CLINICAL AND FORENSIC IMPORTANCE OF S100β PROTEIN FOR PREDICTION OF OUTCOME AND EVALUATION OF MEDICAL CARE IN MILD TO MODERATE HEAD INJURIES

BY

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ABSTRACT

The incidence of minor and mild to moderate traumatic brain injuries (TBI) have increased in the recent years, mainly at the expense of grave and moderate to severe injuries. The protein S100β is a sensitive biomarker to head injury. The aim of this study is to investigate importance of S100β protein as a new biomarker yielding a more informative diagnostic and prognostic technique to be added to the working protocols of dealing with TBIs. Fifty one patients with mild or moderate head injury were included in this study. Sociodemographic data, clinical data and computerized tomography (CT) findings were recorded in addition to measuring serum S100β levels within 6 hours after trauma. There was a significant increase of S100β levels in non survivors compared with survivors (P <0.001). There was a significant negative correlation between the levels of S100β and survival period in cases that died (r = -0.887, P <0.001). The protein S100β had a good predictive power for mortality (AUC = 0.803, cut off value > 1.205 ug/L, sensitivity = 100%, specificity = 54.55%). Adding S100β levels to Glasgow coma score and CT scan findings increased the accuracy of prediction of outcome from 64.7% to 82.4%. However, there were no significant differences in S100β levels as regards categories of severity or types of CT findings. It could be concluded that S100β serum level is a good predictor of outcome in cases of mild and moderate head injuries and its use is recommended both in clinical guidelines and in forensic practice.

Keywords: Head trauma, S100β protein, biological markers, GCS, medicolegal evaluation.

INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of death and lifelong disability in young adults worldwide and it is increasing in the elder population (Steyerberg et al., 2008; Roozenbeek et al., 2013). The term "traumatic brain injury" encompasses a heterogeneous group of pathological disorders, each with its

own clinical presentation, pathophysiology, natural history, treatment, and prognosis. TBI may be categorized by mechanism of injury, clinical severity, radiological appearance, pathology, or focal versus diffuse distribution (Levine and Kumar, 2013).

The socioeconomic consequences of TBI have ignited widespread research aiming at decreasing the burden of the disease (Czeiter et al., 2012). A major field to be explored is the establishment and construction of reliable prognostic tools that will facilitate more efficient design of clinical trials and improve individualized patient management (Menon and Zahed, 2009). There are three different approaches to outcome prediction following TBI. The first is based on admission characteristics such as the age, the reaction of pupils, Glasgow Coma Scale (GCS) score, GCS motor score, body temperature, blood glucose level, and significant non-cranial injuries, in addition to other factors (Hukkelhoven et al., 2005; Mushkudiani et al., 2008). The second approach is based on the pathological findings seen on the first available computerized tomography scan (CT), and is represented by the Marshall CT classification (Marshall et al., 1992), and Rotterdam score (Maas et al., 2005). The third utilizes blood and/or cerebrospinal fluid (CSF) levels of biomarkers of brain injury (Svetlov et al., 2009; Kovesdi et al., 2010).

The protein S100β is one of the calmodulin/troponin C superfamily of calcium binding proteins that has shown promise as a biochemical marker of outcome after mild head injury (Townend et al., 2002). The protein S100β has high specificity for nervous tissue although it is recognized that non-nervous tissues such as fat and muscle also release protein S100β (Netto et al., 2006). However, results reported by Pham et al. (2010) showed that extra-cranial sources of S100β do not affect serum levels. Thus, the diagnostic value of S100β is not compromised in the clinical setting.

The protein S100β is a member of the S100 family which was termed "S100" because it was soluble in 100% saturated ammonium sulfate solution (Moore, 1965). It is an acidic protein with a molecular weight of 21 KDA existing as a homodimer consisting of two beta subunits (Drohat et al., 1996). It is found mainly in the cytosol of glial cells and is released after glial cell damage leading to increased concentrations in CSF and serum. It has a half-life of 2 - 6 hours and can be measured in both arterial and venous serum. Increased levels of S100β are associated with a poor neurophysiological outcome (Herrmann et al., 2001; Donato, 2003; Stålnacke et al., 2005).

The protein S100β exerts a protective effect as long as it is kept within the cells at

physiological levels. However, once it is secreted or released, its local concentration then dictates its beneficial or detrimental effects. Nanomolar concentrations appear to exert neuroprotective effects, while micromolar concentrations produce neurodegenerative or apoptosis-inducing effects (Matthias et al., 2003). The incorporation of serum S100β levels in clinical guidelines for management of TBI was recommended and validated in many studies (Unde´n and Romner, 2009; Unde´n et al., 2015).

Despite the advances in the field of neurosurgery over the past several decades, neurosurgery is one of the top specialties with malpractice claims made against it. As healthcare policy and medical training evolve, incorporating this information on rates and risk of malpractice claims should impact the preparation in the future to avoid and minimize malpractice suits altogether (John, 2011).

Some reports have discussed the increased incidence of minor and mild to moderate craniocerebral injuries mainly at the expense of grave and moderate to severe injuries (Khaes and Cheprov, 1998). However, inconsistencies between clinical diagnosis and forensic medical recognition of TBI, especially cases of concussion, were observed in 69.53% in a study by Bloch-Boguslawska and Wolska (2004). This inconsistency may reflect itself on forensic medical diagnosis of lethal and non-lethal injuries to the head, evaluation of the quality of medical care, and qualification of the severity of harm to health (Isaev et al., 2002).

Hence, the aim of this study was to investigate the clinical and forensic importance of S100β as a new biomarker yielding a more informative diagnostic and prognostic technique to be added to the working protocols dealing with TBIs.

PATIENTS AND METHODS

This study was conducted on admitted patients with traumatic head injury in neurosurgery department, Tanta University hospital in the period between May 2015 to October 2015. The study was approved by Research Ethics committee of Tanta Faculty of Medicine and a written informed consent was obtained from each participant or relatives of the patients.

Patients
All patients above 18 years old, of either sex, who had traumatic brain injuries within less than 6 hours on admission and had GCS 9-15 were included in this study. Patients were excluded if they: 1) had comorbid associated disorder as heart, renal, liver diseases, chronic inflammatory disease and malignancies; 2) had a history of previous neurological illness or psychiatric impairment; 3) trauma affecting also other body regions.

The data collection sheet included personal data: (patient code, age, sex, residence, occupation and date of admission); circumstances of trauma (type, manner and time of injury and time elapsed between infliction of injury and admission "pre-hospitalization period"). The method of treatment (either conservative or operative), hospitalization period and patient outcome (either survivor or not survivor) were recorded also in data sheet.

Physical examination was performed for all patients. Glasgow Coma Scale assessed the initial severity of traumatic head injury at the time of emergency admission to the hospital. Patients were categorized into two groups: GCS 9-12 represented moderate and 13-15 represented mild degree of severity (Lee et al., 2005). Moreover, head computerized tomography (CT) scan was performed within 24 hours after admission to determine the presence and types of intracranial injuries.

The CT findings were recorded according to presence or absence of the clinically important brain injuries; hemorrhage, contusion, skull fracture and brain edema (Stiell et al., 2001).

Methods:
Three ml venous blood samples for estimation of S100β were collected from each patient in the studied groups within the first six hours after head trauma. As S100β

had a half-life of 6 hours in serum and is readily excreted in urine (Donato, 2003), so this time window for sampling was recommended in some studies (Lomas and Dunning, 2005; Zongo et al, 2012).

Quantitation of S100β was performed by a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) using Human (S100β) ELISA Kit (Shanghai Sunred Biological Technology Co., Ltd, shanghai, China) according to the manufacturers' instructions.

The range for serum S100β adopted was S100β > 0.10 µg/L as reference cut-off for diagnostic purpose (Unde´n et al., 2015).

Statistical analysis:
The collected data were organized and statistically analyzed using SPSS software statistical computer package version 22. For quantitative data, the median and interquartile range were calculated. For comparison between groups in quantitative data, Mann-Whitney U and Kruskal-Wallis tests were used as indicated. Receiver operating characteristics (ROC) curve and binary logistic regression were performed to determine cut off value, sensitivity, specificity and accuracy of prediction. For qualitative data, comparison between two or more groups was done using Chi-square or Fisher Exact tests. Significance was adopted at $p < 0.05$ for

interpretation of results of tests (Dawson-Saunders and Trapp, 2001).

RESULTS

Fifty one patients were included in this study. The majority of patients were young (age group 18-40 years) and only three patients were over 60 years old ($p < 0.001$). Males significantly outnumbered females ($p = 0.003$). As regards the circumstances of trauma, all cases were accidental and the majority of cases (82.35 %) occurred in the street either due to falls (47.06 %) or during road traffic accidents (pedestrians in 23.53 %, passengers in 11.76 % and motorcyclists in 5.88 %) (Table 1).

The majority of patients had a mild head trauma (88.24 %) based on Glasgow coma scale. As regards the findings of CT scan of the head, fissure fractures were present in 29.41% of cases, the most encountered intracranial hemorrhages were extradural (EDH) followed by subarachnoid hemorrhages (SAH) (in 23.53 % and 11.76 % of cases respectively), and both brain edema and brain contusion were detected in 23.53% of cases (Figure 1). All cases received conservative treatment. As regards outcome, most patients were improved (64.71 %), while 35.29 % of cases died (Table 2).

As regards serum S100β level, there was no statistically significant difference between the two studied categories of head injury severity ($p = 0.809$) or in the different findings of CT scan of the head ($p = 0.276$). However, patients that died had significantly higher levels of S100β than those who survived ($p < 0.001$) (Table 3).

There was strong negative correlation between serum level of S100β and the duration of hospital stay (survival) in patients who died ($r = -0.887$, $p < 0.001$) (Table 4).

Analysis of receiver operating characteristics (ROC) curve of serum S100β level as a predictor of outcome (Figure 2) showed an area under the curve (AUC) = 0.803, $p < 0.001$. At a cut off value > 1.205 ug/L, serum S100β had a sensitivity of 100% (were able to predict all cases that died) and a specificity of 54.55%.

Binary logistic regression analysis (Table 5) demonstrated that adding the serum level of S100β level to GCS and CT findings resulted in a higher accuracy of prediction of outcome (64.7% versus 82.4%).

Table (1) : Characteristics of all studied patients (n=51).

		n	%	Chi-square goodness of fit test	
				X^2	P
Age group	18-40	33	64.71%	26.824	<0.001*
	41-60	15	29.41%		
	>60	3	5.88%		
Gender	Male	36	70.59%	8.647	0.003*
	Female	15	29.41%		
Time of trauma	Day	27	52.94%	0.176	0.674
	Night	24	47.06%		
Place of trauma	Street	42	82.35%	55.412	<0.001*
	Home	6	11.76%		
	Work	3	5.88%		
Cause of trauma	Fall	24	47.06%	27.529	<0.001*
	RTA Pedestrian	12	23.53%		
	Violence	6	11.76%		
	RTA Passenger	6	11.76%		
	RTA Motorcycle	3	5.88 %		

n: number, RTA: Road Traffic Accident, *: significant at p < 0.05.

Table (2) : Clinical and CT scan of the head findings and course of all studied patients (n=51).

		Severity Of Head Trauma (GCS)				Total		Fisher's exact test	
		Mild (13-15)		Moderate (9-12)					
		n	%	n	%	n	%	X^2	p
Fissure fracture		12	26.67%	3	50.00%	15	29.41%	1.388	0.343
Intracranial hemorrhage	EDH	12	26.67%	0	0.00%	12	23.53%	4.088	0.307
	SAH	6	13.33%	0	0.00%	6	11.76%		
	SDH	3	6.67%	0	0.00%	3	5.88%		
	Intraventricular	3	6.67%	0	0.00%	3	5.88%		
Brain	Brain Edema	9	20.00%	3	50.00%	12	23.53%	8.359	0.01*
	Contusion	9	20.00%	3	50.00%	12	23.53%		
Treatment	Conservative	45	88.24%	6	11.76%	51	100%		
Hospital Stay	< 7 days	18	40.00%	0	0.00%	18	35.3%	12.185	0.002*
	7 - 14 days	15	33.33%	0	0.00%	15	29.4		
	15-21 days	9	20.00%	6	100.00%	15	29.4		
	22 – 28 days	3	6.67%	0	0.00%	3	5.9%		
Outcome	Improved	27	60.00%	6	100.00%	33	64.71%	2.164	0.141
	Died	18	40.00%	0	0.00%	18	35.29%		
Total		45	88.24%	6	11.76%	51	100%		

n: number; EDH: extradural hemorrhage; SAH: subarachnoid hemorrhage; SDH: subdural hemorrhage;

* significant at p<0.05.

Table (3) : Serum levels of S100β in all studied patients (n=51).

		Serum S100β (ug/L)		Test of Significance	
		Median	**IQR**	**Test Statistic**	**p**
GCS Category[a]	**Mild (13-15)**	1.369	1.143 - 1.987	126	0.809
	Moderate (9-12)	1.435	1.107- 1.763		
CT scan of the head[b]	**Brain Edema**	1.696	1.175 - 2.786	2.574	0.276
	Fissure fracture	1.365	1.083 - 1.646		
	Hemorrhage/contusion	1.369	1.143 - 1.762		
Outcome[a]	**Improved**	1.204	1.084 - 1.646	477	<0.001*
	Died	1.865	1.301 - 3.056		

CT: computerized tomography; a: Mann Whitney test; b: Kruskal-Wallis test; *significant at p < 0.05.

Table (4) : Correlation between S100β level and hospital stay.

	Spearman's correlation (between S100β and hospital stay)	
	Correlation coefficient	p
Improved	0.018	0.920
Died	-0.887	<0.001*

*significant at p < 0.05.

Table (5) : Binary logistic regression analysis of outcome.

	Using GCS and CT findings only	**Adding S100β**
Nagelkerke R Square	0.297	0.536
Percentage accuracy	64.7%	82.4%

GCS: Glasgow Coma Score; CT: computerized tomography.
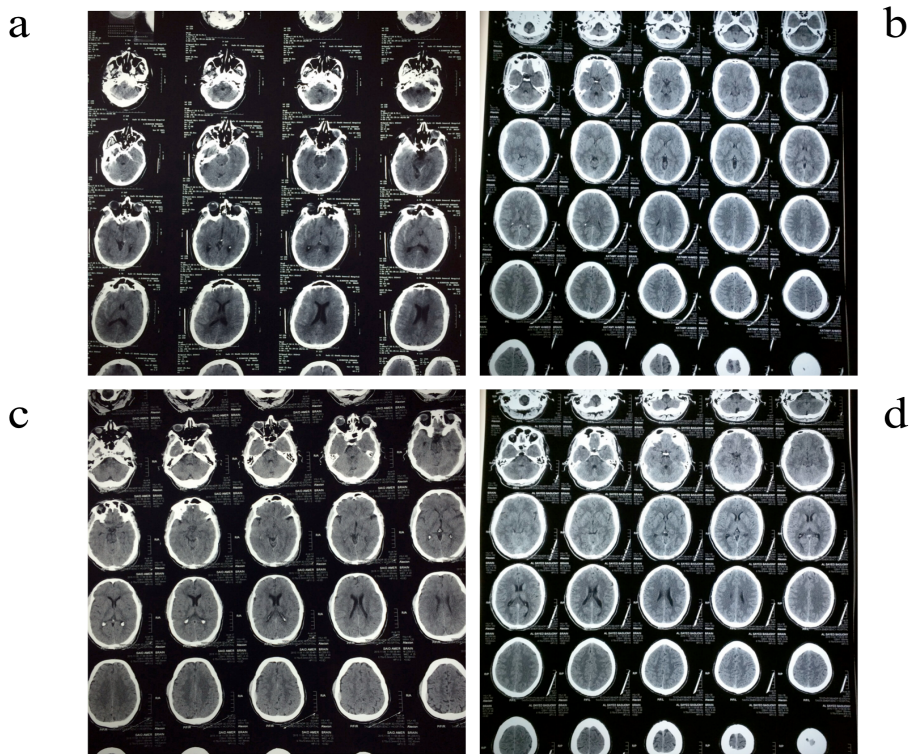
a

b

c

d

Figure (1) : Examples of CT findings in patients: a: Left occipital fissure, subarachnoid hemorrhage; b: Left temporal fissure; c: Right extradural hemorrhage 1 cm; d: Just brain edema.
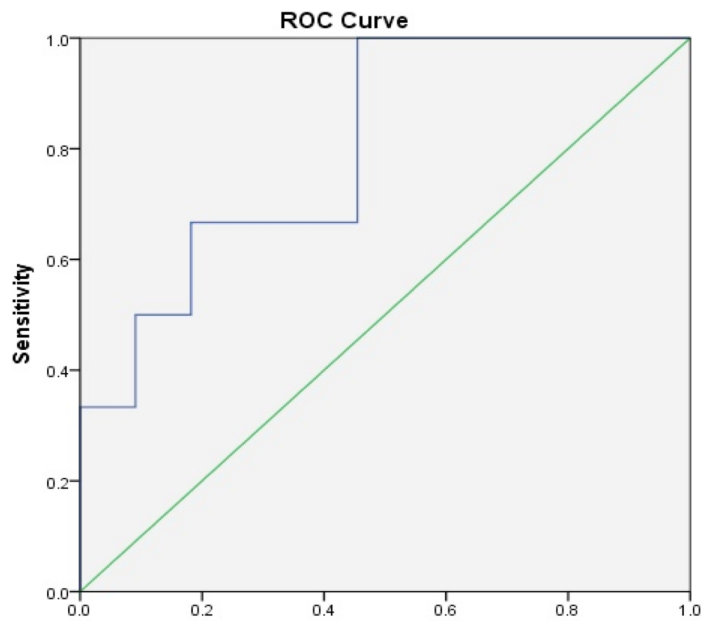

Figure (2) : Receiver operating characteristic (ROC) curve analysis (S100β as predictor of outcome). Area under the curve = 0.803, p <0.001, sensitivity 100% and specificity 54.55% at cut off value > 1.205 ug/L.

DISCUSSION

Head injury is a significant cause of mortality and morbidity in adults and is the leading cause of death in young individuals. Management guidelines have been introduced and later evaluated with respect to safety and economy (Jennett, 1998).

In the present study, fifty one patients admitted with minor to moderate traumatic head injury to Neurosurgery Department, Tanta University were included. Males significantly outnumbered females and all cases were accidental.

As regards serum S100β level in the present study, there was no statistically significant difference between the two studied categories of head injury severity or in the different findings of CT scan of the head. This finding is in line with Akhtar et al. (2003) who found that there was no statistically significant difference in S100β protein concentrations in patients with a positive magnetic resonance image and those with a negative magnetic resonance image. Moreover, Kotlyar et al. (2011) reported a poor predictive power of S100β as regards the presence of intracranial lesions on CT scan.

This finding contradicts results reported by Cervellin et al. (2012), Egea-

Guerrero et al. (2012) and Mercier et al. (2013). Cervellin et al. (2012) and Egea-Guerrero et al. (2012) stated that patients with intracranial lesions detected by CT scan had significantly higher S100β protein levels than those without lesions. Mercier et al. (2013) concluded that measuring the S100β protein could be useful in evaluating the severity of traumatic brain injury patients with moderate and severe injury. This controversy could be attributed to the absence of cases with severe TBI in the current study.

However, patients who died in the present study had significantly higher levels of S100β than those who survived proving the good prognostic value of S100β. This goes hand in hand with results reported by Böhmer et al. (2011), Mercier et al. (2013), Winter et al. (2013) and Nimer et al. (2015). The results revealed significant positive association between S100β protein concentrations and mortality.

In the study herein, there was strong negative correlation between serum level of S100β and the duration of hospital stay (survival) in patients who died. This indicates that the higher the S100β level, the shorter the duration of survival in head injured patients.

This result is in agreement with Li et al. (2006) who found that the level of S100β

was significantly higher in cases that died acutely within short time period as compared with cases that survived for a longer duration.

Analysis of ROC curve of serum S100β level as a predictor of outcome showed a good prediction power of the outcome. At a cut off value > 1.205 ug/L, serum S100β had a sensitivity of 100% (was able to predict all cases that died), but it had a relatively low specificity (54.55%) meaning that only 54.55 % of survivors had S100β levels below the cut off value and were correctly identified.

In most guidelines of the management of TBI, the level of consciousness as assessed by GCS and the findings of CT scan of the head are relied upon for assessment of patients and decision making. In this study, binary logistic regression analysis demonstrated that the use of GCS and CT findings predicted outcome in 64.7% of cases, while adding the serum level of S100β resulted in a higher accuracy of prediction of outcome (82.4%).

This finding is supported by results reported by Lesko et al. (2014) which concluded that adding S100β to clinical predictors is a better prognostic tool than using either of them alone (accuracy of prediction: 75% versus 70%). Rainey et al. (2009) stated that a lower cut-off value of 0.53 ug/L with a sensitivity of 83% and

specificity of 49% can predict death after head trauma, while Böhmer et al. (2011) reported a much higher cut off value for prediction of mortality (14.34 ug/L with a specificity ratio of 100% and 60% sensitivity). These differences in cut off values to predict outcome could be attributed to different time points of sampling in each study.

Zaba et al. (2007) discussed the problem of differential diagnostics and forensic medical expertise of various forms of craniocerebral injuries and concluded that clinical and laboratory studies are insufficient to objectively estimate the results of the examination.

Establishing a breach in the standard of care is a key in litigating medical malpractice claims under the negligence standard (Recupero, 2008). Studies have shown that clinical practice guidelines have an impact on the outcomes of these cases (Hyams et al., 1995). The use of clinical practice guidelines can promote efficiency in malpractice litigation by eliminating the need to establish the appropriate standard of care in each case (LeCraw, 2007; Mackey and Liang, 2011).

Hence, it is of great importance to incorporate new modalities of diagnosis and prognosis in forensic evaluation of medical care. The protein S100β has been proved by this study and other studies to

be good predictor biomarker of bad outcome in cases of mild to moderate head injuries.

In a study of malpractice data in USA from 1991 through 2005 for all physicians representing 25 specialties, 7.4% of all physicians had a malpractice claim of which 19.1% were neurosurgeons facing a claim each year (Chandra et al., 2011). According to the present study and the aforementioned, discussed studies, it could be assumed that high levels of serum S100β above the cut off value indicates a high probability of bad outcome or death in cases of TBI. This should direct the neurosurgeons to recognize such cases at high risk and exert the best available standard of care. In addition, forensic experts can infer in these cases that the poor outcome of victims was related primarily to the effects of trauma and its consequences, provided that breach of the standard of care is suspected, but could not be proved.

From the present study, it is concluded that S100β is a good predictor of the outcome in cases of mild and moderate head injuries and for forensic evaluation of medical care in these cases.

It is recommended to include S100β in the routine investigations requested for patients of mild and moderate head injuries on admission.

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الأهمية السريرية والطبية الشرعية لبروتين S100β في التنبؤ بالنتائج وتقييم الرعاية الصحية لمرضى إصابات الرأس الخفيفة إلى معتدلة

المشتركون فى البحث

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لقد زادت معدلات وقوع إصابات الرأس الطفيفة والخفيفة إلى المعتدلة في السنوات الأخيرة وذلك على حساب حدوث الإصابات المعتدلة والشديدة. يعد بروتين S100β من الدلالات البيولوجية الحساسة لإصابات الرأس.

تهدف هذه الدراسة إلى التعرف على الأهمية السريرية والطبية الشرعية لبروتين S100β كأحد الدلالات البيولوجية الجديدة الذي قد يسفر عن معلومات تفيد في التشخيص والتنبؤ بالنتائج إذا ما أضيف إلى بروتوكولات التعامل مع إصابات الرأس. تم ادراج واحد وخمسون من المرضى الذين يعانون من إصابات في الرأس خفيفة أو معتدلة في هذه الدراسة.

سجلت البيانات الاجتماعية والديغرافية والبيانات السريرية ونتائج الأشعة المقطعية بالإضافة إلى قياس مستويات بروتين S100β في غضون ٦ ساعات بعد الإصابة. كان هناك زيادة كبيرة في مستويات بروتين S100β في غير الناجين مقارنة مع الناجين (P<0.001). كان هناك ارتباط سلبي ذو دلالة احصائية بين مستويات بروتين S100β وفترة البقاء على قيد الحياة في الحالات التي توفيت (معامل الارتباط "r": = ٠,٨٨٧– ، P<0.001). كانت قوة تنبؤ S100β جيدة (AUC المساحة تحت المنحني = ٠,٨٠٣ والحد الادني > ١,٢٠٥ميكروغرام / لتر والحساسية = ١٠٠٪ والنوعية = ٥٥,٥٤٪). إضافة مستويات بروتين S100β الى مقياس جلاسجو للغيبوية GCS ونتائج مسح الأشعة المقطعية زادت دقة التنبؤ بنتيجة المرضي من ٦٤,٧٪ إلى ٨٢,٤٪ مع ذلك لم يكن هناك اختلافات ذات دلالة احصائية في مستويات بروتين S100β بالنسبة لشدة الإصابة أو أنواع الإصابات المختلفة في نتائج الأشعة المقطعية.

ويمكن أن نخلص إلى أن مستوى بروتين S100β هو مؤشر جيد للنتائج في حالات إصابات الرأس الخفيفة والمتوسطة و يُوصى باستخدامه في كل من التقييم السريري أو الطبي الشرعي.