E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.01.472

**Research Article**

# Multisystem Determinants of Ischemic Stroke in a Population-Based Cohort

**Muhammad Waqas[1], M. Rizwan Ishaque[2], Masood Uz Zaman Babar[3], Zahid Ahmad Khan[4], Faraz Ahmed[5], Muhammad Wajahat Gohar Qureshi[6]**

1. Assistant Professor, Neurosurgery, MBBS Medical College, Divisional Headquarters Hospital, Mirpur AJK, Pakistan.
2. Assistant Professor, Medicine, Sahiwal Medical College, Sahiwal, Pakistan.
3. Associate Professor, Department of Neurology, Isra University, Hyderabad, Pakistan.
4. Assistant Professor, General Medicine, Mohtarma Benazir Bhutto Shaheed Medical College, Mirpur, Pakistan.
5. Assistant Professor, Neurology, Isra University Hospital, Hyderabad, Pakistan.
6. Senior Registrar, Neurology, Shalamar Medical and Dental College, Lahore, Pakistan.

**Muhammad Waqas: Corresponding author**

**Abstract:** Ischemic stroke remains a leading cause of mortality and long-term neurological disability worldwide. Emerging evidence indicates that cerebrovascular disease is not solely confined to cerebral vascular pathology but rather reflects complex interactions among cardiovascular, metabolic, inflammatory, and renal systems. The objective of the present study was to evaluate multisystem determinants associated with ischemic stroke occurrence and severity in a population-based cohort and to identify statistically significant predictors that may improve early risk stratification. A prospective observational cohort study was conducted among 420 adults recruited from tertiary healthcare institutions and community health centers between January 2023 and February 2025. Participants were categorized into ischemic stroke and non-stroke control groups following neuroimaging confirmation. Demographic variables, cardiovascular parameters, inflammatory biomarkers, renal indices, and metabolic profiles were analyzed using multivariable statistical models. Hypertension, diabetes mellitus, atrial fibrillation, elevated high-sensitivity C-reactive protein, chronic kidney disease, dyslipidemia, and smoking status demonstrated statistically significant associations with ischemic stroke incidence ($p<0.05$). Multivariate regression analysis identified atrial fibrillation (adjusted OR 3.82, 95% CI 2.11–6.94), elevated hsCRP (adjusted OR 2.94, 95% CI 1.76–4.88), and reduced estimated glomerular filtration rate (adjusted OR 2.47, 95% CI 1.41–4.33) as independent predictors. These findings emphasize the synergistic contribution of

inflammatory, metabolic, cardiovascular, and renal dysfunction to ischemic stroke pathogenesis. The study highlights the clinical importance of integrated multisystem assessment in identifying high-risk individuals and demonstrates a novel population-based analytical model that combines systemic biomarkers with conventional cerebrovascular risk factors for improved preventive strategies.

**Keywords**: ischemic stroke; multisystem determinants; population-based cohort

## Introduction

Ischemic stroke represents one of the most clinically significant neurological disorders because of its substantial contribution to mortality, chronic disability, cognitive decline, and socioeconomic burden. The condition results from interruption of cerebral blood flow due to thrombotic or embolic occlusion of cerebral arteries, leading to neuronal ischemia and irreversible tissue injury. Despite advancements in neuroimaging techniques, thrombolytic therapy, and stroke prevention programs, ischemic stroke continues to account for a considerable proportion of global healthcare expenditure and long-term functional impairment. Contemporary epidemiological data indicate a progressive increase in stroke incidence among younger and middle-aged populations, suggesting that modern lifestyle patterns, metabolic abnormalities, and systemic inflammatory conditions are increasingly contributing to cerebrovascular disease progression [1-3].

Traditional stroke research has primarily focused on isolated vascular risk factors such as hypertension and diabetes mellitus. However, current scientific evidence increasingly supports the concept that ischemic stroke should be considered a multisystem disorder involving integrated dysfunction of cardiovascular, renal, inflammatory, endocrine, and metabolic pathways. Persistent hypertension induces endothelial dysfunction, arterial stiffness, cerebral small vessel disease, and impaired autoregulation, thereby predisposing individuals to ischemic cerebral injury. Similarly, diabetes mellitus accelerates oxidative stress, endothelial damage, platelet activation, and atherosclerotic plaque instability. These metabolic and vascular abnormalities collectively increase susceptibility to thromboembolic events and worsen neurological outcomes after stroke [2-5].

Inflammation has emerged as a critical determinant in ischemic stroke pathogenesis. Elevated concentrations of inflammatory biomarkers such as high-sensitivity C-

reactive protein, interleukin-6, and fibrinogen have demonstrated significant associations with endothelial dysfunction, enhanced thrombotic activity, vascular instability, and cerebral ischemia. Chronic systemic inflammation contributes to accelerated atherosclerosis, vascular remodeling, and impairment of cerebral autoregulation mechanisms. Recent studies published after 2022 have emphasized the interaction between inflammatory pathways and atrial fibrillation in increasing the likelihood of cardioembolic stroke [4-7]. These findings indicate that inflammatory biomarkers may provide additional clinical value for identifying high-risk individuals before the occurrence of irreversible neurological injury.

Cardiovascular abnormalities remain among the most important contributors to ischemic stroke development. Atrial fibrillation has consistently demonstrated strong associations with cardioembolic stroke, recurrent vascular events, and increased mortality. Irregular atrial contraction promotes blood stasis and thrombus formation within the left atrium, substantially increasing the probability of cerebral embolization. In addition, structural cardiac dysfunction, impaired ventricular performance, and vascular stiffness frequently coexist in patients with ischemic stroke. Contemporary investigations have reported that the coexistence of hypertension, diabetes mellitus, and atrial fibrillation markedly amplifies cerebrovascular risk and contributes to poor neurological recovery [6-8]. These observations highlight the importance of multidimensional cardiovascular assessment in stroke prevention strategies.

Renal dysfunction has recently gained considerable attention as an independent determinant of cerebrovascular disease. Reduced estimated glomerular filtration rate and chronic kidney disease are associated with endothelial injury, systemic inflammation, oxidative stress, vascular calcification, and impaired autoregulatory mechanisms. Chronic renal impairment additionally contributes to dyslipidemia, anemia, and arterial stiffness, thereby increasing susceptibility to cerebral hypoperfusion and thromboembolic events. Population-based studies conducted during recent years have demonstrated that renal dysfunction significantly increases the risk of recurrent ischemic stroke and major adverse cardiovascular outcomes [7-9]. Nevertheless, limited evidence remains available regarding the combined interaction of renal, inflammatory, metabolic, and cardiovascular

abnormalities within a single population-based cohort.

Lifestyle-related determinants such as smoking, obesity, and physical inactivity also contribute substantially to ischemic stroke burden. Smoking promotes endothelial toxicity, platelet aggregation, oxidative stress, and prothrombotic activity, while obesity is associated with insulin resistance, chronic inflammation, dyslipidemia, and hypertension. Recent evidence indicates that the coexistence of obesity, smoking, and metabolic syndrome substantially accelerates vascular injury and increases stroke severity [8-10]. These multidimensional interactions suggest that ischemic stroke cannot be adequately explained by isolated risk factors alone and instead requires integrated multisystem evaluation.

Although several investigations have explored individual stroke determinants, comprehensive analyses evaluating simultaneous multisystem interactions remain limited, particularly in population-based settings involving diverse cardiovascular and metabolic profiles. Most available studies have concentrated on isolated predictors rather than evaluating the synergistic effects of inflammatory biomarkers, renal dysfunction, atrial fibrillation, and metabolic abnormalities within the same analytical model. Furthermore, there is insufficient regional evidence assessing how these combined systemic determinants influence ischemic stroke susceptibility and severity. Therefore, the present study was designed to evaluate multisystem determinants associated with ischemic stroke in a population-based cohort using a comprehensive statistical approach. The study additionally aimed to identify independent predictors that may improve early risk stratification and contribute to the development of more effective preventive strategies in high-risk populations [1-10].

**Methodology**

A prospective population-based observational cohort study was conducted Divisional Headquarters Hospital after approval from the ethical committee. The study population consisted of adults aged 35–80 years who underwent neurological assessment for suspected cerebrovascular disease. Participants were categorized into ischemic stroke and non-stroke control groups following radiological confirmation using computed tomography or magnetic resonance imaging. The study design was structured to evaluate the association between multisystem clinical determinants and ischemic stroke occurrence through comprehensive demographic, cardiovascular,

inflammatory, renal, and metabolic assessment.

Sample size calculation was performed using OpenEpi version 3.01 software by considering a confidence level of 95%, statistical power of 80%, anticipated exposure frequency among controls of 30%, odds ratio of 2.0, and equal ratio of cases to controls. The minimum required sample size was calculated as 384 participants. However, to improve statistical precision and compensate for incomplete data or participant withdrawal, a total of 420 individuals were ultimately enrolled, including 210 ischemic stroke patients and 210 age-matched controls.

Inclusion criteria consisted of adults with first-episode ischemic stroke confirmed within 72 hours of symptom onset by neuroimaging. Age-matched community participants without previous cerebrovascular disease were included in the control group. Exclusion criteria included hemorrhagic stroke, transient ischemic attack without radiological evidence, malignancy, severe hepatic dysfunction, autoimmune disease, pregnancy, active infection, recent major surgery, and incomplete laboratory investigations. Participants with recurrent stroke or severe cognitive impairment preventing clinical evaluation were also excluded from the study.

Verbal informed consent was obtained from all participants or legally authorized attendants before enrollment. Confidentiality of participant information was maintained throughout the study period. Ethical approval was obtained from the institutional ethical review committee according to the principles outlined in the Declaration of Helsinki for human subject research.

Detailed demographic and clinical information including age, gender, smoking history, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and chronic kidney disease was recorded using structured questionnaires and verified through medical records. Anthropometric assessment included body mass index calculation and standardized blood pressure measurements. Stroke severity at admission was assessed using the National Institutes of Health Stroke Scale.

Venous blood samples were collected after overnight fasting for measurement of fasting blood glucose, serum creatinine, lipid profile, and high-sensitivity C-reactive protein. Estimated glomerular filtration rate was calculated using the CKD-EPI equation. Electrocardiography was performed for detection of atrial fibrillation and associated

cardiac abnormalities. All laboratory investigations were performed in standardized institutional laboratories using calibrated automated analyzers.

Data analysis was performed using SPSS version 26.0. Quantitative variables were expressed as mean ± standard deviation, whereas categorical variables were summarized as frequencies and percentages. Independent sample t-tests were applied for comparison of continuous variables between study groups, while chi-square tests were used for categorical variables. Multivariate logistic regression analysis was conducted to identify independent predictors of ischemic stroke after adjustment for confounding variables. Odds ratios with 95% confidence intervals were calculated. A p value less than 0.05 was considered statistically significant for all analyses.

## Results

**Table 1. Demographic and Clinical Characteristics of Study Participants**

| Variable | Stroke Group (n=210) | Control Group (n=210) | p-value |
|---|---|---|---|
| Age (years) | 64.8±9.7 | 57.1±8.5 | <0.001 |
| Male gender | 132 (62.9%) | 118 (56.2%) | 0.172 |
| Hypertension | 156 (74.3%) | 92 (43.8%) | <0.001 |
| Diabetes mellitus | 118 (56.2%) | 70 (33.3%) | <0.001 |
| Smoking | 92 (43.8%) | 58 (27.6%) | 0.001 |
| Atrial fibrillation | 68 (32.4%) | 24 (11.4%) | <0.001 |
| Chronic kidney disease | 54 (25.7%) | 26 (12.4%) | 0.002 |
| BMI (kg/m²) | 28.4±3.9 | 26.2±3.1 | <0.001 |

Table 1 demonstrates the demographic and clinical characteristics of study participants. Patients with ischemic stroke showed significantly higher frequencies of hypertension, diabetes mellitus, smoking, atrial fibrillation, chronic kidney disease, and elevated body mass index compared with controls. Mean age was also significantly higher among stroke patients.

**Table 2. Laboratory and Physiological Findings**

| Biochemical Parameter | Stroke Group | Control Group | p-value |
|---|---|---|---|
| Fasting glucose (mg/dL) | 164.5±34.2 | 128.1±26.8 | <0.001 |
| Total cholesterol (mg/dL) | 224.8±39.1 | 196.7±31.2 | <0.001 |
| LDL cholesterol (mg/dL) | 142.2±30.4 | 118.4±24.1 | <0.001 |
| hsCRP (mg/L) | 8.4±2.9 | 4.1±1.7 | <0.001 |
| eGFR (mL/min/1.73m²) | 63.7±16.1 | 82.5±14.8 | <0.001 |
| Systolic BP (mmHg) | 154.7±18.4 | 136.5±15.2 | <0.001 |

Table 2 summarizes laboratory and physiological findings. Significantly elevated fasting glucose, lipid levels, hsCRP, and systolic blood pressure were observed in the stroke group, whereas estimated glomerular filtration rate was significantly reduced. These findings support the interaction between inflammatory, renal, and metabolic dysfunction in ischemic stroke pathogenesis.

**Table 3. Multivariate Logistic Regression Analysis of Independent Predictors**

| Independent Predictor | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| Hypertension | 2.31 | 1.42–3.76 | 0.001 |
| Diabetes mellitus | 1.88 | 1.16–3.05 | 0.011 |
| Smoking | 1.74 | 1.01–2.99 | 0.044 |
| Atrial fibrillation | 3.82 | 2.11–6.94 | <0.001 |
| Elevated hsCRP | 2.94 | 1.76–4.88 | <0.001 |
| Reduced eGFR | 2.47 | 1.41–4.33 | 0.002 |

Multivariate logistic regression analysis identified atrial fibrillation as the strongest independent predictor of ischemic stroke followed by elevated hsCRP and reduced renal function. All predictors retained statistical significance after adjustment for confounding variables.

**Discussion**

The present population-based cohort study demonstrated that ischemic stroke is strongly

associated with multisystem dysfunction involving cardiovascular, inflammatory, metabolic, and renal abnormalities. Hypertension was highly prevalent among stroke patients and retained independent significance after multivariate adjustment. Persistent elevation in blood pressure contributes to endothelial injury, arterial remodeling, cerebral microangiopathy, and disruption of vascular autoregulation, all of which increase vulnerability to ischemic cerebral injury. Contemporary studies have similarly identified hypertension as the leading modifiable determinant of stroke incidence and recurrence across diverse populations [11-12]. The present findings reinforce the importance of aggressive blood pressure control in high-risk populations.

Diabetes mellitus also demonstrated a statistically significant association with ischemic stroke occurrence. Hyperglycemia accelerates oxidative stress, endothelial dysfunction, platelet activation, and atherosclerotic progression, thereby increasing susceptibility to cerebral ischemia. Elevated fasting blood glucose observed in the present cohort further supports the contribution of metabolic dysregulation to vascular injury. Recent investigations published between 2021 and 2024 have consistently reported that diabetes increases the risk of both primary and recurrent ischemic stroke while adversely affecting neurological recovery and mortality outcomes [12-14]. The current findings therefore support integrated metabolic monitoring as an essential component of stroke prevention strategies.

One of the most clinically significant observations of the present study was the strong independent association between atrial fibrillation and ischemic stroke. Patients with atrial fibrillation demonstrated markedly increased odds of stroke occurrence even after adjustment for confounding variables. This observation is consistent with the pathophysiological role of atrial blood stasis and thrombus formation leading to cardioembolic cerebral occlusion. Recent cohort analyses have highlighted the temporal relationship between atrial fibrillation episodes and acute ischemic events, emphasizing the importance of early rhythm monitoring and anticoagulation therapy [13-15]. The present findings additionally indicate that atrial fibrillation frequently coexists with hypertension and diabetes, suggesting a synergistic interaction among cardiovascular determinants.

Inflammatory activity represented another important determinant in the current cohort. Significantly elevated hsCRP levels were

observed among ischemic stroke patients, and multivariate regression confirmed hsCRP as an independent predictor of stroke occurrence. Chronic inflammation promotes endothelial dysfunction, vascular instability, and enhanced thrombotic activity through activation of inflammatory cytokines and coagulation pathways. Contemporary evidence has increasingly recognized inflammatory biomarkers as clinically relevant indicators of cerebrovascular risk and disease severity [14-16]. The present study supports the hypothesis that systemic inflammatory activation may contribute substantially to ischemic stroke pathogenesis and should be considered during cardiovascular risk assessment.

Renal dysfunction was also independently associated with ischemic stroke in the current study. Reduced estimated glomerular filtration rate demonstrated a significant inverse relationship with stroke occurrence. Chronic kidney disease contributes to oxidative stress, vascular calcification, endothelial dysfunction, and persistent inflammatory activation, thereby facilitating cerebral vascular injury. Several recent studies have similarly demonstrated that impaired renal function and variability in renal indices increase the risk of recurrent stroke and major adverse cardiovascular outcomes [15-17]. The present findings therefore emphasize the need for integrated renal assessment in cerebrovascular risk stratification models.

Dyslipidemia and obesity additionally contributed to ischemic stroke susceptibility within the study population. Elevated low-density lipoprotein cholesterol and body mass index observed among stroke patients indicate that lipid abnormalities and adiposity remain important contributors to atherosclerotic plaque formation and vascular inflammation. Smoking further intensified cerebrovascular risk through endothelial toxicity and prothrombotic mechanisms. Previous investigations have shown that the coexistence of smoking, dyslipidemia, and hypertension markedly accelerates vascular injury and worsens clinical outcomes following ischemic stroke [16-18]. The combined influence of these determinants observed in the current study highlights the importance of multidimensional lifestyle and metabolic interventions.

The present study possesses several strengths including its population-based design, comprehensive multisystem assessment, and evaluation of statistically significant independent predictors using multivariate regression analysis. However, certain

limitations should be acknowledged. The study was conducted within a limited geographic region, which may reduce generalizability to broader populations. Inflammatory biomarkers beyond hsCRP were not extensively evaluated, and long-term neurological follow-up was not available for all participants. Despite these limitations, the study provides clinically relevant evidence supporting integrated cardiovascular, inflammatory, metabolic, and renal assessment for early identification of individuals at elevated risk of ischemic stroke [18-20].

**Conclusion**

Ischemic stroke was significantly associated with multisystem dysfunction involving cardiovascular, inflammatory, metabolic, and renal abnormalities. Atrial fibrillation, elevated hsCRP, hypertension, diabetes mellitus, and reduced renal function emerged as major independent predictors of stroke occurrence. The findings address an important research gap by demonstrating the synergistic contribution of multiple systemic determinants and support future large-scale longitudinal investigations focusing on integrated risk prediction models.

**References**

1. Feigin VL, Brainin M, Norrving B, et al. World Stroke Organization global stroke fact sheet 2022. Int J Stroke. 2022;17(1):18-29. DOI: https://doi.org/10.1177/17474930211065917
2. Kablak-Ziembicka A, Przewlocki T. Clinical significance of carotid intima-media complex and carotid plaque assessment by ultrasound for the prediction of adverse cardiovascular events in primary and secondary care patients. J Clin Med. 2021;10(20):4628. DOI: https://doi.org/10.3390/jcm10204628
3. Ziegler L, Wallén H, Aspberg S, et al. IL6 trans-signaling associates with ischemic stroke but not with atrial fibrillation. BMC Neurol. 2021;21:306. DOI: https://doi.org/10.1186/s12883-021-02321-6
4. Xu C, Fu Z, Wu W, et al. Association between high-sensitivity C-reactive protein and blood pressure variability in subacute stage of ischemic stroke. Brain Sci. 2023;13(7):998. DOI: https://doi.org/10.3390/brainsci13070998
5. Guo J, Tian M, Li Y, et al. Exploring clinical indicator variations in stroke patients with multiple risk factors: focus on hypertension and inflammatory reactions. Eur J Med Res. 2024;29:81. DOI: https://doi.org/10.1186/s40001-024-01653-6
6. Singer DE, Ziegler PD, Koehler JL, et al. Temporal association between episodes of atrial fibrillation and risk of ischemic stroke. JAMA Cardiol. 2021;6(12):1364-1369. DOI:

https://doi.org/10.1001/jamacardio.2021.3702

7. Wang X, Sin CF, Teo KC, et al. Impact of renal function variability on long-term prognosis in ischemic stroke patients with atrial fibrillation. Front Neurol. 2024;15:1294022. DOI: https://doi.org/10.3389/fneur.2024.1294022
8. Liu Q, Wu S, Shao J, et al. Metabolic syndrome parameters' variability and stroke incidence in hypertensive patients: evidence from a functional community cohort. Cardiovasc Diabetol. 2024;23:203. DOI: https://doi.org/10.1186/s12933-024-02282-3
9. Rathfoot C, Edrissi C, Sanders CB, et al. Gender differences in comorbidities and risk factors in ischemic stroke patients with a history of atrial fibrillation. BMC Neurol. 2021;21:209. DOI: https://doi.org/10.1186/s12883-021-02214-8
10. Peter A, Ayaz SB, Aadil M. Association of atrial fibrillation with age, gender, hypertension, and diabetes mellitus in cases of ischemic stroke. Pak Armed Forces Med J. 2023;73(Suppl-1):S229-S233. DOI: https://doi.org/10.51253/pafmj.v73iSUPPL-1.4267
11. Elkind MSV, Boehme AK, Smith CJ, et al. Infection as a stroke risk factor and determinant of outcome after stroke. Stroke. 2022;53(10):3150-3159. DOI: https://doi.org/10.1161/STROKEAHA.122.036859
12. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2023 update. Circulation. 2023;147(8):e93-e621. DOI: https://doi.org/10.1161/CIR.0000000000001123
13. Yaghi S, Kamel H. Stratifying stroke risk in atrial fibrillation: beyond clinical risk scores. Stroke. 2022;53(8):2665-2673. DOI: https://doi.org/10.1161/STROKEAHA.121.036859
14. Kelly DM, Rothwell PM. Disentangling the multiple links between renal dysfunction and cerebrovascular disease. J Neurol Neurosurg Psychiatry. 2022;93(1):88-97. DOI: https://doi.org/10.1136/jnnp-2021-327123
15. Arnett DK, Blumenthal RS, Albert MA, et al. Guideline on the primary prevention of cardiovascular disease: implications for stroke prevention. Circulation. 2022;146:e78-e114. DOI: https://doi.org/10.1161/CIR.0000000000000678
16. Tu WJ, Zhao Z, Yin P, et al. Estimated burden of stroke in China in 2020. JAMA Netw Open. 2023;6(3):e231455. DOI: https://doi.org/10.1001/jamanetworkopen.2023.1455

17. Towfighi A, Ovbiagele B. Elusive connection between obesity and stroke. Stroke. 2021;52(5):1675-1682. DOI: https://doi.org/10.1161/STROKEAHA.120.033534
18. Campia U, Gerhard-Herman M, Piazza G, et al. Smoking, cardiovascular disease, and stroke: a review. J Am Coll Cardiol. 2022;80(17):1688-1701. DOI: https://doi.org/10.1016/j.jacc.2022.08.759
21. .
19. Diener HC, Hankey GJ. Primary and secondary prevention of ischemic stroke and cerebral hemorrhage. J Am Coll Cardiol. 2023;81(12):1231-1248. DOI: https://doi.org/10.1016/j.jacc.2023.01.042
20. Norrving B, Barrick J, Davalos A, et al. Action plan for stroke in Europe 2018-2030: update and future directions. Eur Stroke J. 2024;9(1):5-22. DOI: https://doi.org/10.1177/23969873231214567