

# To study the correlation of serum S-100 protein level with the severity of stroke and its prognostic implication

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## ABSTRACT

**Objective:** This study investigated correlation between mortality, stroke subtype and stroke severity with serum S-100 protein level prior to the treatment of the patients admitted to the emergency department and diagnosed with a stroke. **Methods:** Pretreatment sample were collected from the patients ( $n = 142$ ) to determine S-100 protein level, age and sex-matched healthy individuals ( $n = 40$ ) served as control. All patients had cranial computerized tomography scan/magnetic resonance imaging in the first 24 h. The neurological evaluation was made with the National Institute of Health Stroke Scale (NIHSS) in the acute stage. **Results:** Compared with controls, S-100 protein level were significantly higher in the stroke groups. In stroke groups, S-100 protein level was more significantly higher in the ischemic group than hemorrhage and transient ischemic attack group and highest in expired patients. **Conclusion:** Serum S-100 protein measurement can be used as an early marker of brain damage. There is a role of S-100 protein as a co-predictor of outcome in patients with acute stroke.

**Key word:** National Institute of Health Stroke Scale, prognosis, S-100 protein, stroke

## Introduction

Stroke is a devastating condition encompassing a wide range of pathophysiological entities that include thrombus, hemorrhage, and embolism. Currently, diagnosis of stroke relies on physical examination and is further supplemented with various neuro imaging technique. A single set or multiple set of blood biomarkers that could be used differentiate between stroke subtypes or even predict an initial/reoccurring stroke could be extremely valuable.

In recent year, neurobiochemical markers have gained particular attention in the determination of brain damage from stroke. Stroke is a third leading cause of morbidity

and mortality in the world. Hence, there is a need of determination of these markers make it possible to reach a faster diagnosis and to start treatment earlier. Elevated S-100 protein level in cerebrospinal fluid (CSF) in acute cerebral damage have been reported earlier in stroke,<sup>[1-3]</sup> but the difficulty in collecting CSF sample make researchers to examine the biochemical markers in the blood.

S-100 protein is a low molecular weight protein (approximately 10 kda) that belong to a multigenic family of calcium-mediated protein, so named their solubility in 100% ammonium sulfate.<sup>[4]</sup> S-100 protein is released into CSF upon structural damage to the neuronal cells, but the underlying mechanism of passage through the blood-brain barrier has not seen clearly elucidated. The correlation of S-100 is 40 fold higher in CSF then serum. The biomarkers is not affected by hemolysis and has exceptional stability<sup>[5]</sup> giving it appeal for use as clinical biomarkers.

Several studies have demonstrated the serum S-100 protein concentration are increased significantly following stroke.<sup>[6-13]</sup> S-100 protein level measure

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before specific treatment was given and mortality stroke subtype and severity were examined in patients with stroke admitted to hospital emergency department.

## Patients, Methods, and S-100 Protein Measurement

This was a prospective observational study with a definite diagnosis of stroke made both clinically and radiologically, conducted among patients admitted in Mahatma Gandhi Hospital (MGH) Jodhpur.

This study was approved by the Local Research Ethics Committee. Inclusion criteria for the study were patients of acute stroke admitted within 48 h of onset, diagnosis confirmed by computerized tomography/magnetic resonance imaging and patients above the age of 18 years. Exclusion criteria were patients with peripheral vascular disease, systemic inflammatory disorder or tumor, patients whose National Institute of Health Stroke Scale (NIHSS) score could not be calculated at the time of admission. Venous samples were drawn within 48 h of the onset of symptoms and sent for routine blood examinations including measurement of the protein level. The concentration of protein in blood samples was measured in electrochemiluminescence immunoassay is intended for use on Elecsys and cobas E-immunoassay analyzers. Clinical outcome was recorded at 1-week and graded according to Modified Rankin Scale.

### Statistical analysis

Parametric data are expressed as mean value  $\pm$  standard deviation (SD) and categorical variables as percentages. The Chi-square test was used for the comparison of dichotomous variables and the Student's *t*-test for continuous variables. One-way ANOVA was used to test differences on multiple levels by a single factor (independent) variable.  $P < 0.05$  was considered statistically significant. All statistical analysis was performed using SPSS Windows (SPSS version 17.0.2009).

## Results

The study included 142 patients with acute stroke who fulfilled inclusion criteria were admitted the MGH attached to Dr. Sampurnanand Medical College Jodhpur. Out of total 80 (56.33) male and 62 (43.66) were female. In addition, 38 healthy volunteers (25 female and 13 females) similar to the patients cohort in term of age and sex formed the central group. The mean  $\pm$  SD age

of the total patients was  $63.73 \pm 14.11$  years and of the control was  $57.94 \pm 10.66$ .

### Types of strokes and serum S-100 protein level

The most common type of stroke in our study was ischemic (66.19) followed by hemorrhage (24.64) and transient ischemic attack (TIA) (9.15). The most common condition in stroke patients was HTN (68.30), followed by ischemic heart disease (47.8%) diabetes mellitus was seen in 28.87% and dyslipidemia in 23.94%. Seven patients had rheumatic heart disease (RHD) 5%. Serum S-100 protein concentration were increased above the normal value ( $0.1782 \pm 0.1622$  ng/ml) in both ischemic ( $1.12 \pm 1.58$ ) and hemorrhage ( $0.6317 \pm 0.782$ ) stroke group which was statistically significant ( $P < 0.001$ ) when compared to TIA ( $0.22 \pm 0.25$ ) which was not significant ( $P = 0.23$ ). When within patients group, comparison were made there was a statistically significant difference in serum S-100 protein level between the group according to stroke subtype. Serum S-100 level were significantly higher in the cardioembolic stroke and hemorrhage stroke group than in than TIA group. In our study, serum S-100 level was significantly higher in the ischemic group than in other group of stroke. Atherosclerosis (82.5%) 78 was the most common etiology of the ischemic stroke, followed by ischemic cardio embolism (9.3%) and rheumatic cardio-embolism (8.2%). S-100 protein level maximum for RHD (1.523).

Patients followed by IHD (1.342) and atherosclerosis (1.062) patients [Table 1, Figures 1 and 2].

### Severity of stroke and serum S-100 protein level

According to the NIHSS score<sup>[14]</sup> stroke group were compared with control according to low (NIHSS 1–7) moderate<sup>[8-15]</sup> high (>15) severity stroke had significantly higher serum S-100 protein level ( $P < 0.001, 0.001, 0.0001$ ) respectively and S-100 protein level (all comparison  $P < 0.001$ ), when within patients group comparison

**Table 1: S-100 protein level in hemorrhagic and ischemic stroke**

Causes	n	S-100 concentration ( $\mu\text{g/L}$ ) mean $\pm$ SD	P versus control
Controls	38	0.1782 $\pm$ 0.1622 (0.0509-0.901)	
Ischemic stroke			
Atheroembolic	94	1.1231 $\pm$ 1.5864	<0.001
Cardioembolic	78	1.062 $\pm$ 1.60	
Rheumatic	07	1.523 $\pm$ 1.91	
IHD	09	1.342 $\pm$ 0.87	
Hemorrhagic			
Parenchymal	35	0.6317 $\pm$ 0.7820	<0.001
TIA	13	0.2229 $\pm$ 0.2523 (0.012-1.01)	0.231 NS

SD: Standard deviation, IHD: Ischemic heart disease, TIA: Transient ischemic attack, NS: Not significant

were made for stroke severity there was a statistical difference for S-100 protein level were significantly higher in patients with high severity stroke compared those who had low and moderate severity (S-100 median 0.157, 0.270, 1.21). Thus mean S-100 level significantly higher in the stroke patients who belong to NIHSS > 15 [Table 2 and Figure 3].

### Mortality and serum S-100 protein level

In total, 30 (21.9%) patients died during the study. Demographic and clinical difference between patients who died and those who survived age are given in Table 3. There was a significantly higher value of serum S-100 protein level in patients who expired after stroke than in patients who survive ( $P < 0.0001$ ). Of the 30 patients who died, 24 patients had NIHSS score  $\geq 15$  ( $P < 0.001$ ). Of the 30 died patients 21 patients was ischemic and 9 patients was a hemorrhagic stroke group and no one died in TIA

group. The S-100 protein level was significantly higher in patients who died of ischemic stroke than hemorrhagic stroke [Figure 4, Tables 3 and 4].

### Discussion

S-100 protein is such a neurochemical marker of brain damage which is a major component of the cytosol, particularly in the astroglial cells and is released in the CSF and peripheral blood due to disruption of blood brain barrier after the brain damage. The present study primarily confirmed that S-100 protein level are higher in patients with stroke compared with healthy volunteers. The high level of S-100 protein in acute stroke was also observed with other studies in the literature.<sup>[15,16]</sup> This study

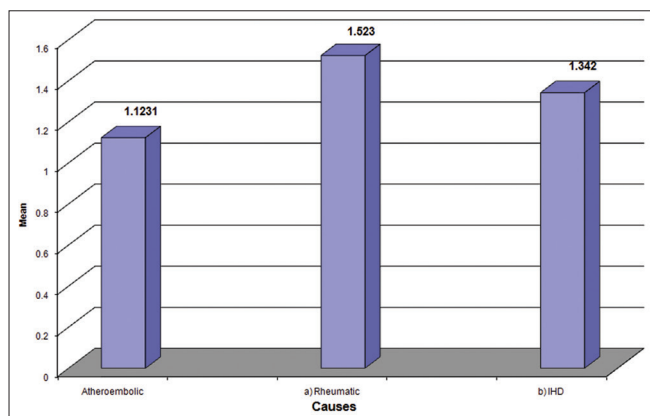


Figure 1: Serum S-100 protein level in stroke patients

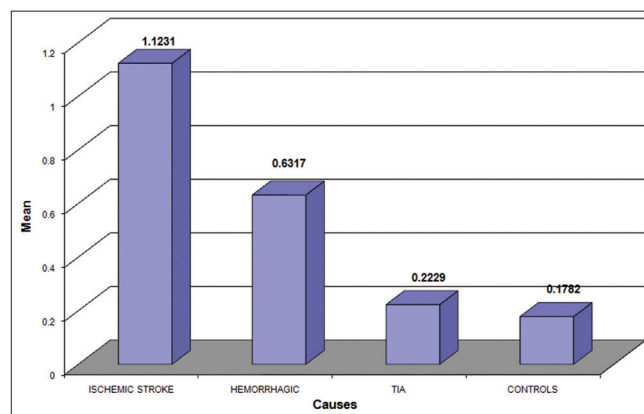


Figure 2: Serum S-100 protein level in subtype of stroke

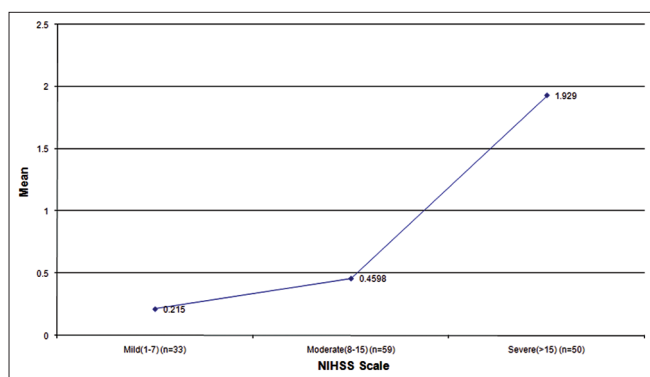


Figure 3: Serum S-100 level with severity of stroke according to National Institute of Health Stroke Scale

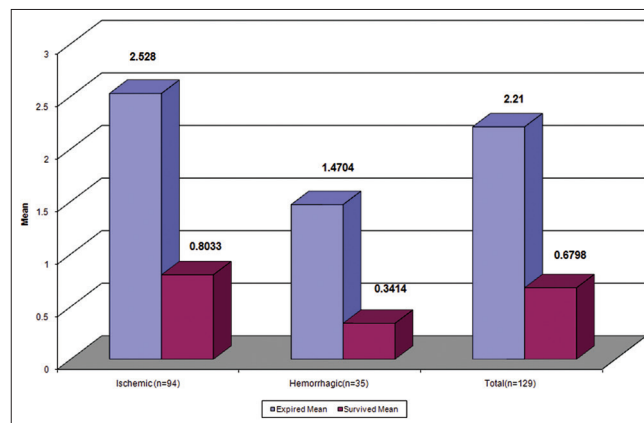


Figure 4: Serum S-100 level in survived and expired patients

Table 2: S-100 B protein according to the severity of NIHSS classification on admission

Biomarker	NIHSS scale		
	Mild (1-7) (n=33)	Moderate(8-15) (n=59)	Severe (>15) (n=50)
Median (minimum-maximum)	0.2150±0.254	0.4598±0.531	1.929±1.826
	0.157 (0.0121-1.51)	0.2705 (0.112-2.85)	1.21 (0.156-8.52)

NIHSS: National Institute of Health Stroke Scale

**Table 3: Relationship of serum S-100 protein in expired and survived patients of stroke**

	Expired		Survived		P
	n	Mean±SD	n	Mean±SD	
Ischemic (n=94)	21	2.528±2.651	73	0.8033±1.043	<0.0001
Hemorrhagic (n=35)	9	1.4704±1.1247	26	0.3414±0.2933	<0.0001
Total (n=129)	30	2.210±2.305	99	0.6798±0.9258	<0.0001

SD: Standard deviation

**Table 4: Clinical characteristics of the stroke patients who survived and expired and severity according to NIHSS**

Characteristic	Expired (n=30)	Survived (n=112)	P
Age years	63.37±15.79	63.77±13.76	
Sex: Male/female (n)	17/13	63/49	
Ischemic stroke (n)	21	73	
Atheroembolic	16	62	
IHD	2	7	
RHD	3	4	
TIA	0	13	
Hemorrhagic stroke			
Parenchymal	9	26	
S-100 mean±SD	2.012±2.166	0.628±0.886	<0.0001
NIHSS score (n)			
Low (1-7)	00	33	<0.001
Moderate (8-15)	06	53	
High (>15)	24	26	

SD: Standard deviation, IHD: Ischemic heart disease, TIA: Transient ischemic attack, NIHSS: National Institute of Health Stroke Scale, RHD: Rheumatic heart disease

also gives the information that S-100 protein level is much higher in ischemic stroke group than other. S-100 protein level was significantly higher in the athero embolic stroke group than in the TIA, cardio embolic and lacunar stroke. S-100 protein level was significantly higher in the patients who died compared with survivors. In predicting stroke subtype and severity although S-100 protein was more valuable for mortality.

An elevated level of S-100 protein was not diagnostic of stroke as it is elevated in all the stroke patients irrespective of types as compared to control. However, S-100 protein can only predict the presence of neuronal damage in the brain but does not specify the cause for it. Hence, S-100 protein has high sensitivity with low specificity in stroke. In other studies also elevated levels was not diagnostic of stroke, the negative predictive value was 0.92.<sup>[17]</sup> However, it is definitely predicted the prognosis of the patients.

The importance of S-100 protein in acute stroke also confirmed with other studies.<sup>[15,18]</sup> Person *et al.*,<sup>[6]</sup> Kim *et al.*<sup>[19]</sup> and Missler *et al.*<sup>[20]</sup> report an association between single biochemical marker

from blood in the acute phase of stroke and functional outcome of infarction.

Foerch *et al.*<sup>[21]</sup> measured single S-100 protein in acute stroke within 12–24 h and found it as a valuable marker in guiding clinical and therapeutic aspects in stroke. Herrmann *et al.*<sup>[22]</sup> found serum S-100 protein level with the size of the brain lesion and neurological status at discharge. In this study, there is a correlation between serum S-100 protein level, infarct size and outcome.<sup>[17,23]</sup> Kenangil *et al.*<sup>[23]</sup> who found that size of the infarct in middle cerebral artery (MCA) territory correlation with the level of S-100 protein. A patient with large MCA infarction had highest serum S-100 level, and their short and long prognosis was the worst. Similar report presented by Buttner *et al.*<sup>[8]</sup> Rainer *et al.*<sup>[24]</sup> report that within first 24 h there was increased the level of S-100 protein level in stroke patients.

## Conclusion

Serum S-100 protein level significantly rises in patient with acute stroke due to ischemia and hemorrhage, but not significant in TIA. It helps in the diagnosis of stroke and the severity of stroke as it is significant increases according to the size of the lesion thus it is more valuable for the prognosis. S-100 protein levels have a positive correlation with NIHSS. Finally, we conclude that serum S-100 protein measurement can be used as an early marker of brain damage. There is a role of S-100 protein as a co-predictor of outcome in patients with acute stroke.

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