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Neuronal and Glial Biomarkers Research for Traumatic Brain Injury

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Abstract

The potential of early neurological inaccurate assessment of severity in patients with traumatic brain injury (TBI) has been highlighted; in some cases, for example, the severity of the injury is overestimated or underestimated. These findings have led to the search of biomarkers associated with early brain injury. Research in this field has exponentially increased over the past 20 years, with most publications on the subject in the last 10 years, whose results range from promising findings to other sometimes inconclusive one. An ideal biomarker should be able to demonstrate high sensitivity and specificity for brain injury, among other aspects. Literature has shown that there is not a single biomarker that predicts the patient's clinical decline with high sensitivity and specificity. Instead, it is required to use a panel of markers that reflect different aspects of head trauma. This chapter gives a review of the most promising biomarkers studied as predictors of severity of TBI, with a special focus on their nature, location, basal concentrations, and methods by which they can be quantified in blood samples.

Keywords: acute brain injury, biomarkers, blood-brain barrier, prognosis, Glasgow Coma Scale

1. Introduction

Every year, 1.1 million Americans are treated in emergency rooms for traumatic brain injury (TBI): 235,000 are hospitalized for nonfatal TBI and 50,000 died. In Finland, a prospective study found that 3.8% of the population had experienced at least one hospitalization due to traumatic brain injury before 35 years of age. Similarly, another study in New Zealand found that at 25 years of age, 31.6% of the population had experienced at least one TBI that required medical attention (hospitalization, emergency department, or doctor's office). It is estimated that 43.3% of Americans have residual disability 1 year after the damage. The most recent estimate of the prevalence of the US civilian residents living with disability after hospitalization with TBI is 3.2 million [1].

TBI is assessed and classified clinically according to the Glasgow Coma Scale (GCS) [2] and by imaging: axial computed tomography (CT) and magnetic resonance imaging (MRI). However, the use of GCS as a diagnostic tool is subject to important limitations, and it is difficult to assess the eye opening in patients with serious lesions on the face; likewise, the verbal response cannot be correctly estimated in individuals who are under the influence of psychoactive drugs

and/or alcohol, and in those who are intubated or sedated will have limited linguistic capacities [3]. Given that the severity of the neurological injury may be underestimated in some cases and overestimated in others, attention has been focused on early assessment strategies in patients with TBI and their inaccuracy in special and frequent circumstances [4].

In view of the high rate of intubation and difficulties in the proper evaluation of the eye opening, Stocchetti et al. concluded that motor GCS score was more important than eye opening or verbal responses to predict the severity of the neurological injury. Other recent research has provided evidence that the use of sedative drugs avoids the accurate assessment of GCS during the first 24 h [5].

Other challenges for diagnosis are presented by the progressive nature of some brain injuries, which can lead to further neurological deterioration. In addition, neurological responses after TBI may vary over time for reasons unrelated to the injury. For example, trauma is frequently associated with alcohol and drug intoxication [6]. These factors together place the GCS in a position full of limitations that diminish its reliability as a highly sensitive test in specific and not infrequent circumstances such as those already mentioned.

On the other hand, neuroimaging techniques are used to provide objective information about the injury and its location [7] and are not influenced by the aforementioned confounding factors. However, the CT scan has a low sensitivity for diffuse brain injury, when the TBI is mild [8] and the availability and usefulness of MRI in the acute stage is limited. These facts, among others, have led to the search for alternative methods to assess the damage, being of special interest, the search for biomarkers, which are more reliable indicators of neuronal injury, due to its molecular context and its early expression.

Research in this field has increased exponentially in the last 20 years, with most publications on the subject in the last 10 years. Most markers are associated with cell damage. **Table 1** presents a summary of the TBI biomarkers most studied to date, including information about their nature, tissue location, molecular weight, half-life, basal levels, and physiopathological significance.

The main physiopathological mechanisms reflected by the glial or neuronal biomarkers are the disruption of the blood-brain barrier (BBBD) and neuronal injury, respectively. Taking into account this basis, it would be advantageous to have a panel of complementary biomarkers that show different temporal profiles and that reflect different physiopathological conditions subsequent to TBI. In a parallel manner, Papa et al. [9] propose that an ideal biomarker should have the following characteristics:

1. demonstrate high sensitivity and specificity for brain injury;

2. stratify the patients according to the severity of the injury;

3. have rapid appearance in the accessible biological liquid;

4. provide information about injury mechanisms;

5. have biokinetic properties;

6. monitor the progress of the disease and the response to the treatment;

7. predict the functional result; and

8. easily measured by simple techniques widely available.

Biomarker	Location	Molecular mass [KDa]	Nature	Half life	Basal concentrations	Significance
UCH-L1	Neuronal	20 [41] 24 [42]	Ubiquitination enzyme	20 minutes [43]	0.12 ng/mL [44]	Neuronal injury
NSE	Neuronal	90 [45] 78 [46]	Enzyme	24 h [46] 48 h [41]	<12.5 ng/mL [47] ≤15 ng/mL [46]	Neuronal injury
αII-espectrina	Neuronal	280 [41]	Cytoskeleton component protein	2.9 h [48]	—	Apoptosis
SBDP		120 [41]		1.5 days [49]		
		145 [41]		1 day [49]		
		150 [41]		1 day [49]		
S-100B	Glial (astrocytes)	21 [50]	Calcium binding protein	97 minutes [47] 112 minutes [43]	0.328–0.01 pg/mL [11]	BBBD
MBP	Glial (oligodendrocytes and Schwann cells)	18.5 [50]	Myelin sheath component protein	12 h [43]	<0.3 ng/mL [50]	White matter injury
GFAP	Glial (astrocytes)	40–53 [30]	Cytoskeleton component protein	—	<0.03 ng/mL [30]	BBBD and neuronal injury

Table 1.
Main biomarkers in TBI and their properties.

In this chapter, we present a compendium of the most studied biomarkers in the TBI, its possible applications, and the current techniques for its detection.

2. Most studied biomarkers in TBI

As explained in previous paragraphs, there is no single biomarker that is sufficiently sensitive and specific to study the physiopathological mechanisms that derive from head trauma. Next, we will mention some of the most studied biomarkers given its rapid elevation after trauma and its relationship with the mechanism of injury. One of the most studied biomarkers is the Ca binder protein S-100β, a glial protein at the astrocyte level that is related to alterations in the blood-brain barrier [10]. Its rapid elevation and its considerable concentration release in the serum facilitate the study of the protein and its correlation with the severity of the injury. Due to the type of cells found in the central nervous system, it is necessary to study biomarkers that allow us to demonstrate not only glial injury but also neuronal. One of the most studied biomarkers in this sense is the C-terminal hydrolase of ubiquitin-L1, which is a highly specific cytoplasmic neuronal enzyme [11, 12]. Finally, we will delve into glial fibrillary acidic protein (GFAP), which is also a glial protein and is part of the cytoskeleton of astrocytes and is also related to the disruption of the blood-brain barrier [11, 13].

2.1 The Ca binder protein S-100β

S-100 β is a central nervous system (CNS) protein found predominantly in astrocytes and is the most studied peripheral biomarker of BBBD. This calcium binding protein (CBP) S-100β increases initially after the accident and then decreases rapidly after the traumatic injuries. In cell models, their release has been demonstrated from the first 15 seconds after the trauma. In humans, the earliest that has been detected is 30 minutes posttrauma. The approximate half-life of this protein is 97 minutes [10], the peak occurs on day 0, and the concentrations decrease toward the sixth day in both CSF and serum.

Goyal et al. [14] reported basal levels of S-100β in healthy CSF controls of 0.0754–0.0034 ng/mL and in serum of 0.328–0.101 pg/mL. This protein has been studied extensively in mild TBI (mTBI), so that high levels in serum are associated with an increase in the incidence of post-concussion syndrome [15] and neurological dysfunction. There are also several studies that have reported a correlation between serum levels of S-100β and the presence of pathological findings in cerebral magnetic resonance imaging (MRI), as well as abnormalities in neuropsychological exploration after mTBI [16].

Most studies show that the S-100β measurement can distinguish injured patients from noninjured patients with an uncertain degree of utility in predicting mortality either acutely or at several points in time (**Table 2**) [17–19]. In general terms, S-100β is a sensitive but not specific predictor of CT abnormalities. Using low serum cut-off values, the sensitivity oscillates between 90 and 100% with a specificity between 4 and 65%.

Müller et al. [17] reported a sensitivity of 0.95 (95% CI 0.76–1.0) for S-100β measured within the first 12 h with a specificity of 31% (95% CI 0.25–0.38) relative to abnormal findings on skull CT scan in a study of 226 adult patients admitted to the hospital with a diagnosis of mild TBI (GCS 13–15). Biberthaler et al. [19] found similar results using a cut-off level of S-100β of 0.1 ng/mL, measured within the first 3 h posttrauma in 1309 patients with mTBI and correlating them to head CT findings. The sensitivity was 99% (95% CI 0.96–1.0), and the specificity was 30% (95% CI 0.29–0.31).

Reference	Detection method	Sample	Findings
Goyal et al. [14]	ELISA	CSF and serum	Increase in CSF and serum first 6 days post-trauma Correlation between serum and CSF levels decreased over time Level in CSF is a potential predictor of GOS and DRS Mean and peak are predictors of mortality in severe TBI
Berger et al [51]	Automated LIAISON system [AB DiaSorin, Bromma, Sweden]	Serum	Significantly elevated in intracranial injury It cannot replace the clinical examination or the use of CT in mTBI It can serve as support for the selection of patients for TC S: 90–100%, E: 4–65%
Biberthaler et al [19]	Elecsys S100 [Roche Diagnostics, Mannheim, Germany]	Serum	Increase was related to findings in the CT scan S: 99%, E: 30%
Biberthaler et al [52]	Long term and Rapid test	Serum	Concentrations were significantly correlated using the two measurement techniques; cut-off value calculated: 0.18 ng/mL. S: 100%, E: 46%
Bazarian, et al [21]	ELISA	Serum	S: 80%, E: 40%

Table 2.
Summary of the evidence reported in the literature on biomarkers in S-100B.

The usefulness of S-100β as a marker does not seem to be affected by the concomitant consumption of alcohol. Mussack et al. conducted a study in which they included patients with mild TBI with demonstrated blood alcohol levels (mean = 182 mg/dL), and found that the sensitivity of S-100β in the first 3 h posttrauma was 100% (95% CI 0.83 a 1.0) and the specificity was 50% (95% CI 0.41–0.59) [20].

On the other hand, Bazarian et al. studied 96 patients with TBI, GCS 13–15 who also presented trauma of extracranial localization, and found a sensitivity of 80% (95% CI 0.36–0.96) and a specificity of 40% (95% CI 0.01–0.09) for S-100β with a cut-off value of 0.08 ng/mL [21].

From the studies described above, it can be deduced that the sensitivity increases as the time elapsed between the trauma and the sample taking (window) decreases, as well as an increase in specificity is observed when the cut-off value increases. In contrast, the limitations of the use of S-100β as a marker are due to the marked decrease in sensitivity and specificity in the context of the polytraumatized patient, since the presence of concomitant extracranial trauma also causes the release and plasma elevation of this protein. The presence of S-100β has been reported in tissues other than the nervous one, mainly in adipose tissue [22]. From this observation, a negative effect on the specificity of this marker is expected, due to the increase that would occur in the context of extracranial lesions, as occurs in the polytraumatized patient.

Pham et al. [22] characterized the tissue specificity of S-100β and evaluated the extracranial sources of this marker and how they affect serum levels of this marker. For this purpose, they performed the extraction of proteins from nine different human tissues (liver, bladder, kidney, colon, lung, muscle, pancreas, adipose tissue, brain, tonsils, stomach, and skin) and their subsequent analysis through ELISA

and Western blot in 200 subjects receiving chemotherapy for the management of CNS lymphomas. A dose of mannitol (1.4M) was administered intra-arterially in the carotid or vertebral artery, subsequently confirming the presence of BBBD by a head CT performed immediately after chemotherapy.

The results presented in that study showed that extracranial sources of S-100β do not affect serum levels. Therefore, the diagnostic value and the negative predictive value of S-100β are not compromised in the context of patients with neurological diseases, but without traumatic lesions, whether cerebral or extracranial.

Goyal et al. [14] also evaluated S-100β as a prognostic biomarker in adult subjects with severe TBI (sTBI) by comparing the results with the S-100β temporal profiles in both CSF (n = 138 subjects) and serum (n = 80 subjects) for 6 days. The variables used to evaluate the extracerebral sources of S-100β in serum were: long bone fracture, Injury Severity Score (ISS), and isolated skull trauma. After TBI, levels of S-100β in CSF and serum were increased compared to healthy controls during the first 6 days after TBI ($p \leq 0.005$ and $p \leq 0.031$). Although levels in CSF and serum had a high correlation at the early post-TCE time points, this association decreased with time. The bivariate analysis showed that subjects who had temporary CSF profiles with higher concentrations of S-100B had higher acute mortality ($p < 0.001$) and worse Glasgow Outcome Scale (GOS; $p = 0.002$) and disability scores (DRS) ($p = 0.039$) 6 months after the injury. Temporary profiles in serum were associated with acute mortality ($p = 0.015$), possibly as a result of the extracerebral sources of S-100β in the serum, represented by high ISSs ($p = 0.032$).

Due to its temporal elevation profile, and the pathophysiological mechanisms that cause its release toward serum, S-100β constitutes an excellent candidate as an early biomarker of TBI, with the possible limitation in patients with concomitant trauma in other sites that leads to the serum elevation of S-100β from extracranial sources.

2.2 Ubiquitin C-terminal hydrolase-L1 (UCH-L1)

The C-terminal hydrolase of ubiquitin-L1 (ubiquitin C-terminal hydrolase-L1, UCH-L1) is an E2 conjugation enzyme present in the cytoplasm of almost all neurons [13] and has previously been used as a neuronal histological marker due to its great abundance and specific expression in these cells [11]. Its location has also been shown in neurons of the peripheral nervous system, particularly in the neuromuscular junction [12], as well as in cells of the neuroendocrine system. In addition, the presence of UCH-L1 has been demonstrated in aortic endothelial cells and in smooth muscle and tumor cells [23]. This enzyme accomplishes the function of adding and removing ubiquitin from proteins in order to promote its degradation via the proteasome-dependent pathway [24].

UCH-L1 is one of the most recent biomarkers proposed for TBI, and for this reason, there are still limited data that demonstrate its usefulness (**Table 3**).

Three isoenzymes of UCH (UCH-L1, UCH-L2, and UCH-L3) have been identified, being UCH-L1, the only one present in high concentrations in the central nervous system [24]. In a prospective case-control study with 66 patients, Papa et al. [24] obtained ventricular CSF samples for each patient after 6, 12, 24, 48, 72, 96, 120, 144, and 168 h after TBI for the UCH-L1 detection by ELISA. The severity was determined by the Glasgow Scale (GCS) and CT findings. Mortality and neurological sequelae were evaluated at 6 months. This study showed that patients with TBI had a significant elevation of CSF UCH-L1 levels at each point in time compared to controls, with total mean in TBI patients = 44.2 ng/mL (±7.9) vs. 2.7 ng/mL (±0.7) in controls ($p < 0.001$). Significantly elevated levels of UCH-L1 were found in

Reference	Detection method	Sample	Findings
Papa et al. [24]	ELISA	CSF	Increase at 6, 12, 24, 48, 72, 96, 120, 144, and 168 h post-trauma, X = 44.2 ng/mL (±7.9), versus controls X = 2.7 ng/mL (±0.7) (p < 0.001). Also elevated when it exists: lower GCS at 24 h, post-trauma complications, deaths in the first 6 weeks, or serious sequelae at 6 months.
Brophy et al. [53]	ELISA	CSF and serum	Significant correlation between biokinetics and means of (UCH-L1) in CSF and serum in severe TBI (rs = 0.59, p < 0.001) (AUC, rs = 0.3, p = 0.027). Increased levels <24 h posttrauma, statistically significant in Cmax (0–24 h) in CSF and serum in those who died.
Mondello et al. [26]	Sandwich ELISA	CSF and serum	It remains elevated up to 7 days after TBI, serum AUC and statistically significant CSF at all-time points up to 24 h (p < 0.001). Levels in <12 h in GCS 3–5 > GCS 6–8 (p = 0.07 and p = 0.02, Mann-Whitney test, respectively). Significantly higher and prolonged serum and CSF levels in non-survivors. A level of >5.22 ng/mL was a predictor of mortality (OR 4.8).
Papa et al. [11]	ELISA	Serum	Elevated in GCS 15 vs. controls without trauma (AUC 0.8) and controls with trauma. Higher elevation in GCS 15 plus TAC or neurosurgical intervention requirement. It provides evidence as a potential marker of mild TBI.
Kou et al. [27]	Electrochemiluminescence immunoassay (ECL-IA)	Serum	Complements brain MRI in the detection of injury. Significantly elevated levels in patients in the acute state of mild TBI.
Diaz-Arrastia et al. [28]	Sandwich ELISA	Serum	Measurement <24 h posttrauma distinguished presence and absence of intracranial lesions (AUC of 0.713). No correlation between levels in mild TCE and recovery at 6 months. Significant increase in levels in moderate/severe TCE compared with mild TBI. Good sensitivity to discriminate between TCE and controls (AUC 0.87). Combination with GFAP showed greater sensitivity and specificity for the diagnosis of TBI (AUC 0.94).
Puvenna et al. [15]	ELISA	Serum	There were no significant differences between the levels of negative controls and TCE <6 h posttrauma, independent of the CT. The levels were high after each game but without correlation with the number of hits received.

Table 3.
Summary of the evidence reported in the literature on UCH-L1.

patients with a lower score in the GCS at 24 h, in those who had presented post-trauma complications, in those who died within the first 6 weeks, and in those with severe sequelae at 6 months. These data suggest that this marker would be useful in determining severity in patients with TBI. Similar studies with larger samples are required to validate these findings.

Additional studies have confirmed the positive correlation between the concentrations of UCH-L1 at the CSF level and serum samples [25]. Similarly, Mondello

et al. [26] conducted a case-control study with 95 patients with severe TBI in order to evaluate the CSF and serum concentrations of UCH-L1 by sandwich ELISA and its association with clinical results. The temporal profile of the marker in both CSF and serum was studied during the first 7 days following the trauma and compared with controls showing significantly higher levels compared to the controls throughout the 7-day period, also confirming a high sensitivity and specificity for the diagnosis of TBI versus controls, with statistically significant serum AUC and CSF values at all-time points up to 24 h ($p < 0.001$).

The levels of UCH-L1 in the first 12 h in both CSF and serum in patients with GCS 3–5 were also significantly higher than in those with GCS 6–8. In addition, UCH-L1 levels in CSF and serum appeared to distinguish between patients with severe TBI survivors and nonsurvivors within the study, such that those who died had significantly higher CSF and serum UCHL1 levels, as well as greater permanence of these levels over time. In this study, a serum level of UCH-L1 > 5.22 ng/mL was a predictor of mortality (OR 4.8).

Papa et al. [11] also analyzed UCH-L1 in serum taken in the first 4 h posttrauma in patients with mild (n = 86) and moderate (n = 10) TBI, as well as in controls with trauma and controls without trauma. For patients with a GCS of 15, serum UCH-L1 was significantly elevated compared to controls without trauma, with an AUC of 0.87, and was also compared with controls with trauma, and was even higher in those patients with GCS of 15 who also had positive findings on the CT scan or required some neurosurgical intervention, suggesting that UCH-L1 may be a potential marker of mild TBI. Additionally, 5% of patients with GCS of 15 (4/77) required neurosurgical intervention, which was higher than the 1% found in patients with GCS 14–15 reported in the study by Jagoda et al., in which the samples were taken within the first 24 h posttrauma [10].

It is inferred from these data that the earlier it is detected posttrauma, the sensitivity of this marker increases. In a smaller study (n = 9), serum UCHL1 (taken <6 h posttraumatic) was found to be significantly elevated in patients with mild TBI [27].

In another study focused on all levels of severity of TBI, serum UCH-1 measured before 24 h posttrauma could distinguish patients with intracranial lesions from those without intracranial lesions with an AUC = 0.713 [28]. However, there was no correlation between UCH-L1 levels in patients with mTBI and recovery at 6 months as measured by the GOSE scale. While there was a significant increase in UCH-L1 levels in patients with moderate/severe TBI compared to mild TBI, patients with mild TBI were not compared with controls.

In a research carried out in a secondary school, Puvenna et al. [15] selected 15 American football players; they obtained serum samples before and after each of two different games. They did not observe significant differences between the levels of UCH-L1 between the negative controls and the positive individuals for mild TBI within the first 6 h posttrauma, regardless of whether or not positive CT findings existed. In addition to this, there was no correlation between the serum levels of UCH-L1 and the number of impacts received. The levels of UCH-L1 and S-100β, markers of neuronal injury and BBBD, respectively, were both elevated after each game. However, only S-100β, unlike UCH-L1, was correlated with the number of hits received and the UCH-L1 elevation did not correlate with the S-100β increments. The authors suggest that elevated postgame UCH-L1 levels may be due to the release of this protein from the neuromuscular junction.

It can be concluded that there are very divergent data regarding the use of UCH-L1 as a serum biomarker of mild TBI. Some studies suggest that it is a promising marker, while others do not find a correlation with the lesion. Release from sources other than the central nervous system could contribute to elevated serum levels.

2.3 The fibrillary acid glial protein (GFAP)

Glial fibrillary acidic protein (GFAP) is a protein derived from glial cells, which is a part of the intermediate filament of the cytoskeleton of astrocytes, where it is the most abundant protein. It is considered a specific marker of CNS diseases, and is also related to several neuronal processes' harmful agents that compromise the integrity of the blood-brain barrier [29], and has been shown to be a potentially useful biomarker for predicting clinical outcomes in TBI. Its normal level in serum is <0.03 ng/mL [30], so any elevation thereof will indicate BBBD (**Table 4**).

Due to its great immunoreactivity, GAFP has been used as an indicator of brain injury in experimental models of mTCE [31]. The first successful measurement of GFAP in human blood was made in 1999 in 12 of 25 patients with severe TBI [32]. Using a weight drop model with mice [33] to evaluate two levels of mTBI, one with hemorrhage (complicated mTBI) and another without bleeding (uncomplicated mTBI), Yang et al. [34] found that serum GFAP was significantly elevated in both injury models at 90 minutes and 6 h after injury, but had returned to normal at 24 h.

In the study of Kou et al. [27], significantly elevated serum levels of GFAP in the first 24 h posttrauma in 9 mTBI patients was also reported; this elevation being even more significant in those with hemorrhagic lesions; however, the small size of the sample does not allow the conclusions to be validated.

In another study, Mondello et al. [35] evaluated whether the relationship between a neuronal marker (UCH-L1) and a glial marker (GFAP) correlates with the presence of different intracranial pathologies after brain trauma. They obtained serum samples from 59 patients with sTBI on admission to the hospital and measured levels of UCH-L1 and GFAP. The glial/neuronal ratio (GNR) was measured as the quotient between the concentrations of GFAP and UCH-L1. Logistic regression analysis identified variables associated with the type of injury. The increase in GNR was associated independently with the type of injury, but not with the age, gender, GCS, or trauma mechanism. This quotient was significantly higher in the patients who died, but it was not an independent predictor of mortality. The GNR had a median of 0.85 and correlated positively with age.

When evaluating the CT scan of the skull on admission, 29 patients presented a diffuse lesion and 30 localized lesions. The GNR was significantly higher in the group with focal lesions compared to the group with diffuse lesions. The receiver operating characteristic (ROC) analysis showed that the GNR discriminated between the two types of injury. GNR was more accurate when performed early than when it was done late (**Table 4**).

These data indicate that the GNR provides valuable information about the different types of injury, which is of great clinical utility. In addition, the GNR can help to identify the pathophysiological mechanisms subsequent to the different types of TBI. This is very useful when implementing therapeutic measures.

In an investigation carried out by Papa et al. [36], the capacity of the GFAP taken <4 h posttrauma was compared to predict intracranial lesions in the CT compared to S-100β. Although patients had GCS 9–15, only 3 of 209 patients had GCS <13 and only 10% had intracranial lesions, both S-100β and GFAP were significantly elevated in all patients, and even more so in those with intracranial lesions. For those patients with GCS 14–15, the AUC for the identification of intracranial lesions was 0.82 for GFAP and 0.77 for S-100β.

In the presence of extracranial lesions and using a cut-off value of 0.067 ng/mL, GFAP was 100% sensitive and 55% specific in the prediction of intracranial lesions. With a cut-off value of 0.20 ng/mL, S-100β also had 100% sensitivity but only 5% specificity. This study concludes that GFAP exceeds S-100β in the identification of intracranial lesions in mild and moderate TBI, even in the presence of extracranial lesions.

Reference	Detection method	Sample	Findings
Kou et al. [27]	Electrochemiluminescence immunoassay (ECL-IA)	Serum	Significantly elevated in all cases of intracranial hemorrhage, with potential screening capacity. Small size of the sample does not allow to validate the conclusions.
Mondello et al. [35]	Sandwich ELISA	Serum	Evaluation of GNR (GFAP/UCH-L1): Median = 0.85, positive correlation with age (R = 0.45, p = 0.003). Greater in focalized lesions vs. diffuse lesion (1.77 vs. 0.48, respectively, p = 0.003). Different type of lesions (AUC = 0.72, p = 0.003). More precise early measurement (<12 h posttrauma) vs. late (AUC = 0.80, p = 0.002). Independent association with the type of injury, but not with the GCS. Independent predictor of mortality.
Papa et al. [36]	ELISA	Serum	S-100B and GFAP significantly elevated in all patients, especially in intracranial injuries. For GCS 14–15, AUC = 0.82 in identification of intracranial lesions for GFAP (0.77 for S-100B). With extracranial lesions and cut-off 0.067 ng/mL, GFAP: S = 100% and E = 55% to predict intracranial lesions. GFAP outperforms S-100B in the identification of intracranial lesions in mild and moderate TBI, even in the presence of extracranial lesions.
Papa et al. [54]	ELISA	Serum	GFAP-BDP significantly elevated in mild TCE vs. controls with or without trauma. AUC = 0.88 to identify brain injury in GCS 15. Higher levels in GCS 15 with positive CT.
Okonkwo et al. [55]	ELISA	Serum	GFAP-BDP <24 h posttrauma distinguished between mild and moderate/severe TBI (AUC of 0.87). Controls were not included, mild to moderate TCE was not compared, and most of the statistical analysis was made with all levels of severity at the time.

Table 4.
Summary of the evidence reported in the literature on GFAP in TBI.

In general, GFAP seems to increase in TBI and could represent a more sensitive marker than S-100β for the identification of intracranial lesions. However, for further validation, more studies are needed that focus specifically on mTBI (GCS 13–15), which include appropriate controls and adequate statistical comparisons.

3. Discussions and conclusions

One of the main purposes of the search for potential biomarkers in the TBI is to predict the presence of pathological findings in head CT and brain MRI; however, the studies published in this regard are inconclusive, and the evidence favors the use of S-100β over other markers in mTBI, as a predictor of negative-CT.

For example, Posti et al. [37] showed that patients with orthopedic trauma had higher levels of GFAP at admission, than those with mTBI and negative-CT (p = 0.026), and did not show that UCH-L1 levels presented significant differences in both groups, performing measurements at different time points, which suggest that these markers are not useful for distinguishing patients with negative-CT mTBI from patients with orthopedic trauma, and that high levels of UCH-L1 or GFAP can

lead to a false diagnosis of mTBI in polytraumatized patients, leading to the unnecessary use of neuroimaging.

On the other hand, the use of the S-100β marker has been recommended in the Scandinavian guidelines for the initial management of minimal, mild, and moderate head injuries in adults [38] as an alternative to reduce the number of CT in the subgroup of mTBI with low risk of intracranial complications or surgical interventions. More studies are needed that show the usefulness of S-100β as a predictor of neurodeterioration in moderate TBI.

The use of neuroimaging is necessary to improve the accuracy of biomarkers in the diagnosis and prognosis of patients who have suffered a TBI, with CT being the first option and the one with the most studies in relation to the release and correlation of biomarkers. Some reviews report higher serum S-100β levels in more severe, focal lesions, compared to diffuse lesions using Marshall scale, and a strong correlation between S100B increasing and the severity of the CT finding when using the sum of Rotterdam CT score and Stockholm CT score [54].

Olivecrona et al. reported how S-100β and neuronal specific enolase (NSE) levels correlate with CT findings using the aforementioned scales. Specifically, S-100β levels, but not to the NSE levels, correlates with Morris-Marshall score for the classification of traumatic subarachnoid hemorrhage (tSAH). This is probably associated with the physiopathological pathways described by each of these biomarkers after a neurotrauma. Likewise, the volume of the parenchymal contusions is also associated with the S-100β levels. Furthermore, in mild TBI, initial low levels of S-100β can be used as a predictor of a stationary injury, suggesting that the CT classification does not evolve [55].

Diagnosis of severity and prognosis of CT findings cannot be performed by a single biomarker test. Instead, a combination of biomarkers of diverse origins and pathways displays a better performance. Thereby, the joint use of GFAP, heart fatty acid binding protein (H-FABP), S-100β, and IL-10 results in a more efficient diagnostic tool with a 46% specificity and 100% sensitivity for predicting CT injuries. This biomarker panel increases specificity by 14% compared to the best single biomarker [56].

The ALERT-TBI study, developed in 22 centers in USA and Europe, validated the ability of the combination of UCH-L1 and GFAP to predict CT injuries within 12 h of mTBI, resulting in a sensitivity of 97.6%, a negative predictive value (NPV) of 99.6%, and a specificity of 36.4%. Therefore, when indicating CT only in those patients with a positive GFAP and UCH-L1 test, the CT use could be reduced by approximately one-third. The extent of these findings to patients with moderate TBI is uncertain [57].

The study of the available evidence on the different serum markers in TBI presented in this chapter allows us to conclude that, currently, there is not a single biomarker capable of predicting the clinical deterioration of patients with high sensitivity and specificity. However, the pathophysiological mechanisms of TBI suggest that instead, a panel of markers that reflect different aspects of traumatic injury should be available, including BBBD and neuronal injury.

The literature has shown that the joint use of S-100β and GFAP or UCH-L1 would represent a valuable early prognostic and follow-up tool in TBI in addition to the GCS and the CT, thus guiding the decisions of initial management and aggressive interventions.

Likewise, given that the kinetic profile of these markers is different, since it presents peaks of appearance earlier than others and different times of permanence in serum, its usefulness would also be correlated with different post-traumatic stages, so that S-100β and UCH-L1 are better early markers [24, 25], whereas GFAP is a better predictor of CT lesions and surgical interventions in the first 7 days post-trauma in mild and moderate TBI [27].

In addition to the above, the literature also shows that these biomarkers are being measured with techniques that demand the use of complex equipment and procedures (such as ELISA) in which the use of labels is necessary [6, 39], displaying the need for the development of rapid and cost-effective techniques that allow the implementation of biomarkers in the clinical setting.

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Conflict of interest

The authors declare no conflict of interest.

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