

Review

From the Emergency Department to Follow-Up: Clinical Utility of Biomarkers in Mild Traumatic Brain Injury

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Abstract

Mild traumatic brain injury (mTBI) remains a clinical challenge, particularly in cases with normal computed tomography (CT) findings but persistent or evolving symptoms. Conventional diagnostic approaches relying solely on clinical criteria and neuroimaging often lack adequate sensitivity and may lead to unnecessary radiation exposure. Recent advances in biomarker research have identified several blood-based proteins such as glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), S100 calcium-binding protein B (S100B), Tau protein, neuron-specific enolase (NSE), and neurofilament light chain (NFL) as potential tools for improving diagnostic precision and guiding clinical decisions. In this study, we synthesize current evidence evaluating the diagnostic and prognostic utility of these biomarkers using sensitivity, specificity, negative predictive value (NPV), and area under the receiver operating characteristic curve (AUC). GFAP and UCH-L1 have shown high sensitivity in detecting intracranial lesions and are now FDA-cleared for emergency department triage within 12 h of injury. While S100B remains widely investigated, its low specificity limits its application beyond select clinical scenarios (i.e., in patients without polytrauma). Additionally, Tau, NSE, and NFL are emerging as prognostic markers, with studies suggesting associations with persistent symptoms and long-term neurocognitive outcomes. Overall, the integration of biomarker-based data into clinical workflows may enhance early mTBI diagnosis, reduce reliance on imaging, and enable individualized follow-up and prognostic stratification. Future research should refine optimal sampling windows and explore multimarker panels to maximize diagnostic and prognostic performance.

Keywords: mild traumatic brain injury; biomarkers; GFAP; UCH-L1; S100B; Tau; NSE; NFL; diagnosis; follow-up; prognosis; emergency medicine



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1. Introduction

Mild traumatic brain injury (mTBI), commonly referred to as concussion, constitutes the majority of traumatic brain injury (TBI) cases globally, and 85–90% of TBI are treated in the ED [1]. A major challenge in evaluating the literature on mTBI lies in the heterogeneity of its definition; furthermore, significant variability exists across hospital centers in the

definition, diagnostic guidelines, admission, and follow-up policies for mTBI management, highlighting a need for standardized practices and further outcome-focused research [2]. The US National Institutes of Health-National Institute of Neurological Disorders and Stroke proposed a multidimensional classification system that integrates clinical evaluation, biomarkers, imaging, and individual modifiers to improve diagnostic precision and support personalized care and research [3]. Furthermore, despite its “mild” classification, mTBI can lead to significant long-term consequences, including cognitive, emotional, and physical impairments [4]. The 2022 update of The Lancet Neurology Commission on TBI highlights that approximately 50% of adults with mTBI do not return to their pre-injury health status within six months. Additionally, less than 10% [5] of patients discharged after emergency department visits for TBI in Europe receive follow-up care, underscoring a significant gap in post-acute management. According to available data, only 16% of mild TBI patients have demonstrable intracranial lesions on CT imaging [6]. Moreover, the estimated lifetime risk of cancer-related mortality from whole-body exposure to low-dose ionizing radiation is approximately 5% per sievert, and for the most frequently performed CT scans, such as those of the neurocranium, the effective radiation dose is approximately 1.6 millisieverts [7]. Alongside, blood-based biomarkers are increasingly recognized as effective tools in the diagnostic evaluation of traumatic brain injury, minimizing subjectivity in interpretation [5].

This study primarily focuses on the clinical utility of several blood-based biomarkers, including glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), S100 calcium-binding protein B (S100B), tubulin-associated unit protein (referred to in this review as Tau), neuron-specific enolase (NSE), and neurofilament light chain (NFL), in the context of mTBI. Emphasis is particularly placed on their clinical utility in the early diagnosis of traumatic brain injury, the risk stratification in mTBI, and the diagnosis of mTBI itself. By tracing the path from the biological definition and molecular role of each biomarker, the analysis progresses toward evaluating their clinical relevance, particularly in the early diagnosis of post-traumatic intracranial lesions, the stratification of risk in patients with mTBI, and the diagnosis of mTBI itself. Among the most promising biomarkers for mTBI are glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1). GFAP, an intermediate filament protein expressed by astrocytes, is released into the bloodstream following astroglial injury. UCH-L1, a neuronal enzyme involved in the ubiquitin-proteasome system, is similarly released upon neuronal damage [8–10]. Both GFAP and UCH-L1 have demonstrated utility in the early detection of mTBI. Studies have shown that these biomarkers are detectable in serum within an hour of injury, with GFAP peaking at approximately 20 h and UCH-L1 peaking at around 8 h post-injury. Their levels correlate with injury severity and the presence of intracranial lesions on CT scans. The U.S. Food and Drug Administration (FDA) has approved the combined use of GFAP and UCH-L1 as a blood-based assay to aid in the evaluation of mTBI, potentially reducing the need for unnecessary CT scans [11–13]. Upon acute brain injury, elevated serum S100B is released into the bloodstream, reflecting blood–brain barrier permeability and astroglial activation. It is the most extensively validated biomarker for ruling out intracranial hemorrhage in mTBI, with sensitivity and negative predictive value often approaching 100% when measured within approximately three hours of injury [14]. However, its specificity is limited and influenced by extracranial sources such as soft-tissue trauma [14]. NSE, an enzyme found in neurons, serves as an indicator of neuronal damage, elevated serum levels of NSE are associated with neuronal injury, making it a potential indicator of the severity of brain damage [15]. NFL, a structural component of the neuronal cytoskeleton, reflects axonal injury. Its presence in blood or cerebrospinal fluid reflects axonal damage and has emerged as a promising biomarker for detecting and monitoring neurodegeneration following mTBI [16,17]. Tau, a microtubule-associated protein, is associated with neuronal

degeneration and cytoskeletal disruption. Increased levels of Tau in the blood are indicative of neuronal disruption and have been associated with both acute and chronic outcomes after head trauma [18].

However, challenges remain in integrating these biomarkers into routine clinical practice, including the need for standardized assay platforms, understanding the kinetics of biomarker release, and establishing clear clinical guidelines for interpretation.

2. Materials and Methods

This study aims to assess the individual biological mechanisms underlying each marker (mainly the tissue localization and the functional significance) and the clinical utility of serum biomarkers in the clinical management of mTBI, defined as a GCS between 13 and 15. The biomarkers involved in this review are the following: GFAP, UCH-L1, S100B, NSE Tau protein, and NFL. A comprehensive literature search was conducted using the PubMed and Mendeley electronic databases. The following keywords and Medical Subject Headings (MeSH) terms were employed: “mild traumatic brain injury”, “mTBI”, “GFAP sensitivity and specificity”, “glial fibrillary acidic protein”, “UCH-L1 sensitivity and specificity”, “ubiquitin carboxy-terminal hydrolase L1”, “biomarkers in TBI”, “NSE sensitivity and specificity for mTBI”, “NFL sensitivity and specificity for mTBI”, “Tau protein sensitivity and specificity for mTBI”, “serum biomarkers for mTBI”, and “diagnostic tools for mTBI”. The search was limited to peer-reviewed articles published in English, with a preference for studies published within the last 10 years to ensure contemporary relevance. Articles were selected based on their relevance to the specific focus of this review, particularly those addressing the diagnostic and prognostic value of serum biomarkers in the context of mTBI. To evaluate the clinical utility of selected blood-based biomarkers in the context of mild traumatic brain injury (mTBI), a systematic analysis was conducted focusing on their diagnostic performance. Specifically, the sensitivity, specificity, negative predictive value (NPV), and area under the receiver operating characteristic curve (AUC) were assessed for each biomarker. Whenever available, biomarker thresholds, timing of sample collection, and population characteristics (e.g., age and time since trauma) were also recorded to contextualize and compare diagnostic performance. Both human (including adult and pediatric populations, without restrictions on participants’ sex or ethnicity) and animal studies were included. Studies that did not include mTBI cases were excluded.

3. Results

This section will address the biomarkers GFAP, UCH-L1, S100B, Tau, NSE, and NFL, discussing for each their underlying biological mechanisms, clinical utility (as diagnostic and prognostic performance), and key supporting studies.

3.1. GFAP

3.1.1. Gene and Protein Overview

GFAP is encoded by the *GFAP* gene, which belongs to the intermediate filament protein family (class III). The gene produces at least 17 known transcript variants via alternative splicing, leading to multiple distinct isoforms. GFAP serves as a highly specific marker for astrocytes and plays a fundamental role in the structural organization of the cytoskeleton within these glial cells. The protein’s function is especially critical during the development of the central nervous system (CNS), where it aids in distinguishing astrocytes from other glial populations [12,13].

3.1.2. Protein Localization, Expression, and Functional Significance

GFAP displays a distinct cytoplasmic distribution within astrocytes and is mainly integrated into the intermediate filament framework of these cells. Subcellularly, it is concentrated in specific intracellular regions, particularly within the astrocytic soma and endfeet. Evidence from both immunohistochemical and transcriptomic studies indicates that GFAP is highly expressed in various parts of the central nervous system, such as the cerebral cortex, hippocampus, amygdala, basal ganglia, thalamus, cerebellum, spinal cord, and visual pathways including the retina. As a structural component of the intermediate filament system, GFAP plays a key role in maintaining cellular architecture, shaping astrocyte morphology, and supporting their physiological functions. It is essential during central nervous system development and is actively involved in the cellular response to neural injury. Genetic alterations in the GFAP gene have been linked to Alexander disease, a rare and often lethal leukodystrophy marked by the accumulation of Rosenthal fibers within astrocytes [12,13].

3.1.3. Clinical Relevance and Disease Association

GFAP is markedly overexpressed in several pathological conditions, particularly gliomas. It is a recognized cancer-enriched marker in glioblastoma multiforme and has prognostic significance in kidney renal clear cell carcinoma. Elevated levels of GFAP have been observed in a broad spectrum of CNS tumors (e.g., pediatric astrocytic tumors, neuroblastoma, and retinoblastoma), systemic inflammatory disorders (e.g., multiple sclerosis, rheumatoid arthritis, and Sjögren's syndrome), and infectious diseases (e.g., dengue fever and *Staphylococcus aureus* bacteremia). Moreover, its upregulation has been noted in conditions such as metabolic syndrome, type 2 diabetes, and liver disease [12,14].

3.1.4. Detection in Blood and Biomarker Potential

The detection of GFAP in peripheral blood has become achievable thanks to the development of highly sensitive immunoassay techniques [19,20]. While conventional ELISA remains effective for analyzing GFAP in cerebrospinal fluid or brain tissue, its sensitivity is insufficient for accurate quantification in serum [21,22]. Currently, the preferred method in clinical research is the Single Molecule Array platform, which allows for detection of GFAP at concentrations below the picogram-per-milliliter range [23,24]. A promising alternative is the second-generation microfluidic immunoassay system, which demonstrates excellent agreement with the Single Molecule Array platform results (Pearson's $r \approx 0.9$), along with robust analytical performance characterized by low intra-assay variability (coefficient of variation $\sim 10\%$) and a detection threshold around 0.9 pg/mL [23,24]. These features suggest that the second-generation microfluidic immunoassay system could be well suited for routine clinical applications in neurological conditions such as traumatic brain injury. Moreover, the i-STAT TBI Plasma cartridge, used with the i-STAT Alinity point-of-care platform, provides a rapid, semi-quantitative measurement of GFAP, enabling timely identification of patients with mTBI and supporting more selective use of head CT imaging [25,26].

3.1.5. GFAP Diagnostic Performance in Mild Traumatic Brain Injury

Following mTBI, GFAP becomes detectable in peripheral blood within the first hour post-injury. Its concentration increases progressively, reaching a peak approximately 20 h after the traumatic event. Thereafter, GFAP levels begin to decline steadily over the subsequent 72 h. Despite this decline, the protein remains detectable up to 168 h post-injury and continues to be present at lower concentrations through at least 180 h. No significant differences in GFAP levels were observed between male and female patients at any point

during the monitoring period, indicating a consistent temporal profile of GFAP release irrespective of sex [27].

The ALERT-TBI study was a prospective, multicenter observational investigation aimed at assessing the diagnostic utility of serum GFAP in excluding intracranial lesions in adults with mild to moderate TBI. Participants were 18 years or older, presented to emergency departments with suspected blunt TBI, and had a GCS score between 9 and 15. Blood samples were collected within 12 h following the injury, and all patients underwent head CT scans as part of routine clinical care. GFAP concentrations were measured using a predefined threshold of 22 pg/mL. The findings showed that GFAP had high sensitivity and a strong negative predictive value for ruling out intracranial damage. Cases with negative GFAP levels were rarely associated with abnormal CT results, supporting its effectiveness in identifying patients unlikely to have clinically significant brain injuries. [28].

A meta-analysis evaluating GFAP serum levels across 11 studies reported an area under the curve (AUC) of 0.75 (95% CI: 0.71–0.78), with a sensitivity of 83% and specificity of 38% at a cut-off of <100 pg/mL [29]. The findings suggest that GFAP may aid in identifying intracranial injuries in mTBI and potentially reduce CT overuse.

A prospective study involving 277 participants [30] reported strong diagnostic accuracy for GFAP, with an area under the curve (AUC) of 0.93 in differentiating individuals with mTBI from healthy controls, and an AUC of 0.77 for detecting CT-detectable lesions, underscoring its clinical relevance in acute care settings. Additionally, a meta-analysis of 14 studies identified that a GFAP threshold of 68.5 pg/mL provided a sensitivity of 75% and a specificity of 73%, supporting its applicability as a screening marker for CT-relevant abnormalities in mTBI cases [31]. In another prospective cohort of 377 patients, GFAP concentrations exceeding 67 pg/mL were linked to a sensitivity of 87%, a specificity of 65%, and a high negative predictive value of 99%. With an AUC of 0.83, these findings suggest that GFAP meaningfully improves clinical protocols for determining the necessity of CT imaging [11].

Prehospital measurement of GFAP within 30–60 min of injury also showed high diagnostic performance. A study reported an AUC of 0.88, with a sensitivity of 98.1% at a 30 pg/mL cut-off (within 30 min the traumatic event), highlighting its utility even in emergency and field settings. GFAP emerged as the strongest independent predictor of CT-positive findings and diffuse injury severity [10].

In pediatric populations (birth to 21 years old), GFAP outperformed the traditional marker S100β in detecting traumatic intracranial lesions. A prospective study of 155 children and adolescents reported an AUC of 0.85, indicating high diagnostic value across age groups [32]. Finally, a study involving 247 participants found an AUC of 0.70 for GFAP in distinguishing mTBI from non-mTBI cases, underscoring its potential role in early injury stratification when measured within six hours of trauma [33].

See Table 1 for a summary of supporting scientific evidence.

Table 1. GFAP Diagnostic Accuracy in mTBI for Intracranial Injury Detection.

Study Type	Cut-Off	Sensitivity	Specificity	NPV	AUC
Meta-analysis (2023) [29]	<100 pg/mL	83%	38%	—	0.75 (95% CI: 0.71–0.78)
Meta-analysis (2025) [31]	68.5 pg/mL	75%	73%	—	—
GFAP vs. Clinical Rules (2022) [11]	67 pg/mL	87%	65%	99%	0.83 (95% CI: 0.73–0.93)
^a GFAP within 30 min (2024) [10]	30 pg/mL	98.1%	34.4%	—	0.88 (95% CI: 0.85–0.92)
^a GFAP within 60 min (2024) [10]	30 pg/mL	98.7%	36.4%	—	0.89 (95% CI: 0.86–0.92)
GFAP in Pediatrics (2016) [32]	0.15 ng/mL	100%	36%	100%	0.85 (95% CI: 0.72–0.98)

NPV: Negative Predictive Value; AUC: Area Under the Curve; CI: Confidence Interval; “—”: denotes that the data were either unspecified or not reported within the study; ^a the study included also patients with GCS < 13.

3.2. UCHL1

3.2.1. Functional and Clinical Overview

UCH-L1, also referred to as PARK5, PGP9.5, or UCHL1, is a neuron-specific thiol protease belonging to the peptidase C12 family. This deubiquitinating enzyme is critically involved in the maintenance of ubiquitin homeostasis by hydrolyzing the C-terminal glycine residue of ubiquitin, thereby generating a stable pool of monoubiquitin essential for proteasomal degradation and autophagic processes [12,22].

3.2.2. Expression and Localization

UCHL1 is selectively expressed in the central nervous system (CNS), with notable enrichment in neuronal soma, axons, and synapses. Its expression extends to peripheral tissues such as distal renal tubules, islets of Langerhans in the pancreas, and spermatogonia in the testis. At the subcellular level, the protein predominantly localizes to the cytosol, with additional presence in the nucleoplasm. Transcriptomic data indicate group-enriched RNA expression in the brain and pituitary gland, while single-cell analyses highlight elevated expression in oocytes and differentiated neuronal subtypes. Despite broad tissue distribution, UCHL1 is not expressed in immune cell populations under physiological conditions [19,34,35].

3.2.3. Biological Function

Functionally, UCHL1 has been shown to regulate key signaling molecules through deubiquitination, including EGFR, HIF1A, WWTR1/TAZ, and BACE1 [36,37]. These interactions implicate the protein in diverse physiological processes such as synaptic function, immune modulation, cardiac function, and osteoclastogenesis [38]. UCH-L1-mediated degradation of BACE1 contributes to reduced amyloid-beta production, linking it to the pathophysiology of neurodegenerative diseases, including Alzheimer's disease. Furthermore, its role in stabilizing HIF1A under hypoxic conditions and preventing EGFR degradation underscores its involvement in cellular stress responses and tumorigenesis [19,37].

3.2.4. Genetic and Clinical Insights

Clinically, UCH-L1 has emerged as a prognostic biomarker in several cancers, including kidney renal clear cell carcinoma, liver hepatocellular carcinoma, and lung squamous cell carcinoma. Notably, its expression is markedly upregulated in glioblastoma multiforme [19,39]. From a pathological perspective, mutations in UCH-L1 have been associated with familial forms of Parkinson's disease, reflecting its critical role in neuronal proteostasis. Due to its multifactorial involvement in both neurodegeneration and oncogenesis, UCH-L1 is increasingly recognized as a potential therapeutic target in both neurological and malignant diseases [19,40].

3.2.5. Detection in Blood and Biomarker Potential

The measurement of UCH-L1 levels in peripheral blood has significantly advanced with the introduction of highly sensitive immunoassay technologies. Earlier studies relied on conventional sandwich ELISAs, which generally offer a detection threshold around 30 pg/mL and restrict their utility in identifying subtle neuronal damage [41]. In comparison, modern digital platforms such as Simoa enable detection of UCH-L1 at concentrations below one picogram per milliliter, making them particularly well-suited for research involving low-abundance neurological biomarkers [42]. Additionally, diagnostic tools authorized by the FDA, such as the i-STAT Alinity system [43,44], facilitate rapid, point-of-care assessment of both UCH-L1 and GFAP. These assays have demonstrated robust diagnostic accuracy, with reported sensitivities approaching 97% and negative predictive values ex-

ceeding 99%, especially when performed within 12 h following a mild traumatic brain injury [28]. Furthermore, the i-STAT Alinity point-of-care system rapidly quantifies UCH-L1, potentially leading to prompt and reliable detection of acute intracranial injury with CT imaging [25,26].

3.2.6. UCH-L1 Diagnostic Performance in Mild Traumatic Brain Injury

UCH-L1 is detectable in peripheral blood shortly after the traumatic event. Its concentration increases rapidly, reaching a peak approximately 8 h post-injury. Following this peak, UCH-L1 levels decline steadily over the next 48 h. Although the overall temporal trend is similar in both male and female individuals, UCH-L1 concentrations tend to be higher in males at several time points, particularly within the first 72 h after injury. This suggests potential sex-related differences in the biomarker response, despite the shared pattern of early elevation and subsequent decline [27]. The observed kinetics of UCH-L1 underscore its potential utility as an early biomarker for mild traumatic brain injury, with a distinct peak in the acute phase and a relatively rapid clearance profile.

A 2025 meta-analysis showed that UCH-L1, at a 237.7 pg/mL threshold, offers 89% sensitivity and 36% specificity for detecting intracranial lesions in mild TBI (GCS 13–15), highlighting its value as a dependable rule-out tool [31]. The ALERT-TBI trial (2018), a key multicenter study, highlighted the diagnostic value of UCH-L1, particularly in combination with GFAP. Together, the two biomarkers showed 97.6% sensitivity and a 99.6% negative predictive value, indicating their usefulness in limiting unneeded CT scans during mild TBI assessment [28].

Evidence supporting the use of UCH-L1 in pediatric populations has also been robust. A 2017 study on children and adolescents with GCS scores of 15 reported that a UCH-L1 cut-off of 0.18 ng/mL resulted in 100% sensitivity and NPV, albeit with a specificity of 48%, highlighting its capacity to effectively rule out intracranial injury even in young, high-functioning patients [45].

The biomarker's relevance in prehospital and early emergency settings was further validated by a 2024 study, which found that UCH-L1 levels were significantly associated with both traumatic brain lesions and CT-based indicators of diffuse injury severity. The AUC was 0.75 (95% CI: 0.70–0.80), supporting its integration into early triage and transport decision protocols [10].

Combining biomarkers with clinical decision rules has shown additional benefits. A 2022 study demonstrated that UCH-L1 (cut-off: 189 pg/mL) achieved 96% sensitivity and 99% NPV, with an AUC of 0.72. The integration of UCH-L1 improved the diagnostic accuracy of existing clinical algorithms in determining the necessity for CT imaging following mTBI [11]. Despite its high sensitivity, UCH-L1's specificity and overall predictive power have shown variability across different studies. For instance, a 2017 investigation reported a lower AUC of 0.65 and a modest NPV of 31%, suggesting limited utility when used in isolation and emphasizing the importance of context-specific application [33]. In contrast, a 2024 meta-analysis reported a pooled AUC of 0.81 (95% CI: 0.74–0.87) and a sensitivity of 81%, confirming that UCH-L1 maintains good overall diagnostic performance, albeit with some heterogeneity across studies [46].

Further research into the timing and demographic modifiers of biomarker performance has revealed key insights. A 2023 study examining acute (<6 h) and subacute sampling windows showed that UCH-L1 has a moderate discriminative ability between mTBI and controls (AUC: 0.79, 95% CI: 0.70–0.88), with observed variations in diagnostic performance according to sex and time since injury [33]. Finally, recent evidence supports the use of age-adjusted cut-off thresholds to improve specificity without compromising sensitivity. A 2024 study proposed an elevated cut-off of 335 ng/L for patients over 65 years, achieving

a sensitivity of 100% and improving specificity to 30.6%. These findings suggest that biomarker performance can be enhanced through demographic stratification, refining the test’s utility in older populations [47]. Furthermore, UCH-L1 showed good diagnostic performance in identifying mildTBI within 6 h post-injury, with an AUC of 0.79 (95% CI: 0.70–0.88), indicating moderate sensitivity and specificity. Its performance was consistent regardless of sex or presence of loss of consciousness/post-traumatic amnesia [48]. Refer to Table 2 for a summary of the supporting literature.

Table 2. UCH-L1 accuracy across studies in mild traumatic brain injury.

Study Type	Cut-Off	Sensitivity	Specificity	NPV	AUC (95% CI)	Purpose
^a Meta-analysis (2025) [31]	237.7 pg/mL	89%	36%	—	—	Intracranial injury
^b UCH-L1 in Pediatrics (2017) [45]	0.18 ng/mL	100%	48%	100%	0.83 (0.72–0.94)	Intracranial injury
UCH-L1 vs. Clinical Rules (2022) [11]	189 pg/mL	96%	29%	99%	0.72	Intracranial injury
UCH-L1 for mTBI Diagnosis and Stratification (2017) [33]	—	—	—	31%	0.65	mTBI vs. no mTBI
Meta-analysis (2024) [46]	—	81%	—	—	0.81 (0.74–0.87)	TBI severity and evolution
^c UCH-L1 in CT-Negative mTBI (2023) [48]	4.96 pg/mL	79%	75%	—	0.79 (0.70–0.88)	mTBI vs. no mTBI
^d Age-adjusted Cut-off (2024) [47]	335 ng/L (≥65 yrs)	100%	30.6%	100%	—	mTBI vs. no mTBI
^d Age-adjusted Cut-off (2024) [47]	335 ng/L (<65 yrs)	98.4%	64.8%	98.8%	—	mTBI vs. no mTBI

NPV: Negative Predictive Value; AUC: Area Under the Curve; CI: Confidence Interval; “—”: indicates that data is not specified or not reported in the study; ^a in patients presenting with a GCS score between 13 and 15, the optimal serum cutoff value for UCH-L1 was identified as 237.7 pg/mL. ^b regarding children and youth, involved in this study, presenting with an intracranial lesion and a GCS of 15; ^c the data reported in the table correspond to values obtained within 6 h following the mTBI; ^d this study considered UCH-L1 combined with GFAP.

3.3. S100B

3.3.1. Gene and Protein Structure

The *S100B* gene is located on chromosome 21q22.3 and encodes a small protein with two EF-hand calcium-binding domains. While it binds calcium weakly, it exhibits a high affinity for zinc [40]. These ions bind at distinct sites on the protein, and their interaction is modulated by physiological levels of potassium ions, which can antagonize calcium binding [19].

3.3.2. Localization and Expression

S100B is primarily localized in the cytosol and nucleus but also associates with cellular structures such as the primary cilium, microtubules, vesicles, and basal bodies [35]. Although secreted, its extracellular destination remains unclear. Within the CNS, it is expressed in astrocytic soma and endfeet, neuronal soma, ependymal cells, and endothelia [19]. S100B expression is enriched in brain tissue, with high levels in the cerebral cortex, hippocampus, cerebellum, basal ganglia, and hypothalamus [35]. It is also detectable in peripheral tissues, including the adrenal gland, thyroid, adipose tissue, and epithelial surfaces [19]. At the single-cell level, Schwann cells and melanocytes show the highest expression. Within the brain, its expression is mostly associated with white matter and oligodendrocyte-related myelination clusters. Despite its CNS predominance, S100B is also

found in various epithelial, glandular, and stromal cells, albeit at lower levels [19,20]. S100B is not exclusively expressed in the central nervous system; it is also found in several extracerebral tissues, including adipocytes, chondrocytes, and melanocytes, which can contribute to elevated serum levels independent of brain injury [49,50]. These extracranial sources must be considered to avoid false-positive interpretations, especially in contexts involving polytrauma, physical exertion, or comorbid conditions affecting peripheral tissues [49,50].

3.3.3. Functional Roles

S100B serves multiple functions, both intracellular and extracellular [19,51]: acts as a neurotrophic factor, promoting astrocytosis and axonal outgrowth; supports sympathetic innervation of thermogenic adipose tissue, functioning as an adipocyte-derived signaling molecule; interacts with various proteins, including STK38, modulating their activity by releasing autoinhibitory interactions; may regulate apoptosis in cardiac myocytes after myocardial infarction through interactions with AGER and subsequent ERK1/2 and p53 activation; facilitates proper processing of cytoplasmic proteins like ATAD3A, aiding in mitochondrial localization.

3.3.4. Clinical Relevance and Detection in Blood

S100B has been implicated in numerous neurological conditions. Elevated levels are associated with Alzheimer's disease, Down syndrome, epilepsy, and amyotrophic lateral sclerosis [40]. Due to its presence in astrocytes and its release upon glial injury, it serves as a biomarker for traumatic brain injury [19]. Most clinical and research assessments of S100B use the traditional ELISA format. Serum or plasma samples are analyzed using monoclonal and polyclonal antibodies specific to S100B, typically achieving detection down to ~0.10 µg/L (100 ng/L) or lower [52]. This assay format is established in practice and forms the basis for many clinical decision algorithms. Automated plasma-based S100B assays offer rapid turnaround (≤ 30 min) for emergency department use. These are integrated into clinical workflows to accelerate triage and reduce unnecessary CT imaging for low-risk mTBI patients [53].

3.3.5. S100B Diagnostic Performance in Mild Traumatic Brain Injury

A recent meta-analysis reported a sensitivity of 98% (95% CI: 92–99%) and NPV of 99% for intracranial injury post-mTBI, with a cut-off value of 0.05 µg/L considered optimal within three hours post-injury [54]. Another meta-analysis comparing S100B with NSE found that S100B had superior diagnostic performance, with an AUC of 0.89 (95% CI: 0.86–0.91), sensitivity of 99%, and specificity of 76% [55].

In pediatric patients, S100B demonstrated perfect sensitivity (100%) and NPV (100%), although with a modest specificity of 41%, confirming its utility for ruling out intracranial injury while reducing CT use [56]. Among elderly patients, S100B maintained high sensitivity (97.4%), but its specificity dropped significantly (17.3%), suggesting limited ability to reduce CT use in this group [57]. Notably, a subanalysis within a prospective cohort study revealed that S100B still achieved a high NPV (99.1%) despite a lower sensitivity of 66.7%, underscoring variability depending on population characteristics for ruling-out intracranial injury [58].

Further support comes from studies involving patients on antiplatelet therapy or aged over 65, where S100B demonstrated 98% sensitivity and 99.6% NPV for intracranial lesion after the traumatic event [59]. However, its low specificity (35.3%) remained a limitation. In the emergency setting, S100B reached a sensitivity of 93.2% and NPV of 93%, though specificity was again poor (15.7%) [60]. When integrated into clinical protocols, S100B achieved 100% sensitivity, 100% NPV, and an AUC of 0.79 (95% CI: 0.71–0.86), suggesting improved diagnostic performance when guideline-adherent [60].

The supporting scientific data are summarized in Table 3.

Table 3. S100B diagnostic accuracy across studies in mild traumatic brain injury.

Study Type	Cut-Off	Sensitivity (%)	Specificity (%)	NPV (%)	AUC (95% CI)	Purpose
^a Sytematic Review (2025) [54]	0.05 µg/L	98 (92–99)	32 (26–39)	99	—	Intracranial lesion
S100B vs. NSE Meta-analysis (2024) [55]	—	99 (4–100)	76 (51–91)	—	0.89 (0.86–0.91)	Intracranial lesion
Pediatric Meta-analysis (2024) [56]	—	100 (98–100)	41 (26–57)	100 (99–100)	—	Intracranial lesion
Elderly Patients (2024) [57]	0.105 µg/L	97.4 (83.3–100)	17.3 (9.5–29.3)	—	—	Intracranial lesion
^b Subanalysis Cohort (2021) [58]	—	66.7 (9.4–99.2)	93.7 (87.4–97.4)	99.1 (94.8–99.9)	—	Intracranial lesion
Platelet Inhibitors/>65 yrs (2015) [59]	0.105 µg/L	98 (89.5–99.7)	35.3 (31.9–38.8)	99.6 (97.9–99.9)	—	Intracranial hemorrhage
ED Screening (2022) [61]	0.105 µg/L	93.2	15.7	93	—	Intracranial lesion
Routine Care/Guidelines (2022) [60]	0.10 µg/L	100 (76.8–100)	47 (37.7–56.5)	100	0.79 (0.71–0.86)	Intracranial lesion

ED: Emergency Department; NPV: Negative Predictive Value; AUC: Area Under the Curve; CI: Confidence Interval; “—”: indicates that data is not specified or not reported in the study; “yrs”: years old; ^a the study considered mTBI as a GCS between 14 and 15. ^b The blood samples were obtained in the first six hours following trauma to assess the presence of brain injury.

3.4. Neuron-Specific Enolase

3.4.1. Functional and Clinical Overview

NSE, a key enzyme involved in glycolysis, is predominantly present in neurons and neuroendocrine cells. When neuronal injury occurs, NSE may enter the bloodstream, positioning it as a possible indicator of brain damage. Interest in its application for diagnosing and forecasting outcomes in mTBI has grown. However, inconsistent results among studies have left its clinical relevance still under debate [62].

3.4.2. Pathophysiological Correlations and Limitations

While most research undermines NSE’s clinical diagnostic or prognostic value, some findings suggest its relevance in the context of neural connectivity changes. In a 2021 study published, higher acute-phase NSE levels were associated with reduced efficiency and centrality in the anterior default mode network (DMN) at three months post-injury. These functional connectivity alterations correlated with working memory deficits, suggesting NSE may serve as an indirect marker of post-injury network reorganization [63].

However, the utility of NSE is constrained by its limited specificity to cerebral injury. Thelin et al. [64], in their study published in 2016, demonstrated that NSE levels are influenced by extracranial injuries, thus reducing its specificity as a brain injury biomarker. While there was some correlation between NSE levels and long-term outcomes, its predictive value was consistently lower than that of S100B, a more brain-specific marker [65].

3.4.3. NSE Diagnostic Performance in Mild Traumatic Brain Injury

Amoo et al. (2022) [14] conducted a systematic review and meta-analysis on biomarkers for detecting CT abnormalities in mild TBI. Due to limited data on NSE, it could not be analyzed quantitatively. The study concluded that evidence for NSE as an independent diagnostic tool remains inadequate and requires further research [14].

Mercier et al. (2018) [15] reported a transient correlation between elevated NSE and cognitive impairment at two weeks post-injury, which was not sustained at six weeks. The study concluded that NSE is not a dependable predictor of clinical outcome in mTBI [15].

Overall, current evidence does not support the use of NSE as a primary diagnostic or prognostic biomarker in mild traumatic brain injury. Although NSE may reflect certain

aspects of neuronal injury and functional connectivity changes, its diagnostic performance is undermined by low specificity and variability due to extracranial injury. Further large-scale, standardized studies are needed to clarify its role, particularly in conjunction with other markers or advanced neuroimaging; an overview of the evidence base can be found in Table 4.

Table 4. NSE Diagnostic Accuracy across studies in Mild Traumatic Brain Injury for Intracranial Injury Detection.

Study Type	Purpose	Comments
Systematic review (diagnostic) (2022) [13]	Intracranial lesions	Limited data prevented meta-analysis; inconclusive diagnostic value
Observational MRI-connectivity (2021) [62]	Cognitive recovery following mTBI	NSE linked to DMN connectivity and cognitive deficits
Observational outcome comparison (2016) [64]	Clinical outcomes, severity of the injury, and whether biomarker concentrations were affected by extracranial influences	Influenced by extracranial trauma and predictive power inferior to S100B

DMN: default mode network.

3.5. Tau

3.5.1. Functional and Clinical Overview

Tau is a neuronal microtubule-associated protein predominantly localized in the axons of central nervous system neurons. Encoded by the *MAPT* gene on chromosome 17q21, Tau is produced in six different isoforms in the adult brain, arising through alternative mRNA splicing. These isoforms differ in their number of microtubule-binding domains and N-terminal inserts, which modulate their interaction with the cytoskeleton and their physiological function [65]. Under normal conditions, tau stabilizes microtubules and maintains axonal transport, contributing to neuronal architecture and function. However, in pathological states, tau undergoes hyperphosphorylation or cleavage, leading to its detachment from microtubules and aggregation into insoluble filaments—features commonly seen in tauopathies such as Alzheimer’s disease and chronic traumatic encephalopathy (CTE). In the context of TBI, including mTBI, neuronal damage triggers the release of Tau into extracellular fluids, where it becomes detectable in serum and cerebrospinal fluid. Several studies have shown that elevated serum tau levels correlate with axonal injury and adverse neurological outcomes following head trauma, supporting its use as a potential biomarker for early diagnosis and prognosis in mTBI. Particularly, tau has shown utility in identifying Diffuse Axonal Injury (DAI), even in patients with negative CT scans [18,66].

3.5.2. Tau Diagnostic Performance in Mild Traumatic Brain Injury

Serum cleaved Tau protein has been extensively studied as a biomarker for detecting intracranial lesions in patients with mild or minor traumatic brain injury TBI. In a cohort of patients presenting with minor head trauma, Tau demonstrated a sensitivity of 92%, specificity of 100%, and an NPV of 98% for the detection of intracranial injuries, underscoring its high diagnostic accuracy in this clinical setting [66]. This indicates that Tau can effectively rule out significant brain injury in patients with low-severity trauma.

A longitudinal prospective study assessing plasma biomarkers in mild TBI patients reported an AUC of 0.70 during the acute phase, improving to 0.80 when patients exhibited additional lesions. Sensitivity ranged from 78% to 79%, while specificity varied between 60% and 85%. Importantly, the study emphasized that tau’s diagnostic capability was enhanced when combined with other central nervous system (CNS) biomarkers such as GFAP and NFL, suggesting a synergistic effect in multimarker panels [67]. Again, the use

of a multi-marker approach (heart fatty-acid binding protein + S100B + Tau) improved differentiation between patients with and without mTBI, supporting the utility of multiplex biomarker strategies in clinical diagnostics [68].

In the context of DAI—a form of microstructural brain damage not typically detected by CT but identifiable through magnetic resonance imaging (MRI)—tau has shown promising diagnostic utility. With a threshold value of >1.5 pg/mL, Tau demonstrated a sensitivity of 74% and a specificity of 69% for the detection of DAI, indicating a moderate but clinically meaningful ability to identify these subtle injuries [69]. These results highlight Tau’s potential relevance in the assessment of complex brain injury phenotypes, beyond the scope of CT-visible lesions and mild traumatic brain injury.

The diagnostic performance across studies varies, but generally, serum tau exhibits high sensitivity (78–94.7%) and moderate to high specificity (60–100%), with NPV reaching as high as 98% in minor head trauma cohorts. The AUC values reported range from approximately 0.70 to 0.80, reflecting moderate discriminative power that improves significantly when tau is combined with complementary biomarkers; Table 5 provides an overview of the scientific evidence.

Table 5. Tau accuracy across studies in mild traumatic brain injury.

Study Type	Cut-Off	Sensitivity	Specificity	NPV	AUC (95% CI)	Purpose	Comments
Observational, minor trauma (2020) [66]	—	92%	100%	98%	—	Intracranial hemorrhage	High accuracy in minor head trauma
Prospective, 1-year follow-up (2021) [67]	3.00 pg/mL	^a 78–79%	^a 60–85%	—	^a 0.70–0.80	mTBI vs. no mTBI	Improved with GFAP and NFL panels
^b Correlative biomarker-CT study, ^c isolated mTBI patients (2019) [68]	—	94.7%	69.4%	—	—	mTBI vs. no mTBI	Improved with multimarker approach

NPV: Negative Predictive Value; AUC: Area Under the Curve; CI: Confidence Interval; “—”: indicates that data is not specified nor reported in the study; ^a Tau exhibited discriminatory power in differentiating mTBI patients from trauma controls group (sensitivity: 79%, specificity: 85%, AUC: 0.80) rather than patients with mTBI from combined controls group (sensitivity 78%, specificity: 60%, AUC: 0.70); ^b the study includes Tau in combination with other biomarkers (heart fatty-acid binding protein + S100B + tau), and the reported values refer to the highest specificity achieved among the various biomarker combinations; ^c: patients presenting with mild traumatic brain injury only.

3.6. Neurofilament Light Chain

3.6.1. Functional and Clinical Overview

NFL is a structural protein of the neuronal cytoskeleton, classified as the smallest subunit of neurofilaments, which also includes medium and heavy chains. Composed of a central α -helical rod domain flanked by non-helical head and tail regions, NFL assembles into heteropolymers that form the backbone of the axonal cytoskeleton, providing tensile strength and maintaining axonal caliber [16,17,70]. NFL is predominantly expressed in large-caliber myelinated axons within the central and peripheral nervous systems. Under physiological conditions, NFL remains compartmentalized within neurons; however, axonal injury or degeneration—such as that seen in mTBI, multiple sclerosis, or neurodegenerative diseases—results in its release into interstitial fluid, cerebrospinal fluid (CSF), and eventually into the bloodstream. This makes the NFL a highly sensitive, though not disease-specific, biomarker of neuroaxonal damage. In the context of TBI, elevated serum NFL levels have been consistently observed and correlated with injury severity, symptom duration, and long-term outcome [16,48]. Importantly, its concentration tends to peak in the subacute phase, offering diagnostic value even when initial neuroimaging is inconclusive. Furthermore, due to its stability and detectability in blood using ultrasensitive immunoassays, NFL is gaining prominence as a practical biomarker for diagnosis and monitoring in patients with mTBI.

3.6.2. NFL Diagnostic Performance in Mild Traumatic Brain Injury

In the acute setting, NFL appears to offer limited diagnostic utility. A 2023 study published in *Neurology* evaluating CT-negative mTBI patients found that serum NFL levels measured within 6 h post-injury lacked discriminative power. However, at 7 days post-injury, NFL effectively differentiated between mTBI patients and healthy controls, achieving an AUC of 0.81, with 65% sensitivity and 91% specificity, suggesting significant value in the subacute phase for confirming brain injury [48]. In a pediatric cohort of 302 patients with mTBI, serum NFL demonstrated a sensitivity of 100% in identifying intracranial injury, making it a potentially powerful tool to exclude clinically significant lesions. Nevertheless, its specificity remained low ($\leq 30\%$), which limits its role as a standalone diagnostic tool. This study, published in 2025 in *Frontiers in Neurology*, underlines the utility of NFL in safely ruling out injury but emphasizes the need for a combination with other markers or clinical indicators [71].

Beyond diagnosis, the NFL may hold prognostic value. In a 2020 study, serum NFL levels correlated strongly with cerebrospinal fluid concentrations ($r = 0.71$) and were able to discriminate between patients with post-concussive symptoms lasting longer than one year versus those with shorter symptom durations (AUC = 0.80). This suggests the NFL as a viable marker for tracking injury severity and recovery [16].

In preclinical settings, NFL also shows potential as an indicator of neurological vulnerability. A 2023 study in *Translational Research* used an animal model to demonstrate that serum NFL measured at the time of a second mTBI could predict neurological deterioration, with an AUC of 0.73, sensitivity of 64%, and specificity of 78% [70].

Finally, a 2021 meta-analysis including 24 studies concluded that serum NFL levels were significantly elevated in individuals with concussion compared to controls ($p = 0.0023$), further validating NFL as a general biomarker of axonal injury in mild TBI, particularly in sport-related contexts [17].

Serum NFL is a dynamic biomarker whose clinical utility in mTBI varies with time post-injury and patient context. While it lacks early diagnostic strength, its performance in subacute and chronic phases, along with its high sensitivity in pediatric populations, supports its inclusion in multimodal diagnostic frameworks. Future work should refine its temporal thresholds, combine it with complementary biomarkers such as GFAP or tau, and validate its role in prognostication and repeated trauma assessment; see Table 6 for a summary of supporting scientific evidence.

Table 6. NFL accuracy across studies in mild traumatic brain injury.

Study Type	Cut-Offs	Sensitivity	Specificity	AUC	NPV	Purpose	Comment
Human, adult mTBI (7-day NFL) (2023) [48]	7.40 pg/ml	65%	91%	0.81 (95% CI)	—	mTBI vs. no mTBI	High subacute diagnostic value
Pediatric mTBI (<24 h, TBI-to-sample interval) (2025) [71]	13.12 pg/ml	100%	24.7%	74.5 (95% CI)	—	Intracranial lesions	Strong for ruling out intracranial injury post mTBI
Pediatric mTBI (<6 h, TBI-to-sample interval) (2025) [71]	13.12 pg/ml	100%	30.56%	58.7 (95% CI)	—	Intracranial lesions	Strong for ruling out intracranial injury post-mTBI
^a Human, chronic symptoms (2020) [16]	—	—	—	0.80 (95% CI)	—	Post-concussive symptoms	Tracks long-term symptom duration
^b Animal, repeated mTBI (2023) [70]	33.3 pg/ml	64%	78%	0.73 (95% CI)	—	Axonal injury	Predicts vulnerability to repeated trauma

NPV: Negative Predictive Value; AUC: Area Under the Curve; CI: Confidence Interval; “—”: indicates that data is not specified nor reported in the study; ^a serum NFL levels discriminated between hockey players with persistent Post-Concussive Symptoms (PCS) as PCS >1 year and those with PCS $\leq$ 1 year, with an Area Under the Curve of 0.80; ^b the animals involved in the study were Sprague-Dawley rats.

4. Discussion

Blood-based biomarkers such as GFAP, UCH-L1, S100B, NFL, Tau, and NSE represent a promising strategy to advance the diagnosis and clinical management of mTBI, a potential that is well supported by an extensive literature [4,72]. These biomarkers provide distinct advantages over conventional diagnostic methods like CT scans, which involve radiation exposure and incur significant costs [7], by providing a more timely and sensitive assessment of brain injury.

GFAP shows a consistent temporal pattern after mTBI, detectable within an hour and peaking around 20 h, with strong sensitivity and negative predictive value for ruling out intracranial lesions, helping reduce unnecessary CT scans [28,47]. UCH-L1 demonstrates high sensitivity, and its combined use with GFAP significantly enhances diagnostic accuracy [9,28,48]. S100B is a sensitive rule-out biomarker within 3 h post-injury but has limited specificity, especially in older or multi-injured patients [54,56,58]. NSE typically demonstrates lower diagnostic performance compared to other biomarkers [62–64]. Its utility may be more pronounced in prognostic contexts, such as assessing risk for post-concussive syndrome [15]. Tau shows elevated serum levels following mTBI and may serve as a prognostic biomarker, especially in patients experiencing persistent post-concussive symptoms [18,65,66]. Despite its promise, Tau’s utility is somewhat hindered by data heterogeneity, likely attributable to rapid protein degradation and methodological differences in assay techniques across studies. The NFL has emerged as a biomarker indicative of axonal injury, reflecting the underlying pathophysiology of mTBI [16,73]. Recent investigations have demonstrated that elevated NFL levels correlate with poorer prognosis and increased risk of long-term complications, as well as heightened susceptibility to subsequent brain injuries [17,70,71]. However, clinical application of NFL is currently limited by variability in release kinetics and longer assay times compared to GFAP and UCH-L1.

Overall, GFAP, UCH-L1, and S100B emerge as the most robust and clinically applicable biomarkers for early diagnosis and exclusion of intracranial injury in patients with mild TBI, supporting the implementation of algorithms that reduce unnecessary CT scans, thereby enhancing patient safety and reducing healthcare costs [11,28]. Conversely, NFL, Tau, and NSE hold greater potential in prognosis and long-term monitoring but require further validation before widespread clinical adoption. See Table 7 for an overview of the biomarkers in mTBI.

Table 7. Comparative Summary Table of Biomarkers in mTBI.

Biomarker	Cellular Origin	AUC	Key Clinical Utility	Limitations	Optimal Sampling Time
GFAP	Astrocytes [9,12,30]	0.83–0.89 [14,29,31]	High sensitivity for intracranial injury; NPV 99.6% with UCH-L [28,47] 1	Short half-life; altered in other glial states [9,10]	<12 h post-injury [9,10]
UCH-L1	Neurons [37,74]	0.65–0.83 [33,45]	Enhances lesion exclusion with GFAP (NPV > 99%) [9,28,47]	Lower specificity; extracranial increases [14]	<6 h post-injury [28,47]
S100B	Astrocytes (primarily) [19,49,50]	0.89 [55]	Used in European guidelines to avoid unnecessary CT scans in low-risk patients [54,56,58]	Low specificity; false positives in extracranial trauma and elderly [49,54,57]	Within 3 h post-injury [49,54,58]
NSE	Neurons [55,62]	—	Historical marker; limited acute specificity [64]	Confounded by extracranial injury, hemolysis [14,55]	Acute phase [62,64]
Tau	Neuronal microtubules [66]	0.70–0.80 [66,67]	Early detection post-impact in sports [18]	High variability; lack of standardization [66]	Early post-injury [18]
NFL	Axonal protein [67]	0.81 [48]	Useful in prognosis, subacute/chronic phases [16,17]	Limited acute utility (<6 h) [17]	Weeks after injury [16,17,67]

NPV: Negative Predictive Value; AUC: Area Under the Curve; “—”: indicates that data is not specified nor reported in the above-mentioned studies.

The integration of blood-based biomarkers in the evaluation of mTBI represents a significant advancement in improving patient stratification and clinical decision-making. Unlike conventional CT, which is primarily limited to detecting intracranial hemorrhage and fails to identify diffuse parenchymal injuries characteristic of TBI, biomarkers provide objective molecular data that reflect underlying neuronal and glial damage. This capability is particularly valuable for detecting subtle microinjuries that are otherwise invisible on imaging, thereby enhancing diagnostic accuracy. A notable 27% of patients with normal CT scans had MRI abnormalities [75], findings like subarachnoid hemorrhage, brain contusions, and hemorrhagic axonal injury were independently associated with poorer outcomes at three months.

Moreover, biomarkers offer critical benefits in the assessment of challenging patient populations, such as those presenting with intoxication, where clinical evaluation is often confounded, and in identifying individuals at heightened risk for long-term sequelae following mTBI. Their high sensitivity makes biomarkers an effective tool for ruling out significant brain injury, which can contribute to reducing unnecessary head CT scans [76]. This reduction not only decreases patient exposure to ionizing radiation but also has the potential to improve emergency department workflow and reduce length of stay by facilitating faster and more informed decision-making. The authors have offered some initial suggestions on the potential indications for using biomarkers in mTBI, see Table 8 for further details.

Table 8. Indications for the use of the biomarkers in specific clinical scenarios following mTBI.

Clinical Scenarios Where biomarker Use Should Be Recommended	Clinical Scenarios Where Biomarker Use Should Be Not Recommended
Patients with unclear clinical presentation and altered mental status that may affect clinical assessment, such as drug intoxication or chronic neurological or cognitive deficits prior to the injury.	Patients with severe TBI requiring immediate neurosurgical intervention or patients with moderate TBI.
Patients unable to undergo neuroimaging promptly, taking into account the associated benefits and risks (e.g., due to contraindications or resource limitations).	Not plausible mechanism of injury (minor trauma).
	* Evidence of a lacero-contusive wound or contusion or any other skin lesion suggestive of underlying intracranial injury.

* Clinical assessment is crucial in determining the need for brain CT imaging.

However, it is essential to recognize that biomarkers should not be used in isolation nor applied indiscriminately to all patients with suspected mTBI [77]. Given their high sensitivity, the risk of false positives exists, and clinical judgment remains paramount. Biomarkers are most effective when integrated into a comprehensive clinical framework that includes patient history, physical examination, and established decision rules. Such an approach ensures that biomarker data complement rather than replace clinical assessment, ultimately optimizing patient care and resource utilization.

5. Conclusions

A diagnostic biomarker identifies or confirms a disease or its subtype, and effective validation ensures that it can be measured accurately, consistently, and cost-effectively [78]. However, a lack of proper validation can lead to overestimating its clinical usefulness. Looking forward, the combination of multiplex biomarker panels with artificial intelligence and machine learning offers significant potential to improve diagnostic accuracy and risk stratification in mTBI, facilitating more personalized patient care and more efficient use

of healthcare resources. The integration of these tools into routine clinical workflows represents a significant but achievable challenge in the future.

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