Section: Biochemistry

Original Research Article

# A CASE-CONTROL STUDY INVESTIGATING THE ASSOCIATION BETWEEN ELEVATED C-REACTIVE PROTEIN LEVELS AND RISK OF STROKE

**Madhavi Latha Jaladurgam[1], Prathyusha Prathivadi Bhayankara[2], Sateesh Koppula[3], Ramesh Kandimalla[4]**

[1]Associate Professor, Department of Biochemistry, Kurnool Medical College, Kurnool, Andhra Pradesh, India
[2]Senior Resident, Department of Biochemistry, Kakatiya Medical College, Warangal, Telangana, India
[3]Assistant Professor, Department of Biochemistry, Government Medical College, Suryapet, Telangana, India
[4]Associate Professor, Department of Biochemistry, Government Medical College, Narsampet-Warangal, Telangana, India

*Received* : 02/05/2024
*Received in revised form* : 30/06/2024
*Accepted* : 15/07/2024

*Keywords:*
*C-Reactive Protein, Stroke, Hypertension, Smoking, Biomarker, Risk Factor.*

Corresponding Author:
**Dr. Ramesh Kandimalla,**
Email: ramesh.kandimalla@gmail.com

DOI: 10.47009/jamp.2024.6.4.19

Source of Support: Nil,
Conflict of Interest: None declared

*Int J Acad Med Pharm*
2024; 6 (4); 87-91

## Abstract

**Background:** Elevated C-Reactive Protein (CRP) levels have been suggested as a potential risk factor for stroke. This case-control study aims to investigate the association between elevated CRP levels and the risk of stroke. **Materials and Methods:** A total of 100 participants were enrolled, comprising 50 cases (stroke patients) and 50 controls (non-stroke patients). Demographic data, clinical characteristics, CRP levels, hypertension status, and smoking status were collected and analyzed. Chi-square tests were used to determine the significance of associations, and odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess the strength of associations. **Result:** The mean age of cases was 68.2 years (SD = 5.1) compared to 66.5 years (SD = 5.8) for controls (p=0.144p = 0.144p=0.144). Gender distribution was similar between groups (60% males in cases, 56% in controls, p=0.682p = 0.682p=0.682). Hypertension was significantly more prevalent in cases (80%) than controls (50%), p=0.0016p = 0.0016p=0.0016. Elevated CRP levels were observed in 70% of cases and 40% of controls (p=0.002p = 0.002p=0.002), with an OR of 3.5 (95% CI, 1.6 to 7.7). Smoking status did not significantly differ between groups (50% smokers in cases, 40% in controls, p=0.3173p = 0.3173p=0.3173). **Conclusion:** This study identified a significant association between elevated CRP levels and an increased risk of stroke, with participants having elevated CRP levels showing 3.5 times higher odds of experiencing a stroke. Hypertension was also significantly associated with stroke, while smoking status showed no significant association. These findings underscore the importance of CRP as a potential biomarker for stroke risk assessment.

## INTRODUCTION

Stroke is a major cause of morbidity and mortality worldwide, posing significant healthcare challenges.[1] Despite advances in understanding its pathophysiology and treatment, stroke remains a leading cause of long-term disability. Identifying modifiable risk factors is crucial for the prevention and management of stroke.[2,3]

C-Reactive Protein (CRP) is an acute-phase reactant produced by the liver in response to inflammation.[4] Elevated CRP levels have been associated with an increased risk of cardiovascular events, including myocardial infarction and stroke.[5] CRP is not only a marker of inflammation but also believed to play a direct role in atherogenesis and plaque instability, contributing to the pathogenesis of stroke.[6]

Several epidemiological studies have suggested a link between elevated CRP levels and the risk of stroke.[7] However, the nature and strength of this association remain to be fully elucidated. Understanding the role of CRP in stroke risk could provide valuable insights for risk stratification and preventive strategies.

In addition to CRP, other factors such as hypertension and smoking status are well-established risk factors for stroke. Hypertension is a leading modifiable risk factor, significantly contributing to the development of ischemic and hemorrhagic strokes. Smoking, on the other hand, exacerbates vascular inflammation and atherosclerosis, further increasing the risk of stroke.


ISSN (O): 2687-5365; ISSN (P): 2753-6556

This case-control study aims to investigate the association between elevated CRP levels and the risk of stroke, controlling for other confounding factors such as hypertension and smoking status. By examining these associations, this study seeks to enhance the understanding of CRP as a potential biomarker for stroke risk and its role in stroke pathophysiology. The findings could have significant implications for clinical practice, particularly in the identification and management of individuals at high risk for stroke.

## MATERIALS AND METHODS

**Study Design and Setting:** This case-control study was conducted at Kakatiya Medical College, Warangal, from June 2023 to May 2024. The study aimed to investigate the association between elevated C-Reactive Protein (CRP) levels and the risk of stroke.

**Participants:** A total of 100 participants were recruited for the study, comprising 50 cases and 50 controls. The cases included patients who were diagnosed with stroke during the study period. The controls were age- and sex-matched individuals who had not experienced a stroke, selected from the general population attending the outpatient department of Kakatiya Medical College for routine check-ups.

**Inclusion and Exclusion Criteria:** Participants aged 18 years and older were eligible for inclusion. Cases were confirmed by clinical diagnosis and imaging studies (CT/MRI) indicating stroke. Controls were individuals without a history of stroke or other major cardiovascular events. Exclusion criteria for both cases and controls included chronic inflammatory diseases, autoimmune disorders, recent infections, and malignancies, as these conditions could confound CRP levels.

**Data Collection:** Demographic and clinical data were collected using a structured questionnaire. Information on age, gender, medical history, hypertension status, and smoking status was obtained. Blood samples were collected from all participants to measure CRP levels. CRP was quantified using a high-sensitivity CRP (hs-CRP) assay.

**CRP Measurement:** Elevated CRP levels were defined as CRP concentrations above 3 mg/L, based on the American Heart Association guidelines. Normal CRP levels were defined as CRP concentrations of 3 mg/L or lower.

**Statistical Analysis:** Data were analyzed using SPSS software (version 25.0). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Chi-square tests were performed to examine the associations between categorical variables. The odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the strength of the association between elevated CRP levels and stroke. Logistic regression analysis was conducted to adjust for potential confounders, including age, gender, hypertension, and smoking status. A p-value of less than 0.05 was considered statistically significant.

**Ethical Considerations:** The study was approved by the Institutional Ethics Committee of Kakatiya Medical College. Informed consent was obtained from all participants before their inclusion in the study. Participants were assured of the confidentiality of their data and their right to withdraw from the study at any time without any consequences.

## RESULTS

The study included 100 participants, equally divided into 50 cases (stroke patients) and 50 controls (non-stroke patients). The demographics and clinical characteristics of the participants are presented in [Table 1].

**Demographics and Clinical Characteristics:** The mean age of the cases was 68.2 years (SD = 5.1), while the controls had a mean age of 66.5 years (SD = 5.8), with no statistically significant difference between the two groups (p=0.144p = 0.144p=0.144). The gender distribution was similar between the groups, with 60% males in the cases and 56% males in the controls (p=0.682p = 0.682p=0.682). Hypertension was significantly more prevalent among the cases (80%) compared to the controls (50%), and this difference was statistically significant (p=0.0016p = 0.0016p=0.0016). The smoking status did not differ significantly between cases and controls, with 50% of the cases and 40% of the controls being smokers (p=0.3173p = 0.3173p=0.3173) [Table 1].

**C-Reactive Protein (CRP) Levels:** Elevated CRP levels were observed in 70% of the cases and 40% of the controls, a difference that was statistically significant (p=0.002p = 0.002p=0.002). Conversely, normal CRP levels were found in 30% of the cases and 60% of the controls [Table 2].

**Association Between CRP Levels and Stroke:** The odds ratio (OR) for the association between elevated CRP levels and stroke was 3.5, with a 95% confidence interval (CI) of 1.6 to 7.7, indicating a statistically significant association (p=0.002p = 0.002p=0.002) [Table 3]. This suggests that participants with elevated CRP levels had 3.5 times higher odds of having a stroke compared to those with normal CRP levels.

**Hypertension and Stroke:** The presence of hypertension was significantly higher among the cases (80%) compared to the controls (50%) (p=0.0016p = 0.0016p=0.0016) [Table 4]. This underscores the strong association between hypertension and the risk of stroke in this study.

**Smoking Status and Stroke:** There was no significant association between smoking status and stroke in this sample. The proportion of smokers among the cases was 50%, compared to 40% among the controls (p=0.3173p = 0.3173p=0.3173) [Table 5].


ISSN (O): 2687-5365; ISSN (P): 2753-6556

**Table 1: Demographics and Clinical Characteristics.**

| Characteristic | Cases (n = 50) | Controls (n = 50) | p-value |
|---|---|---|---|
| Mean Age (years) | 68.2 (SD = 5.1) | 66.5 (SD = 5.8) | 0.144 |
| Male | 30 (60%) | 28 (56%) | 0.682 |
| Female | 20 (40%) | 22 (44%) | |
| Hypertension | 40 (80%) | 25 (50%) | 0.0016 |
| Smoker | 25 (50%) | 20 (40%) | 0.3173 |
| Non-smoker | 25 (50%) | 30 (60%) | |

**Table 2: C-Reactive Protein (CRP) Levels**

| CRP Levels | Cases (n = 50) | Controls (n = 50) | p-value |
|---|---|---|---|
| Elevated CRP | 35 (70%) | 20 (40%) | 0.002 |
| Normal CRP | 15 (30%) | 30 (60%) | |

**Table 3: Association Between CRP Levels and Stroke**

| Measure | Value |
|---|---|
| Odds Ratio (OR) | 3.5 |
| 95% Confidence Interval (CI) | 1.6 to 7.7 |
| p-value | 0.002 |

**Table 4: Hypertension and Stroke**

| Hypertension Status | Cases (n = 50) | Controls (n = 50) | p-value |
|---|---|---|---|
| Hypertension | 40 (80%) | 25 (50%) | 0.0016 |
| No Hypertension | 10 (20%) | 25 (50%) | |

**Table 5: Smoking Status and Stroke**

| Smoking Status | Cases (n = 50) | Controls (n = 50) | p-value |
|---|---|---|---|
| Smoker | 25 (50%) | 20 (40%) | 0.3173 |
| Non-smoker | 25 (50%) | 30 (60%) | |

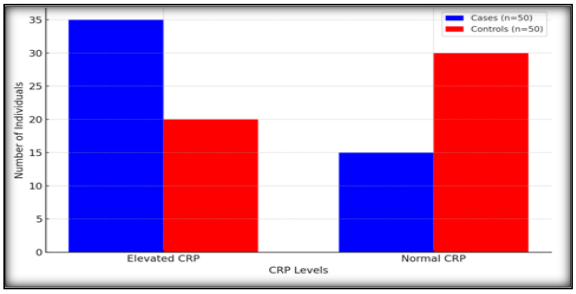


**Figure 1: CRP Levels in Cases and Controls**

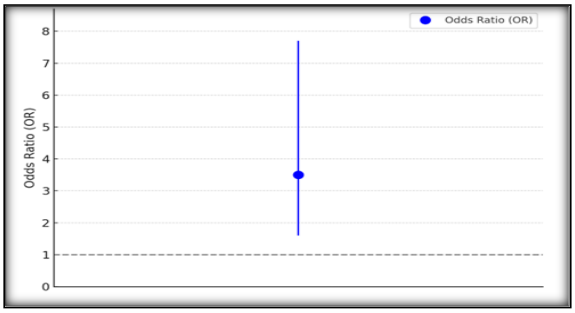


**Figure 2: Association Between CRP Levels and Stroke**

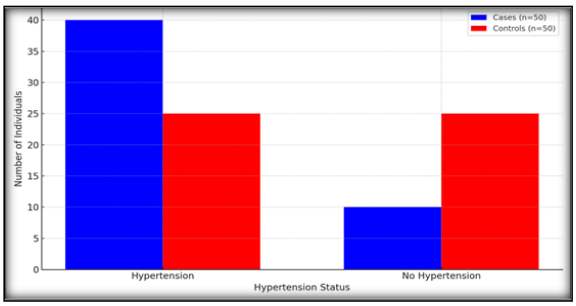


**Figure 3: Hypertension Status in Cases and Controls**

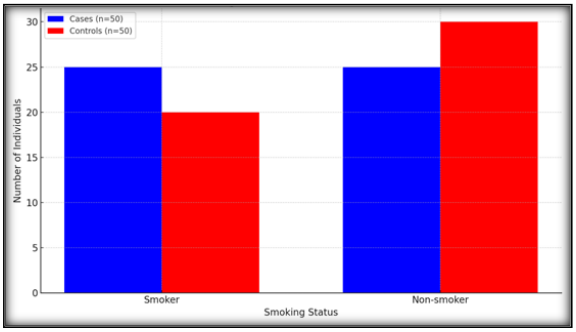


**Figure 4: Smoking Status in Cases and Controls**

## DISCUSSION

This case-control study, conducted at Kakatiya Medical College, Warangal, from June 2023 to May 2024, investigated the association between elevated C-Reactive Protein (CRP) levels and the risk of stroke. The findings demonstrate a significant association, with elevated CRP levels conferring a 3.5-fold increased risk of stroke. This aligns with existing literature that implicates inflammation, as indicated by CRP, in the pathogenesis of stroke.

The results highlight the potential role of CRP as a biomarker for stroke risk. Elevated CRP levels were significantly more prevalent among stroke patients compared to controls, suggesting that systemic inflammation may contribute to stroke occurrence. This is consistent with previous studies that have linked higher CRP levels to an increased risk of cardiovascular events, including stroke. Kaptoge et al,[8] (2010) conducted a meta-analysis and found that elevated CRP levels were associated with an


ISSN (O): 2687-5365; ISSN (P): 2753-6556

increased risk of coronary heart disease, stroke, and mortality. Our findings support these results, emphasizing the role of CRP as an important inflammatory marker in stroke risk assessment (Kaptoge et al 2010).[8]

Hypertension was also found to be significantly associated with stroke in this study. This finding underscores the critical importance of managing hypertension as a key modifiable risk factor for stroke prevention.[9] Elevated CRP levels combined with hypertension can exacerbate stroke risk, as demonstrated by Chen et al,[10] (2022) in their nationwide prospective cohort study (Chen et al 2022).[10] The lack of a significant association between smoking status and stroke in this study may be due to the relatively small sample size or other confounding factors not accounted for.

Several studies have reported similar associations between elevated CRP levels and stroke risk. For instance, Chaudhuri et al,[9] (2013) found that high-sensitivity CRP levels were elevated in patients with acute ischemic stroke, further supporting our findings (Chaudhuri et al 2013).[9] Additionally, VanGilder et al,[11] (2014) reported that elevated CRP levels were associated with worse long-term prognosis in ischemic stroke patients (VanGilder et al 2014).[11] These studies collectively highlight the significance of CRP as a predictor of stroke and its potential impact on patient outcomes.

Our study adds to this body of evidence by confirming these findings in an Indian population, thereby contributing to the global understanding of stroke risk factors. The Emerging Risk Factors Collaboration, as analyzed by Kaptoge et al (2010),[8] included diverse populations and indicated the universal relevance of CRP as a risk marker for cardiovascular diseases, including stroke (Kaptoge et al 2010).[8]

McCabe et al,[12] (2021) conducted a systematic review and meta-analysis that also supported the association between inflammatory markers such as CRP, interleukin-6, and fibrinogen, and the risk of recurrence after ischemic stroke (McCabe et al 2021).[12] Chen et al,[13] (2023) further corroborated the role of high-sensitivity CRP serum levels in the prognosis for stroke patients through a meta-analysis, emphasizing the prognostic value of CRP in stroke outcomes (Chen et al 2023).[13]

Additionally, Luan and Yao,[14] (2018) highlighted the clinical significance and potential role of CRP in chronic inflammatory and neurodegenerative diseases, which aligns with our findings on the inflammatory basis of stroke (Luan & Yao 2018).[14] Dhingra et al,[15] (2007) also discussed the broader implications of CRP and inflammatory conditions in cardiovascular disease risk, which underscores the importance of addressing inflammation in stroke prevention strategies (Dhingra et al 2007).[15]

In summary, this study reinforces the association between elevated CRP levels and stroke risk, highlighting the importance of CRP as a biomarker for identifying individuals at higher risk. It underscores the need for comprehensive management of hypertension and other modifiable risk factors to mitigate the overall stroke risk.

**Clinical Implications:** The identification of elevated CRP levels as a significant risk factor for stroke has important clinical implications. Measuring CRP levels could be a useful addition to current stroke risk assessment protocols, helping to identify individuals at higher risk who may benefit from more aggressive preventive measures.

**Strengths and Limitations:** One of the strengths of this study is the use of a well-defined case-control design, which allowed for the comparison of CRP levels between stroke patients and matched controls. Additionally, the study accounted for major confounding factors such as hypertension and smoking status.

However, there are limitations to consider. The sample size was relatively small, which may limit the generalizability of the findings. Additionally, the cross-sectional nature of the study precludes the establishment of a causal relationship between elevated CRP levels and stroke. Future studies with larger sample sizes and prospective designs are needed to confirm these findings and elucidate the underlying mechanisms.

## CONCLUSION

This study provides evidence of a significant association between elevated CRP levels and the risk of stroke, highlighting the role of inflammation in stroke pathogenesis. Hypertension was also identified as a key risk factor. These findings suggest that CRP could serve as a valuable biomarker for stroke risk assessment and underscore the importance of managing inflammation and hypertension to prevent stroke. Further research with larger, prospective studies is warranted to confirm these results and explore the potential benefits of targeting inflammation in stroke prevention.

## REFERENCES


1. Wang L, Yang L, Liu H, Pu J, Li Y, Tang L, et al. C-Reactive Protein Levels and Cognitive Decline following Acute Ischemic Stroke: A Systematic Review and Meta-Analysis. Brain Sci. 2023 Jul 17;13(7):1082. doi: 10.3390/brainsci13071082. PMID: 37509012; PMCID: PMC10377587.
2. Ahmadi-Ahangar A. Predictive ability of C-reactive protein for stroke. Caspian J Intern Med. 2016 Summer;7(3):151-152. PMID: 27757197; PMCID: PMC5062170.
3. Mengozzi M, Kirkham FA, Girdwood EER, Bunting E, Drazich E, Timeyin J, et al. C-Reactive Protein Predicts Further Ischemic Events in Patients With Transient Ischemic Attack or Lacunar Stroke. Front Immunol. 2020 Jul 7;11:1403. doi: 10.3389/fimmu.2020.01403. PMID: 32733466; PMCID: PMC7358589.
4. Finck T, Sperl P, Hernandez-Petzsche M, Boeckh-Behrens T, Maegerlein C, Wunderlich S, et al. Inflammation in stroke: initial CRP levels can predict poor outcomes in endovascularly treated stroke patients. Front Neurol. 2023 Jun 9;14:1167549. doi: 10.3389/fneur.2023.1167549. PMID: 37360331; PMCID: PMC10289003.




ISSN (O): 2687-5365; ISSN (P): 2753-6556

5. Bian J, Guo S, Huang T, Li X, Zhao S, Chu Z, et al. CRP as a potential predictor of outcome in acute ischemic stroke. Biomed Rep. 2023 Jan 17;18(2):17. doi: 10.3892/br.2023.1599. PMID: 36776580; PMCID: PMC9892964.
6. Hong SI, Kim JS, Bae HJ, Kim WY. C-reactive Protein for Stroke Detection in the Emergency Department in Patients With Dizziness Without Neurological Deficits. Front Neurol. 2021 May 31;12:662510. doi: 10.3389/fneur.2021.662510. PMID: 34135849; PMCID: PMC8200534.
7. Liu Y, Wang J, Zhang L, Wang C, Wu J, Zhou Y, et al. Relationship between C-reactive protein and stroke: a large prospective community based study. PLoS One. 2014 Sep 5;9(9):e107017. doi: 10.1371/journal.pone.0107017. PMID: 25191699; PMCID: PMC4156395.
8. Emerging Risk Factors Collaboration; Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010 Jan 9;375(9709):132-40. doi: 10.1016/S0140-6736(09)61717-7. Epub 2009 Dec 22. PMID: 20031199; PMCID: PMC3162187.
9. Chaudhuri JR, Mridula KR, Umamahesh M, Swathi A, Balaraju B, Bandaru VC. High sensitivity C-reactive protein levels in Acute Ischemic Stroke and subtypes: A study from a tertiary care center. Iran J Neurol. 2013;12(3):92-7. PMID: 24250912; PMCID: PMC3829297.
10. Chen X, Liu S, Chu J, Hu W, Sun N, Shen Y. Joint effect of elevated-c-reactive protein level and hypertension on new-onset stroke: A nationwide prospective cohort study of CHARLS. Front Public Health. 2022 Oct 3;10:919506. doi: 10.3389/fpubh.2022.919506. PMID: 36262245; PMCID: PMC9573958.
11. VanGilder RL, Davidov DM, Stinehart KR, Huber JD, Turner RC, Wilson KS, et al. C-reactive protein and long-term ischemic stroke prognosis. J Clin Neurosci. 2014 Apr;21(4):547-53. doi: 10.1016/j.jocn.2013.06.015. Epub 2013 Aug 23. PMID: 24211144; PMCID: PMC4394376.
12. McCabe JJ, O'Reilly E, Coveney S, Collins R, Healy L, McManus J, et al. Interleukin-6, C-reactive protein, fibrinogen, and risk of recurrence after ischaemic stroke: Systematic review and meta-analysis. Eur Stroke J. 2021 Mar;6(1):62-71. doi: 10.1177/2396987320984003. Epub 2021 Jan 5. Erratum in: Eur Stroke J. 2023 Mar;8(1):398. doi: 10.1177/23969873221133904. PMID: 33817336; PMCID: PMC7995315.
13. Chen L, Wang M, Yang C, Wang Y, Hou B. The role of high-sensitivity C-reactive protein serum levels in the prognosis for patients with stroke: a meta-analysis. Front Neurol. 2023 Jun 5;14:1199814. doi: 10.3389/fneur.2023.1199814. PMID: 37342777; PMCID: PMC10278886.
14. Luan YY, Yao YM. The Clinical Significance and Potential Role of C-Reactive Protein in Chronic Inflammatory and Neurodegenerative Diseases. Front Immunol. 2018 Jun 7;9:1302. doi: 10.3389/fimmu.2018.01302. PMID: 29951057; PMCID: PMC6008573.
15. Dhingra R, Gona P, Nam BH, D'Agostino RB Sr, Wilson PW, Benjamin EJ, et al. C-reactive protein, inflammatory conditions, and cardiovascular disease risk. Am J Med. 2007 Dec;120(12):1054-62. doi: 10.1016/j.amjmed.2007.08.037. PMID: 18060926; PMCID: PMC2215387.


ISSN (O): 2687-5365; ISSN (P): 2753-6556