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# AN INVESTIGATIONAL STUDY ON ASSOCIATION OF HIGH HS-CRP LEVELS WITH ISCHEMIC STROKE

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## ABSTRACT

It is postulated that, elevated CRP levels independently predict the risk of future stroke and transient ischemic attack in the elderly. This study was intended to find association of hs-CRP (>3 mg/L) with acute ischemic stroke. This one year prospective study was done in under the Department of Neurology, Ankineedu Stroke Center, Lalitha Super Specialities Hospital, Guntur, Andhra Pradesh on 100 patients presenting with acute ischemic brain stroke from 1st February, 2017 to 31st January 2019. Most of the patients presentated with Hemiparesis (80%) followed by Dysarthria (61%). Majority of the patients presented with hypertension as risk factor (81%) followed by ischemic heart disease (72%). The GCS score between 3 to 8 on day one was noted among 56% of the patients while on day 7 and day 30, GCS was > 8 in 70% and 77% of the patients. hs-CRP levels were > 3 on day one in majority of the patients (88%). On day seven, hs-CRP levels were > 3 in 62% of the patients and on day 30, 58% of the patients has hs-CRP levels of < 3. NIHS score of > 15 was noted on day 1 in 55% of the patients while 7, 39% of the patients had NIHS score of < 5 while on day 30 and 59% of the patients had NIHS score of < 5. The mean hs-CRP levels were significantly high in patients with severe NIHS scores (>15) compared to patients with moderate (5 to 15) and mild (< 5) NIHS scores on day one (14.14 ± 4.51; $p<0.001$), day seven (11.95 ±2.31; $p<0.001$), and day 30 (9.49 ± 2.45; $p<0.001$). Furthermore, mean Age, mean SBP,

mean DBP, mean Neutrophils, mean ESR, mean blood urea, mean serum creatinine, mean total cholesterol, mean GCS and mean NIHS on day 1, 7 and 30 differed significantly ($p<0.050$).

**Keywords: High sensitive C-reactive protein, National Institute of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), Acute Ischemic Stroke**

## INTRODUCTION

A stroke, or cerebrovascular accident, is defined as abrupt onset of a neurologic deficit of vascular origin. World Health Organization defines the clinical syndrome of "stroke" as, rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin **[1]**. Majority of stroke are ischemic (80%); while others result from primary hemorrhage either intracerebral or into the subarachnoid space. Acute ischemic stroke is result of stroke caused by thrombosis or embolism and is more common than hemorrhagic stroke **[2]**. Numerous risk factors are involved in the development of stroke, such as hypertension, cigarette smoking, hyperlipidemia and diabetes mellitus **[3]**.

C-reactive protein (CRP) is an acute phase protein produced in response to inflammatory process and therefore it is regarded as a well-known marker of inflammation. CRP is currently being investigated as a probable marker of generalized atherosclerosis. Atherosclerosis is considered a chronic inflammatory response by arterial endothelium **[4]**. Infections and inflammation play a vital role in the pathophysiology of atherosclerosis **[5]**. High sensitive C-reactive protein (hs-CRP) is a sensitive marker of inflammation and tissue injury in the arterial wall **[6]**. CRP is a glycoprotein produced by the liver and plays a vital role in the development of atherosclerotic disease in cardiac and cerebral circulation **[7]**. Hence, the present research study reflects the association of high hs-CRP (> 3 mg/L) levels with ischemic stroke.

## PATHOPHYSIOLOGY

When an ischemic stroke occurs, the blood supply to the brain is interrupted, and brain cells are deprived of the glucose and oxygen they need to function. Ischemic stroke is a complex entity with multiple etiologies and variable clinical manifestations. Approximately 45% of ischemic strokes are caused by small or large artery thrombus, 20% are embolic in origin, and others have an unknown cause. Thrombosis can form in the extracranial and intracranial arteries when the intima is roughened and plaque forms along the

injured vessel. The endothelial injury (roughing) permits platelets to adhere and aggregate, then coagulation is activated and thrombus develops at site of plaque. Blood flow through the extracranial and intracranial systems decreases, and the collateral circulation maintains function. When the compensatory mechanism of collateral circulation fails, perfusion is compromised, leading to decreased perfusion and cell death **[8]**.

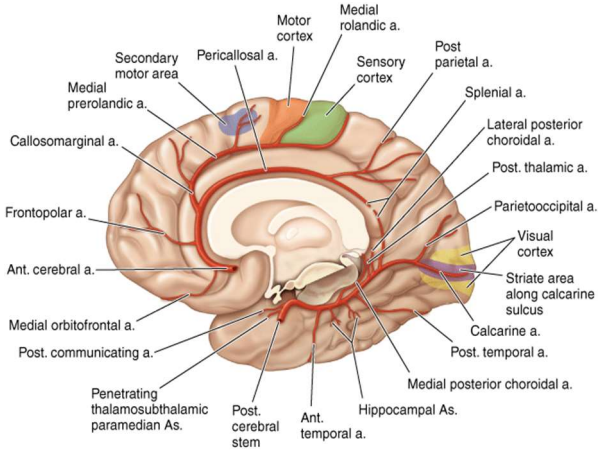



**Figure 1: Cerebral hemisphere showing medial aspect - Branches of ACA [9]**

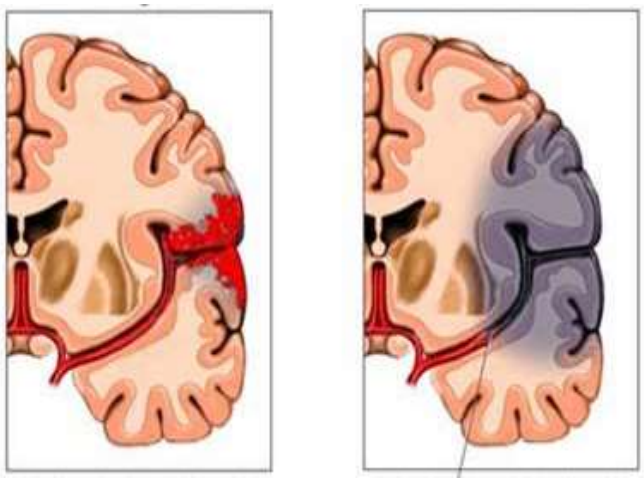


**Figure 2: Pathology of hemorrhagic and ischemic stroke [10]**

## METHODOLOGY

**Study design:** The study design was a one year prospective study.

**Study period and duration:** This study was conducted for the period of Two years, from 1st February, 2017 to 31st January 2019. Study was done in the Department of Neurology, Ankineedu Stroke Unit, Lalitha Super Specialities Hospital, Guntur, Andhra Pradesh.

**Source of Data:** This study comprised of patients presenting with acute ischemic brain stroke.

**Sample size**

In this study as the proportion of patients with acute ischemic stroke was not known in the study area hence it was considered as 50%. Thus the sample size would be $n = Z^2 p q / E^2$

$n = (1.96)^2 * (0.50) * (0.50) / (0.10)^2$

Therefore $0.96 / 0.01 = 96 \approx 100$ hence a total of 100 patients with Acute Ischemic Stroke.

**Selection criteria**

Inclusion

- Patients presenting with history of focal neurological deficit of acute onset in the form of hemiparesis, hemianaesthesia , aphasia or having

evidence of the presence of ischemic infarct in CT scan of the brain will be included in this study.

- Patients aged above 18 years of both sexes.

Exclusion

- The patients with infectious pathology, arthritis, cancer, history of recent MI or acute coronary syndrome, those in hepatic failure were excluded from this study.
- Patients presenting with focal neurological deficit after 72 hrs and on drugs, e.g., NSAIDs, statins, hormone replacement therapy were excluded.

**Method of Data collection**

Patients were screened for the eligibility and those fulfilling the selection criteria were briefed about the nature of the study. Demographic data such as age and sex were recorded. A Detailed history of regarding stroke, its onset, duration, time of presentation, focal neurological deficits, any association with seizure, headache, vomiting, or deviation of mouth was taken and other co-morbid conditions such as, hypertension, diabetes mellitus, previous stroke, smoking and alcohol intake was considered to ascertain the presence of any risk factors. Clinical examination included vitals, i.e., pulse, blood pressure, and detailed examination of the neurological system. A thorough physical examination was conducted for vitals (pulse rate, blood pressure and respiratory rate) followed by systemic examination. The diagnosis of stroke was entertained after fulfilling WHO definition of stroke by the patient **[11]**. The ischemic nature of stroke was established by computed tomographic / magnetic resonance imaging scan. Evaluation of stroke severity was carried out based on NIHSS and GCS **[12]**.

**Estimation of hs-CRP**

Levels of hs-CRP are estimated by VITROS 5.1 chemistry system and VITROS 5600 integrated system to quantitatively measure CRP in human serum or plasma. As per the normative data from VITROS 5600 system manual and current literature, the cardiovascular risk was determined as low risk with hs-CRP levels < 1.0 mg/L, medium risk if 1.0-3.0 mg/L, high risk when > 3.0 mg/L **[13]**. For our study we considered hs-CRP level of ≥ 3 mg/L as high risk and ≤ 3 mg/L as low risk **[14]**.

**Statistical analysis**

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The data was analysed using SPSS statistics software version 20.0. The

categorical data was expressed in terms of rates, ratios and proportions and comparison was done using chi-square test or Fisher's exact test. The continuous data was expressed as mean ± standard deviation (SD) and the comparison was done using independent sample't' test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

**RESULTS:**

In the present study most of the patients were males (71%). The male to female ratio was 2.44:1 **(Graph 1, 2)**.

In this study most of the patients were aged between 41 to 50 years (37%) followed by 51 to 60 years (25%). The mean age was 58.24 ± 10.99 years and the median age was 58 years with range 26 to 92 years **(Graph 3)**.

In the present study the commonest clinical presentation was Hemiparesis (80%) followed by Dysarthria (61%) and reeling sensation (20%). The other presentations were hemiplegia (13%), Facial palsy (10%), Dysphagia (9%), Headache, Vomiting (6% each), Diplopaia (5%) Aphasia (4%) and Numbness (3%) **(Graph 4)**.

In this study majority of the patients presented with hypertension as risk factor (81%) followed by ishaemic heart disease (72%) **(Graph 5)**.

In the present study most of the patients had GCS score between 3 to 8 on day one (56%) while on day 7 and day 30, GCS was > 8 in 70% and 77% of the patients **(Graph 6)**.

In this study hs-CRP levels were > 3 on day one in majority of the patients (88%). On day seven, hs-CRP levels were > 3 in 62% of the patients and on day 30 58% of the patients has hs-CRP levels of ≤ 3 **(Graph 7)**.

In the present study, NIHSS score of > 15 was noted on day 1 in 55% of the patients. On day 7, 39% of the patients had NIHSS score of < 5 while on day 30 59% of the patients had NIHSS score of < 5 (**Table 1**).

***Chi-square test #Fishers exact test**

The association of hs-CRP levels with GCS score is as shown in table 8. It was observed that, significantly higher number of patients with higher hs-CRP levels (>3) had severe stroke based on GCS (3-8) on day one (100%; p<0.001), day seven (100%; p<0.001) and day 30 (100%; p<0.001) **(Table 2)**.

**#Fishers exact test**

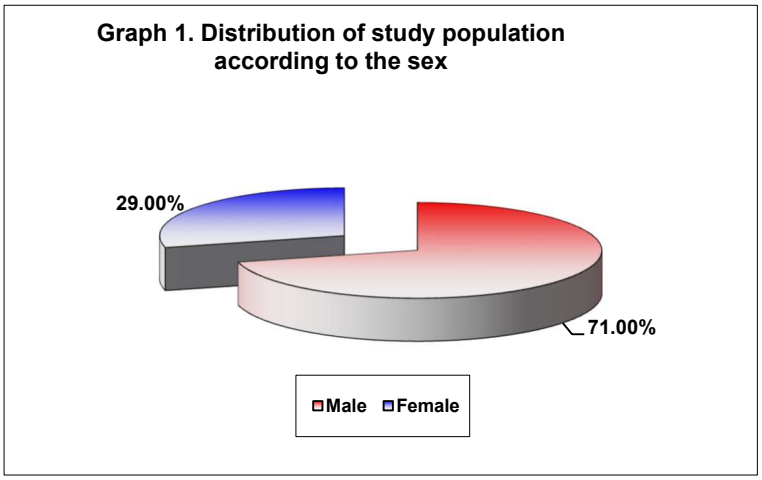
In this study, on Day one, significantly higher number of patients with severe NIHSS score (98.18%) had raised hs-CRP levels (>3) (p<0.001). Similar observations were noted on Day seven

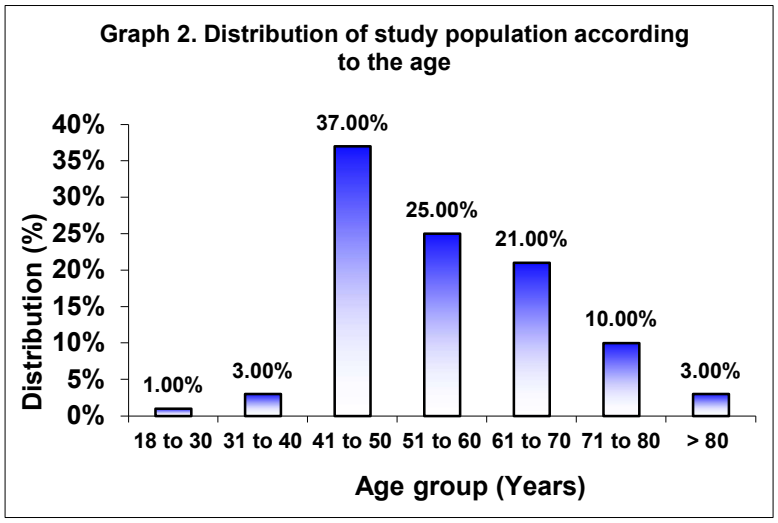
(100%; p<0.001) and Day 30 (100%; p<0.001) **(Table 3)**.

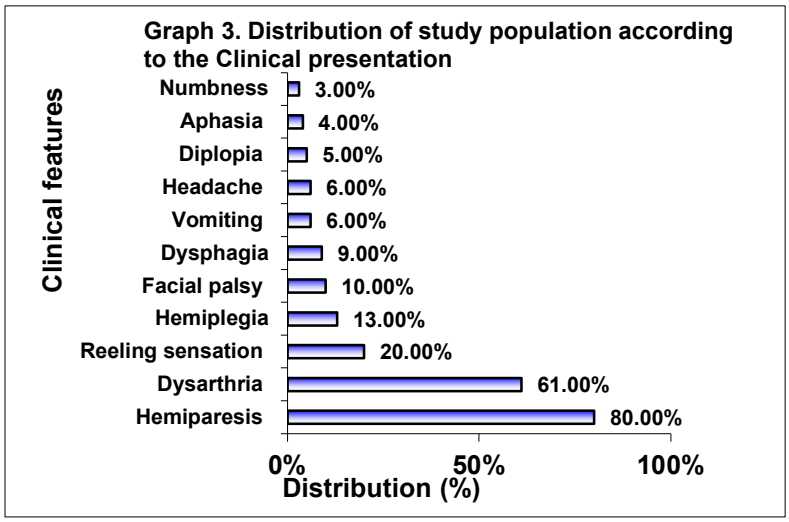
In this study the mean hs-CRP levels were significantly raised in patients with GCS score of 3 to 8 compared to those patients who has GCS score of > 8 on day one (14.13 ± 4.28 vs 5.13 ±3.40; p<0.001), Day seven (12.19 ± 2.10 vs 3.64 ±3.28; p<0.001) and Day 30 (9.81 ± 2.11 vs 2.11 ± 2.54; p<0.001) **(Table 3)**.

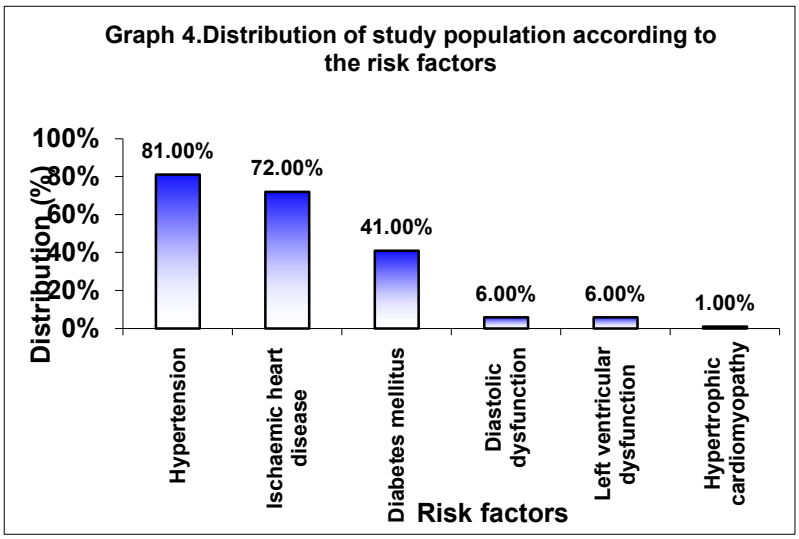
In this study, the mean hs-CRP levels were significantly high in patients with severe NIHSS scores (>15) compared to patients with moderate (5 to 15) and mild (< 5) NIHSS scores on day one (14.14 ± 4.51; p<0.001), day seven (11.95 ±2.31; p<0.001), and day 30 (9.49 ± 2.45; p<0.001) **(Table 4)**.

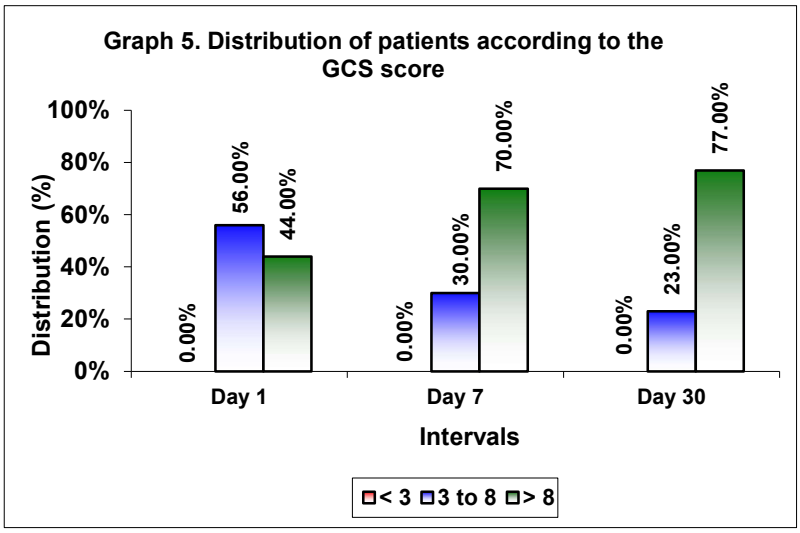
**Table 5** shows Comparison of clinical characteristics of study population with normal and raised hs-CRP levels it was observed that, mean Age, mean SBP, mean DBP, mean Neutrophils, mean ESR, mean blood urea, mean serum creatinine, mean GCS and mean NIHSS on day 1, 7 and 30 differed significantly (p<0.050).

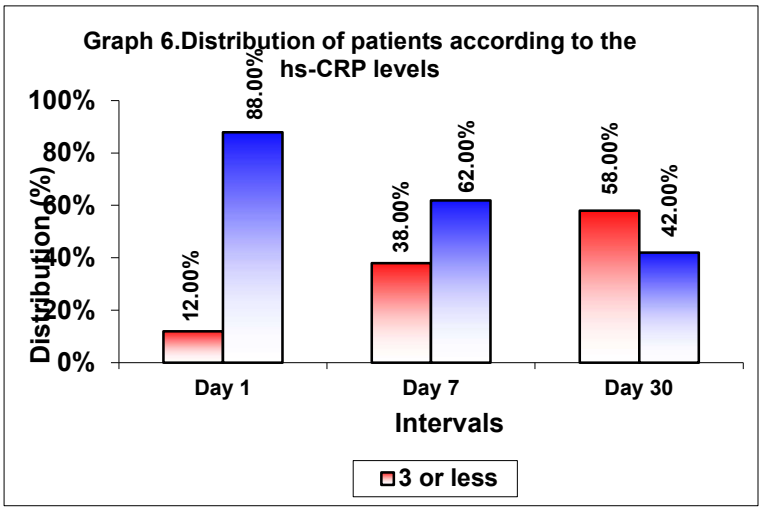



Graph 3. Distribution of study population according to the Clinical presentation
Clinical features
Numbness 3.00%
Aphasia 4.00%
Diplopia 5.00%
Headache 6.00%
Vomiting 6.00%
Dysphagia 9.00%
Facial palsy 10.00%
Hemiplegia 13.00%
Reeling sensation 20.00%
Dysarthria 61.00%
Hemiparesis 80.00%
0%
50%
100%
Distribution (%)


Graph 4.Distribution of study population according to the risk factors
Distribution (%)
100%
80%
60%
40%
20%
0%
81.00%
72.00%
41.00%
6.00%
6.00%
1.00%
Hypertension
Ischaemic heart disease
Diabetes mellitus
Diastolic dysfunction
Left ventricular dysfunction
Hypertrophic cardiomyopathy
Risk factors


Graph 5. Distribution of patients according to the GCS score
Distribution (%)
100%
80%
60%
40%
20%
0%
0.00%
56.00%
44.00%
0.00%
30.00%
70.00%
0.00%
23.00%
77.00%
Day 1
Day 7
Day 30
Intervals
< 3
3 to 8
> 8



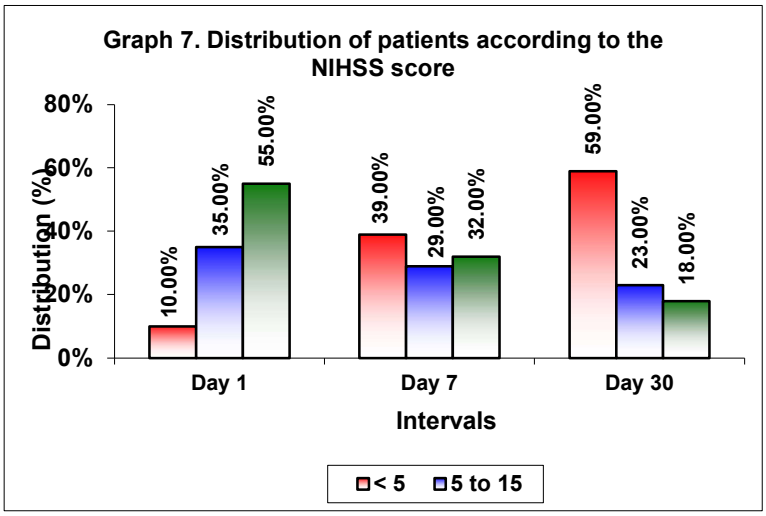




**Table 1: Association of hs-CRP with GCS score on different intervals**

| Intervals | GCS score | hs-CRP | | | | $x^2$ | DF | p value |
|---|---|---|---|---|---|---|---|---|
| | | >3 | | ≤3 | | | | |
| | | No | % | No | % | | | |
| Day 1 | 3 to 8 | 56 | 100.00 | 0 | 0.00 | 17.35 | 1 | < 0.001* |
| | > 8 | 32 | 72.73 | 12 | 27.27 | | | |
| | Total | 88 | 88.00 | 12 | 12.00 | | | |
| Day 7 | 3 to 8 | 30 | 100.00 | 0 | 0.00 | 26.67 | 1 | < 0.001* |
| | > 8 | 32 | 45.71 | 38 | 54.29 | | | |
| | Total | 62 | 62.00 | 38 | 38.00 | | | |
| Day 30 | 3 to 8 | 23 | 100.00 | 0 | 0.00 | - | - | < 0.001# |
| | > 8 | 19 | 24.68 | 58 | 75.32 | | | |
| | Total | 42 | 42.00 | 58 | 58.00 | | | |

**Table 2: Association of hs-CRP with NIHSS on different intervals**

| Intervals | NIHSS score | hs-CRP | | | | p value# |
|---|---|---|---|---|---|---|
| | | >3 | | ≤3 | | |
| | | No | % | No | % | |
| Day 1 | Mild (< 5) | 6 | 60.00 | 4 | 40.00 | < 0.001 |
| | Moderate (5 to 15) | 28 | 80.00 | 7 | 20.00 | |
| | Severe (> 15) | 54 | 98.18 | 1 | 1.82 | |
| | Total | 88 | 88.00 | 12 | 12.00 | |
| Day 7 | Mild (< 5) | 7 | 17.95 | 32 | 82.05 | < 0.001 |
| | Moderate (5 to 15) | 23 | 79.31 | 6 | 20.69 | |
| | Severe (> 15) | 32 | 100.00 | 0 | 0.00 | |
| | Total | 62 | 62.00 | 38 | 38.00 | |
| Day 30 | Mild (< 5) | 5 | 8.47 | 54 | 91.53 | < 0.001 |
| | Moderate (5 to 15) | 19 | 82.61 | 4 | 17.39 | |
| | Severe (> 15) | 18 | 100.00 | 0 | 0.00 | |
| | Total | 42 | 42.00 | 58 | 58.00 | |

**Table 3: Comparison of mean hs-CRP with GCS score**

| Intervals | GCS score | hs-CRP | |
|---|---|---|---|
| | | Mean | SD |
| Day 1 | 3 to 8 | 14.13 | 4.28 |
| | > 8 | 5.13 | 3.40 |
| | 't' value | 11.702 | |
| | DF | 97.978 | |
| | 'p' value | <0.001 | |
| Day 7 | 3 to 8 | 12.19 | 2.10 |
| | > 8 | 3.64 | 3.28 |
| | 't' value | 15.587 | |
| | DF | 83.430 | |
| | 'p' value | < 0.001 | |
| Day 30 | 3 to 8 | 9.81 | 2.11 |
| | > 8 | 2.11 | 2.54 |
| | 't' value | 14.588 | |
| | DF | 42.795 | |
| | 'p' value | < 0.001 | |

**Table 4: Association of mean hs-CRP with NIHSS score**

| Intervals | NIHSS score | hs-CRP | |
|---|---|---|---|
| | | Mean | SD |
| Day 1 | Mild (< 5) | 3.60 | 1.88 |
| | Moderate (5 to 15) | 5.81 | 3.45 |
| | Severe (> 15) | 14.14 | 4.51 |
| | 'F' value | 61.979 | |
| | 'p' value | <0.001 | |
| Day 7 | Mild (< 5) | 1.81 | 1.26 |
| | Moderate (5 to 15) | 5.79 | 3.62 |
| | Severe (> 15) | 11.95 | 2.31 |
| | 'F' value | 148.420 | |
| | 'p' value | <0.001 | |
| Day 30 | Mild (< 5) | 1.14 | 1.35 |
| | Moderate (5 to 15) | 6.52 | 3.45 |
| | Severe (> 15) | 9.49 | 2.45 |
| | 'F' value | 120.966 | |
| | 'p' value | < 0.001 | |

**Table 5: Comparison of clinical characteristics of study population with hs-CRP**

| Clinical characteristics | hs-CRP | | | | p value |
|---|---|---|---|---|---|
| | <3 | | >3 | | |
| | Mean | SD | Mean | SD | |
| Age (Years) | 53.92 | 6.46 | 58.83 | 11.37 | 0.038 |
| Pulse rate (/minute) | 82.67 | 4.77 | 83.88 | 9.00 | 0.479 |
| Systolic BP (mm Hg) | 130.83 | 16.76 | 143.41 | 24.58 | 0.035 |
| Dialostic BP (mm Hg) | 83.33 | 6.51 | 88.43 | 14.20 | 0.044 |
| Respiratory rate (/Minute) | 20.75 | 0.87 | 20.65 | 1.16 | 0.718 |
| Temperature ($^0$C) | 98.58 | 0.67 | 98.29 | 0.60 | 0.170 |
| Hb (g/dL) | 14.03 | 1.95 | 13.34 | 2.07 | 0.268 |
| WBCs (cell/cumm) | 8759.17 | 2864.68 | 12505.00 | 17400.37 | 0.068 |
| Neutrophils (%) | 60.33 | 8.78 | 70.99 | 14.14 | 0.002 |
| Lymphocytes (%) | 29.25 | 6.82 | 24.59 | 11.66 | 0.059 |
| ESR (%) | 21.25 | 12.93 | 31.67 | 27.05 | 0.036 |
| Platelets (Lacks/cumm) | 504.97 | 1171.97 | 3.16 | 1.44 | 0.166 |
| Fasting RBS (mg/dL) | 125.42 | 41.86 | 148.97 | 67.73 | 0.110 |
| Random RBS (mg/dL) | 166.00 | 81.62 | 173.06 | 68.57 | 0.779 |
| HbA1c (%) | 7.42 | 2.18 | 8.08 | 1.90 | 0.334 |
| Blood urea (mg/dL) | 24.92 | 7.27 | 30.98 | 16.14 | 0.033 |
| Serum creatine (mg/dL) | 1.00 | 0.00 | 1.06 | 0.25 | 0.043 |
| Total cholesterol (mg/dL) | 161.33 | 28.63 | 147.88 | 32.47 | 0.154 |
| LDL (mg/dL) | 58.33 | 29.82 | 75.11 | 27.69 | 0.087 |
| HDL (mg/dL) | 36.08 | 6.65 | 38.31 | 9.38 | 0.318 |
| Triglycerides (mg/dL) | 169.75 | 73.35 | 148.76 | 88.05 | 0.379 |
| Prothrombin time (sec) | 14.38 | 1.40 | 15.14 | 4.63 | 0.233 |
| Intgernational normalised ratio | 1.01 | 0.03 | 1.06 | 0.33 | 0.126 |
| Activated prothrombin time (sec) | 26.83 | 6.09 | 24.77 | 4.59 | 0.279 |
| GCS Day 1 | 12.67 | 1.50 | 8.33 | 2.93 | <0.001 |
| GCS Day 7 | 14.75 | 0.87 | 10.76 | 3.38 | <0.001 |
| GCS Day 30 | 17.13 | 8.28 | 5.92 | 3.53 | <0.001 |
| NIHSS Day 1 | 10.84 | 7.55 | 2.58 | 1.83 | <0.001 |
| NIHSS Day 7 | 7.75 | 8.26 | 0.50 | 0.67 | <0.001 |
| NIHSS Day 30 | 17.13 | 8.28 | 5.92 | 3.53 | <0.001 |

## CONCLUSION

Based on the results of this study it may be concluded that, there raised hs-CRP levels are highly associated with acute ischemic stroke. Furthermore, raised hs-CRP levels are highly associated with severity of stroke and outcome of stroke as measured by GCS and NIHS. Hence hs-CRP levels might be included as a health screening protocols.

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