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Original Research Article

ROLE OF C REACTIVE PROTEIN AS PREDICTOR OF EARLY MORTALITY IN ISCHEMIC STROKE

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ABSTRACT

Background: A stroke or cerebrovascular accident is defined as an abrupt onset of neurological deficit that is attributable to a focal vascular cause. Prevalence of stroke is increasing among developing countries. C Reactive Protein (CRP) is a pentameric protein which may be used as a prognostic marker in ischemic stroke. This study was done to determine the predictive role of CRP in early mortality in acute ischemic stroke and the relation between CRP and National Institutes of Health Stroke Scale (NIHSS) score in ischemic stroke.

Materials and Methods: This was a prospective observational done in 50 acute ischemic stroke patients admitted in medicine wards of a government medical college in Kerala from December 2020 November 2021(12 months). Information was collected using structured proforma and NIHSS score. Data collected were analysed using the SPSS software.

Results: Among the 50 ischemic stroke patients, majority were found to be of age group between 51 – 70 years (72%) and 46.0% were females and 54% were males. There was significant relation between CRP and type of stroke. The median NIHSS score of alive patients(n=44) was 10 and expired patients(n=6) was 20. The NIHSS score > 15 in 83% patients who died. There was significant relation between CRP and stroke severity (NIHSS score) as p value <0.001. High NIHSS score patients had high CRP. All 8 patients who had CRP >24 had NIHSS score >15. Mean CRP of expired patients was 26.3±3.8 and alive patients was 6.6±6.9. Cut off point for predicting mortality in this study for CRP was 18 with 100% sensitivity and 93.18 % specificity and cut off point for NIHSS score was 13 with 83.33% sensitivity and 90.91% specificity.

Conclusion: There is significant relation between CRP and stroke severity (NIHSS score). Both CRP and NIHSS score are good predictors of early mortality in acute ischemic stroke.

Keywords: C Reactive Protein, NIHSS score, Acute Ischemic Stroke, Predictor.

INTRODUCTION

A stroke or cerebrovascular accident is defined as an abrupt onset of neurological deficit that is attributable to a focal vascular cause.[1] 85% of stroke occurs due to ischemia when there is cessation of blood flow for more than a few minutes. Stroke is the second most leading cause of death in all countries except low-income countries where it ranks fifth. Inflammation plays a key role in pathogenesis of cerebrovascular disease via mechanisms including development of atherosclerosis, plaque instability, and triggering of plaque rupture.[2] C Reactive Protein (CRP) is an acute-phase reactant protein that has rapid induction with long half-life (19 hours) and lack of alteration during day and night which makes it an important factor for evaluation in inflammatory and infectious diseases.[3] Increases in CRP may reflect systemic inflammatory response following stroke, tissue damage and its extent, or concurrent infections. There are studies proving that CRP can be used as a prognostic marker in ischemic stroke. National Institutes of Health Stroke Scale (NIHSS) is the most widely used deficit rating scale in modern neurology which can be useful as a worthful predictor of stroke

outcome.[4,5] The NIHSS score strongly predicts the likelihood of a patient's recovery after stroke. A score of ≥16 forecasts a high probability of death or severe disability whereas a score of ≤ 6 forecasts a good recovery.[6] It has been found that deceased patients have higher levels of CRP and NIHSS on admission.4 Early identification of patients with greater chance of early mortality helps in providing better care for this patients. This study was done to determine the predictive role of CRP in early mortality in acute ischemic stroke and to assess the relation between CRP and NIHSS score in ischemic stroke.

MATERIALS AND METHODS

This was a prospective observational study done for a period of 12 months from December 2020-November 2021 in the inpatients admitted with acute ischemic stroke of Department of Medicine of a Government Medical College in Central Kerala after getting clearance from the Institutional Review Board (IRB 29/2020 dated 15/09/2020). According to a study Sharma S et al the prevalence of normal serum C – reactive protein in ischemic stroke was 18 %, so a sample size of 44 was calculated.6 Inclusion criteria was any patient >18 years with first episode of ischemic stroke with neurological signs and confirmed by CT brain or MRI and focal neurological deficits not exceeding 72 hours. Those with hemorrhagic brain stroke, impaired renal function, elevated Erythrocyte Sedimentation rate, severe sepsis, peritonitis, pancreatitis and other systemic inflammatory conditions and ischemic stroke patients who underwent thrombolysis were excluded from the study. All patients included in the study were examined on the day of admission and NIHSS score and admission time CRP values were entered in the proforma. Patients were followed up for 7 days to determine the outcome -whether alive or expired. Data were entered in Microsoft excel and analysed using IBM SPSS version 24 software. Association between categorical variables analysed by Fischers exact test. Comparison of quantitative variables between 2 groups was analysed by unpaired t test. Comparison of continuous variables among more than 2 group was analysed by ANOVA. The level of statistical significance will be p value less than 0.05.

RESULTS

We included 50 patients with acute ischemic stroke in this study and majority were in the age group 51-70(n=36, 72%) followed by equal numbers(n=7, 14%) in the 31-50 and >71 years age groups. There were 27 (54%) males as compared to 23(46%) females. 40(80%) of the patients in the study population had small vessel disease, 8(16 %) had large artery stroke and 2 (4%) had cardioembolic stroke. The outcome at the end of 7th day was that 44(88%) survived and 6(12%) died. Table 1 summarizes the comorbidies of the patients enrolled in the study. As shown in table 1 33(66%) had hypertension of which 19(38%) had a BP 140-160/90-100 mm Hg and 14(28%) had >160/>100 mm Hg at the time of admission. The other important comorbidies were diabetes mellitus and dyslipidemia.

Table 1: Profile of patients admitted with acute ischemic stroke

Comorbidities	**n=50(%)**
Diabetics Mellitus	27(54)
Hypertension	33(66)
Coronary Artery Disease	4(8)
Chronic Liver Disease	1(2)
Dyslipidemia	10(20)
Smoking	3(6)
Atrial Fibrillation	2(4)

Table 2: C Reactive Protein and its distribution with age, gender and TOAST Classification

		Gender		**Age**			**TOAST Classification**			**7th day Outcome**	
CRP	**N =50(%)**	**Males N=27**	**Females N=23**	**31-50 years N=7**	**51-70 years N=36**	**>70 years N=7**	**Large artery Stroke N=8**	**Cardio embolic Stroke N=2**	**Small Vessel Disease N=40**	**Alive N=44**	**Dead N=6**
<6	33(66)	14	19	6	23	4	0	0	33	33	0
6-12	5(10)	4	1	1	4	0	1	0	4	5	0
12-24	4(8)	3	1	0	3	1	1	0	3	3	1
>24	8(16)	6	2	0	6	2	6	2	0	3	5
Fishers		0.179		0.042			<0.001			<0.001	

TOAST- Trial of ORG 10172 in Acute Stroke Treatment

The mean CRP of the study population was 8.9±9.3 with minimum value of 2 and maximum 30. As shown in table 2 the values of CRP was significantly related to age, Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification as well as 7th day outcome and it was not related to gender. CRP >24 was seen in 8 patients of which 6 were males,6 were in the age groups 31-50 years, 6 had large artery stroke, 5 were dead at 7th day. Table 3 summarises the relation of CRP with various comorbidities. Mean CRP of expired patients were 26.3±3.8 and alive patients was 6.6±6.9.

Table 3: CRP and its relation with comorbidities

CRP	N=50(%)	Diabetes N=27	Hypertension N=33	Coronary Artery Disease N=4	Chronic Liver Disease N=1	Dyslipidemia N=10	Smoking N=3	NIHSS severity Score		
								Mild <6	Moderate 6-15	Severe >15
<6	33(66)	18	22	2	0	7	1	10	23	0
6-12	5(10)	3	1	0	0	0	1	0	4	1
12-24	4(8)	2	3	1	1	0	0	0	4	0
>24	8(16)	4	7	1	0	3	1	0	0	8
Fishers		1.000	0.09	0.33	0.08	0.35	0.264	<0.001		

As shown in table 3, there was significant relation between CRP and stroke severity (NIHSS score) as p value was <0.001. Those patients with severe NIHSS score had high CRP levels, all 8 patients who had CRP >24 had NIHSS score >15. There was no significant relation of CRP levels with other comorbidities.

Table 4: Relation of NIHSS score with TOAST and 7th day Outcome

	TOAST			7th day Outcome	
NIHSS score	Large artery stroke(n-8)	Cardioembolic stroke(n=2)	Small Vessel disease stroke(n=40)	Alive N=44	Dead N=6
Mild <6	0	0	10	10	0
Moderate 6-15	1	0	30	30	1
Severe >15	7	2	0	4	5
Fisher's exact	<0.001			<0.001	

The median NIHSS score was 10 with Interquartile range (9.5,10). The median NIHSS score of alive patients was 10 and expired patients was 20. As shown in table 4, there was significant relation between TOAST classification and outcome with stroke severity as p value was <0.001. Those with large artery stroke had severe stroke according to NIHSS score. 83%,5 among 6 patients who died had NIHSS score > 15.

Table 5: Cut off values of NIHSS and CRP for predicting bad outcome

Area under the ROC curve (AUC)	AUC	Standard Error	95% Confidence Interval	Optimum cut off	Sensitivity	Specificity	+LR	-LR	+PV	-PV
CRP values	0.962	0.0256	0.86-0.99	>18	100	93.18	14.67	0	66.7	100
NIHSS score	0.907	0.0682	0.79-0.97	>13	83.33	90.91	9.17	0.18	55.6	97.6

The cut off point for predicting bad outcome in this study with CRP was 18 with 100% Sensitivity and 93.18% Specificity while that with NIHSS Score was >13 with 83.33% Sensitivity and 90.91% Specificity.

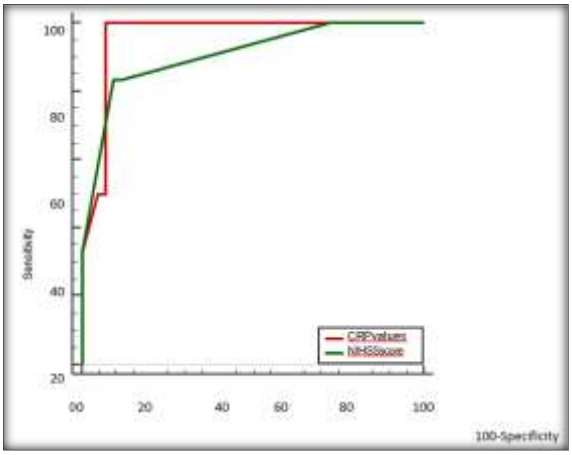

Figure 1: ROC Curve of NIHSS and CRP

DISCUSSION

This study was aimed at estimating the predictive ability of C Reactive Protein for early mortality in ischemic stroke and to assess the relation between CRP and NIHSS score in ischemic stroke patients admitted in Medical Wards of a Government Medical College over a period of 12 months.

In this study population, among the 50 ischemic stroke patients, majority of patients were found to be of age group between 51-70 years (72%). This is in concurrence with the study by Sharma et al in which the most common age group among patients of Acute ischemic stroke (AIS) was 50-70 years(72%).6 Among the study population 46.0% were females and 54% were males with a male to female ratio 1.17:1 which is different from 2.1:1 in the study by Sharma et al.[6] In the study by Shah et al., the majority of participants were in the 51-70 years(43.2%) and

males were more (58%) compared to females. This is in line with our study.

The mortality at 7 days was 12% in this study. Shah et al., reports a higher in hospital mortality rate of 20.5% in their 5 year retrospective study done in Nepal and Sharma et al., reports a rate of 34% in an Indian study while a rate of 4.5% has been reported by Heuschmann et al done in Germany.[6-8] This difference in the mortality rate might be due to several factors in a resource poor country which needs to be addressed by improvising the stroke care. 80% of the patients in the study population had small vessel disease, 16 % had large artery stroke and 4% had cardio embolic stroke. In the study by Dewan and Rana et al; majority had small vessel disease 45%, 36% had large artery atherosclerosis stroke and 19% had cardioembolic stroke.[9] In the study by Mohebbi et al., large vessel atherosclerosis was seen in 58.6%, cardioembolic in 6.8% and small vessel occlusion in 35%.4We found that there was significant relation between CRP and type of stroke. Patients with large artery stroke had high CRP values. CRP values > 6 was seen in 34% and we could not find any association of elevated CRP values with gender or comorbidities like diabetes, hypertension, coronary artery disease, dyslipidemia, smoking or chronic liver disease. We found that there was an association between CRP>6 with age, TOAST classification, NIHSS score and 7th day outcome. Dewan and Rana et al., found that a positive level of CRP was noted in 63% and unrelated to the presence or absence of risk factors of obesity, smoking, alcohol abuse, hypertension, diabetes mellitus and coronary artery diseases.9 Similar to our study elevated CRP levels was associated with large artery atherosclerosis , high NIHSS score and 7th day outcome in some of the published research.[9-11] Mengozzi et al., found that eventhough higher CRP levels were associated with risk of diabetes CRP was an independent predictor pointing to the fact that low level inflammation is associated with cardiovascular risk.[12] In the present study, mean CRP of expired patients was 26.3±3.8 and alive patients was 6.6±6.9. In the study by Mohebbi et al., the mean of CRP in died patients was 8.9 ± 7 mg/dl and in survived patients was 2.2 ± 5 mg/dl (P = 0.0001).4In the study by Sharma et al., the mean CRP level in discharged patients was 10.51 ± 13.21 mg/l whereas it was 44.11 ± 29.7 mg/l in those who died in the hospital. In this study also mean CRP of died patients was significantly higher than mean CRP of discharged patients.[6]

The median NIHSS score of alive patients was 10 and expired patients was 20. In the study by Caso et al, the median NIHSS was 10 which is similar to our study.[11] In this study there was significant relation between TOAST classification, Outcome at 7th day with stroke severity (NIHSS score) as p valve <0.05. Those with large artery stroke and 83% patients who died had NIHSS score >15. In the study by Mohebbi et al mean of NIHSS Score was 9.5 which is relatable to our study.[4] In the study by Idicula et al., they found that high CRP was associated with high NIHSS (p = 0.01) and high long-term mortality (p < 0.0001). After adjusting for confounding variables, high CRP remained to be associated with high NIHSS (p = 0.02) and high long-term mortality (p = 0.002).[11] This is in line with the present study which showed that there was significant relation between CRP and stroke severity (NIHSS) as p valve <0.001. Those patients with high NIHSS score had high CRP. All the 8 patients who had CRP >24 had NIHSS score >15. Mazya et al., showed that mortality at 7 days (29.5% vs 12.7%) and 3 mon>ths (50.4% vs 26.9%) was higher in the NIHSS 25 group.13 The increased mortality in patients with NIHSS >25 in their study was explained by the higher stroke severity itself reflected by decreased consciousness level at presentation and presence of comorbidities. Dewan and rana found that 13% expired by 7th day and even though severity of stroke, fever, atrial fibrillation, hypertension at admission and early neurological deterioration were related to early 7-day mortality in univariate analysis only NIHS score was significantly correlated with early mortality on doing multivariate analysis.[9]

Cut off points for predicting mortality in this study for CRP was 18 with 100% sensitivity and 93.18 % specificity. Cut off point for NIHSS score was 13 with 83.33% sensitivity and 90.91% specificity. Mohebbi et al., found that High Sensitivity-CRP levels>2.15 were considered as cut of point for predicting mortality.[4] Using a ROC curve the identified a cut-off of CRP of 3.25µg/ml, measured within 14 days from onset, as an independent predictor of further events was found in study by Mengozzi et al.[12] Cut-off of values of 4.1µg/ml and > 4.85µg/ml (top quartile) have been identified in studies by Purroy et ala and Elkind at al in predicting further events.[13,14] While our study which showed high cut off of CRP 18 for predicting mortality these studies showed that even low levels of inflammation should be considered a vascular risk factor both in primary prevention and for stroke recurrence.[12,14,15] Fonarrow et al., found that there was a strong graded relation between increasing NIHSS score and higher 30-day mortality and a model with NIHSS alone provided excellent discrimination whether included as a continuous variable (c-statistic 0.82 [0.81 to 0.83]) or 4 categories variable (c-statistic 0.80 [0.79 to 0.80].[16] Dawodo and Danesi et al., found that patients with NIHSS score of 20 and above had mortality of 56.5%.[17] They also found that if initial NIHSS score remained static or worsened, prognosis was worse as patients those with initial NIHSS score of 20 and above all died, compared with those with NIHSS score of less than 20 who had mortality of 70%.[17]

Limitations of this study include the small sample size, the limited duration of 12 months, single measurement of CRP levels which may be influenced by factors such as stress, infection, timing of measurements. Large population based cohort studies with serial measurements of CRP need to be done in

the future. High Sensitivity CRP measurements were not taken which could be better than CRP levels.

CONCLUSION

There is significant relation between CRP and stroke severity NIHSS score. Both CRP and NIHSS score are good predictors of early mortality in acute ischemic stroke. Cut off point for predicting mortality in this study for CRP was 18 with 100% sensitivity and 93.18 % specificity. Cut off point for NIHSS score was 13 with 83.33% sensitivity and 90.91% specificity.

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