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Role of serum Hs-CRP in evaluatingIschemic strokes as compared to healthy population

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ABSTRACT: Introduction: Stroke designates any abnormality of the brain resulting from pathologic vascular processes like luminal occlusion by embolus or thrombus, rupture of a vessel, an altered permeability of the vessel wall or increased viscosity or other change in the quality of the blood flowing through the cerebral vessels. An increasing body of evidence has linked inflammation with the pathogenesis of atherothrombotic stroke.Recent use of highly sensitive CRP assays has enhanced the usefulness of CRP as a reliable predictor of cardiovascular events. At present, there are very few documented studies from India comparing the association of hs-CRP with ischemic stroke, henceforth, we methodically studied these variables (hs-CRP) in stroke patients and compared them with data from age- and sex-matched control subjects.

Objectives/Aim: To study the serum concentration of hs-CRP in patients of acute ischemic stroke, and compare it with that of age and sex matched controls.

Materials and Methods: Ahospital based case control study including 100 cases each of ischemic stroke and age and sex matched controls was undertaken and prognostic significance was found with reference to their hs-CRP levels.

Results: Stroke patients were found to have a significantly higher hsCRP levels when compared to the controls (7.30 ± 2.34 mg/dl vs. 2.58 + 0.88 mg/di, p <0.001).

Conclusion: We herein conclude that hsCRP levels are increased in cases of ischemic stroke. Furthermore, the increased levels correlated with severe neurological deficit and worse outcome. Therefore hs-CRP can be used for risk stratification after stroke.

I. INTRODUCTION

Among all the neurologic diseases of adult life, stroke clearly ranks first in frequency and importance. Also, it's the first leading cause for disability, second leading cause of dementia and third leading cause of death. This group of diseases has provided the most instructive approach to localization in neurology.

Stroke designates any abnormality of the brain resulting from a pathologic process of the blood vessels including occlusion of the lumen by embolus or thrombus, rupture of a vessel, an altered permeability of the vessel wall or increased viscosity or other change in the quality of the blood flowing through the cerebral vessels. These are two main types –ischemic (with or without infarction) and hemorrhage—and unless one or the other occurs, the vascular lesion usually remains silent.

In the last two decades, extraordinary imaging technology has been introduced that allows the physician to identify the ischemic salvageable and infracted brain tissue in the acute phase of stroke, which virtually defines the goal of modern acute stroke treatment.

However, an increasing body of evidence has linked inflammation with the pathogenesis of atherothrombotic stroke. Infections and inflammation may promote atherosclerosis and thrombosis by elevating serum levels of fibrinogen, leukocytes, clotting factors, and cytokines and by altering the metabolism and functions of endothelial cells and monocyte macrophages. C-reactive protein (CRP) are acute-phase reactants, are indicators of underlying systemic inflammation and novel plasma markers for atherothrombotic disease.

Recent use of highly sensitive CRP assays, with international reference standards set by the World Health Organization (WHO), has enhanced the usefulness of CRP as a reliable predictor of cardiovascular events.

At present there are very few documented studies from India comparing the association of hs-CRP with ischemic stroke. Hence we planned to study these variables (hs-CRP,) using a precise methodology in stroke patients and compare them with data from age- and sex-matched control subjects.

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II. AIMS & OBJECTIVES

This study is aimed at

- To study the serum concentration of hs-CRP in patients of acute ischemic stroke.
- To compare it with that of age and sex matched control.

Rationale of the study

High sensitive C-reactive protein (hsCRP) is a sensitive marker of inflammation and tissue injury in the arterial wall, playing a vital role in the development of coronary and cerebral atherosclerotic disease. So we aimed to study the serum concentration of hs-CRP in patients of acute ischemic stroke and its role in predicting the survival.

III. MATERIAL AND METHODS

Study Design — Hospital based case control study.
Study Place - S.M.S Medical College and hospital, Jaipur.
Study Duration — June 2017 to Dec 2018 or up to sample size completed.
Study Population — Cases- All patients of clinical and CT scan brain confirmed first ischemic stroke admitted within 72hrs of symptom onset in wards of Department of Medicine were taken for the study.
Controls—Healthy, age and sex matched controls not having any evidence of stroke or CAD or previous history of TIAs were also studied for valid comparison.
Sample size — The sample size required is 11 cases in each group at 95% confidence limit and 80% power to detect the difference of 6.4±5 in mean hsCRP level in both group. The sample size would be enhanced to 100 in each group. This is adequate to cover other studying variable.
Design: Hospital based case control study.

SELECTION OF PATIENTS:

INCLUSION CRITERIA

1. All patients of clinical and CT scan brain confirmed firstischemic stroke admitted within 3 days of symptom onset.
2. Healthy age and sex matched volunteers who are relatives of the patient.
3. Informed consent to participate in the study.

EXCLUSION CRITERIA

1. Acute infectious disease e.g. Tuberculosis.
2. All patients of stable or unstable angina, acute myocardial infarction, Immunological disorders.
3. Known or suspected neoplastic disorders e.g. multiple myeloma.
4. Recent [less than 3 months] major trauma, surgery, burns
5. Osteoarthrosis, costochondritis, rheumatoid arthritis, ankylosing spondylitis.
6. Unwillingness to participate in study.

IV. METHODOLOGY: -

After taking clearance from ethics committee of our tertiary care hospital, patients/relatives were explained about the study, given complete information regarding the procedures undertaken and taken written consent in their local language (Appendix 2). Patients were enrolled into two groups after matching confounding factors like age, sex etc.

Applying inclusion and exclusion criteria patients were categorized into Group A (patients with Acute ischemic stroke) and Group B (age and sex matched control).

The following clinical and demographic parameters were recorded: age, sex, hypertension (known hypertension treated with antihypertensive drugs OR 2 or more blood pressure recordings greater than 140/90 mm Hg), diabetes mellitus (known diabetes treated with diet or drugs or both; or either a fasting serum glucose >126 mg/dl) and BMI.

Hematological markers, Renal function tests, Liver function tests, glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride levels, and HsCRP were measured in all patients and control participants.

Statistical Analysis :

Statistical analyses were done using computer software (SPSS version 20 and primer). The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analysed by using chi square test and the difference in means were analyzed by using student T Test .and Correlation analyses by using Pearson correlation coefficient. Significance level for tests was determined as 95% ($P< 0.05$).

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V. OBSERVATIONS AND RESULTS

Table No. 1

Age wise distribution of Cases and controls subjects

	Case		Controls	
	No	%	No	%
36-45	11	11	9	9
46-55	26	26	22	22
56-65	25	25	31	31
66+	38	38	38	38
Total	100	100	100	100
Mean ± SD	61.02 ± 11.81		60.77 ± 9.76	

Chi-square = 1.1762 with 3 degrees of freedom; P-value 0.75872 (p>0.05)
Mean age for cases was 61.02±11.81years when compared to 60.77±9.76 years in controls; the difference was not statistically significant with P value >0.05 i.e. cases and controls were matched for age.

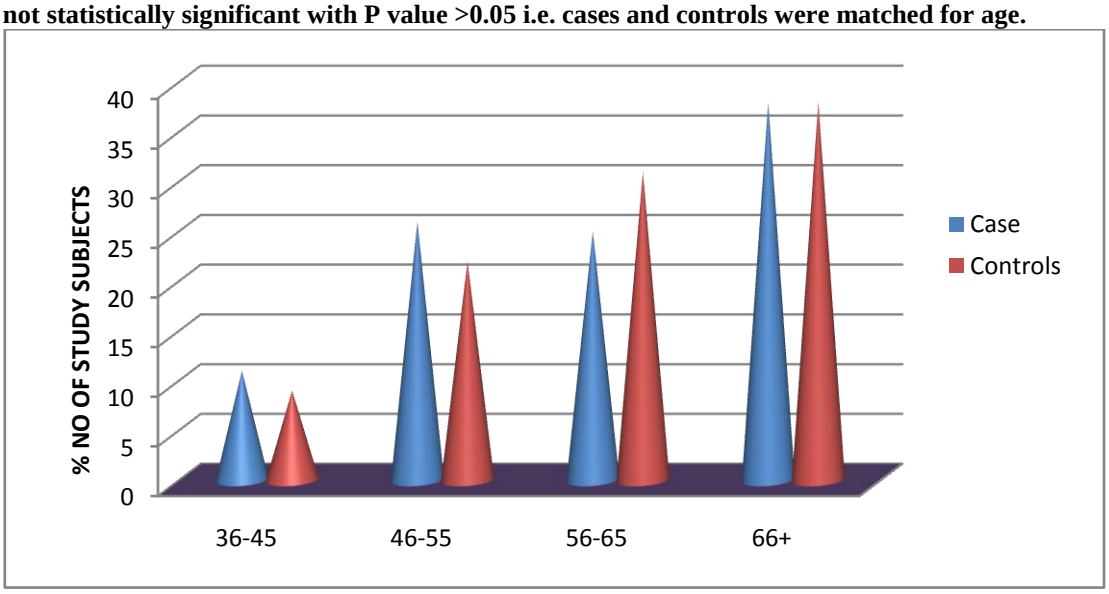

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Table No. 2
Gender wise distribution of cases and controls subjects

	Case		Controls	
	No	%	No	%
Male	73	73.00	74	74.00
Female	27	27.00	26	26.00
Total	100	100.00	100.00	100

Chi-square = 0.0257 with 1 degree of freedom; P-value 0.872 (p>0.05)
Males were 73% and 74% among cases and controls respectively and females were 27% and 26% among cases and controls respectively. Gender wise among cases and controls no significant difference was found i.e. samples were matched for gender (P>0.05)

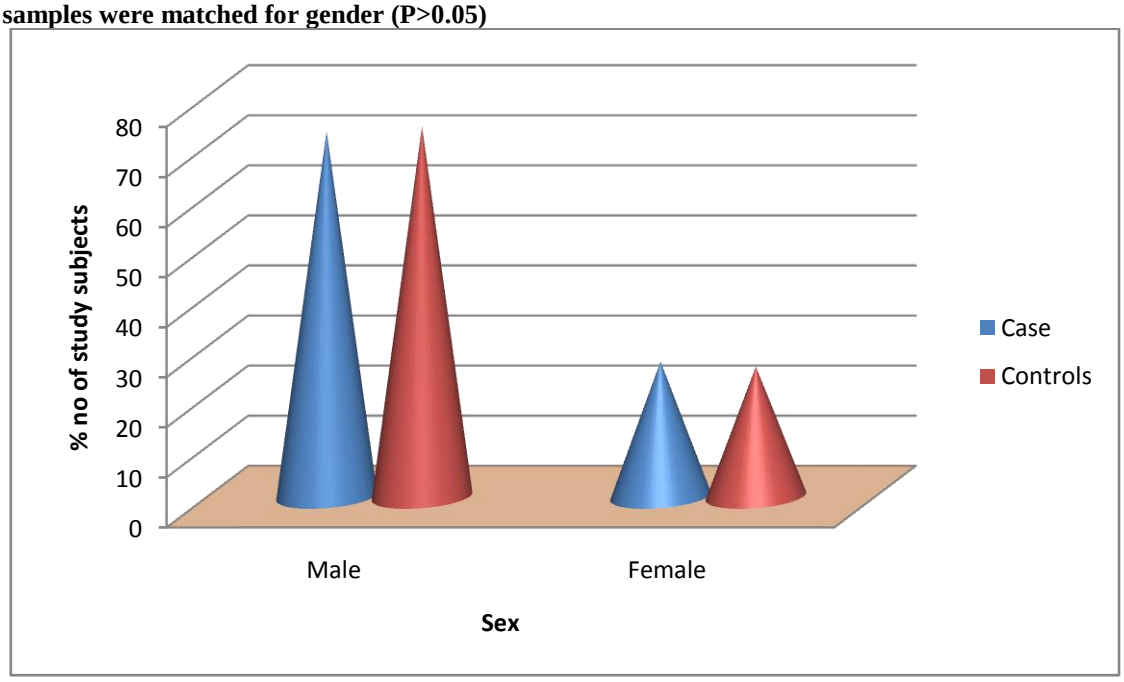

Table No. 3
Mean ± Sd of BMI of case & Control subjects

	Mean ± Sd		P-value	Significance
	Case	Control		
BMI	23.43 ± 3.02	22.18 ± 2.15	> .05	NS

A measurement of BMI was done in both the groups. In the cases group BMI ranged from 17.1 to 29.8 kg/m^2 with a mean of 23.43 ± 3.02 kg/m^2. In the control group BMI ranged from 17.8 to 29.87kg/m^2 with a mean of 22.18 ± 2.15 kg/m^2 the difference was not statistically significant with P value of >.05 i.e. cases and controls were matched for BMI.

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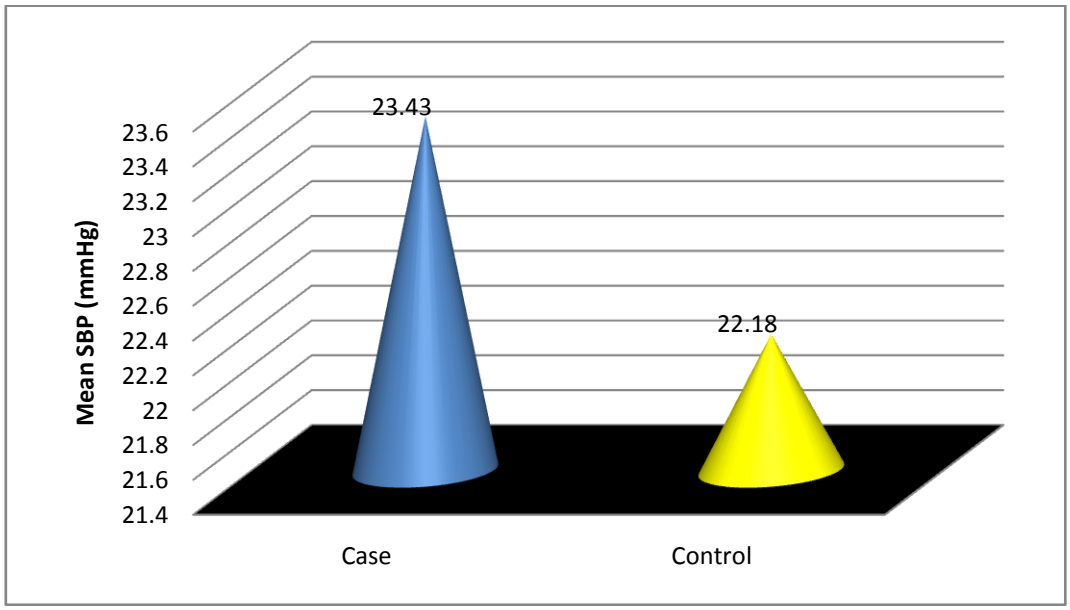

Table No. 4
Mean ± Sd of SBP of case & Control subjects

	Mean ± Sd		P-value	Significance
	Case	Control		
SBP	146.06 ± 21.52	121.92 ± 14.37	< .05	SIGNIFICANT

A measurement of SBP was done in both the groups. In the cases group SBP mean was 146.06 ± 21.52 mmhg. In the control group SBP mean was 121.92 ± 14.37 mm/hg Significantly higher mean SBP was observed in cases as compared to controls. (P<0.05).

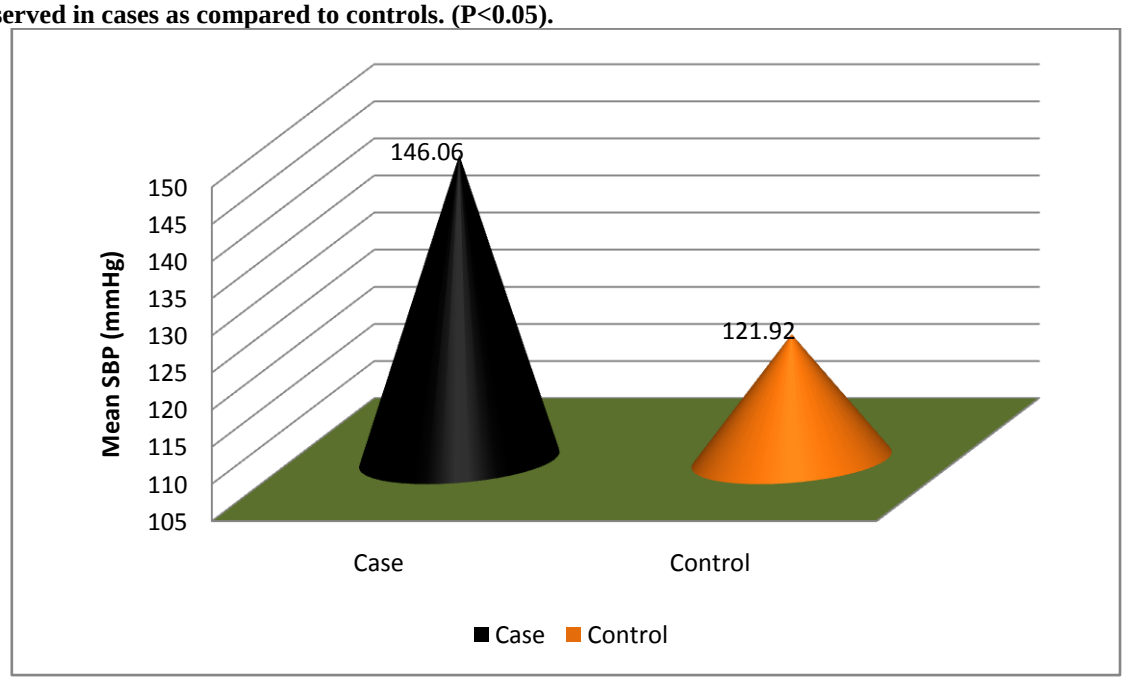

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Table No. 5
Mean ± Sd of DBP of case & Control subjects

	Mean ± Sd		P-value	Significance
	Case	Control		
DBP	99.76 ± 20.53	77.14 ± 9.55	<.05	SIGNIFICANT

A measurement of DBP was done in both the groups. In the cases group DBP mean was 99.76 ± 20.53 mmhg. In the control group DBP mean was 77.14 ± 9.55 mmhg Significantly higher mean DBP was observed in cases as compared to controls. (P<0.05).

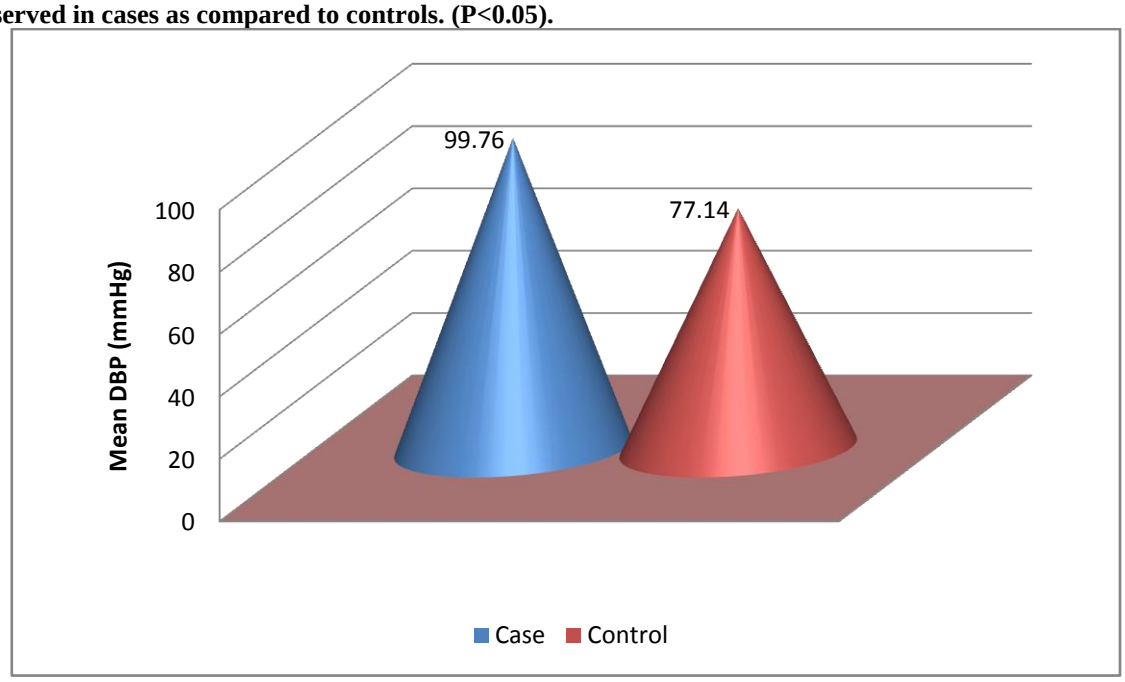

Table No. 6
Presenting symptoms amongst cases at the time of admission.

Weakness	Altered sensorium (%)		Total
	Yes	No	
Left Side	38	35	73
Right Side	17	10	27
Total	55	45	100

Aphasia	Case (%)
Yes	18
No	82
Total	100

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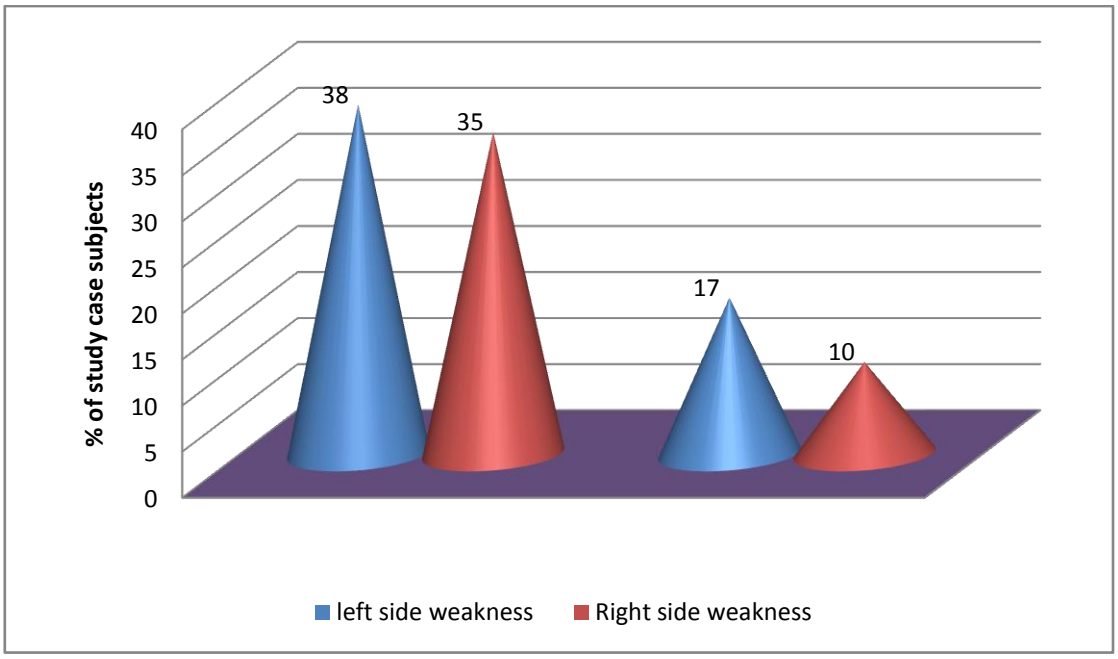
The most common presentation in our study was Left side weakness with altered sensorium (38%) followed by Left side weakness without altered sensorium (35%), Right side weakness with altered sensorium (17%).
Aphasia were studied in case groups. There were 18 out of 100 patients found with Aphasia while 82 patients were found without Aphasia.
Presenting symptoms amongst cases at the time of admission.



(AS = Altered sensorium, NAS=Non-altered sensorium

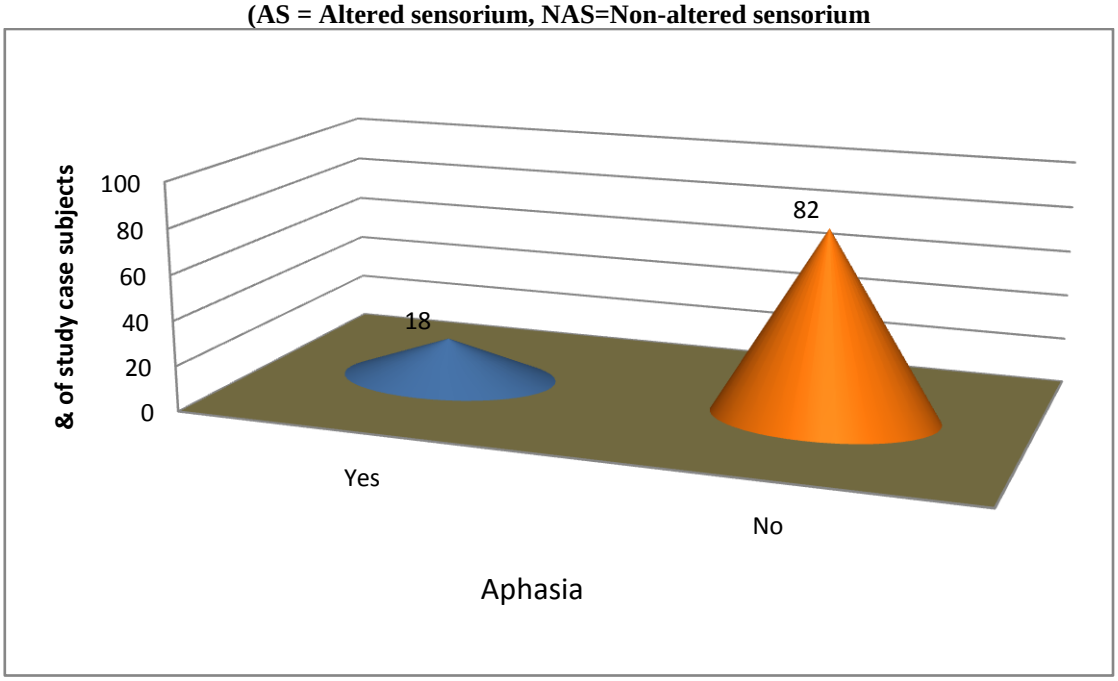


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Table No. 7
Risk factors for strokes amongst study subjects

Risk Factors	Case		Controls		P-value
	No	%	No	%	
HT	55	55	7	7	<0.001(SIG)
DM	21	21	9	9	<0.01 (SIG)
Smoking	27	27	6	6	<0.001 (SIG)
Dyslipidemia	42	42	13	13	<0.05 (SIG)

Out of many risk factors for stroke hypertension was the most prevalent risk factor in case group subjects.

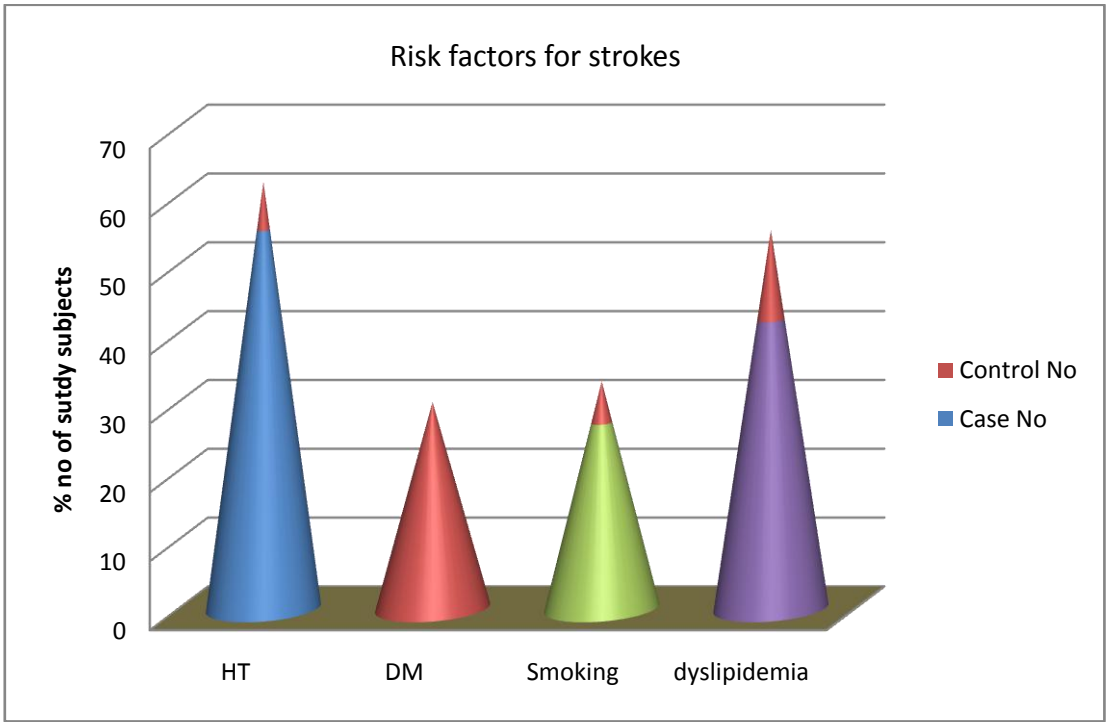

Table No. 8
Mean ± Sd of GCS of case & control group subjects

	Mean ± Sd		P-value	Significance
	Case	Control		
GCS	7.57 ± 1.73	15.00 ± 0.00	< .001	HIGHLY SIGNIFICANT

Highly significant difference was observed in the mean of GCS of case and control group subjects. (p <.001)

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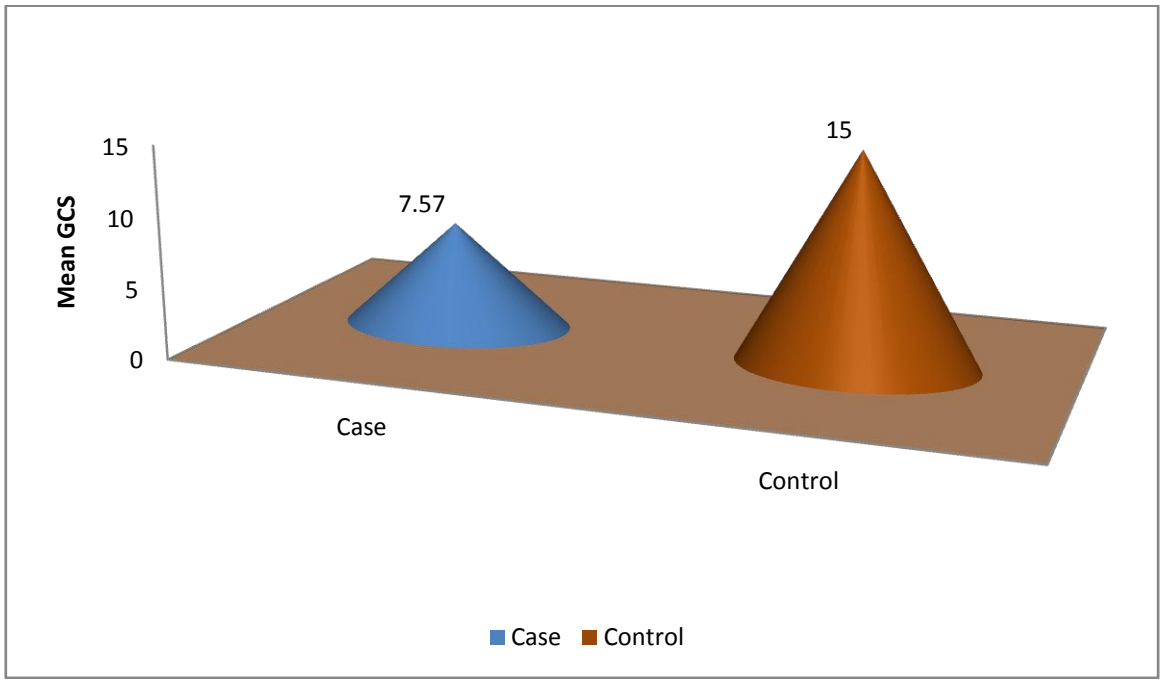

Table No. 9
Mean ± Sd of age according outcome case group subjects

	Mean ± Sd		P-value	Significance
	Survivor	Non-Survivor		
Mean age	58.0 ± 11.83	66.38 ± 11.80	< .001	HIGHLY SIGNIFICANT

In case groups, non-survivors were found to have significantly older age, mean age being 66.38 ± 11.80 years as compared to survivor (58.0 ± 11.83). (p value <0.001)

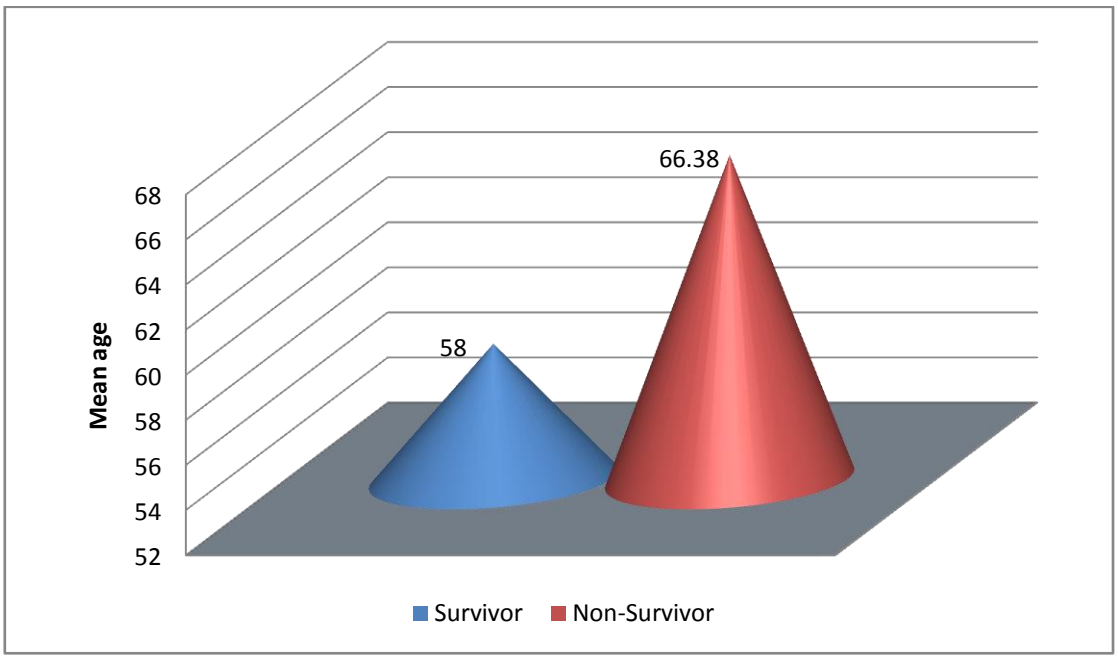

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Table No. 10
Mean ± Sd of FBS of case & control group subjects

	Mean ± Sd		P-value	Significance
	Case	Control		
FBS	119.72 ± 43.40	100.95 ± 20.72	< .001	HIGHLY SIGNIFICANT

Highly significant difference was observed in the mean of FBS of case and control group subjects. (p <.001).

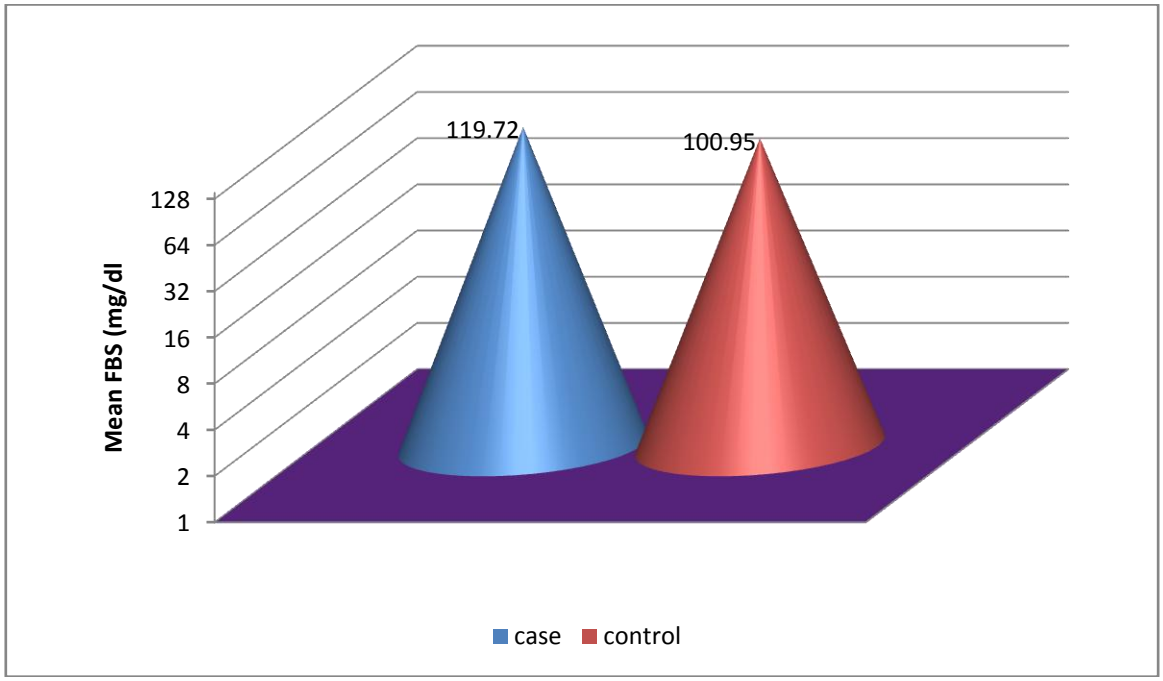

Table No. 11
Mean ± Sd of HsCRP of case & control group subjects

	Mean ± Sd		P-value	Significance
	Case	Control		
HsCRP	7.30 ± 2.34	2.58 ±.0.88	< .001	HIGHLY SIGNIFICANT

Highly significant difference was observed in the mean of HsCRP of case and control group subjects. (p <.001).

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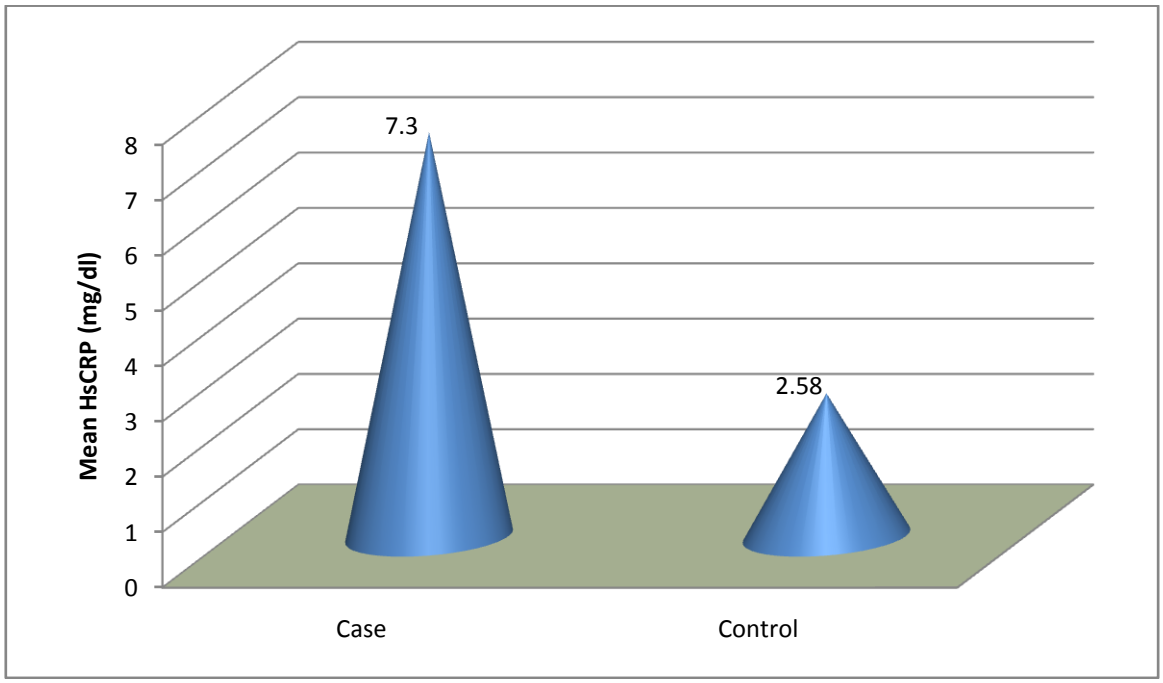

Table No. 12
Mean ± Sd of Lipids of case & control group subjects

	Mean ± Sd		P-value	Significance
	Case	Control		
HDL	41.50 ± 5.90	48.56 ± 7.05	< .001	HIGHLY SIGNIFICANT
LDL	100.71 ± 21.81	88.68 ± 14.07	<.001	HIGHLY SIGNIFICANT
TG	144.76 ± 33.98	125.26 ± 17.78	<.001	HIGHLY SIGNIFICANT

HDL Cholesterol level in cases and controls were 41.50 ± 5.90 mg/dl and 48.56 ± 7.05 mg/dl respectively. HDL Cholesterol was highly significant in stroke cases compared to controls (p value <0.001).
LDL Cholesterol level in cases and controls were 100.71 ± 21.81 mg/dl and 88.68 ± 14.07 mg/dl respectively. LDL Cholesterol was highly significant in stroke cases compared to controls (p value < 0.001). Triglyceride (TG) level in cases and controls were 144.76 ± 33.98 mg/dl and 125.26 ± 17.78 mg/dl respectively. Triglyceride was highly significant in stroke cases compared to controls (p value <0.001).
Mean ± Sd of Lipids of case & control group subjects

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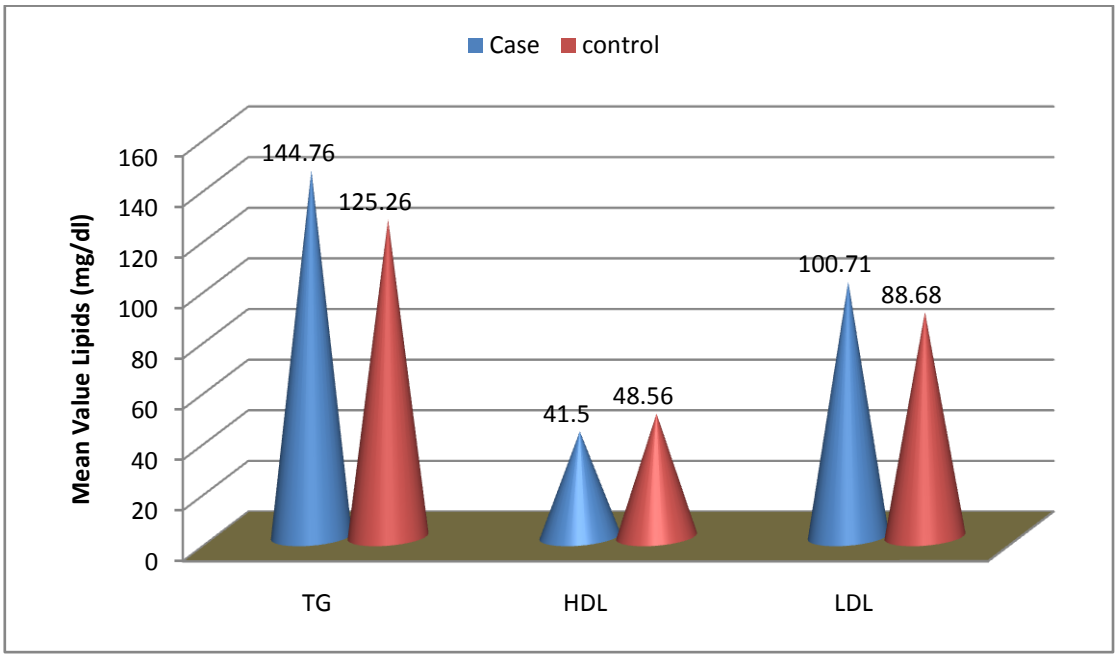

Table No. 13
Mean ± Sd of HsCRP according to GCS of case group subjects

	Mean ± Sd		P-value	Significance
	< 6 GCS(n=30)	< 6 GCS(n=70)		
HDL	9.32 ± 2.38	6.45 ± 2.35	<.001	HIGHLY SIGNIFICANT

All stroke cases who had highly hsCRP, also had low GCS (6) (n=30)

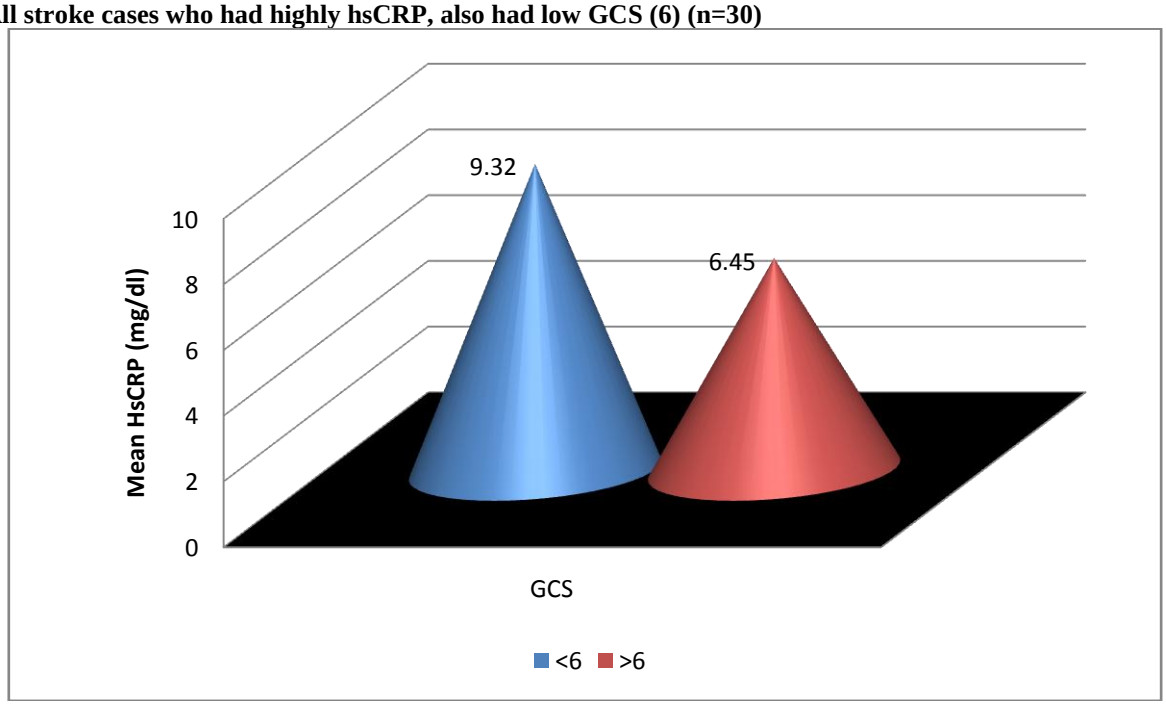

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Table No. 14
Mean ± Sd of HsCRPaccording outcome case group subjects

	Mean ± Sd		P-value	Significance
	Survivor (n=64)	Non-survivor (n=36)		
HDL	5.98 ± 1.79	9.66 ± 0.90	< .001	HIGHLY SIGNIFICANT

Non-survivor patients (36) had high HsCRP (9.66±0.90) as compared to survivor patients.

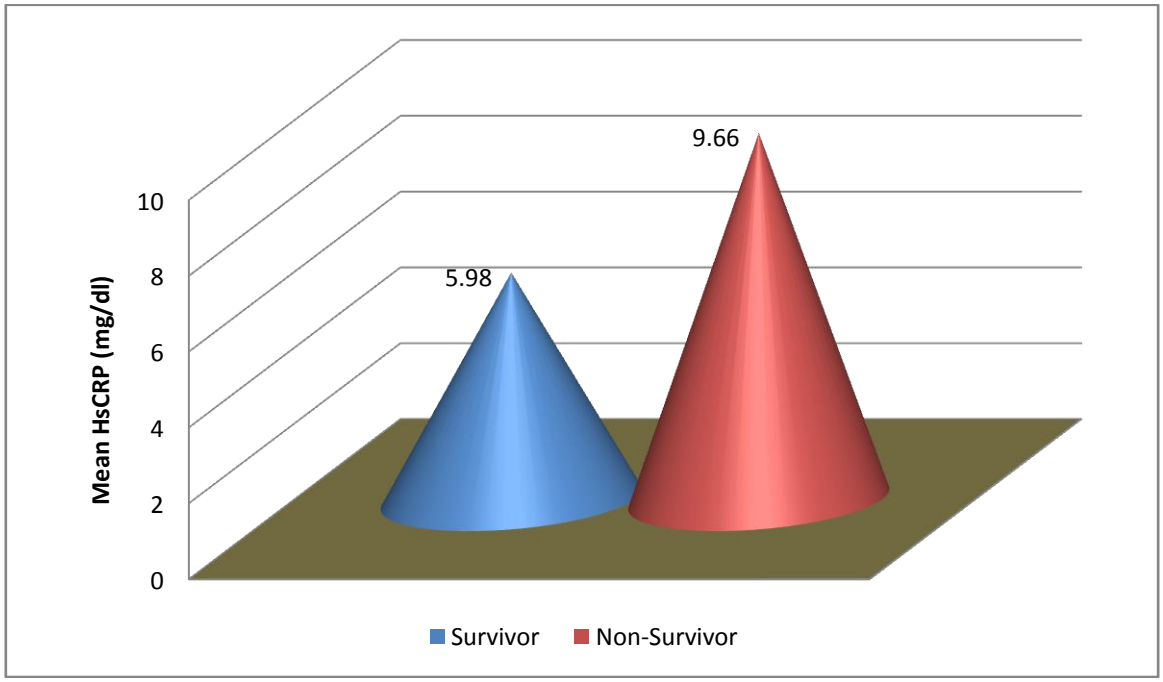

Table No. 15
Mean ± Sd of hs-CRP according risk factor among case group subjects

	Mean ± Sd of hs-CRP		P-value	Significance
	Yes	No		
Smoking	9.27 ± 1.87	6.58 ± 2.09	< .001	HIGHLY SIGNIFICANT
Diabetes	8.30 ± 2.27	7.04 ± 2.32	<.05	SIGNIFICANT
HT	7.91 ± 2.20	6.57 ± 2.35	<.01	SIGNIFICANT
Dyslipidemia	7.79 ± 2.35	6.95 ± 2.31	>.05	NOT SIGNIFICANT

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Significant difference in Mean Serum hs-CRP Level was found between Smokers and Non Smokers, diabetic and non-diabetic, hypertensive and non-hypertensive in case group subjects.

No significant difference in Mean Serum hs-CRP Level was found between dyslipidemic and non-dyslipidemic in case group subjects.

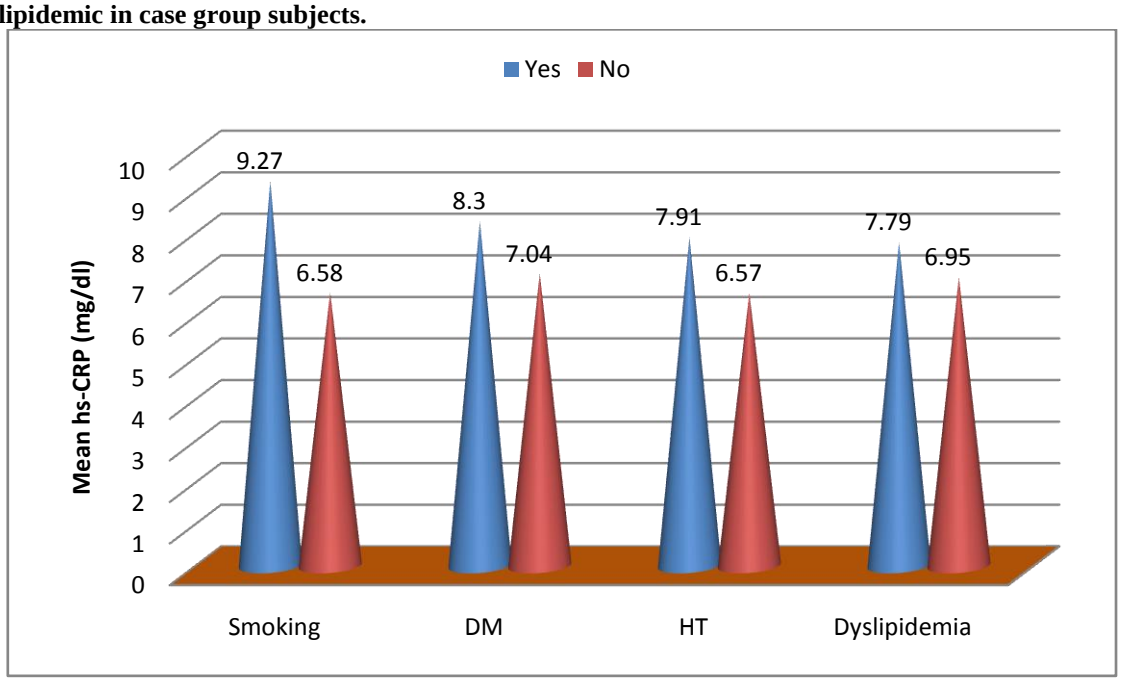

Table No. 16
Correlation between GCS &HsCRP of case group subjects

Correlation	R-value	P-value	Significance
GCS &HsCRP	-0.791	<.001	HIGHLY SIGNIFICANT

A negative correlation was identified between the GCS and hsCRP levels (r -0.791; p <0.001) by using Pearson's correlation coefficient. The r2= 0.625, it means 62.5 % of the total variation in hs-CRP was explained by the linear relation with GCS.

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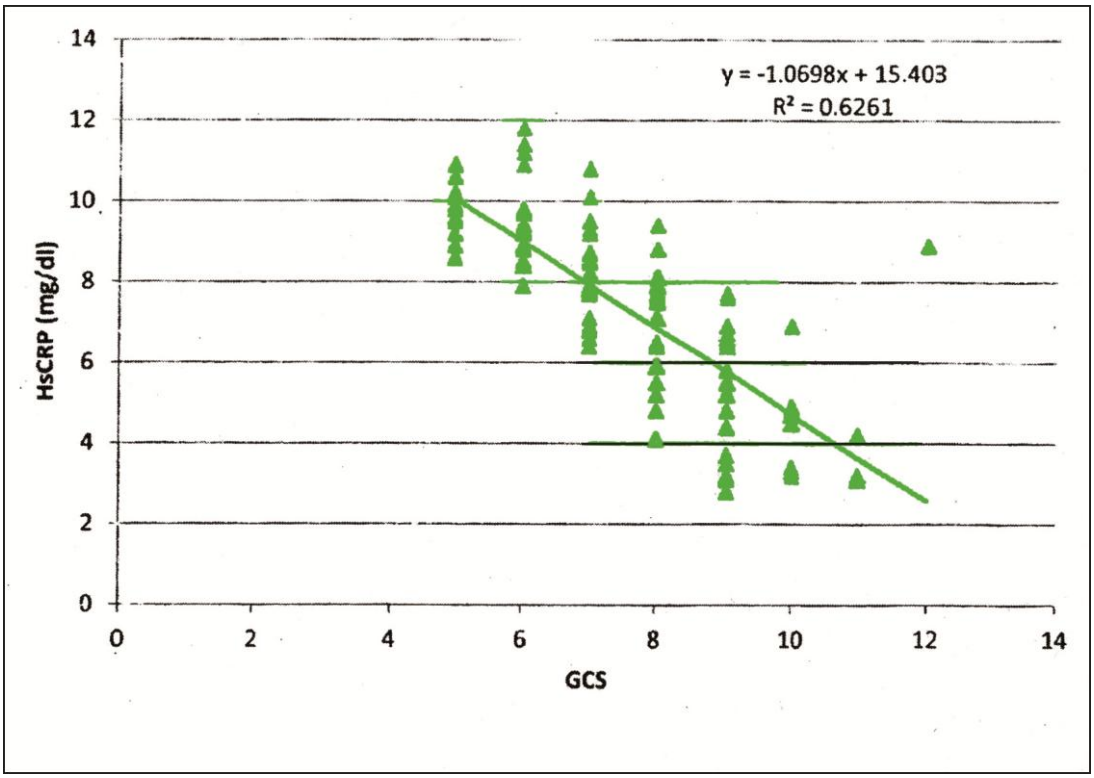

Table No. 17 Correlation between FBS &HsCRP of case group subjects

Correlation	R-value	P-value	Significance
FBS &HsCRP	+0.326	<.05	Sig

A positive correlation was identified between the FBS and hs-CRP levels (r=0.326; p <0.05).by using Pearson's correlation coefficient. The r2= 0.106, it means 10.6 % of the total variation in hs-CRP was explained by the linear relation with FBS.

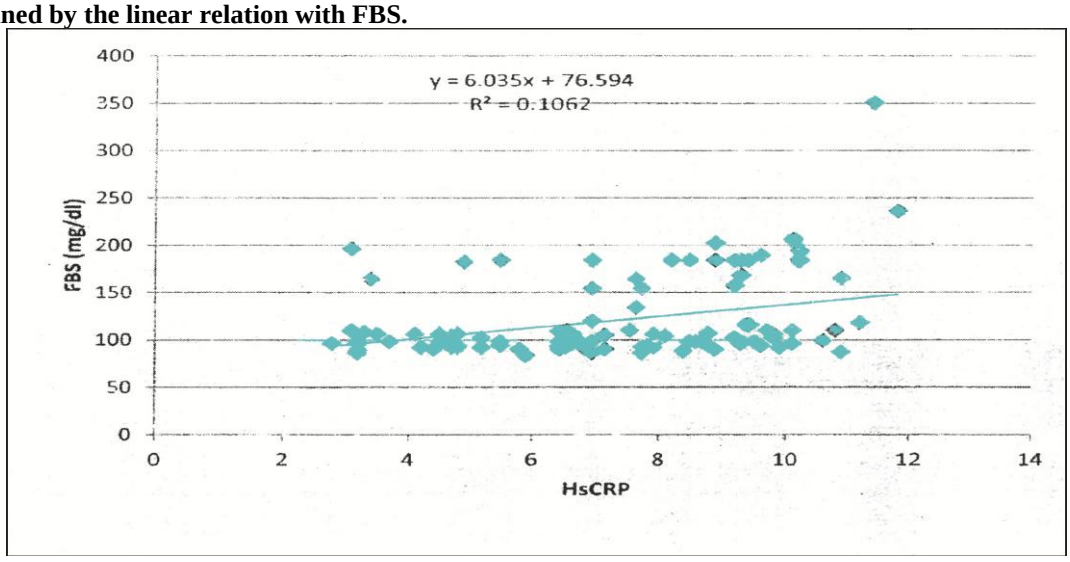

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Table No. 18 Correlation between BMI &HsCRP of case group subjects

Correlation	R-value	P-value	Significance
BMI &HsCRP	+0.544	<.01	Sig

A positive correlation was identified between the BMI and hs-CRP levels (r= +0.544); p <0.01) by using Pearson's correlation coefficient. The r2= 0.295, it means 29.5 % of the total variation in hs-CRP was explained by the linear relation with BMI.

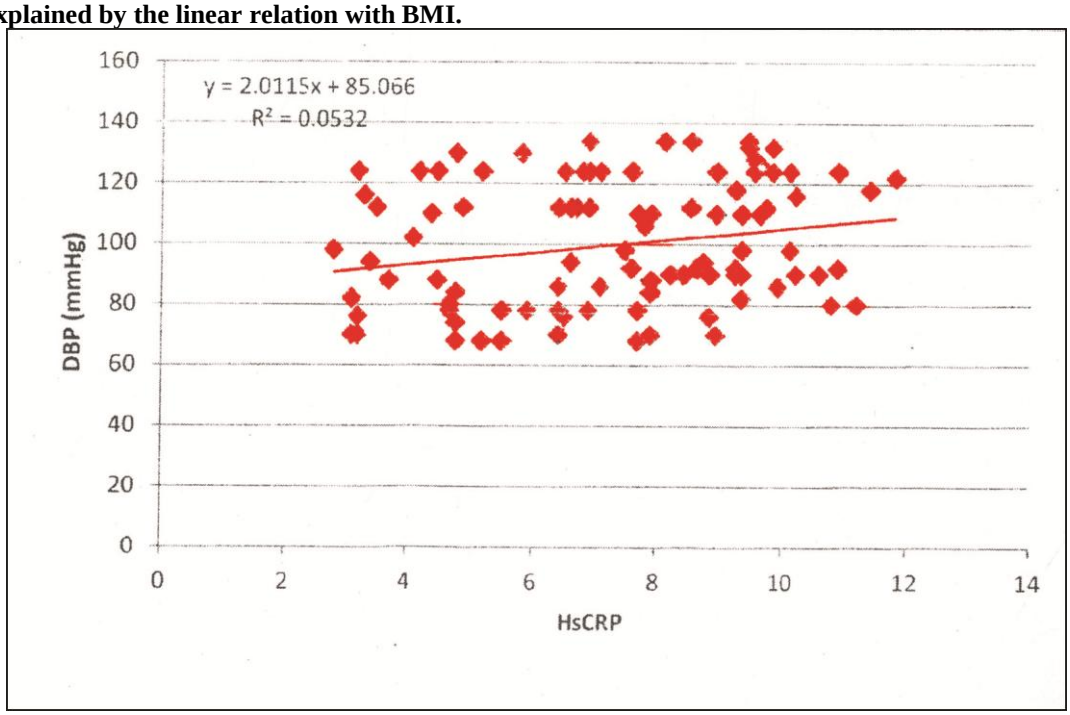

Table No. 19 Correlation between SBP &HsCRP of case group subjects

Correlation	R-value	P-value	Significance
SBP &HsCRP	+0.276	<.05	Sig

A Significant positive fair correlation was observed between the SBP and HsCRP (r=0.276, p <0.05 S) by using Pearson's correlation coefficient. The r2= 0.076, it means 7.6 % of the total variation in HsCRP was explained by the linear relation with SBP. The relationships between the variables in the patient group were considered by using Pearson's correlation coefficient.

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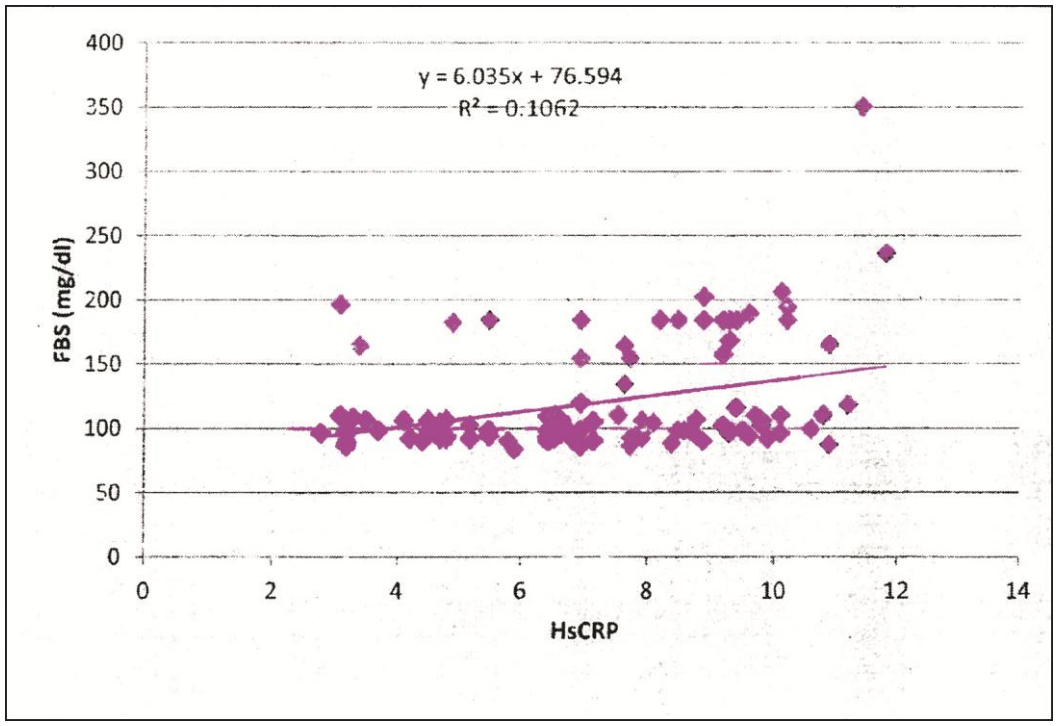
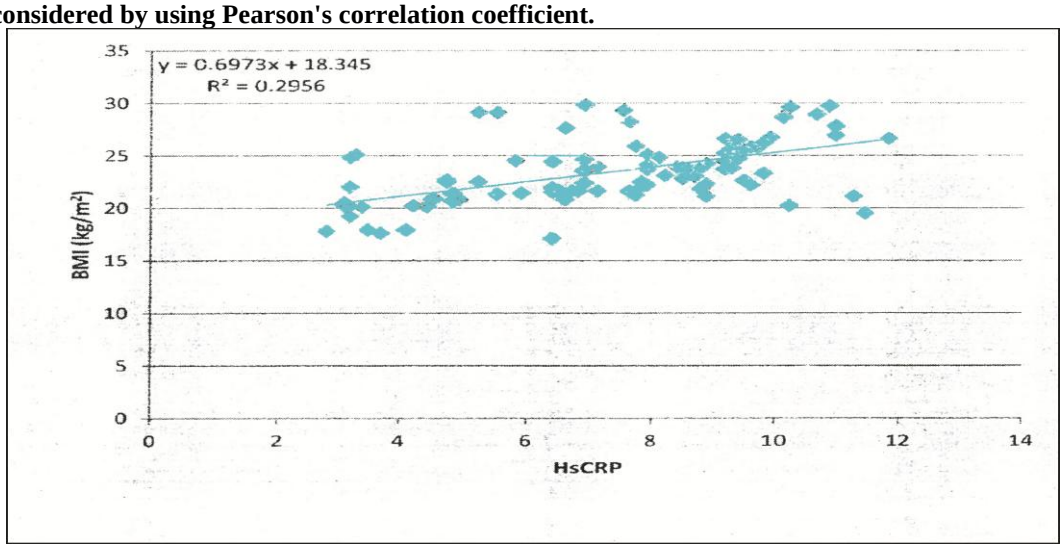


Table No. 20
Correlation between DBP &HsCRP of case group subjects

Correlation	R-value	P-value	Significance
DBP &HsCRP	+0.231	>.05	NS

A positive fair correlation was observed between the DBP and HsCRP (r=0.231, p >0.05 NS) by using Pearson's correlation coefficient. The r2= 0.053, it means 5.3 % of the total variation in HsCRP was explained by the linear relation with DBP. The relationships between the variables in the patient group were considered by using Pearson's correlation coefficient.



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VI. DISCUSSION

Our study was a prospective case control study carried out from June 2014 to December 2015 at Sawai Man Singh Medical College and Hospital, Jaipur. Patients of acute ischemic stroke admitted to the medical and neurology wards within 24 hrs of the onset of symptoms were taken as cases, taking into consideration the already mentioned inclusion and exclusion criteria's. 100 stroke patients with age and sex matched controls were recruited for study. We compared risk factors for stroke, vitals, biochemical parameters, hsCRP between cases and controls.

In a study by Di Napoli et al. from Italy, 95 patients (74.2%) with acute ischemic stroke had high CRP levels (>0.5 mg/dl) at admission. Muir et al. had detected elevated CRP (> 10 mg/L) levels in 96 out of the 228 (42.1%) patients admitted with acute ischemic stroke in the UK. This variance may be explained partly by the different definitions of high CRP in various studies. The hsCRP levels are now becoming universally standardised and most centres accept a value above 3 mg/dl as high.

Zacho et al., in his population based study found a high frequency of ischemic heart disease (32%) and ischemic stroke (25%) among patients with high levels of CRP in Denmark. Ridker et al. from the US, showed high CRP to be a predictor of risk for future stroke in healthy men. Among the Japanese population Arima et al. showed a significant association between high hsCRP and future risk of stroke. Thus,s there is increasing evidence that hsCRP is a risk as well as prognostic factor for ischemic stroke.

HS-CRP LEVEL in STROKE:

Highsensitive C-reactive protein (hsCRP) is a sensitive marker of inflammation and tissue injury in the arterial wall. CRP is a glycoprotein produced by the liver and plays a vital role in the development of atherosclerotic disease in cardiac and cerebral circulation. As a marker of infection and inflammation, high hsCRP has been associated with acute stroke. When the hsCRP levels were measured within 72 hours of admission, it was found to be high in cases (7.30 ± 2.34) as compared to control (2.58 ± 0.88) (Table no. 11). Similar observations have been reported by various other workers also like Di Napolil et al.

HS-CRP LEVEL and SURVIVAL

We found that hs-CRP level was higher in non-survival as compared to survival. Value of hs-CRP was 9.66 ± .90 mg/L in non-survival as compared to 5.98 ± 1 .79mg/L in survival case group. High hs-CRP level in non-survival stroke cases was found statistically significant. (p value <0.001). Thus, there was a relation between the hsCRP level and mortality. Higher the hsCRP level more is the chance of mortality.

Correlation of various parameters (SBP, DBP, **GCS, DYSLIPIDEMIA, DM and hs-CRP) in Acute Iscliemic Stroke**

A negative correlation was identified between the GCS and hsCRP levels (r= -0.791; p <0.001) **(Table no. 16)** by.using Pearson's correlation coefficient. While a positive correlation was identified between the FBS and hs-CRP levels (1=0.326; p <0.05) **(Table no. 17),** BMI and hs-CRP levels (r= +0.544); p <0.01) **(Table no. 18),** SBP and hsCRP (r=0.276, p <0.05 S) (Table no. **19)** and DBP and hsCRP 0-0.23 1, p >0.05 NS) **(Table no. 20)** by using Pearson's correlation coefficient. Dewan and Rana et al. reported same results in their study.

LIMITATIONS OF THE SUTDY There are few limitations in this study:

1. There were only 100 patients and 100 controls in this study. Sample size was calculated and found adequate for such a study. But the sample was smaller than some of the western studies.
2. The controls have been matched only for age and sex and not for the other risk factors which would have been ideal. However almost all the western literature reviewed has also compared only for age and sex.

This study only demonstrates that raised hs-CRP is associated with stroke, however being an observational study it does not demonstrate whether the increase in hs-CRP has contributed to the development of stroke or is simply a consequence of the acute event itself.

VII. SUMMARY

This study was conducted at the upgraded Department of General Medicine, SMS medical college & Hospital, Jaipur. It was Hospital based case control analytical type of observational study. After applying inclusion and exclusion criteria, 100 cases of Acute Ischemic Stroke were selected as cases. Age and sex matched healthy controls were taken for each case.

The aim of our study was to assess the difference in serum hs-CRP levels among ischemic stroke patients and age and sex matched healthy subjects.

The mean age of both the case and control group was 61 .02 ± 11.81 and 60.77 ± 9.76 years respectively with the range (36 to 90 years) (p>0.05 NS). The male and female were 73% and 27% in case groups and the M: F ratio 2.7:1.

Mean BMI of cases and control was 23.43 ± 3.00 kg/m^2 and 22.18 + 2.15 kg/m^2 respectively. Mean values of both these variables were non-significant among cases as compared to controls. (p for BMI :>.05).

Among cases, mean SBP was 146.06 ± 21.52mmHg, mean DBP was 99.76 ± 20.53, mean FBS was 119.72 ± 43.40, mean HDL was 41.50 ± 5.9, mean LDL was 100.71 ± 21.81 and mean TG was 144.76 ± 33.98. The mean value of all these variables was significantly higher among cases as compares to controls. (p for all variables <0.001, p for SBP & DBP <0.05)

To study relationships among various variables in patient group, Pearson's correlation coefficient was applied and it was found that there is statistically significant positive fair correlation between hs-CRP& SBP(r=+0.276,p<0.05) and hs-CRP& FBS. (r=+0.326, p<0.05). Statistically significant moderately strong positive correlation was seen between hsCRP& BMI (r=+0.544, p<0.01) while significant moderately strong inverse correlation was observed between hs-CRP & GCS levels (r= -0.791, p<0.001). No significant correlation was found between hs-CRP & DBP. (r=+0.231, p>0.05).

We found that stroke patients had a significantly higher hsCRP levels when compared to the controls (7.30 ± 2.34 mg/dl vs. 2.58 + 0.88 mg/di, p <0.001).

CONCLUSION: From this study we conclude that hsCRP levels are increased in cases of ischemic stroke. Furthermore, the increased levels correlated with severe neurological deficit and worse outcome. Therefore hs-CRP can be used for risk stratification after stroke.

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ABBREVIATIONS

BMI	Body Mass Index
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
FBS	Fasting Blood Sugar
HDL	High Density Lipoprotein
HTN	Hypertension
LS	Level of Significance
SBP	Systolic Blood Pressure
SD	Standard Deviation
TC	Total Cholesterol
TG	Triglyceride
hS-CRP	High sensitivity C-reactive protein