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ORIGINAL RESEARCH

To Evaluate The Role Of C-Reactive Protein's As Prognostic Relevance In Acute Ischaemic Stroke Patients

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ABSTRACT

Aim: To evaluate the role of C-reactive protein's as prognostic relevance in acute ischaemic stroke patients.

Materials and methods: one hundred patients who had been diagnosed with first ischaemic stroke by clinical criteria and CT of the brain. Patients admitted to the hospital with a diagnosis of first ischaemic stroke within 72 hours of symptom onset were considered for inclusion. If the patient was unable to give consent, their legal guardian gave permission instead.

Results: The severity of stroke was determined using the CNSS score, and the mean CNSS score was 6.98±1.63 in the low CRP group and 5.97±1.55 in the high CRP group. The value difference is statistically significant (p=0.011). The mean BI score in the low CRP group is 35.88±5.87, whereas it is 31.36±4.98 in the high CRP group (p=0.021). The mean infarct size in the low CRP group is 3.1±0.58 mm and 4.2±0.69 mm in the high CRP group (p=0.011). (Table 4) The severity of the stroke, the level of impairment, and the size of the infarct were all substantially larger in the high CRP group (Table 5). Out of 70 patients in the high CRP group, 25 (35.71%) had fatal events and 25 (35.71%) had non-fatal events. As a result, 50 patients (71.42%) had adverse effects, which were statistically significant when compared to the low and high CRP groups. The biggest number of incidents occurred in the high CRP level group, i.e., 40%, while the RR was highest in the CRP level >5, i.e., 6.3, which is significant.

Conclusion: The present investigation shown that individuals with ischemic stroke had elevated levels of CRP, an inflammatory marker. Stroke severity and bad outcomes are proportional to the degree of CRP elevation. In terms of mortality and morbidity, CRP after discharge is preferable to CRP at admission.

Keywords: Inflammation, Prognosis, Stroke outcome

INTRODUCTION

"rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin," is how the World Health Organization (WHO) describes a stroke. [1] An acute ischaemic stroke results when blood supply to the brain is suddenly cut off. Most cases of severe acute

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ischaemic stroke are caused by embolic or thrombotic occlusion (70-80% of cases). [2] The functions of endothelial cells are altered, and the serum levels of cytokines, fibrinogen, clotting factors, and leukocytes are all raised, all of which have been shown in multiple studies to play a major role in the pathogenesis of atherosclerotic stroke.[3]

The development of thrombosis is caused by a systemic inflammatory response after ischemic episodes. A number of studies have linked increased levels of inflammatory biomarkers like C-reactive protein and Interleukin-6 (IL-6) to an increased risk of ischaemic events. 3 C-reactive protein was found to be a strong predictor of ischemic stroke and TIA in the Framingham study (TIA).[4] High sensitivity C-reactive protein (hs-CRP) levels at baseline are associated with an increased risk of ischaemic stroke but have no discernible effect on the risk of hemorrhagic stroke. [5]

Two scientists, Tillet WS and Francis T, found CRP in 1930.[6] In reaction to IL-1, IL-6, and Tumor Necrosis Factor (TNF), hepatocytes generate high levels of C-reactive protein (CRP), a systemic inflammatory marker. [7,8] C-reactive protein (CRP) has been established as a significant factor for assessment in inflammatory and infectious disorders due to its rapid induction, long half-life (19 hours), and lack of variation over day and night in contrast to other acute phase reactants. Important components of atheroma include inflammation, which is linked to the activation and proliferation of macrophages, endothelial cells, and smooth muscle cells.[9] An rise in its concentration occurs in response to injury, infection, or inflammation, making it an archetypal member of the family of proteins known as acute phase proteins. Cigarette smokers, those with atherosclerosis, people under emotional stress, those with type 2 diabetes, those who are overweight, and the elderly all have higher than normal CRP levels. Acute phase reactants, such as CRP and ESR in the serum, rise first during an inflammatory reaction. However, a serum CRP level that can be easily measured by nephelometry is now the best single diagnostic of acute inflammation. [10] C-reactive protein values in the blood are usually about 0.8 mg/L. 90% of seemingly healthy people had concentrations below 3 mg/L, suggesting that even very low concentrations are within the normal range. [11] Within hours of an acute injury or the beginning of inflammation, humoral mediators including leucocyte endogenous pyrogen and Prostaglandin E likely stimulate an increase in the rate of CRP synthesis and release (PGE). Within 24 to 48 hours, the serum CRP concentration may reach peak values of up to 300mg/mL. Recent prospective studies have shown that CRP is therapeutically useful for predicting the risk of subsequent cardiovascular disorders[12,13] and it is a proven diagnostic marker for patients with Cerebrovascular Accident (CVA). [14] Clinically significant correlations between CRP readings and stroke severity and disability have been found across several studies including individuals who have had a stroke. As a result, a raised CRP is a prognostic marker for future cardiovascular events, albeit it is unclear when in relation to the qualifying incident CRP examination should take place. In light of this information, the purpose of the current research was to assess the prognostic value of C-reactive protein (CRP) as an inflammatory marker in cases of acute cerebral ischemic stroke.

MATERIALS AND METHODS

One hundred patients who had been diagnosed with first ischaemic stroke by clinical criteria and CT of the brain participated in this prospective single-center observational study.

INCLUSION CRITERIA

Patients admitted to the hospital with a diagnosis of first ischaemic stroke within 72 hours of symptom onset were considered for inclusion. If the patient was unable to give consent, their legal guardian gave permission instead.

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EXCLUSION CRITERIA

Patient exclusion criteria included those with conditions such as acute infectious disease, stable or unstable angina, acute myocardial infarction, immunological disorders, known or suspected neoplastic disorders, recent history (3 months) of major trauma, surgery, burns, osteoarthritis, costochondritis, rheumatoid arthritis, ankylosing spondylitis, renal failure, haemorrhagic stroke, collagen vascular disease, liver disease, etc.

If the patient was unable to communicate, medical history was obtained from his or her family members. Neurology interns conducted the physical exam. Patients were analysed for demographic factors such as age and sex as well as medical conditions such as diabetes, high cholesterol, heart disease, high blood pressure, stroke, and smoking. All patients had routine blood work, a brain MRI, a TTE, and a carotid doppler ultrasonogram performed.

METHODOLOGY

The Canadian Neurological Stroke Scale (CNSS) and the Barthel Index (BI) were used to assess the severity and disability of the initial stroke at the time of admission. 15 In addition to other routine laboratory tests, the CRP level in patients with acute ischaemic stroke was quantified at the time of admission and discharge. Patients were checked in one month, three months, and six months. The disability score was calculated using BI during each follow-up visit. The CRP level was related to the size of the infarct. The CRP was linked to mortality and morbidity (disability, vascular events). Every week, the patients were contacted by phone to learn about their mortality and morbidity. Death or any new nonfatal vascular events (recurrent stroke, unstable angina, myocardial infarction, whichever occurred first) recorded during the six-month follow-up period were considered end events. All blood samples were collected from patients at the time of admission and again at discharge, and hs-CRP was measured on an Architect c16000 chemistry analyzer using an immunoturbidimetry assay. The results were given in milligrams per litre. CRP was less than 5 mg/L in the normal range. CT scans were performed on each patient at the Department of Radiodiagnosis, Regional Diagnostic Centre, SCB Medical College, Cuttack, at the time of admission. A CT scan was used to distinguish between a haemorrhagic and an ischaemic stroke. The American Heart Association (AHA) and American Stroke Association (ASA) emphasise the importance of a rapid brain imaging study prior to administering stroke-specific treatment, and a non-enhanced CT scan provides sufficient information for clinical decision-making in this setting. Because CT scans are more widely available and have a shorter acquisition time than MRIs, they are the most routinely utilised diagnostic imaging technique in acute ischemic stroke. In MRI, more time is spent screening for contraindications and placing the patient on the table.[15] Furthermore, as technology advances, ultrafast CT scans are as effective as MRI in detecting ischemic alterations and viable brain parenchyma. In the current investigation, CT scan was favoured over MRI due to the aforementioned characteristics.

STATISTICAL INVESTIGATION

SPSS version 25.0 was used for statistical analysis of the data. Proportions, the Chi-square test for association, Analysis of Variance (ANOVA) for assessing the difference between means, and logistic regression for determining the Relative Risk (RR) are among the statistical techniques used.

RESULTS

The patient population's demographic profile is shown in (Table 1). In the current research, the age group 60-70 years had the highest number of patients (40%). Males outnumber females (61%) in terms of incidence (Table-1). Hypertension is the most common risk factor,

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accounting for 68% of all cases, and the incidence was greatest with CRP levels over 5. (Table 2), which is followed by dyslipidaemia. In the current investigation, the incidence of atrial fibrillation (7%), peripheral arterial disease (10%), left ventricular hypertrophy (45%), and carotid stenosis (6%) was not substantially different between the two groups. (Table 3)
The severity of stroke was determined using the CNSS score, and the mean CNSS score was 6.98±1.63 in the low CRP group and 5.97±1.55 in the high CRP group. The value difference is statistically significant (p=0.011). The mean BI score in the low CRP group is 35.88±5.87, whereas it is 31.36±4.98 in the high CRP group (p=0.021). The mean infarct size in the low CRP group is 3.1±0.58 mm and 4.2±0.69 mm in the high CRP group (p=0.011). (Table 4)
The severity of the stroke, the level of impairment, and the size of the infarct were all substantially larger in the high CRP group (Table 5). Out of 70 patients in the high CRP group, 25 (35.71%) had fatal events and 25 (35.71%) had non-fatal events. As a result, 50 patients (71.42%) had adverse effects, which were statistically significant when compared to the low and high CRP groups. The biggest number of incidents occurred in the high CRP level group, i.e., 40%, while the RR was highest in the CRP level >5, i.e., 6.3, which is significant.
A statistically significant 50 (71.42%) of patients in the high CRP group had fatal and nonfatal events. A high CRP upon discharge is linked with a statistically significant 20.22 times increased risk of adverse outcomes. 15 of the 25 nonfatal occurrences had high CRP levels, whereas 10 had low CRP levels. Both the BI at admission and the BI at 6 months are lowest in the high CRP at admission group. These are statistically significant values. The high CRP at discharge group had the lowest BI at admission and six months, which is extremely significant. As a result, BI at admission was shown to be more significantly linked with CRP at discharge (p=0.006) than CRP at admission (p=0.011). Furthermore, BI at six months was much more strongly connected with CRP at discharge (p=0.002) than CRP at admission (p=0.02).

Table 1: Demographic profile of the patients

Parameter	Number	%
Mean age (years)	55.85±5.85	
Male gender	61	61
Hypertension	68	68
Diabetes	30	30
Dyslipidemia	43	43
Chronic heart disease	19	19
Smoking	17	17
Previous ischaemic stroke	13	13
History of antiplatelet use	17	17

Table 2: Risk factors in relation to level of CRP at admission

	CRP value (mg/L)			
Risk factors	**<5 =30**	**>5=70**	**Total= 100**	**p-value (Chi-square test)**
Hypertension	38	30	68	0.81
Diabetes	18	12	30	0.39
Dyslipidaemia	23	20	43	0.49
CHD	9	10	19	0.44
Smoking	8	9	17	0.69

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Table 3: Cardiovascular features in relation to CRP value at admission.

Cardiovascular features	CRP value (mg/L)			p-value (Chi-square test)
	<5	>5	Total	
Atrial fibrillation	7	0	7	0.61
Peripheral arterial disease	4	6	10	0.59
Left ventricular hypertrophy	20	25	45	0.81
Carotid stenosis	3	3	6	0.42

Table 4: Comparision of neuroradiological features with CRP at time of admission.

Neuroradiological features	CRP value (mg/L)		p-value (Chi- square test)
	<5	>5	
CNSS (mean)	6.98±1.63	5.97±1.55	0.011
Barthel Index (mean)	35.88±5.87	31.36±4.98	0.021
Infarct size in mm (mean)	3.1±0.58	4.2±0.69	0.011

Table 5: Comparison of CRP at admission and Relative Risk (RR) of end points at 6 months.

CRP (mg/L)	Event	RR	p-value (Chi-square test)
<5	6(20%)	1.2	-
>5	50(71.42%)	6.3	0.04

DISCUSSION

The majority of participants in this analysis were between the ages of 60 and 70 (40%). Statistically, ischemic stroke occurs most often in those aged 60 to 69, therefore our finding jives with the findings of other research. [16] Half of the patients were above the age of 60. Stroke has been shown to be more prevalent among the elderly, which is consistent with previous research. [17] The current investigation confirms the findings of Bejot Y et al., finding a gender gap of 61(61%) in male and 39(39%) in female. [18] Hypertension (68%) was the leading risk factor, followed by dyslipidaemia (43%) and diabetes (30%). Di Napoli M et al., Winbeck et al., found similar results. Patients were placed into three groups based on their CRP levels for each risk factor. All p values generated for the comparisons between the three groups of CRP levels were more than 0.05, indicating that there was no statistically significant difference in the incidence of risk factors between the groups. Since CRP was shown to be unrelated to the aforementioned risk variables in both the current study and prior research, it is now recognised as an independent factor. [19,20]

Notably, the current investigation demonstrated no statistically significant difference in the incidence of atrial fibrillation (7%), peripheral arterial disease (10%), Left ventricular hypertrophy (45%), or carotid stenosis (6%). The CNSS score was used to determine the severity of the stroke, and it was found to be 6.98±1.63 in the low CRP group and 5.97±1.55 in the high CRP group. There is a statistically significant difference in the results (p=0.011). Comparing the two groups, those with low CRP have a mean BI of 35.88±5.87 (p=0.021), whereas those with high CRP have a mean BI of 31.36±4.98). As a whole, infarct sizes are larger in the high CRP group, at 4.2±0.69 mm (p=0.011), than in the low CRP group, at 3.1±0.58 mm. As a result, a rise in CRP substantially heightens the risk of stroke, disability, and infarct size. These results are consistent with those found by Shoaeb MA et al., who found that a patient's blood CRP level upon admission may be utilised to predict stroke severity and early prognosis. Serum C-reactive protein levels were shown to be substantially

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linked with disease severity and outcome in ischemic stroke by 21 authors when tested within 24 hours after stroke start. After stroke, several researchers have identified variable increases in CRP. According to research published in 2011 by Di Napoli M et al.,[21] it was discovered that CRP concentration increased in the first 24 hours after stroke, and that this increment was associated with the size of the infarction, so rising CRP levels in the first 24 hours were synchronised to poor prognosis.[22, 23] There is yet no explanation for the correlation between elevated CRP and severe stroke. Cerebral artery atherosclerosis is thought of as an inflammatory condition because of the production of acute phase reactant proteins in the initial few hours. An increased risk of vascular problems has been connected to a higher inflammation level as measured by CRP levels. [24] The degree of damage to brain tissue may be reflected in the level of CRP elevation. High CRP levels may be linked to underlying mechanisms that lead to more severe strokes because of the role CRP plays as an inflammatory marker. Another connection is that increased CRP levels activate coagulation through the crucial function of tissue factor expression. Stroke patients with activated coagulation factors have a higher risk of dying, and fibrinogen may play a part in this. [25]
Patients with high CRP levels were much more likely to have adverse outcomes, with 50 (71.42%) of them experiencing either fatal or nonfatal events. Statistics show that the probability of adverse outcomes is significantly increased by 20.22 times if CRP is high upon discharge. The C-reactive protein levels in 15 of the 25 nonfatal incidents were high, whereas C-reactive protein levels in 10 of the events were low. The group with high CRP at admission also had the lowest BI at admission and after 6 months. These numbers have a high probability of being correct. The high CRP at discharge group had the lowest BI at admission and six months, which is extremely significant. The correlation between BI and CRP at discharge ($p=0.006$) was statistically significantly higher than the correlation between CRP and BI ($p=0.011$). Six-month BI was also significantly connected with CRP at discharge ($p=0.002$), albeit the correlation was less ($p=0.04$) at admission. In addition, similar findings were made by other researchers. [26]

CONCLUSION

The present investigation shown that individuals with ischemic stroke had elevated levels of CRP, an inflammatory marker. Stroke severity and bad outcomes are proportional to the degree of CRP elevation. In terms of mortality and morbidity, CRP after discharge is preferable to CRP at admission. The severity of impairment is also correlated with CRP levels. Patients who were identified as high-risk were subject to stricter and more frequent monitoring.

REFERENCES

1. Krishna Murthy HA, Renuka Prasad YS. Study of prognostic significance of serum c-reactive protein and ESR in acute ischaemic stroke. Int J Cur Res Rev. 2013;05(02):129.
2. Yoldas T, Gonen M, Godekmerdan A, Ilhan F, Bayram E. The serum high-sensitive C reactive protein and homocysteine levels to evaluate the prognosis of acute ischaemic stroke. Mediators Inflamm. 2007;2007:15929. Doi: 10.1155/2007/15929.
3. Mohebbi S, Ghabaee M, Ghaffarpour M, Meisami AP, Siah RS, Mirkala MR, et al. Predictive role of high sensitive C-reactive protein in early onset mortality after ischaemic stroke. Iranian Journal of Neurology. 2012;11(4):135-13.
4. Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, et al. Plasma concentration of C-reactive protein and risk of ischaemic stroke and transient ischaemic attack: The Framingham study. Stroke. 2001;32:2575-79. Doi: 10.1161/hs1101.098151.
5. Zhou Y, Han W, Gong D, Man C, Fan Y. hs-CRP in stroke: A meta-analysis. Clin Chim Acta. 2016;453:21-27. Doi: 10.1016/j.cca.2015.11.027.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 07, 2022

6. Tillet WS, Francis T. Serological reactions in peneumonia with a non protein somatic fraction of pneumococcus. J Exp Med. 1930;52;561-57.
7. VanGilder RL, Davidov DM, Stinehart KR, Huber JD, Turner RC, Wilson KS, et al. C-reactive protein and long-term ischaemic stroke prognosis. Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia. 2014;21(4):547-53. Doi: 10.1016/j.jocn.2013.06.015.
8. Gong P, Liu Y, Huang T, Chen W, Jiang T, Gong Y, et al. The association between high-sensitivity C-reactive protein at admission and progressive motor deficits in patients with penetrating artery infarctions. BMC Neurol. 2019;19:346. https:// doi.org/10.1186/s12883-019-1538-5.
9. Ridker PM, Peter WF, Wilson, Grundy SM. Should C-Reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation. 2004;109:2818-25.
10. Keren DF, Warren JS. Diagnostic Immunology, p 57-58. Baltimore, MD,Williams & Wilkins, 1992.
11. Pepys MB. The acute phase response and Creactive protein. Chapter 11, 13.3 in Oxford Text book of Medicine, 3rd Edition, Weathurall DJ, Ledingham JGG, Warrell DA, Tokyo: Oxford University Press, 1906; 1527-1533.
12. Kushner I, Feld Man G. Control of acute phase response Demonstration of C-reactive protein sysnthesis and secretion by hepatocytes during acute inflammation in the rabbit. J. Exp Med. 1978;148:466-77.
13. Merriman CR, Pulliam LA, Kampschmidt RF. Effect of leukocytic endogenous mediator on C-reactive protein in rabbits. Proc Soc Exp Bio Med. 1975;149:782-84
14. Smith WS, Hauser SL, Easton D. Cerebrovascular diseases. Harrison's principles of Internal Medicine. 16th edition. (Eds). Casper DL, Fauci AL, Longo DL, Braunwald E, Hauser SL. McGraw-Hill 2004
15. Cotè R, Hachinski VC, Shurvell BL, Norris JW, Wolfson C. The Canadian Neurological Scale: A preliminary study in acute stroke. Stroke.1986;17:731-37
16. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischaemic stroke: An independent prognostic factor. Stroke. 2001;32:917-24. 10.1161/01.str.32.4.917. Chen RL, Balami JS, Esiri MM, Chen LK, Buchan AM. Ischaemic stroke in the elderly: An overview of evidence. Nat Rev Neurol. 2010;6(5):256-65. Doi: 10.1038/nrneurol.2010.36.
17. Béjot Y, Bailly H, Graber M, Garnier L, Laville A, Dubourget L, et al. Impact of the ageing population on the burden of stroke: The Dijon Stroke Registry. Neuroepidemiology. 2019;52(1-2):78-85. Doi: 10.1159/000492820.
18. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circ Res. 2017;120(3):472-95. ahajournals.org/doi/abs/10.1161/ CIRCRESAHA.116.308398, 2017,120,472-495
19. Di Napoli M, Papa F, Bocola V. Prognostic influence of increased c-reactive protein and fibrinogen levels in ischaemic stroke. Stroke. 2001;32:133-38. 10.1161/01.STR.32.1.133.
20. Shoaeb MA, Shehata MA, Taema KM, Hammouda MA. CRP in cerebrovascular stroke: Prognostic implications. The Egyptian Journal of Critical Care Medicine. 2014;2(1):43-52. ISSN 2090-7303.
21. Pedersen ED, Waje-Andreassen U, Vedeler CA, Aamodt G, Mollnes TE. Systemic complement activation following human acute ischaemic stroke. Clin Exp Immunol. 2004;137(1):117-22.
22. Di Napoli M. Early inflammatory response in ischaemic stroke. Thromb Res. 2001;103(3):261-64.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 07, 2022

23. Bahadursingh S, Beharry K, Maharaj K, Mootoo C, Sharma P, Singh J, et al. C-reactive protein: Adjunct to cardiovascular risk assessment. West Indian Med J. 2009;58(6):551-55.
24. Audebert HJ, Rott MM, Eck, Haberl RL. Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. Stroke. 2004;35(9):2128-33.
25. Feinberg WM, Erickson LP, Bruck D, Kittelson J. Hemostatic markers in acute ischaemic stroke. Association with stroke type, severity, and outcome. Stroke. 1996;27(8):1296-300
26. Wu X, Liu G, Zhou W, Ou A, Liu X, Wang Y, et al. Outcome prediction for patients with anterior circulation acute ischaemic stroke following endovascular treatment: A single-center study. Experimental and Therapeutic Medicine. 2019;18(5):3869- 76. https://doi.org/10.3892/etm.2019.8054