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The role of s100b as a predictor of the functional outcome in geriatric patients with acute cerebrovascular stroke

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Introduction

Ischemic stroke is one of the leading causes of disability worldwide [1]. Though clinical assessment of stroke and evaluation of stroke etiology are always sufficient, reliable biomarkers to support the diagnosis and predict the outcome are not well-established [2]. Identification of biomarkers that can predict the outcome would be beneficial in stroke management and monitoring the course of stroke therapy. It can also help to direct a specific or personalized therapy to a subgroup of patients most likely to benefit [3]. Many biomarkers are known to increase during early neurological deterioration (END); or worsening of neurological status from admission to 48–72 h after admission, especially the S100B [3–5]. Identifying patients at risk of END may be useful for initiating therapies to prevent such worsening. S100B is a calcium-binding protein that was found primarily in glial and Schwann cells. It possesses many of the ideal characteristics of a biochemical marker such as high organ specificity, low molecular size, and a high degree of solubility. S100B acts in bimodal manner. At nanomolar concentrations, S100B stimulates neurite outgrowth in cerebral cortex neurons in vitro and enhances survival of neurons in various systems during development [6]. SB100 has also a neurotrophic activity during the neuronal maturation and glial cell proliferation [7]. S100B decreases cell death and protects against mitochondrial function loss resulting from glucose deprivation [6, 8]. With its neurotrophic and gliotrophic actions, S100B plays an important role in normal CNS development and recovery after injury.

In contrast to the stated effects of nanomolar levels of S100B, micromolar levels of extracellular S100B are known to have deleterious effects [9]. At these concentrations, extracellular S100B stimulates the expression of proinflammatory cytokines and induces apoptosis in vitro [8]. S100B exerts its neurotoxic effects in vitro by inducing apoptosis in neurons. The short biological half-life of S100B (between 30 and 60 min) and its renal clearance (2 h) imply that any persistent elevation of S100B concentration in the blood reflects a continuous active secretion or passive release from damaged tissues [10]. During the last few years, several studies [8, 11–14] have investigated release and kinetics of protein S-100B after acute stroke and their association with lesion volume, clinical status, and outcome.

The purpose of the present study was to investigate the relation between release pattern and serum concentration of protein S100B and short-term functional outcome after stroke in elderly patients.

Patients

The study was carried out on 40 elderly patients above 65 years of both sexes diagnosed as acute cerebrovascular stroke (ischemic and hemorrhagic) within 24 h of the onset admitted to the Main university hospital and Hadara hospital, and it was conducted for 14 days, Patients' functional outcomes were classified according to Modified Rankin scale (MRS) into two groups: group I included 28 patients of good outcome MRS (1,2,3), and group II included 12 patients with poor outcome MRS (4,5,6). All were selected with exclusion criteria, age less than 65 years; advanced renal, pulmonary, and liver disease; and patients with recurrent stroke, fractures, and psychiatric disorders.

Methods

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and an informed consent was obtained from the patients or next of kin.

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Table 2 Comparison of the S100B levels on day 1 and 3 between the two studied groups

	Group I (Good outcome)	Group II (Poor outcome)	*t*	P1
S 100B Day 1				
Range	28.30–94.40	35.20–249.70	2.33	0.0241
Mean	49.29	63.98		
S.D.	18.76	26.11		
S 100B Day 3				
Range	15.20–177.20	11.50–391.00	20.475	0.0001
Mean	53.15	180.83		
S.D.	43.87	135.56		
P2	0.211	0.001		

Thorough history was taken as regard demographic data, medical history, and drug history. Complete physical examination and neurological examination was taken; the neurological deficit was quantified by the use of the National institute of health stroke scale (NIHSS) [15]. Short-term outcome was determined by the use of (MRS) [16] scores at 14 days after symptom onset. Good outcome group was defined as patients with MRS 0–3, whereas poor outcome group was defined as patients with MRS 4–6. Glasgow coma scale was done daily during the period of the study.

Routine Lab investigations were done on admission and every other day for correction of any abnormal values. Serum level of S100B level was measured using the enzyme-linked immunosorbent assay (ELISA) technique using commercially available kits day 1 and 3 [17] (normal range 50 ± 15 pg/mL, pathological limit > 75 pg/mL).

All neuroradiological examinations were based on cranial CT scans. All scans were performed in standardized slices without contrast enhancement soon after admission and were repeated after 48 h and when needed, magnetic resonance imaging brain scan (MRI) was done.

All calculations were performed on a personal computer with IBM SPSS software package (version 20.0) for Windows [18].

Qualitative data were presented as percentages (%) and numbers (*n*). Quantitative data were presented as standard deviation (SD) and means. One-way ANOVA (*F* test) was used for comparison between means. Pearson or Spearman correlation coefficients were used for studying the correlation between variables according to the distribution of variables (continuous or discontinuous quantitative variables respectively). *P* value ≤ 0.05 was accepted as statistically significant.

Results

Regarding diagnosis, ischemic CVS in group I was 25 (89.3%) and in group II was seven (58.3%), hemorrhagic stroke in group I was three (10.7%) and in group II was five (41.7%), and total ischemic stroke was 80% and hemorrhagic stroke 20%.

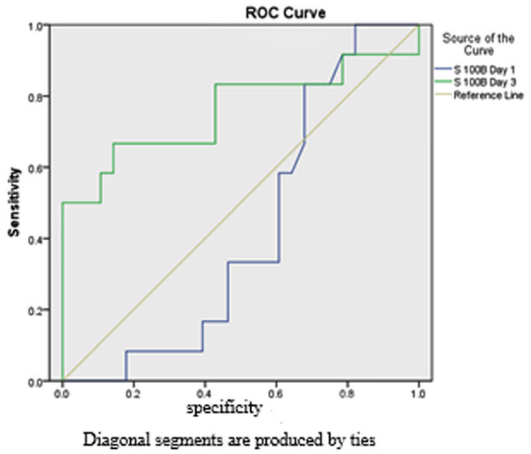
Regarding comorbidities, diabetes mellitus (DM) in group I was 13 (46.4%) and in group II was six (50%). Hypertension (HTN) was 26 (92.9%) and eight (66.7%) in two groups respectively. Cardiac disease (ischemic heart disease and atrial fibrillation) was five (17.9%) and four (33.3%) in two groups respectively. There was no statistically significant difference regarding DM and cardiac disease while there was statistically significant difference regarding HTN, total hypertensive patients 34 (85%).

Regarding NIHSS, there was statistical significant difference between NIHSS in group I and II in the same day (P1 < 0.05) group I range 0–14 in day 1 (minor-moderate stroke) and group II range 7–23 in day 1 (moderate-moderate to severe stroke); there was statistical significant difference between day 1 and 3 in two groups(P2 < 0.05) ranging 0–14, 0–10 respectively in group I and 7–23, 10–21 respectively in group II; there was statistical significant difference between day 1 and day 14 in two groups (P3 < 0.05) ranging 0–14, 0–8 respectively in group I and 7–23, 12–26 respectively in group II, while there was no statistical significant difference between day 3 and 14 in two groups(P4 > 0.05) (Table 1).

Regarding S100B in day 1 in group I, it ranged from 28.30 to 94.40 with mean value of 49.29 ± 18.76, and in group II it ranged from 35.20 to 349.70 with mean value of 63.98 ± 26.11. S100B day 3 in group I ranged from 15.20 to 177.20 pg/ml with mean value of 53.15 ± 43.87

Table 1 Comparison of the NIHSS scores on day 1, 2 and 3 between the two studied groups

	Group I Good outcome	Group II Poor outcome	*t*	P1
NIHSS Day 1				
Range	3–14	7–23	26.034	0.0001
Mean	6.86	14.17		
S.D.	3.45	5.51		
P2	0.021	0.033	0.001	
NIHSS Day 3				
Range	0–10	10–21	14.824	0.0001
Mean	4.71	17.00		
S.D.	2.71	3.59		
P3	0.0045	0.016	0.065	
NIHSS Day 14				
Range	0–8	12–26	31.632	0.0001
Mean	3.68	19.83		
S.D.	2.42	4.61		
P4	0.081	0.077	0.001	



Test Result Variable(s)	Cut off value	Sensitivity	Specificity	PPV	NPV
S 100B Day 1	54.3000	53.3	47.9	50.1	45.0
S 100B Day 3	66.7500	91.0	80.00	90.0	85.0

Fig. 1 ROC curve to determine the sensitivity and specificity of S100B in different period in prediction the outcome

pg/ml, and in group II it ranged from 11.50 to 391 pg/ml with mean value 180.83 ± 135.56 pg/ml. There was statistically significant difference between the two studied groups at the same period (P1 < 0.05). There was no statistically significant difference between day 1 and day 3 in group I (P2 > 0.05) while there was statistically significant difference regarding group II (P2 < 0.05) (Table 2).

When correlating S100B level day 1 with the short-term functional outcome measured by clinical scales NIHSS and MRS day 14, there was no significant correlation between S100B at day 1 and other variables, while correlating S100B day 3 with the same variables, there was statistically significant correlation between them (Table 3).

From ROC curve, it was found that the cut-off value of S 100 B at day 1 was 54.3 (AUC of 0.423); at this point, the sensitivity was 53.3%, specificity was 47.9%, PPV was 50.1%, and the NPV was 45.05, while the cut of value of S100 B at day 3 (AUC of 0.759) was 66.75, and show a high sensitivity, specificity, PPV, and NPV more than the S100 B at day 1; the sensitivity was 91.0%, specificity 80.0%, PPV 90.0%, and NPV was 85.0% (Fig 1).

Table 3 Correlation between S100B day 1 and 3 with NIHSS, GCS, and MRS

		NIHSS Day 14	GCS	MRS
S100B Day 1	R (p)	− 0.155 (0.341)	0.070 (0.667)	− 0.148 (0.362)
S100B Day 3	R (p)	0.722** (0.000)	− 0.786**(0.000)	0.688**(0.000)

Discussion

The major finding of the present study was that protein S100B measured at day 3 after acute cerebrovascular stroke was significantly correlated with short-term functional outcome at day 14 determined by MRS and NIHSS scores with high sensitivity 91% and specificity 80% as shown by the ROC curve, while S100B day 1 was not significantly correlated (Table 3).

In agreement with our study, Wunderlich et al. [19] found that serum concentrations and kinetics of protein S100B have a high predictive value for early neurobehavioral outcome after acute stroke, and that protein S100B concentrations at days 2 to 4 after acute stroke may provide valuable information for both neurological status and functional impairment at discharge from the acute care hospital; the neurological status was evaluated by (NIHSS) on admission, at days 1 and 4 on the stroke unit, at day 10, and at discharge from the hospital; those results agreed with the present study in the significance of correlation between S100B day 3 and the short-term functional outcome.

In the present study, there was statistically significant difference between the two studied groups at the same period showing more elevated level of S100B in group II. There was no statistically significant difference between day 1 and day 3 in group I, while there was statistically significant difference regarding group II showing that worsening of the neurological state in the group of poor

outcome is accompanied by significant elevation in S100B level (Table 2).

In contrast to our study, Park et al. [20] in their study on 111 acute ischemic stroke patients, measurement of plasma H-FABP (heart type fatty acid binding protein) and S100B levels done during acute phase (< 24 h) of stroke and clinical severities were evaluated by the use of NIHSS scores at the time of admission and MRS at 3 months after onset, found that S100B was correlated with initial NIHSS score, and agreeing with the present study that S100B was significantly higher in patients with poor clinical outcome with increased MRS score.

In agreement with our study, González-García et al. [21] reported that there was no significant association on admission between S100B concentrations and stroke severity as measured by the NIHSS. Even though, S100B was not found to be associated with functional neurological deficit at 60 days outcome either in IS nor in HS.

The release patterns of protein S100B in the present study confirm the results of previous clinical studies that had examined sequential S100B levels after stroke. Kim et al. [22] measured S100B protein in serum on days 1, 3, and 7 after infarction and found peak values after 3 days agreed with the present study. Missler et al. [23] in their study found that concentration of S100B protein in blood peaks 2.5 ± 1.3 days after infarction and concluded that the concentration of S100B protein in blood during acute stroke is a useful marker of infarct size and of long-term clinical outcome agreeing to the present study.

In contrast to the present study, Buttner et al. [24] in their study reported a significant correlation between protein S100B and neurological status at admission. They failed, however, to calculate significant correlations between protein S-100B values and the functional outcome 4 weeks after stroke onset.

Agreeing with the present study, Abraha et al. [25] found that S100B protein concentration was also significantly related to clinical outcome at 3 months measured using three disability and handicap scales with high values associated with poor clinical outcome; their study concluded that measurement of serum S100B protein could be a useful prognostic marker of clinical outcome in acute stroke.

Jauch et al. [26] in their study found that patients with favorable outcomes had smaller changes in S100B concentrations in the first 24 h, agreeing with the present study as no significant change in level of S100B was found between day 1 and 3 in group I.

Regarding NIHSS, which quantify the neurological deficit, there was statistical significant difference between NIHSS in group I and II in the same day showing the starting clinical neurological state of the group I minor-moderate stroke and in the group moderate to severe stroke, there was statistical significant difference between day 1 and 3 in two groups showing that the improvement or worsening of the neurological state apparently started to show by the day 3, there was statistical significant difference between day 1 and day 14 in two groups showing that the improvement or worsening of the neurological state already established by day 14, while there was no statistical significant difference between day 3 and 14 in two groups showing that improvement or worsening of the neurological state signs appear as early as day 3 without marked change upon reaching day 14.

We concluded that the severity of stroke quantified by using NIHSS is probably the most important clinical predictor of short-term outcome as significant change in the score between admission and discharge (day 14) was found (Table 1). Frankel et al. [27] found that patients with a severe neurologic deficit after acute ischemic stroke, as measured by the NIHSS, have a poor prognosis agreeing with the presented study.

Regarding comorbidities, there was no statistical significant difference between the two groups regarding DM and cardiac disease while there was statistical significant difference regarding HTN, 92.9% and 66.7% in two groups respectively, total hypertensive patients 85%, confirming that arterial hypertension (HTN) is the single most important modifiable risk factor for stroke with high prevalence among patients with a recent ischemic stroke [28, 29], agreed upon by O'Donnell et al. [30] in their study about risk factors for ischemic and intracerebral hemorrhagic stroke in 22 countries, and González-García et al. [21] where hypertension prevalence among ischemic stroke patients was 81.8% and 58.8% among hemorrhagic stroke.

The major limitation of the study is that longer follow up duration for the patients is needed.

Conclusions

Protein S100B measured at day 3 after acute cerebrovascular stroke was significantly correlated with short-term functional outcome at day 14. Significant elevation in S100B level accompanied worsening of the neurological state in the group of poor outcomes showing that S100B has a good prognostic value.

Abbreviations

ALT: Alanine transaminase; ANOVA: Analysis of variance; AST: Aspartate transaminase; AUC: Area under curve; CNS: Central nervous system; CT: Computed tomography; DM: Diabetes mellitus; ELISA: Enzyme-linked immunosorbent assay; END: Early neurological deterioration; GCS: Glasgow coma scale; GOS: Glasgow outcome scale; HTN: Hypertension; MRI: Magnetic resonance imaging; MRS: Modified Rankin scale; NIHSS: National institute of health stroke scale; NPV: Negative predictive value; *P* value: Probability value; PPV: Positive predictive value; ROC: Receiver operating characteristic curve; SD: Standard deviation; SPSS: Statistical Package for the Social Sciences

Authors' contributions
WE conducted neurological examination, scoring, sampling, followed the recruited patients up, wrote the paper material, and she is the corresponding author for editing. SA participated in creating the idea and principle of the conducted research. EM created the study design, methodology, supervised, and revised the written material. AE revised the writing process. ME revised the writing process. DH laboratory analysis of samples. All authors read and approved the final manuscript.

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Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

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