

Preoperative Serum S100 B Protein as a Prognostic Marker for Traumatic Brain Injury Patients

Ali E. Seif El-Deen MD, Said Hammad MD*, Amal El-Bendary MD*

Departments of Neurosurgery & Clinical Pathology*,
Faculty of Medicine, Tanta University

ABSTRACT

Objectives: The preoperative estimation of serum levels of protein S100 B in patients with traumatic brain injury (TBI) as a prognostic marker for their outcome is evaluated in this study, considering TBI as any blow to the head causing a clinical diagnosis of head injury to be made, even if insufficient to cause definite loss of consciousness. **Patients & Methods:** The study included 40 patients with TBI of varied severity and 10 volunteers as a control group. The initial severity of the injury was assessed using the Glasgow coma score (GCS), and neurological assessment were performed at the emergency department. Cranial CT scans without contrast enhancement were performed soon after admission. All patients received measures to decrease intracranial pressure and phyntoin for posttraumatic seizures and as a neuroprotector. Operative procedures were conducted according to the type of post-traumatic lesion. Follow-up was conducted monthly and the final outcome at six months was assessed using the Expanded Disability Status Scale (EDSS) and the final outcome was considered unfavorable if the patient had $EDSS \geq 5$. **Results:** The study comprised 40 patients with a mean age of 42.7 ± 8.8 years; 17 patients (42.5%) had loss of consciousness at the scene of the accident; 9 patients (22.5%) arrived unconscious and 26 patients (65%) had posttraumatic amnesia. Twenty-one patients (52.5%) had isolated TBI, while 19 patients (47.5%) had TBI associated with multiple trauma. Mean initial GCS score was 11.1 ± 3 and normal CT was reported in 14 patients (35%). Throughout ICU stay 15 patients died for a mortality rate of 37.5% and 9 of the survivors (36%) had unfavorable outcome with $EDSS \geq 5$. Serum S100B levels were significantly higher in patients compared to control levels, in non-survivors compared to survivors and in patients with unfavorable compared to favorable outcome. There was a negative significant correlation between serum S100B levels and both GCS and survival, while survival showed a positive significant correlation with GCS. Moreover, serum S100B levels showed negative significant correlation with clinically evaluated neurological outcome. Using ROC curve, serum S100 B levels were found to be the most specific predictor of mortality ($AUC=0.960$), followed by time lag between trauma affliction and sampling ($AUC=0.532$) and was the most specific predictor of unfavorable neurological outcome ($AUC=0.844$) followed by age ($AUC=0.622$). ROC curve analysis defined serum level of S100B at cutoff point of ≤ 0.52 ($AUC=0.697$) as the most appropriate cutoff point for identification of patients with predicted survival and favorable neurological outcome with specificity rate of 55.6% and 66.7%, respectively and accuracy rate of 70% and 80%, respectively. **Conclusion:** It could be concluded that preoperative estimation of serum S100B protein in patients with TBI could be used as a prognostic predictor for postoperative survival and neurological outcome. Serum levels of ≥ 0.52 $\mu\text{g/L}$ indicated bad prognosis.

INTRODUCTION

Protein S100 is a dimeric acidic calcium-binding protein with a molecular mass of 10–12 KD. It was

termed "S100" because it is partially soluble in a 100% saturated solution of ammonium sulfate, ⁽¹⁾. Protein S100 constitutes a major component of the cytosol of various cell types, but

protein S100B ($\beta\beta$ subunits) and S100A1 ($\alpha\beta$) are predominantly present in astrocytes and Schwann cells⁽²⁾. This protein has been implicated in the Ca^{2+} -dependent regulation of a variety of intracellular functions such as protein phosphorylation, enzyme activities, cell proliferation and differentiation, dynamics of cytoskeleton constituents, structural organization of membranes, intracellular Ca^{2+} homeostasis, inflammation, and protection from oxidative cell damage⁽³⁾.

The released S100B exerts paracrine and autocrine effects on neurons and glia. On the other hand, elevations of S100B levels in blood or cerebrospinal fluid have been observed in patients with Alzheimer's disease, Down's syndrome, amyotrophic lateral sclerosis, multiple sclerosis, schizophrenia, depression, cerebral stroke and traumatic brain injury⁽⁴⁾. It has been documented that the excessive S100 B promotes the expression of inducible nitric oxide synthase or pro-inflammatory cytokines and exhibits detrimental effects on neurons⁽⁵⁾. On studies using some animal models of the cerebral stroke or Alzheimer's disease, it is suggested that the excessive S100 B produced by activated astrocytes precedes neurodegenerations⁽⁶⁾.

Protein S100 B can be both actively secreted into the extracellular space and passively released by cell death. It has been reported that S100 B protein is an early marker for cerebral injury and the appearance of S100 B in serum indicates both neuronal damage and increased permeability of the blood-brain barrier⁽⁷⁾.

Rapid detection of tissue injury is very important for stratifying patients for treatment and for improved clinical outcome. Therefore, research in the

field of brain-specific proteins as biochemical plasma markers for neurologic disorders or brain injury is expanding. The proteins S100 B, neuron specific enolase, myelin basic protein, and glial fibrillary acidic protein are currently being evaluated as protein markers in cerebrospinal fluid and/or blood for detection of brain injury in neurologic patients, and patients with cerebrovascular accidents, traumatic brain injury, stroke, global cerebral ischemia attributable to cardiac arrest or cardiopulmonary bypass surgery, tumor cerebri, or dementia, with the aim to eventually locate the site of injury (neuron, glia, or myelin),^(8,9).

The diagnosis of acute cerebral injury currently relies on clinical neurological examination, computed axial tomography or magnetic resonance imaging. However, these methods are not always suitable for the unconscious and artificially ventilated, or hemodynamically unstable and thus unable to cooperate. The identification of a biochemical serum marker to assist in diagnosis and predicting the outcome of acute traumatic brain injury would be potentially useful,⁽¹⁰⁾. Thus, the current study was designed to evaluate the prognostic yield of preoperative estimation of serum levels of protein S100B in patients with TBI, so as to be used as prognostic marker for postoperative outcome of TBI cases.

PATIENTS & METHODS

This prospective double-blinded study was conducted at Neurosurgery Department, Tanta University Hospital, since Jan 2006 till March 2008 to allow a minimum follow-up period of 6 months for the last case

operated upon. After obtaining approval of the study protocol from the Local Ethical Committee and fully informed written consent from the patients or their nearest relative, 40 patients with TBI of varied severity, either isolated injury secondary to head trauma or as a part of multiple trauma, were enrolled in the study. The study comprised 10 volunteers to donate blood as a control group.

Inclusion criteria were head injury and presentation to the emergency department within six hours of injury. The definition of head injury used for this study was "any blow to the head causing a clinical diagnosis of head injury to be made, even if insufficient to cause definite loss of consciousness"⁽¹¹⁾. A six hour cutoff was chosen as it is thought that S-100B is rapidly cleared from the serum, with a half-life estimated at around six hours⁽¹²⁾. Patients with history of Alzheimer's disease, Down's syndrome, multiple sclerosis, schizophrenia, depression, cerebral stroke, spinal cord injury were excluded off the study because these diseases are associated with elevated serum S100 protein".

Base line demographic data, time and mechanism of injury, relevant symptoms and signs were recorded. Clinical information was obtained, including information necessary to determine the severity of illness and use of intensive care resources. Initial injury severity was assessed at admission using the Glasgow coma score (GCS) that evaluates eye response (eye open spontaneously=4, eye opening on verbal command = 3, eye opening to painful stimuli = 2 & no eye opening = 1), verbal response (orientated = 5, confused, disorientated=4, incoherent, inappropriate words = 3,

incomprehensive sounds=2 & no verbal response=1) and motor response (obeys commands=6, localizes pain=5, withdraws to pain=4, decorticate posture=3, decerebrate posture=2 & no motor response=1), the summation of the three responses equals the total score with score of 15 is the best and trauma was classified as mild; GCS=13-15, moderate; GCS=9-12 and severe; GCS \leq 8, ⁽¹³⁾. All patients were cared at Surgical ICU irrespective of the severity of trauma or the initial GCS. Neurological assessment was performed at emergency department prior to transfer to ICU and initiation of therapy. Also, cranial CT scans without contrast enhancement were performed in standardized slices soon after admission and lesions were evaluated with respect to lesion topography and territories of vascular supply on the basis of *Damasio & Damasio*⁽¹⁴⁾. CT findings were defined as pathological (CT+) if intracranial hemorrhage, skull fracture, brain edema, or contusions were detected. Post-traumatic lesions included: depressed skull fracture; intracerebral hematoma/brain contusion(s); subarachnoid hemorrhage; subdural hematoma; epidural hematoma; and intraventricular hemorrhage, ⁽¹⁵⁾.

Therapeutic measures

First-aid Measures

1. All patients received general measures to decrease intracranial pressure: elevation of the head of the bed for 30° with keeping the neck straight and avoiding hypotension and controlling hypertension if present.
2. Ventilation in sever head injured patients to maintain normocabnia (P_{CO_2} = 35-40 mmHg), light sedation using intramuscular codeine sulphate 30-60 mg/4 hrs and dehydration measures in the

form of mannitol intravenous infusion in a loading dose of 0.25-1 mg/kg, followed 0.25 mg/kg/6 hrs.

3. If intracranial hypertension persisted, patients were heavily sedated using intravenous fentanyl 1-2 ml or magnesium sulphate 2-4 mg or pancornium 3-5 mg intravenous, increased doses of mannitol and lastly cerebrospinal fluid drainage via interventricular catheter.
4. Phynytoin was used for posttraumatic seizures and as a neuroprotector in a loading dose as 20 mg/kg within 24 hrs after injury and high therapeutic levels were maintained in presence of acute subdural, epidural or intracerebral hematoma, GCS \leq 10 on admission, open depressed skull fracture with parenchymal injury, cortical contusion on CT examination, penetrating brain injury, or the development of seizures within the first 24 hrs after injury.

Operative measures

Operative procedure varied according to clinico-radiological assessment:

1. Cases with compound depressed skull fracture underwent adequate exposure with elevation of all bone fragments, excision of foreign bodies, repair of dural tear if present and dealing with underlying pathology as contusion or hematoma.
2. Extra-axial mass with a definite shift of the midline, clearly identifiable extra-axial lesion of increased or decreased density and the midline is seen to be shifted on computed tomographic scan more than 4 mm, the lesion should be evacuated.
3. Midline shift without extra- or intra-axial clot seen on computed tomographic scan of 5mm or more, craniotomy even if high density

masses are not seen on computed tomographic scan.

4. Intra-axial mass in presence of focal neurologic deficit associated with large hematoma in an appropriate anatomical location, loss of consciousness, deteriorating or unimproved neurological status, intractable elevation of ICP or significant midline shift on CT scanning. For such cases hematoma evacuation, localization of the source of hemorrhage and securing hemostasis was performed.
5. Multiple intra-axial lesions with midline shift, the primary lesion or lesions producing the shift should be evaluated.
6. Cases with cerebral contusion with progressive neurological deterioration or intractable uncontrolled elevation or of ICP underwent cranial decompression with removal of contused brain tissue

Follow-up

Follow-up was conducted monthly and the final outcome at six months was assessed using the Expanded Disability Status Scale (EDSS). It is a ten point scale derived from severity scores in each of 6 systems (sensory, motor, sphincteric, brain stem, vision, cerebral), ambulation and work ability with 0=no symptoms or signs, 1=mild disability with no or minimal impairment of ambulation, 3.5-5.5=moderate disability and impairment of gait, 6-9.5= severe disability ending in a bed-ridden helpless patient and 10=death due to MS. The final outcome was considered unfavorable if the patient had EDSS \geq 5⁽¹⁶⁾.

Serum S100 B protein estimation

Sampling:

A venous blood sample was collected at admission and blood was allowed to clot, and after centrifugation

within 30 minutes (1000g, 10 minutes), serum was collected and stored at -80°C for later analysis. Time lag between trauma affliction and sampling was identified.

Assay:

Micro titer ELISA plates coated with 10 μL of anti-S-100 β chain (Sigma) in 20 ml phosphate buffer (0.05 mol/L, pH 8.6) were incubated with 200 μL per well of S-100 calibrators, controls, and samples for 120 minutes. Biotin-labeled rabbit anti-S-100 antibody (DAKO) in a Tris 0.05 mol/L, NaCl 0.15 mol/L, CaCl_2 10 mmol/l, NaN_3 0.15 mmol/l buffer was added, and plates were incubated for another hour. After the plates had been washed, 200 μL of streptavidin-europium in assay buffer (Tris 0.05 mol/L, NaCl 0.15 mol/L, bovine serum albumin 1 g/L, bovine gamma globulin 0.5 g/L, both from Sigma, NaN_3 0.15 mmol/L) was added to each well, and the plates were incubated for 30 minutes. As a last step, 200 μL of enhancement solution (acetic acid 0.01 mol/L, tri-*n*-octyl phosphine oxide 38 mg/L, potassium phtalate 1.3 g/l, thenoyltrifluoroacetone 222 mg/l, Triton X-100 2 ml/L) was added to each well, and the plates were incubated for 15 minutes,⁽¹⁷⁾ Serum S100 B levels >0.1 $\mu\text{g/L}$ are considered pathologic depending on the work of *Biberthaler et al.*,⁽¹⁸⁾ who ascertained that a cut-off point at a concentration of 0.1 $\mu\text{g/L}$ of S 100 B, which was the highest level measured in healthy volunteers without any sign of intracranial injury, is an accurate discriminative cutoff point.

RESULTS

The study comprised 40 patients; 31 males (77.5%) and 9 females

(22.5%). The Patients' mean age was 42.7 ± 8.8 ; within a range of 26–61 years. There were 29 patients (72.5%) who had a car accident, 7 patients (17.5%) had fallen from a height and 4 patients (10%) had motorbike accident. Seventeen patients (42.5%) had loss of consciousness at the scene of the accident and 9 patients (22.5%) arrived unconscious; while the other 23 patients (57.5%) did not lose consciousness at all, 26 patients (65%) had posttraumatic amnesia, while 14 patients (35%) did not have. Twenty-one patients (52.5%) had isolated TBI, while the other 19 patients (47.5%) had TBI associated with multiple trauma, (Table 1).

The mean initial GCS score was 11.1 ± 3 ; range: 5–15. There were 14 patients (35%) with mild trauma and a mean GCS score was 14.1 ± 0.9 ; range: 13–15; 17 patients (42.5%) with moderate trauma and a mean GCS score was 11.1 ± 0.9 ; range: 10–12 and 9 patients (22.5%) with severe trauma and a mean GCS score was 6.3 ± 1.1 ; range: 5–9, (Table 2).

Normal CT was reported in 14 patients (35%); however, CT scanning detected fissure skull fracture in 4 patients (10%), fissure basal skull fracture in 2 patients (5%) and depressed skull fracture in 4 patients (10%); extradural hemorrhage in 6 patients (15%), subdural hemorrhage in 7 patients (17.5%), 2 patients (5%) had subarachnoid hemorrhage and the last patients had intracerebral hemorrhage, (Table 3; case presentation).

Throughout ICU stay 15 patients died for a mortality rate of 37.5% after a mean duration of ICU stay of 2.2 ± 0.8 ; range: 1–3 days. On contrary, the 25 survivors had a mean ICU stay of 11.3 ± 3.9 ; range: 6–20 days. There was a non-significant difference

between survivors and non-survivors as regards age, gender, time of sampling or presence of multiple trauma, (Table 4).

Survivors had significantly higher frequency ($X^2=3.322$, $p<0.05$) of mild and moderate trauma with less frequency of severe trauma and showed significantly higher GCS ($Z=3.305$, $p=0.001$) at time of arrival compared to non-survivors, (Table 4, Fig. 1). Throughout follow-up period 16 of the 25 survivors (64%) had favorable outcome (EDSS<5); 4 patients (16%) had EDSS=0, 7 patients (28%) had EDSS=1, 2 patients (8%) had EDSS=2 and 3 patients (12%) had EDSS=3, while the other 9 survivors (36%) had unfavorable outcome with EDSS \geq 5, (Table 6). Mean EDSS was significantly lower ($Z=2.67$, $p=0.008$) in patients had favorable outcome compared to those had unfavorable outcome, (Fig. 2).

The estimated serum levels of S100B (Fig. 3) were significantly higher in patients compared to control levels, in non-survivors compared to survivors and were significantly higher in patients with unfavorable outcome (EDSS \geq 5) compared to those with favorable outcome (EDSS<5), (Table 6, Fig. 4).

There was a negative significant correlation between serum S100B levels and both GCS, ($r=-0.452$,

$P=0.003$) and survival, ($r=-0.795$, $P<0.001$), (Fig. 5), while survival showed a positive significant correlation with GCS, ($r=0.397$, $P=0.011$), (Fig. 6). Similarly, serum S100B levels showed negative significant correlation ($r=0.546$, $P=0.005$) with clinically evaluated neurological outcome, (Fig. 7).

Using ROC curve, plotted for various patients' characters, time of sampling, GSC and serum levels of S100B for identification of the specific predictor of mortality, serum levels of S100 B was found to be the most specific for the prediction of mortality with AUC=0.960, followed by time lag between trauma affliction and sampling with AUC=0.532. On the other hand, serum S100B level was the most specific for the prediction of unfavorable neurological outcome with AUC=0.844 followed by age with AUC=0.622, (Table 7, Fig. 8 & 9). Using ROC curve analysis of estimated serum levels of S100 defined serum level of S100B protein at cutoff point of ≤ 0.52 (AUC=0.697) as the most appropriate cutoff point for identification of patients with predicted survival and favorable neurological outcome with specificity rate of 55.6% and 66.7%, respectively and accuracy rate of 70% and 80%, respectively, (Fig. 10).

Table (1): Demographic and initial clinical data of studied patients

Age (years)		38.8±13.9 (18-62)
Sex; M:F		28:12
Cause of trauma	Car accident	29 (72.5%)
	Fall from height	7 (17.5%)
	Motorbike accident	4 (10%)
Loss of consciousness	No	23 (57.5%)
	At scene of accident only	8 (20%)
	At scene of accident till admission	9 (22.5%)
Posttraumatic amnesia	No	14 (35%)
	Present	21 (65%)
Type of trauma	Isolated TBI	21 (52.5%)
	Multiple trauma including TBI	19 (47.5%)

Data are presented as mean±SD, ratios and numbers; ranges and percentages are in parenthesis.

Table (2): Initial GCS score of studied patients and type of trauma

Severity of trauma	Number (%)	GCS score
Mild trauma	14 (35%)	14.1±0.9 (13-15)
Moderate trauma	17 (42.5%)	11.1±0.9 (10-12)
Severe trauma	9 (22.5%)	6.3±1.1 (5-8)
Total	40 (100%)	11.1±3 (5-15)

Data are presented as mean±SD and numbers; ranges and percentages are in parenthesis.

Table (3): Patients' distribution according to CT findings

CT findings	Number (%)
Normal	14 (35%)
Fissure skull fracture only	4 (10%)
Basal skull fracture only	2 (5%)
Depressed skull fracture	4 (10%)
Extradural hemorrhage	6 (15%)
Subdural hemorrhage	7 (17.5%)
Subarachnoid hemorrhage	2 (5%)
Intracerebral hemorrhage	1 (2.5%)

Data are presented as numbers and percentages are in parenthesis.

Table (4): Preliminary data of studied patients categorized according to survival outcome

Severity of trauma		Survivors	Non-survivors
Age (years)		42.9±9.5 (26-61)	42.3±7.8 (32-53)
Male: Female (%)		76:24	80:20
Time of sampling (min)		138.2±59.7 (30-240)	156±86.5 (30-240)
Type of trauma	Isolated TBI	14 (56%)	7 (46.7%)
	Multiple trauma including TBI	11 (44%)	8 (53.3%)
Trauma severity	Mild	10 (40%)	4 (26.7%)
	Moderate	11 (44%)	6 (40%)
	Severe	4 (16%)	5 (33.3%)
GSC at time of arrival		12±2.6 (7-15)	9.5±3.2 (5-13)

Data are presented as mean±SD and numbers; ranges and percentages are in parenthesis.

Table (5): Patients' distribution according to Follow-up outcome evaluated as EDSS

Outcome		Number (%)
Favorable	Good recovery with no symptoms or signs (EDSS=0)	4 (16%)
	No disability with minimal impairment of ambulation (EDSS=1)	7 (28%)
	Mild disability with minimal gait impairment (EDSS=2)	2 (8%)
	Moderate impairment of ambulation (EDSS=3)	3 (9%)
Unfavorable (EDSS ≥5)		9 (36%)

Data are presented as numbers and percentages are in parenthesis.

Table (6): Serum S100 levels estimated in studied patients categorized according to survival and neurological outcome of survivors compared to control levels

Group			Serum level (µg/L)
Control			0.166±0.033 (0.12-0.22)
Patients	Total		0.756±0.334 (0.25-1.48)*
	Survivors	Total	0.553±0.16 (0.25-0.88)*
		Favorable	0.489±0.104 (0.36-0.75)*
		Unfavorable	0.667±0.183 (0.25-0.88)* ‡
	Non-survivors		1.095±0.266 (0.65-1.48)*†

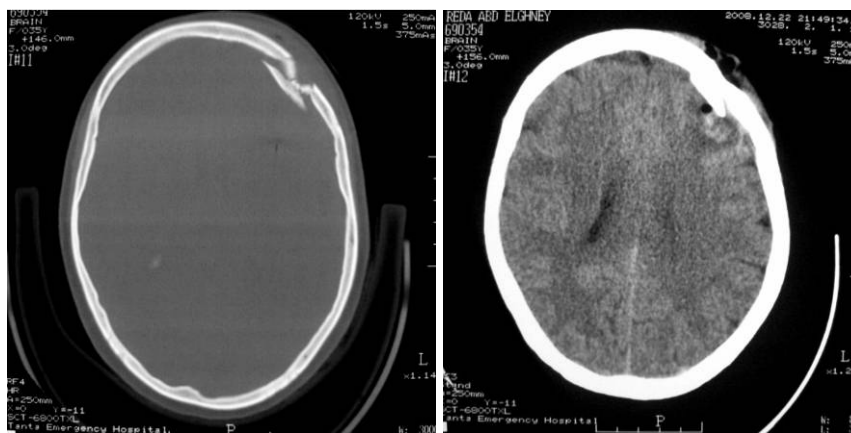
Data are presented as mean±SD, ranges are in parenthesis

*: Significant versus control levels †: Significant versus survivors

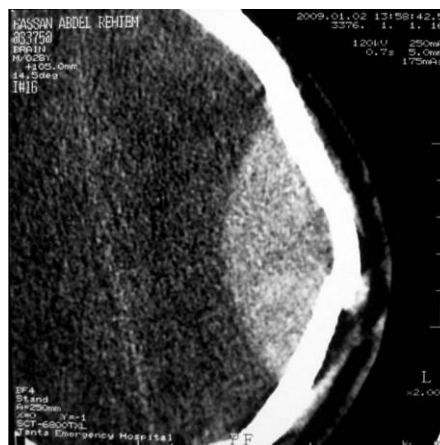
‡: Significant versus patients had favorable outcome

Table (7): Specificity of various parameters for prediction of mortality and unfavorable neurological outcome presented as AUC

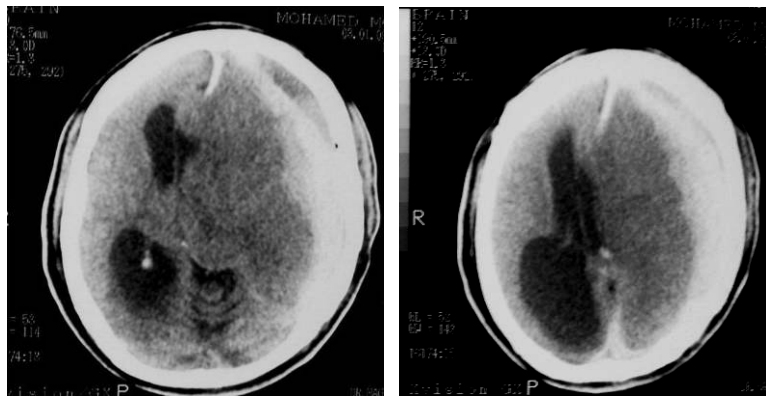
Data	Mortality	Unfavorable outcome
Age (years)	0.498	0.622
Male gender	0.520	0.514
Initial GCS	0.277	0.597
Time lag till sampling (min)	0.532	0.493
Serum S100 level	0.960	0.844

CASE PRESENTATION

Case (1): Male patient aged 35 years with history of local head trauma, patient was conscious, presented by frontal scalp wound with +VE halo sign, CT brain showed compound depressed skull fracture with underlying brain laceration and pneumocephalus. The depressed fractured bone was elevated and after dealing with the brain laceration, and dural repair; the extracted bone was repositioned.



Case (2): Male patient aged 28 years old with history of local head trauma; GCS=13, presented by parietal scalp wound, repeated vomiting with GCS=13. CT brain showed an epidural hematoma. Patient had been operated upon by craniotomy flap and hematoma evacuation.



Case (3): Male patient aged 37 years, presented by history of MVA, GCS=7, unequal pupils, CT brain showed left fronto-temporo-parietal acute subdural hematoma with marked mass effect and midline shift, and early signs of brain herniation. Patient had been operated upon by craniotomy flap and hematoma evacuation.

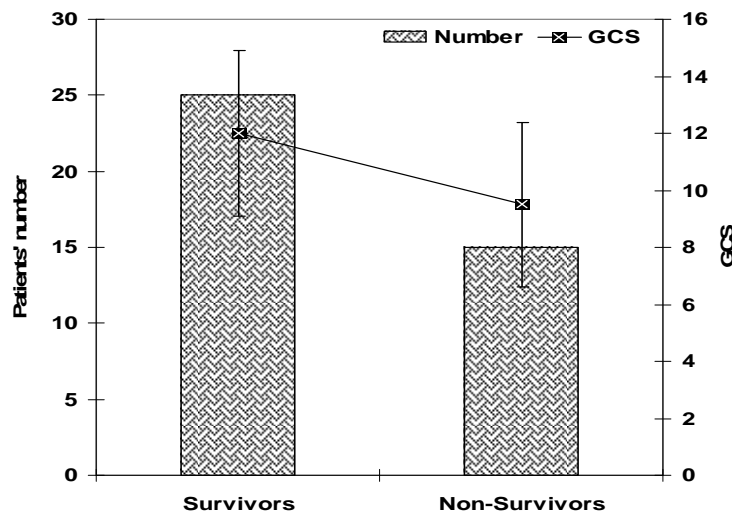


Fig. (1): Patients' distribution according to survival in relation to initial GCS determined at time of arrival

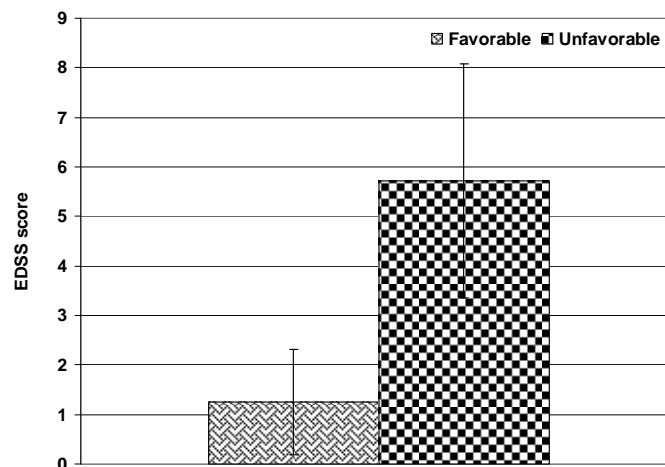


Fig. (2): Mean EDSS of survivors categorized according to neurological outcome

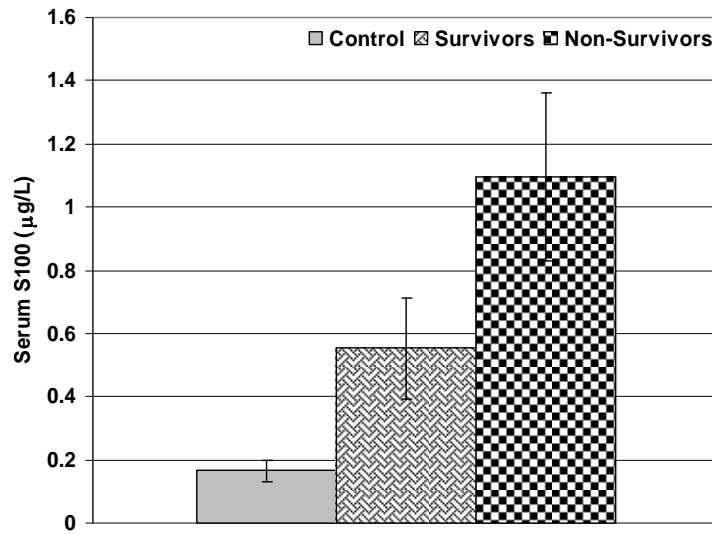


Fig. (3): Mean (\pm SD) of serum S100 levels estimated in patients categorized according to survival and compared to control levels

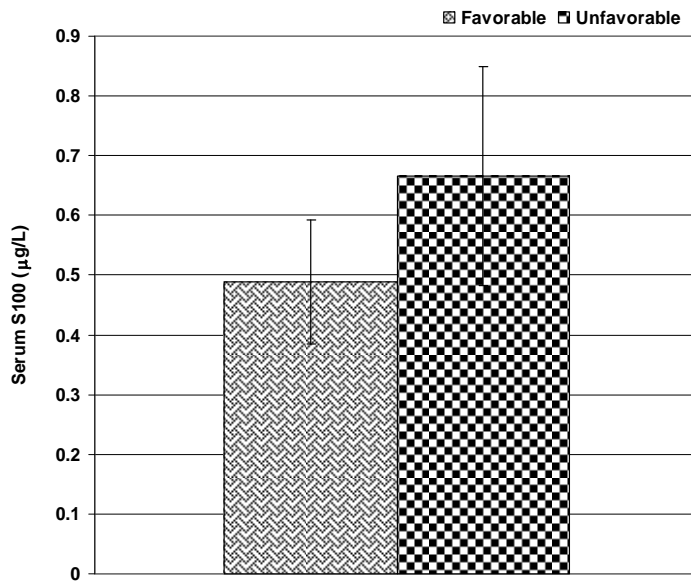


Fig. (4): Mean (\pm SD) of serum S100 levels estimated in survivors categorized according to neurological outcome

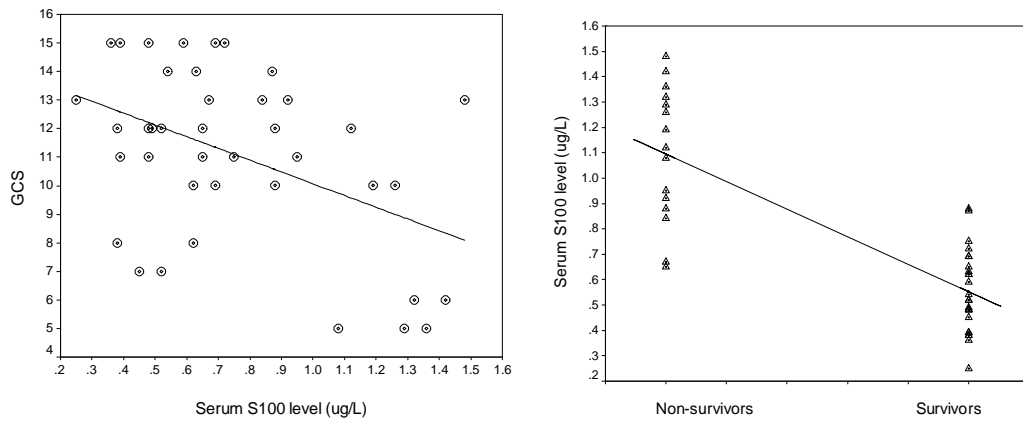


Fig. (5): Correlation between serum S100B level and both GCS and survival in studied patients

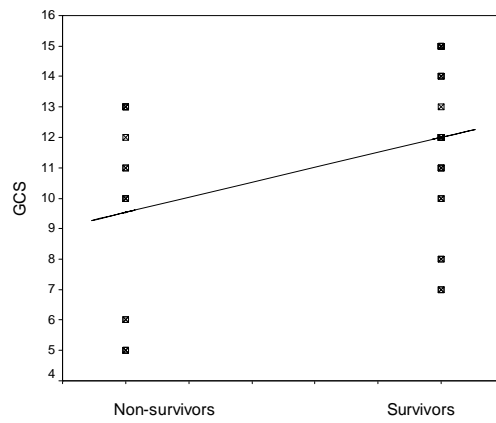


Fig. (6): Correlation between survival and GCS in studied patients

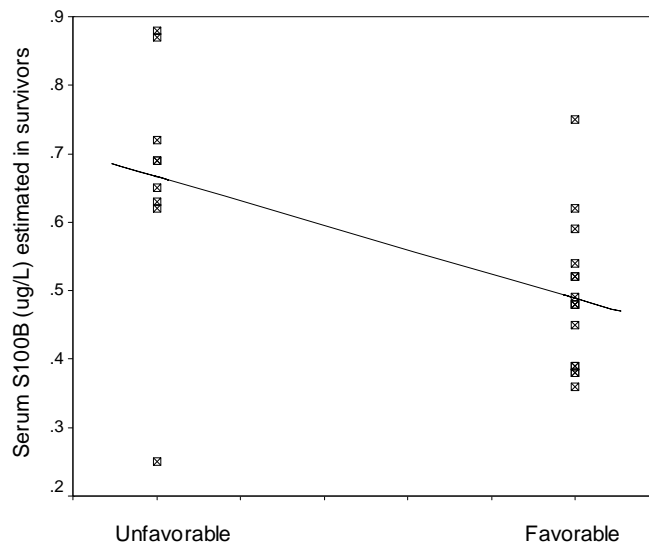


Fig. (7): Correlation between serum S100B and neurological outcome of survivors

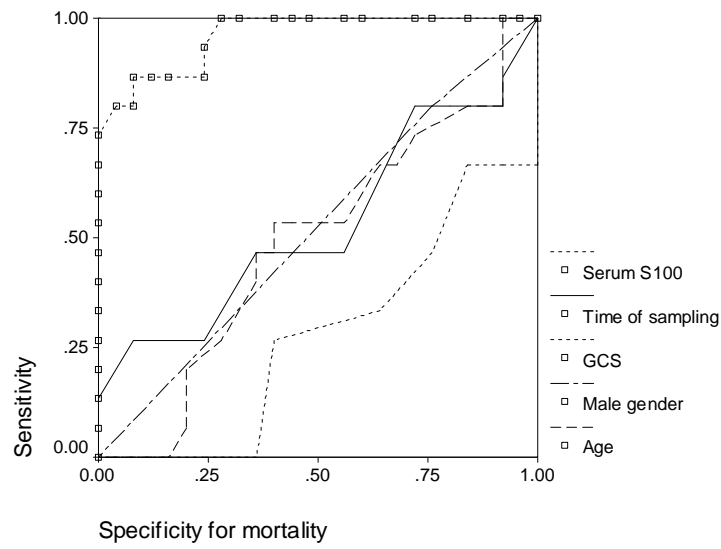


Fig. (8): ROC curve analysis of studied parameters as predictors for mortality after TBI

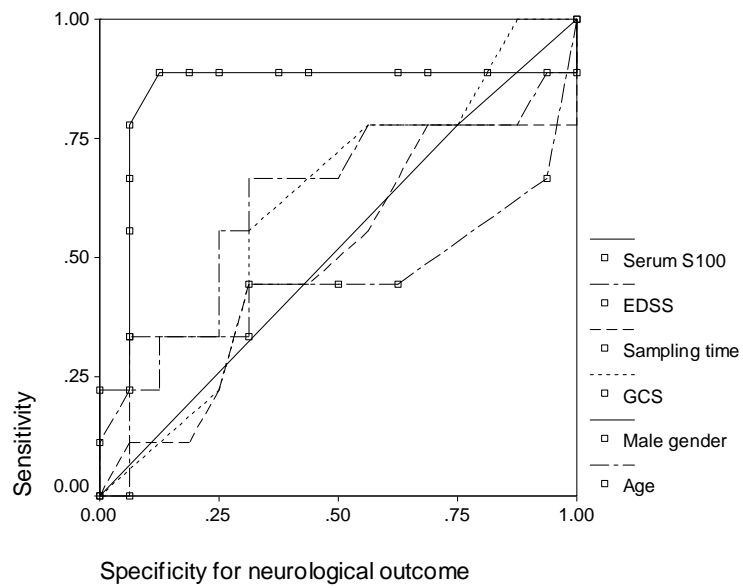


Fig. (9): ROC curve analysis of studied parameters as predictors for mortality after TBI

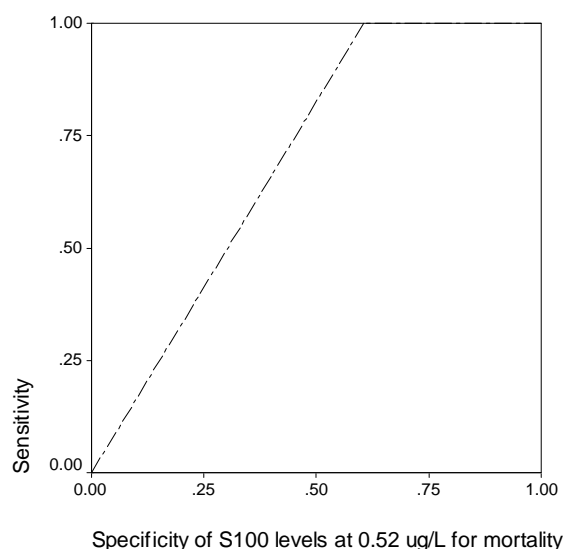


Fig. (10): ROC curve analysis of serum S100 level at 0.52 µg/L as predictor for mortality after TBI

DISCUSSION

The members of the S100 protein family are multifunctional proteins with a regulatory role in a variety of cellular processes. They exert their actions usually through calcium binding, although Zn^{2+} and Cu^{2+} have also been shown to regulate their biological activity. The most studied member, protein S100B, exhibits neurotrophic (at physiologic concentration) or neurotoxic (at higher concentration) activity and its immunohistochemical expression or serum levels have been determined in various clinical disorders,⁽¹⁹⁾

The current study was designed to evaluate the prognostic yield of estimation of serum levels of protein S100B in patients with TBI, so as to be used as prognostic markers for cases admitted to ICU after TBI.

Estimated serum levels of S100B were significantly higher in TBI patients, irrespective of the trauma severity or being isolated or a part of

multiple trauma, compared to the control levels. This finding signified that S100B was released early after TBI and could be considered as an early marker. This finding agreed with *Biberthaler et al.*,⁽¹⁸⁾ who found the initial S100B serum levels of mild head trauma patients were significantly higher than those of the negative control group and with *Hayakata et al.*,⁽²⁰⁾ who found CSF concentrations of S100B peak within 24 h after severe traumatic brain injury and decrease gradually thereafter and could be useful as predictors of outcome in cases of severe TBI. *Song et al.*,⁽²¹⁾ evaluated serum levels of S100B protein after acute radiation induced brain injury in astrocytoma patients and reported that high levels of serum S100B protein are associated with radiation-induced brain injury in astrocytoma patients and may serve as the marker for early diagnosis of the injury. Moreover, *Berger et al.*,^(22, 23) found serum S100B levels are increased in the majority of children

with acute traumatic brain injury, including well-appearing children in whom the diagnosis might otherwise be missed. Furthermore, *Springborg et al.*⁽²⁴⁾ reported that the high sensitivity and high negative predictive value of S100B for brain damage is clinically useful and integration of S100B into existing management routines can reduce the need for CT scans or admission by over 30%.

Also, the estimated serum levels of S100B were significantly higher in non-survivors compared to survivors and in patients with unfavorable outcome compared to those with favorable outcome. These results illustrated the prognostic yield of estimation of serum S100B levels at time of admission. In support of these data, serum S100B levels showed a positive significant correlation with the initial GCS and a negative significant correlation with both the frequency of survival and favorable outcome. Moreover, ROC curve analysis for various patients' characteristics, initial GCS and serum S100B as predictors for prognosis defined estimated serum S100B level as the most specific predictor for both survival and neurologic outcome.

These findings go in hand with various previous studies; *da Rocha et al.*⁽²⁵⁾ tried to determine whether S100B serum levels correlate with primary outcome following isolated severe TBI or multitrauma in males and found mean S100B concentrations were significantly increased in the patient with TBI compared with the control group and patients with fatal outcome had higher mean S100B concentrations when compared with survivors with a significant correlation between higher initial S100B concentrations and fatal outcome. *Watt et al.*⁽²⁶⁾ examined the relationship

between serum concentrations of protein S-100B and neuropsychological functioning following severe traumatic brain injury and found early measurement of S-100 not only reflected overall brain injury severity, but also related to neuropsychological deficits, with higher serum concentrations associated with poorer performance across most cognitive domains. Also, *Townend & Ingebrigtsen*,⁽²⁷⁾ found patients with high levels of S-100B at initial assessment may represent a high risk group for disability after head trauma and *Berger et al.*,⁽²⁸⁾ reported that S100B concentrations obtained at the time of TBI may be useful in predicting outcome of pediatric traumatic brain injury.

ROC curve analysis of estimated serum levels of S100B defined ≤ 0.52 $\mu\text{g/L}$ as the most appropriate cutoff (AUC=0.679) for identification of patients with predicted survival and favorable neurological outcome with specificity rate of 55.6% and 66.7%, respectively and accuracy rate of 70% and 80%, respectively. Such cutoff point coincided with that reported by *Korfias et al.*⁽²⁹⁾ who reported that patients with initial serum S-100B levels above 1 $\mu\text{g/L}$ had a nearly threefold increased probability of death within 1 month and serum S-100B alteration indicated neurological improvement or deterioration. Surgical treatment reduced S-100B levels and concluded that serum S-100B protein reflects injury severity, improves prediction of outcome after severe TBI and may also have a role in assessing the efficacy of treatment after severe TBI. *Rainey et al.*⁽³⁰⁾ who found the cutoff point of 0.53 $\mu\text{g/L}$ has sensitivity of >80% and specificity of 60% to predict unfavourable outcome and 49% to predict death.

Various studies tried to elucidate the causal relationship between S100B and exacerbation of brain damage and bad prognosis; *Tateishi et al.*,⁽⁵⁾ suggested that released S100B exerts paracrine and autocrine effects, on neurons and glia, implicated in the Ca²⁺-dependent regulation of a variety of intracellular functions such as protein phosphorylation, enzyme activities, cell proliferation and differentiation, dynamics of cytoskeleton constituents, structural organization of membranes, intracellular Ca²⁺ homeostasis, inflammation, and protection from oxidative cell damage; but excessive S100B release promotes the expression of inducible nitric oxide synthase or pro-inflammatory cytokines and exhibits detrimental effects on neurons. *Mori et al.*⁽³¹⁾ using transgenic mice overexpressing human S100B provided genetic evidence that overexpression of human S100B acts to exacerbate brain damage and peri-infarct reactive gliosis (astrocytosis and microgliosis) during the subacute and acute phases of ischemic brain injury.

It could be concluded that preoperative estimation of serum S100B protein in patients with TBI could be used as a prognostic predictor for postoperative survival and neurological outcome and serum levels of ≥ 0.52 $\mu\text{g/L}$ indicated bad prognosis.

REFERENCES

1. **Zimmer DB, Cornwall EH, Landar A, Song W:** The S100 protein family: History, function, and expression. *Brain Research Bulletin*, 1995; 37: 417-29.
2. **Kligman D, Hilt DC:** The protein S 100 family. *Trends Biochem Sci*, 1998; 11: 437-43
3. **McAdory BS, Van Eldik LJ, Norden JJ:** S100B, a neurotropic protein that modulates neuronal protein phosphorylation, is upregulated during lesion-induced collateral sprouting and reactive synaptogenesis. *Brain Res*. 1998; 813:211-7.
4. **Delgado P, Alvarez Sabin J, Santamarina E, Molina CA, Quintana M, Rosell A, Montaner J:** Plasma S100B level after acute spontaneous intracerebral hemorrhage. *Stroke*, 2006; 37(11):2837-9.
5. **Tateishi N, Shimoda T, Yada N, Shinagawa R, Kagamiishi Y:** S100B: astrocyte specific protein. *Nihon Shinkei Seishin Yakurigaku Zasshi*. 2006; 26(1):11-6.
6. **Tanaka Y, Koizumi C, Marumo T, Omura T, Yoshida S:** Serum S100B is a useful surrogate marker for long-term outcomes in photochemically-induced thrombotic stroke rat models. *Life Sci.*, 2007; 81(8):657-63.
7. **Foerch C, Wunderlich MT, Dvorak F, Humpich M, Kahles T, Goertler M, Alvarez-Sabín J, Wallesch CW, Molina CA, Steinmetz H, Sitzer M, Montaner J:** Elevated serum S100B levels indicate a higher risk of hemorrhagic transformation after thrombolytic therapy in acute stroke. *Stroke*, 2007; 38(9):2491-5.
8. **Kirchhoff C, Buhmann S, Braunstein V, Leidel BA, Vogel T, Kreimeier U, Mutschler W, Biberthaler P:** Cerebrospinal s100-B: a potential marker for progressive intracranial hemorrhage in patients with severe traumatic brain injury. *Eur J Med Res.*, 2008; 13(11):511-6.
9. **Ishibashi H, Funakoshi Y:** Serum S-100B protein levels in left- and

- right-hemisphere strokes. *J Clin Neurosci.*, 2008; 15(5):520-5.
10. **Lima DP, Simão Filho C, Abib Sde C, de Figueiredo LF:** Quality of life and neuropsychological changes in mild head trauma. Late analysis and correlation with S100B protein and cranial CT scan performed at hospital admission. *Injury.* 2008; 39(5):604-11.
 11. **Wade DT, Crawford S, Wenden FJ:** Does routine follow up after head injury help? A randomised controlled trial. *J Neurol Neurosurg Psychiatry*, 1997; 62: 478-84.
 12. **Usui A, Kato K, Abe T:** S100 protein in blood and urine during open heart surgery. *Clin Chem.*, 1989; 35: 1942-4.
 13. **Teasdale G, Jennett B:** Assessment of coma and impaired consciousness: a practical scale. *Lancet*, 1974; ii: 81-4.
 14. **Damasio H, Damasio AR:** *Lesion Analysis in Neuropsychology.* New York, Oxford University Press, 1989.
 15. **Stiell IG, Wells GA, Vandemheen K:** The Canadian CT head rule for patients with minor head injury. *Lancet*, 2001; 357:1391-6.
 16. **Othman AM:** The extended disability status score. In: *Postgraduate Neurology*, Othman AM (ed), 1st ed., 2002; Pp: 573.
 17. **Abdul-Khaliq H, Schubert S & Stoltenburg-Didinger G (2000):** Protein S-100B in brain and serum after deep hypothermic circulatory arrest in rabbits: relationship to perivascular astrocytic swelling. *Clin Chem Lab Med.*; 38: 1169-72.
 18. **Biberthaler P, Mussack T, Wiedemann E, Kanz KG, Koelsch M, Steppert GC, Jochum M:** Evaluation of S-100b as a specific marker for neuronal damage due to minor head trauma. *World J Surg.*, 2001; 25(1): 93-7.
 19. **Sedaghat F, Notopoulos A:** S100 protein family and its application in clinical practice. *Hippokratia.* 2008; 12(4):198-204.
 20. **Hayakata T, Shiozaki T, Tasaki O, Ikegawa H, Inoue Y, Toshiyuki F & Sugimoto H:** Changes in CSF S100B and cytokine concentrations in early-phase severe traumatic brain injury. *Shock*, 2004; 22(2): 102-7.
 21. **Song WS, Guo LB, Hong ZY, Li JJ, Wu J:** Serum S100 protein and radiation-induced brain injury in astrocytoma patients. *Di Yi Jun Yi Da Xue Xue Bao.*, 2005; 25(6): 723-5.
 22. **Berger RP, Adelson PD, Pierce MC, Dulanti T, Cassidy LD & Kochanek PM:** Serum neuron-specific enolase, S100B, and myelin basic protein concentrations after inflicted and noninflicted traumatic brain injury in children. *J Neurosurg.* 2005; 103(1 Suppl.): 61-8.
 23. **Berger RP, Dulanti T, Adelson PD, Leventhal JM, Richichi R & Kochanek PM:** Identification of inflicted traumatic brain injury in well-appearing infants using serum and cerebrospinal markers: a possible screening tool. *Pediatrics*, 2006; 117(2): 325-32.
 24. **Springborg JB, Undén J, Ingebrigtsen T, Romner B:** Brain injury marker S100B can reduce the use of computer tomography in minor head injuries--secondary publication. *Ugeskr Laeger.* 2009; 171(12):978-81.
 25. **da Rocha AB, Schneider RF, de Freitas GR, André C, Grivicich I, Zanoni C, Fossá A, Gehrke JT, Pereira Jotz G, Kaufmann M, Simon D, Regner A:** Role of
-

- serum S100B as a predictive marker of fatal outcome following isolated severe head injury or multitrauma in males. *Clin Chem Lab Med.*, 2006;44(10):1234-42.
- 26. Watt SE, Shores EA, Baguley IJ, Dorsch N, Fearnside MR:** Protein S-100 and neuropsychological functioning following severe traumatic brain injury. *Brain Inj.* 2006; 20(10):1007-17.
- 27. Townend W, Ingebrigtsen T:** Head injury outcome prediction: a role for protein S-100B? *Injury*, 2006; 37(12):1098-108.
- 28. Berger RP, Beers SR, Richichi R, Wiesman D, Adelson PD:** Serum biomarker concentrations and outcome after pediatric traumatic brain injury. *J Neurotrauma.*, 2007;24(12):1793-801.
- 29. Korfiatis S, Stranjalis G, Boviatis E, Psachoulia C, Jullien G, Gregson B, Mendelow AD, Sakas DE:** Serum S-100B protein monitoring in patients with severe traumatic brain injury. *Intensive Care Med.* 2007; 33(2):255-60.
- 30. Rainey T, Lesko M, Sacho R, Lecky F, Childs C:** Predicting outcome after severe traumatic brain injury using the serum S100B biomarker: results using a single (24h) time-point. *Resuscitation.* 2009; 80(3):341-5.
- 31. Mori T, Tan J, Arendash GW, Koyama N, Nojima Y, Town T:** Overexpression of human S100B exacerbates brain damage and periinfarct gliosis after permanent focal ischemia. *Stroke.* 2008; 39(7):2114-21.
-