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# ORIGINAL ARTICLE

## STUDY OF C-REACTIVE PROTEIN IN ACUTE ISCHEMIC STROKE

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**ABSTRACT:** Ischemic stroke is the 3rd leading cause of death after AMI and cancer. Stroke is also the leading cause of hospital admission causing disability. The study was based on 100 patients with ischemic stroke admitted to the JJM Medical College, Davangere. This study was done to estimate the role of C-reactive protein as a marker of acute inflammation following ischemic stroke and also to determine, its prognostic role, by assessing the functional outcome of patient using modified Barthel index scoring (ADL). Patients with CRP <6 mg/dl suffered mild disease, showed good prognosis, their Barthel scores improved with follow up. Patients with CRP levels >6 mg/dl suffered severe disease with poor functional outcome. P value <0.05, significant, suggests CRP is a good tool for prognostic indicator.

**KEYWORDS:** C-reactive protein, Modified Barthel Index Scoring, Acute Ischemic Stroke.

**INTRODUCTION:** Cerebrovascular diseases include some of the most common and devastating disorders like ischemic stroke, hemorrhagic stroke and cerebrovascular anomalies such as intracranial aneurysms and arterio-venous malformations (AVMs). Globally, approximately 15 million new acute stroke events occur every year. Two thirds of these individuals live in low-and middle income countries such as India.[1] About 80percent of all first ever-in-life time strokes are ischemic, 10percent are due to primary intracerebral hemorrhage, and in remainder there is uncertenity.[2] For India, community survey have shown a crude prevalence rate of 'hemiplegia' in the range of 200 per 100, 000 persons, nearly 1.5% of all urban hospital admissions, 4.5% of all medical admission and around 20% of neurological cases.[3] Despite a growing literature on the role of acute phase protein, particularly CRP and other inflammatory markers, risk stratification and predictors of outcome among patients with cardiovascular disease, very little is known about the role of the inflammatory markers in predicting outcome in patients with cerebrovascular disease.CRP fulfils most of the requirements of a new risk and prognostic predictor. The present study attempts to investigate prognostic importance of C-reactive protein in acute ischemic stroke. Mario de Napoli showed that after acute stroke an increase level of CRP measured at discharge predicts unfavorable outcome and recurrence.[4]

**AIMS AND OBJECTIVE:** To evaluate C-reactive protein as a prognostic tool in ischemic stroke by using Modified Barthel Index Scoring.

**INCLUSION CRITERIA:** Cases of acute ischemic stroke admitted to the department of medicine in Chigateri General Hospital and Bapuji Hospital attached to JJM Medical College, Davangere documented by CT brain as established ischemic stroke are only included.

**EXCLUSION CRITERIA:**

1. Patients admitted with CVA diagnosed as intracranial bleed are not taken into study.

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2. Patients admitted with features of neurological deficit or coma secondary to intracranial infections, subdural hematoma, intracranial tumour, meningitis are not considered into the study.
3. Patients admitted with neurological deficits due to old CVA following cerebral ischemia are also not considered.
4. Patient with neurological deficit due to transient ischemic attack are not included.

After admission a detailed history regarding the temporal profile of stroke including history of risk factors like hypertension, diabetes mellitus, smoking, history of coronary heart disease and RHD were obtained. Detailed neurological examination including fundoscopy and other systemic examination was carried out in all cases. The diagnosis of stroke was made on the basis of temporal profile of clinical symptoms, clinical examination and CT scan of brain. Patient's functional status scored according to Modified Barthel Score at the time of admission on 5$^{th}$ day and at the time of discharge. All the patients are followed up after 3months by personal interview, telephonic conversation or postal correspondence and functional status are again scored as per Modified Barthel score. The Barthel index is compared with initial CRP level and correlation noted.

| Items | Unable to perform task | Attempts task but unsafe | Moderate help required | Minimal help required | Fully independent |
|---|---|---|---|---|---|
| Personal hygiene | 0 | 1 | 3 | 4 | 5 |
| Bathing self | 0 | 1 | 3 | 4 | 5 |
| Feeding | 0 | 2 | 5 | 8 | 10 |
| Toilet | 0 | 2 | 5 | 8 | 10 |
| Stair climbing | 0 | 2 | 5 | 8 | 10 |
| Dressing | 0 | 2 | 5 | 8 | 10 |
| Bowel control | 0 | 2 | 5 | 8 | 10 |
| Ambulation (wheelchair) | 0 (0) | 3 (1) | 8 (3) | 12 (4) | 15 (5) |
| Chair-bed Transfers | 0 | 3 | 8 | 12 | 15 |

TABLE 1: Modified Barthel index scoring

Patients are divided into 3 groups according to Modified Barthel index.

**Barthel index:** < 41 severely disabled
41 to 60 moderately disabled
>60 mildly disabled**.**

Routine investigations were also done before enrolling the patient into study. CRP levels were estimated in every patient at the time of enrolment of patient in the study. The Barthel index is compared with initial CRP level and correlation noted.

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**ETHICS:** While performing this study on human subjects, the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (instrumental or regional) and with Helsinki Declaration of 1975 that was revised in 2000.

**STATISTICAL METHODS:** Chi-square and Fisher exact test have been used to test the significance of study parameters between Group A and Group B. Odds ratio has been used to find the strength of relationship between study parameters and the groups. Student's t test (independent samples) has been used to find the significance of investigations between the two groups.

1. Chi-Square Test

$\chi^2 = \frac{\sum(Oi - Ei)^2}{Ei}$, Where Oi is observed frequency and Ei is Expected frequency

2. Fisher Exact Test

| | Class1 | Class2 | Total |
|---|---|---|---|
| Sample1 | A | B | a+b |
| Sample2 | C | D | c+d |
| Total | a+c | b+d | n |

Fisher Exact Test statistic= $\sum p = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{n!} \frac{1}{\sum a!b!c!d!}$

3. Odds Ratio OR=ad/bc
4. Student t test (Independent)

**Objective:** To investigate the significance between the means of two populations.

$$t = \frac{(\bar{x}_1 - \bar{x}_2) - (\mu_1 - \mu_2)}{\sqrt{s^2(1/n1 + 1/n2)}}$$

$$\text{Where } s^2 = \frac{(n1-1)\sum_{i=1}^{n1}(x1 - \bar{x}1)^2 + (n2-1)\sum_{i-1}^{n2}(x2 - \bar{x}2)^2}{n1 + n2 - 2}$$

**STATISTICAL SOFTWARE:** The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

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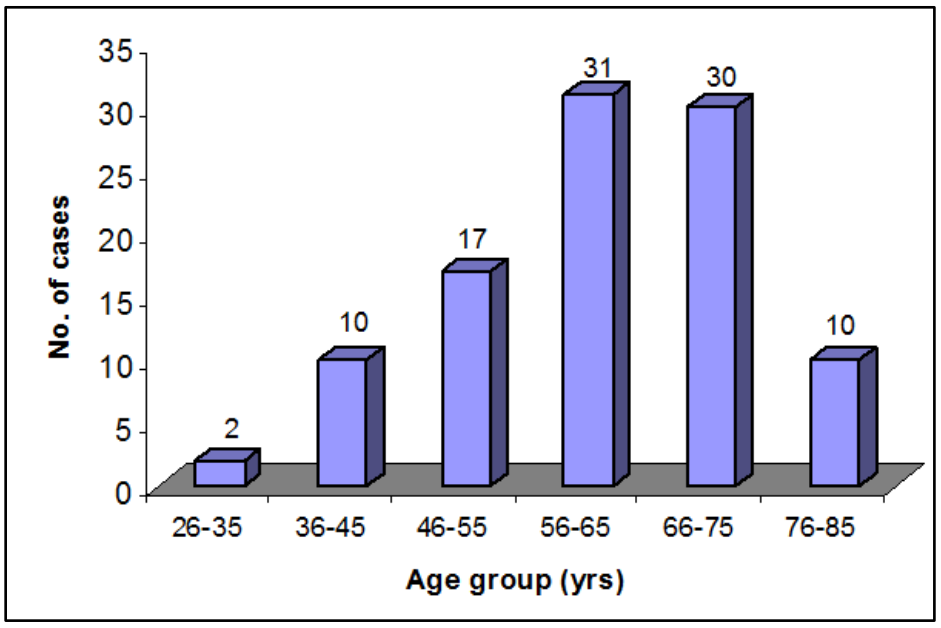
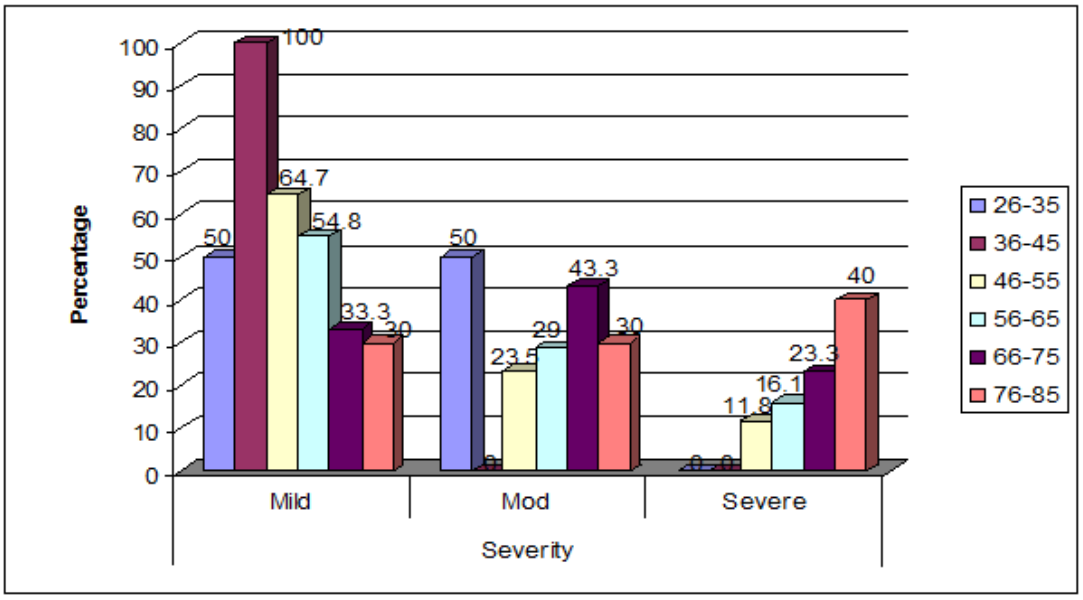
**RESULTS:**




**GRAPH 1: Age distribution**




**GRAPH 2: Barthel Index-age**

Chi-Square - 19.0 $p < 0.05$

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| Severity | Day 1 n (%) | Day 5 n (%) | On discharge n (%) | 3M n (%) |
|---|---|---|---|---|
| Mild | 52 | 80 | 83 | 84 |
| Moderate | 30 | 6 | 4 | 3 |
| Severe | 18 | 14 | 10 | 10 |
| Death | - | - | 3 | 3 |
| Total | 100 | 100 | 100 | 100 |

TABLE 2: Severity (based on Barthel index)

| Severity | Number of cases | CRP | |
|---|---|---|---|
| | | < 6 n (%) | > 6 n (%) |
| Mild | 52 | 52 (100) | - |
| Moderate | 30 | 29 (96.7) | 1 (3.3) |
| Severe | 18 | 5 (27.8) | 13 (72.2) |
| Total | 100 | 86 | 14 |

TABLE 3: Barthel index and CRP

$\chi^2 = 61.9$ $p < 0.05$, significant

**DISCUSSION:**

**Age:** In the present study, the age group analysis was between 26 to 85years. The peak incidence of CVA was between 56-75years. K.K. Sikka et al (1960, Kanpur) in their study of ischemic cerebrovascular disease (cerebral thrombosis) found, maximum number of cases fell in 5th to 6th decades with mean age 61.8 years, this study also confirms the same.[5]

**Sex:** In our study the sex ratio analysis is 3.5:1 with male predominance. This ratio resembles the epidemiological study done in Western European region, male stroke incidence was 33% higher and stroke prevalence was 41% higher than the female, with large variations between age bands and between population World wide, stroke is more common among men, but women are more severely ill.[6]

**Age and severity:** In this study maximum numbers of patients are in 5th and 6th decade of life. Also there is increasing trend of severity above 7th decade of life. The P-value is <0.05, showing a significant risk association. In Copenhangen stroke study reported that age independently influenced initial Barthel Index (BI) (–4 points per 10 years, P < 0.01) and discharge BI (–3 points per 10 years, p < 0.01). ADL improvement was influenced independently by age (–3 points per 10 years, p <0.01) whereas age had no influence on neurological improvement or on speed of recovery.[7]

In Rotterdam study they concluded that stroke incidence increases with age, also in the very old[8].Our study also had similar results.

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**Barthel index and CRP:** In this study, there were 52(100) mild cases on day 1 according to Barthel Index. Their CRP values at admission was <6 mg/dl. These patients have shown improvement in Barthel scores on day 5, at discharge and at 3 months.

There were 30 patients on day 1 with moderate disability. 29 (96.7) patients had CRP value <6 and one patient >1(3.3). Among these 30 patients, 29patients showed improvement in their Barthel scores by day 5, and flowingly. 18 patients on day one in the study group were severely disabled and 13(72.2) patients had CRP value >6 on day one. P values in this study of CRP is <0.05 $\chi^2$ = 61.9 showing a significant indicator of stroke outcome.

Similar results were observed by Kerstin Winbeck et al in his study of multiple logistic regression analysis identified. Barthel Index score at admission and CRP at 12 and 24hours after symptoms onset predicts an unfavorable outcome and is associated with an increased incidence of cerebrovascular and cardiovascular events.[9]

In a study conducted by Loewen and Anderson on predictors of stroke outcome, using modified motor assessment scale (motor status) and the Barthel index (functional outcome) they tested 50 stroke patients ≤ 3 days, 1 week and 1month after their stroke and at discharge from hospital. They found both measures reliable and valued. They suggested that these objective predictors of recovery be used as adjuncts in prioritizing and directing the rehabilitation management of patients with stroke.[10]

Panicker JN et al studied morbidity prediction in ischemic stroke. The functional status was analyzed using Barthel Index of Activities of Daily Living. Patients were grouped in 3 categories using Barthel index as mild, moderate and severe CRP, measured at admission. Follow up of the patients was achieved through telephone in most of the cases or postal correspondence. They concluded that CRP is an index of increased risk for cardiovascular disease and patients can be targeted with more aggressive therapy for plaque stabilization.[11]

The "Bergen stroke study" by Titto T idicula et al showed that high CRP was associated with poor short-term functional outcomes (BI <95) (p = 0.03). Hence CRP is an independent predictor of long-term mortality after ischemic stroke.[12]

In the study by Mario Di Napoli et al, the study of C-reactive protein in ischemic stroke; CRP at admission Hazard ratio (HR) 2.78, 95% CI, 1.45 to 5.33 (p = 0.0021) and discharge (HR 9.42, 95% CI 4.27 to 19.05 p <0.0001) were predictors of the combined end point of new vascular events or death at 1year. CRP at discharge is better related to later outcome and could be of greater utility for risk stratification predicts future cardiovascular events or death.[13]

Study by Gussekloo et al showed that CRP is a strong but non-specific risk factor of fatal stroke and the risk of death from stroke increased linearly up to 10folds in subject with highest levels of CRP at baseline (p <0.001) after adjusting for age, sex, smoking, medication, total cholesterol, diabetes and hypetension.[14]

**SUMMARY:** Main objective of this present study was to estimate C-reactive protein level as a marker of acute inflammation. In this study, patients with CRP <6 mg/dl suffered mild disease. They also showed good prognosis, their Barthel scores improved with follow up. Patients with CRP levels >6 mg/dl suffered severe disease and did not show any improvement in their Barthel scored. P value <0.05, significant, suggests inflammation following ischemic stroke. The association of CRP values at admission and its correlation with Barthel scores to assess the functional outcome of patient

following ischemic stroke, suggest CRP as a good prognostic tool. The rise in CRP following ischemic stroke suggest its role in inflammation.

**CONCLUSION:** Modified Barthel index is a good tool to assess the functional outcome of patients following ischemic stroke, in co-relation with CRP levels. Elevated CRP is highly sensitive, non specific and an independent risk factor for prediction of ischemic stroke

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