

## Original Research Article

# Reliability of C-reactive protein as a predictor of early neurological deficit in acute ischemic stroke: is it only to be blamed? a retrospective observational study

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## ABSTRACT

**Background:** Ischemic Stroke is a common cause of morbidity and mortality. Various parameters, both clinical and laboratory have been studied as markers of Early Neurological Deterioration (END) out of which CRP has been the most important. This retrospective study of ours is an attempt to study its influence on END by minimizing other variables as much as possible.

**Methods:** 50 patients were chosen retrospectively strictly according to laid down inclusion and exclusion criteria, their data recorded and analyzed with 17.0 SPSS software. Any p value <0.05 was taken as significant.

**Results:** Significantly raised CRP values were found in elderly patients (p=0.0001) and in males (p=0.003). Higher incidences of ENDs were also found in elderly patients (p=0.326) and males (p=0.846) and patients with raised CRP levels (p=0.057).

**Conclusions:** Higher Values of CRP are associated with increased frequency of ENDs. But in patients with multiple factors which can influence both CRP and END, CRP alone should not be thought of as the only culprit.

**Keywords:** C-reactive protein level, Early neurological deterioration, High sensitivity CRP, National institute of health stroke scale

## INTRODUCTION

Ischemic stroke, characterized by the sudden loss of blood circulation to an area of the brain is among the major causes of morbidity and mortality.<sup>1-3</sup> Many factors help us predict the both the short and long term outcome in acute ischemic stroke patients one of them being the CRP (C- Reactive Protein) which has been found to have significant impact both in terms of Early Neurological Deterioration (END) and early and late mortality.<sup>4,5</sup>

But we wished to study effect of CRP on END (Early Neurological Deterioration). So, the aim of this study was to see the implications predominantly of CRP on END.

Aims and objectives were to correlate retrospectively CRP levels taken during admission within 24 hours of onset of acute ischemic stroke with END (Early Neurological Deterioration) by calculating the NIHSS both at the time of admission and at 72 hours post admission.

## METHODS

Neurological assessment and definition of END-Stroke severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS).<sup>6</sup> In this study, END was defined as an increment of at least one point in motor power or total NIHSS score deterioration  $\geq 2$  points within the first 72 hours after admission.<sup>7-12</sup> Trained

physicians and intensivists assessed the neurological status of the patients on a daily basis. CRP values (Normal <5 mg/L) checked during admission were recorded along with daily NIHSS and later correlated.

**Study design**

A total of 50 patients fulfilling the criteria were taken up in this single centre, retrospective observational study

Study area was Hospital Stroke Unit and ICU. Study duration was 3 Months From- November 2019 to January 2020.

**Inclusion criteria**

- 18 years of age or older.
- Acute ischemic stroke diagnosed via computed tomography and/or magnetic resonance imaging.
- Did not undergo any therapeutic intervention like thrombolysis or mechanical thrombectomy.
- First-ever ischemic stroke presenting within 24 hours of admission.
- Presenting NIHSS 9-15.

**Exclusion criteria**

- Diagnosis of transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage, brain tumors or unspecified stroke.
- History of more serious medical disease other than ischemic stroke, such as cancer, renal failure, and Parkinson’s disease.
- The interference of CRP level by any disorder, including asthma, arthritis, liver disease, bronchitis, sinus infection, aspiration pneumonia or urinary tract infection on acute stroke phase.
- Death during the hospital admission.
- Incomplete clinical data.

**Statistical methods**

Data Analysis was done with the help of 17.0 SPSS Statistical Software. p value less than 0.05 was taken as significant.

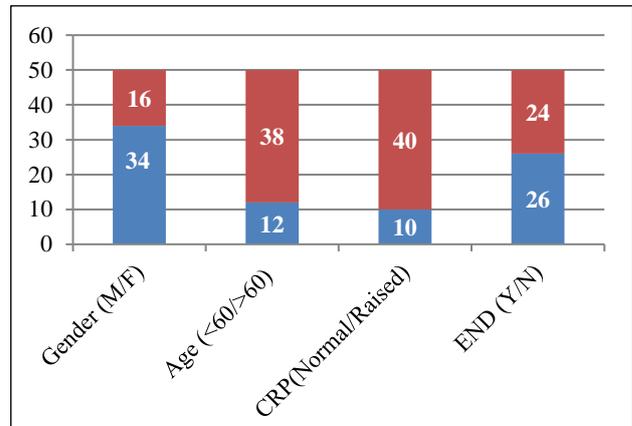
**RESULTS**

Distribution of various parameters like number of patients enrolled, age, gender, CRP values and Incidence of Early Neurological deficits (END) against each other has been shown in the tabular form and bar charts along with p value (Significant <0.05).

Distribution of various qualitative parameters with respect to total number of patients (Figure 1).

Out of 50 patients, 34 were male and 16 were female with significant p value as stroke is usually found more in

males than females. Also, stroke being disease of the elderly, more males in the senior citizen group were affected whereas this number was similar for females. (Table 1).



**Figure 1: Distribution of gender, age, CRP level and frequency of end.**

**Table 1: Gender v/s Age.**

Age (years)	Male (34)	Female (16)	p value
<60	4	8	0.003
> 60	30	8	

**Table 2: Gender v/s CRP Distribution.**

CRP (mg/L)	Male (34)	Female (16)	p value
Normal (<5)	3	7	0.003
Raised (>5)	31	9	

In this study, both gender showed rise in CRP but the number of patients’ showing rise were found to be more in males which was significant. In females there were near equal patients both with normal and raised CRP thus implying that males show more significant rise in CRP. (Table 2).

**Table 3: Gender v/s END (Early Neurological Deficit).**

END	Male (n=34)	Female (n=16)	p value
Yes	18	8	0.846
No	16	8	

Early Neurological Deficit (END) was found to be more in males as compared to females which was more than double. But if compared within the gender there is almost no difference at all as similar number of males and females show and did not show END thus giving an insignificant p value (Table 3).

Overall 80% (40/50) of patients showed raised CRP out of which nearly 90% (35/40) were present in age group >60 which was significant thus showing that raised CRP

values are found more in elderly strokes. 20% (10/50) of patients didn't show any rise in CRP in stroke (Table 4).

**Table 4: Age v/s CRP.**

Age (Years)	Normal CRP	Raised CRP	p value
<60	7	5	0.0001
>60	3	35	

**Table 5: Age v/s END.**

Age (Years)	N=50	END (n=26)	p value
<60	12	9	0.326
>60	38	17	

From the previous table, we saw that high CRP values were found in elderly patients. A little more than half of the patients (26/50) showed END out of which almost double the number were present in elderly age group. In age group <60, around 75% (9/12) showed END and age group >60, nearly half of them (17/38) showed END, which was insignificant overall (Table 5).

**Table 6: CRP v/s END.**

CRP Level	END (n=26)	p value
Normal (n=10)	1	0.057
Raised (n=40)	25	

Comparing only patients showing END (Early Neurological Deficit) with CRP levels, it was found that almost all the patients (25/26) had raised CRP. If seen only among patients who had raised CRP i.e. 80 % (40/50), 25 out of 40 (62.5%) showed END giving p value of 0.057 (Table 6).

**Table 7: CRP v/s Total N v/s END.**

CRP Level (mg/l)	N = 50	END	p value
<5	10	1	0.144
5-10	12	9	
>10	28	16	

Authors also had END studied according to CRP severity levels distributed into 3 categories as shown above. It was seen that higher CRP values (>10) were seen in more than half of the total number of patients (28/50) out of which more than half of them (16/28) showed END. Similar was the case in high CRP group (5-10) in which 75% (9/12) showed END whereas only 10% patients (1/10) showed END in normal CRP group. The overall p value was insignificant (Table 7).

## DISCUSSION

In this retrospective study of ours, the most important finding was that END (Early Neurological Deficit) occurs significantly which was found to the tune of around 50 % which has also been seen in previous studies.<sup>13-15</sup> Large

NIHSS scores along with other systemic factors like Diabetes Mellitus, hypertension during presentation have larger chances of END and also patients with greater ENDS were found to have larger NIHSS scores at the onset, retrospectively.<sup>16-18</sup> These factors altogether are responsible for END and early mortality in acute stroke. Therefore, a moderate value of NIHSS of 9-15 was chosen so that at least one of the major determinants of END was removed and better effect of CRP on END could be studied. Similarly an increment of 2 NIHSS points was chosen as it is a sensitive indicator.<sup>19</sup> Choosing 4 or more point increment or 1 point increment could result in false negative ENDS or false positive ENDS, respectively as most of the patients show some degree of minor deterioration when they land in the hospital within 24 hours of inciting event which was one of the inclusion criteria in this study. Also, all patients may not show that major neurological deterioration amounting to 4-point increment in NIHSS scale thus making them more vulnerable to getting neglected.

This study found direct correlation of CRP with END. CRP level is an important prognostic indicator for ischemic stroke.<sup>20-23</sup> Similar to this study, Seo et al, found that CRP level at admission was significantly associated with END in acute ischemic stroke.<sup>23</sup> Moon AR et al, found the association of hs (high sensitivity) CRP and Mean Platelet Volume (MPV) as one of the predictors of long term clinical outcomes in post Percutaneous Transluminal Coronary Angioplasty (PTCA) patients.<sup>24</sup> Jimenez MC et al, also found significant association between hs CRP and stroke severity in hypertensive patients.<sup>25</sup> addition, it can also be used for the prediction of future development of atherosclerotic diseases including stroke and cardiovascular disease.<sup>23-25</sup> But wide variation in the results between this study and other studies could also be due to different definitions of END, time scale of assessment of acute stroke and varied process of selection of patients.

Though, all these studies indicate an association between serum CRP and END and future stroke suggesting a link, but the other side of the coin should also be seen. Several common clinical conditions also confound the results intended to be studied. Heidari B et al, found that CRP and ESR are raised in patients with Rheumatoid Arthritis and Chronic Kidney Disease on Chronic Hemodialysis as these are chronic inflammatory states, and thus, in such patients presenting with stroke, CRP obviously would lose its prognostic and predictive value for END, morbidity and mortality.<sup>26,27</sup> Hajian-Tilaki K et al, found that in urban population, the prevalence of various parameters such as hypertension, diabetes, hyperlipidemia and central obesity, thus contributing to metabolic syndrome is quite high and these patients usually have raised CRP due to baseline high inflammatory state which can also cause biased results.<sup>28</sup> Firouzjahi A et al, also found raised CRP values in COPD (Chronic Obstructive Pulmonary Diseases) as compared to that in healthy controls.<sup>29</sup> These factors may

increase the risk of stroke and affect the outcome regardless of inflammatory state. Apart from this, many other chronic clinical diseases that are associated with low grade systemic inflammation usually coexist in elderly subjects. In addition, asymptomatic latent and undiagnosed local or systemic infection may be a cause of increased serum CRP and confound the results. This could also be one of the reasons for having significantly raised CRP levels in patients and thus increased incidences of ENDS. Therefore, we tried to remove all these variables as much as possible by strictly laying down the exclusion criteria.

This study also has several limitations. First, this is a retrospective study. Unknown but potentially important factors might have confounded these results. Retrospective identification of patients might cause a selection bias. Secondly, stricter inclusion and exclusion criteria need to be followed as there are many factors which can influence both the CRP and incidence of END simultaneously as discussed. So, all these factors should be removed as much as possible which we tried in every possible way. Thirdly, long term follow up couldn't be done to understand the late effects of raised CRP. Fourthly, sample size should be larger to better ascertain the effects of CRP on END.

## CONCLUSION

Higher Values of CRP are definitely associated with increased frequency of ENDS. But in patients with multiple factors which can influence both CRP & END, CRP alone should not be thought of as the only culprit. Therefore, further stricter studies need to be done which should include patients with as much minimal influencers of END as possible.

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