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KEY WORDS: Ischaemic stroke, haemorrhagic stroke, hsCRP level.

A STUDY OF HIGH SENSITIVITY C - REACTIVE PROTEIN IN ISCHEMIC STROKE

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ABSTRACT

Aim: To investigate the association of high hsCRP (> 3 mg/L) levels with ischemic stroke and its subtypes in Indian patients.
Study design: Randomized control trial.
Place and duration of study: General Medicine Department, Maharaja's Institute of Medical Sciences, Nellimarla, Vizianagaram, Vizianagaram Dist, India from October 2014 to September 2016.
Methodology: 60 patients ischemic stroke were selected who were admitted in to ICU and Medical wards, Maharaja's Institute of Medical Sciences, Nellimarla, Vizianagaram from October 2014 to September 2016. This study is a duration based, done over a period of 24 months with 60 patients who attended the hospital on admission and diagnosed on the basis of CT/MRI in Department of Medicine in Maharajah's Institute of Medical Sciences and evaluated with general and systemic examination and Laboratory studies including estimation of hs-CRP value. Controls were healthy subjects chosen from patients with no present or past history of stroke, transient ischemic attack (TIA), or cardiac disease.
Results: Most of the patients (53.3%) were in the age group of 60 - 70 years. Left-sided hemiparesis with altered sensorium with facial palsy was the most common presenting symptom. hsCRP levels were found to be increased in stroke patients and on comparison with controls, the values were found to be significant ($p < 0.001$). Also, the values were found to be more in haemorrhagic than ischaemic stroke. No significant correlation was seen with other risk factors like diabetes, dyslipidaemia. It was also seen that patient with low GCS score had high levels of hsCRP in both types of stroke. Mean hsCRP level was 14.8 ± 6.2 in non-survivors of haemorrhagic and 10.7 ± 5.4 in ischaemic stroke. These values were found to be statistically significant ($p < 0.001$).
Conclusion: From this study we concluded that hsCRP level is increased in cases of stroke – ischaemic as well as haemorrhagic, suggesting an inflammatory response in acute stroke. Furthermore, the increased levels correlated with larger infarct and bleed, severe neurological deficit and worse outcome.

I. Introduction

Cerebrovascular disease includes some of the most common and devastating disorders like ischemic stroke and hemorrhagic stroke. Stroke is the second leading cause of death worldwide, causing 6.2 million deaths in 2011[1]. India and other developing countries, is in the midst of a stroke epidemic.[2]

Developing countries like India are facing a double burden of communicable and non-communicable diseases.[3] Stroke is one of the leading causes of death and disability in India. Stroke is becoming an important cause of premature death and disability in low income and middle-income countries like India, largely driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors.[4]

As a result developing countries are exposed to a double burden of both communicable and non-communicable diseases. Majority of stroke survivors continue to live with disabilities, and the costs of ongoing rehabilitation and long term-care are largely undertaken by family members, which increases their family expenditure.[5]

The metabolic consequences associated with changes in diet and lifestyle has increased the number of hyperlipidemia individuals who are at risk of a number of adverse effects such as stroke.[6] On the other hand, case-control studies of stroke which examined cholesterol as a risk factor have generally failed to show a direct and strong association.[7]

Several case-control studies with ischemic stroke, there is increasing evidence that inflammatory processes are involved in cerebral ischemia. Ischemic brain injury secondary to an arterial occlusion is characterized by acute local inflammation and changes in levels of inflammatory cytokines in body fluids of patients.[8]

The presence of inflammatory markers such as hs-CRP before a clinical event, is likely to indicate ongoing inflammation associated with vascular events likely a plaque becoming unstable. Increased hs-CRP is an important prognostic indicator of Ischemic stroke.[9]

Some investigations have suggested that hs-CRP predicts prognosis,[10] few other studies have also tend to assess mortality alone as an outcome.[11] As hs-CRP is an acute-phase reactant, it might be expected to increase after stroke, and this increase is likely to correlate with stroke severity. hs-CRP itself a marker for prognosis of stroke. C-reactive protein (CRP), an acute-phase reactant, is an indicator of underlying systemic inflammation and a plasma marker for athero thrombotic disease.[12]

Inflammation plays a key role in the pathogenesis of atherothrombosis, and measurement of high-sensitivity C-reactive protein (hs-CRP)—a sensitive marker for systemic inflammation—can identify individuals at high risk of developing ischemic stroke.[13]

Since etiopathogenesis of stroke is complex and multiple factors have been attributed, the present study aims to investigate the association of hs-CRP levels in patients with ischemic stroke. This study was conducted in department of general medicine in Maharajah's Institute of Medical Sciences, a tertiary hospital, having all superspeciality units including neurology, which caters to large number of stroke patients in its Intensive care units, inpatient department and physiotherapy department.

II. Aims And Objectives

1. To observe on hs-CRP rise in ischemic stroke
2. To evaluate role of hs-CRP as a diagnostic aid in ischemic stroke.

III. Materials And Methods

60 patients ischemic stroke were selected who were admitted in to ICU and Medical wards, Maharaja's Institute of Medical Sciences, Nellimarla, Vizianagaram from October 2014 to September 2016. This study is a duration based, done over a period of 24 months with 60 patients who attended the hospital on admission and diagnosed on the basis of CT/MRI in Department of Medicine in Maharajah's Institute of Medical Sciences and evaluated with general and systemic examination and Laboratory studies including estimation of hs-CRP value. Controls were healthy subjects chosen from patients with no present or past history of stroke, transient ischemic attack (TIA), or cardiac disease.

3.1 Inclusion criteria

All patients aged 30-75 years with clinically and radiologically diagnosed as ischemic stroke.

3.2 Exclusion criteria

- Patients of age>75 yrs and <30 yrs were excluded
- Patients with hypertension, diabetes, hyperlipidemia, tuberculosis, h/o TIA, Obesity and those who have received treatment with aspirin
- Patients with head injury, meningitis, brain abscess ,arteritis and infectious diseases

This study is a duration based, done over a period of 24 months with 60 patients who attended the hospital on admission and diagnosed on the basis of CT/MRI in Department of Medicine in Maharajah's Institute of Medical Sciences. Clinical history was taken from the patient or their attendants. Brief history regarding presence or absence of vomiting, headache and convulsion within 2hrs. post ictus and Past history of hypertension, diabetes, CAD , RHD, TIA, Collagen diseases, meningitis, intermittent claudication, tuberculosis, endocrine disorders, congenital disorders were taken. Personal history with particular regards for dietary habits, smoking and socioeconomic status were noted.

General examination with height, weight, BMI, waist / Hip ratio, markers of atherosclerosis (arcus seniles, locomotor brachialis), blood pressure were noted. Neurological examination based on performa was done within 2hrs. of admission.

All other systems like cardio vascular system, gastrointestinal system, respiratory system, were examined in detailed, Investigations including hs- CRP, FBS, lipid Profile, X ray, CT scan after 24 hrs after onset of symptoms, HS- CRP estimation was done within 24 hrs.

3.3 Materials Used :

Reagents:

Diluent Ultra 1	Tris buffer 20 mmol/l, pH 8.2 Sodium azide 0.95 g/l.
Latex-ultra(R2)	Latex particles coated with goat IgG anti- human
	CRP, pH 7.3. Sodium azide 0.95 g/l.
U-CRP Cal	Liquid Calibrator. CRP concentration is as stated on the vial label
Optional	Ref.:43036 CRP Ultra control

3.4 Investigations used

CT Scanning :

CT Scanning was done 24 hrs. post ictus Schimadzu CT 3000 T CT scanners were used which belong the third generation of CT scan machine. In all cases only plain CT(NCCT) was done.

The patients was kept in supine potion and 15^0 tilt upwards was given along the orbito meateals line to prevent radiation to the face and 8mm section was taken infratentiorial & 10mm section supratentorially.

CT Scan Finding in Cerebral Infarct :

Hyper acute (< 12hrs)
normal (50-60%)
Hyperdense MCA artery (25-90%),
obstruction of lentiform nuclei .

Acute (12-24hrs) Low density basal ganglia, loss of gray white matter interface (insular ribbon sign) and sulcal effacement.

1-7 days-- Mass effect , wedge-shaped low density area, involving white gray matter gyral effacement.

1-8 days --contrast enhancement persist mass effect resolves.

Months to years-- Encephalomalacia, volume loss and calcification.

3.5 Method:

HS CRP assay is based on its understanding of structure and function, particularly in context of stroke.

ESTIMATION OF HIGH-SENSITIVITY C- REATIVE PROTEIN

Determined by turbidometric immunoassay using commercially available kit (Erba) and Humastar 300 chemistry analyzer (Human gmbh Germany).

Principle

The CRP-ultrasensitive is a quantitative turbidimetric test for the measurement of low levels of C- reactive protein (CRP) in human serum or plasma.

3.6 Calculations

Calculate the absorbance difference (A2-A1) of each point of the calibration curve and plot the values obtained against the CRP concentration of each calibrator dilution. CRP concentration in the sample is calculated by interpolation of its (A2-A1) in the calibration curve.

3.7 Reference Values

Below 3 mg/L is considered normal. Each laboratory should establish its own reference range.

3.8 Interferences

Bilirubin (20 mg/dl), lipemia (10 g/l) and rheumatoid factors (75 IU/ml), hemoglobin (10 g/l), do not interfere. Other substances may interfere. hs-CRP assay is highly sensitive and is expressed in mg/dl.

IV. Observation And Results

The 60 patients admitted in our hospital selected for study are divided into two equal and comparable groups. Those patients who were subjected were considered as Cases, and Controls were included in group2.

Table 1Comparison of Age Distribution between Study & Control Group

Age in Yrs	Cases	Controls
<50	6	6
50-60	12	12
60-70	32	32
≥70	10	10
Total	60	60

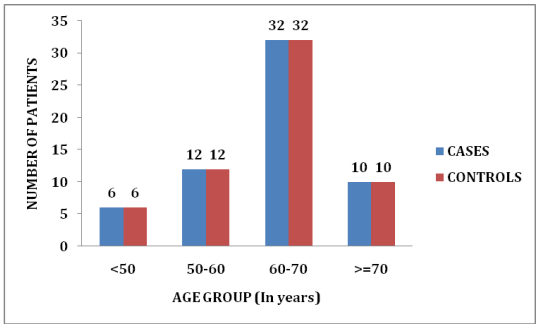


Table 2 : Comparison Of Sex Distribution Between Study And Control Group

	Female	Male
Cases	29	31
Controls	31	29

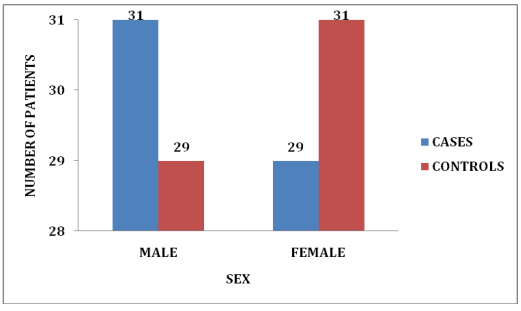


Table 3 :Comparison Of anthropometric parameters between controls and cases

	GROUP	N	Mean	Std. Deviation	P VALUE
AGE	CONTROL	60	61.10	9.573	1
	CASES	60	61.10	9.573	
WEIGHT	CONTROL	60	60.02	3.501	0.007
	CASES	60	62.03	4.521	
BMI	CONTROL	60	21.95	2.251	0.013
	CASES	60	21.11	1.193	

TABLE 4 Comparison of Blood Pressure Between Controls And Cases(N=120)

Blood Pressure	GROUP	N	Mean	Std. Deviation	P VALUE
SBP	CONTROL	60	124.50	4.935	
	CASES	60	124.85	5.045	0.702
DBP	CONTROL	60	80.02	5.111	
	CASES	60	79.67	5.262	0.712

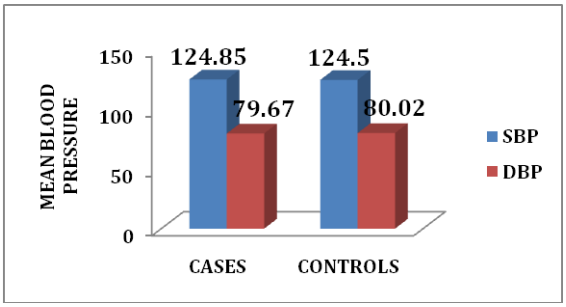


Table 5 : Comparison Of Routine Laboratory Parameters Between Controls And Cases

CLINICAL PARAMETERS	GROUP	N	Mean	Std. Deviation	P VALUE
FBS	CONTROL	60	86.77	7.14	
	CASES	60	85.17	8.30	0.260
SR.UREA	CONTROL	60	20.87	2.3	0.001
	CASES	60	19.67	1.52	
SRCREATINE	CONTROL	60	.7400	.21	0.744

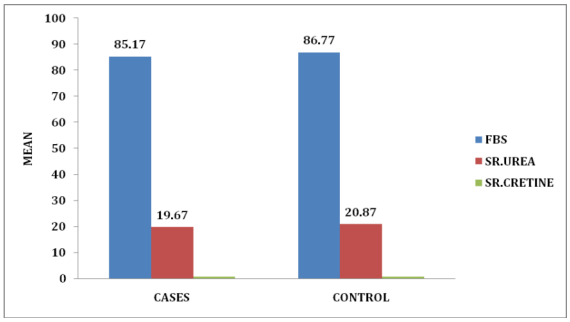


Table 6 : Comparison Of Lipid Profile Parameters Between Controls And Cases (N=120)

LIPID PROFILE	GROUP	N	Mean	Std. Deviation	P VALUE
SR.CHOLESTRAL	CONTROL	60	161.07	22.135	0.596
	CASES	60	158.90	22.516	
HDL	CONTROL	60	43.92	10.154	0.005
	CASES	60	48.32	6.387	
LDL	CONTROL	60	88.72	20.049	0.787
	CASES	60	87.87	13.713	
TGL	CONTROL	60	144.73	38.029	0.186
	CASES	60	132.73	58.517	

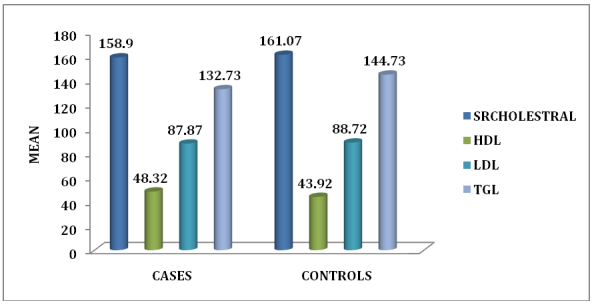


Table 7 : Logistic Regression Analysis For Prediction Of Ischemic Stroke With Measured Parameters(N=120)

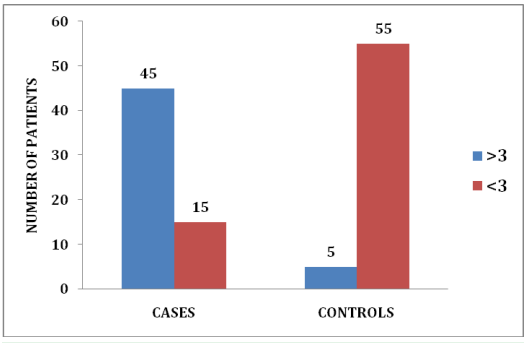
Parameters	B	S.E.	Wald	df	P value.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
AGE	.003	.024	.014	1	.905	1.003	.956	1.052
SEX	.006	.437	.000	1	.989	1.006	.428	2.368
WEIGHT	-.152	.056	7.454	1	.006	.859	.771	.958
BMI	.269	.155	2.989	1	.084	1.308	.965	1.774
SBP	-.018	.046	.163	1	.686	.982	.898	1.074
DBP	.000	.043	.000	1	.984	.999	.919	1.087
FBS	.040	.028	1.987	1	.159	1.041	.985	1.100
SRURIEA	.405	.151	7.164	1	.007	1.499	1.114	2.016
SRCRETINE	.406	1.251	.105	1	.746	1.500	.129	17.419
SRCHOLESTRAL	-.004	.011	.116	1	.733	.996	.976	1.018
HDL	-.067	.027	6.222	1	.013	.935	.887	.986
LDL	-.003	.013	.039	1	.844	.997	.972	1.024
TGL	.008	.005	2.720	1	.099	1.008	.998	1.018
Constant	-3.367	9.034	.139	1	.709	.034		

Table 8 Distribution of study subjects according to localization of lesions

Anatomical sites	Frequency	Percent
Frontal	8	13.3%
Parietal	3	5.0%
Temporal	12	20.0%
Frontoparietal	1	1.7%
Parietotemporal	3	5.0%
Subcortical	3	5.0%
Basal ganglia	7	11.7%
Internal caspsule	1	1.7%
Periventricular	7	11.7%
Multiple infarct	5	8.3%

Table 9: Hs-CRP In Cases And Controls

Hs-CRP	CASES	CONTROLS	P VALUE
>3	45	5	0.001
<3	15	55	



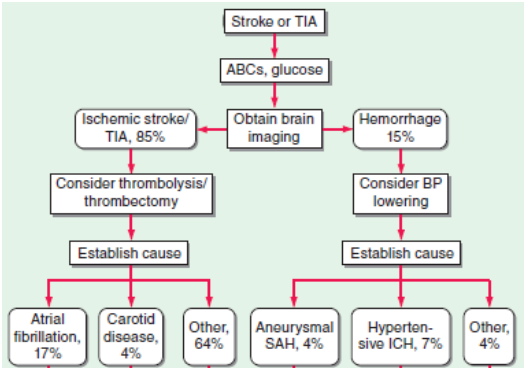


Fig-1 : Algorithm for stroke

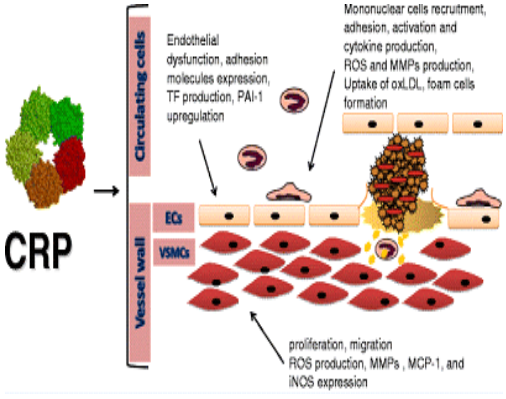


Fig-2: Role of hs-CRP in atherosclerosis

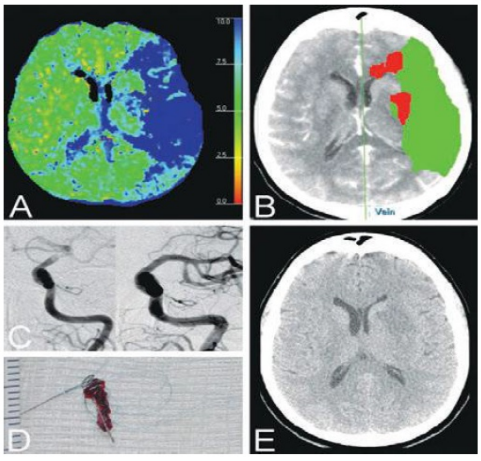


Figure 3:CT Angiogram, B:CT image showing infarct(red), penunmbra(green).

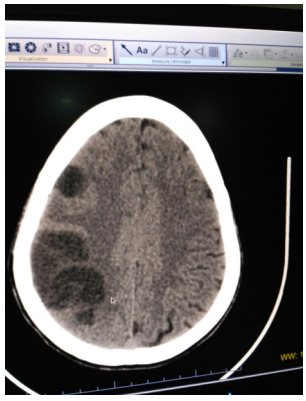


Figure 4: CT image showing infarct Analysis of the data

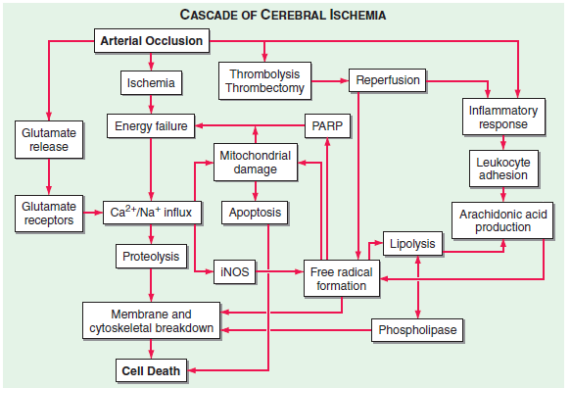


Figure 5:Cascade of cerebral ischemia

v. Discussion

Study of hs-CRP in ischemic stroke was carried out in the Department of General Medicine at Maharajah's institute of medical sciences, Nellimarla .During the study period October 2014 – September 2016

hs- CRP may reflect inflammations related to pathophysiology of ischemic stroke. However, many patients (26%) in this study had normal levels of hs-CRP after stroke, implying that ischemic stroke itself does not induce a full-blown acute-phase response.

5.1 Age Distribution:

In this study youngest patient was female (40 years) and oldest patient was male (75years). Maximum number of cases were observed between age group of 60-70 (53.3%) Similar to study by **Jaydip Ray Chaudhuri et al.(2013),** Abraham et al and, Razadan et al .Mean age in males 61.1 ± 9.99 yrs , female 61.1 ± 9.13 yrs, 10% patients were under the age of 50 i.e young stroke.[35,36] discussed in table no.10

Table.10 : comparison of age distribution

Age in yrs	Chauduri et al	Abraham et al	Razdan et al	Present study
40-50	11.3%	7.5%	5.6%	10.3%
50-60	28.4%	37.2%	36.1%	36.4%
60-70	60.3%	55.3%	58.3%	53.3%

5.2 Sex Ratio:

In the present study 51.7% patients were male, 48.3% were female, male to female ratio was **0.52:0.48**, so males had higher incidence of stroke, these results were comparable with that of **Jaydip Ray Chaudhuri et al. study(2013)**. **Wolf et al (2001**) showed relative risk of stroke was twice in male and 3 times in female in highest quartile (2.11mg/L) compared with the lowest quartile (0.55mg/L).

Similar results were observed in the Framingham study conducted by **Kannel WB et al.**[37] asdiscussed in table no 11.

Table.11 comparison of sex distribution

Gender	Chaudhuri et al	Wolf et al	Present study
Male	59.6%	54.3%	51.7%
female	40.4%	45.7%	48.3%

5.3 CT Evaluation of site of lesion:
In the present study Frontal and Fronto parietal involvement was observed in 20%, basal ganglia 13.3% and thalamus 1.7% were involved, cortical involvement was seen in 11.7%, which are similar to study conducted by NINDS stroke data Bank 1999.[38]

5.4 Clinical Profile:
In this present, study mode of onset was sudden in 87.5% of cases, gradual in 12.5% cases. Cases Presented with altered sensorium, stupor or confused in 23.3%, coma in 12.5% cases, headache and vomiting are present in 21.7% similar to **Poungvarin et al**. discussed in table no 12.

Table 12 : comparision of clinical profile

Clinical features	Poungvarin et al	Present study
Stupor	27.3%	23.3%
Coma	18.4%	12.5%
Headache &vomiting	28.6%	21.7%

5.5 BMI and Weight
The mean BMI in the stroke patients was 21.11 ± 1.19kg/m^2 and control group 21.95± 2..25 kg/m^2 (p > 0.013). This difference is statistically insignificancant. This is similar to study conducted by **P.M.Ridker et al , M.A. Mandell et al**, 2001. In present study 42 of 55 male cases and 22 of 25 female cases has no central obesity (waist/hip ratio >0.95 and >0.85) respectively.[39]

In this present study, 17 patients (28.3%) were below 60kg, 43 patients (71.3%) were above 60 kgs. Mean weight of the study group was 62.03 ± 4.0.3 kg and the control group was 60.02 ± 3.05 kg (P>0.07). The difference was statistically insignificant.

5.6 Blood Pressure
In this study, mean systolic BP is 124.85± 5.04mm Hg, Diastolic BP is 79.67±5.26mmHg in study group and in control group mean systolic BP is 124.05±4.94 mm Hg, mean diastolic BP is 80.02±5.1mmHg, which is similar to the study conducted by **Mandal et al**[41], **P.Patel et al, Ridker P.M. et al**[42]

5.7 FBS and Serum Creatinine:
Mean FBS in cases was 85.17mg/dl and in controls was 86.77mg/dl, Mean Serum Creatinine of cases was 0.72mg/dl and in controls was 0.74mg/dl. The difference between them were statistically insignificant. These values are comparable with study conducted by **M.A. Madall,P.Patel (2001)** [41]**P.M. Ridker**[42] **(1997), Cambien et al**discussed in table no.13

Table 13 :comparison of FBS, Sr.creatinine,mean BP

Variables	M.A. Madall	Ridker	Cambien	Present study
Mean FBS [mg/dl]	78.6	98.2	86.3	85.7
Mean Sr.creatinine [mg/dl]	0.76	0.83	0.65	0.72
Mean SBP[mm of hg]	130±6	118±3	126±4	124±5
Mean DBP[mm of hg]	82±2	80±7	78±3	80±5

5.8 Lipid Profile
The mean lipid profile of study and control group were total cholesterol 159.95± 22.13mg%,p value 0.596 , serum HDL 46.12± 8.03,**P VALUE < 0.05** , Serum LDL 87.5±16.05 mg% PVALUE=0.787 Ns, triglyceride 138.73± 48..05mg% p=0.186. similar results were observed in **Ronald B et al. study (2010)** [x]

5.9 hs-CRP Analysis in Study and Control Group:
In the present study, hs CRP value > 3mg/L was present in 45 of the 60 ischemic stroke patients(75% of study group) compared to the controls(8% of control group) X^2= 27.8 (p<0.001). these results were similar to **Jaydip Ray Chaudhuri et al.** study(2013) where the frequency of hs-CRP in stroke patients was 61.9% compared to controls 6.6% p value (p<0.001)

Ridker P.M.et al, Ridker showed that men with highest quartile of baseline hs-CRP value (5.7mg/L) had twice the risk of future ischemic stroke (RR-1.9) compared with lowest quartile (0.55mg/dl) with risk of future ischemic stroke (RR- 0.8) This was independent of lipid profile , FBS, BP. Similar results were observed in Wolf PA et al, Grussekloo et al, Fragmingham study (1999).[43]

Rajput et al. concluded that, 132 (88%) had elevated CRP (CRP > 10 mg/L) among stroke patients from Pakistan. [44]

Moreover, in a study by **Di Napoli et al**. from Italy, 95 patients (74.2%) with acute ischemic stroke had high CRP levels. [45]

Muir et al. had detected elevated CRP (> 10 mg/L) levels in 96 out of the228 (42.1%) patients admitted with acute ischemic stroke in the UK. [46]

On the other hand, only 22% of stroke patients and 14% of myocardial infarction patients had high CRP (> 7 mg/l) levels in a study from Netherlands by **den Hertog HM et al.**[47]discussed in table no.14

Table.14: comparing association of hs C-RP with ischemic stroke

	Chaudhuri et al	Ridker P.M.et al	Rajput et al	Di Napoli et al	Muir et al	Present study
hs-CRP	61.9%	82%	88%	74.2%	42.1%	75%

This variance may be explained partly by the different definitions of high CRP in various studies. **The hs-CRP levels are now becoming universally standardized and most centers accept a value above 3 mg/dl as high.** [48]

In present study raised HS-CRP levels in 40-50 age group was 23.3%, in 50-60 age group was 34.3% and in 60-70 age group was 42.4% which are similar to studies conducted by chaudhuri et al, Rider P.M et al and Muir et al. compared in Table 15

Table 15 : comparing age with hs-CRP

	RAISED hs-CRP LEVELS			
Age group	Chaudhuri et al	Ridker P.M et al	Muir et al	Present study
40-50	27.9%	25.5%	15.4%	23.3%
50-60	32%	31.4%	38.2%	34.3%
60-70	40.1%	43.1%	46.4%	42.4%

In present study raised hs-CRP levels in male was 54.6% and in female was 45.4% which are similar to studies conducted by chaudhuri et al, Rider P.M et al and Muir et al. compared in Table 16

Table 16: comparing gender with hs-CRP

	Raised hs-CRP LEVELS			
Gender	Chaudhuri et al	Ridker P.M et al	Muir et al	Present study
Male	58.8%	57.6%	56.8%	54.6%
Female	41.2%	42.4%	43.2%	45.4%

5.10 Limitations of the present study:
though hs-CRP is found to be most suitable and sensitive parameter helping in diagnosis, prognosis and outcome of ischemic stroke. hs-CRP level at the time of discharge which gives significant information has not been carried in this study ,and the study population is small.

VI.Conclusion
The high sensitive c- reactive protein was significantly elevated in patients with Ischemic stroke . There is a positive correlation of hs-CRP with old age and male sex

The increase of hs-CRP value predicts the risk of future ischemic stroke due to atherosclerosis. hs-CRP might prove to be helpful to predict the future risk of ischemic stroke in elderly population especially sixth decade and later. Male sex, Elderly age, and

Decreased HDL Value has been associated with positive correlation with incidence of Ischemic Stroke.

hs-CRP is elevated by underlying conditions other than acute stroke, such as infection, surgery, and Malignancy. These predisposing factors were excluded from this study. However, it is possible that some of the patients had unrecognized conditions that elevate their inflammation marker levels and also increased the risk of vascular events.

hs-CRP appears to be a good marker of Ischemic Stroke because of its high sensitivity .and being independent of other known cardiovascular risk factors.

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