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Biomarkers in Acute Traumatic Brain Injury: A Systematic Review and Meta-Analysis

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Abstract

Traumatic brain injury (TBI) stands as a significant contributor to traumatic death and disability worldwide. In recent years, researchers have identified biomarkers to gauge useful outcomes in TBI patients. However, the enigma of timely sample collection to measure the biomarkers remains a controversial point in the case of TBI, unlike other degenerative diseases like Alzheimer's disease and Parkinson's disease, where we can collect the sample at any point in time. The purpose of this study is to evaluate the sensitivity of biomarkers in TBI concerning time of injury by analyzing recent available data on biomarkers in the medical literature. A total of 2,256 studies were initially retrieved from the search engine. After an initial screening, only 1,750 unique articles remained. After excluding review articles, animal studies, meta-analysis, and studies with children (screened by title and abstract), 30 kinds of literature were found relevant to search the required variables. Further 16 studies were excluded due to the nonavailability of complete variables or data. Finally, 14 studies remained and were included in the analysis. This study has analyzed the four most commonly described biomarkers for TBI in the literature: glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B, ubiquitin carboxy-terminal hydrolase L1, and Tau. According to this statistical analysis, all biomarkers included in the study have shown their serum levels after trauma. So, all these biomarkers can be used for further study in the outcome prediction and diagnosis of TBI patients. The meta-analysis suggests that the best biomarker for TBI is Tau in cases where sample collection is done within 24 hours, while GFAP is the best biomarker to be studied for TBI if sample collection is done 24 hours after trauma.

Categories: Neurosurgery, Trauma
Keywords: tau protein, uchl-1, s100b, gfap, biomarkers, acute traumatic brain injury

Introduction And Background

Traumatic brain injury (TBI) is a significant cause of death and disability. In the last few years, many advances have been made to elucidate the anatomical, cellular, and molecular mechanisms of TBI. However, these advances have not yet yielded significant improvements in treatment. Some of the barriers identified to developing recent treatment include heterogeneity of the disease, difficulty stratifying patients by injury severity, and a lack of definite markers of injury [1]. Unlike other emergency diseases, such as myocardial ischemia, where rapid diagnosis with the biomarkers from blood tests proves invaluable to guide diagnosis and management, no such rapid and definitive diagnostic tests exist for TBI currently. Therefore, the measurement of biomarkers measurable in CSF and blood can significantly contribute to the diagnosis, prognosis, and clinical research of TBI.

Recent reviews of biomarkers in brain injury have highlighted the need for biomarker development [1]. Most of the research on potential biomarkers for brain injury has been conducted over the last 10 years. The most studied potential biomarkers for TBI are glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), neurofilament L (NF-L), and Tau protein. GFAP and S100B are released from astrocytes, while UCH-L1, NF-L, and Tau are released from neurons [2]. After TBI, biomarkers can diffuse through the extracellular space of the brain and enter the bloodstream via a disrupted blood-brain barrier, intramural periarterial drainage system, or glymphatic system [3]. The kinetic studies of these biomarkers showed that the Tmax of all the above biomarkers except Tau protein is less than 24 hours and T1/2 is less than 36 hours [4]. GFAP is detectable within one hour after injury, rises and seems to peak within 20-24 hours, and subsequently drops over 72 hours with a 24-hour sampling time of 48 hours [5]. S100B is released within minutes of an injury, rises sharply, and settles to homeostatic levels one to two hours later [6]. Based on their approximate Tmax, it is predicted that the time for S100B is between 0 and 4 hours, four to 12 hours for UCH-L1 and Tau, and 12-36 hours for GFAP [6]. So it seems that the biggest limitation to the practical utility of biomarkers is the timely arrival of head injury patients to trauma centers and the in-time collection of samples for biomarker studies to define the severity and prognosis of TBI. Empirical studies are needed to confirm the best sampling times for blood biomarkers after TBI, depending on the intended context of use. This study aims to identify the pragmatic utility of GFAP,

S100B, UCH-L1, and Tau protein biomarkers in acute TBI and their clinical significance in the form of sensitivity, specificity, and the area under the curve (AUC) of each biomarker concerning time: early phase (less than 24 hours of trauma) vs. late phase (more than 24 hours of trauma). The authors also analyzed the serum value of the above four biomarkers as a whole without segregating them into early and late phases and their usefulness in the management of acute TBI.

Review

Methodology

Information Source

The two panelists allocated to each population, intervention, control, and outcomes (PICO) question were given the duty of scoping the literature to finalize PICO specifics, picking the search terms for the PICO question, and choosing two to three major articles thought to be extremely pertinent to the subject. The search was conducted by utilizing the databases MEDLINE/PubMed, SCOPUS, and Google Scholar and using the search criteria to choose the relevant articles. The search included all the published articles from 1998 until 2023.

Study Selection

A four-tier system was followed for screening purposes. 2,256 records were identified in Tier I through a database search, and after the removal of duplicates, 1,750 studies remained. In Tier II, screening was done based on title, and 337 suitable articles were found. The next exclusion was done through the screening of abstracts, which led to 70 studies at the end of Tier II screening. The Tier III exclusion was done based on eligibility and a full-text review, and only 30 kinds of literature were found to be relevant enough to be tested for the qualifying criteria. The qualifying criteria applied were adult population (⩾15 years of age), injury reported in less than 24 hours, English language of articles, randomized controlled trials, prospective or retrospective observational studies, case-control studies, and case series with a sample size greater than 20 patients. Case reports and reports that were published only as an abstract or supplement were not included. In Tier IV, finally, 14 studies remained and were included in the meta-analysis (Figure *1*). The quality assessment of the included studies was done using the Newcastle-Ottawa Scale (NOS), as shown in Table *1*.

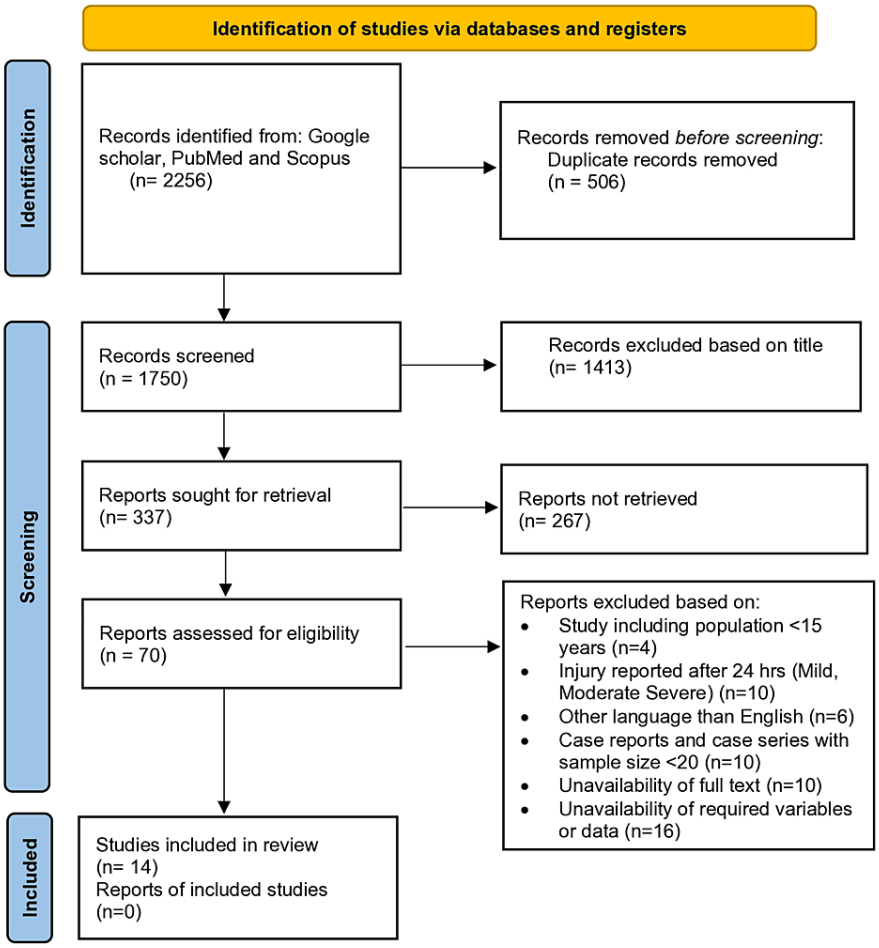

FIGURE 1: PRISMA flow chart showing identification of publications, screening, qualifying criteria, and final selection of publications for meta-analysis

PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses

Authors	Representativeness of the sample	Ascertainment of the exposure (disease)	Assessment of the outcome	Statistical test	Quality score
Welch et al. (2017) [4]	2	1	2	2	7
Diaz-Arrastia et al. (2014) [7]	2	2	2	2	8
Czeiter et al. (2020) [8]	2	2	1	2	7
Okonkwo et al. (2013) [9]	2	2	1	2	7
Hellewell et al.	2	2	2	1	7

(2020) [10]					
McMahon et al. (2014) [11]	2	2	1	2	7
Raheja et al. (2016) [12]	1	1	2	2	6
Lei et al. (2015) [13]	2	1	1	2	6
Anderson et al. (2020) [14]	2	1	2	2	7
Shahim et al. (2014) [15]	2	1	2	2	7
Rainey et al. (2009) [16]	2	1	2	2	7
Olivecrona et al. (2009) [17]	2	1	1	2	6
Müller et al. (2007) [18]	2	1	2	2	7
Liliang et al. (2010) [19]	1	2	1	2	6
-	*2: Truly representative of the average in the target population (all subjects or random sampling); *1: somewhat representative of the average in the target population (nonrandom)	*2: Secure record (medical charts) or validated measurement tool; *1: self-report	*2: Independent structured assessment; *1: not done	*2: The statistical test used to analyze the data clearly described appropriate variables; *1: not mentioned	

TABLE 1: Quality assessment of the studies using the NOS

NOS, Newcastle-Ottawa Scale

Data Synthesis and Statistical Analysis

To assess the significance of the biomarkers on the outcome, the individual effects of all biomarkers were estimated. The pooled AUC and the 95% CI were calculated with the help of the AUC and their standard error. In the studies where information on standard error was not available, the approximation method was used. For the initial phase, the authors calculated the pooled AUC for each biomarker (GFAP, UCH-L1, S100B, and Tau) based on the number of patient samples collected within 24 hours of trauma, while the pooled AUC of all biomarkers for the late phase was calculated using the patient's sample collected after 24 hours of trauma mentioned in the studies. The level of significance was set at a p-value of <0.05. Whether to use a fixed effect or random effects model was decided based on heterogeneity, which was evaluated by Cochran's Q test and Higgins I^2 statistics. If the statistical heterogeneity was significant ($p < 0.10$ or $I^2 > 50\%$), a random effects model was used; otherwise, the fixed effects model was used. Meta-analysis was performed using MedCalc Version 22 (MedCalc Software Ltd, Ostend, Belgium) and MS Office (Microsoft Corporation, Redmond, United States).

Results

The results were analyzed for GFAP, UCH-L1, S 100B, and Tau separately as well as combined for the early phase (less than 24 hours) and late phase (more than 24 hours).

GFAP

GFAP data were extracted from nine studies for the early phase and eight studies for the late phase, comprising 4,685 and 4,641 cases, respectively (Table *2*). The pooled AUC for GFAP in the early phase exhibited heterogeneity among the studies (Q = 97.69, I^2 = 91.8%, p < 0.001), prompting the use of a random effects model. The estimated pooled AUC for GFAP was 0.84 (95% CI 0.79-0.89, p < 0.001). Conversely, the AUC for GFAP in the late phase showed homogeneity (Q = 11.88, I^2 = 41.07%, p = 0.105), leading to the application of a fixed effects model, with a pooled AUC of 0.88 (95% CI 0.86-0.91, p < 0.001) (Figure *2*). Analysis of the combined GFAP data demonstrated homogeneity (Q = 1.1378, I^2 = 12.11%, p = 0.286), and a fixed effects model yielded a pooled AUC of 0.86 (95% CI 0.83-0.89, p < 0.001). The overall sensitivity percentage for the entire GFAP biomarker in the AUC analysis was 86%.

Authors and statistical metrics	<24 hours of TBI, 95% CI	Sensitivity (%)	Specificity (%)	>24 hours of TBI, 95% CI	Sensitivity (%)	Specificity (%)
Welch et al. (2017) [4]	0.900 (0.860-0.940)	97	18	0.870 (0.775-0.965)	100	42
Diaz-Arrastia et al. (2014) [7]	0.910 (0.880-0.940)	91	88	0.740 (0.610-0.870)	74	61
Czeiter et al. (2020) [8]	0.720 (0.690-0.750)	71	75	0.900 (0.870-0.930)	92	89
Okonkwo et al. (2013) [9]	0.870 (0.810-0.930)	80	81	0.840 (0.770-0.910)	73	89
Hellewell et al. (2020) [10]	0.730 (0.580-0.880)	82	50	-	100	100
McMahon et al. (2014) [11]	0.880 (0.830-0.930)	67	89	0.960 (0.855-1.000)	45	99
Raheja et al. (2016) [12]	0.870 (0.755-0.985)	53.1	80	0.880 (0.735-1.000)	90	90
Lei et al. (2015) [13]	0.823 (0.700-0.946)	84.6	69.2	0.761 (0.605-0.917)	85.3	77.4
Anderson et al. (2020) [14]	0.801 (0.718-0.884)	87	60	0.867 (0.720-1.000)	71	80
Pooled AUC	0.840 (0.793-0.888)	-	-	0.884 (0.860-0.908)	-	-
Cochran Q	97.69	-	-	11.88	-	-
I^2	91.81%	-	-	41.07	-	-
p-value (heterogeneity)	<0.001	-	-	0.105	-	-

TABLE 2: Comparison of AUC and statistical metrics of GFAP biomarker between <24 hours and >24 hours of trauma

AUC, area under the curve; GFAP, glial fibrillary acidic protein; TBI, traumatic brain injury

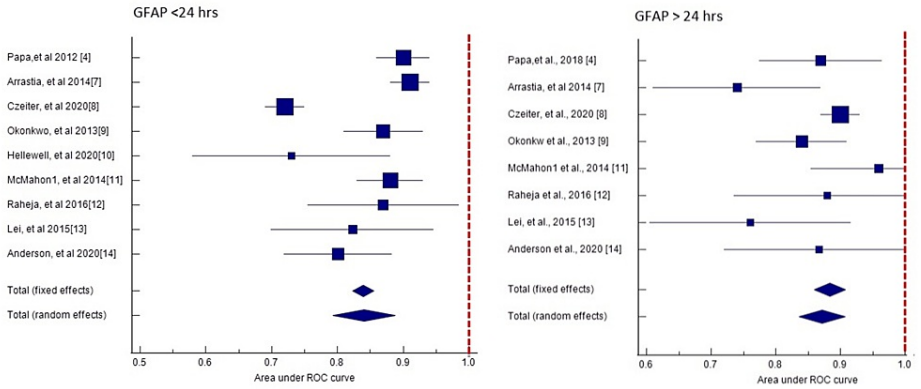

FIGURE 2: Area under the ROC curve for biomarker GFAP in the (A) first 24 hours of TBI (early phase) and (B) >24 hours of TBI (late phase)

GFAP, glial fibrillary acidic protein; ROC, receiver operating characteristic; TBI, traumatic brain injury

S100B

S100B data were extracted from four studies, with a cumulative sample size of 662 cases for both the early and late phases (Table *3*). The pooled AUC for S100B in the early phase exhibited homogeneity among the studies (Q = 2.46, I^2 = 0%, p = 0.48), leading to the application of a fixed effects model. The estimated pooled AUC for S100B was 0.657 (95% CI 0.59-0.72, p < 0.001). In the late phase, the AUC for S100B also showed homogeneity (Q = 1.44, I^2 = 0%, p = 0.69), resulting in a pooled AUC of 0.73 (95% CI 0.67-0.79, p < 0.001) (Figure *3*). The combined analysis of S100B data exhibited heterogeneity (Q = 2.7439, I^2 = 63.56%, p < 0.001), prompting the use of a random effects model with a pooled AUC of 0.696 (95% CI 0.64-0.74, p < 0.001). The overall sensitivity percentage for the entire S100B biomarker in AUC analysis was 70%.

Authors and statistical metrics	<24 hours of TBI, 95% CI	Sensitivity (%)	Specificity (%)	>24 hours of TBI, 95% CI	Sensitivity (%)	Specificity (%)
Shahim et al. (2014) [15]	0.670(0.515-0.825)	67	52	0.68 (0.495-0.865)	68	87
Rainey et al. (2009) [16]	0.690 (0.575-0.805)	80	60	0.77 (0.680-0.860)	83	49
Olivecrona et al. (2009) [17]	0.552 (0.405-0.699)	91.3	28	0.687 (0.549-0.825)	40	75
Müller et al. (2007) [18]	0.680 (0.565-0.795)	95	31	0.72 (0.600-0.840)	-	-
Pooled AUC	0.657 (0.592-0.721)	-	-	0.732 (0.672-0.792)	-	-
Cochran Q	2.457	-	-	1.435	-	-
I^2	0.00%	-	-	0.00%	-	-
p-value (heterogeneity)	0.483	-	-	0.697	-	-

TABLE 3: Comparison of AUC and statistical metrics of S100B biomarker between <24 hours and >24 hours of trauma

AUC, area under the curve; S100B, S100 calcium-binding protein B; TBI, traumatic brain injury

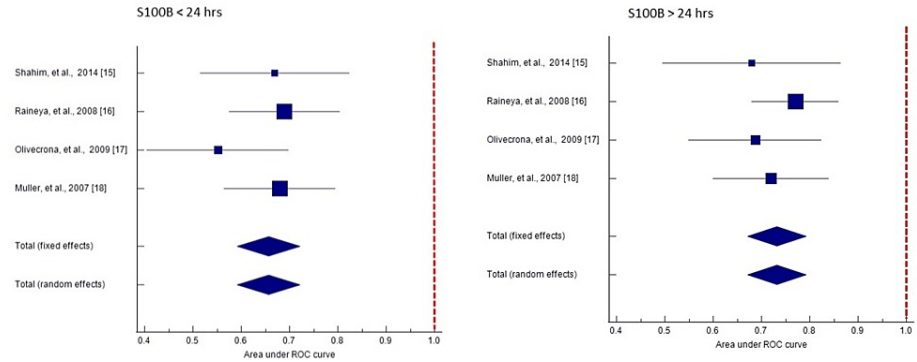

FIGURE 3: Area under the ROC curve for S100B in the (A) first 24 hours of TBI (early phase) and (B) >24 hours of TBI (late phase)

ROC, receiver operating characteristic; S100B, S100 calcium-binding protein B; TBI, traumatic brain injury

UCH-L1

UCH-L1 data were extracted from two studies, with a cumulative sample size of 377 cases for both the early and late phases (Table 4). The pooled AUC for UCH-L1 in the early phase exhibited heterogeneity among the studies (Q = 14.01, I^2 = 92.86%, p < 0.001), leading to the application of a random effects model. The estimated pooled AUC for UCH-L1 was 0.78 (95% CI 0.64-0.92, p < 0.001). In the late phase, the AUC for UCH-L1 showed homogeneity (Q = 0.42, I^2 = 0%, p = 0.52), prompting the use of a fixed effects model with a pooled AUC of 0.82 (95% CI 0.74-0.90, p < 0.001) (Figure 4). Combined analysis of UCH-L1 data demonstrated homogeneity (Q = 0.2531, I^2 = 0%, p = 0.244), resulting in a pooled AUC of 0.81 (95% CI 0.74-0.87, p < 0.001). The overall sensitivity percentage for the entire UCH-L1 biomarker in AUC analysis was 81%.

Authors and statistical metrics	<24 hours of TBI, 95% CI	Sensitivity (%)	Specificity (%)	>24 hours of TBI, 95% CI	Sensitivity (%)	Specificity (%)
Diaz-Arrastia et al. (2014) [7]	0.870 (0.835-0.905)	87	83	0.800 (0.700-0.900)	80	70
Anderson et al. (2020) [14]	0.665 (0.564-0.766)	60	75	0.854 (0.724-0.984)	68	79
Pooled AUC	0.779 (0.639-0.919)	-	-	0.820(0.741-0.899)	-	-
Cochran Q	14.129	-	-	0.419	-	-
I^2	92.92%	-	-	0.00%	-	-
p-value (heterogeneity)	<0.001	-	-	0.518	-	-

TABLE 4: Comparison of AUC and statistical metrics of UCH-L1 biomarker between <24 hours and >24 hours of trauma

AUC, area under the curve; TBI, traumatic brain injury; UCH-L1, ubiquitin carboxy-terminal hydrolase L1

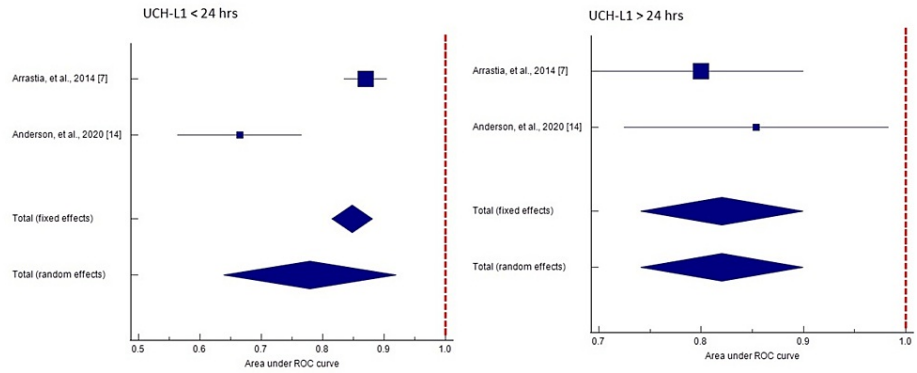

FIGURE 4: Area under the ROC curve for UCHL-1 in the (A) first 24 hours of TBI (early phase) and (B) >24 hours of TBI (late phase)

ROC, receiver operating characteristic; TBI, traumatic brain injury; UCH-L1, ubiquitin carboxy-terminal hydrolase L1

Tau Protein

Tau protein data were extracted from two studies, with a cumulative sample size of 377 cases for the early phase only (Table 5). No studies were found for the late phase. The pooled AUC for Tau protein in the early phase exhibited heterogeneity among the studies (Q = 2.8, I^2 = 64.7%, p = 0.092), leading to the application of a random effects model. The estimated pooled AUC for Tau protein was 0.88 (95% CI 0.75-1.0, p < 0.001) (Figure 5). The overall sensitivity percentage for Tau protein in the AUC analysis was not provided.

Authors and statistical metrics	<24 hours of TBI, 95% CI	Sensitivity (%)	Specificity	>24 hours of TBI	Sensitivity (%)	Specificity (%)
Shahim et al. (2014) [15]	0.800 (0.655-0.945)	80	65	-	91	100
Liliang et al. (2010) [19]	0.939 (0.867-1.000)	88	94	-	90	100
Pooled AUC	0.884 (0.751-1.00)	-	-	-	-	-
Cochran Q	2.832	-	-	-	-	-
I^2	64.69%	-	-	-	-	-
p-value (heterogeneity)	0.092	-	-	-	-	-

TABLE 5: Comparison of AUC and statistical metrics of Tau protein biomarkers between <24 hours and >24 hours of trauma

AUC, area under the curve; TBI, traumatic brain injury

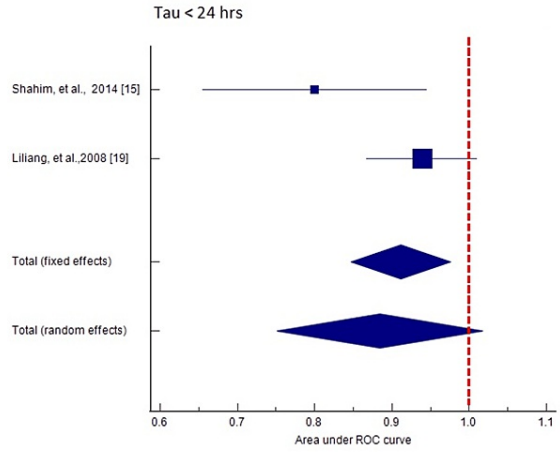

FIGURE 5: Area under the ROC curve for Tau protein in the first 24 hours of TBI (early phase)

ROC, receiver operating characteristic; TBI, traumatic brain injury

Comparison of Pooled AUC Among All Biomarkers (<24 Hours and >24 Hours)

A comparison of the combined AUC values for all biomarkers in both the early (<24 hours) and late (>24 hours) phases reveals that Tau protein exhibited the highest AUC in the early phase, making it the most effective for early TBI diagnosis, while S100B had the lowest AUC, indicating the least effectiveness. In the late phase, GFAP had the highest pooled AUC, proving to be the most reliable for diagnosing TBI at this stage, whereas S100B again showed the lowest AUC (Figure *6*, Figure *7*). This analysis underscores that Tau protein offers the best predictive, diagnostic, and clinical utility for TBI patients shortly after injury, while GFAP provides the greatest diagnostic accuracy in the later phase of trauma.

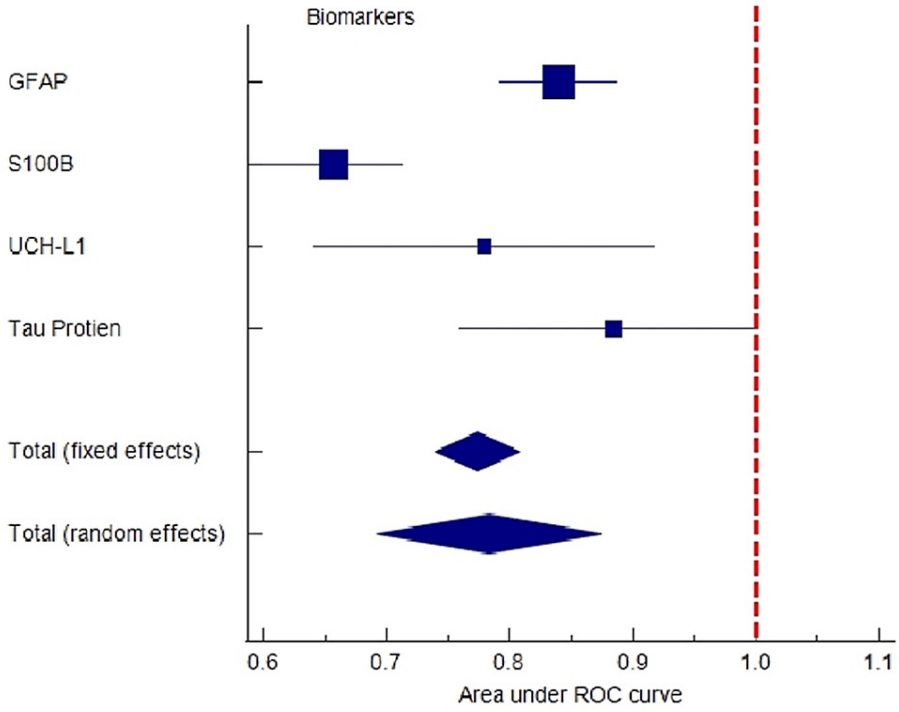

FIGURE 6: Comparison of pooled AUC among all biomarkers (<24 hours)

AUC, area under the curve

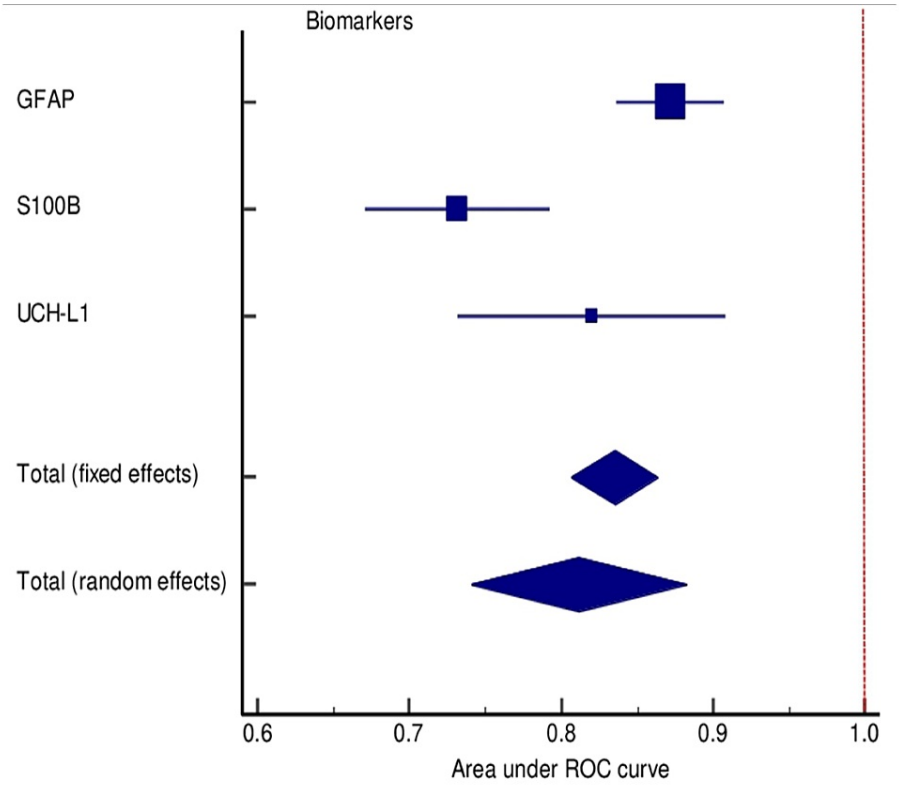

FIGURE 7: Comparison of pooled AUC among all biomarkers (>24 hours)

AUC, area under the curve

Detection of Bias

The statistical analyses of biomarkers in TBI reveal varied findings based on timing and measurement methods. Within 24 hours post-injury, GFAP levels show no significant publication bias (Egger's test, p = 0.947), with a moderate correlation suggested by Begg's test (Kendell's tau = -0.479, p = 0.072). Similarly, S100B levels within the first 24 hours exhibit no bias (Egger's test, p = 0.384) but a moderate negative correlation (Kendell's tau = -0.547, p = 0.264) according to Begg's test. Conversely, UCH-L1 demonstrates significant bias (Egger's test, p < 0.001) and a strong negative correlation (Kendell's tau = -1.00, p = 0.317) within 24 hours, whereas after this period, bias remains significant (Egger's test, p < 0.001) with a strong positive correlation (Kendell's tau = 1.00, p = 0.317). Tau protein also shows significant bias early on (Egger's test, p < 0.001) and a strong negative correlation (Kendell's tau = -1.00, p = 0.317) (Figure *8*). These results underscore the critical impact of sampling timing on biomarker analyses in TBI research, necessitating careful consideration of both statistical biases and correlation strengths in interpreting diagnostic and prognostic utility.

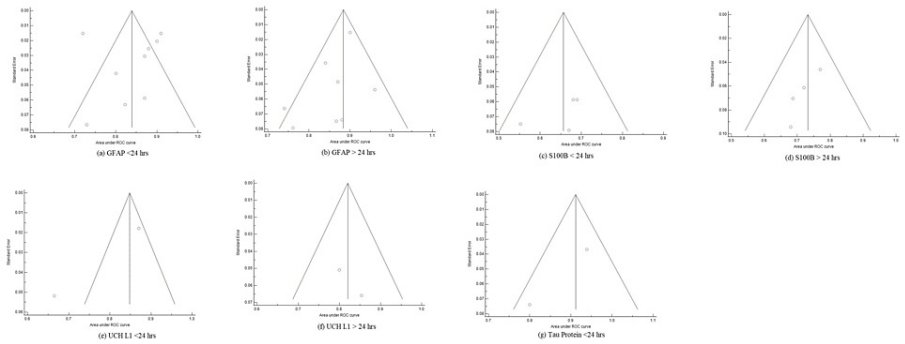

FIGURE 8: Funnel plots for studies for different biomarkers: (a) GFAP <24 hours, (b) GFAP >24 hours, (c) S100B <24 hours, (d) S100B >24 hours, (e) UCH-L1 <24 hours, (f) UCH-L1 >24 hours, and (g) Tau protein <24 hours

GFAP, glial fibrillary acidic protein; S100B, S100 calcium-binding protein B; UCH-L1, ubiquitin carboxy-terminal hydrolase L1

Discussion

Biomarkers in TBI are indicators that can measure the biological condition or state of the brain by using blood, urine, or soft tissue to examine normal biological processes, pathogenic processes, or pharmacologic responses to a traumatic injury to the brain [20]. Currently, GFAP, UCH-L1, Tau, S100B, and NF-L are the most effective biomarkers for the detection of TBI. They can be detected in the bloodstream on the day of the trauma and are associated with the severity of brain injuries. The relationship (linear or nonlinear) between the number of biomarkers released in serum and the force of impact due to trauma has not been established yet because the rise of biomarker levels after head injury was multimodal rather than unimodal. After TBI, levels of biomarkers in the CSF rise rapidly, suggesting that these biomarkers have easy access to the CSF from the interstitial fluid. Biomarkers can reach the CSF by transependymal flow into the ventricles or transpial flow into the subarachnoid space and finally enter the blood [3]. The other mode by which biomarkers can enter the bloodstream is via direct diffusion through the extracellular space of the brain by penetrating blood vessels if the blood-brain barrier is disrupted. The exact mechanism and route of absorption and their relative contribution in the bloodstream by different mechanisms are still unsettled [8]. Once biomarkers reach the blood, they get eliminated by various methods like redistribution to other compartments, renal excretion, hepatic metabolism, or intravascular proteolysis [8]. Studies have suggested that the elimination of biomarkers is likely renal and that the rate of elimination is inversely proportional to the molecular weight of biomarkers. Time concentration curves of biomarkers can be created by repeated sampling, which allows for the calculation of the Tmax and $T_{1/2}$ of biomarkers (Table *6*). Comorbid conditions, such as polytrauma and chronic neurodegenerative diseases, can alter biomarker levels in the blood, complicating the interpretation of results specifically for TBI. It may also lead to variability in biomarker readings, complicating diagnosis and prognosis. Interpretation of TBI biomarkers with these underlying conditions may lead to confusion in identifying the source of the biomarkers, resulting in poor reliability.

Biomarker	Normal serum value (pg/ml)	T_{max}	$T_{1/2}$
GFAP	60-70 (65)	24 hours	36 hours
S-100B	50-60 (55)	2 hours	1.5 hours
UCH-L1	8-10 (9)	8 hours	8 hours
Tau	1-5 (3)	8 hours	10 hours

TABLE 6: Time concentration curves of biomarkers with Tmax and T1/2

GFAP, glial fibrillary acidic protein; S100B, S100 calcium-binding protein B; UCH-L1, ubiquitin carboxy-terminal hydrolase L1

McDonald et al. have emphasized that whether a biomarker is released all at once at impact or is released in

a delayed or continuing manner after TBI is another known unknown fact, complexing the interpretation of patterns for the rise and fall of serum biomarkers's levels concerning time [20]. Overall, the enigma of timely sample collection remains a controversial point in the case of TBI, unlike other degenerative diseases like Alzheimer's disease, and Parkinson's disease. So, the practical utility of biomarkers for assisting in diagnosis, risk categorization, and the management of TBI is discussed below for each biomarker based on studies included and analyzed with the abovementioned objectives.

GFAP

This crucial human astrocyte intermediate filament supports and fortifies the cellular framework of the cell. Another way in which GFAP is implicating CNS functions is through its involvement in processes such as cellular communication and blood-brain barrier function. Several illnesses, such as traumatic spinal cord injury, neurological disorders, cerebrovascular disease, and TBI, can be diagnosed by testing the blood GFAP level [21]. Following brain cell damage, there is the release of the breakdown product GFAP-BDP into the CSF and blood. Following traumatic brain damage, GFAP is probably secreted from astrocytes and found to increase in both the blood and the CSF during astrogliosis. When a TBI compromises the blood-brain barrier, GFAP is released into the interstitial fluid and enters the bloodstream through the lymphatic system or another pathway [22]. It is one of the biomarkers approved by the US FDA for TBI.

Within an hour of the damage, GFAP was found in the serum. This protein is linked to measures of injury severity, such as the Glasgow Coma Scale score, CT lesions, and neurological treatments. When it came to predicting the presence of CT abnormalities, GFAP had the maximum discrimination; clinical features performed better than other biomarkers. GFAP alone did not contribute any utility for predicting CT positivity when compared with other biomarkers [23]. Diaz-Arrastia et al. state that GFAP may help diagnose and predict poor outcomes, but it is not appropriate for predicting intracranial CT abnormalities or incomplete recovery [7]. The increased GFAP level can be measured in both blood and CSF after TBI [10]. Monitoring GFAP could aid in prognosticating outcomes in patients with acute severe TBI.

Further study is needed for a better understanding of the pathophysiology of severe TBI and for choosing potential therapeutic targets [24]. Nine major studies were analyzed on GFAP to conclude the clinical utility of GFAP. In our meta-analysis, the overall statistical sensitivity of GFAP was found to be more than 86%, and its sensitivity performance concerning time is measured using the area under the receiver operating characteristic (ROC) curve and pooled values, which show a value of 0.84 (95% CI 0.79-0.88) and 0.87 (95% CI 0.83-0.90) in the early and late phases, respectively (Table *1*). This indicates that the sensitivity of GFAP increases after 24 hours of TBI.

S100B

S100B is the most studied protein for both structural and functional recovery in TBI. This protein belongs to a family of intracellular calcium-binding proteins primarily expressed in mature perivascular astrocytes. However, it is also present in other cells within the CNS, including neural progenitor cells, oligodendrocytes, and specific neuronal populations. S100B serves essential functions such as cell trafficking, growth, energy metabolism regulation, and the maintenance of calcium homeostasis, thereby facilitating signal transfer from second messengers. While highly specific for nervous tissue, S100B can also be found in chondrocytes, melanocytes, Langerhans cells, adipocytes, skeletal muscle, and cardiac muscle. The protein may exist as soluble in the cytoplasm, associated with the plasma membrane, other intercellular membranes, and the cytoskeleton [25]. Patients with polytrauma may not be suitable candidates to perform a study on S100B for TBI. As an intracellular regulator, S100B interacts with a broad range of proteins in a limited number of cell types to regulate energy metabolism, transcription, protein phosphorylation, cell proliferation, survival, differentiation, and motility, as well as Ca2+ homeostasis [26].

Four studies observed that the overall statistically calculated percentage for S100B is 70%. The performance in the early phase was compared to the late phase, as measured by the AUC. The pooled value is 0.65 (95% CI 0.59-0.72) for the early phase and 0.73 (95% CI 0.67-0.79) for the late phase of TBI (Table *2*). These findings suggest an increase in S100B sensitivity after 24 hours of TBI. In a utility-wise comparison, S100B is ranked fourth best.

The increasing level of S100B biomarkers indicates that we can develop a tool or medical device to monitor axonal injury and astroglial injury. According to Rainey et al., S100B biomarkers do not show good prognostic performance for TBI patients [16]. At three and 12 months after trauma, no differences in prognostic values between markers were apparent, nor was there any clinically significant value of the marker as a predictor of clinical outcomes. Determining serum S100B cannot replace a clinical examination or the use of a CT scan for patients. Measurements in clinical evaluation might support the selection of patients for a CT scan [18].

UCH-L1

UCH-L1 makes up between 1% and 5% of all the proteins found in neurons, rendering it a very prevalent

protein in the brain. Additionally, UCH-L1 is present at a reduced concentration in the gonads, in certain cells under particular circumstances (such as certain fibroblasts and clonal cells during wound healing), and in malignant cells. Although its precise actions are still unknown, it acts as a ligase to extend Lys polyubiquitin chains on an alpha-synuclein and prevent the breakdown of neuronal proteins via ubiquitin-proteasome pathways. Ubiquitination can be divided into three crucial steps: activation, conjugation, and ligation, catalyzed by the enzymes ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3), respectively. It is necessary to preserve the health and stability of axons and may be crucial for the healing process following an injury through various processes, which could account for its high levels following TBI. UCH-L1 increases in serum levels within the first 24 hours of trauma compared to control [27].

Two studies observed that UCH-L1's overall statistically calculated percentage is 81%, and its performance in the early phase of traumatic head injury compared to the late phase of injury was determined through statistical analysis of the data. The measured area under the ROC curve and pooled value are 0.779 (95% CI 0.639-0.919) for the early phase of TBI and 0.820 (95% CI 0.742-0.899) for the late phase of TBI (Table *3*). These results define that UCH-L1 increases after 24 hours of TBI. In the comparison of all biomarkers' utility, UCH-L1 is the third best biomarker.

In a study by Anderson et al., they found that at six months, 34% had GOS-E scores ⩽4, with mortality rates at 7% and 13%. ELISA was used for biomarker measurements, suggesting the potential use of these biomarkers for lesion prediction compared to CT scans [14]. According to Diaz-Arrastia et al., UCH-L1 was deemed suitable for predicting and diagnosing poor outcomes but was not suitable for predicting intracranial CT abnormalities or incomplete recovery [7]. UCH-L1 is also a US FDA-approved biomarker for TBI [23].

Tau Protein

Tau is a microtubule-associated protein primarily expressed in neurons of the CNS, playing a crucial role in axonal maintenance and transport [28]. It serves as a biomarker for neurodegenerative diseases due to its presence in abnormal intraneuronal aggregates observed in tauopathies, including Alzheimer's disease. The molecular diversity of Tau proves valuable when analyzing it in the brain or peripheral fluids [29]. According to certain research, tau is produced at the synaptic terminus when synaptic activity is normal [29]. Although the long-term implications of physiologically produced tau are unknown, this constitutive and physiological tau secretion has not been explicitly connected to the spread of pathogenic forms of tau to nearby neurons. Moreover, secreted monomeric tau might have some unidentified physiological signaling function. However, other research indicates that presynaptic neural activity might control pathogenic tau release and transsynaptic transfer [29].

Two studies observed that Tau protein's overall statistically calculated sensitivity percentage is 88%, and its performance in the early phase of TBI compared to the late phase was measured using the ROC, with a pooled value of 0.884 (95% CI 0.751-1.000) for the early phase of TBI (Table *4*). There is no evidence of Tau protein increasing after 24 hours of trauma. The increasing level of biomarkers was found, and it was suggested that a tool or medical device could be developed to monitor axonal injury and astroglial injury. This study found 88% sensitivity and 94% specificity for predicting a poor outcome, suggesting that Tau protein may serve as an indicator for predicting outcomes following severe TBI [6].

When all four biomarkers, GFAP, S100B, UCH-L1, and Tau protein, are compared, irrespective of sample collection time, Tau protein exhibits the highest significant AUC (0.884, 95% CI (0.759-1.00)), followed by GFAP (0.860, 95% CI (0.832-0.888)), UCH-L1 (ranked third) with 0.810 (95% CI (0.743-0.878) and S100B (0.696, 95% CI (0.644-748)) when compared to the other three biomarkers. These findings are shown graphically in Figure *9*.

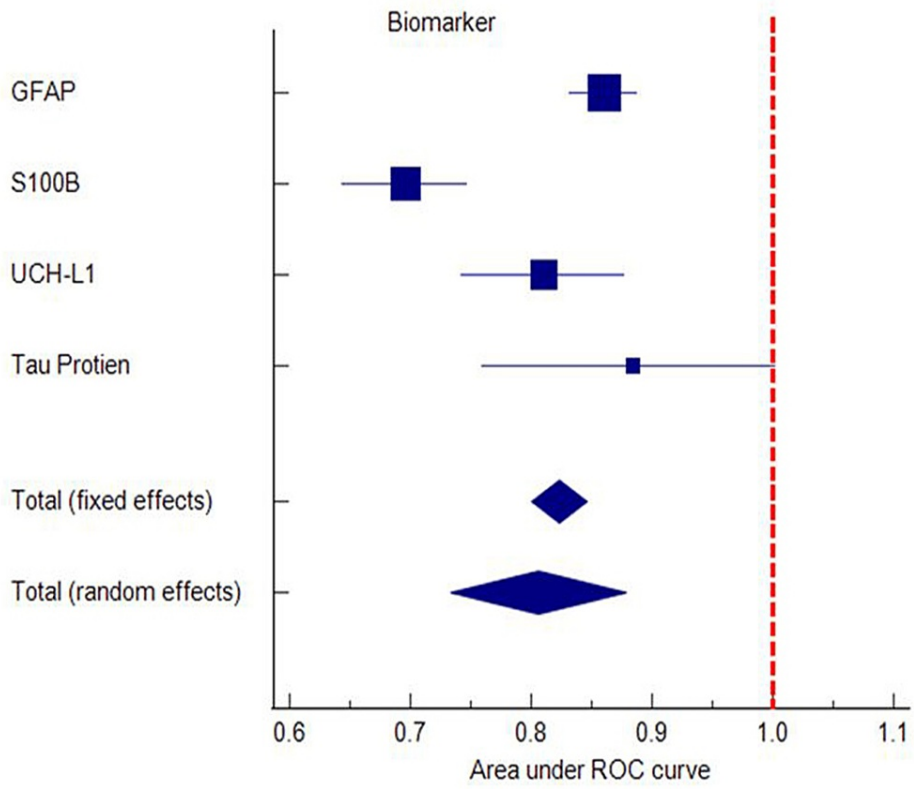

FIGURE 9: Comparison of pooled AUC among all biomarkers (irrespective of time)

AUC, area under the curve; ROC, receiver operating characteristic

Upon comparison, it was found that in the early phase (<24 hours), Tau protein exhibited the highest pooled AUC, followed by the pooled values of GFAP, UCH-L1, and S100B; however, for the late phase (>24 hours), the pooled AUC of GFAP was the highest, followed by the polled value of UCH-L1. The pooled value of S100B was the lowest when compared to all other biomarkers (Table 7).

Pooled outcome						
Biomarkers	**<24 hours of trauma**	**95% CI**	**p-value <24 hours**	**>24 hours of trauma**	**95% CI**	**p-value**
GFAP	0.84	0.793-0.888	<0.001	0.872	0.836-0.907	<0.001
S100B	0.657	0.592-0.721	<0.001	0.732	0.672-0.792	<0.001
UCH-L1	0.779	0.639-0.919	<0.001	0.82	0.741-0.899	<0.001
Tau protein	0.884, 95% CI: 0.751-1.000	-	<0.001	-	-	-

TABLE 7: Pooled AUC value (total random effects) of biomarkers measured statistically

AUC, area under the curve; GFAP, glial fibrillary acidic protein; S100B, S100 calcium-binding protein B; UCH-L1, ubiquitin carboxy-terminal hydrolase L1

The meta-analysis has shown the pooled value of all studied (GFAP, S100B, UCH-L1, and Tau protein) biomarkers increases after 24 hours, suggesting the multimodal and/or continuous release of biomarkers after head injury. It indicates the fact that a detailed and thorough prospective study on the set of biomarkers may be crucial to guide the prognosis and monitor the management of TBI even after the early phase of the disease course. It is also evident that, out of all the trauma biomarkers (GFAP, S100B, UCH-L1, and Tau protein), Tau is still the best TBI biomarker to investigate within the first 24 hours of trauma. After

statistically analyzing 377 individual cases for this investigation, it was found that the Tau protein had the greatest pooled value. Upon conducting statistical analysis on 662 instances from four distinct pieces of literature, the authors discovered that S100B had the lowest pooled value among the four biomarkers. This outcome remains consistent for all biomarkers when comparing cases with trauma victims. In the early phase, 4,641 individual cases were examined, and in the late phase, statistical analyses showed that GFAP had the highest pooled value. Based on these findings, it is determined that GFAP is the most effective biomarker for TBI in a period exceeding 24 hours. Finally, as per the study, it is evident that Tau is the best biomarker within 24 hours of TBI and GFAP is best after 24 hours of trauma.

Conclusions

This meta-analysis highlights that biomarkers effectively identify TBI, with their diagnostic accuracy improving over time, particularly for GFAP, S100B, and UCH-L1, which showed increased levels beyond 24 hours post-injury. This increase indicates that these biomarkers might be more detectable and become more reliable indicators of TBI severity or injury progression as time progresses. The study also highlights the feasibility and practicality of using blood-based biomarkers for assessing TBI and exploring the underlying mechanisms in different TBI scenarios. The ease of using blood-based biomarkers for TBI assessment supports their widespread adoption in clinical research. This review emphasizes the evolving use of biomarkers for TBI diagnosis, tracks recovery, and provides insight for future research in predicting outcomes and better managing TBI patients.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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