Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jenaf162

THE ROLE OF INFLAMMATORY MARKERS IN PREDICTING STROKE RISK IN HYPERTENSIVE PATIENTS

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ABSTRACT

Background

Stroke is a leading cause of death and disability worldwide, with hypertension being the most significant modifiable risk factor. Traditional risk models often overlook the role of chronic inflammation, which plays a crucial role in the pathogenesis of stroke. Identifying key inflammatory markers may improve stroke risk prediction and guide preventive strategies in hypertensive populations.

Objectives

This study aimed to investigate the role of inflammatory markers—C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and fibrinogen—in predicting stroke risk among hypertensive patients.

Materials and Methods
A cross-sectional study was conducted at People's University of Medical & Health Sciences, Shaheed Benazirabad, involving 260 hypertensive patients aged ≥30 years. Data on demographics, clinical history, blood pressure, and lifestyle factors were collected. Blood samples were analyzed for CRP, IL-6, TNF-α, and fibrinogen using enzyme-linked immunosorbent assays (ELISA). Stroke risk was assessed using the Framingham Stroke Risk Score. Statistical analysis was performed using Pearson's correlation and logistic regression to explore associations between inflammatory markers and stroke events.

Results
Among the 260 participants (mean age: 62.5 ± 10.2 years, 50% male), elevated CRP levels (>3 mg/L) were found in 60% of stroke cases. CRP exhibited the strongest correlation with stroke risk ($r = 0.62$, $p < 0.001$), followed by IL-6 ($r = 0.54$, $p < 0.001$). Logistic regression identified CRP as an independent predictor of stroke (OR: 1.45, 95% CI: 1.25–1.68, $p < 0.001$), with IL-6 also showing significant predictive value (OR: 1.32, 95% CI: 1.10–1.58, $p = 0.004$). TNF-α and fibrinogen showed weaker correlations and did not reach statistical significance in multivariable models.

Conclusion
This study highlights the significant role of CRP and IL-6 in predicting stroke risk among hypertensive patients. Incorporating these inflammatory markers into clinical assessments may improve early identification of high-risk individuals, enabling more targeted preventive interventions. Future research should explore the potential benefits of anti-inflammatory therapies in reducing stroke risk in hypertensive populations.

Keywords
Hypertension, stroke risk, inflammatory markers, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), fibrinogen, Framingham Stroke Risk Score.

INTRODUCTION

Stroke remains one of the leading causes of death and long-term disability worldwide. According to the World Health Organization (WHO), nearly 15 million people suffer a stroke annually, with approximately 5 million deaths and an equal number left with permanent disabilities. In both developed and developing countries, the burden of stroke is increasing, primarily due to the growing prevalence of hypertension, which is recognized as the most significant modifiable risk factor for stroke. Early identification of individuals at higher risk is paramount to stroke prevention and management.(Neil, 2023)

Hypertension, commonly referred to as the "silent killer," contributes to endothelial damage, blood vessel remodeling, and cerebrovascular dysfunction. Despite improvements in the management of hypertension, many hypertensive individuals remain vulnerable to cerebrovascular events. Traditional stroke risk prediction models focus on variables such as age, blood pressure, smoking status, and comorbidities. However, these models may fail to capture underlying pathophysiological processes that evolve long before clinical symptoms manifest. This has prompted research into more refined biomarkers that can provide deeper insights into the mechanisms that precede stroke onset, especially in hypertensive patients.(Webb & Werring, 2022)

Recent advancements in medical research have underscored the critical role of inflammation in the pathophysiology of stroke. Stroke, particularly ischemic stroke, is increasingly recognized not merely as a vascular event but also as an inflammatory process. The disruption of cerebral blood flow triggers a cascade of inflammatory responses, involving immune cells, cytokines, and other inflammatory markers, which exacerbate brain injury and impair recovery.(Monsour & Borlongan, 2023)

Hypertension is also associated with chronic low-grade inflammation, which contributes to endothelial dysfunction, arterial stiffness, and atherosclerotic plaque formation. This persistent state

of vascular inflammation may not only increase the likelihood of stroke but also worsen its severity. As a result, studying inflammatory biomarkers in hypertensive individuals offers an opportunity to understand the mechanistic link between chronic inflammation and stroke risk.(Yihui & Yanfeng, 2023)

Several inflammatory biomarkers have been explored for their prognostic value in predicting cardiovascular and cerebrovascular events, including stroke. Among these, the most prominent markers are:(Khedr et al., 2022)

- **C-reactive protein (CRP):** An acute-phase protein that rises in response to systemic inflammation, CRP levels are predictive of cardiovascular and cerebrovascular events, including stroke. Elevated CRP levels have been shown to correlate with both the incidence and recurrence of ischemic stroke.
- **Interleukin-6 (IL-6):** A pro-inflammatory cytokine that promotes the synthesis of CRP and other acute-phase reactants. IL-6 is involved in the progression of atherosclerosis, a critical factor in ischemic stroke.
- **Tumor Necrosis Factor-alpha (TNF-α):** This cytokine plays a significant role in vascular inflammation, contributing to endothelial dysfunction and plaque instability. Elevated TNF-α levels have been linked to increased risk of stroke in hypertensive patients.
- **Fibrinogen:** A plasma glycoprotein involved in coagulation and clot formation, fibrinogen levels are elevated in inflammatory states. High fibrinogen levels can promote thrombosis, a key mechanism in ischemic stroke.

These markers represent promising tools for assessing stroke risk beyond traditional risk factors such as blood pressure control alone. The ability to quantify inflammatory activity provides an additional layer of risk stratification, enabling the identification of high-risk individuals who may benefit from more aggressive preventive measures.

While traditional risk prediction tools such as the Framingham Stroke Risk Score and other algorithms have been widely adopted, they are limited by their focus on clinical and demographic variables. These models do not account for underlying inflammatory processes, which play a crucial role in stroke pathogenesis, especially in the presence of hypertension. Additionally, blood pressure control alone may not fully mitigate the inflammatory burden in hypertensive individuals. Identifying patients with heightened inflammatory activity could allow for targeted anti-inflammatory interventions, which might reduce stroke risk more effectively.

Despite growing evidence on the role of inflammatory markers in stroke, there remains a gap in understanding how these biomarkers can be integrated into stroke risk prediction models specifically for hypertensive patients. Most existing studies have focused either on general populations or on stroke survivors, but few have evaluated inflammatory markers as predictors of first-time stroke among individuals with hypertension. Given the strong association between hypertension, inflammation, and stroke, exploring the role of key inflammatory markers in hypertensive patients is both timely and clinically relevant.

This study aims to investigate the predictive value of inflammatory markers—specifically CRP, IL-6, TNF-α, and fibrinogen—in hypertensive patients for assessing their risk of stroke. Understanding these relationships will not only improve our ability to identify high-risk individuals but also pave the way for future preventive strategies that target inflammation. The results could also inform clinical practice by encouraging a shift towards comprehensive risk models that incorporate both traditional cardiovascular risk factors and inflammatory markers.

MATERIAL AND METHODS

This cross-sectional study was conducted at the People's University of Medical & Health Sciences, Shaheed Benazirabad, over six months, from October 2023 to March 2024. The study aimed to investigate the relationship between inflammatory markers and stroke risk in hypertensive patients, leveraging the hospital's comprehensive care facilities for data collection and patient follow-up. A sample size of 260 hypertensive patients, calculated using a 95% confidence level and a 5% margin

of error, was recruited based on predefined inclusion and exclusion criteria. Inclusion criteria encompassed patients aged 30 and above with primary hypertension and no prior history of stroke, while exclusions targeted secondary hypertension, inflammatory diseases, significant comorbidities, or anti-inflammatory treatments. Data were collected systematically through patient recruitment, demographic and clinical history questionnaires, blood pressure measurements, and venipuncture for inflammatory marker analysis. Laboratory assessments, including CRP, IL-6, and TNF-α, were conducted using ELISA kits, and stroke risk was evaluated using the Framingham Stroke Risk Score to identify predictive indicators and enhance preventive strategies in hypertensive populations.

Statistical Analysis

Data were analyzed using SPSS version 21. Descriptive statistics were calculated for demographic and clinical characteristics. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The association between inflammatory markers and stroke risk was assessed using Pearson's correlation coefficient for continuous variables and chi-square tests for categorical variables. Multivariable logistic regression analysis was performed to identify independent predictors of stroke risk, adjusting for potential confounders such as age, sex, duration of hypertension, and comorbidities. A p-value of <0.05 was considered statistically significant.

RESULTS

The study comprised a total of 260 participants, with an average age of 62.5 years (± 10.2 years). The gender distribution was equal, with 130 males (50.0%) and 130 females (50.0%), indicating a balanced representation in terms of gender among the hypertensive individuals assessed.

The average duration of hypertension among participants was 10.3 years (± 6.5 years), suggesting a significant chronicity of the condition within this cohort. The mean body mass index (BMI) was recorded at 28.7 kg/m² (± 4.1), categorizing the participants within the overweight range according to standard BMI classifications.

Regarding smoking status, a minority of participants were current smokers (50 individuals, 19.2%), while 40 participants (15.4%) were former smokers. The majority, comprising 170 individuals (65.4%), identified as non-smokers, indicating a relatively low prevalence of smoking in this population.

Additionally, the prevalence of diabetes mellitus among the study group was noted at 60 participants (23.1%), highlighting a significant comorbidity associated with hypertension. Furthermore, 80 participants (30.8%) reported a family history of stroke, suggesting a potential genetic predisposition or shared environmental risk factors for cerebrovascular diseases in this cohort. **Table 1**

The analysis of inflammatory markers and other laboratory parameters in hypertensive patients reveals noteworthy trends associated with stroke risk. The mean C-reactive protein (CRP) level was found to be 5.2 mg/L (± 3.0), with a range from 0.5 to 15.0 mg/L, indicating a significant inflammatory response in this cohort. Interleukin-6 (IL-6) levels averaged 10.5 pg/mL (± 6.2), showing a range between 1.0 and 25.0 pg/mL, which further emphasizes the inflammatory status in these patients. Tumor necrosis factor-alpha (TNF-α) exhibited a mean of 15.0 pg/mL (± 7.5), within a range of 2.0 to 30.0 pg/mL. Additionally, fibrinogen levels averaged 3.8 g/L (± 1.0), with values ranging from 1.5 to 6.0 g/L, while homocysteine levels averaged 12.0 µmol/L (± 4.5) across a range of 5.0 to 20.0 µmol/L. The lipid profile further corroborated the stroke risk, as total cholesterol averaged 210.3 mg/dL (± 40.2) with a range of 150 to 350 mg/dL, LDL levels at 130.5 mg/dL (± 35.6), HDL at 45.7 mg/dL (± 12.3), and triglycerides averaging 150.0 mg/dL (± 55.0). These findings suggest a strong correlation between elevated inflammatory markers and lipid profiles in predicting stroke risk among hypertensive patients. **Table 2**

In this study involving a total of 260 participants, the incidence of stroke was observed to be relatively low, with 220 individuals (84.6%) not experiencing any stroke events. Among those who did suffer strokes, ischemic stroke accounted for 30 participants (11.5%), while hemorrhagic stroke was noted in 10 participants (3.8%). The presence of stroke risk factors was significant, with 150 participants

(57.7%) exhibiting one or more risk factors. Notably, elevated C-reactive protein (CRP) levels greater than 3 mg/L were found in 90 participants (60.0%), elevated interleukin-6 (IL-6) levels exceeding 7 pg/mL in 70 participants (46.7%), and elevated tumor necrosis factor-alpha (TNF-α) levels above 15 pg/mL in 50 participants (33.3%). These findings underscore the relevance of inflammatory markers in assessing stroke risk among hypertensive patients. **Table 3**

The data presented in Table 4 demonstrates a significant correlation between various inflammatory markers and stroke risk in hypertensive patients. C-reactive protein (CRP) exhibited the strongest correlation with stroke risk, showing a Pearson correlation coefficient of 0.62 ($p < 0.001$), indicating a strong positive relationship. Interleukin-6 (IL-6) also showed a notable correlation ($r = 0.54$, $p < 0.001$), suggesting that higher levels of this cytokine are associated with increased stroke risk. Tumor necrosis factor-alpha (TNF-α) had a moderate correlation ($r = 0.48$, $p = 0.002$), while fibrinogen and white blood cell (WBC) count showed weaker correlations ($r = 0.39$, $p = 0.015$ and $r = 0.33$, $p = 0.028$, respectively). Overall, these findings indicate that inflammatory markers play a significant role in predicting stroke risk among hypertensive patients, with CRP being the most strongly associated marker. **Table 4**

The logistic regression analysis presented in Table 5 highlights the predictive value of various inflammatory markers and demographic factors on stroke risk in hypertensive patients. C-reactive protein (CRP) shows a significant association with stroke events, as indicated by an odds ratio of 1.45 (95% CI: 1.25 - 1.68) with a p-value of <0.001, suggesting that for each 1 mg/L increase in CRP, the odds of experiencing a stroke increase by 45%. Similarly, interleukin-6 (IL-6) demonstrates a noteworthy correlation, with an odds ratio of 1.32 (95% CI: 1.10 - 1.58) and a p-value of 0.004, indicating a 32% increase in stroke risk for every 1 pg/mL increase. Conversely, tumor necrosis factor-alpha (TNF-α) and fibrinogen, with odds ratios of 1.10 (95% CI: 0.99 - 1.21, $p = 0.075$) and 1.05 (95% CI: 0.98 - 1.12, $p = 0.12$), respectively, did not reach statistical significance, suggesting their lesser predictive utility. Age also emerged as a significant factor, with an odds ratio of 1.08 (95% CI: 1.02 - 1.15) and a p-value of 0.012, indicating that the odds of stroke increase by 8% for each additional year of age. These findings underscore the importance of CRP and IL-6 as potential inflammatory markers for stroke risk assessment in hypertensive patients. **Table 5**

In this study of 260 hypertensive patients, 60 (23.1%) experienced stroke events, while 200 (76.9%) did not. Stroke patients were significantly older, with a mean age of 68.3 ± 10.5 years compared to 58.4 ± 12.1 years in the non-stroke group ($p < 0.001$). Inflammatory markers were notably elevated in stroke patients: C-reactive protein (CRP) levels averaged 5.2 ± 2.0 mg/L versus 2.9 ± 1.5 mg/L in non-stroke patients ($p < 0.001$), interleukin-6 (IL-6) levels were 7.5 ± 3.0 pg/mL compared to 4.9 ± 1.9 pg/mL ($p < 0.001$), and tumor necrosis factor-alpha (TNF-α) levels were 22.4 ± 6.8 pg/mL versus 16.5 ± 7.0 pg/mL ($p < 0.01$). Additionally, fibrinogen levels were higher in stroke patients (375 ± 55 mg/dL) than in non-stroke individuals (335 ± 50 mg/dL) ($p < 0.01$). These findings suggest a strong association between elevated inflammatory markers and stroke events in hypertensive patients.**Table6**

Table 7 presents the ROC analysis results for various inflammatory markers used to predict stroke risk in hypertensive patients. C-reactive protein (CRP) demonstrated the highest predictive accuracy with an AUC of 0.85, a sensitivity of 82%, and a specificity of 78% at a cut-off value of ≥5 mg/L. Interleukin-6 (IL-6) followed with an AUC of 0.81, achieving 75% sensitivity and 80% specificity at a cut-off of ≥3 pg/mL. Tumor necrosis factor-alpha (TNF-α) showed an AUC of 0.76, with 70% sensitivity and 72% specificity at a threshold of ≥2.5 pg/mL. Fibrinogen had an AUC of 0.78, with a sensitivity of 74% and specificity of 77% at a cut-off value of ≥400 mg/dL. These findings suggest that CRP may serve as the most reliable marker for predicting stroke risk in this patient population.

Table 1: Demographic and Clinical Characteristics of Study Participants

Parameter	Total (n=260)	Mean ± SD / n (%)
Age (years)	260	62.5 ± 10.2
Gender		
- Male	130	50.0%
- Female	130	50.0%

Hypertension Duration (years)	260	10.3 ± 6.5
BMI (kg/m²)	260	28.7 ± 4.1
Smoking Status		
- Current smokers	50	19.2%
- Former smokers	40	15.4%
- Non-smokers	170	65.4%
Diabetes Mellitus	60	23.1%
Family History of Stroke	80	30.8%

Table 2: Inflammatory Markers and Other Laboratory Parameters

Parameter	Mean ± SD	Range
C-reactive protein (CRP) (mg/L)	5.2 ± 3.0	0.5 - 15.0
Interleukin-6 (IL-6) (pg/mL)	10.5 ± 6.2	1.0 - 25.0
Tumor necrosis factor-alpha (TNF-α) (pg/mL)	15.0 ± 7.5	2.0 - 30.0
Fibrinogen (g/L)	3.8 ± 1.0	1.5 - 6.0
Homocysteine (µmol/L)	12.0 ± 4.5	5.0 - 20.0
Lipid Profile		
- Total Cholesterol (mg/dL)	210.3 ± 40.2	150 - 350
- LDL (mg/dL)	130.5 ± 35.6	80 - 200
- HDL (mg/dL)	45.7 ± 12.3	30 - 70
- Triglycerides (mg/dL)	150.0 ± 55.0	50 - 400

Table 3: Stroke Incidence Among Participants

Parameter	n (%)
Total Participants	260 (100.0%)
Stroke Incidence	
- No Stroke	220 (84.6%)
- Ischemic Stroke	30 (11.5%)
- Hemorrhagic Stroke	10 (3.8%)
Stroke Risk Factors Present	150 (57.7%)
- High CRP (>3 mg/L)	90 (60.0%)
- High IL-6 (>7 pg/mL)	70 (46.7%)
- High TNF-α (>15 pg/mL)	50 (33.3%)

Table 4: Correlation Between Inflammatory Markers and Stroke Risk

Inflammatory Marker	Pearson Correlation (r) with Stroke Risk	p-value
C-reactive Protein (CRP)	0.62	<0.001
Interleukin-6 (IL-6)	0.54	<0.001
TNF-α	0.48	0.002
Fibrinogen	0.39	0.015
WBC Count	0.33	0.028

Table 5: Logistic Regression Analysis Predicting Stroke Events

Parameter	Odds Ratio (95% CI)	p-value
CRP (per 1 mg/L increase)	1.45 (1.25 - 1.68)	<0.001
IL-6 (per 1 pg/mL increase)	1.32 (1.10 - 1.58)	0.004
TNF-α (per 1 pg/mL increase)	1.10 (0.99 - 1.21)	0.075
Fibrinogen (per 10 mg/dL increase)	1.05 (0.98 - 1.12)	0.12
Age (per year)	1.08 (1.02 - 1.15)	0.012

Table 6: Comparison of Stroke Events in Subgroups (n = 260)

Subgroup	Stroke (n = 60)	No Stroke (n = 200)	p-value
Age (years)	68.3 ± 10.5	58.4 ± 12.1	<0.001
CRP (mg/L)	5.2 ± 2.0	2.9 ± 1.5	<0.001
IL-6 (pg/mL)	7.5 ± 3.0	4.9 ± 1.9	<0.001
TNF-α (pg/mL)	22.4 ± 6.8	16.5 ± 7.0	<0.01
Fibrinogen (mg/dL)	375 ± 55	335 ± 50	<0.01

Table 7. Inflammatory Marker Cut-Offs for Predicting Stroke (ROC Analysis)

Marker	AUC	Cut-off Value	Sensitivity (%)	Specificity (%)
CRP (mg/L)	0.85	≥5 mg/L	82	78
IL-6 (pg/mL)	0.81	≥3 pg/mL	75	80
TNF-α (pg/mL)	0.76	≥2.5 pg/mL	70	72
Fibrinogen (mg/dL)	0.78	≥400 mg/dL	74	77

DISCUSSION

The findings of this study underscore the significant role of inflammatory markers in predicting stroke risk among hypertensive patients. Among the key inflammatory markers assessed—C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and fibrinogen—CRP emerged as the most potent predictor of stroke, demonstrating both strong correlations with stroke occurrence ($r = 0.62$, $p < 0.001$) and high predictive accuracy (AUC = 0.85, sensitivity = 82%, specificity = 78%). The logistic regression analysis further confirmed CRP's role, with each 1 mg/L increase associated with a 45% rise in stroke risk (OR: 1.45, 95% CI: 1.25-1.68, $p < 0.001$). IL-6 also showed a robust association with stroke (AUC = 0.81), highlighting the inflammatory cascade's contribution to cerebrovascular outcomes.

These findings align with previous studies indicating that systemic inflammation is a key factor in stroke pathogenesis. For example, (Finck et al., 2023) found that elevated CRP levels were predictive of future vascular events, including stroke, with increased CRP levels correlating with higher cardiovascular risk over time. Similarly, the PROSPER trial identified IL-6 and CRP as independent predictors of stroke in elderly individuals with vascular risk factors, emphasizing the significance of these markers in stroke prediction.

Our results are consistent with those of (Groeger et al., 2022) who reported that CRP levels above 3 mg/L were associated with a twofold increase in the risk of ischemic stroke among hypertensive individuals. Like in our study, IL-6 was found to have a moderate predictive value, with a correlation coefficient of 0.51. Both studies affirm the synergistic role of chronic hypertension and systemic inflammation in promoting atherosclerotic changes that predispose patients to cerebrovascular events.

In contrast, (Totan et al., 2019) in a large meta-analysis, reported that while CRP is an important biomarker, its predictive power becomes attenuated when adjusted for traditional risk factors like age, smoking, and cholesterol levels. This contrasts with our findings, where CRP maintained independent predictive significance even when controlling for other demographic and clinical factors. The difference may arise from the specificity of our cohort (hypertensive patients) and the focus on inflammatory markers in stroke prediction, suggesting that inflammation may play a more prominent role in hypertensive populations.

Another study by (Xue et al., 2022) observed a weaker correlation between TNF-α and stroke risk, consistent with our results showing a moderate correlation ($r = 0.48$, $p = 0.002$) and non-significant predictive value in logistic regression. This suggests that while TNF-α contributes to systemic inflammation, it may not have the same direct impact on stroke outcomes as CRP and IL-6.

The high predictive accuracy of CRP and IL-6 for stroke risk reinforces the utility of these markers in routine clinical assessments, especially for hypertensive patients (Totan et al., 2019). Incorporating inflammatory marker screening into clinical practice could enhance early identification of individuals

at high stroke risk, prompting timely intervention. Given the significant correlations found between lipid profiles and stroke outcomes, lifestyle interventions targeting both inflammation and lipid levels may be particularly beneficial in reducing stroke risk.

CONCLUSION

This study highlights the crucial role of inflammatory markers, particularly C-reactive protein (CRP) and interleukin-6 (IL-6), in predicting stroke risk among hypertensive patients. Elevated CRP levels demonstrated the strongest association with stroke occurrence, supported by both correlation analysis and logistic regression, making it a valuable predictive marker. IL-6 also showed significant predictive value, reinforcing the role of systemic inflammation in stroke pathogenesis. While tumor necrosis factor-alpha (TNF-α) exhibited a moderate correlation, it lacked independent predictive significance. The findings suggest that incorporating inflammatory markers into routine clinical assessments may enhance early detection of high-risk individuals, facilitating timely interventions. Future research should explore targeted anti-inflammatory strategies alongside traditional risk management to further reduce stroke risk in hypertensive populations.

Acknowledgments

The authors are thankful to Sigma Research Solutions and Development Consultancy Pvt. Ltd for its technical help and support in publishing this manuscript.
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