

## Original Research

### Exploring the Relationship Between C-Reactive Protein Levels, Carotid Intimal Thickness, and Patient Outcomes in Ischemic Stroke

Sonu Birender Singh Yadav

Assistant Professor, Department of General Medicine, Gouri Devi Institute of Medical Sciences & Hospital, Durgapur, West Bengal, India

#### ABSTRACT:

**Background:** Stroke stands as the third leading cause of death, accounting for 9% of all fatalities in industrialized nations, and remains a major contributor to global disability. The carotid intima-medial thickness (IMT) has emerged as a reliable independent indicator of cardiovascular conditions. C-reactive protein (CRP) has been established as a significant contributing factor to cardiovascular disease. The link between CRP and stroke becomes more substantial when coupled with an elevated carotid IMT. **Methods:** This study is a prospective cross-sectional investigation conducted over a one-year period, involving a cohort of 200 patients. **Results:** A total of 200 participants were included in the study. The mean levels of carotid intimal thickness and C-reactive protein were  $0.823 \pm 0.25$  mm and  $7.867 \pm 3.76$  mg/dl, respectively. Among the participants, 100 out of 200 reported carotid intima medial thickness exceeding 0.8 mm. There was a highly significant association between carotid intima thickness and patient outcomes ( $p < 0.003$ ), with 65% of participants reporting CRP levels greater than 6 mg/dl ( $p < 0.001$ ). Additionally, there was a significant correlation between carotid medial thickness and C-reactive protein levels ( $p < 0.001$ ). **Conclusion:** Supplementing conventional risk factors with the inclusion of C-reactive protein (CRP) and carotid intima-medial thickness demonstrated a modest improvement in predicting cerebrovascular accidents. Regular monitoring of identified risk factors in high-risk individuals, along with broader acceptance of the expected course of treatment in tertiary centers equipped with emergency intensive care units, has the potential to reduce episodes leading to morbidity and mortality.

**Keywords:** CRP, Stroke, carotid

Received: 11-07-2019

Accepted: 15-08-2019

**Corresponding author:** Sonu Birender Singh Yadav, Assistant Professor, Department of General Medicine, Gouri Devi Institute of Medical Sciences & Hospital, Durgapur, West Bengal, India

**This article may be cited as:** Yadav SBS. Exploring the Relationship Between C-Reactive Protein Levels, Carotid Intimal Thickness, and Patient Outcomes in Ischemic Stroke. J Adv Med Dent Sci Res 2019;7(9):287-292.

#### INTRODUCTION

Stroke, ranking as the third leading cause of death in industrialized countries and accounting for 9% of all fatalities, stands as a significant public health concern with far-reaching implications. Ischemic stroke, the predominant subtype comprising 87% of cases, is intricately linked to the pathophysiological process of atherosclerosis. Atherosclerosis, characterized by the gradual buildup of plaque in arterial walls, serves as a pivotal contributor to ischemic strokes, disrupting blood flow to the brain. Within the realm of risk factors, the distinction between adjustable and non-modifiable factors takes center stage<sup>1</sup>. Adjustable risk factors, notably diabetes, hypertension, smoking, and hyperlipidemia, play a substantial role in shaping the atherosclerotic burden and, consequently, stroke risk. These factors, subject to modification through

lifestyle interventions and medical management, underscore the importance of targeted preventive measures. Concurrently, non-modifiable factors such as age, gender, and family history contribute to the overall risk profile, necessitating a holistic understanding of individual susceptibility. Recognizing the nuanced interplay between these factors is essential for tailoring effective stroke prevention strategies. In the quest for proactive healthcare, routine monitoring of identified risk factors emerges as a linchpin in early intervention. Additionally, the integration of expected treatment protocols in tertiary centers, equipped with emergency intensive care units, underscores the urgency and gravity of stroke-related episodes. This multifaceted approach not only seeks to curb the incidence of strokes but also aims at mitigating the associated

morbidity and mortality. In conclusion, the comprehensive understanding of stroke's prevalence, subtypes, underlying pathophysiology, and risk factors lays the foundation for a robust public health response. By addressing both modifiable and non-modifiable elements, the medical community can deploy more effective strategies, reducing the burden of stroke on individuals, families, and healthcare systems. The carotid intima-media thickness (IMT) has emerged as a robust and independent marker in the evaluation of cardiovascular health. This measurement holds particular significance due to the pivotal role of the carotid artery in supplying blood to the cerebrovascular arterial system. By scrutinizing the extent of arteriosclerosis in the carotid artery, clinicians can gain valuable insights into the potential risks of developing ischemic cerebrovascular conditions, including transient ischemic attacks and cerebral infarctions<sup>2</sup>. Essentially, the IMT becomes a predictive gauge, allowing for early identification of vascular changes that may precede adverse cerebrovascular events. In parallel, C-reactive protein (CRP) has been recognized as a key contributory factor in cardiovascular disease. Its association with inflammation and its correlation with overall vascular health make CRP a crucial biomarker. When exploring the relationship between CRP and stroke, the synergy becomes apparent, especially when considered alongside a higher carotid IMT. The presence of elevated CRP levels in conjunction with an increased carotid IMT reinforces the credibility of this association, signifying a potential heightened cardiovascular risk, specifically for stroke. The comprehensive evaluation of both CRP and carotid IMT, therefore, offers a more nuanced and holistic approach to cardiovascular risk assessment. This integrated analysis not only enhances the precision of prognostication but also provides clinicians with a more detailed understanding of the patient's vascular health. This dual assessment strategy empowers healthcare professionals to make more informed decisions regarding preventive interventions and management strategies, ultimately contributing to a more personalized and effective approach to cardiovascular care. Recent infections have emerged as a potential risk factor for ischemic stroke, as indicated by various case-control studies involving patients who experienced such strokes. The mounting evidence underscores the significant role of inflammatory processes in contributing to cerebral ischemia. In cases of ischemic brain injury resulting from arterial occlusion, acute localized inflammation and changes in the levels of inflammatory cytokines in body fluids have been consistently observed among affected individuals<sup>3</sup>. Moreover, prospective studies have revealed that individuals at risk of experiencing their first myocardial infarction (MI) or stroke in the future often exhibit elevated levels of inflammation markers, with particular emphasis on C-reactive protein (CRP). The presence of heightened inflammation markers

serves as a predictive indicator for future cardiovascular events. Notably, in cases where thrombolytic drugs have been administered, elevated CRP levels have proven to be a more accurate predictor of outcomes than peak creatine kinase. This finding holds significance not only in assessing the effectiveness of thrombolytic interventions but also in predicting mortality rates among MI patients. The ability of CRP to serve as a robust prognostic marker highlights the intricate interplay between inflammatory responses, cardiovascular events, and the overall prognosis of individuals who have experienced ischemic events<sup>4</sup>. In summary, the link between recent infections, inflammatory processes, and ischemic stroke is gaining prominence in the medical landscape. Elevated levels of inflammation markers, particularly CRP, not only signal potential cardiovascular risks but also offer valuable insights into the outcomes of thrombolytic treatments and the prognosis of individuals recovering from myocardial infarctions. This evolving understanding holds promise for more targeted interventions and improved patient management in the realm of ischemic events.

#### **MATERIALS AND METHODS**

This study represents a prospective cross-sectional investigation conducted over a span of one year, involving a cohort of 200 patients who sought medical attention at the Department of General Medicine. The aim of the study was to comprehensively examine and analyze various aspects of health, symptoms, and conditions presented by these patients during the specified timeframe. By adopting a prospective approach, the researchers sought to capture real-time data and observations, offering a dynamic snapshot of the patient population over the course of the study duration. The choice of the Department of General Medicine suggests a broad focus on diverse health issues, emphasizing the inclusivity of the study and the potential to gain insights into a wide range of medical conditions. This methodology allows for a thorough exploration of prevalent health concerns, contributing to a more comprehensive understanding of health patterns within the studied patient population.

#### **INCLUSION CRITERIA**

The inclusion criteria for this study encompass stroke patients aged 18 years or older who present themselves to the hospital within 72 hours of the onset of symptoms. This selection criteria is designed to capture a specific subset of individuals, namely those who have recently experienced a stroke and seek medical attention in the early phase of symptom manifestation. The emphasis on the age criterion ensures that the study focuses on adult populations, while the requirement of presentation within 72 hours aims to gather data from the acute phase of stroke, enabling a closer examination of the early clinical course and potentially influencing treatment

strategies. By delineating these specific inclusion criteria, the study aims to provide a targeted and time-sensitive analysis of stroke cases within the specified demographic.

### EXCLUSION CRITERIA

The exclusion criteria for this study involve two key parameters: age and pre-existing medical conditions. Specifically, individuals below 18 years of age are excluded from the study. Additionally, patients with known autoimmune diseases or inflammatory conditions are also excluded. The age criterion ensures that the study remains focused on adults, aligning with the inclusion criteria. Excluding individuals under 18 helps maintain consistency in the targeted age group and ensures that the study findings are relevant to the adult population. The exclusion of patients with known autoimmune diseases or inflammatory conditions indicates an intention to isolate cases specifically related to stroke without the potential confounding influence of pre-existing autoimmune or inflammatory disorders. This exclusion criterion allows for a more accurate assessment of stroke-related factors and outcomes within the studied population. By clearly defining these exclusion criteria, the study aims to enhance the homogeneity of the participant group, facilitating a more precise analysis of the factors and characteristics associated with strokes in adults without autoimmune diseases or inflammatory conditions.

The data collection process commenced following the acquisition of informed consent from participants and a detailed explanation of the study's objectives. To confirm the diagnosis of ischemic stroke, each patient underwent either a CT head or MRI Brain scan<sup>5</sup>. These imaging studies provided a comprehensive evaluation of cerebral structures and assisted in confirming the presence of ischemic stroke. In addition to the neuroimaging, a set of investigations, including a complete blood count and renal function tests, were conducted to gather pertinent information about the patients' overall health and potential contributing factors. C-reactive protein (CRP) levels, a key inflammatory marker, were measured to assess the systemic inflammatory response. This involved obtaining blood samples for laboratory analysis. Furthermore, carotid-intima medial thickness (IMT) was measured using carotid arterial Doppler in the department of radio-diagnosis, once the patients were stabilized. This non-invasive ultrasound technique allowed for the evaluation of the carotid

artery's structural integrity and the detection of any abnormalities in the intima-medial thickness. In the subsequent analysis, carotid IMT exceeding 0.8mm and CRP levels surpassing 6mg/L were considered significant parameters. These thresholds were established to identify and emphasize cases where both structural changes in the carotid artery and elevated inflammatory markers were present. The combination of these criteria aimed to enrich the dataset with clinically relevant information, providing a more detailed understanding of the association between carotid health, inflammatory status, and ischemic stroke within the studied population.

### RESULTS

In this study, a total of 200 participants were enrolled, and their demographic characteristics were analyzed. The mean age of the study participants was determined to be  $56.54 \pm 10.23$  years, as outlined in Table 1. Noteworthy proportions of the participants exhibited common cardiovascular risk factors: 63% were hypertensive, 49% were diabetic, 57% were smokers, and 63% were dyslipidemic. Further investigation into the vascular health of the participants revealed a mean carotid intimal thickness of  $0.833 \pm 0.24$  mm and a mean C-reactive protein level of  $7.877 \pm 3.76$  mg/dl. Within the cohort, 50 out of 100 patients reported carotid intima medial thickness exceeding 0.8 mm. The significance of these findings was underscored by a highly significant association between carotid intima thickness and patient outcomes ( $p < 0.003$ ). Additionally, 65% of the participants reported C-reactive protein levels greater than 6 mg/dl, demonstrating a substantial inflammatory component in the study population, and this association was statistically significant ( $p < 0.001$ ). The correlation analysis revealed a significant relationship between carotid medial thickness and C-reactive protein levels ( $p < 0.001$ ). This implies that as carotid intima-medial thickness increased, so did the levels of C-reactive protein, suggesting a potential link between structural changes in the carotid artery and systemic inflammation. These findings collectively suggest a complex interplay between cardiovascular risk factors, carotid health, and inflammatory markers within the studied population. The observed associations highlight the importance of considering multiple factors in assessing the risk and outcomes associated with ischemic stroke, offering valuable insights for further research and clinical management strategies.

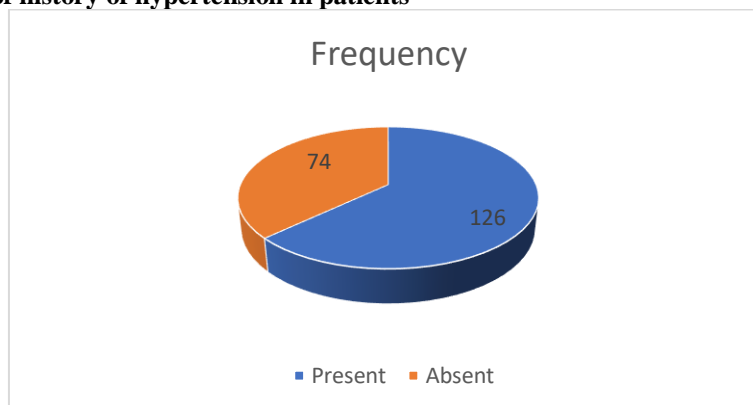
**Table 1: Distribution of study participants on the basis of their age**

Sl. No	Age in Years	Frequency
1	≤50	40
2	51-60	74
3	61-70	68
4	71-80	14
5	> 80	4
	Total	200

**Table 2: Distribution of study participants on the basis of presence of hypertension**

Sl. No.	History of HTN	Frequency	Percentage %
1	Present	126	63
2	Absent	74	37
	Total	200	100

**FIG 1: frequency of history of hypertension in patients**



**Table 3: Distribution of study participants on the basis of history of Diabetes**

Sl. No.	History of Smoking	Frequency	Percentage
1	Present	98	49.0
2	Absent	102	51.0
	Total	200	100.0

**Table 4: Distribution of study participants on the basis of history of smoking**

Sl. No.	History of Smoking	Frequency	Percentage
1	Present	114	57.0
2	Absent	86	43.0
	Total	200	100.0

**Table 5: Distribution of study participants on the basis of Carotid intima-medial thickness**

Sl. No.	Carotid intima medial thickness (in mm)	Frequency	Percentage
1	≤ 0.8	100	50%
2	>0.8 – 1.0	64	32%
3	>1.0 – 1.2	26	13%
4	>1.2 – 1.4	10	5%
	Total	200	100%

**Table 6: Distribution of study participants on the basis of Levels of C Reactive Protein**

Sl. No.	Levels of C Reactive Protein (in mg/dl)	Frequency	Percentage
1	< 3	6	3%
2	3-6	64	32%
3	>6 – 10	98	49%
4	>10	32	16%
	Total	200	100%

**DISCUSSION**

This investigation was undertaken with the primary objective of unraveling the correlation between C-reactive protein (CRP) levels and carotid intima-medial thickness (IMT) in individuals who have experienced ischemic stroke. In addition to scrutinizing this key association, the study extended its focus to explore correlations with other routine laboratory parameters. The findings of this study substantiate a compelling link between elevated CRP

levels, heightened carotid IMT values, and the occurrence of ischemic stroke<sup>6</sup>. Beyond the specific markers, the study delved into the broader context of atherosclerotic risk factors, including hypertension, diabetes, smoking, and dyslipidemia. By meticulously correlating these risk factors with CRP levels and carotid IMT, the research aimed to provide a comprehensive understanding of the intricate network of factors contributing to ischemic stroke. The mean carotid intima-medial thickness level, determined to

be  $0.823 \pm 0.24$  mm, serves as a pivotal metric, underlining the prevalence of atherosclerotic changes within the studied population. Notably, half of the participants reported carotid IMT values exceeding the clinically significant threshold of 0.8 mm, emphasizing the clinical relevance of carotid IMT as a measurable parameter for assessing vascular health. Statistical analyses conducted in this study revealed a highly significant association between carotid intima-medial thickness and patient outcomes ( $p < 0.003$ ). This robust correlation underscores the potential of carotid IMT as a predictive marker for both the occurrence and severity of ischemic stroke, offering valuable insights for risk assessment and prognostication. Furthermore, the study reaffirms the well-established connection between elevated CRP levels and the incidence of ischemic stroke, reinforcing the pivotal role of inflammation in the pathophysiology of vascular events. In summary, the comprehensive approach of this study, encompassing CRP levels, carotid IMT, and routine laboratory parameters, contributes significantly to our understanding of the multifaceted nature of ischemic stroke. The demonstrated associations not only enhance our comprehension of risk factors but also have implications for risk assessment, preventive strategies, and the development of targeted interventions for individuals at risk of or recovering from ischemic stroke.

The findings from this study are in alignment with the outcomes reported by several notable studies conducted in recent years. Notably, Satoko Oet al<sup>7</sup> and Virendra Atamet al in 2018 observed mean intimal thickness values of  $0.76 \pm 0.13$  mm and  $0.708 \pm 0.128$  mm, respectively. These results provide a context for understanding the variability in intimal thickness measurements across different study populations. Furthermore, Shovan Kumar Daset al (2014) reported higher carotid intima-medial thickness (CIMT) among patients with acute ischemic stroke compared to healthy controls ( $0.849 \pm 0.196$  vs  $0.602 \pm 0.092$ ;  $p < 0.001$ ). This observation corroborates the current study's findings, emphasizing the significance of elevated CIMT in individuals with ischemic stroke.

The mean C-reactive protein (CRP) level of  $7.877 \pm 3.76$  mg/dl in the present study aligns with the broader scientific literature. The significance of this alignment is reinforced by the p-value of  $< 0.001$ , indicating a substantial association between CRP levels exceeding 6 mg/dl and the outcomes of the patients. This corroborates with Maria Totan et al's study, where correlations were drawn between CRP values and the risk of death<sup>8</sup>. Moreover, the present study notes a strong correlation between higher levels of CRP and CIMT with common cardiovascular risk factors such as hypertension, diabetes, history of smoking, and dyslipidemia. This concurrence with established risk factors adds depth to the study's findings, highlighting the interconnectedness of these variables in the

context of ischemic stroke. In summary, the consistent patterns observed across these studies, including the present one, strengthen the evidence supporting the correlation between elevated CIMT, CRP levels, and the risk and outcomes of ischemic stroke. These findings collectively contribute to the growing body of knowledge, providing valuable insights into the complex interplay of vascular and inflammatory factors in the context of cerebrovascular health.

The association between C-reactive protein (CRP) levels and prognosis in the context of stroke remains somewhat enigmatic from a pathophysiological standpoint. However, one potential link lies in the role of tissue factor expression in the coagulation process, which may be influenced by increased CRP levels. Tissue factor plays a crucial part in initiating the coagulation cascade, and alterations in its expression may contribute to the observed associations between elevated CRP levels and the prognosis of stroke patients. Regarding carotid intima-media thickness (IMT), studies have demonstrated its significance in predicting the risk of stroke. Increased IMT has been consistently linked to an elevated risk of stroke, as evidenced by case-control studies and investigations into incident stroke risk. The linear rise in relative risk with increased IMT, comparable in magnitude to the risk associated with myocardial infarction, underscores the importance of IMT as a predictive marker for cerebrovascular events.

Studies by Touboul et al<sup>9</sup> have further emphasized the value of carotid IMT in identifying individuals at high risk for brain infarction. Elevated common carotid artery-IMT (CCA-IMT) was associated with both overall brain infarctions and major subtypes. However, it's crucial to note that the potential value of CCA-IMT and plaque score has been more conclusively established for certain stroke subtypes, specifically atherothrombotic infarction and lacunar infarction, rather than other subtypes like cardioembolic infarction, cerebral hemorrhage, or other/unclassified strokes. Interestingly, these studies highlight that cerebral hemorrhage, other or unclassified stroke, and cardioembolic infarction may not significantly involve atherosclerosis. This implies that while carotid IMT is a valuable predictor for certain ischemic stroke subtypes, its utility may be limited in assessing the risk of stroke subtypes primarily driven by non-atherosclerotic mechanisms. In summary, the intricate interplay between CRP levels, carotid IMT, and stroke prognosis underscores the multifaceted nature of cerebrovascular events. While CRP may impact coagulation pathways, carotid IMT serves as a valuable marker for atherothrombotic and lacunar infarctions but may have limited applicability in other stroke subtypes driven by diverse pathophysiological mechanisms.

## CONCLUSION

The comprehensive analysis of various clinical and

laboratory parameters in relation to the outcome of ischemic stroke led to the conclusion that C-reactive protein (CRP) and carotid intima-media thickness (IMT) stand out as significant markers for predicting ischemic stroke compared to other parameters. Elevated levels of both CRP and carotid IMT were independently correlated with the disease state, highlighting their potential roles as valuable indicators in assessing the risk and outcomes of ischemic stroke. This study underscores the importance of considering multiple conventional risk factors in understanding the causation of stroke episodes. The recognition of risk factors such as hypertension, diabetes, smoking, and dyslipidemia, in addition to CRP and carotid IMT, provides a more holistic perspective on the complex interplay of factors contributing to ischemic stroke. Moreover, the addition of CRP and carotid IMT to conventional risk factors demonstrated a modest increase in the ability to predict ischemic stroke events. This suggests that incorporating these markers into the overall risk assessment provides incremental value in enhancing the precision of prognostication. The study emphasizes the potential impact on reducing episodes leading to morbidity and mortality through routine monitoring of identified risk factors among high-risk individuals. Furthermore, the wider acceptance of expected treatment protocols, especially in tertiary centers equipped with emergency intensive care units, is highlighted as a crucial step in optimizing outcomes for individuals experiencing ischemic stroke. In conclusion, this research contributes valuable insights into the predictive value of CRP and carotid IMT in the context of ischemic stroke. By recognizing their significance and integrating them with conventional risk factors, healthcare professionals can enhance risk assessment, optimize treatment strategies, and ultimately contribute to the reduction of morbidity and mortality associated with ischemic stroke.

## REFERENCES

1. Hashimoto H, Kitagawa K, Hougaku H, Shimizu Y, Sakaguchi M, Nagai Y et al. C-reactive protein is an independent predictor of the rate of increase in early carotid atherosclerosis. *Circulation*. 2001;104(1):63-7.
2. Hakimelahi R, Vachha BA, Copen WA, Papini GDE, He J, Higazi MM et al. Time and diffusion lesion size in major anterior circulation ischemic strokes. *Stroke*. 2014;45:2936–2941.
3. Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Production of C-reactive protein and risk of coronary events in stable and unstable angina. *Lancet*. 1997;349:462-6.
4. Cao JJ, Thach C, Manolio TA, Psaty BM, Kuller LH, Chaves PH et al. C-reactive protein, carotid intima-media thickness, and incidence of ischemic stroke in the elderly: the Cardiovascular Health Study. *Circulation*. 2005;108:166-70.
5. Singh AS, Atam V, Jain N, Yathish BE, Patil MR, Das L. Association of carotid plaque echogenicity with recurrence of ischemic stroke. *North American journal of medical sciences*. 2013;5(6):371.
6. Das SK, Sarkar A, Pramanik S, Bandyopadhyay M, Mondal K, Singh SK. Carotid artery intima-media thickness in patients with acute ischemic stroke and its correlation with risk factors for atherosclerosis and/or stroke. *Asian Journal of Medical Sciences*. 2015;6(1):22-7.
7. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. *Stroke*. 2001;32(4):917-24.
8. Van Der Meer IM, Bots ML, Hofman A, Iglesias del Sol A, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. *Circulation*. 2004;109(9):1089-94.
9. Lee EJ, Kim HJ, Bae JM, Kim JC, Han HJ, Park CS, Park NH, Kim MS, Ryu JA. Relevance of common carotid intima-media thickness and carotid plaque as risk factors for ischemic stroke in patients with type 2 diabetes mellitus. *American journal of neuroradiology*. 2007;28(5):916-9.