Assessment of Hs-CRP (high sensitive c-reactive Protein) as a prognostic indicator in acute ischemic stroke

Shridhar Patil[1], Anuja Kadagud[2], Ravi Kattimani[3], Muddasir Indikar[4]

[1,2,3]Department of Medicine, [4]Department of Geriatric Medicine, BLDE Medical College Vijayapur, Karnataka, India.

Abstract

Introduction: The measurement of markers of inflammation or thrombosis has been proposed as a method to improve the prediction of risk in patients with vascular disease. The role of High sensitive C-reactive protein (Hs-CRP) as a novel plasma marker of atherothrombotic disease is currently under investigation. We related plasma Hs-CRP levels to first ever ischemic stroke and its role as a diagnostic aid.

Aim And Objectives: In view of the different observations by various studies about the source of inflammatory stimulus and significance of value of High sensitive C-reactive protein in thrombotic stroke and relation between different risk factors, the present study was undertaken with the following aims and objectives. To determine the levels of Hs-CRP levels in acute ischemic stroke. To compare the Hs-CRP levels in patients of acute ischemic stroke with healthy controls. To determine the role of Hs-CRP in predicting the outcome in patients with acute ischemic stroke.

Methods: Fifty patients with first ever acute ischemic stroke patients were examined with the exclusion from the exclusion criteria. CT scan of brain was done to confirm the diagnosis. Plasma Hs-CRP level was determined after 12 hours and before 72 hours of onset of symptoms in all CT confirmed ischemic stroke patients. This clinical study was done during September 2022 to February 2024. Hs-CRP was randomly measured in 50 age and sex matched individuals matched in all possible criteria except the disease under study as a control group.

Results: The Hs-CRP concentration in ischemic strokes independent of infarction site, the value was more between 51-70 years of age group and male predominance. All of the 50 ischemic strokes studied had CRP value >1 mg/l and chi square test value is 66.14 which is statistically significant. Only 9 of the 50 control group had CRP >1mg/l, which is insignificant.

Conclusion: The Hs-CRP level is significantly higher in ischemic strokes and by its elevation between 12-72 hours of symptom onset was a bad prognostic indicator. Elevated Hs-CRP values were also raised in all the patients who expired.

Keywords: High sensitive C-reactive protein; Ischemic stroke.

Introduction

Stroke remains a major cause of human mortality and morbidity. Cardiovascular and cerebrovascular diseases appear to be very frequently encountered now and responsible for great deal of morbidity. In spite of our increasing understanding of the pathophysiology and epidemiology of cardiovascular diseases and stroke and continuing advances in prevention and treatment, the burden of above said diseases is high[1].

Furthermore traditional atherogenic risk factors such as hypertension, smoking, hyperlipidemia, diabetes mellitus do not fully account for the clinical occurrence of CHD and stroke in different populations[2]. There is no surprise that extensive search study is necessary for potential risk factors.

At the turn of 20th century, Sir Williams Osler (1908) and Ophulus (1921) proposed that infection could be a casual factor in pathogenesis of atherosclerosis. Infarct research of more than a century has implicated various microorganisms as potential link between inflammation and the pathogenesis of atherosclerosis. Indeed atherosclerosis is now accepted as an

Address for Correspondence:

Dr. Muddasir Indikar

Department of Geriatric Medicine,
Amina Manzil Darbar Galli J M Road,
Email: drmuddasir12@gmail.com

inflammatory disease, possible infections include chlamydia, H-pylori, Herpes and CMV[3]. Researchers found a protein in their several years study in first attack of myocardial infarction or stroke and this is C reactive protein.

Apparently measuring C-reactive protein might provide novel method to detect worrisome level of atherosclerosis in otherwise healthy persons. This new finding assumed importance to researchers as they raised the possibility that atherosclerosis may be at least partly and inflammatory process disease[4]. Antimicrobial and antiviral therapy may someday become the part and parcel of therapies to prevent heart attack and stroke. Limited works have been published on CRP changes in stroke in India despite high incidence of CVA in India.

Materials And Methods

The study "Plasma High sensitive C Reactive Protein levels as a prognostic and diagnostic marker in first ever acute ischemic stroke" was carried out in shri B M Patil medical college hospital and research centre Vijayapura during the period from September 2022 to February 2024.

Selection of Patients: The study was conducted on patients admitted with clinically first attack of stroke to medicine intensive care unit or acute medical ward of shri B M Patil medical college hospital and research centre.

Period of Study: September 2022 to February 2024.

Sample Size: 100 patients admitted with stroke (CT proved) were selected for the study. Out of this 50 were selected after exclusion of patients having heart disease, infection, tuberculosis, malignancies anywhere in the body, previous history of stroke, TIA and other factors known to alter Hs-CRP value as the study group. 50 age and sex matched control subjects were selected from patients in other wards matched in every possible aspect except for the disease under study.

Study Group: Of 100 stroke patients, 50 were selected as the study group strictly adhering to the inclusion criteria.

Inclusion criteria: Patients of first ischemic stroke admitted within 72hrs of symptom onset and healthy controls

Exclusion Criteria: Patients with Acute infectious disease, Immunological disorders, known or suspected neoplastic disorders and recent (<3 months) major trauma, surgery, burns, osteoarthritis, ankylosing spondylitis, rheumatoid arthritis.

Study Protocol:

Clinical history was taken from either the patient or his/her relatives or attender, while taking history importance was given regarding presence or absence of vomiting, headache and convulsions. Past history of hypertension, diabetes, CAD, RHD, TIA, 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, gastrointestinal system, and respiratory system were examined in detail. Detailed routine investigations were done including blood haemoglobin, TLC, DC, urine routine, FBS, lipid profile, ECG, chest X-ray, 2D-ECHO.

CT scan after 24 hours after onset of symptoms and C-reactive protein estimation was done anytime between 12-72 hours of symptom onset.

Hyper acute (<12 hours):	Normal (50-60%)
	Hyperdense MCA artery (25-90%)
	Obscuration of lentiform nuclei
Acute (12-24 hrs)	Low density basal ganglia
	Loss of gray white matter interface
1-7 days	Mass effect
	Wedge shaped low-density area involving white grey matter. Gyral effacement
1-8 weeks	Contrast enhancement persist
	Mass effect resolves
Months to years	Encephalomalacia
	Volume loss, Calcification.

Statistics:

Data were presented as mean±SD values were called significant (if $p<0.005$). The chi square test was used in most cases to compare frequency distribution.

Sample Size Estimation

Sample size estimation formula: $n=z^2pq/d^2$

Confidence limit is 95%

Z=1.96 at 95% confidence

Prevalence of ischemic stroke in India(p)=5.45%

Q=100-5.45=94.55%

Precision=d=10%

$N=(1.96)^2*5.45*94.55/10^2$

=19.79 approximately 20

Results

Descriptive and inferential statistical analysis has been carried out in the present study. The results were analysed by using SPSS version 18 (IBM Corporation, SPSS Inc., Chicago, IL, USA).

Microsoft word and Excel was used to generate graphs, tables etc. Results on continuous measurements were presented on Mean SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance.

Normality was assessed using Shapiro-Wilk Test. Mann-Whitney Test, Chi-square test with Yate's correction and Fisher Exact test was used to find the significance difference of study parameters between the two groups.

Table 1: Comparison between the groups

VARIABLES	STUDY GROUP		CONTROL GROUP		Mann-Whitney Test
	RANGE	MEAN± SD	RANGE	MEAN± SD	P value
AGE	30-85	58.68±13.18	35-80	60.20±11.93	0.526
NIH SCALE	06-22	13.40±4.56	-	-	-
Systolic	110-210	161.32±22.34	110-140	124.60±7.19	<0.001*
Diastolic	70-120	92.68±12.64	08-90	75.44±11.33	<0.001*
FBS	89-341	158.04±75.70	77-112	88.42±8.32	<0.001*
UREA	16-124	38.34±20.45	14-29	20.14± 2.78	<0.001*
CREAT	01-04	1.43±0.63	0.10-1.20	0.88±0.18	<0.001*
CHOLESTROL	70-285	177.86±54.45	106-198	163.28±19.93	0.412
HDL	15-72	35.20±11.75	35-56	43.04±5.08	<0.001*
LDL	31-225	112.54±49.49	50-165	91.80±19.56	0.284
TG	41-342	117.98±62.49	69-212	139.48±40.63	0.002*
Hs-CRP	2.78-10.80	7.05±1.89	0.50-3.90	1.07± 0.75	<0.001*
Inference	There is significant difference between the groups for all values except AGE, Total Cholesterol and LDL				

Table 1 shows that there was a significant difference between study and control groups in terms of systolic and diastolic blood pressures, fasting blood sugars, urea, creatinine, HDL & Hs-CRP with p value of <0.001 whereas stastically there was no difference between the study and control groups in terms of age, Total Cholesterol and LDL with p values of >0.001.

Table 2: Gender-wise comparison

Gender	Study group	Control group	P value
FEMALE	16(32)	20(40)	0.53
MALE	34(68)	30(60)	
Total	50(100)	50(100)	
Inference	Both the groups are homogeneous for age distribution		

Table 2 shows the study group had 32% of females and 68% of males whereas the control group had 40% of females and 60% of males.

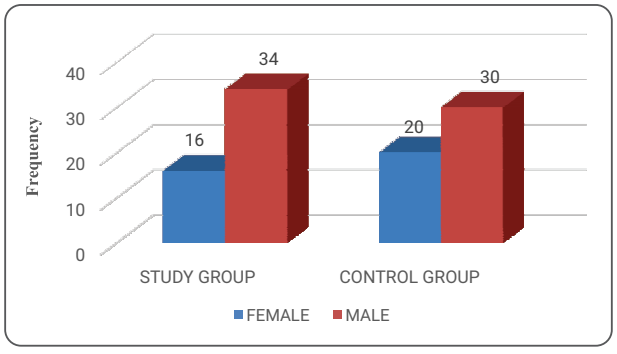

Figure 1: Diagram showing gender - wise comparison between study and control groups

Table 3: Distribution of Gender According to Age-Wise

Age Group (Years)	Study Group		Control Group	
	Female	Male	Female	Male
31-40	01	04	0	04
41-50	01	08	04	04
51-60	07	07	04	08
61-70	05	11	06	08
71-80	02	02	06	06
81-90	0	02	0	0
Total	16	34	20	30

Table 3 shows maximum stroke patients were in the age group 61-70 years constituting 32% of the study group and 28% of them were in the age group of 51-60 years. Only 2 females had stroke in age <50 years. Young stroke (age<40 years) was found in 10% of the study group. Control group also had majority of patients in age group 61-70 followed by 51-60 and 71-80 years.

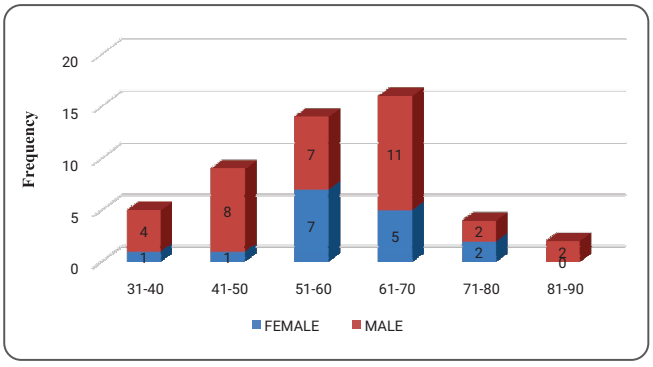

Figure 2a: Diagram showing age - wise distribution of gender among study group

Table 4: CON A/D/C

Con	Frequency	Percentage
A	09	18
C	10	20
D	31	62
Total	50	100

Table 4 shows 18% of the study group patients were Alert and 62% were Drowsy and 20% of them were Comatose on admission.

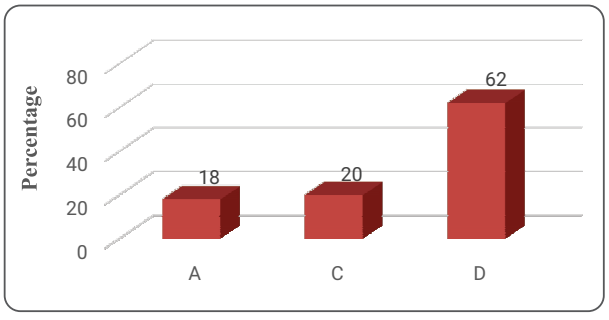

Figure 3: Diagram showing level of consciousness

Table 5: Motor Weakness

	Frequency	Percentage
L-H	27	54
R-H	23	46
Total	50	100

Table 5 shows that 54% of the study group had right sided hemiparesis whereas 46% had left sided hemiparesis.

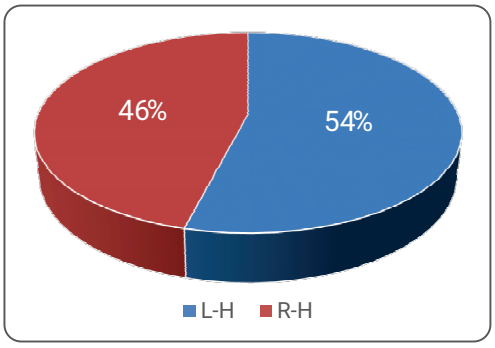

Figure 4: Pie-chart showing predominant motor weakness

Table 6: Others

	Frequency	Percentage
Headache	08	16
Seizure	04	08
Vomiting	05	10
Total	17	

Table 6 shows 16% of the study group had headache while 8% had seizures and 10% had vomiting at the time of admission

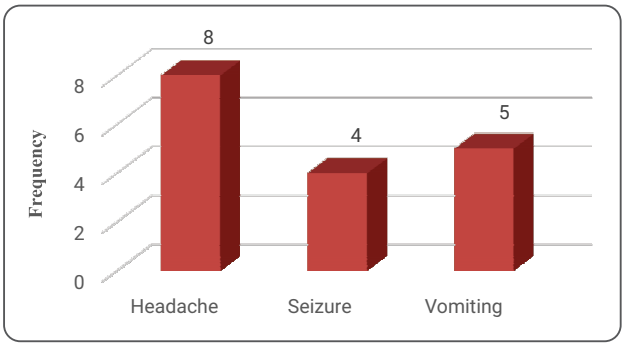

Figure 5: Diagram showing frequency of other clinical features among study group

Table 7: Gender-Wise Distribution of NIH Score

NIH	Female n (%)	Male n (%)	Total n (%)
Minor Stroke (1-4)	0	0	0
Moderate Stroke (5-15)	13(26)	20(40)	33(66)
Moderate - Severe Stroke (16-20)	03(06)	11(22)	14(28)
Severe Stroke (>20)	0	03(06)	03(06)
TOTAL	16(32)	34(68)	50(100)

Table 7 shows no patient in the study group had minor stroke whereas 33 patients (both males and females) had moderate stroke and 14 patients had moderate-severe stroke and 3 patients (males) had severe stroke.

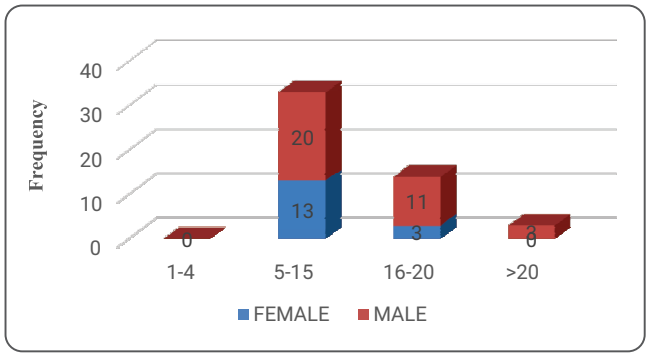

Figure 6: Diagram showing genderwise distribution of NIH SCORE

Table 8: Dietary habits

	Frequency	Percentage
MIXED	30	60
VEG	20	40
Total	50	100

Table 8 shows that 60% of the study consisted of patients with mixed diet whereas 40% of them were vegetarians.

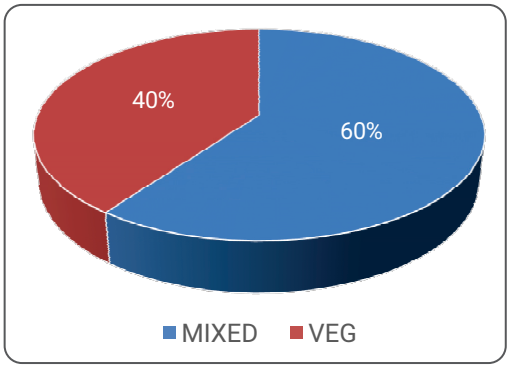

Figure 7: Pie - chart depicting dietary habits among study group

Table 9: Deleterious Habit

	Frequency
Smoking	28
Alcohol	18
Tobacco	05

Table 9 shows 56% of the study group patients were smokers and 36% were alcoholics and 10% were tobacco chewers.

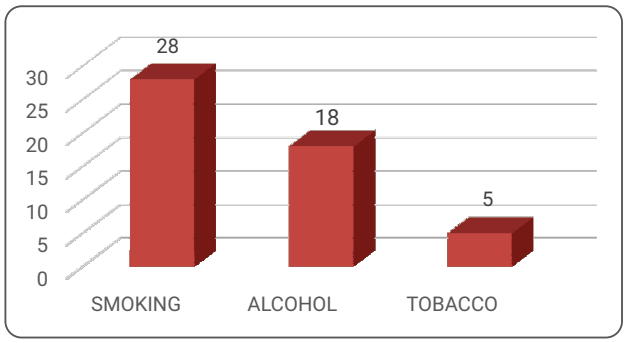

Figure 8: Diagram showing frequency of deleterious habits among study group

Table 10: CVS FINDINGS

	Frequency (n)	Percentage (%)
ECTOPICS	01	
ESM	05	
Total	06	

Table 10 shows 1 patient from the study group had ectopics whereas ESM was present in 5 patients from the study group.

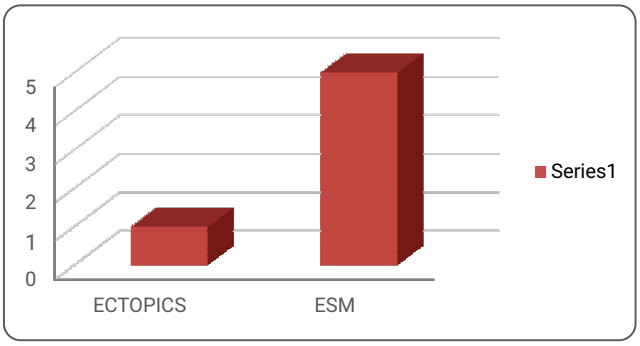

Figure 9: Diagram showing incidental CVS findings in study group

Table 11: CT Scan Diagnosis

	Frequency (n)	Percentage (%)
BG	10	20
FR	06	12
FR,PA	09	18
FR,TE	02	04
PA	04	08
PA, TE	10	20
TE	09	18
Total	50	100

Table 11 shows that infarcts involving basal ganglia and parieto-temporal areas consisted of 20% patients each from study group whereas those involving fronto-parietal and temporal areas accounted for 18% each and frontal area infarcts were 12% and those involving parietal and fronto-temporal areas accounted for 8% and 4% respectively.

Table 12: Comparison of Hs-CRP Values among different groups

Groups	<1	>1	Total	Chi-square
Study Group	0	50	50	X2=66.14
Control Group	41	09	50	P=<0.001
Total	41	59	100	
Inference	There is significant difference between the groups for Hs-CRP values			

Table 12 shows Hs-CRP values of >1 in all the patients of study groups and only 9 patients had values of Hs-CRP >1 which implies statistically significant differences between study and control groups. Chisquare value of 66.14 is also statistically very significant.

Table 13: Age distribution of mortality cases

Age Group (Years)	No. of Deaths (n)	Percentage (%)
31-40	02	25
41-50	0	0
51-60	02	25
61-70	03	37.5
71-80	0	0
81-90	01	12.5
Total	08 (100)	100

Table 13 shows that among 8 patients of study group where death was the final outcome 37.5% mortality in age group 61-70 years and 25% mortality each for 51-60 & 31-40 years age group. 12.5% mortality was also observed in age group of 81-90 years age group.

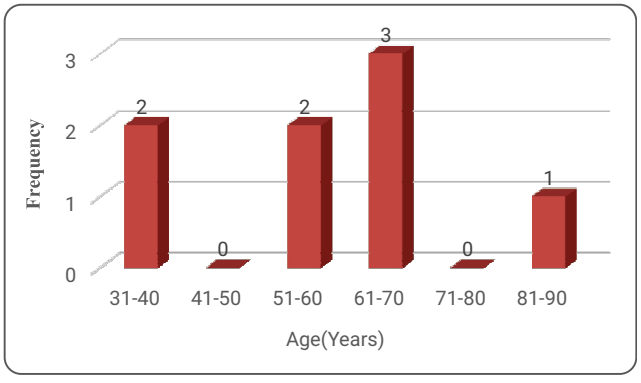

Figure 10: Diagram depicting age - wise distribution of mortality

Table 14: Sex distribution of mortality cases

Gender	No. of Deaths (n)	Percentage (%)
Female	0	0
Male	08	100
Total	08	100

Table 14 shows among 8 patients of study group where death was the final outcome 100% of them were males.

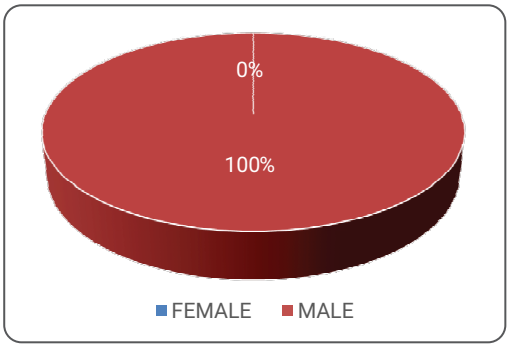

Figure 11: Pie - chart depicting gender - wise distribution of mortality

Discussion

Strokes kill 5 million people each year. Cerebrovascular disease is the second cause of death world wide[5,6].

Kristensen B et al documented young ischemic strokes occuring in patients younger than 45 years old was rare and less than 5 percent of all cerebral infarctions[7]. A recent stroke registry study by T.Song - Hai Lee et al revealed that the incidence of young stroke was 6.8% of all strokes[8].

In our study young ischemic stroke less than 40 years of age constitutes 10% of all strokes and highest incidence in males was noticed after the age of 61-70 years i.e.22% and in females also the incidence was highest in the age group of 51-60years i.e.14%.

The greater prevalence of stroke in men is well known, but recent issues emphasize the importance of stroke in women[9]. Over the entire life time, 16% of women but only 8% of men will die of stroke[10]. Knowledge of sex differences might be of interest in improving preventive strategies and the in-hospital management of stroke patients. JaumeRoquer et al documented mean age for stroke was higher in women than in men[11].

In contrast to above studies, we documented the increased incidence of acute thrombotic stroke in both males and females after the age of 50 years with slight predominance in males. We also documented the incidence of thrombotic stroke after 50 years of age in males and females were 60% and 40% respectively.

PinkyTalreja Mishra et al concluded that most of the patients (65%) were in the age group of 50 - 70 years. Left-sided hemiparesis with altered sensorium with facial palsy was the most common presenting symptom. Hs-CRP levels were found to be increased in stroke patients and on comparison with controls, the values were found to be significant ($p < 0.001$)[12].

Our study correlated well with the above study with increased incidence of acute thrombotic stroke in both males and females after the age of 50 years with slight predominance in males. Left sided hemiparesis

was also most common among our study group.

Thomas S.Bowman et al 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 ischemic stroke[13].

In contrast to the above study we did notice the much significance rise in TG and decrease in HDL in relation to ischemic stroke when compared to controls in our study.

Jaydip Ray Chaudhuri et al concluded that on comparison between high and low Hs-CRP groups it was found that hypercholesterolemia, older age, and mortality were significantly associated with high Hs-CRP levels[14].

Our study also correlated with the above study such that high Hs-CRP were associated with hypercholesterolemia, older age and mortality.

CRP, one of the acute phase reactants, is an indicator of underlying systemic inflammation and a novel plasma marker of atherothrombotic disease[15]. It is likely that CRP has many pathophysiological roles in the inflammatory process, including binding of phosphocholine and recognition of foreign pathogens and phospholipid constituents of damaged cells.

Kerstin winbeck et al study documents, raised CRP in 127 patients without thrombolysis with a first ischemic stroke no more than 12 hours after symptom onset[16]. In contrast, a CRP increase between 12 and 24 hours after symptom onset predicts an unfavourable outcome and is not a best parameter to predict outcome which is estimated before 12 hours of onset of symptoms.

In the present study, CRP was measured only after CT image confirmation of infarction which was done after 24 hours of onset of symptoms. So CRP level was estimated after CT confirmation and before 72 hours of onset of symptoms.

Rathore HS et al 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[17]. 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 6 mg/L, observed rise of CRP in 12% cases of lacunar infarct and 88% cases of cortical infarct.

In the present study the CRP rise was 80% in cortical and 20% in subcortical. It was clearly observed in our study that Hs-CRP was raised in all subtypes of cerebral infarct without much difference.

In Irene M et al 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 predicts myocardial infarction and stroke[18].

In our control study involved age and sex matched healthy individuals; the rise of Hs-CRP level was noted in 18% of cases. The prediction of myocardial infarction and stroke couldn't be done since it needs longer follow-up.

In L.Masoti et al study they retrospectively measured CRP values in 196 elderly patients for relationship between CRP and short term prognosis and concluded that elevation of CRP could represent a negative prognosis in elderly patients with ischaemic stroke, in particular, for short term prognosis[19].

In the present study, there were 8 deaths, all of them were males and in all of them Hs-CRP was raised which is in terms with that of the above study reiterating that elevated Hs-CRP levels were a bad prognostic indicator.

Conclusion

In this study mean High sensitive C-Reactive protein levels were significantly higher in patients with ischemic stroke when compared to controls. It is also observed that by elevated High sensitive C-Reactive protein in ischemic stroke can be diagnosed positively but subtypes (cortical, subcortical) of cerebral infarction cannot be differentiated at the time of early diagnosis. High sensitive C-Reactive protein levels being raised within 72 hours of an acute ischemic stroke is poor prognostic indicator. High sensitive C-Reactive protein levels were raised in all cases who expired.

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