



Role of Serum HsCRP in Predicting Outcome after One Week in Ischemic Stroke Patients

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Abstract

Introduction: A stroke is a medical condition in which poor blood flow to the brain results in cell death. There are two main types of strokes: Ischemic and hemorrhagic. Both results in parts of the brain not functioning properly. CRP is not only a sensitive marker of inflammation but also a novel plasma marker of atherosclerosis in disease. Ischemic brain injury is characterized by acute local inflammation and changes in levels of inflammatory cytokines, such as IL-6, IL-2, IL-10, fibrinogen, ferritin and high sensitivity C reactive protein (hsCRP). Recent studies have shown hsCRP as a potential prognostic biomarker of ischemic stroke.

Aims and objectives

To Evaluate The Role Of Serum HsCRP Assay Within 24 Hours Of Stroke Onset As A Biomarker For Predicting Short Term Outcome (Modified Rankin Score And Barthel Index) After 1 Week In Kashmiri Population.

Materials and Methods

The present prospective observational study was conducted on 102 in the postgraduate Department of Medicine, Government S.M.H.S. Hospital, an associated hospital of Government Medical College, Srinagar. After obtaining the ethical clearance from the Institutional Ethical Committee, patients fulfilling the inclusion and exclusion criteria were included in the study after obtaining the proper informed consent in local language. The study was conducted over a period of two years. Serum hsCRP levels were assessed at admission and its levels were compared with Barthel index and modified Rankin score after one week.

Conclusion

All ischemic stroke patient had increased high sensitive CRP levels. High levels of hsCRP were directly correlated with high MRS score. Hence directly related to poor outcome of ischemic stroke in the form of increased disability and increased mortality after one week ($r=0.651$; $p < 0.001$) and High levels of hsCRP were inversely correlated with Barthel index. Hence high

levels of serum hsCRP related to poor outcome of ischemic stroke in the form of increased disability and increased mortality both after one week ($r=-0.756$; $p<0.001$).

Keywords: hsCRP, Stroke, Cytokines, Disability

Introduction

Stroke is a major cerebrovascular disease threatening human health and life with high morbidity, disability and mortality [1]. According to the data from Global Burden of Disease Study [2], worldwide in 2010 there were an estimated 11,569,538 incident ischemic strokes and 5,324,997 events of incident hemorrhagic stroke; furthermore, 2,835,419 individuals died from ischemic stroke and 3,038,763 from hemorrhagic stroke. Stroke is the number cause of the death in several countries such as China [3]. Stroke was defined as a sudden onset of loss of global or focal cerebral function persisting for more than 24 h [4]. Biomarkers that predict the occurrence and outcome from ischemic stroke are critical for prevention and treatment. Serum biomarkers are considered to be the most valuable adjunct to routine clinical examination and imaging data [5]. Inflammation has an important role in the development of atherosclerosis and during the ischemic event. Inflammatory markers such as fibrinogen and hsCRP have been reported as a predictable marker for the stroke severity and outcome [6]. It has been reported that it is possible to use the increase in the concentration of acute phase reactants especially the hsCRP to help predict cerebrovascular mortality [7]. CRP is an acute phase reactant that is rapidly produced by the liver after tissue injury or infection [5,7]. CRP is a sensitive indicator of inflammation [8,9]. Although many inflammatory biomarkers have been reported to be useful in predicting clinical outcome after stroke, hsCRP remains one of the most widely used in clinical practice [8–12]. Increased hsCRP has been associated with the

development of atherosclerosis, ischaemic attacks, hemorrhagic stroke, as well as disease outcomes [13–17]. Studies suggest that post-stroke inflammatory responses may exacerbate tissue damage after cerebral infarction and affect clinical outcomes [18,19]. Recent studies have shown that elevated hsCRP values independently predict the risk of future cardiovascular diseases and ischemic cerebrovascular diseases, including transient ischemic attack in the elderly [20–22]. After acute ischemic stroke (AIS), a sustained inflammatory response indicated by increased level of CRP has been reported in about 75% of patients. A strong and persistent inflammatory response is associated with a worse outcome. Moreover, CRP at discharge has been shown to be related to a 1-year outcome [23–25]. Recently, a meta-analysis suggested that elevated baseline hsCRP levels are independently associated with excessive ischemic stroke risk. However, the physiologic role of CRP is not well understood; it potentially has anti-inflammatory properties as well as proinflammatory effects [26]. Inflammation may not only be the consequence of brain infarction, it may also contribute to ischemic damage. In addition, the role of inflammatory markers in predicting functional outcome in stroke remains controversial [27]. Several studies have assessed the value of CRP in the very early phases of stroke as a prognostic factor of functional outcome. Many of these studies evaluated only the relation between the CRP and mortality instead of functional outcome. Some found a positive association but others did not. Napoli MD et al (2001) [28] found that CRP is a marker of increased 1 year risk in ischemic stroke. Also they found that CRP at discharge is better related with outcome. Chaudhuri JR et al (2013) [29] their study demonstrated that high levels of hsCRP are prevalent in all ischemic stroke subtypes, and are independently associated with large artery atherosclerosis and cardio embolic stroke.

Shoaeb M A et al (2014) [30] concluded that hs-CRP can be used to predict severity and early outcome in ischemic stroke but not in hemorrhagic stroke. Pandey S et al (2018) [31] found that hs-CRP is 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. Wang Y et al (2022) [32] concluded that elevated levels of hsCRP measured in the first 72 hours after ischemic stroke or transient ischemic attack but not 72 hours to 8 days, were associated with an increased risk of 1-year stroke recurrence. In search for the further clarification of its role in cerebrovascular stroke, we sought to evaluate hsCRP level as an early prognostic factor of functional outcome after stroke and its association with severity of stroke.

Materials and methods

The present prospective observational study was conducted in the Postgraduate Department of Medicine, Government S.M.H.S. Hospital, an associated hospital of Government Medical College, Srinagar. After obtaining the ethical clearance from the Institutional Ethical Committee, patients fulfilling the inclusion and exclusion criteria were included in the study after obtaining the proper informed consent in local language. The study was conducted over a period of two years.

Inclusion criteria:

- Patients admitted with first-ever stroke
- Patients admitted within first 24 hours of symptom onset
- Age >45

Exclusion criteria

- Patients with old stroke
- Patients with Liver disease

- Patients with acute coronary syndrome
- Patients with Renal disease
- Patients with traumatic brain injury

A complete history, physical examination, and systemic examination was done in all patients. Five millilitres venous blood was taken at the time of hospital admission for subsequent measurement of admission blood glucose level, hsCRP, and other routine examinations. Blood samples were taken for baseline investigations and hsCRP levels. NCCT head was done to rule out Hemorrhagic stroke. The severity of neurologic impairment was evaluated by the National Institutes of Health Stroke Scale (NIHSS) score on admission. The functional status was evaluated by Barthel Index and Modified Rankin Scale (MRS) on day 7. A poor functional outcome was defined as death (MRS 6) or dependency (MRS 2-5) and BI of less than 20 signifies total dependency, 20-60 signifies severe dependency.

Observations and Results

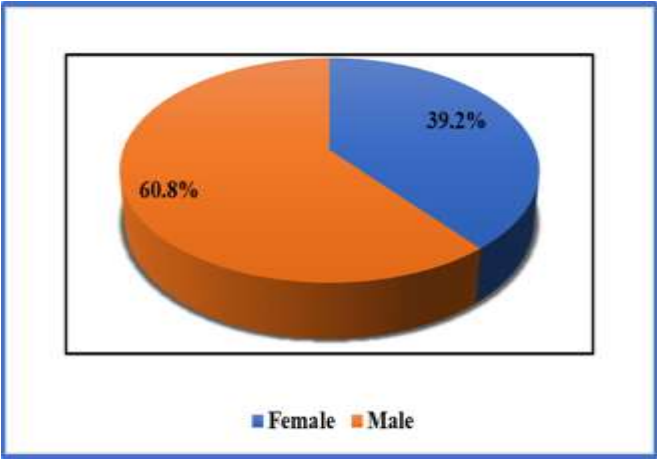
The results of the study conducted on 102 patients are presented here

Table 1: Gender distribution of study patients

Gender	Frequency	Percentage
Female	40	39.2
Male	62	60.8
Total	102	100

Males outnumbered females in our study with 62 (60.8%) males versus 40 (39.2%) females.

The male to female ratio was 1.55:1.

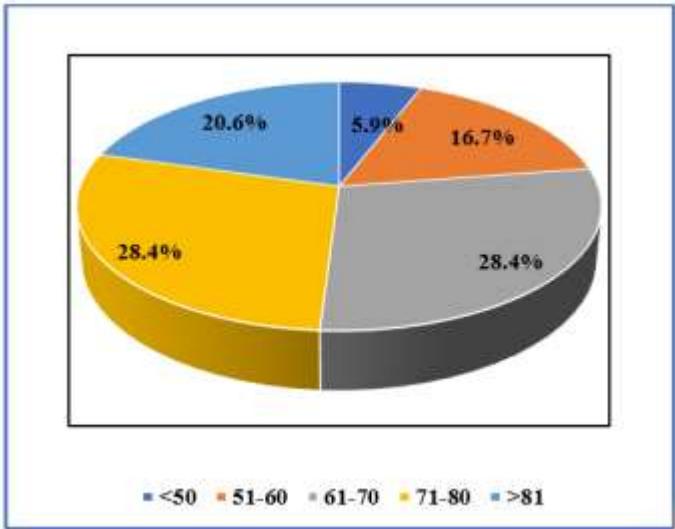


Graph 1: Gender distribution

Table 2: Age distribution of study patients

Age (in years)	Frequency	Percentage
<50	6	5.9
51-60	17	16.7
61-70	29	28.4
71-80	29	28.4
>81	21	20.6
Total	102	100

Most common age group in our study was 61-80 years (58/102, 56.8%) followed by 21 (20.6%) patient who belonged to >81 years age group. There were 1716.7%) patients aged between 51-60 years while as 6 (5.9%) patients belonged to <50 years age group.

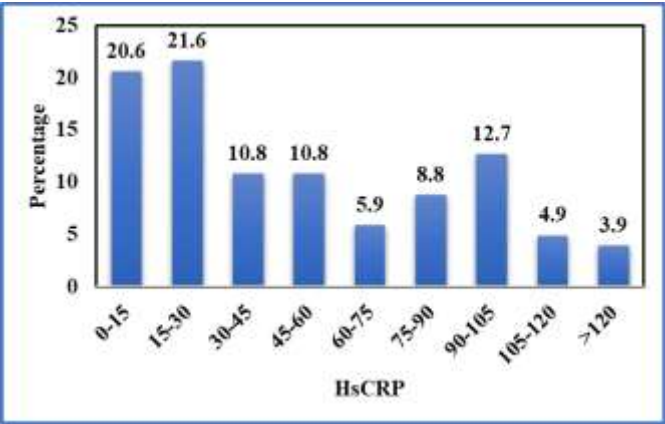


Graph 2: Age distribution

Table 3: HsCRP distribution

HSCRCP	Frequency	Percentage
0-15	21	20.6
15-30	22	21.6
30-45	11	10.8
45-60	11	10.8
60-75	6	5.9
75-90	9	8.8
90-105	13	12.7
105-120	5	4.9
>120	4	3.9
Total	102	100

All of the patients had increased hsCRP levels. Most of the patients had hs CRP levels in the range of 0-60.



Graph 3: HsCRP

Table 4: BI-1 week

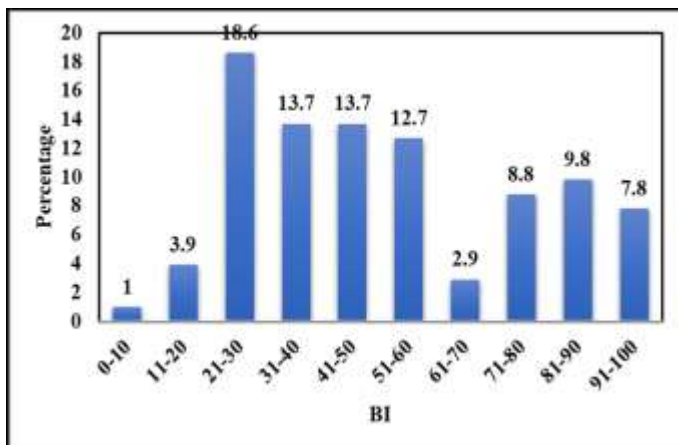
BI	Frequency	Percentage
0-10	1	1
11-20	4	3.9
21-30	19	18.6
31-40	14	13.7
41-50	14	13.7
51-60	13	12.7
61-70	3	2.9
71-80	9	8.8
81-90	10	9.8

91-100	8	7.8
Total	102	100

Most the patients (48%) had Barthel index between 21-60.

7(6.9%) patients died within 7 days.

Among these 7 patients 6 had hs CRP levels of more than 60mg/l.



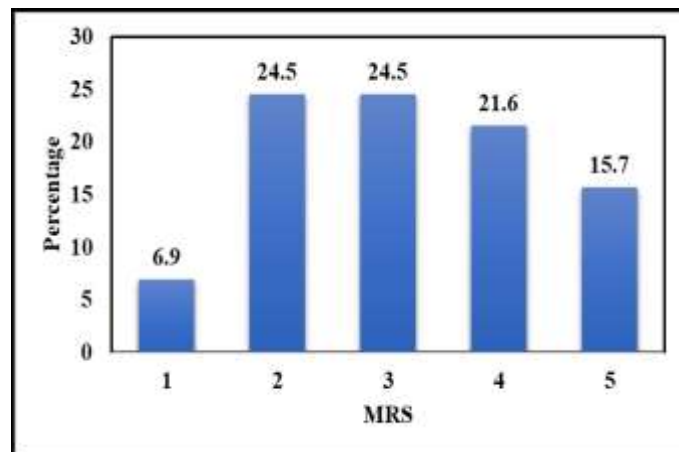
Graph 4: BI-1 week

Table 5: MRS-1 week

MRS	Frequency	Percentage
1	7	6.9
2	25	24.5
3	25	24.5
4	22	21.6
5	16	15.7
Dead	7	6.8
Total	102	100

Out of 102 patients, 7(6.9%) had MR score of 1, 25(24.5%) patients had MR score of 2, 25(24.5%) patients had MR score of 3, 22(21.6%) patients had MR score of 4, 16(15.7%) had MR score of 5, 7(6.8%) patients died within one week.

Most of the patients (49%) had MR score of 2 and 3.



Graph 5: MRS-1 week

Table 6: Mean BI and mean MRS-1 week

HSCRP (mean)	Mean BI-1 week	Mean MRS-1 week
0-15 (8)	80.8	2
15-30 (21)	70.2	3
30-45 (37.5)	45.0	4
45-60 (52.4)	38.2	3
60-75 (66.7)	36.4	4
75-90 (82.8)	30.0	5
90-105 (94.9)	37.3	4
105-120 (113)	22.0	5
>120 (134)	28.3	5
Pearson's correlation coefficient	-0.756; p <0.001	0.651; p <0.001

Mean hsCRP is positively correlated with mean MRS at 1 week ($r=0.651$; $p <0.001$)

Mean hsCRP is negatively correlated with mean Barthel index at 1 week ($r=-0.756$; $p <0.001$)

Discussion

This study was conducted on 102 patients. Participants of these were evaluated in IPD and data was collected on admission. HsCRP levels assessed at admission. Patients were followed after one week for further data collection. After one week Barthel index and MRS was calculated.

In this prospective study, most common age group in our study was 61-80 years (58, 56.8%) followed by 21 (20.6%) patient who belonged to >81 years age group. There were 17(6.7%) patients aged between 51-60 years while as 6 (5.9%) patients belonged to <50 years age group. Males Outnumbered females in our study with 62 (60.8%) males versus 40 (39.2%) females. The male to female ratio was 1.55:1.

In our study all patients with ischemic stroke had increased levels of hsCRP. Rajput et al.⁴⁶ had found that among stroke patients from Pakistan, 132 (88%) had elevated CRP (CRP > 10 mg/L). Moreover, in a study by Di Napoli et al.³⁸ from Italy, 95 patients (74.2%) with acute ischemic stroke had high CRP levels (> 0.5 mg/dl) at admission. Muir et al.⁴⁷ had detected elevated CRP (> 10 mg/L) levels in 96 out of the 228 (42.1%) patients admitted with acute ischemic stroke in the UK. On the other hand, only 22% of stroke patients and 14% of myocardial infarction patients had high CRP (> 7 mg/l) levels in a study from Netherlands.⁴⁸

Both scores (MRS and BARTHEL INDEX) were grouped in various classes and mean for each group was calculated. Mean of hsCRP was compared with mean MRS after one week. Mean hsCRP and mean MRS were correlated by Pearson's correlation coefficient. MRS was positively correlated after one week ($r=0.651$; $p<0.001$). Mean of hsCRP was compared with mean Barthel index after one week. Mean hsCRP and mean Barthel index were correlated by Pearson's correlation coefficient. Both were negatively correlated after one week (-0.756 ; $p<0.001$). Hence high levels of hsCRP are associated with poor outcome both after one week. One study done by Shoaeb M A³⁸ et al, they found that in the Ischemic stroke group, serum CRP level on admission was predictive of stroke severity, positively correlated with NIHSS ($r=0.337$, $p=0.02$). A CRP level of 10.25 mg/L

was predictive of a severe ischemic stroke with a sensitivity of 80% and a specificity of 75%. as well as a poor outcome using mRS with a sensitivity of 75% and a specificity of 82%. Serum hsCRP levels of more than 10.25mg/dl can predict severity of stroke with sensitivity of 80% and specificity of 75%.

Subbarayan MK et al³⁵ conducted a study in which they found that 78% of patients had hsCRP levels of > 10.1mg/dl and 22% of the patients had hs CRP of < 10.1mg/dl. In 90% of patients with glasgow outcome score of 5 have CRP detected by high sensitive method (i.e. <10.1mg/L). In 96.1% of patients with have Glasgow outcome score 1-3, have hsCRP ≥ 10.1 mg/L. They found that there is an association between Glasgow outcome Score and hsCRP. The study concludes that high sensitive CRP level predicts the severity of acute ischaemic stroke and guides us in the prognosis. Pandey S et al (2018)³⁹ found that hs-CRP levels in Acute ischemic stroke increased significantly (within 24 hours of stroke) and continued to increase further at discharge, while decreased significantly during 3 months follow up. hs-CRP > 7mg/dl of at admission had 3.5fold higher risk of mortality.

The mechanisms underlying the association between CRP and stroke are not well defined, although atherosclerotic pathways are hypothesized. CRP may induce atherogenesis by activating the inflammatory cascade and interacting with endothelial and smooth muscle cells, resulting in foam cell formation, endothelial dysfunction, and plaque destabilization. Whether CRP plays a causal role or serves as a marker of subclinical disease remains under debate. It is also unclear whether CRP significantly improves long-term prediction of stroke. Current guidelines do not support CRP measurement for stroke risk assessment in healthy or high-risk population, however, our data suggest that

elevated CRP concentrations were associated with poor outcomes and more disability. There are some limitations in our study. This study is a relatively small study since only 102 patients were included. Blood sample was taken at different times after onset of stroke as time of presentations was variable.

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