

Original Research Article

Prognostic significance of hs-CRP in acute ischemic stroke patients

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ABSTRACT

Background: Stroke, a serious neurological disease is a major cause of death and disability throughout world. The pathophysiology of stroke involves inflammatory pathways, oxidative damage, apoptosis, angiogenesis and neuroprotection. High sensitivity C - reactive protein (hs-CRP) is associated with atherosclerosis and predict incident stroke in many patients. Objective of present study was to find out change in pattern of hs-CRP in acute ischemic stroke (AIS) patients during 3-months follow up and its prognostic significance.

Methods: Single centre prospective cross-sectional time bound study. 256 were screened and 130 meet the inclusion and exclusion criteria, of which 100 gave informed consent and 80 patients completed the study at 3 months. Demographic, clinical parameters including NIHSS scoring, biochemical analysis was collected at enrolment, discharge and at end of the study.

Results: hs-CRP levels in AIS increased significantly (within 24 hours of stroke) and continued to increase further at discharge, while decreased significantly during 3 months follow up. >7mg/dl hs-CRP at admission had 3.5 fold higher risk of mortality. Age >60 years, metabolic syndrome, hyperlipidemic, SBP >160mmHg and hs-CRP > 7 mg/dL increases relative risk in AIS stroke patients by 1.42, 1.09, 1.11, 1.577 and 3.23 fold respectively.

Conclusions: hs-CRP increased significantly in AIS patients during 1st weeks of stroke with subsequent gradual decrease by the end of 3 months, the severity scoring system could determine prognosis on admission to ICU while hs-CRP is the main factor determining short as well as long term prognosis. We recommend serial measurements of hs-CRP for prognostication in AIS subjects.

Keywords: Acute ischemic stroke, hs CRP, National Institute of Health Stroke Scale

INTRODUCTION

Stroke is the leading cause of death worldwide and one of the main causes of long-term disability. According to the World Health Organization, 15 million people suffer from stroke each year.¹ About 85-90% of all ischemic stroke is due to compromised vascular supply.² Two-thirds of all strokes occur in people over age 65, with men affected more than women, although women are more likely to die from stroke. There is increasing evidence that inflammatory processes are involved in cerebral ischemia.³ Ischemic brain injury is characterized

by acute local inflammation and changes in levels of inflammatory cytokines, notably C reactive protein. Elevated stroke risk has been linked to high levels of C-reactive protein. Many patients with elevated CRP levels within 72 hours of stroke have increased risk of death.⁴ CRP serves as biomarker for systemic inflammation. However vascular inflammation is more related to high sensitive CRP.⁵ The association between hs-CRP and higher stroke severity remains unexplained. There is a distinct possibility that elevated hs-CRP may be a direct response to the extent of cerebral tissue injury.¹ High Sensitivity C-reactive protein, hs-CRP is an acute- phase and is produced not only by the liver but also in vascular

smooth muscle cells and adipocytes. It is also a novel plasma marker of athero-thrombotic disease. Because it is a stable protein, its measurement is not greatly affected by the freezing cycle. Elevated plasma levels of CRP are not disease specific but are sensitive markers which are produced in response to tissue injury, infectious agents, and inflammation. Although infarct size and stroke severity are major determinants of short-term prognosis after ischemic stroke, hs CRP predicts prognosis, in particular mortality or new vascular events during the first year independent of infarct size and stroke severity.⁶ It was the only inflammatory marker that independently predicted the risk of stroke. Therefore, this study was done firstly to find out the pattern of changes of hs-CRP in acute ischemic stroke patients during 3 month follow up, secondly to study the effect and prognostic value of hs-CRP and NIHSS severity scoring system in AIS patients and to find out any correlation between hs-CRP and severity scoring system in ischemic stroke patients.

METHODS

A Single centre cross-sectional prospective analytical hospital-based time bound study. 256 AIS patients diagnosed by imaging, were screened in medicine emergency Gandhi Medical college and Hamidia Hospital Bhopal, India. Out of which 130 were meeting inclusion and exclusion criteria. 100 patients gave informed consent and were recruited for the study, 80 completed the study with 3 months follow up. The study was approved by institute ethical committee for human research. All patients who were admitted with first episode of AIS with imaging (CT/MRI) evidence of infarction. All patients with haemorrhagic stroke, duration of symptom >24 hours, transient ischemic attack, history of migraine, past history of vascular disease (previous stroke, angina, myocardial infarction, peripheral artery disease), Renal or Hepatic disease and patients on estrogen or lipid altering agents were excluded from the study.

Demographic, clinical, biochemical parameter was collected at enrolment, discharge and at end of the study. The study duration was for 90 days. Detailed history was obtained at enrolment; clinical examination and battery of investigations were done on admission, discharge and at completion of study. NIHSS scoring system was used objectively quantify the impairment caused by stroke. All 11 parameters were individually scored and were summed to calculate total NIHSS score.⁷

Imaging either CT scan or MRI brain for evidence of infarction was done and (hs-CRP) was measured at admission (within 24 hour), on discharge and after 3 months follow up.

Blood was drawn after 8 hour of overnight fasting to measure serum parameters such as serum creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol. Blood pressure was recorded with standard mercury

sphygmomanometer with cuff adapted to arm circumference after the subject had rested in the supine position for 15 minutes.

Statistical analysis

Statistical analysis was performed with the help of SPSS 16.0 software. It included the usual descriptive analysis. Student t test was used to compare continuous variables and χ^2 test used to compare categorical variables. P value less than 0.05 was taken as significant. Dummy variables were used for sex (1 for male, 0 for female), diabetes (0 for no diabetes, 1 for diabetes). Kaplan meier survival plot was used for survival analysis with hs-CRP.

RESULTS

156 acute ischemic stroke patients were screened and 130 were meeting inclusion and exclusion criteria. 100 patients gave informed consent for study. Out of which 20 patients were lost to follow up and 80 patients completed the study protocol at the end of 3 months. Baseline characteristics of study population of 100 acute ischemic stroke patients are shown in Table 1.

Table 1: Patients characteristic of study population at time of admission.

Baseline characteristics	Mean±Std. deviation
Age (yr)	57.12±14.81
SBP (mmHg)	158.04±25.52
DBP (mmHg)	96.8±15.00
NIHSS ad score	15.66±10.69
Hospital stay (days)	6.78±2.55
Total cholesterol (mg/dL)	180.49±18.52
LDL (mg/dL)	108.09±19.43
S. Creatinine (mg/dL)	1.04± 0.82
hs-CRP ad (mg/dL)	7.15±2.69
Sex (M/F)	53 / 47
Diabetes/Non-Diabetes	35 /65
Metabolic syndrome (Y/N)	45/55
Tobacco abuse (Y/N)	40 / 60

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NIHSS: National Institute of Health Stroke Scale; ad: admission; LDL: Low density lipoprotein; M: Male; F: Female; Y: Yes; N: No

The mean age was 57.12 yrs, mean hospital stay was 6.78 days. 53% of patients were male. 60% were non tobacco user, and 65% were non-diabetic. hs-CRP at admission was 7.15 mg/dL.

The Table 2 shows that age >60 years, presence of metabolic syndrome, hyperlipidemic, SBP >160mmHg and hs-CRP >7 mg/dL increases the relative risk in ischemic stroke patients by 1.42 fold, 1.09 fold, 1.11 fold, 1.577 fold and 3.23 fold respectively than patients with age <60 years, not having metabolic syndrome, non-hyperlipidemic patients, SBP <160 mmHg, hs-CRP >9 mg/dL and hs-CRP >7 mg/dL.

Table 2: Odds ratio of different risk factors on Outcome of patients with ischemic stroke.

	Good	Bad	Total	Odds ratio
<60 yrs	37	11	48	1.42
>60 yrs	43	9	52	
Female	47	9	56	0.574
Male	33	11	44	
Non-diabetic	53	12	65	0.764
Diabetic	27	8	35	
Metabolic syndrome (absent)	44	11	55	1.09
Metabolic syndrome (present)	36	9	45	
Hyperlipidemic (absent)	42	11	53	1.106
Hyperlipidemic (present)	38	9	47	
No tobacco abuse	53	7	60	0.274
Tobacco abuse	27	13	40	
SBP <160 (mmHg)	39	12	51	1.577
SBP >160 (mmHg)	41	8	49	
hs-CRP > 7 (mg/dL)	44	16	60	3.23
hs-CRP > 9 (mg/dL)	36	4	40	

Authors found that that there was significant increase in hs-CRP levels at discharge. Hs-CRP level was also higher as compared to baseline but it decreased at 3months in comparison to time of discharge. The change in hs-CRP level at this point of time is statistically significant (Table 3).

Table 3: Follow up hs-CRP levels (mg/dl) in acute ischemic stroke patients.

	Admission	Discharge	Day 90
hs-CRP (mg/dL)	7.16±2.7	26.81±5.06	13.78±3.6
N	100	89	80
		p=0.009*	p<0.0001**

*: significant as compared to admission **: significant as compared to discharge

Mean hs-CRP had weak positive correlation with NIHSS score and was statistically significant, the association is weakest for NIHSS score and hs-CRP at the time of discharge (p= 0.014, r=0.233) as shown in Table 4.

Table 4: Correlation coefficient between admission hs-CRP (mg/dl) and NIHSS score.

		hs-CRP admission (mg/dL)	hs-CRP discharge (mg/dL)	hs-CRP day 90 (mg/dL)
NIHSS score	p	<0.001	0.014	0.037
	r	0.496	0.233	0.293

Table 5 shows that the odds ratio for good outcome is 1.23, 1.30 and 1.65 when NIHSS score at admission is <5, <10 and <15 respectively.

Table 5: Odds ratio of NIHSS score on outcome of patients with ischemic stroke.

Outcome				Odd ratio (good)
NIHSS admission	Mortality	Un-complicated	Total	
<5	1	17	18	1.23
>5	19	63	82	
<10	1	26	27	1.3
>10	19	54	73	
<15	5	61	66	1.65
>15	15	19	34	

The NIHSS score significantly increased in subjects who died in comparison to those who remained alive. hs-CRP levels showed significant increase in deceased subjects compared to uncomplicated subject (Table 6).

Table 6: Prognostic effect of NIHSS score and hs-CRP on mortality in ischemic stroke patients.

	Uncomplicated subject	Mortality	P
NIHSS score	6.7±2.6	21.69±10.93*	0.001
hs-CRP (mg/dL) admission	4.59±1.06	16.54±5.40*	<.0001
hs-CRP (mg/dL) discharge	12.38±6.38	32.20±8.87*	<.0001
hs-CRP (mg/dL) day 90	6.94±2.14	-	-

*significant as compared to uncomplicated subjects

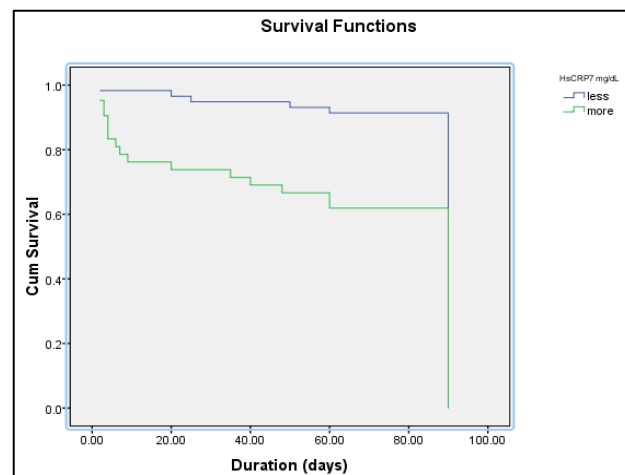


Figure 1: Kaplan Meier survival graph OF hs-CRP at admission.

The Kaplan-Meier survival graph plotted for hs-CRP at admission clearly showing better cumulative survival if hs-CRP <7mg/dl at admission (Figure 1).

DISCUSSION

Stroke is the third leading cause of mortality in the western world and also a major cause of disability. There is growing evidence that C-reactive protein (CRP), a peripheral marker of vascular inflammation, is also a marker of generalized atherosclerosis.⁸ It was shown that elevated CRP levels independently predict the risk of future stroke and transient ischemic attack in the elderly.

Therefore, this study was conducted to find out the pattern of changes of hs-CRP in acute ischemic stroke patients during follow up of 3 months and study the prognostic value of hs-CRP and severity scoring system (NIHSS score). Our study showed significant changes in levels of hs-CRP of acute ischemic stroke patients during follow up within 3 months. Level of hs-CRP was increased on admission within 24 hours and more significant increase was found on discharge. But there was significant decrease during follow up after 3 months. Similar result was obtained by Titto et al they reported that admission CRP is associated with stroke severity and long-term mortality when measured at least 24 hours after onset.⁹ CRP is an independent predictor of long-term mortality after ischemic stroke and might be used as a marker of prognosis after stroke.

The current study showed that admission levels of hs-CRP >7mg/dl increase risk of mortality and morbidity by 3.23 fold this was in agreement with Corso et al they reported that CRP levels >9 mg/L, predict a higher risk of further ischemic events and mortality.⁹ Similar results were documented by Elkind et al while discharge levels of hs-CRP >7 mg/dl increase risk of mortality and morbidity by 3.5 fold.¹⁰ The results of our study were in accordance with Huang Y et al they reported that higher levels of hs-CRP is a strong risk factor for Death after Acute Ischemic stroke, hs-CRP in our study showed significant positive correlation with NIHSS score.¹¹ Therefore hs-CRP is an important predictor of prognosis for patients with ischemic stroke. Libby P et al concluded that CRP concentration is an independent predictor for inflammation in acute ischemic stroke and a key prognostic factor in such conditions.¹² Authors found similar results in our study ($p < 0.0001$). Mahapatra SC et al studies the role of CRP in ischemic stroke and revealed a positive correlation between persistent increase of CRP titer and ischemic stroke.¹³ Authors found that serum Hs-CRP >7 mg/dL is associated with increased risk of stroke and showing significant positive correlation with NIHSS score ($p = 0.001$; $r = 0.496$).

Arevalo-Lorido JC et al found increased levels of CRP in the non-favorable stroke category that was related with neurological and functional disabilities and radiological findings mainly when the levels were greater than

3.6mg/dl.¹⁴ Napoli et al, Massoti et al studied CRP levels in acute ischemic stroke and found that elevated CRP levels added to the existing prognostic markers and concluded that increased values at hospital admission could represent a negative prognostic index in elderly patients with ischemic stroke.¹⁵ Increased Hs-CRP values at admission had negative prognostic index in all ages with ischemic stroke in present study. Keith in Ischemic stroke mean CRP concentration was 10.1 mg/L.¹⁶ Survival was significantly worse with CRP >10.1 mg/L ($p = 0.00009$, log-rank test). Higher CRP concentration was independent predictor of mortality (hazard ratio, 1.23; 95% CI, 1.13 to 1.35; $p = 0.02$), together with age and stroke severity. Very similar results were seen in our study with mean Hs-CRP at admission was 7.15 ± 2.69 mg/dL and higher mortality at day 90 seen in those having values >7 mg/dL ($p < 0.0001$). Kaplan-Meier survival plot for Hs-CRP >7 mg/dL (63.02 days; 95% CI = 51.77-74.26 days) compared to <7 mg/dL was (84.95 days, 95% CI = 80.39-89.51 days) which was statistically significant ($p < 0.0001$).

Our present study has some advantage as all patients with onset of symptoms >48 hrs were excluded from the study. Hs-CRP was measured longitudinally over 3 month period. This study has evaluated hs-CRP as prognostic marker in patients with varied age group. There were some limitations in our study. Present study was a single centre study with small sample size. Because current study was nested one, we had limited data about chronic inflammatory diseases or clinical infections. Rates of infection at the time of stroke range from 6% to 25%, depending upon the population studied and methods used to detect infection.^{17,18}

CONCLUSION

Authors can conclude that cerebral ischemia could trigger an acute response monitored by significant increase in levels of hs-CRP in AIS patients especially during early days of stroke with subsequent gradual decrease by the end of 3 months. hs-CRP followed by NIHSS scoring system are the most important risk factor for morbidity and mortality in AIS patients. Therefore, serial measurements of circulating hs-CRP in ischemic patients is indicated for better analyzing its impact on both short and long term prognosis.

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