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Correlation of Serum S100B with the Severity and Outcome of Traumatic Brain Injury: A Cohort Study

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Abstract

Background: The contribution of blood biomarkers and clinical indices following traumatic brain injury (TBI) may provide diagnostic and predictive tools. S100b is one of the extensively studied blood biomarkers of TBI but has led to inconclusive reports of its contribution to discriminating the severity and outcomes of injury. This investigation seeks to verify S100B concentrations in blood as severity and outcome predictors of TBI.

Methods: Eighty-five patients sustaining TBI (Glasgow Coma Scale score [GCS] 3-15) getting admitted to the neurosurgery department were included in the study. Serum was collected within 48 hours of trauma and was analysed for S100B concentration. Demographic details of patients were collected, along with data on injury mechanisms, CT brain findings, and GCS. The outcome was assessed using the Glasgow Outcome Scale Extended (dichotomised in unfavourable vs favourable and death vs alive), 3- and 6-months post-injury.

Results: On admission, serum level of S100B was significantly different in mild, moderate and severe TBI groups (p=0.000). However, the post hoc test confirmed a significant difference in the protein concentration between mild vs severe (p=0.000) and moderate vs severe (p=0.004) TBI. S100B concentrations collected on admission were able to efficiently differentiate between favourable and unfavourable groups at three months follow-ups (p=0.000). Median serum levels were significantly higher among deaths. The protein inversely correlated with GCS on admission, and the GOS E outcome scores at 3 and 6 months dichotomised as favourable (GOS E5-8) and unfavourable (GOS E 1-4) outcomes. A positive correlation was observed with total scores of Rotterdam CT Brain categorisation (ρ= 0.289, p=0.005). S100B showed a moderate discriminative ability with the sensitivity of 72%, 71%, 72% and 74% in severity, mortality, and three- and six-months poor outcome prediction, respectively.

Conclusion: Including on-admission S100B in the investigation panel for TBI may aid as an extra reliable tool to predict patient outcomes and strategies for treatment accordingly.

Key-words: S100B, TBI, Glasgow Coma Score, Glasgow Outcome Score (Extended), clinical outcome.

Introduction

India's socio-demographic and epidemiological landscape is rapidly changing due to rapid urbanisation, industrialisation, motorisation and lifestyle changes [1,2]. This transition has given rise to many problems, including Traumatic brain injury (TBI). TBI is an alarming issue in India, as it causes mortality and morbidity in the population's young, productive age group [3]. According to epidemiological data, there are 1.6 million TBI cases every year in India. Additionally, 200,000 people die yearly from brain injuries, and around 1 million people will require access to rehabilitation programmes [4]. Being called the 'silent epidemic' clinical recovery after a TBI varies widely, with some patients making remarkable progress and others dealing with significant handicaps [5]. Developing a suitable prognostic model and treatment strategy becomes important by utilising data available on admission. There are extensive studies headway on board in this regard. Serum biomarkers are extensively being researched as a handier tool for prognostic utilisation, thus contributing to patient outcomes, drug discovery and therapeutics.

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One of the most extensively researched proteomic indicators for TBI is the S100B calcium-binding protein, primarily found in white matter and synthesised in astroglia and Schwann cells and helps regulate the intracellular levels of calcium [6,7]. Astrocytes will release accumulated S100B when under the influence of injury or metabolic strain, assessed extracellularly as quickly as 15 s after a lesion is produced [8]. Soon after the injury, the level of S100B mRNA will also rise, indicating that the protein is still being synthesised inside the cell [9]. As a result, the amounts detected in the blood come from both secreted and freshly synthesised sources. Most S100B is released into the serum from CSF through arachnoid villi. As a result, there is a correlation between the CSF: S100B ratio and the time following a TBI [10]. Due to its rapid detection in serum after injury, the protein has been incorporated in Scandinavian guidelines for head injury management since 2013 [11].

The utilisation of the protein in injury research comes with an advantage as it is stable and relatively unaffected by storage and temperature fluctuations due to repeated freeze-thaw cycles, which makes its handling hassle free and, at the same time, assures reliable results [12]. Unaffected by haemolysis is another advantage worth noting down [13].

The ability of S100B to discriminate injury severity and predict outcomes has been widely discussed for several years. However, the conclusion is limited and confusing as the optimal time between the trauma and sampling is different and inconclusive. In this study, we aimed at the analysis of serum S100B on hospital admission as a marker for the severity of the TBI and as a marker to predict outcomes in terms of GOS E at three- and six months post-TBI.

Materials and Methods

Study design, ethics and setting

The enquiries were collected as a part of a prospective cohort study. Head-injured patients visiting the emergency department and seeking further treatment in Justice KS Hegde Charitable Hospital, in the Neurosurgery department, between December 2019 till September 2021 were included in the study. Ethical approval was provided by the Central Ethics Committee NITTE (Deemed to be University) Ref; NU/CEC/2019/0250. The next of kin issued the consent as per the Declaration of Helsinki.

Study population, sample and data collection

During the sample collection period, there were 111 patients deemed potentially eligible. As the study comprised of follow-up till six months post-TBI, there were dropouts due to loss to follow-up (n=7), late admissions beyond 48 hours of injury (n=5), systemic hypertension and uncontrolled diabetes(n=2), retro positive reports (n=2), Covid19 positive (n=1), spinal injury (n=7) and patients diagnosed with cancer (n=2) were excluded. Eighty-five eligible patients were signed up for the study (Figure 1).

The clinical and demographic details and GCS scores were collected on admission for all the patients. CT brain findings were categorised under the Rotterdam CT (R-CT) brain classification (Table 1) [14].

Every head-injured patient included in the study has received treatment according to the standard protocol in our tertiary care hospital.

Table 1: Description of Rotterdam CT (R-CT) Brain score categories.

CT brain features	Score
Basal cistern	
▪ Normal	0
▪ Compressed	1
▪ Absent	2
Midline shift	

▪ No shift or shift ≤ 5mm	0
▪ Shift >5mm	1
Epidural mass lesion	
▪ Present	0
▪ Absent	1
IVH o tSAH	
▪ Absent	0
▪ Present	1
Sum score	+1

IVH: Intraventricular haemorrhage;
tSAH: traumatic subarachnoid haemorrhage.

Biomarker determination

Sample collection and storage

Two ml of blood venous blood was drawn in plain vacutainers from every patient within 48 hours of injury. Collected samples were centrifuged for 10 minutes at 3000 rpm. Separated serum was stored in a -30° C freezer preparatory to the analysis.

S100B assay

The serum S100B was quantitatively determined by the **Enzyme-Linked Immunosorbent Assay (ELISA) method (XEMA Co., Ltd). The detectable concentration of S100B was between 10ng/L to 3500ng/L. 90ng/L was the higher limit of serum concentration detectable among healthy controls.**

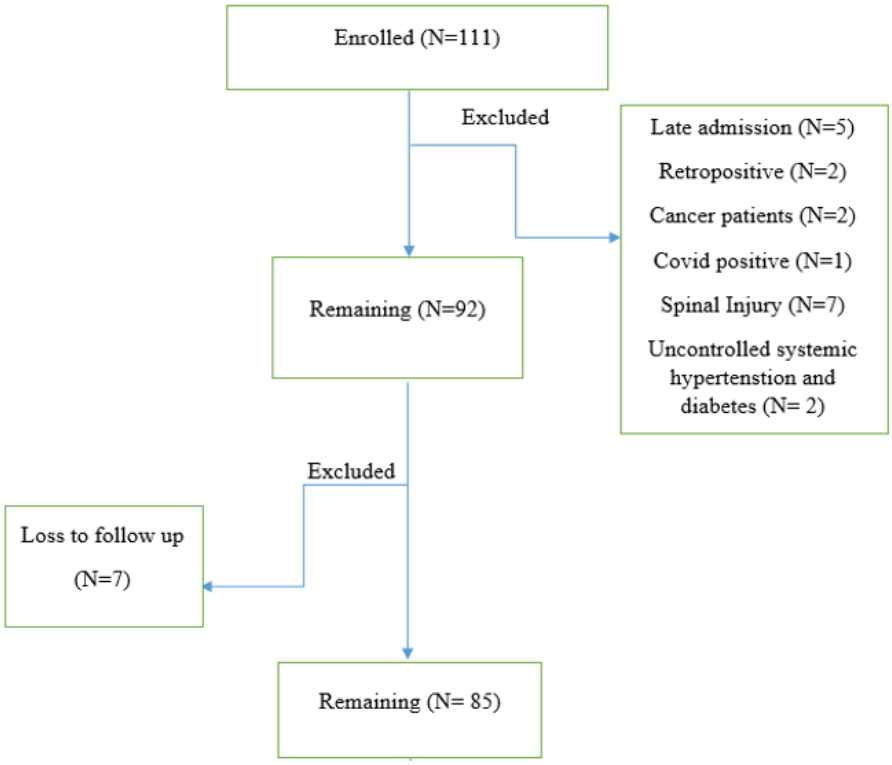

Fig 1. Flow chart depicting patients' enrolment for the study

Outcome assessment

The outcomes were evaluated three and six months after injury by extended Glasgow Outcome Score (GOS E). The GOS E forms eight outcome categories, as described in Table 2. A total GOS E score of 1 = death, 2= vegetative state, 3 = severe disability (completely dependent), 4= severe disability (partial dependency on others), 5= independent but cannot resume work to previous capacity, 6= some disability exists but can partly resume work/ previous activities, 7= good recovery with minor physical deficits that affect daily life, and 8 = good recovery [15]. GOS E score was dichotomised as optimal (GOS E ≥ 5) and suboptimal (GOS E ≤ 4).

Table 2: Description of categories of the Glasgow Outcome Scale Extended

Score	Category	Domain	Criteria
1	Dead		
2	Vegetative state	Consciousness	Not able to look after themselves for 8 hours.
3	Lower SD	Activities at Home	Not able to look after themselves for a day
4	Upper SD	Activities outside home Function	Not able to shop and travel
5	Lower MD	Ability to work or study Social and leisure activities Friction in Family and friendship	Not able to work/ study Not able to participate Constant frictions
6	Upper MD	Work Social and leisure activities Friction in Family and friendship	Reduced work capacity Less participation Frequent frictions
7	Lower GR	Social and leisure activities Friction in Family and Friendship Symptoms affecting daily life	Participate less Occasional problems Yes
8	Upper GR	Symptoms affecting daily life	No problem

SD- Severe disability, MD- Moderate disability, GR- Good recovery

Statistical analysis.

For statistical analysis Statistical Package for the Social Sciences software package (SPSS 23.0, IBM, Chicago, IL, US) and GraphPad Prism 9.4.1. were used. Patient demographics and clinical features on admission were listed and presented as the number of subjects (percentage). The normality of numerical data distribution was tested using Shapiro-Wilk and Kolmogorov Smirnov tests. S100B serum levels were compared across the severity and outcome groups with the Kruskal Wallis test, the Bonferroni post hoc test, and the Mann-Whitney U test. Spearman's correlation was applied to assess the correlation with severity, CT brain and outcome scores. The extent of subjects injured with moderate to severe TBI according to GCS score, experiencing poor functional outcome during three- and six-month follow-up and mortality prediction within six months of TBI were assessed using receiver operator characteristics (ROC). AUC between 0.7-0.8 was acceptable discrimination. A $p < 0.05$ was regarded to be statistically significant.

Results

Demographics, aetiology of TBI and baseline characteristics.

Demographic and clinical characteristics of the head-injured subjects under study are represented in Tables 3 and 4.

The study participants ranged between 19 and 72 years of age (mean ± SD 39.7 ± 14.2). Most of the subjects were males (n= 65, 76.5%), diversely employed, and the common cause of injury was a Road traffic accident (RTA) (n= 61, 71.8 %), followed by fall from height (n= 19, 22.4 %) and other causes (n= 5, 5.9 %).

Table 3: Patient demographics

Variables	N (%)
Age	
≤ 30	28 (32.9)
31-50	41 (48.2)
> 50	16 (18.8)
Gender	
Male	65 (76.5)
Female	20 (23.5)
Employment status	
Agriculturist/ Coolie	26 (30.6)
Employed/ Business	34 (40)
Homemaker	12 (14.1)
Others	13 (15.3)
Mechanism of Injury	
RTA	61 (71.8)
Fall from height	19 (22.4)
Other	5 (5.9)

The mean systolic BP was 128.89 ± 20.8 mmHg, and the mean pulse was 83.7±15.4. About 28.2% of the study population presented with unilateral pupillary responsiveness. Seventy-three per cent of patients presented with loss of consciousness/posttraumatic amnesia (LOC/PTA), 18.8% with seizure, 44.7 % experienced vomiting prior to hospitalisation, and 20% and 33% of TBI survivors presented with ear and nasal bleeding, respectively (Table 4).

Table 4: Clinical features.

Variables	Mean ± SD/ N(%)
Systolic BP	128.89 ± 20.8
Pulse	83.7± 15.4
Pupillary responsiveness	
Bilaterally responsive	61 (71.8)
Unilaterally responsive	24 (28.2)
LOC/PTA experienced	
Yes	62 (72.9)
No	23 (27.1)
Seizure	
Yes	16 (18.8)
No	69 (81.2)

Vomiting	
Yes	38 (44.7)
No	47 (55.3)
Ear bleed	
Yes	17 (20)
No	68 (80)
Nasal bleed	
Yes	28 (32.9)
No	57 (67.1)

Table 5 describes the CT brain findings categorised under the R-CT brain classification. Partial and complete compression of the basal cistern was observed in 4.9% and 2.4% TBI subjects, respectively. The presence of midline shift was noted among 7.1% of the CT brain images. Epidural mass lesions were presented in 83.5% of the CT brain images. The presence of intraventricular haemorrhage (IVH) or traumatic subarachnoid haemorrhage (tSAH) was noted among 52.9% of head-injured patients.

Table 5: CT brain findings under Rotterdam CT Brain (RCT) categorisation.

Variables	**N (%)**
Compression of basal cistern	
0	79 (92.9)
1	4 (4.9)
2	2 (2.4)
Midline shift	
0	79 (92.9)
1	6 (7.1)
Epidural mass lesion	
0	71 (83.5)
1	14 (16.5)
IVH or tSAH	
0	40 (47.1)
1	45 (52.9)
RCT total score	
Abnormal (>1)	79 (92.9)
Normal (0-1)	6 (7.1)

S100B levels were compared between severity and outcome groups.

According to the GCS scores on admission, there were 39 subjects categorised as mildly injured, 25 as moderately injured and 21 as severely injured. Median serum S100B concentrations, with interquartile range, across the three subgroups of injury severity can be seen in Table 6 and Figure 2. Median concentrations were lowest among the mild TBI subgroup. It increased progressively and significantly among moderate and severe TBI subgroups (Kruskal-Wallis p=0.000). On applying the post hoc (Bonferroni) test, the serum concentrations of S100B showed a significant difference between mild vs severe (p=0.000) and moderate vs severe (p=0.004) TBI.

Table 6: Comparison of S100B serum levels between severity groups.

S100B ng/L	Mild TBI	Moderate TBI	Severe TBI	Kruskal Wallis p	Post-hoc (Bonferroni)	p
N	39	25	21		Mild-moderate	1.0
Median	325.7	491.8	753.5	0.000*		
Lower IQR	261.32	317.4	412.8		Mild-Severe	0.000*
Upper IQR	446.5	629.95	1073.1		Moderate-Severe	0.004*

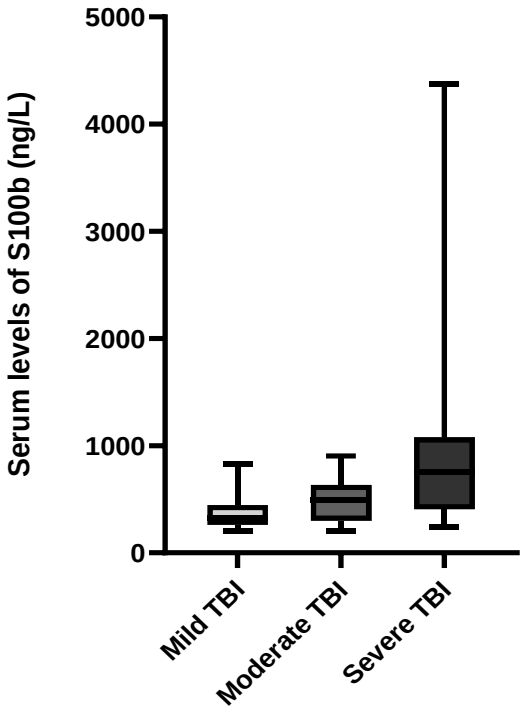

Figure 2: Boxplots showing biomarker concentrations in subjects with mild, moderate, and Severe TBI. The horizontal line customary to the box stands for the median serum S100B values; the inferior and superior of the box appoint the first and third quartiles. The lower and upper whiskers represent the lowest and highest observed values below the upper fence. The first box (mild TBI) consists of 39 subjects, the middlebox (moderate TBI) consists of 26 subjects and the severe TBI group consists of 21 subjects.

The ROC analysis corroborated the ability of S100B to assess severity with the cut-off value of ≥ 378ng/L (Figure 3) with a sensitivity of 72% and specificity of 1-0.308 (70%) with AUC = 0.727 (p=0.000).

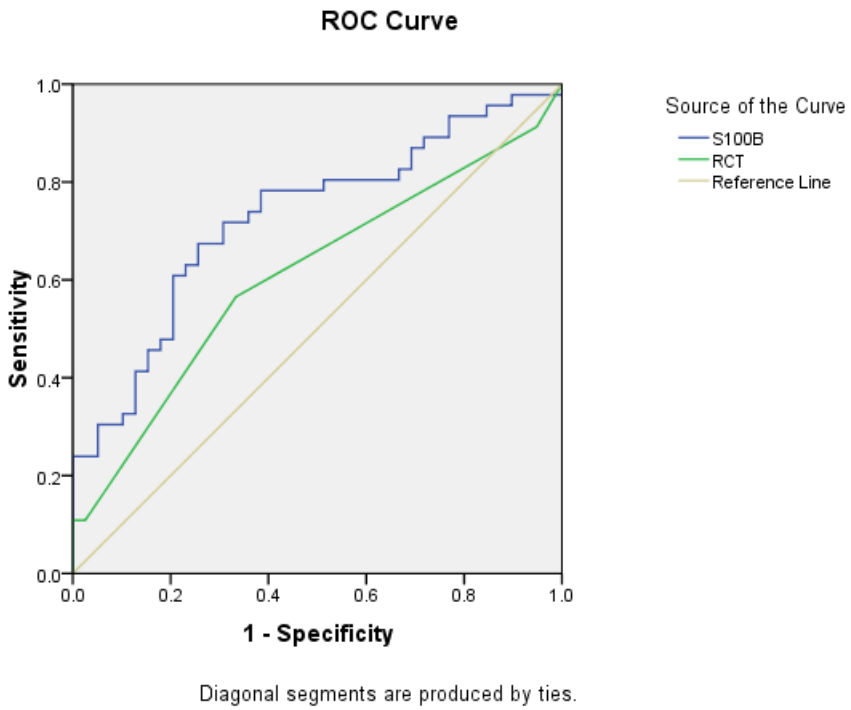

Figure 3: Receiver operating characteristic (ROC) curve for severity prediction in TBI using S100B

During follow-ups, unfavourable outcome was experienced by 32 and 23 subjects, respectively, while 53 and 62 subjects showed favourable outcomes in terms of three and six months GOS E scores (Table 7). The median values of serum S100B on admission showed significantly higher levels among the unfavourable outcome posers during the third-month follow-up (p=0.000). However, the sixth-month outcome groups owned no statistically significant difference (p=0.63). The areas under the ROC curves for three and six months of poor functional outcomes were 0.729 (cut-off value ≥ 406 ng/L; sensitivity= 72%; specificity= 68%; p=0.000) (Figure 4a) and 0.731 (cut-off value ≥ 406 ng/L; sensitivity= 74%; specificity= 63%; p=0.001) (Figure 4b) respectively.≥ 406 ng/L; sensitivity= 74%; specificity= 63%; p=0.001) (Figure 4b) respectively.

The 14 non-survivors had a significantly elevated concentration of S100B on admission than the rest of the survivors (p=0.012), as elaborated in Table 8. The TBI patients who experienced mortality within six months of injury had higher S100B concentration with a cut-off value of ≥ 487.7 ng/L (Figure 5) with (AUC= 0.714, sensitivity 71%, specificity 65% and p=0.012).

The total Rotterdam CT (R-CT) brain scores did not show a significant cut-off value except for three months follow up with AUC= 0. 673, a cut-off value of ≥ 2.5, sensitivity=65%, specificity= 66% and p=0.008 (Figure 4a) predicting the probability of a poor outcome for patients scoring a total R-CT score >2.5 in on-admission brain imaging.

Table 7: Comparison of S100B serum levels between outcome groups during 3- and 6-month follow-up.

S100B ng/L	Unfavourable outcome GOSE (1-4)	Favourable outcome GOSE (5-8)	Mann-Whitney U p
Three months outcome			
N	32	53	
Median	570.18	334.98	0.000*

Lower IQR	370.9	264.9	
Upper IQR	945.57	483.7	
Six months outcome			
N	23	62	
Median	612.3	342.5	0.63
Lower IQR	399.75	275.16	
Upper IQR	1073.1	275.16	

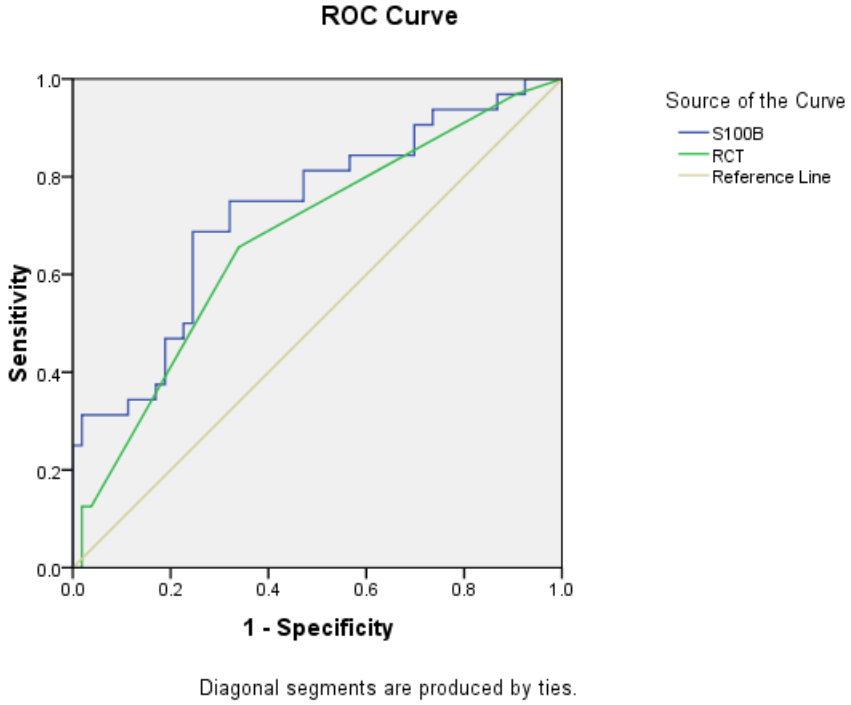

Figure 4a

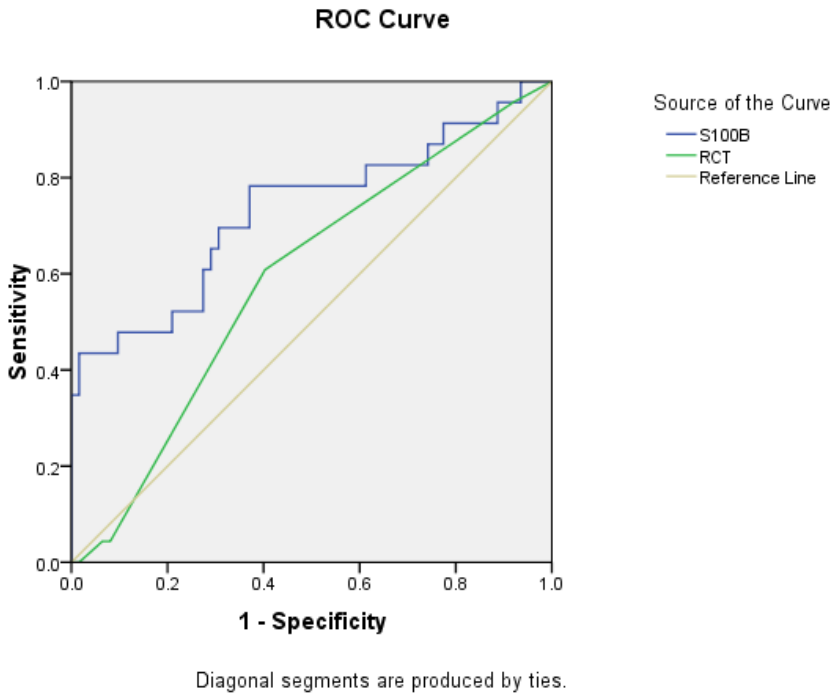

Figure 4b

Figure 4a and 4b: Receiver operating characteristic (ROC) curve for outcome prediction in TBI with S100B levels measured <48 h and Glasgow outcome score extended (GOS E) for poor outcome scores at three months (4a) and six months (4b) follow-ups in 85 TBI patients.

Table 8: Comparison of S100B serum concentration between non-survivors and survivors six months post-TBI.

S100B ng/L	**Non-survivors GOSE (1)**	**Survivors GOSE (2-8)**	**Mann-Whitney U p**
N	14	71	
Median	662.35	348.02	0.012*
Lower IQR	399.75	280.53	
Upper IQR	1123.8	595.1	

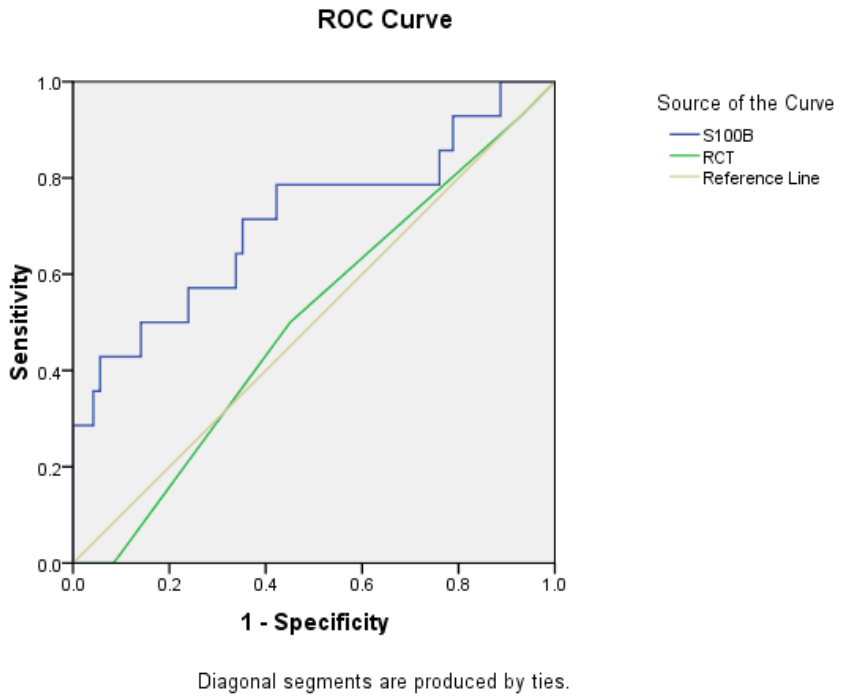

Figure 5: Receiver operating characteristic (ROC) curve for mortality prediction in TBI using S100B.

S100B correlates with severity, CT brain, and adverse outcomes.
On analysing the serum S100B levels of the entire population, we found a significant negative correlation (Table 9) with the on-admission GCS score (ρ= -0.3991, p= 0.0002), three - and six-months GOS E outcome scores (ρ= -0.436, p=<0.0001 and ρ=-0.388, p=0.0002 respectively).

S100B with on-admission R-CT total score showed a significant positive correlation (ρ= 0.289, p=0.005). However, the S100B levels among different groups divided depending on radiological features of basal cistern compression, midline shift, and epidural mass lesion did not show significant statistical correlation except for the IVH or tSAH group, which correlated positively (ρ=0.313, p=0.003).

Table 9: Correlation of S100B serum levels on admission with injury severity, CT brain (Rotterdam scores) and outcomes.

Variables	Spearman's ρ	p
Glasgow Coma Score (admission)	-0.3991	0.0002*
Rotterdam CT Brain Score		
Compression of basal cistern	0.1378	0.20
Midline shift	0.1385	0.20
Epidural mass lesion	0.05688	0.60
IVH or tSAH	0.3138	0.003*
Total score	0.2894	0.005*
Glasgow Outcome Score Extended		
Three months follow-up	-0.436	<0.0001*
Six months follow-up	-0.388	0.0002*

Discussion

Differences in S100B levels across the severity groups

The serum S100B concentrations from our study population showed the ability to stratify patients based on their injury severity, i.e. GCS scores (Kruskal-Wallis p=0.000) (Table 6). Similarly, several studies have reported the utilisation of S100B collected within 6 and 24 hours of injury to stratify patients based on severity [16-20]. Koivikko et al., in their recently published work, reported that S100B significantly differed between the severity groups but did not show a difference between moderate and severe TBI [17]. A similar finding was reported by Hellwell et al. [21]. Our study showed a significant difference between the three severity groups. Further confirmation by the Bonferroni post hoc test showed the ability of S100B to differentiate between mild and severe and moderate and severe TBI groups (Table 6). Our data did not significantly differentiate between mild and moderate TBI groups. Contrastingly, Fathi M et al. [20] showed that S100B significantly categorised mild from moderate TBI.

Correlation of S100B with GCS scores

We found a significant negative correlation between the protein level and the hospital admission GCS. However, some authors found no correlation between the same [22]. A significant negative correlation with GCS on admission proves S100B to be an excellent supplementary marker for injury severity (Table 9). Shakeri et al. reported a negative correlation between GCS and S100B collected within 48 hours of TBI, a finding common with our finding [23]. Few studies, including serial sampling procedures, also have achieved a significant negative correlation between the GCS on hospital admission and serum S100B collected on days 0, 3, and 7 of TBI [24], 1st and 3rd days [25].

Comparison of S100B on admission with outcome groups

Our study showed comparable results at three months follow up with Mann Whitney u p=0.000. Not many works report the difference in on-admission serum levels of S100B between the poor and good outcome groups. However, according to Hellwell et al., day one serum S100B levels in moderate to severe TBI cohort were higher in poor outcomes (GOS E 1-4) compared to good outcomes (GOS E 5-8), with p=0.008 [21], which is in line with our findings.

Correlation with CT brain findings

Our study sample achieved a significant positive correlation with the CT brain findings categorised under Rotterdam CT scores (Table 9) with Spearman ρ= 0.2894, p=0.005. Similar findings were recently reported in a study on the Chinese population by Yin W et al. [26]. Thelin et al. reported a correlation with the radiographic image of the second peak of S100B at 48 hours post-injury [27].

Correlation with the outcome

During outcome measurement, we considered the population as continuous data and followed uniform dichotomisation of GOS E scores as good (GOS E 5-8) and poor (GOS E 1-4) outcomes. However, many studies reported have applied outcome measurements after grouping their study population under GCS scores, as discussed below.

Our TBI population demonstrated a negative correlation of S100B serum levels on admission with 3 and 6 months GOS E outcomes. Townend W et al. found a similar correlation at one-month follow-up with the study population of all three severity categories [28]. While another study of severe TBI subjects, with serial sample collection, the 48 hours serum S100B negatively correlated with three months' GOS E scores [29]. A cohort of severe TBI subjects with serial sampling for 5 days. The three months follow-up with GOS E showed a significant negative correlation with initial, 72 hours, maximum release, and total (bulk) release of S100B [30]. Metting Z. et al., included only mild TBI patients in their study and thus dichotomised GOS E and optimal=8, and suboptimal<8. They reported no correlation between the biomarker released on admission with six months' outcome [31].

The predictive ability

We found moderate discriminative ability (AUC= 0.714, sensitivity 71%, specificity 65% and p=0.012) of S100B serum levels between non-survivors and survivors of TBI with the Mann Whitney p =0.012 and serum levels being significantly higher in non-survivors. Rodríguez-Rodrigueza et al. published comparable results. They explained that serum samples collected within 48 hours of injury were a better predictor of mortality with

higher levels of S100b among the non-surviving participants [32]. An increase in the protein around 2.1 fold was reported by a study[22]. The probability of mortality prediction within 48 hours of injury by S100B was a notable finding in our study with a small population of mixed severity.

Earlier works have claimed the short half-life of S100B. It has been shown that within 7 hours following brain injury, the S100B levels recover to baseline, resulting in a limited window for serum collection [33,34]. However, the Maximum number of patients we received in our tertiary care setup was brought to us beyond 24 hours of TBI after receiving primary care at their local nursing homes or PHCs. Their financial burden also adds to it [35]. In a review work addressing the distribution of neurologists and neurosurgeons in India, Ganapathy K mentioned that about 700 million rural Indian residents must travel more than 75- 100km for tertiary consultations [36], which is true in the majority of our study subjects. Thus practically, it requires more than 24 hours for a patient from a rural setup to reach a tertiary care hospital. There were not many studies to our knowledge addressing <24 hours of biomarker levels and correlation of the same with severity and outcome using the GOS E scale.

Diverse researchers agree that the best moment to measure a biomarker in sTBI is from 24 to 48 h post-accident, once the injury is well established and the organism has generated a response (successful or unsuccessful) to the initial damage [37-39]. This discussion gives a new vision towards the diagnostic and prognostic tool for those less privileged rural patients who may find it difficult to commute within a brief time gap from the injury setup to tertiary care hospitals. Along with other regular prognostic tools, one-time sampling of S100B biomarker level within 48 hours also may play a promising role in injury severity and outcome prediction, thus helpful in treatment modalities contributing to designing personalised care and medication for TBI patients.

Conclusion

In conclusion, the eventual correlation between S-100B levels and Rotterdam CT Brain classification scores may improve prognostication accuracy and aid in determining the severity of intracranial injuries. The bulk release of serum S100B in the first 48 hours following a TBI appears to be the most accurate time to diagnose the degree of injury at the time of admission and predict death and unfavourable or favourable outcomes three and six months after the TBI.

Limitations of the study

We would like to list a few limitations of this study.

1. We did not attempt a statistical analysis on pupillary responsiveness data with the serum S100B in predicting outcomes associated with TBI.
2. Speed of recovery is different for every TBI case. In this study, we did not dichotomise the population according to the severity group (GCS) and segregate it as Mild and Moderate+Severe TBI. Performing 3- and 6-month follow-ups by applying the GOS E score as per the requirement of the severity of injury would have given us a much clearer insight into predicting the ability of S100B.

Future goals

Serum biomarkers of head injury are not much explored in India. In the present study, we have only considered GOS E scores to assess the functional outcome of head-injured subjects. This scoring system takes account of individuals' physical well-being. A person having suffered from TBI undergoes great difficulty with respect to his emotional and social aspects of life, which is less discussed in the Indian (rural) setup. In our future research, we would like to investigate serum biomarkers' ability to predict the neurocognitive functioning/outcomes and other emotional trauma they experience due to TBI.

Declaration of interest

The authors report no disclosures relevant to the manuscript.

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