Original Article

Association of C - reactive protein with Severity of Acute Ischemic Stroke in a Tertiary Hospital, Bangladesh

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Background : The aim of the study to assess the association of C-reactive protein (CRP) with severity of acute ischemic stroke (AIS). Materials and Methods: This study was a hospital based cross-sectional descriptive study and conducted in the department of Neurology& Medicine in Sir Salimullah Medical College & Mitford Hospital, Dhaka during January 2018 to December 2018. Clinically and radiologically diagnosed 100 admitted AIS patients were assessed and interviewed according to prefix selection criteria. Serum CRP assay was done within 24 hour of hospitalization. The severity of stroke was evaluated by using National Institutes of Health Stroke Scale (NIHSS). Interpretation of NIHSS were correlates with CRP. Results: Out of 100 patients, Mean age of group A and group B were respectively 61.18±10.48 years and 60.40 ± 10.58 years with no significant difference (p>0.05). Distribution of gender, occupation, economic status and risk factors were similar across the group (p>0.05). Mean CRP level of group A and group B were 14.07 ± 4.69 and 3.67 ± 1.29 mg/dl, respectively. Severity of stroke which was measured by NIHSS score were significantly higher in CRP raised group than others (p<0.05). Similarly, lower GCS score were observed in group A patients than group B ((p<0.05). Moreover, CRP positive stroke patients had significantly higher number of deaths at day 7 follow up after stroke than CRP negative patients (Group A-14% *versus* group B-2%, p <0.05). Conclusion : CRP is elevated in the acute phase of AIS and elevated CRP level is significantly associated with severity of AIS patients.

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Key words **: C-reactive protein, Stroke, Atherosclerosis.**

Stroke is a worldwide health problem. It is a major cause of morbidity, mortality and disability in developed as well as developing countries. Ischemic strokes, which account for 80% of strokes, are caused by the obstruction or clogging of the major arteries in the cerebral circulation. Cerebral atherosclerosis, a major cause of ischemic stroke, can be divided into extracranial atherosclerosis (ECAS) and intracranial atherosclerosis (ICAS), and anterior and posterior circulation atherosclerosis[1]. Inflammation plays a major role in all phases of pathophysiology in atherosclerosis[2,3]. Therefore, it might be hypothesized that a more severe stroke is associated with greater inflammatory response. High-sensitivity C-reactive protein (hsCRP) is a sensitive marker of inflammation and tissue injury. Stable plaques are characterized by a chronic inflammatory infiltrate, whereas vulnerable and ruptured plaques are characterized by an "active"

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Editor's Comment :

- **High CRP is associated with a greater risk for ischemic stroke or Transient Ischaemic Attack (TIA).**
- **C-reactive protein is elevated in the acute phase of acute ischaemic stroke**
- **Elevated CRP level is significantly associated with severity of AIS patients.**
- **CRP positive stroke patients had significantly higher number of deaths at day 7 follow up after stroke than CRP negative patients.**

inflammation involved in the thinning of the fibrous cap, predisposing the plaque to rupture[4]. Although a single vulnerable atherosclerotic plaque rupture may cause the event, there are many other types of plaques, several of which are vulnerable. The existence of multiple types of vulnerable plaques suggests that atherosclerosis is a diffuse inflammatory process[2]. CRP is a phylogenetically highly conserved plasma protein, with homolog in vertebrates and many invertebrates, and it participates in the systemic response to inflammation[5]. The role of CRP as a marker during and after stroke is less extensively studied in comparison to coronary artery disease. The Rotterdam study shows that although high CRP is associated with the risk for future stroke, it is not useful for individual stroke prediction[6]. On the other hand, the Framingham study shows that high CRP is associated with a greater risk for ischemic stroke or TIA[5]. Acute ischemic stroke may trigger an inflammatory response that leads to increased levels of C-reactive protein (CRP). High levels of CRP may be associated with poor outcome because they reflect either an inflammatory reaction or tissue damage[7]. Several studies have found an association between increased CRP levels and clinical outcome in the ischemic stroke. The results of previous studies that have aimed to assess the prognostic value of CRP in the very early phase of stroke are ambiguous. Two prospective studies did not observe a relation between CRP levels obtained within 6 or 12 hour after symptom onset and death or dependency at follow-up[8,9]. Increased CRP levels following ischemic stroke may also reflect concurrent infections. Secondary infections are common in the first week of stroke and are associated with poor outcome but they usually occur more than 12 h after stroke onset[10,11]. In another study, only two clinically overt infections were reported within 24 hour after stroke onset. In addition, only few studies have analyzed the relationship between elevated admission CRP levels and stroke severity[12]. The aim of our study was therefore to determine the prognostic value of CRP measured in the very early phase of ischemic stroke for poor functional outcome in patients with acute ischemic stroke.

Materials and Methods

This study was a hospital based cross-sectional descriptive study and conducted in the department of Neurology & Medicine in Sir Salimullah Medical College & Mitford Hospital, Dhaka during January 2018 to December 2018 for duration of one year. Clinically and radiologically diagnosed total (admitted) Acute Ischemic Stroke (AIS) patients within 24 hours were assessed and interviewed according to selection criteria. Patients who were admitted more than 24 hours after the onset of symptoms were excluded. Patients who were found with stroke or awoke with stroke were included if it was known that the patient had been normal. A questionnaire was made and pre-tested for data collection. A detailed clinical history including age, sex, socioeconomic status, occupation, duration of symptoms, risk factors, neurological problems were elicited and recorded in all cases.

At admission, plain CT scan of the head was done to rule out haemorrhage. Serum CRP assay was done within 24 h of hospitalization and analyzed by Tina-quant latex method using Modular P (Roche Diagnostics). The NIH stroke score (NIHSS) was assessed by a neurologist at the time of admission. The NIHSS was categorized as 0, 1–4, 5– 15, 16-20 & 21-42 and the NIHSS score were correlates with CRP. For analysis of these subjects were stratified into two groups: group A- AIS with raised CRP and Group B consist of AIS without raised CRP. Both groups of the patients were observed in similar manner and outcome assessment was also done in according to the protocol. Total follow up was done up to 7 days from admission. Severity was evaluated by using National Institutes of Health Stroke Scale (NIHSS).

Their informed written consent was taken in a consent form before collecting data. Proper permission was taken from the concerned departments and local ethical committee.

Exploratory data analysis were carried out to describe the study population where categorical variables were summarized using frequency tables while continuous variables were summarized using measures of central tendency and dispersion such as mean, median, percentiles , standard deviation and Chi-square test. All statistical analysis were performed using SPSS 23.0 for Windows (SPSS Inc, Chicago, Illinois, USA) level of significance was set at .05 and p-value <0.05 was considered significant

Operational Definitions :

Stroke[13] : Stroke is defined by the World Health Organization as a clinical syndrome consisting of 'rapidly developing clinical signs of focal (aphasia/ dysphasia/ dysarthria/ dysphasia/any cranial nerve palsy/weakness) (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin. In the spring of 2013, the AHA/ASA published an expert consensus document with a new definition of stroke. The major fundamental change compared with older definitions is that the new broader definition of stroke includes any objective evidence of

permanent brain, spinal cord or retinal cell death due to a vascular cause.

Acute Stroke[14,15]: The acute phase of stroke includes 24 hours to weeks of post acute period. This time is to the key interventions involved in the assessment, treatment or management, and early recovery in the first days after stroke onset. This may represent initial diagnostic procedures undertaken to identify the nature and mechanism of stroke, inter-professional care on designated care units to prevent further complications and promote early recovery. At the "acute" stage, the following neurologic and medical complications have been recorded: stroke progression; seizures; increased intracranial pressure; fever; urinary and chest infections; severe hypertension; congestive heart failure; falls; and deep vein thrombosis and pulmonary embolism. The presence of these complications is associated with deterioration and higher mortality. Previous studies focused on the first week after stroke. Broadly speaking it is refers to the first days to weeks of inpatient treatment with stroke.

National Institutes of Health Stroke Scale (NIHSS)[16]:

	Category	Score
1A	Level of consciousness	0-3
1B	Level of consciousness questions	0-2
1C	Level of consciousness commands	0-2
2	Best Gaze	0-2
3	Visual fields	0-3
4	Facial palsy(paresis)	0-3
5A	Motor-left arm	0-4, UN
5B	Motor-right arm	0-4, UN
6A	Motor-left leg	0-4, UN
6B	Motor-right leg	0-4, UN
7	Limb ataxia	0-2, UN
8	Sensory	0-2
9	Best language	0-3
10	Dysarthria(articulation of words)	0-2, UN
11	Extinction	0-2

Severity of Stroke[17]: The National Institutes of Health Stroke Scale (NIHSS) is considered as the Gold Standard systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

Score	Stroke severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

Results and Observations

100 patients with AIS were included in the study 64(64.00%) males and 36(36%) females were included in the study, female-to-male ratio of 1:1.8.

In Table 1 the distribution was same in both group A and group B. The difference in distribution was not statistically significant (p>0.05).

This Table 2 shows that the mean age of presentation was 60.79 ± 10.49 years. Mean age of group A and group B were respectively 61.18±10.48 years and 60.40±10.58 years. There was no statistically significant difference between those two groups (p>0.05). Majority of the patients were aged between 61-70 years in both groups (44%).

This Table 3 shows among all patients 58% had hypertension, 24% had DM, 10% had dyslipidemia, 11% had obesity and 24% had smoking habit. The difference in distribution of risk factors between two groups was not statistically significant (p>0.05).

Table 1 — *Distribution of the study subjects according to sex (n=100)*

Sex	Group A (CRP positive) (n=50)		Group B (CRP negative) (n=50)		Total (n=100)		P value
	n	%	n	%	n	%	
Male	32	64	32	64	64	64	1.00NS
Female	18	36	18	36	36	36	

NS = Not significant ; P-value reached from χ^2 test

Table 2 — *Distribution of the study subjects according to age (n=100)*

Age in years	Group A (CRP positive) (n=50)		Group B (CRP negative) (n=50)		Total (n=100)		P value
	n	%	n	%	n	%	
41 – 50	10	20	12	24	22	22	0.445NS
51 – 60	12	24	14	28	26	26	
61 – 70	22	44	22	44	44	44	
71 – 80	6	12	2	4	8	8	
Mean ± SD	61.18±10.48		60.40±10.58		60.79±10.49		0.712NS
Range	(42-80)		(41-75)		(41-80)		

NS = Not significant ; P-value reached from χ^2 test

Table 3 — *Distribution of the study subjects according to Risk factors (N=100)*

Risk factors	Group A (CRP positive) (n=50)		Group B (CRP negative) (n=50)		Total (n=100)		P value
	n	%	n	%	n	%	
Hypertension	30	60	28	56	58	58	0.685NS
DM	16	32	8	16	24	24	0.061NS
Dyslipidaemia	7	14	3	6	10	10	0.182NS
Obesity	6	12	5	10	11	11	0.749NS
Smoking	11	22	13	26	24	24	0.640NS

NS = Not significant ; P-value reached from χ^2 test

Table 4 — *CRP level of the study subjects (N=100)*

CRP level	Group A (CRP positive) (n=50)	Group B (CRP negative) (n=50)	Total (n=100)
Mean ± SD	14.07 ± 4.69	3.67 ± 1.29	8.87 ± 6.25
Median	13.33	3.75	6.25
Min-Max	6.80 – 25.31	1.27 – 5.70	1.27 – 25.31

In Table 4 shows mean CRP level of group A patients was 14.07±4.69 and of group B was 3.67 ± 1.29 and of all was 8.87 ± 6.25. Less than 6 mg/dl CRP was considered negative CRP.

In Table 5 shows among patients who were CRP positive (group A) 26% had NIHSS between 21 – 42, 30% had 16 – 20, 34% had 5 -15 and 10% had 1- 4. While among those who had CRP in negligible amount (group B) 10% had NIHSS 21 – 42, 18% had 16 – 20, 42% had 5 – 15 and 30% had 1 – 4. The difference in distribution of NIHSS score between two groups was statistically significant (p<0.05).

In Table 6 shows CRP positive stroke patients had significantly higher number of deaths at day 7 after stroke than CRP negative patients (14% vs 2% deaths among group A and group B respectively, p <0.05).

In Table 7 shows Descriptive analysis of CRP values in relation to admission NIHSS score and outcome of patients shows that mean CRP values increased with increasing NIHSS score and CRP values was significantly higher among patients who were dead than those who were alive after stroke.

Table 5 — *NIHSS score of the study subjects in relation to CRP (N=100)*

Age in years	Group A (CRP positive) (n=50)		Group B (CRP negative) (n=50)		Total (n=100)		P value
	n	%	n	%	n	%	
1 – 4	5	10	15	30	20	20	0.015S
5 – 15	17	34	21	42	38	38	
16 – 20	15	30	9	18	24	24	
21 – 42	13	26	5	10	18	18	

NS = Not significant ; P-value reached from χ^2 test

In Table 8 shows univariate regression analysis of different risk factors for dying at follow-up after stroke was done. Patients with age >60 years, being male, CRP positive, HTN, DM, dyslipidaemia, smoking and obesity had higher odds of dying at 7 days after stroke. But none of the factors were significant at 0.05 level. At <0.1 level age > 60 years, CRP positivity and DM was found to be significant predictor of death at 7 days in stroke patients.

In Table 9 shows multivariate regression analysis of different risk factors for dying at follow-up after stroke was done. Only those risk factors found significant (at <0.1 level) in univariate analysis was included. When adjusted for other factors, patients with CRP positivity was found to have higher odds of dying at 7 days after stroke (OR 6.99; 95%CI 0.81- 60.18, p=0.076). It was

Table 6 — *Outcome of study subjects at day 7 after stroke in relation to CRP (N=100)*

Age in years	Group A (CRP positive) (n=50)		Group B (CRP negative) (n=50)		Total (n=100)		P value
	n	%	n	%	n	%	
Alive	43	86	49	98	92	92	0.027S
Dead	7	14	1	2	8	8	

NS = Not significant ; P-value reached from χ^2 test

Table 7 — *CRP level in relation to admission NIHSS score and outcome of patients (N=100)*

Outcome	NIHSS score		CRP value (mean ± SD)	
	Category	n	In relation to NIHSS score	In relation to outcome
Alive	1 – 4	20	5.02±2.66	7.87±5.16
	5 – 15	38	7.25±4.94	
	16 – 20	23	9.22±4.71	
	21- 42	11	12.36±6.77	
Dead	16 – 20	1	19.61	20.37±6.43
	21 – 42	7	20.48±6.94	
P value				<0.001

P value determined by Student's t test

Table 8 — *Univariate analysis risk factors for dying at 7 days after stroke (n=100)*

Variables	Odds ratio	95% CI	p-value
Age >60 years	7.31	0.86 – 61.81	0.068*
Sex (Male)	4.29	0.51 – 36.42	0.181
CRP positive	7.97	0.05- 7.97	0.057*
Hypertension	1.22	0.27 – 5.44	0.788
DM	3.60	0.82 – 15.68	0.088*
Dyslipidaemia	1.31	0.14 – 11.95	0.806
Smoking	2.02	0.44 – 9.20	0.945
Obesity	3.07	0.53 – 17.54	0.206

*p value significant at <0.1 level

Table 9 — *Multivariate analysis of risk factors for dying at 7 days after stroke (n=100)*

Variables	Odds ratio	95% CI	p-value
Age >60 years	1.31	0.27 – 6.25	0.735
CRP positive	6.99	0.81 – 60.18	0.076*
DM	2.84	0.61 – 13.15	0.182

* p value significant at <0.1 level

significant at <0.1 level.

Discussion

Total 100 patients of acute ischaemic stroke were studied. Among them 50 patients were CRP positive and another 50 patients had negligible CRP. The mean age of all patients was 60.79±10.49 years. This is nearly similar to the finding of a stroke registry conducted by Bhowmik and colleagues (2016)[18]. They included 679 patients of ischaemic stroke and found a mean age of 60.6 years. In the present study majority patients were aged between 61 to 70 years (44%). In comparison Siddiqui *et al* (2013) studied all types of stroke and found majority patients aged between 51 to 60 years (29%) followed by 22% aged between 61 – 70 years19.The difference could be attributed to the difference in study population. But, overall 69% were aged =50 years in their study which is similar to the findings (78% aged =50 years) of this study. The majority patients were male (66%) and rest (34%) were female with similar sex distribution across groups in this study. This is also similar to the findings of Bhowmik *et al* (2016) who reported 67.7% patients being male in their study[18]. Another study conducted by Islam *et al* (2013) reported a male-female ratio of 3.44:2.41 among stroke patients[20]. Mohammad *et al* (2014) noted in review that one of the risk factor of stroke is male sex[21]. Therefore, findings of the present study are consistent with previous findings. The most common risk factor found in this study was HTN (58%) followed in decreasing order by DM (24%), smoking habit (24%), obesity (11%) and dyslipidaemia (10%) 20. Islam *et al* (2013) found majority 86.3% cases of hypertension, 55% cases of smoking, 11.3% cases of diabetes among ischemic stroke cases[20]. Mohammad *et al* (2014) found that hypertension was the most common modifiable risk factor found in stroke patients (57.6%) followed by smoking (44.6%), tobacco use (24.3%), Oral Contraceptive Pill (OCP) use in female (40% of female stroke), diabetes (23%), ischemic heart disease (17.1%), obesity (10.6%) and dyslipidaemia (5.3%) [21]. Sharmin *et al* found 46% diabetic patients among their study population[22]. Siddiqui *et al* (2013) found that about 77% of patient had history of hypertension, 22% diabetes mellitus, 20% dyslipidaemia, 13% previous history of stroke and 27% ischaemic heart disease[19]. Badiuzzaman *et al* (2009) fond 58.62% patients had hypertension with other risk factors in their study and this was followed by risk factors associated with smoker (53.9%), lipid disorder (48.01%), heart diseases (25.75%), diabetes mellitus (20.01%) and previous history of stroke (10.61%)[23]. All the above comparison implies that HTN was the most common risk factor with ischemic stroke. Among others, diabetes and dyslipidaemia are also common.

In this study, CRP positivity was found to be significantly associated with poor outcome in follow-up at 7 days ($p<0.05$). CRP positive stroke patients had significantly higher number of deaths at day 7 after stroke than CRP negative patients (14% vs 2% deaths among group A and group B respectively, $p <0.05$). Similar result was encountered by Dewan and Rana (2011) in their study 3. In their study total 13 out of 100 stroke patients died. Among them 12 (92.3%) were CRP positive and 1 (7.7%) were CRP negative and the difference was statistically significant.

Univariate analysis showed that CRP positivity is associated with higher odds of dying at 7.97 (95% CI 0.05-7.97; p value =0.057). When adjusted for other significant (at <0.1 level) risk factors of stroke including age >60 years, and DM the OR of dying for CRP positive ischemic stroke remains similar OR 6.99 (95%CI 0.81-60.18, p=0.076), in which CRP positivity at 24 hours after admission in ischemic stroke patients is an important prognostic factor of death at 7 days after discharge from hospital. Dewan and Rana (2011) followed up patients for 18 months and found that an increasing CRP values at discharge predicted adverse prognosis and had strongest association with outcome at one year in a multivariate model 3. Di Napoli *et al* (2001) followed up 193 ischemic stroke patients for 1-year. They found that CRP at hospital discharge was the strongest independent marker of adverse outcome (HR 7.42, 95% CI 2.75 to 20.03; P=0.0001) 24.In spite of small number of cases studied within 7 days, findings of this study supported the previous observations that an elevated CRP reflects the severity and the extent of brain infarct and is related to early mortalities[24-26].

Conclusion :

In our present study, mean CRP levels were significantly higher in patients with ischemic stroke when compared to controls. This study confirms that C-reactive protein is elevated in the acute phase of ischaemic stroke and could present a prognostic marker.

Limitations :

This study has small sample size and study populations were confined to only one tertiary care hospital and the long term follow up were not assessed.

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Conflict of interest : None declared

Recommendation: Further population based study is necessary to infer the findings over the general population.

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