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Assessment of risks with acute ischemic stroke in association with CRP levels

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***Abstract*---**Background: There is growing evidence of the prognostic importance of C-reactive protein (CRP) in ischemic stroke. However, the independent value of CRP at different stages after stroke has not been established. Therefore, we assessed the prognostic values of CRP in ischemic stroke. C- reactive protein (CRP), an acute phase reactant and a marker for underlying systemic inflammation has been reported to be elevated in acute coronary syndromes. It has been reported that concentrations of C-reactive protein is directly correlated with the presence and severity of atherosclerosis and are predictors of coronary events and mortality in patients with acute coronary syndromes. Aims and Objectives: The primary aim of this study was to systematically and critically review the relationship between CRP and long-term functional outcome in ischemic stroke patients to evaluate the current state of the literature and also risks involved in it. Materials and methods: This is a prospective study carried out in the Department of Medicine, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpet, Tamilnadu. Personal history regarding dietary habits, smoking, alcohol consumption and tobacco chewing were noted. NIH Stroke Scale was assessed in all patients to assess the neurological disability and its prognosis. Detailed neurological examination was done based on proforma, among 72 patients who had first ever acute ischemic stroke CRP level was measured and it was > 6 mg/dl in 50 patients constituting 69% of total study population and CRP level of < 6mg/dl was seen in 22 patients constituting 31%. The mean of CRP level at admission was 25.3 Results and Observations: Results indicate a significant association between elevated baseline high sensitivity CRP and unfavorable long-term functional outcome. Our results emphasize the need for additional research to characterize the relationship between

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acute inflammatory markers and long-term functional outcome using well-defined diagnostic criteria. In our study, among 72 patients only 22 patients are alcoholic constituting 31% and 50 are non-alcoholic constituting 69% , patients who are smokers, among 72 patients 20 patients are smokers constituting 28% of study group and 52 are non-smokers constituting 72%, association between the CRP level and NIH score at the end of three months of follow-up, this also showed a positive correlation with a “p” value of. Conclusion: C-reactive protein being elevated within 72 hours of an acute ischemic stroke is an indicator of poor prognosis. It is also observed that raised plasma levels of Creactive protein can be used to diagnose ischemic. Stroke positively but subtypes (cortical, subcortical) of cerebral infarction cannot be differentiated at the time of diagnosis.

***Keyword*---**CRP, Prognosis, C- reactive protein, NIH Stroke Scale, Risk factors, positive correlation.

Introduction

Cerebrovascular stroke (CVS) is a common cause of death and disability. The C-reactive protein increases in response to stroke and may be used as a predictor for stroke outcome. Some studies have investigated the relationship between acute biomarkers and functional outcome following stroke. A potential prognostic biomarker of ischemic stroke (IS) is C-reactive protein (CRP), which is currently used for evaluating pathological inflammation and has been extensively studied in relationship to the progression of atherosclerosis [2]. Baseline inflammatory levels of CRP can predict patient outcomes in cardiovascular disease [1, 3,4,5] including myocardial infarction [6,7]. At the turn of 20th century, Sir Williams Osler and Ophulus proposed that infection could be a causal factor in the pathogenesis of atherosclerosis. In fact research of more than a century has implicated various microorganisms as a potential link between inflammation and pathogenesis of atherosclerosis. Indeed atherosclerosis is now accepted as an inflammatory disease, possibly infections include Chlamydia, H-pylori, Herpes and CMV. Researchers found a protein in their several years of study in the first attack of myocardial infarction or stroke and this is C- reactive protein.[8] In the last few decades, inflammation has been proposed to play an important role in the pathogenesis of acute ischemic stroke (AIS). C-reactive protein (CRP), which is the classical acute-phase reactant protein, is viewed as the most extensively studied marker of inflammation. Undoubtedly, it is also one of the most widely studied inflammatory biomarkers in cardiovascular disease and ischemic stroke.[9] In recent years, an increased level of CRP remarkably associated with the functional prognosis of acute ischemic stroke was observed in multiple studies. Nevertheless, most of the previous studies investigating the prognosis of patients with acute ischemic stroke were mainly focused on new stroke attack and mortality. In addition, Halvor et al. found that CRP and homocysteine were associated with long-term mortality in young ischemic stroke patients. Huang et al revealed that hsCRP was related to a worse prognostic risk of all-cause death within three months after acute ischemic stroke in Chinese patients.[10] Apparently, measuring C – reactive protein might provide a novel method to detect

a worrisome level of atherosclerosis in otherwise healthy persons. This new finding assumed importance to researchers as it raised the possibility that atherosclerosis may be atleast partly an inflammatory process disease. Antimicrobial and antiviral therapy may someday become the part and parcel of therapies to prevent heart attacks and stroke. Limited studies have been published on CRP changes in stroke in India despite a high incidence of CVA in India.[11] CRP is a systemic inflammatory marker that is produced in large amounts by hepatocytes in response to IL-1, IL-6 and TNF factor. 3,4 Rapid induction of CRP, its long half-life (19hours) and a lack of alteration during day and night in comparison with other acute phase reactants has introduced CRP as an important factor for evaluation of inflammatory and infectious diseases.[12] Nowadays, CRP is a confirmed diagnostic marker for patients with CVA and recent prospective investigations showed that CRP is clinically helpful in predicting the risk of the future cardiovascular diseases.[13] C- reactive protein was discovered by Tillet and Francis in 1930 . They were investigating serological reactions in pneumonia with various extracts of pneuomococci and observed that a non-type specific somatic polysaccharide fraction, which they designated as fraction 'C' was precipitated by the sera of actually ill patients. After the crisis, the capacity of the patient's sera to precipitate with polysaccharide (CPS) rapidly disappeared, and the C- reactive material was not found in sera from normal healthy individuals.[14] Avery and his collaborators characterised the C- reactive material as a protein which required calcium ions for its reaction with CPS and introduced the term 'acute phase' to refer to serum from patients acutely ill with infectious diseases and containing the C-reactive protein. Lofstorm independently described a non-specific capsular swelling reactions of some strains of pneumococci when mixed with acute phase sera and subsequently showed that the substance responsible was CRP. He detected CRP in noninfectious as well as infectious conditions; and the acute phase reaction, in which the concentration of certain plasma protein increases is now recognised as a general and non-specific response to most forms of infective and non infective inflammatory processes, cellular and/ or tissue necrosis, and malignant neoplasia. Semiquantitative assays for serum CRP were widely used for many years to provide an objective index of the acute phase response and therefore, of disease activity in many clinical conditions. Within the past few years there has been a resurgence of interest in the chemical structure, and biological functions of CRP, and with the advent of more sensitive and precise assays, the measurement of serum CRP levels is proving to be useful in variety of clinical conditions, including ischemic stroke. C- reactive protein (CRP), an acute phase reactant and a marker for underlying systemic inflammation has been reported to be elevated in acute coronary syndromes. It has been reported that concentrations of C-reactive protein is directly correlated with the presence and severity of atherosclerosis and are predictors of coronary events and mortality in patients with acute coronary syndromes. Recently CRP was shown to be a risk predictor for future myocardial infarction, stroke and coronary heart disease death in apparently healthy individuals[14,15]. This potential predictive capacity of CRP warrants further evaluation

Materials and Methods

This is a prospective study carried out in the Department of Medicine, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpet, Tamilnadu, Information was collected through a pretested and structured proforma for each patient. Clinical history was taken from either patient or his/her attendee. While taking history importance was given regarding presence or absence of vomiting, headache and convulsions, past history of hypertension, diabetes, coronary artery disease, rheumatic heart disease, transient ischemic attack, collagen diseases, meningitis, tuberculosis, endocrine disorders and congenital disorders were taken. Personal history regarding dietary habits, smoking, alcohol consumption and tobacco chewing were noted. NIH Stroke Scale was assessed in all patients to assess the neurological disability and its prognosis. Detailed neurological examination was done based on proforma. All other systems like cardiovascular system, respiratory system, gastrointestinal system were examined in detail. Detailed investigations Complete blood count, ESR, Fasting Blood sugar, Serum electrolytes, Lipid profile, Chest X-Ray, Electrocardiography, Transthoracic echocardiography, HIV serology, Prothrombin time, INR,CRP level, CT Brain/MRI Brain was done in all patients. ANA Profile, Homocystiene level, antiphospholipid antibody, were done when clinically required.

Results and Observations

Table 1: Subjects distribution based on alcohol usage

Alcohol Usage	Number	%
Yes	22	31
No	50	69
Total	72	100

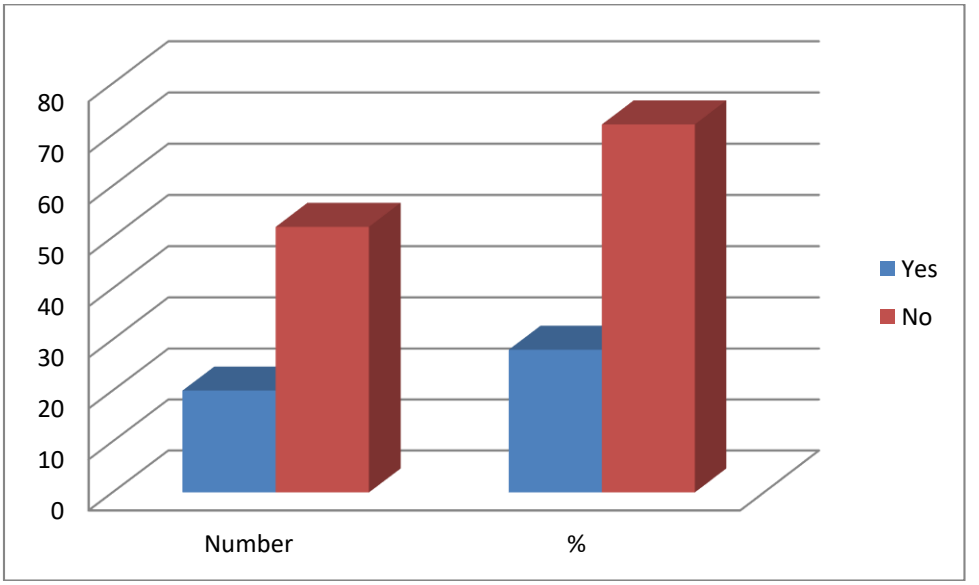

Figure 1: Alcohol usage among the subjects

Table 1 and Figure 1 showing the number of patients who are alcoholic among study group. Among 72 patients only 22 patients are alcoholic constituting 31% and 50 are non-alcoholic constituting 69%.

Table 2: Subjects distribution based on Smoking

Smoking	Number	%
Yes	20	28
No	52	72
Total	72	100

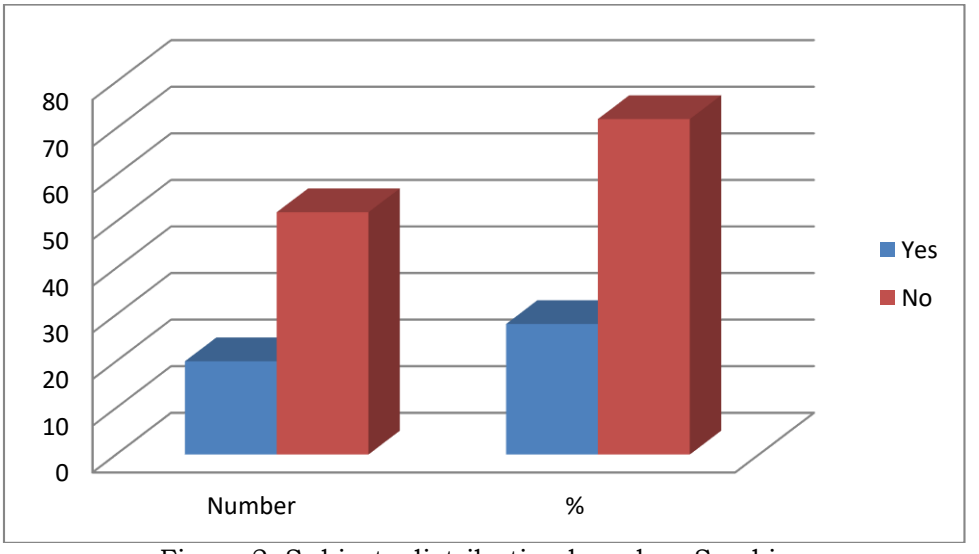

Figure 2: Subjects distribution based on Smoking

Table 2 and Figure 2 showing number of patients who are smokers, among 72 patients 20 patients are smokers constituting 28% of study group and 52 are non-smokers constituting 72%.

Table 3: Subjects distribution based on both Smoking and alcohol usage

Both(Smoking and alcohol)	Number	%
Yes	12	17
Not both	60	83
Total	72	100

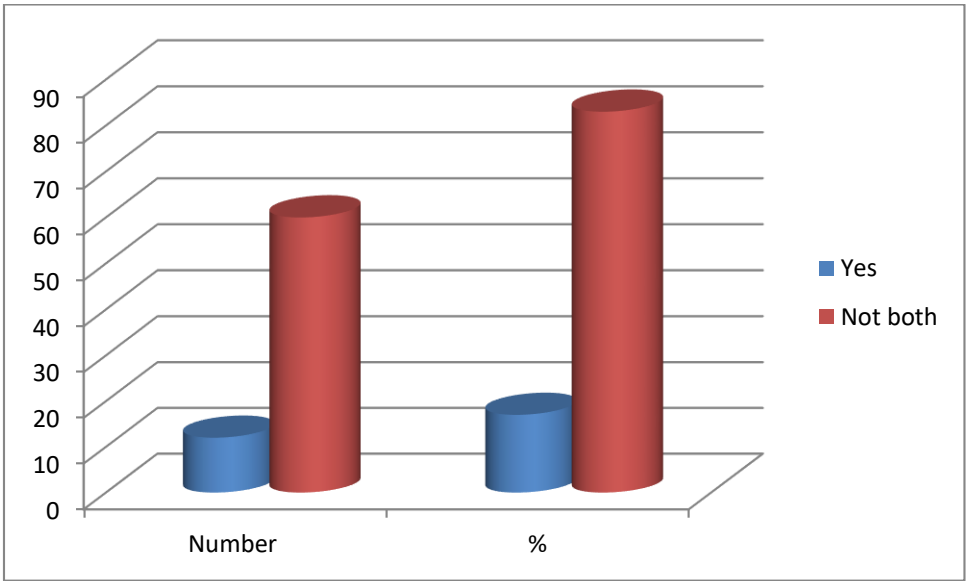

Figure 3: Subjects distribution based on both Smoking and alcohol usage

Table 3 and Figure 3 showing number of patients who had a habit of taking both alcohol and smoking, among 72 patients 12 had habit of taking both alcohol and smoking and 60 patients had no habit.

Table 4: Subjects distribution based on hypertension status

Hypertension	Number	%
Yes	30	42
No	42	58
Total	72	100

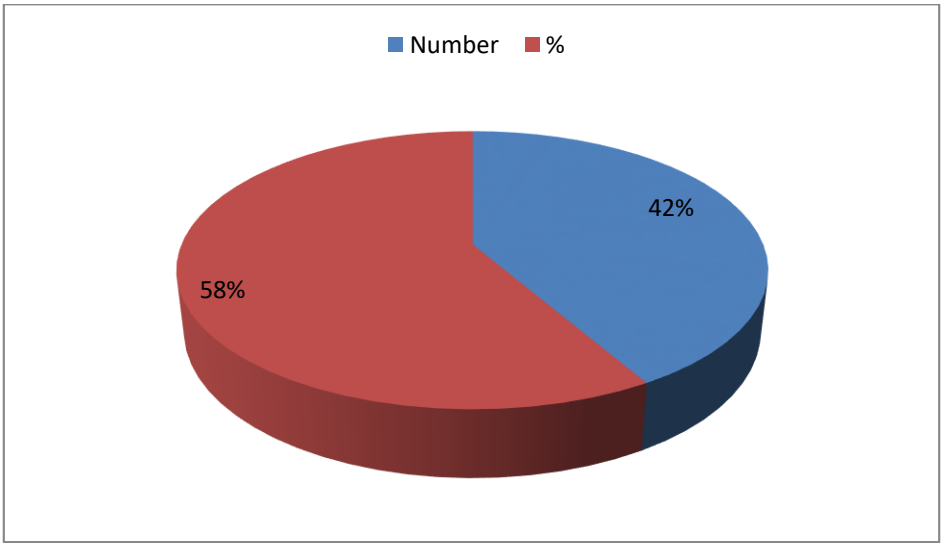

Figure 4: Subjects distribution based on hypertension status

Table 4 and Figure 4 showing distribution of patients based on presence or absence of hypertension. Among 72 patients 30 patients had past history of hypertension constituting 42% and 42 patients had no past history of hypertension constituting 58%.

Table 5: Subjects distribution based on diabetes status

Diabetes Mellitus	Number	%
Yes	14	19
No	58	81
Total	72	100

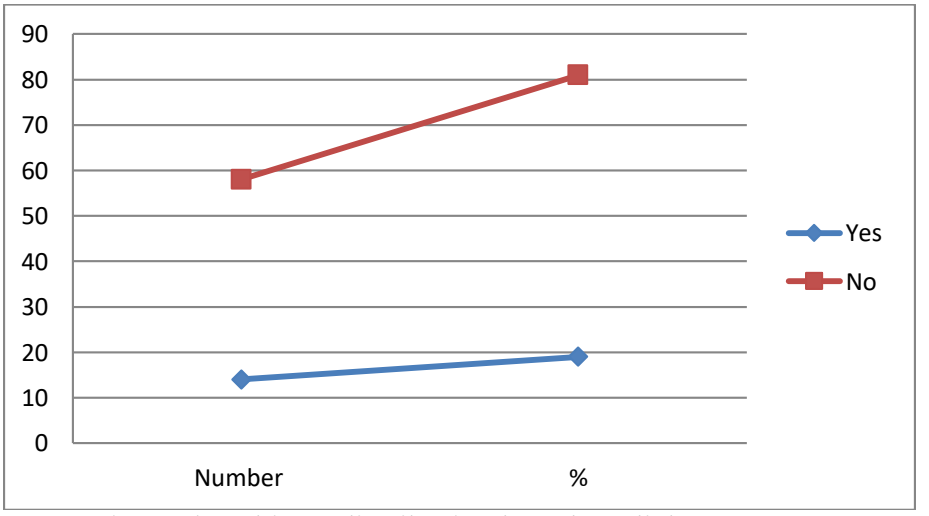

Figure 5: Subjects distribution based on diabetes status

Table 5 and Figure 5 showing distribution of patients based on the presence or absence of diabetes mellitus in the past, among 72 patients of study group only 14 patients had a past history of diabetes mellitus constituting 19% and 58 patient had no past history of diabetes mellitus constituting 81%.

Table 6: Subjects distribution on hypertension and diabetes

Both (Hypertension and Diabetes)	Number	%
Yes	7	10
Not Both	65	90
Total	72	100

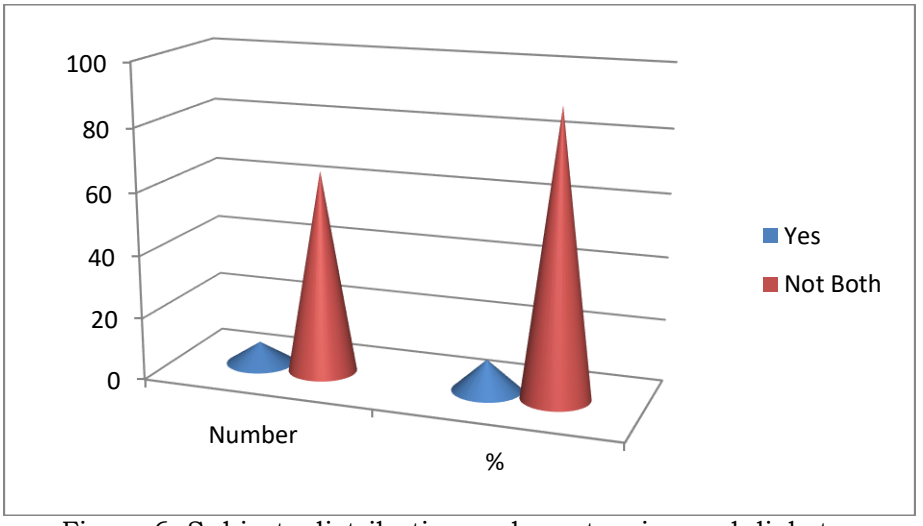

Figure 6: Subjects distribution on hypertension and diabetes

Table 6 and Figure 6 showing distribution of patients who had a past history of both diabetes mellitus and hypertension, among 72 patients studied only 7 patients had past history of both diabetes mellitus and hypertension constituting 10% .

Table 7: Subjects distribution on CRP at the admission category

CRP Level	Number	%
<6	22	31
>6	50	69
	72	100

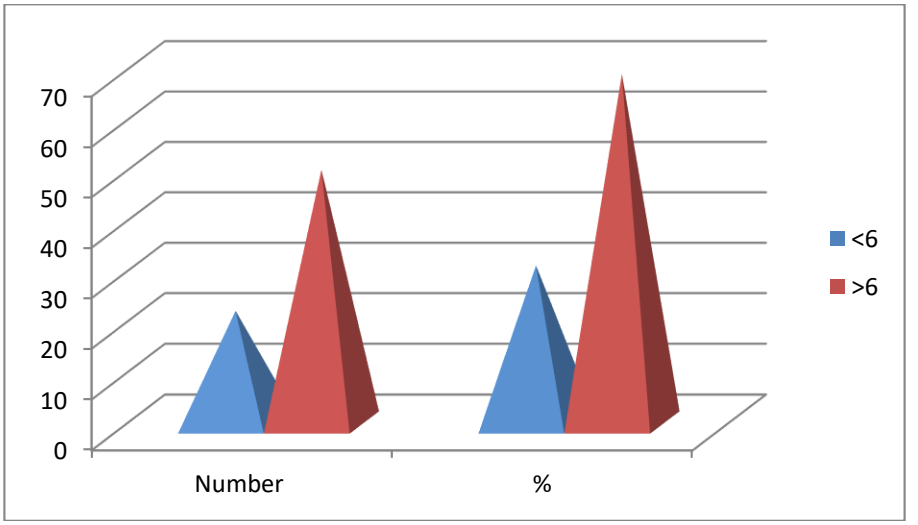

Figure 7: Subjects distribution on CRP at the admission category

Table 7 and Figure 7 showing distribution of patients based on CRP level at admission, in the present study cut off value of 6mg/dl has been taken since in India as a developing nation there is a high incidence of infectious diseases CRP level of 6 mg/dl taken as positive. Among 72 patients who had first ever acute ischemic stroke CRP level was measured and it was >6 mg/dl in 50 patients constituting 69% of total study population and CRP level of <6mg/dl was seen in 22 patients constituting 31%. The mean of CRP level at admission was 25.3.

Table 8: Subjects distribution based on CRP level at the end of 3rd month

CRP Level	Number	%
<6	47	65
>6	19	27
Missing	6	8
Total	72	100

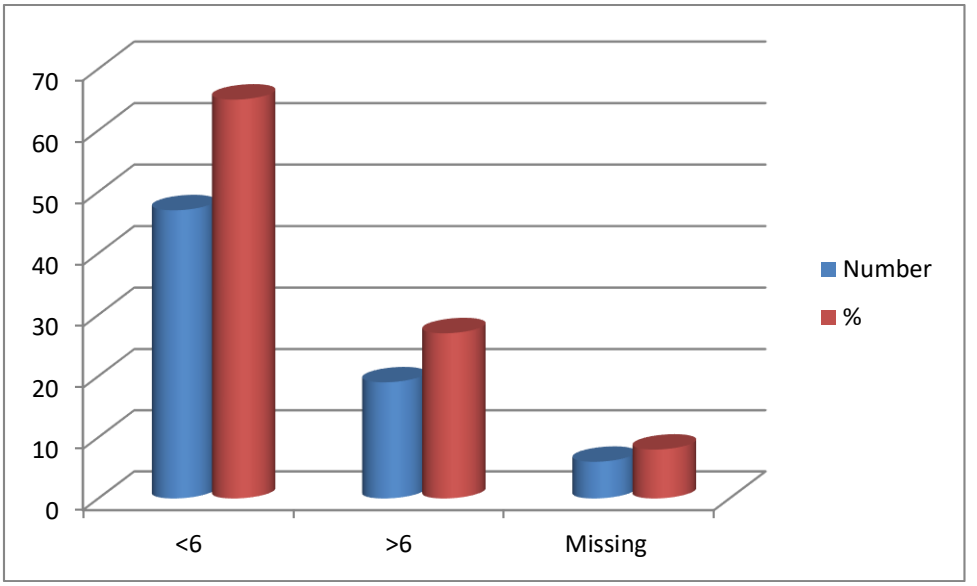

Figure 8: Subjects distribution based on CRP level at the end of 3rd month

Table 8 and Figure 8 showing distribution of patients based on CRP level done after a follow-up period of three months. Among 72 patients studied, 47 patients who had shown significant improvement as assessed by NIHS Scale system, CRP level also reduced to <6mg/dl constituting 65%, and in 19 patients CRP level remained <6mg/dl In 6 patients CRP level could not be done as the patients died within the follow-up period of three months.

Table 9: Correlation with CRP at admission and NIHS Score at admission

CRP Level at admission	NIHSS at admission Mean (SD)	P value (t test)
<6	9.0 (4.69)	0.003
>6	14.1 (6.9)	0.003

Table 9 showing an association between the CRP level at admission time and NIH Score at admission which is an predictor of severity of stroke, there is a positive correlation between CRP level and NIH score with a “p” value of 0.03 which is significant.

Table 10: Correlation with CRP and NIHS at the end of 3rd month

CRP Level at 3rd Month	NIHSS at 3rd Month Mean (SD)	P value
<6	2.98 (1.97)	<0.001
>6	6.32 (4.04)	<0.001

Table 10 shows the association between the CRP level and NIH score at the end of three months of follow-up, this also showed a positive correlation with a “p” value of <0.001 which is significant.

Discussion

The aim of the study was to elucidate the relationship between CRP and prognosis after cerebral ischemia. We adopted strict enrollment criteria to have a homogeneous population: all patients were selected to avoid possible confounding factors capable of increasing inflammation markers. Smoking is widely accepted as one of the risk factors for cerebral infarction in indian populations. Smoking thought to affect lacunar infarction mainly through reversible factors, such as increased platelet aggregation and arterial vasoconstriction induced by sympathetic activity rather than through atherogenic factors and this relationship has not been observed in most japanese epidemiological studies. Hertog, H.M.; Rossum, J.A[16] et al in their study observed that overall 38% of patients with history of acute ischemic stroke were smokers. Hypertension is a well-established risk factor for a first stroke. All forms of hypertension, isolated systolic or diastolic and combined systolic and diastolic hypertension, increase stroke risk. Compared with non hypertensive individuals, people with hypertension are three or four times more likely and people with borderline hypertension about 1·5 times more likely to have a stroke.[17] Roberta Ravenni, Joe F. Jabre, Edoardo Casiglia[18]et al documented that approximately 54% of strokes can be attributed worldwide to high blood pressure (BP) values in both gender and in all ages. As a consequence, hypertensive subjects are 3 to 4 times more likely to have a stroke than the normotensives. In particular, it was established that a 2 mmHg rise in systolic BP in middle age is associated with 10% increase in risk of stroke. In addition the relationship between blood pressure and risk of first stroke is direct, continuous and independent, with the risk increasing continuously above a BP of 115/75 mmHg. High PP(Pulse pressure) is associated with higher incidence of carotid stenosis, and reduction in cerebral flow, and is recognized as an independent predictors of stroke mortality particularly in elderly people from general population. In particular, a 10 mmHg PP increase is associated with 11% increase in stroke. Current international guidelines recommend a systolic/diastolic goal of <140/<90 mmHg in the general population and <130/<80 mmHg in diabetic subjects and in those with renal disease. Brett m. Kissela, Md Jane Khoury, ms[19]et al observed that age-specific incidence rates and rate ratios show that diabetes increases ischemic stroke incidence at all ages, but this risk is most prominent before age 55 in African Americans and before age 65 in whites. One-year case fatality rates after ischemic stroke are not different between those patients with and without diabetes. They estimated that 37–42% of all ischemic strokes in both African Americans and whites are attributable to the effects of diabetes alone or in combination with hypertension. Thomos S. Bowman et al[20] documented that TC, HDL, and Triglyceride level were not independent risk factors for ischemic stroke and TC:HDL ratio did not have a linear association with the risk of ishemic stroke. Acute stroke may trigger an inflammatory response that leads to increased levels of CRP. High levels of CRP may be associatedwith poor outcome because they reflect either an inflammatoryreaction or tissue damage. Elevated serum levels of CRP are found in up-to three quarters of patients with ischemic stroke. Increases in CRP may reflect a systemic inflammatory response following stroke, the extent of tissue injury, or concurrent infections. Several studies have assessed the value of CRP in thevery early phase of stroke as a prognostic factor of functional outcome. Verification of the role of CRP as an early prognosticfactor of functional outcome after ischemic stroke may

beof clinical importance, because it is an easily-measured and readily available inflammatory marker. Titto T Idicula, Jan Brogger[21] et al studied 498 patients, CRP was measured within 24 hours after stroke onset, showed a crude association between high CRP and poor short-term functional outcome. They concluded thatadmission CRP is associated with stroke severity and long-term mortality when measured at least 24 hours after onset. M.A. Shoaeba, M.A. Shehata[22]et al included 50 patients with a first-ever acute stroke admitted within 24 h of onset with a mean age of 59.5 ± 8.6 years. And found that serum CRP level on admission was predictive of stroke severity as well as outcome. They concluded that the serum CRP level on admission can be used to predict severity and early outcome in ischemic but not in hemorrhagic stroke. M.A. Shoaeba, M.A. Shehata[22]et al in their study classified Severity of stroke by using NIHSS, Patients were categorized as mild stroke (NIHSS 0–7), moderate (NIHSS 8–14), or severe stroke (NIHSS >14). Severity of stroke assessed by NIHSS revealed a mean score of 13±14 with 15 patients (30%) stratified as severe, 5 patients (10%) as moderate, and 30 patients (60%) as mild and There was a strong positive correlation between disease severity assessed by NIHSS and Serum CRP level, was positively correlated with NIHSS (r=0.54, P =0.006). Serum CRP level was14.4± 6 mg/L in patients with severe ischemic stroke comparedto 7.7±4.5 mg/L in patients with mild and moderate presentation. (P = 0.01). They detected a CRP level of10.25 mg/L to predict severe ischemic stroke with a sensitivity of 80% and a specificity of 75%. Outcomes assessed 7 days after admission by mRS revealed a poor outcome in 22 patients (44%); however, outcome evaluation by BI revealed a poor outcome in 32 patients (64%). Mario Di Napoli et al[23] studied, the risk of CRP in 72% of patients (p=0.0001) out of 473 first ever ischemic stroke patients and suggested CRP as a independent marker of underlying chronic inflammatory process in atherosclerosis. Recently, Di Napoli M[24] observed an increase of CRP within 3 hours after stroke compared with pre-stroke value. Mahapatra SC et al[25] observed CRP value 76 mg/dl in 64 patients out of 80 total thrombotic stroke patients ($p<0.001$) The study was undertaken to assess the role of inflammation in pathogenesis of ischemic stroke. Rathore HS et al[26] performed a study to measure and compare CRP levels in the cortical and lacunar infarct and to find out their diagnostic importance at an early stage of stroke. CRP was estimated in 25 cases of lacunar and 25 cases of cortical infarct. The CRP was considered positive if its value was more than 6mg/dl, observed rise of CRP in 12% cases of lacunar infarct and 88% cases of cortical infarct. In Irene M et al[27] study, CRP levels were measured in a random sample of 773 subjects >55 years of age and follow-up was done for the next 6.5 years. They documented the progression of subclinical atherosclerosis and CRP predicted myocardial infarction and stroke.

Conclusion

C-reactive protein being elevated within 72 hours of an acute ischemic stroke is an indicator of poor prognosis. It is also observed that raised plasma levels of Creactive protein can be used to diagnose ischemic stroke positively but subtypes (cortical, subcortical) of cerebral infarction cannot be differentiated at the time of diagnosis. Cerebro-vascular stroke is one of the leading causes of death and disability in the elderly.

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Conflict of Interest: None

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