RESEARCH ARTICLE

Utility of S-100B as a Potential Tool for Neuromonitoring and Prediction of Neuroworsening in Acute Phase of Traumatic Brain Injury

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ABSTRACT

Aim: In this review, we summarize the evidence on the use of S-100B in traumatic brain injury (TBI) of all severities, its clinical significance, and its prognostic value in the different posttrauma phases.

Background: Most of the published studies report the serum determination of S-100B in the context of mild TBI as a predictor of positive CT scan, which represents a valuable tool when establishing a criterion to indicate the performance of the CT and decide the medical discharge. Likewise, we have reported several studies that correlate S-100B with the clinical evolution of the patient with severe TBI, showing an excellent indicator of intracranial hypertension. However, there are few studies that report on the impact of S-100B as a predictor of neuroworsening in the acute phase in moderate TBI.

Review results: Traumatic brain injury comprises a heterogeneous group of traumatic injuries that can evolve progressively. Almost 90% of head injuries that reach the hospital are mild head injuries or mild TBI, which is defined by a score of more than 12 on the Glasgow Coma Scale (GCS). Of this, a few can be accompanied by a hemorrhagic lesion that can be detected by further imaging techniques. Still, utilizing these techniques in every single patient that comes to the ER does not only take a toll on the finances of the hospital but, more importantly, also exposes the patients to unnecessary radiation. There are still difficulties to correlate the findings on imaging with secondary injury, and to predict the clinical evolution in the acute phase and in the long-term. Serum S-100B levels have shown high sensibility and negative predictive value (NPV) for intracranial complications after mild head injury. Most of the published studies report that measurement in serum of S-100B in the context of mild TBI, as a predictor of CT findings, represents a valuable tool when establishing a criterion for indication of CT and to decide medical discharge. However, there are few studies that report the impact of S-100B as a predictor of neuroworsening in the acute phase of moderate TBI, which is defined by a score between 9 and 12 on the GCS.

Conclusion: Serum S-100B is a useful marker of brain damage in TBI. Its usefulness has been studied mainly as a support to evaluate the need to perform a CT scan in mild TBI, and to monitor patients with moderate-to-severe TBI, in order to predict the outcome and validate the response to treatment. This review highlights S-100B as a versatile marker whose clinical utility depends on the severity of the head trauma. In this way, S-100B would be a potential predictor of neuroworsening in the acute phase in moderate TBI.

Clinical significance: Despite its valuable utility as a predictor of positive CT in mild TBI, and as a tool for neuromonitoring in established severe TBI, the greater utility of S-100B could be as a predictor of neuroworsening in the acute phase in the moderate TBI.

Keywords: Brain injuries, Intracranial hypertension, Neuromonitoring, Prognosis, S-100B.

RESUMEN

Objetivo: En esta revisión resumimos la evidencia sobre el uso de S-100B en el trauma craneoencefálico (TCE) de todas las severidades, su significado clínico y su valor pronóstico en las diferentes fases postraumáticas.

Antecedentes: la mayoría de los estudios publicados reportan la medición sérica de S-100B en el contexto del TCE leve como predictor de TAC de cráneo positiva, lo que representa una valiosa herramienta a la hora de establecer un criterio para indicar una TAC y decidir el alta médica. Asimismo, varios estudios correlacionan a S-100B con la evolución clínica del paciente con TCE grave, mostrando ser un excelente indicador de hipertensión intracraneal. Sin embargo, existen pocos estudios que informen sobre el impacto de S-100B como predictor de empeoramiento neurológico en la fase aguda del TCE moderado.

Resultados: la lesión cerebral traumática comprende un grupo heterogéneo de lesiones que pueden evolucionar progresivamente. Casi el 90% de los traumas craneoencefálicos que llegan al hospital son leves, lo cual se define por una puntuación de más de 12 en la Escala de coma de Glasgow (ECG). De estos, algunos pueden ir acompañados de una lesión hemorrágica que puede detectarse mediante otras técnicas de imagen. Aun así, la utilización de estas técnicas en cada paciente que llega a la sala de emergencias no solo afecta las finanzas del hospital, sino que, más importante aún, expone a los pacientes a radiación innecesaria. Sigue habiendo dificultades para correlacionar los hallazgos de las imágenes con la lesión secundaria y para predecir la evolución clínica en la fase aguda y a largo plazo. Los niveles séricos de S-100B han mostrado una alta sensibilidad y un valor predictivo negativo (VPN) para las complicaciones intracraneales después de un trauma craneoencefálico leve. La mayoría de los estudios publicados informan que la medición en suero de S-100B en el contexto de un TCE leve, como predictor de hallazgos en la TAC, representa una herramienta valiosa a la hora de establecer un criterio de indicación de TC y para decidir el alta médica. Sin embargo, existen pocos estudios que reporten el impacto del S-100B como predictor de empeoramiento neurológico en la fase aguda del TCE moderado, el cual se define por una puntuación entre 9 y 12 en la ECG.

Conclusión: S-100B sérico es un marcador útil de daño cerebral en el TCE. Su utilidad se ha estudiado principalmente como soporte para evaluar la necesidad de realizar una TAC en el TCE leve, y para monitorizar a los pacientes con TCE moderado-grave, con el fin de predecir el resultado y

validar la respuesta al tratamiento. Esta revisión destaca al S-100B como un marcador versátil cuya utilidad clínica depende de la gravedad del traumatismo craneal. De esta forma, el S-100B sería un potencial predictor de empeoramiento neurológico en la fase aguda en el TCE moderado.

Importancia clínica: a pesar de su valiosa utilidad como predictor de TAC positiva en el TCE leve y como herramienta de neuromonitorización en el TCE severo establecido, la mayor utilidad de S-100B podría ser como predictor de empeoramiento neurológico en fase aguda del TCE moderado.

Palabras clave: Lesiones cerebrales traumáticas, Hipertensión intracraneal, Monitorización, Pronóstico, S-100B.

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BACKGROUND

The term “biomarker” refers to biological substances that serve as indicators of occurrence, status, and/or evolution of a disease or pathological condition. Qualitatively or quantitatively, biomarkers can be measured by molecular biology, chromatographic, spectroscopic, optical, and electrochemical techniques, from tissue samples or body fluids.^{1,2} Specifically, in traumatic brain injury (TBI), the use of biomarkers is proposed as an alternative and/or complement to current diagnostic and prognostic techniques. This could suppose multiple advantages in front of the current methods regarding the management and clinical outcome of patients with TBI.³

Traumatic brain injury comprises a heterogeneous group of traumatic injuries, which can evolve progressively. According to the Glasgow Coma Scale (GCS), TBI is classified as mild, moderate, or severe.⁴ Once the primary lesion occurs, biochemical mechanisms are activated that promote the injury to states of greater severity, which is known as secondary injury.⁵ The primary lesion is evidenced by the appearance of neural injury and hemorrhages at different levels of the intracranial structures, which include subarachnoid hemorrhage (SAH), subdural hematoma (SDH), epidural hematoma (EDH), and intracerebral hematoma (ICH).⁶ These lesions are frequently associated with disruption of the blood-brain barrier (BBB), which become permeable to molecules from nervous tissue to blood and cerebrospinal fluid (CSF), becoming potential biomarkers of brain injury, when it is not evident in the CT.⁷

Current neuromonitoring strategies in TBI include the use of neuroimaging such as computed tomography (CT), nuclear magnetic resonance (NMR), and bedside monitors such as transcranial Doppler (TCD), intracranial pressure (ICP), microdialysis, or brain tissue oxygen. These tools are routinely used for identifying and monitoring temporal trends of anatomical and physiological parameters associated with progressive neurological worsening and mortality.⁸ However, despite the availability of these tools, its remains problematic to correlate the changes detected with the level of secondary injury and predicting the clinical course in acute and in the long-term phase of the illness, given the heterogeneity of the TBI. Additionally, the aforementioned techniques imply high cost and often the mobilization and transfer of the patient.³

In this sense, the use of biomarkers represents a practical and cost-effective alternative to monitoring, especially in situations in which the diagnostic equipment, described above, is not available, such as centers in low- and middle-income countries (LMICs), or during the transfer of patients from remote locations to the specialist centers. The quantification of detectable biomarkers in the early phases after trauma would optimize the times for the timely implementation of specific therapies, becoming a tool for predicting neuroworsening in the acute phase of the illness.

The S-100B protein has been a widely studied candidate. S-100B is a calcium-binding astrocytic protein, which is released just after impact on the skull, as a consequence of BBB, and

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correlates very sensitively with tomographic findings such as brain contusion, EDH, SDH, and SAH, among others.^{9,10} However, S-100B is not released exclusively from the brain. Certain cells, such as adipocytes, epithelial, muscle, cardiac, skeletal cells, chondrocytes, and Langerhans cells are also the source of this protein,^{11,12} so high concentrations of S-100B have been identified in the blood of polytraumatized patients without apparent damage to the central nervous system.^{13–16}

It has been documented that S-100B levels change early and quickly after a central nervous system-related injury.¹⁷ Astrocytes, for example, release the stored S100B in just 15 seconds.¹⁸ Once in blood, S-100B reaches significantly high concentrations if comparing it to the reference value (0.1 ug/L) in the absence of head trauma.^{19,20} S-100B can be completely metabolized and excreted by the kidneys at the level of the proximal tubules;²¹ however, its plasma half-life is not known exactly, due to the interindividual variability among patients, the constant production and release S-100B from the affected tissue, and the variation in the methodological approaches used.^{17,20,22}

Taking into account the release rate of S-100B and the rate of renal elimination, some authors suggest that the half-life of this protein in patients with TBI is short, between 60 and 120 minutes, which suggests that the continuous elevation of the levels of this protein may be associated with brain injury.^{23,24} Although extracranial sources of S-100B may interfere with the evaluation of damage to the central nervous system, it must be taken into account that extracranial blood levels of S-100B are eliminated faster than central nervous system blood levels, as indicated in Figure 1.^{17,25–28} According to this, serum levels of S-100B at 12 hours' posttrauma could be considered a better indicator of post-concussion syndrome and neurological dysfunction in patients with mild TBI trauma.^{17,29}

In fact, most of the published studies report that measurement of serum of S-100B in the context of mild TBI, as a predictor of CT findings, represents a valuable tool when establishing a criterion for indication of CT and to decide medical discharge. Likewise, several studies have reported that correlation of S-100B with the clinical course of the patient with severe TBI, thus showing it to be an excellent indicator of intracranial hypertension (ICH). However, there are few studies that report the impact of S-100B as a predictor of neurological deterioration in the acute phase of moderate TBI. In this review, we summarize the available evidence on the use of S-100B in TBI of all severities, their clinical significance, and their prognostic value in the different post trauma stages (Fig. 1).

MATERIALS AND METHODS

To obtain the information presented in this review, we used the Web of Science, PubMed, and Scopus scientific databases. The search period was from 2010 to 2020, using the following Boolean strings for all the databases: ((s100b[All Fields] OR S-100b[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields])) AND ("brain injuries, traumatic"[MeSH Terms] OR ("brain"[All Fields] AND "injuries"[All Fields] AND "traumatic"[All Fields]) OR "traumatic brain injuries"[All Fields] OR ("traumatic"[All Fields] AND "brain"[All Fields] AND "injury"[All Fields]) OR "traumatic brain injury"[All Fields]) AND ("2010/01/01"[PDAT]: "2020/04/05"[PDAT])).

The downloaded database files were subsequently processed through frequency analysis in Microsoft Excel, and maps based on both bibliographic data and network data were generated using the VOSviewer software. The search gave us a total of 64 articles for PubMed, 1,567 for Web of Science, and 295 for Scopus, for a total of 1,926 articles in all databases. The proportion of MeSH keywords that meet a minimum threshold of occurrences of 5 and the whole number of MeSH keywords was 35/207 for PubMed, 203/1,831 for Web of Science, and 265/1,859 for Scopus. This information regarding the occurrence and total link strength (Fig. 2)

was used to exclude most of the articles and to refine the search, and in addition, we used the following parameters to analyze and select the publications of S-100B over the past 10 years: number of references cited, number of references per article, number of pages per article, authors' performance, and journal publication patterns based on JCR impact factor and journal position by JCR categories. A total of 54 articles were selected to be included in this review.

REVIEW RESULTS

Utility of S-100B as a Predictor of CT Findings in Mild TBI

Almost 90% of patients with head injury who present to the hospital have mild TBI, which is defined by a 13–15 score on the GCS.³⁰ Of this, only a few have a hemorrhagic lesion, which can be detected by further imaging techniques (CT scan). Still, utilizing imaging techniques in every single patient that comes to the ER does not only pose a burden to the finances of the hospital but, more importantly, also exposes the patients to unnecessary radiation.^{30–32} Serum S-100B levels have shown high sensibility and NPV (75–100% and 90–100%, respectively) for intracranial complications after mild head injury.³³ Thus, proving a valuable tool to identify patients who truly merit further imaging studies owing to due to their risk of having a brain bleed.

It has been reported that measurement of S-100B can reduce the use of CT scans and hospital admissions by approximately 30%.^{30,31} S-100B serum levels have already been used as a tool to determine which patients with mild TBI require a posterior CT scan to rule out tissue and hemorrhagic brain lesions. Using a cutoff value of 0.1 µg/L, patients with mild TBI that had a value inferior to this were discharged; a 6-month follow-up period showed no readmissions, missed intracerebral bleeds, or deaths,³¹ showing the effectiveness of serum S-100B levels' NPV for predicting hemorrhagic lesions.

Fig. 1: Schematic representation of the clinical utility of S-100B according to the initial severity of the TBI, in acute and late phase. The panel of the left shows the early elevation of S-100B, the peaks are higher proportionally to the level of actual severity, defined by the process of neuroinflammation and secondary injury, however, the higher the peak, the greater the probability of neurodeterioration in the acute phase, which is particularly critical for moderate TBI, because the actual severity could be underestimated by GCS, while the levels of S-100B indicate that the trauma will actually behave like a severe TBI in the following hours. The panel on the right shows how the S-100B values tend to return to baseline values in the late stage, although the monitoring of their concentrations allows the detection of secondary peaks, which are related to secondary events of brain damage, serving as an indicator of response to treatment. Modified from Reference 12

There is a relationship between the severity of the TBI and the amount of S-100B detected.³⁵ Serum levels of S-100B in severe TBI that surpass the 7 µg/L have been shown to lead to a 100% patient mortality in 2 weeks, while levels over 0.2 µg/L increase the probability for a worse outcome and measurement after 24 hours can help predict brain death in such patients.^{30,36,37} All of this leading us to understand the relation between the presence and magnitude of the brain injury and the amount of serum S-100B.

The subsequent serum values of S-100B predicted the development of elevated ICP in patients with TBI ($p < 0.01$). Patients

with high ICP on day 5 had 11 times more risk for a fatal outcome while those with high ICP on day 6 had a fatal outcome risk, which was 9 times greater.⁴⁰ Olivecrona et al. report that the maximum intracranial pressure (ICPmax) and minimum cerebral perfusion pressure (CPPmin) are clearly correlated with S-100B levels. The correlation was significant for three types of measurements: the initial measurement, the maximum concentration measured in the first 5 days posttrauma, and the total release of the biomarker during the first 72 hours, calculated by the area under the curve. In general, the maximum concentrations ($r = 0.69$, $p = 0.001$) and the total release ($r = 0.68$, $p = 0.0001$) of S-100B correlated better with the ICPmax, compared to the initial measurement ($r = 0.52$, $p = 0.0005$). These results were similar in relation to the CPPmin, and also in function of another biomarker, neuron-specific enolase (NSE).³⁸ Table 1 summarizes main literature available that correlates S-100B with neuromonitoring techniques, such as ICP monitoring, and neuroworsening in moderate to severe TBI.

Utility of S-100B as a Predictor of Neurological Worsening in the Acute Phase

The use of S-100B protein as a tool in the diagnosis, monitoring, and prognosis of TBI has been discussed throughout this review. Still, one point in which studies are still needed is in this protein's ability to predict neuroworsening in early stages, in patients who have suffered a moderate TBI, due to the potential neurological deterioration and the need to implement aggressive management with endotracheal intubation and/or hyperosmolar therapy. The secondary lesions generated by the subsequent inflammatory process after the trauma can take hours to show clinical manifestations, happening when the injury is very extensive, thus worsening the patient's prognosis and increasing mortality before timely interventions can be made.

Andriessen et al. conducted a prospective cohort study with a sample of 508 patients. They found that of the 169 patients diagnosed as moderate at emergency department (ED) evaluation, 39 (24%) deteriorated to a GCS less than or equal to 8 and remained unconscious for more than 6 hours, thus giving room to question the prognostic value of prehospital GCS scores. Interestingly, it can be observed that at least 15% of their cohort's diagnosis changed from the scene of the injury to the ED. Researchers concluded that combining information from both the scene of the injury and ED admission may have additional value for injury severity classification and outcome prediction than just using the GCS. Also, they found that among patients that had 6 or more hours of impaired consciousness, positive CT findings were present in 86% of patients with severe TBI and 76% in patients with moderate TBI. In patients with severe and moderate TBI and impaired consciousness for less than 6 hours, CT findings were 52 and 50%, respectively. This shows that a relatively long time is required for intracranial lesions to appear on CT scan in both severe and moderate TBI.⁴¹ If relevant therapeutic actions had been performed in a timely manner, 26% of the CT findings could have been avoided. They also found three patients with an ED admission diagnosis of moderate TBI who were intubated before GCS evaluation and 77 patients (15%) with a change in injury severity category due to fluctuations in the GCS. This study reports a hospital mortality rate in those patients with mild/moderate TBI that deteriorated to severe TBI (M-S, 14%), and those with mild/moderate TBI at the injury scene and moderate TBI at the ED (M-M, 15%).⁴¹

In another study, Thelin et al. performed a database study of S-100B and NSE levels collected prospectively from patients

admitted to the NICU at Karolinska University Hospital from January 1, 2005, to December 31, 2013. With a sample of 417 patients, they found that patients with favorable outcome have low and rapidly decreasing levels of S-100B and NSE, while S-100B and NSE levels in patients with an unfavorable outcome remain elevated during a longer period of time, presumably indicating an ongoing cerebral injury.¹²

Bouzat et al. carried out a prospective cohort study, with a sample of 67 patients; its objective was to test whether the determination of the serum protein S-100B could predict a secondary neurological deterioration. They defined secondary neurological impairment as a decrease in initial GCS of two points or more, or any treatment for neurological worsening. They identified nine patients with secondary neurological deterioration after trauma. No differences were found in the serum levels of S-100B protein between these patients and those without neurological aggravation ($n = 58$ patients): $0.93 \mu\text{g/L}$ (0.14–4.85) vs $0.39 \mu\text{g/L}$ (0.04–6.40), respectively. They concluded that the measurement of serum protein S-100B at the time of admission was unable to predict patients with risk of neurological deterioration after a mild or moderate TBI. They also remarked that extracranial lesions can increase serum S-100 protein levels limiting the usefulness of this quantification in the prediction of neuroworsening.⁴²

Korfias et al. designed a prospective observational study in a neurosurgical intensive care unit with the aim of examining the relationship between serum S-100B concentrations and injury severity, clinical course, survival, and treatment efficacy after severe TBI with a sample of 102 adult patients with severe TBI, admitted between June 2001 and November 2003. They defined neurological change as improvement or worsening in GCS score, alteration of the pupillary reaction, and presentation of new neurological signs (difficulty in speech-aphasia or motion-hemiparesis, or development of seizures). They found a statistically significant correlation between serum S-100B course and neurological improvement ($n = 21$) or deterioration ($n = 29$) during the 1st week of hospitalization ($p = 0.0002$ and $p = 0.001$, Wilcoxon signed-rank test). Their findings were related to others in the literature that showed that high serum levels of S-100B are well correlated with primary damage, secondary deterioration, and unfavorable outcome in severe TBI and that the quantification of S-100B is a promising serum marker for assessing the extent of primary injury and the time course of secondary damage.⁴³

DISCUSSION

Monitoring ICP remains the main strategy of neuromonitoring in the management of patients with severe TBI.⁴⁴ Chesnut et al. demonstrated that the treatment of severe TBI based on controlled maintenance of $\text{ICP} \leq 20 \text{ mm Hg}$ is not superior to image-based management and clinical examination. In this multicenter controlled trial, conducted in Ecuador and Bolivia, 324 patients with severe TBI treated in the ICU were randomly assigned to one of two groups. In one of the groups, management was based on intraparenchymal monitoring of ICP, while in the other, it was based on imaging and clinical data. Survival and functional status were evaluated at 3 and 6 months and the neuropsychological state at 6 months, showing no evidence of significant difference in terms of mortality ($p = 0.60$) and days of ICU stay ($p = 0.25$). However, it was found that the duration of specific treatments for ICH was lower in the group with ICP monitoring ($p = 0.002$). Complications and adverse events were similarly distributed in both groups.⁴⁵

Table 1: Main literature available, where S-100B levels have been correlated with neuromonitoring techniques, such as ICP monitoring, and neuroworsening in moderate-to-severe TBI

Reference	Type of study	n	Findings
Petzold et al. ⁴⁰	Prospective cohort	34	S-100B predicted the development of elevated ICP in patients with TBI ($p < 0.01$). The average S-100B level measured at admission was 1 ± 3 pg/mL in the control group, and in patients with TBI it was 37 ± 30 and 110 ± 50 pg/mL in those who survived and those who died, respectively.
Olivecrona et al. ³⁸	Prospective cohort	48	In patients with severe TBI, best correlation of ICP with S-100B: maximum concentrations ($r = 0.69, p = 0.001$) and S-100B total release ($r = 0.68, p = 0.0001$). Initial S-100B concentrations, at 72 hours, maximum and total release were 1.04 ± 0.21 ; 0.40 ± 0.04 ; 1.37 ± 0.45 ; and 4.09 ± 1.38 $\mu\text{g/L}$, respectively.
Hendoui et al. ⁴⁸	Clinical trial	33	Negative correlation between serum S-100B level and GCS on 1st ($r = -0.401, p = 0.021$) and 3rd days ($r = -0.469, p = 0.006$).
Shakeri et al. ⁴⁹	Cross-sectional	72	Significant negative correlation between final GCS and protein S-100B level at first ($p = 0.027$), 48 hours later ($p < 0.0005$), and final measurement ($p < 0.0005$).
Andriessen et al. ⁴¹	Prospective cohort	508	Total 169 patients diagnosed as moderate at emergency department (ED) evaluation, 39 (24%) deteriorated to a GCS less than or equal to 8 and remained unconscious for > 6 hours. At least 15% of their cohort, diagnosis changed between injury scene and ED. Total 77 patients (15%), with change in injury severity category due to fluctuations in the GCS.
Thelin et al. ⁵⁰	Database study	417	Hospital mortality rates in patients with mild/moderate TBI deteriorating to severe TBI (14%). High S-100B and NSE levels correlate with poorer long-term health conditions. Being the levels of S-100B those that exhibit a better discrimination between different groups according to the Glasgow results scale (GOS): GOS1 = dead, GOS2 = vegetative state, GOS3 = severe, dependent state, GOS4 = moderately recovered, independent state, and GOS5 = good recovery. Especially when measured between 24 and 36 hours after trauma. The NSE levels only discriminated GOS1 from the rest of the groups.
Bouzat et al. ⁴²	Prospective cohort	67	Nine patients with secondary neurological impairment after trauma were identified. No differences were found in the serum levels of S-100B protein between these patients and those without neurological aggravation ($n = 58$ patients): 0.93 mg/L (0.14–4.85) vs 0.39 mg/L (0.04–6.40), respectively.
Korfias et al. ⁴³	Prospective cohort	102	S-100B at the time of admission did not allow to predict patients with risk of neurological deterioration after a mild or moderate traumatic brain injury. To assess if the S-100B protein is a promising marker of injury severity and outcome after head injury in adult patients, serum S-100B levels were measured on admission and every 24 hours thereafter for a maximum of 7 days. Initial S-100B values ranged from 0.15 to 32.9 $\mu\text{g/L}$ (mean 2.1; median 1.72 $\mu\text{g/L}$); the highest observed value during the first 7 days of hospitalization was 48.6 $\mu\text{g/L}$. A significant relationship was found between initial serum S-100B levels and CT Marshall classification ($p = 0.047$). Subjects with Marshall VI grade (nonevacuated lesions > 25 mL) presented with statistically higher initial serum S-100B levels than those with Marshall grades I or II ($p = 0.032$). Cox's proportional hazard regression analysis shows a threefold increased probability of death within 1 month when initial serum S-100B levels were 1–1.99 vs 2 $\mu\text{g/L}$ or higher.
Doha et al. ⁵¹	Prospective cohort	40	The patients were divided into two equal groups. Group I: patients with traumatic head injury, II: patients with trauma rather than head trauma. Significant difference between the results of S-100B in group I and group II was detected ($p < 0.001$), with higher results of S-100B in TBI patients. Significant difference between the results of S-100B in survival and nonsurvival for patients in group I was detected ($p = 0.002$), with higher results of S-100B in nonsurvival patients. This research also showed a statistically significant difference in Spearman's correlation between S-100B protein and GCS ($p < 0.05$).
Park and Hwang ⁵²	Prospective cohort	15	Total 15 pediatric patients (18 years old) with TBI were enrolled in this study. Median serum concentrations of S-100B, NSE, and IL-6 at admission were 178.12 pg/mL, 16.54 ng/mL, and 15.48 pg/mL. The serum S-100B and NSE level both at admission and 1 week after trauma was significantly higher in the poor GCS group than in the good GCS group ($p < 0.05$). In contrast, the serum IL-6 level in the poor GCS group was slightly lower than in the good GCS group at admission and higher than the good GCS group 1 week after the trauma. However, this difference was not significant ($p = 0.053$).

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Reference	Type of study	n	Findings
Yalcin et al. ⁵³	Prospective cohort	58	Total 58 adult patients (> 18 years) were admitted. Serum S-100B levels were measured prospectively and compared according to clinical findings and outcomes of the patients. According to the ROC analysis, cut-off values for S-100B for the differential diagnosis of patients with and without brain damage were found to be 785.944 ng/mL. The GCS score of the patients varied between 6 and 15. There was a statistical significance between the patients with and without TBI according to GCS. In addition, a negative correlation between GCS and S-100B levels was determined (S100B rho: -0.64).
Vos et al. ⁵⁴	Prospective cohort	79	In 79 patients with TBI (GCS $\leq$ 12), serum, taken at hospital admission, was analyzed for GFAP and S-100B. In patients who died compared with alive patients, median serum levels were increased: GFAP 33.4-fold and S-100B 2.1-fold. In unfavorable compared with favorable outcome, GFAP was increased 19.8-fold and S-100B 2.1-fold. Multivariable analysis showed that models containing mass lesion, pupils, GFAP, and S-100B were the strongest in predicting death and unfavorable outcome. S-100B was the strongest single predictor of unfavorable outcome with 100% discrimination.

The results of this trial, and the fact that ICP monitoring is infrequent in low- and middle-income countries (LMICs), have motivated new research that seeks to define alternative methods that allow patients to follow-up with severe TBI without ICP monitoring. By the time this review was written, the Global Neurotrauma Research Group was developing the Consensus-Based Guidelines (CBG) project in Latin America for the creation and validation of guidelines for the treatment of severe TBI in the absence of ICP monitoring. Partial results of this initiative show the analysis of different predictors using a proportional multivariate probability model in 550 patients. At 6 months' posttrauma, 37% of the patients had died, while 44% reached a GOS-E of 5–8. A high score on the motor Glasgow ([OR 1.41], CI 1.23–1.61) and the finding of EDH ([OR 1.83], CI 1.17–2.86) were significant predictors of a high score in GOS-E, while advanced age ([OR 0.65], CI 0.57–0.73) and the effacement of cisterns ($p < 0.001$) were associated with a low GOS-E score. Strikingly, the site where the study was conducted ($p < 0.001$) and race ($p = 0.004$) were associated with the result in a significant way, surpassing even the clinical variables such as hypotension and pupillary examination, suggesting an important predictive role of sociodemographic factors, although additional research is required to understand these associations.⁴⁶

The only clinical protocol that has been prospectively tested in a clinical trial for the treatment of TBI without control of ICP is the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST TRIP), which used the imaging and clinical examination (ICE) algorithm, reporting a favorable GOS score at 6 months (39%) and a mortality rate (41%) without significant differences compared to the group with treatment based on ICP monitoring. This study strongly supports the idea that the aggressive and diligent treatment of ICH, suspected or monitored, is probably a critical component for the successful management of TBI; so, the aggressiveness of the treatment should not be diminished in the absence of ICP monitoring. The authors also highlight the need for this protocol to be modified to increase efficiency, while including other monitoring tools.⁴⁷

In general, studies in relation to monitoring and predictive models in TBI, in the LMIC, show the need to incorporate new strategies to improve the sensitivity and reduce the window of time in the detection of the neuroworsening processes, imageneological and clinically evident, and in that way to be able to implement specific therapies in a timely manner. Serum biomarkers have been

one of the main candidates for this purpose, with S-100B being one of the most studied.

The variations observed in the different studies in relation to the serum levels of S-100B and its association with the ICP, the findings in the CT, the clinical outcome, and its prognostic value may be due to methodological limitations, such as blood sampling, ICP measuring technique, and CT scan evaluation method. Additionally, it is likely that some treatment strategies may affect S-100B levels,³⁸ an aspect barely discussed in the literature. Treatments that could affect the kinetics of S-100B include sedatives, vasopressors, aggressive fluid replacement, and hyperosmolar therapy. In the latter case, it has been reported that mannitol therapy would increase serum levels of S-100B, since its hyperosmotic action increases the permeability of the BBB.²²

The usefulness of S-100B in TBI has been studied mainly to support the need to perform a CT in mild TBI and to monitor patients with moderate to severe TBI, as a predictor of outcome and elevation of the ICP, as well as a tool for monitoring the response to treatment.¹² However, despite the available evidence as a valuable tool, S-100B is rarely used among clinicians who manage patients with TBI and, to our knowledge, only S-100B has been routinely included in the Scandinavian guidelines for the management of TBI. It is possible that this is due to the fact that published studies show a tendency toward low S-100B specificity, due to the extracranial sources of S-100B in the polytraumatized patient. Therefore, in order to increase the usefulness of S-100B, and extend its use, it is necessary to improve the understanding of the kinetics of this biomarker, so as to discriminate the origin of the ultra-early and late levels of S-100B, in addition to a clearer differentiation in relation to the extracerebral levels of the marker, as well as defining the reference values related to age for the pediatric population.

Future work should also compare S-100B in the context of multivariate analysis, in such a way that other known predictors are included, such as established prognostication models like IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI) or BEST TRIP variables.

CONCLUSION

Clinical data and neuroimaging have been used as prognostic tools, in the detection of findings associated with progressive neuroworsening and mortality. However, given the heterogeneity

of the TBI, there are still difficulties to correlate the findings with secondary injury, and to predict the clinical evolution in the acute phase and in the long-term. Additionally, CT and MRI imply high cost and the mobilization and transfer of the patient.

Serum S-100B is a useful marker of brain damage in TBI. Its usefulness has been studied mainly as a support to define the need to perform a CT scan in mild TBI, and to monitor patients with moderate-to-severe TBI, in order to predict the outcome and validate the response to treatment. This review highlights S-100B as a versatile marker whose clinical significance depends on the severity of the trauma. In this way, S-100B would be a potential predictor of neuroworsening in the acute phase in moderate TBI; however, more studies specifically focused on this subgroup are required.

CLINICAL SIGNIFICANCE

We consider that despite its valuable utility as a predictor of positive CT in mild TBI, and as a tool for neuromonitoring in established severe TBI, the greater utility of S-100B could be as a predictor of neuroworsening in the acute phase in the moderate TBI, due to the great impact on early mortality that would cause the timely implementation of specific therapies.

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