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Blood biomarkers for traumatic brain injury: A narrative review of current evidence

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ABSTRACT

Introduction: A blood-based biomarker (BBBM) test could help to better stratify patients with traumatic brain injury (TBI), reduce unnecessary imaging, to detect and treat secondary insults, predict outcomes, and monitor treatment effects and quality of care.
Research question: What evidence is available for clinical applications of BBBMs in TBI and how to advance this field?
Material and methods: This narrative review discusses the potential clinical applications of core BBBMs in TBI. A literature search in PubMed, Scopus, and ISI Web of Knowledge focused on articles in English with the words "traumatic brain injury" together with the words "blood biomarkers", "diagnostics", "outcome prediction", "extracranial injury" and "assay method" alone-, or in combination.
Results: Glial fibrillary acidic protein (GFAP) combined with Ubiquitin C-terminal hydrolase-L1(UCH-L1) has received FDA clearance to aid computed tomography (CT)-detection of brain lesions in mild (m) TBI. Application of S100B led to reduction of head CT scans. GFAP may also predict magnetic resonance imaging (MRI) abnormalities in CT-negative cases of TBI. Further, UCH-L1, S100B, Neurofilament light (NF-L), and total tau showed value for predicting mortality or unfavourable outcome. Nevertheless, biomarkers have less role in outcome prediction in mTBI. S100B could serve as a tool in the multimodality monitoring of patients in the neurointensive care unit.
Discussion and conclusion: Largescale systematic studies are required to explore the kinetics of BBBMs and their use in multiple clinical groups. Assay development/cross validation should advance the generalizability of those results which implicated GFAP, S100B and NF-L as most promising biomarkers in the diagnostics of TBI.

1. Introduction

Traumatic brain injury (TBI) is a markedly heterogeneous and complex disease that differs in severity from a severe, life-threatening disorder to single or repetitive mild TBI (mTBI) with little to no structural injuries observed on routine neuroimaging. Moreover, TBI can also be classified into focal injuries-including penetrating trauma, cortical/white matter contusion, epi-and subural hematomas-or diffuse injury with wide-spread damage to the cerebrovascular system and/or the white matter (Maas et al., 2017). Not only the heterogeneity of the disease itself, but also the demographic and genetic factors, as well as concomitant extracranial injuries, add further to this complexity (Carney et al., 2017). TBI is most often diagnosed by emergency department (ED) physicians and neurosurgeons and in some countries neurologists are primarily involved in the care of TBI (Foks et al., 2017). A careful and focused medical history, an appropriate neurological examination, and a head computed tomography (CT), if required, are the most crucial initial steps in the assessment of TBI patients. TBI is

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generally classified by Glasgow Coma Scale (GCS) as severe (GCS 3–8), moderate (GCS 9–12) and mild (GCS 13–15) as well as on the basis of cranial CT abnormality (Tenovuo et al., 2021). Although the severity of TBI has been traditionally classified by the GCS, it is not an absolute measure of TBI severity (Zetterberg et al., 2013). An mTBI patient has a small but not negligible risk of developing intracranial lesions, and a large subgroup of these patients develop chronic symptoms (Diaz-Arrastia et al., 2014; Takala et al., 2016; Posti et al., 2017). In a busy ED, an mTBI patient with a negative head CT and no significant neurological symptoms is usually rapidly discharged (Maas et al., 2017; Menon and Maas, 2015). However, neuronal damage may still be present, and the patient could have an incomplete recovery. In current practice, neuroimaging is the main diagnostic tool, however, it is not sensitive enough to diagnose all types of TBIs and to predict the outcome (Eierud et al., 2014; Mohammadian et al., 2020). It is thus difficult to stratify patients in the milder range of TBI, and decide whether they demand further observation and follow-up or not. Concussion, often defined as a mTBI, (Hossain et al., 2022) is common in contact sports such as boxing, American football, ice hockey, rugby, and martial arts, all characterized with high risk for repetitive concussion. Regrettably, there is no robust objective evidence ensuring a safe duration of time for return to play (Shahim et al., 2016a). Not only for the acute diagnostics of milder spectrum of TBI, but also for the monitoring of moderate to severe TBI (sTBI), there is no clinically validated objective test or surrogate marker that could mirror the multidimensional pathophysiology of TBI. Such a test alone or in combination with clinical, physiological, or imaging covariates could help to better stratify the patients with TBI, to perform further interventions as early as possible to prevent any permanent damage, to predict the outcomes and to monitor the treatment effects.

A biological marker (biomarker) of injury is defined as "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Atkinson et al., 2001). Biomarkers of TBI could be proteins, metabolites, or other substances such genetic markers. Since the collection of cerebrospinal fluid (CSF) samples is complicated and not realistic in the routine management of TBI, especially for the milder cases, blood biomarkers are preferred.

1.1. How could blood biomarkers improve the management of TBI

Application of a blood biomarker with high sensitivity, adequate specificity and well-defined bio-kinetic properties would be able to aid in the management of TBI in the following ways:

- To better stratify patients with TBI based on objective measures of brain damage instead of merely clinical symptoms and/or neuroimaging, which might lead to a **more precise classification.**
- To avoid unnecessary CT imaging, which is expensive, time-consuming and involves radiation exposure.
- To predict any intracranial lesions as a surrogate marker of imaging and to be used as a reliable discriminant of CT-positive and CT-negative brain injury in clinical practice.
- To identify patients with TBI in case of polytrauma.
- To decide the group of patients who might need advanced imaging e.g., magnetic resonance imaging (MRI).
- To identify the patients with axonal injury in the acute setting–given that CT/MRI scanning has suboptimal sensitivity and specificity for axonal lesions and MRI in the acute setting is not always feasible.
- To explore the return to play duration for the contact sports and, thus, aiming to reduce the risk of repetitive mTBI with exponentially detrimental effect on outcome.
- To use as an advanced neuromonitoring tool to understand the progress of any secondary insults following TBI and to evaluate treatment effects.
- To be included in a multifactorial prediction model to provide realistic prognosis information to the patients and their families.
- To be included in audit protocols as a measure of actual-, versus expected outcome
- To follow the disease course at the late post-injury phase detecting chronic neurodegenerative complications

1.2. Search criteria

This narrative review sheds light on the six most studied TBI biomarkers due to their potential clinical relevance. A literature search was performed in PubMed, Scopus, and ISI Web of Knowledge for articles in English with the words "traumatic brain injury" together with one or a combination of the words "blood biomarkers", "diagnostics", "outcome prediction", "extracranial injury", and "assay method". Focus was mainly on articles on clinical TBI.

1.3. Most studied biomarkers and their current applications

Table 1 summarizes the main properties of the mostly studied biomarkers in the literature. Figs. 1 and 2 show the expression of different blood biomarkers following TBI and their kinetic properties, respectively.

1.3.1. S100B

S100B is a small protein, belongs to a family of intracellular, calcium-binding proteins, predominantly presents in central nervous system (CNS) astrocytes (Thelin et al., 2017a). Historically, S100B is the mostly studied biomarker for the assessment of TBI, and also applied as an indicator of blood-brain barrier damage. Blood levels of S100B increase within 1 h following TBI and peak at <6 h post-injury (Rodríguez-Rodríguez et al., 2012). It has a half-life of 30 min to 2 h, and blood S100B levels are affected by age (Calcagnile et al., 2013). S100B levels in blood may increase during different athletic strenuous activities, and are also elevated in patients with extracranial injuries (Thelin et al., 2017b; Mehta et al., 2020). Since S100B is present in melanocytes, people of colour as well as melanoma patients might have higher levels (Yang et al., 2021). S100–B release of extracranial origin appears to have a faster clearance from blood than S100–B released from the CNS (Thelin et al., 2017b). CSF and salivary testing for S100B has also been proposed as an alternative to blood testing (Zetterberg et al., 2013; Janigro et al., 2020). In the latest Scandinavian Guidelines for the initial management of minimal, mild and moderate head injuries in adults, the use of S100B in the emergency department was recommended to rule out the need for head CT (using a cut-off in blood of 0.1 μg/L) in patients with isolated mild head injury who are at low risk for intracranial haemorrhage and presented <6 h post-injury. Use of S100B in the Scandinavian guidelines is cost-effective and safe to reduce unnecessary head CT scans (Calcagnile et al., 2016; Minkkinen et al., 2019; Undén et al., 2015). Despite of having excellent negative predictive value (NPV) for head CT under the above application criteria, the clinical utility of S100–B in TBI is limited due to the low brain specificity and the high number of negative CT scans related to this. In addition, due to the rapid clearance of S100B, its performance decreases within the first 24 h from injury. Thus, S100B must be used cautiously together with clinical covariates.

S100B has been also studied for outcome prediction following TBI. S100B levels were predictive of poor outcome and death for patients with moderate and sTBI with area under the receiver operating characteristic curve (AU-ROC) of 0.82 and 0.86, respectively (Mondello et al., 2011). The association of S100B levels at different time points with outcomes was also evaluated (Welch et al., 2017) and S100B levels correlated to long-term functional outcome. It was suggested that S100B levels should be determined at 12–36 h after injury in polytrauma patients (Gardner et al., 2018). Limited information also suggests that S100B could be used as a monitoring tool to enable early detection of secondary injury and to evaluate the treatment efficacy for the patients

Table 1
Main properties of the mostly studied biomarkers in the literature.

Biomarker	Molecular weight (kDa)	Primary origin	Location	Other sources	Half-life (h)	Peak (h)
S100B	11	Astrocytes	Cytoplasm	Adipocytes, melanocytes, muscle, chondrocytes, enteric glial cells	0.5–2	<6
GFAP	50	Astrocytes	Cytoplasm	Schwann cells, chondrocytes, enteric glial cells liver, pancreas	24–48	20–24
UCH-L1	25	Neurons	Cytoplasm	Testis, ovary, kidney	8	7–9
Tau	33–46	Neurons	Axon terminals, unmyelinated axons	Astrocytes and oligodendrocytes, peripheral nervous system, kidneys	Unknown	12–24
NF-L	68	Neurons	Myelinated axons	Peripheral axons	Unknown	Unknown

Glial fibrillary acidic protein (GFAP), Ubiquitin C-terminal hydrolase-L1 (UCH-L1), Neurofilament light (NF-L).

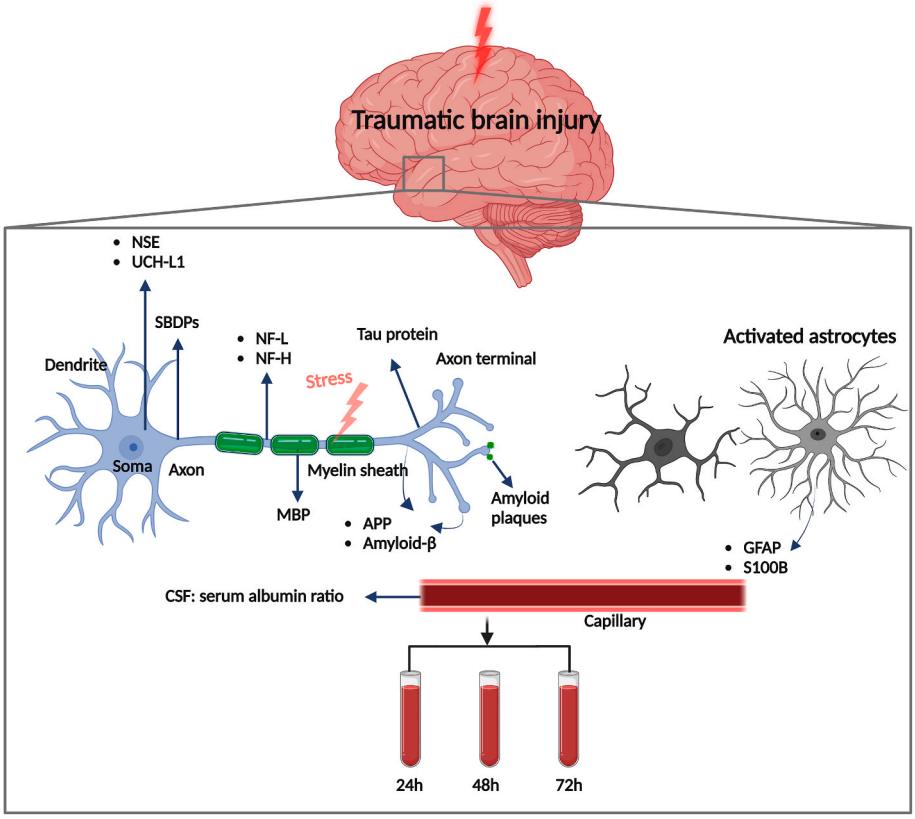

Fig. 1. Expression of different blood biomarkers from neurons and activated astrocytes following traumatic brain injury. The cerebrospinal fluid: albumin ratio is used to determine whether the blood-brain barrier is intact (Dadas and Janigro, 2018). Blood samples obtained at different timepoints indicate the importance of serial biomarker sampling.

with TBI admitted in the neurointensive care unit (NICU). (Thelin et al., 2017b; Lindblad et al., 2022).

1.3.2. GFAP

Glial fibrillary acidic protein (GFAP), a cytoskeletal monomeric filament protein (Eng et al., 1971) present in astrocytes, is located both in white and grey brain matter. GFAP is detectable within 1 h of trauma (Welch et al., 2017) and has a suggested half-life of 24–48 h, depending on the severity of TBI and the assay methods (Thelin et al., 2017a). The levels of GFAP could be affected by age (Gardner et al., 2018) and remain elevated several months after TBI (Posti et al., 2017). GFAP is also located extracranially, for example in Schwann cells, chondrocytes, testicular Leydig cells and enteric glia as well as in liver and pancreatic cells (Janigro et al., 2022). GFAP could serve as a sensitive marker of blood-brain barrier (BBB) disruption after TBI (Abdelhak et al., 2022). In acute diagnostics of TBI, the admission blood levels of GFAP correlated with both the initial GCS scores and brain imaging findings, (Luoto et al., 2017) and serum GFAP levels were increased in mTBI patients with abnormal CT findings when compared to patients with a normal CT scan (Diaz-Arrastia et al., 2014). Additionally, GFAP blood levels were increased in patients with axonal injury, identified by MRI, and in TBI patients requiring neurosurgical intervention (Diaz-Arrastia et al., 2014; Papa et al., 2012). The levels of GFAP could discriminate both patients with mTBI and moTBI from healthy controls and from patients with orthopedic injury without a TBI (Papa et al., 2012). From clinical standpoints, GFAP has a good sensitivity and specificity for predicting lesions on CT in acute TBI (Luoto et al., 2017). Current results of the large-scale, multicenter initiatives CENTER-TBI, and TRACK-TBI, are important in verifying the potential of GFAP as a marker in acute TBI triage. Recently, TRACK-TBI investigators reported that blood levels of GFAP within 24 h of injury have significant discriminative ability to identify MRI abnormalities in patients with normal CT findings (Yue et al., 2019). Even though GFAP is not yet included in any clinical guidelines, the recent results of CENTER-TBI provided strong evidence

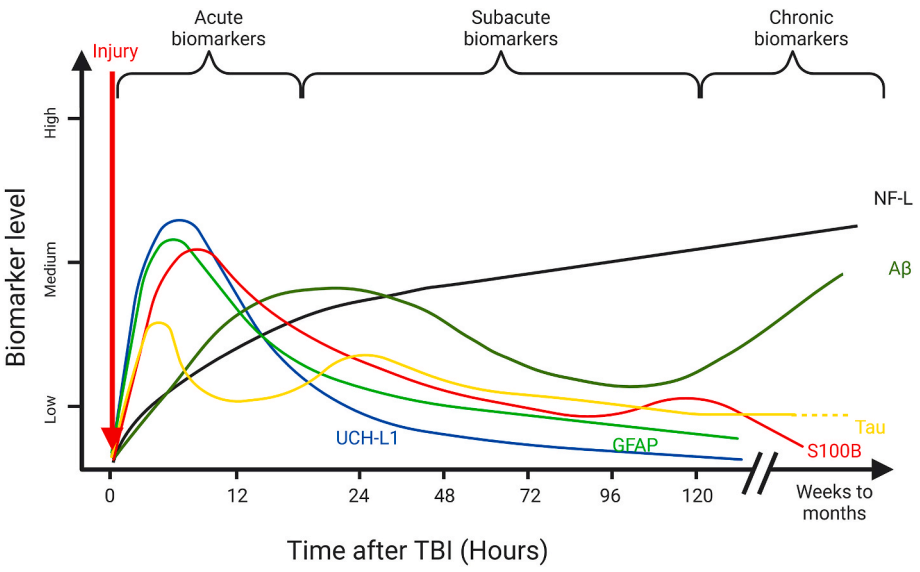

Fig. 2. Approximated kinetic properties of different blood biomarkers from the acute to the chronic phase following traumatic brain injury.

that serum GFAP levels, obtained in the first 24 h post-injury, could be highly predictive for CT positivity, outperforming other markers and adding value to clinical variables considered in latest CT decision rules (Czeiter et al., 2020). To identify patients with traumatic intracranial findings on head CT, GFAP has outperformed (AU-ROCs 0.74–0.89) (Diaz-Arrastia et al., 2014; Czeiter et al., 2020; Papa et al., 2016; Posti et al., 2019; Okonkwo et al., 2020) NF-L (0.81–0.82) (Czeiter et al., 2020; Posti et al., 2019), S100B (0.58–0.76) (Czeiter et al., 2020; Posti et al., 2019; Okonkwo et al., 2020),T-tau (0.78–0.82) (Czeiter et al., 2020; Posti et al., 2019) and UCH-L1 (0.62–0.83). (Diaz-Arrastia et al., 2014; Czeiter et al., 2020; Papa et al., 2016; Posti et al., 2016). From a practical point of view, a rapid capillary blood-based GFAP screening test would facilitate the TBI management in pre-hospital environments (e.g., sideline assessment in sports and emergency medical services). A single marker approach using GFAP could be beneficial for the timely diagnosis and decision making also in the Low-and-Middle Income Countries (LMICs) where routine neuroimaging is often inaccessible and unequally distributed.

GFAP also discriminated favourable and unfavourable outcome in mTBI patients (AU-ROC of 0.76) (Hossain et al., 2019). The day-of-injury GFAP plasma concentrations were good to excellent in predicting death and unfavourable outcome (Korley et al., 2022).

1.3.3. UCH-L1

Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is involved in either adding or removing ubiquitin from proteins targeted for metabolism, abnormal proteins, and proteins damaged by oxidation (Liu et al., 2002). UCH-L1 is detectable within 1 h of TBI, peaks 8 h after injury and has a short half-life of 7–9 h (Papa et al., 2016). UCH-L1 is also expressed in cells outside the CNS, such as in testis, ovary and kidney (Posti et al., 2017; Wilkinson et al., 1989). Given that UCH-L1 is produced by neurons, it is considered a suitable counterpart for GFAP in TBI diagnostics (Diaz-Arrastia et al., 2014; Papa et al., 2016). A superior sensitivity and specificity for diagnosing TBI was obtained when GFAP was combined with UCH-L1, thus supporting the idea that a combination of biomarkers may be ideal in diagnosis and prognostication of TBI. However, unexpected results have been lately reported by the large cohort CENTER-TBI study. This will be discussed in the later section of this manuscript (Bogoslovsky et al., 2016). Patients with mTBI had higher levels of serum UCH-L1 compared to orthopedic trauma patients without brain injury, and to healthy controls. Important to note that UCH-L1 was able to discriminate between CT-positive and CT-negative mTBI and between healthy controls and patients across the full spectrum of TBI (Diaz-Arrastia et al., 2014; Papa et al., 2012, 2016; Yue et al., 2019). Nonetheless, there are contradictory reports in which UCH-L1 was unable to distinguish healthy controls from patients with mTBI (Posti et al., 2017; Dadas et al., 2018). Variations of such results could be for the methodological dissimilarities among the studies.

The latest report by the CENTER-TBI researchers provided strong evidence that integration of serum UCH-L1 in established prognostic models, IMPACT AND CRASH, have incremental prognostic value for functional outcome after TBI.

In a cohort that included all severities of TBI, both UCH-L1 (AU-ROC 0.73) and GFAP (AU-ROC 0.72) at admission discriminated patients with unfavourable outcome from those with favourable outcome. However, in patients with **complete and incomplete recovery**, the discriminatory power of UCH-L1 and GFAP was not clinically useful (Takala et al., 2016). In another study, predictive performance of UCH-L1 and GFAP within 24 h from injury for complete recovery at 3 months was not adequate, 0.59 and 0.65, respectively (Diaz-Arrastia et al., 2014). To date, the knowledge is that these biomarkers provide the most useful prognostic information for patients presenting with a GCS score of 3–12.

1.3.4. Tau

Tau, a microtubule-associated protein that is located in the axons of CNS neurons, serves as a structural element in the axonal cytoskeleton (Olivera et al., 2015; Rubenstein et al., 2015). Though tau is mostly found in the brain, some extracranial sources exist such as in the liver, kidney and testis (Morris et al., 2011). It is identified as a neurodegenerative biomarker, (Jack et al., 2019; Kim et al., 2018) and has been widely investigated for the development of neuronal and axonal pathology following TBI, (Neselius et al., 2013) although its half-life in blood after TBI is not established (Posti and Tenovuo, 2022). Tau serum levels peak at 12–24 h, and decline relatively slowly (Rubenstein et al., 2017; Randall et al., 2013). Blood Tau levels appear increased with aging (Chiu et al., 2017). Phosphorylation of tau is a normal event in healthy neurons, but hyperphosphorylation and aggregation into neurofibrillary tangles is a characteristic of Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) (Zetterberg and Blennow, 2016). Elevated levels of plasma total Tau (T-tau) are correlated with the outcome of repeated mTBI or concussion (Neselius et al., 2013; Shahim et al., 2014). In severe TBI, serum T-tau and admission CSF T-tau levels were significant outcome predictors (Liliang et al., 2010). T-tau was

unable to differentiate CT-positive and CT-negative mTBI groups (Zetterberg et al., 2013). These findings are reasonable, since traditional immunoassay methods are not sensitive enough to analyze, especially, the low levels of tau in blood (Zetterberg and Blennow, 2016). Lately, using an ultrasensitive assay platform, (Kuhle et al., 2016) acute plasma hyperphosphorylated tau protein (P-tau) levels and the P-tau/T-tau ratio outperform T-tau levels for the outcome prediction of TBI, (Rubenstein et al., 2017) a finding that needs validation in independent studies. Furthermore, the acute levels of plasma T-tau could differentiate patients with complicated mTBI (as defined by CT imaging) from controls (Zetterberg and Blennow, 2016). Significantly elevated levels of plasma T-tau were also reported in cases of ice hockey players after concussion compared to their pre-season levels (Shahim et al., 2014). However, there is no evidence that acute levels of plasma T-tau were able to differentiate incomplete and complete recovery in case of single and uncomplicated mTBI. In mTBI, mainly subcortical myelinated axons of the white matter are presumed to be injured (Zetterberg et al., 2013; Shahim et al., 2016a; Neselius et al., 2013). Tau is mainly expressed in unmyelinated cortical axons, (Hossain et al., 2022) which may limit the potential of tau as an axonal injury biomarker for mTBI. Considering the diagnostic accuracy, AU-ROCs for T-tau have varied considerably between similar clinical settings when measured with similar assays (Shahim et al., 2014; Meier et al., 2020). To understand the complex issue of tau pathology, in a recent study (Marklund et al., 2021) young patients with symptomatic repetitive sports-related concussions were found to have increased tau aggregation in the corpus callosum at longer time points after injury. For the detection of abnormal tau pathology, dual PET tracers in combination with biomarkers (CSF and plasma tau), neuropsychological evaluation, and 3 T magnetic resonance (3T MR) scanning were used in this study. Higher exosomal tau concentrations were also associated with chronic symptoms in military personnel after mTBI (Gill et al., 2018). Although the current reports showed several promising aspects of tau as a blood biomarker of concussion, there is still insufficient evidence to support the clinical validity for the bench-to-bedside application of this neurodegenerative biomarker.

1.3.5. NF-L

Neurofilament light (NF-L) protein is a large caliber axonal biomarker that can be measured in blood samples and in CSF (Kuhle et al., 2016; Wilson et al., 2016; Shahim et al., 2017a). It is mainly expressed in the long myelinated white matter (WM) axons of brain, (Zetterberg et al., 2013; Shahim et al., 2016b, 2017a) but may also be expressed in peripheral axons (Sandelius et al., 2018). NF-L protein has been extensively studied as a potential body fluid biomarker to investigate the ongoing axonal injury following TBI (Hossain et al., 2019; Newcombe et al., 2022; Shahim et al., 2020a). Extracranial injury and aging could lead to increased levels of blood NF-L. (Posti and Tenovuo, 2022) The levels of NF-L can remain elevated months to years after TBI (Newcombe et al., 2022). Patients with mTBI or concussion had significantly higher levels of NF-L compared to healthy individuals or orthopedic controls, from the acute to the chronic phase (Shahim et al., 2014, 2017a, 2020a, 2020b). Blood levels of NF-L were significantly elevated in contact sports athletes, for example, professional hockey players who suffered from symptoms after repetitive mTBI (Shahim et al., 2016a, Shahim et al., 2017a). Recently, an association between the early plasma levels of NF-L and the outcome in patients with mTBI was reported (Hossain et al., 2019). The early levels of plasma NF-L could associate with the presence of DAI at a later phase of TBI (Hossain et al., 2023). In addition to the admission levels, the plasma levels of NF-L at several time-points, correlated with the outcome of TBI (Skillbäck et al., 2014). A single mild to moderate TBI may cause long-term neuroaxonal degeneration, for which NF-L could be a surrogate marker, (Shahim et al., 2020a) supported by the association between diffusion tensor imaging (DTI) measures of axonal injury and the serum levels of NF-L following sTBI (Shahim et al., 2016b; Ljungqvist et al., 2017). Serum concentrations of NF-L correlated with the DTI measures of axonal injury in subacute and chronic TBI (Shahim et al., 2020a). The elevated blood levels of NF-L at 6 months was significantly related to the metrics of microstructural injury on DTI (Newcombe et al., 2022). BIO-AX-TBI, (Graham et al., 2020) investigating fluid and imaging markers of axonal injury after moderate to severe TBI, demonstrated that the levels of plasma NF-L and DTI metrics are closely related in quantifying underlying axonal injury subacutely after TBI. In this study, microdialysate taken directly from damaged WM was found to contain very high levels of NF-L and this concentration of NF-L in microdialysis fluid significantly correlated with the levels of NF-L in plasma. Also, the plasma levels of NF-L also correlated with histopathologically defined axonal injury within the WM, which was produced by an experimental injury model (Graham et al., 2021). Thus, the association between the plasma levels of NF-L and DTI metrics indicates that plasma NF-L measurement may reflect the damage of WM of the brain following TBI. The peak of NF-L was between 10 days and 6 weeks following injury and that subacute levels strongly correlated with outcome, which strengthen the concept that DAI is a slow, long-lasting process (Shahim et al., 2020a; Graham et al., 2021).

Latest report of the CENTER-TBI researchers underpinned that day-of-injury NF-L had the greatest additional prognostic value for predicting incomplete recovery after mTBI (Helmrich et al., 2022). Since NFL concentrations are known to peak several days or weeks after injury, subacute measures or trajectory-based analyses from serial samples postinjury could have further predictive value.

1.3.6. Aβ40 and Aβ42

Aβ40 and Aβ42, **which** can be formed as part of normal metabolism, (Shahim et al., 2017b) reflect amyloidogenic amyloid precursor protein (APP) metabolism and may be potential biomarkers of axonal damage in TBI (Zetterberg et al., 2013; Marklund et al., 2014; Hossain et al., 2020). The levels of Aβ40 and Aβ42 becomes elevated within 24 h of injury, however, contradictory results exist (Shahim et al., 2016a; Lippa et al., 2019).Aβ pathology, primarily consisting of aggregated Aβ42 peptides, is a histologic hallmark of AD, and TBI has been suggested to be one of the risk factors for AD. (Ramos-Cejudo et al., 2018) Aβ pathology (amyloid plaques) was found in boxers having dementia pugilistica (Roberts et al., 1990) and in a proportion of other contact sport athletes having CTE (Blennow and Nellgård, 2004). Although ventricular CSF levels of Aβ40 and Aβ42 were elevated during the first week after severe TBI, (Olsson et al., 2004) no changes in Aβ40 or Aβ42 were observed in mTBI where CSF samples were collected by lumbar puncture (Neselius et al., 2013). However, for repetitive mTBI, post-injury subjective symptoms were associated with the reduction of CSF levels of Aβ40 and Aβ42 (Olsson et al., 2004; Tsitsopoulos and Marklund, 2013). There was no correlation between the levels of Aβ40 and Aβ42 and outcome, and these levels are not able to predict complete or incomplete recovery (Marklund et al., 2014; Olsson et al., 2004; Tsitsopoulos et al., 2017). Plasma levels of Aβ40 and Aβ42 did not have a clinical value for the diagnosis and the prediction of outcome of mTBI (Hossain et al., 2020; Lippa et al., 2019). In case of CT-positive TBI, Aβ40 could predict outcome when used in combination with the Helsinki Computed Tomography Score (HCTS) (Posti et al., 2020). Rapid formation of Aβ protofibrils and plaques after sTBI indicate that these potentially toxic Aβ species may aggravate the clinical outcome both in the shorter and longer perspective (Abu Hamdeh et al., 2018).

1.3.7. Other biomarkers

Besides the above-mentioned body fluid biomarkers, neuron specific enolase (NSE), heart-fatty acid binding protein (H-FABP), anti-inflammatory cytokines (e.g., IL-10), spectrin breakdown products (SBDPs), miRNAs and myelin basic protein (MBP) have been also studied for the different severity of biomarkers and provided promising results (Thelin et al., 2017a). However, due to the small to moderate sample sizes such study findings need to be validated in future larger prospectively collected well characterized cohorts to evaluate their

clinical applications.

Unfortunately, overwhelming majority of studies are focused on adult population without assessing extremes of age. Especially little is known about the pediatric population where the performance of the above-detailed core biomarkers is not clarified. An interesting approach is focusing on identification of biomarkers specific for the pediatric age group, including the evaluation of osteopontin as a marker of injury severity (Blackwell et al., 2020, 2023Blackwell et al., 2023).

1.4. *Blood biomarkers for monitoring patients with TBI in neurointensive care unit and the role of panels of biomarkers*

Serial sampling of protein biomarkers could be performed to monitor the progression of lesions or development of new injuries following TBI. The most studied blood biomarker in this context is S100B. Other proteins that have been studied in this setting include NSE, GFAP, tau, NF-L, and UCH-L1. Even relatively modest increases of S100B (>0.05 μg/L), sampled every 12 h, have a robust sensitivity and specificity in order to detect lesions seen on imaging. S100B, could be superior to NF-L in detection of secondary insults when monitoring patients with TBI in NICU. So far, blood biomarkers are not a part of the BTF guidelines (Lindblad et al., 2022).

Since TBI induces a complex cascade of neurometabolic changes, (Zetterberg et al., 2013; Menon and Maas, 2015) theoretically, panels of biomarkers from different cellular origins are needed. Panels of biomarkers from different cellular origins could outperform the ability of single proteins to detect patients requiring head CT scanning after TBI (Posti et al., 2019). A serum protein biomarker panel of different cellular origins (S100B, NSE, NF-L, GFAP, UCH-L1 and tau) improved outcome prediction in human TBI, where 70% of the cohort had severe TBI (Thelin et al., 2019). Blood biomarkers increased the efficacy of the prediction models of TBI, especially in case of severe cases (Czeiter et al., 2012). Note that the recent ALERT-TBI study found that a blood test incorporating GFAP and UCH-L1 in identifying CT-positive findings has better sensitivity (0.98) and specificity (0.36) (Bazarian et al., 2018) than S100B in the validation studies for the Scandinavian guidelines (sensitivity 0.94 and specificity 0.19) (Calcagnile et al., 2016; Minkkinen et al., 2019).Although the U.S. authorities (FDA) approved this test for identifying patients requiring head CT, the role of UCH-L1 in this combination test has been questioned (Maas and Lingsma, 2018). Contrasting the Scandinavian guidelines, the FDA-approved test does not consider clinical covariates such as extracranial injury or other clinical factors such as GCS score, injury mechanism or use of anticoagulants that predispose to intracranial haemorrhage.

Contrary to the expectations, the recent comprehensive evidence from the CENTER-TBI researchers showed that a multi-marker approach applying combinations of biomarkers did not increase the diagnostic value for CT positivity, compared to GFAP alone (Czeiter et al., 2020). These observations do not reject the potential usefulness of combinational approaches in terms of outcome. Similarly, prognostic studies from the same investigators did not prove that a combinational panel of biomarkers would considerably increase the added value of UCH-L1 or GFAP alone to prognostic modelling by IMPACT and CRASH.

1.5. *Pathophysiological mechanisms for release of brain biomarkers after TBI*

The biomarkers reviewed in previous paragraphs have different cellular origin in the brain and degree of brain specificity (i.e., different degree of peripheral expression). They may be grouped into two categories showing either acute changes and a rapid half-life (e.g. S100B, GFAP, T-tau and UCHL-1), and those with a slow and delayed increase peaking at day 7–12 after trauma, followed by a slow normalization (e.g. NF-L). The reason for this difference is not clear but may be related to different pathophysiological mechanisms for release.

The mechanism of the passage of blood biomarkers from the brain to blood is still not completely understood. The blood-brain barrier (BBB) disruption and the glymphatic system are the mostly studied routes.

1.5.1. *BBB*

The BBB is composed of tightly connected endothelial cells and astrocytes, connected by tight junctions, and may become disintegrated in TBI (Dadas and Janigro, 2018). The BBB creates a tightly regulated environment in the CNS by controlling ingress of immune cells and blood-borne metabolites. It also controls the cerebral homeostasis by necessary influx of vital substrates and efflux of waste materials. In transportation across the BBB, the astrocytic podocytes, along with microglial cells and basal cell membrane of the endothelium, act as a bridge between the brain parenchyma and micro vessels. Breakdown of the functional integrity of the BBB due to injury leads to functional changes and raised permeability to high molecular weight protein such as albumin (Lindblad et al., 2020). In TBI studies the gold-standard for assessing BBB disruption is the CSF to blood albumin quotient. However, in humans, elevated albumin CSF:serum ratio, is observed up to a week following TBI (Dadas and Janigro, 2018).

1.5.2. *The glymphatic system*

The glymphatic system is a route that connects the interstitial fluid of the brain, CSF, and venous outflow. We suffer from a paucity of data regarding the role or potential alteration of this system in TBI. It is believed to act as a lymphatic drainage from the brain (Sullan et al., 2018). This para-arterial influx of CSF through brain extracellular fluid to a paravenous outflow, is the principal path of efflux of cerebral protein debris and is driven by arterial pulsations. A recent study reveals the fact that the glymphatic system acts unaided from the BBB integrity following brain injury. It further shows that proteins of cerebral origin mainly drain through the glymphatic system from the injured brain (Sullan et al., 2018; Piantino et al., 2019).

2. Conclusion

Available evidence suggests that serum GFAP levels obtained within 24 h post-injury predict brain lesions on head CT across the full range of TBI severities and thus, it could be used for triaging patients for CT scanning. S100B could aid in refining the indication for head CT scanning if used cautiously in combination with clinical covariates. Regarding outcome prediction, day-of-injury NF-L levels have the greatest additional prognostic value for predicting incomplete recovery after mTBI.

3. Future directions

One of the critical aspects prior to applications of TBI biomarker in the clinical setting is to explore their kinetics. Large and systematic observational studies using serial biomarker sampling with particular focus on age- and sex differences are needed. Another vital step is to develop a validated assay with clearly defined cut-off values for abnormality, having excellent sensitivity and at least good specificity in multiple clinical groups, including those with orthopedic injuries and those with a wide range of pre-existing neurological and medical problems. For the validation of TBI biomarkers, the international research communities need to establish methodological standards and to collect high-quality extensive data by fostering global team science. Hopefully, the ongoing collaborative trials based on the CENTER-TBI and TRACK-TBI studies will provide more evidence for the clinical use of TBI biomarkers.

Ethical approval

Since this was a narrative review, no institutional ethical clearance was required.

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