Unveiling the predictive power of biomarkers in traumatic brain injury: A narrative review focused on clinical outcomes

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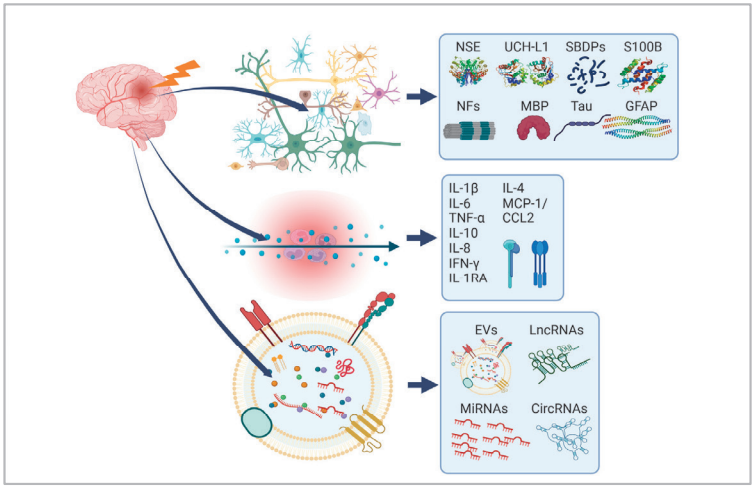
Traumatic brain injury (TBI) has long-term consequences, including neurodegenerative disease risk. Current diagnostic tools are limited in detecting subtle brain damage. This review explores emerging biomarkers for TBI, including those related to neuronal injury, inflammation, EVs, and ncRNAs, evaluating their potential to predict clinical outcomes like mortality, recovery, and cognitive impairment. It addresses challenges and opportunities for implementing biomarkers in clinical practice, aiming to improve TBI diagnosis, prognosis, and treatment.



This graphical abstract shows the diverse TBI biomarkers involved in key processes such as neuronal and glial injury, axonal damage, inflammation, and molecular signaling via extracellular vesicles and non-coding RNAs.

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INTRODUCTION

Traumatic brain injury (TBI) results from external forces impacting the brain, often involving direct trauma, acceleration/deceleration, or rotational forces. This complex interplay generates inertial forces that disrupt brain tissue and cells, leading to a cascade of neurological dysfunction[1]. TBI is a major public health concern, with the highest incidence among common neurological disorders, and poses a substantial global burden. Although traditionally seen as an acute condition, TBI is increasingly recognized for its chronic effects, including a higher risk of neurodegenerative diseases[2]. In 2019, there were 27.16 million new cases and 48.99 million prevalent cases of TBI, leading to 7.08 million years lived with disability (YLDs) (ref.[3]). Despite moderate-to-severe TBI often causing lasting functional impairment, outcomes vary widely among individuals with similar injuries, ranging from full recovery to severe disability or death[4,5]. This variability underscores the need for individualized treatment strategies, recognizing the unique patterns of impairments and their evolution over time[5].

TBI is not a singular event but a complex cascade of pathological processes. The initial impact triggers a chain reaction of secondary injuries, characterized by molecular and cellular responses that persist long after the initial

trauma. These secondary injuries lead to neuronal and astroglial damage, axonal disruption, and inflammation, ultimately contributing to the long-term consequences of TBI. Understanding these intricate processes is crucial for developing effective neuroprotective and therapeutic interventions[6]. Currently, TBI diagnosis relies on the Glasgow Coma Scale (GCS), a clinical assessment tool that classifies TBI severity based on the patient's level of consciousness. The GCS categorizes injuries as severe (GCS 3–8), moderate (GCS 9–13), and mild (GCS 14–15) (ref.[7]). However, despite the use of advanced imaging techniques like CT and MRI, predicting long-term outcomes remains challenging. These methods often fail to detect diffuse axonal injury (DAI), a common TBI characterized by widespread shearing of nerve fibers, which significantly impacts long-term prognosis[8]. Biomarkers offer a promising avenue for improving TBI diagnosis, prognosis, and treatment monitoring. They can reveal injury-induced cellular, biochemical, and molecular changes, often detecting early microlesions that conventional imaging techniques miss[9]. By integrating biomarkers with clinical examination and imaging, clinicians can achieve more accurate severity assessment, predict outcomes more reliably, and evaluate treatment responses effectively[10]. The development of reliable biomarkers is crucial for early and accurate TBI diagnosis, paving the way for timely and effective interventions. The absence of such biomarkers currently limits our ability to provide optimal care for patients with TBI.

This narrative review aims to explore the predictive power of biomarkers in TBI, focusing on their ability to forecast clinical outcomes. We will examine the current landscape of biomarker research, analyzing biomarkers related to neuronal injury, inflammation, extracellular vesicles, and non-coding RNAs. We will critically evaluate the evidence on their predictive value for clinical outcomes, such as mortality, functional recovery, long-term disability, and cognitive impairment. Additionally, we will discuss the challenges and opportunities associated with biomarker use in clinical practice and provide recommendations for future research. By synthesizing current knowledge and highlighting future directions, this review seeks to illuminate the potential of biomarkers as valuable tools for improving TBI diagnosis, prognosis, and personalized treatment strategies.

BIOMARKERS IN TRAUMATIC BRAIN INJURY: A DIVERSE LANDSCAPE

TBI can be classified as mild, moderate, or severe. Mild TBI (mTBI), often caused by head impacts resulting in rotational acceleration of the brain, can also occur without direct impact, such as in motor vehicle crashes with rapid head rotation. While mTBI typically does not produce visible brain damage, it can lead to rapid neurophysiological and neurological dysfunction that often resolves quickly. However, persistent cognitive dysfunction can occur in up to 15% of individuals[11-13].

TBI pathogenesis involves two distinct phases: the primary injury, occurring immediately upon impact, and the secondary injury, encompassing the body's attempts to limit and repair the damage[14,15]. The initial impact causes necrosis, tissue deformation, and shearing of neurons, axons, and glial cells, leading to excitotoxicity, oxidative damage, and cerebrovascular disturbances[16]. Complications include reduced mitochondrial respiration, lipid damage, activation of apoptotic and non-apoptotic cell death pathways, and initiation of inflammatory and protein degradation cascades[17,18]. The initial injury also disrupts the blood-brain barrier (BBB), increasing permeability and allowing further cellular damage and inflammation[19,20]. TBI-induced injury disrupts cerebral vascular autoregulation, leading to an imbalance between cerebral blood flow and metabolism, resulting in cerebral oxygen deprivation (ischemia). This triggers mitochondrial dysfunction, increased lactate levels, elevated intracellular calcium (Ca2+) ions, and reduced ATP production, contributing to the failure of ATP-dependent ion pumps and impaired glutamate uptake[21]. The initial injury sets off a cascade of secondary events, initiated by the release of glutamate from damaged neurons. Glutamate triggers edema, pro-inflammatory cytokine release, and further ischemia, perpetuating the cycle of damage[1,16]. TBI-induced metabolic changes affect amino acid, carbohydrate, and lipid metabolism, impacting both brain and other organ functions[22]. These complex processes manifest in a range of clinical symptoms, from motor deficits to debilitating neurocognitive and personality changes[23].

An ideal and reliable fluid biomarker for TBI, as proposed by Wang et al.[6], should possess several key characteristics to be truly effective. First, it should be released upon injury, meaning that head trauma triggers its release into readily accessible bodily fluids, allowing for non-invasive detection. Second, the biomarker should exhibit elevated levels in TBI patients compared to healthy individuals. Third, its concentration should correlate with the severity of the TBI, both quantitatively and qualitatively. Finally, the biomarker's levels should align with findings from other clinical diagnostic tools, such as the Glasgow Coma Scale (GCS), CT scans, and MRI. Fig. 1 provides an overview of diverse TBI biomarkers, each reflecting a specific aspect of the injury process. These biomarkers encompass markers of neuronal, axonal, myelin, and glial cell damage, inflammatory responses, extracellular vesicles, and a variety of non-coding RNA species.

Neurological biomarkers in traumatic brain injury

A range of protein biomarkers have emerged as potential indicators of TBI, each reflecting damage to specific neurological structures. These include markers for dendrites (MAP2), neuron cell bodies (UCH-L1, NSE), axons (pNF-H, SBDPs, Tau protein), myelin (MBP), synapses (neurogranin, synaptogranin), astroglia (GFAP, S100B), and autoantibodies (anti-GFAP) (Table 1) (ref.[6]). The persistence of these biomarkers in blood and cerebrospinal fluid (CSF) varies. Some, like S-100B and GFAP, show acute elevations and typically return to baseline levels within days, while others, such as Tau protein, exhibit persistent aberrations correlating with long-term sequelae following TBI (ref.[6,24]). Tau, a microtubule-associated

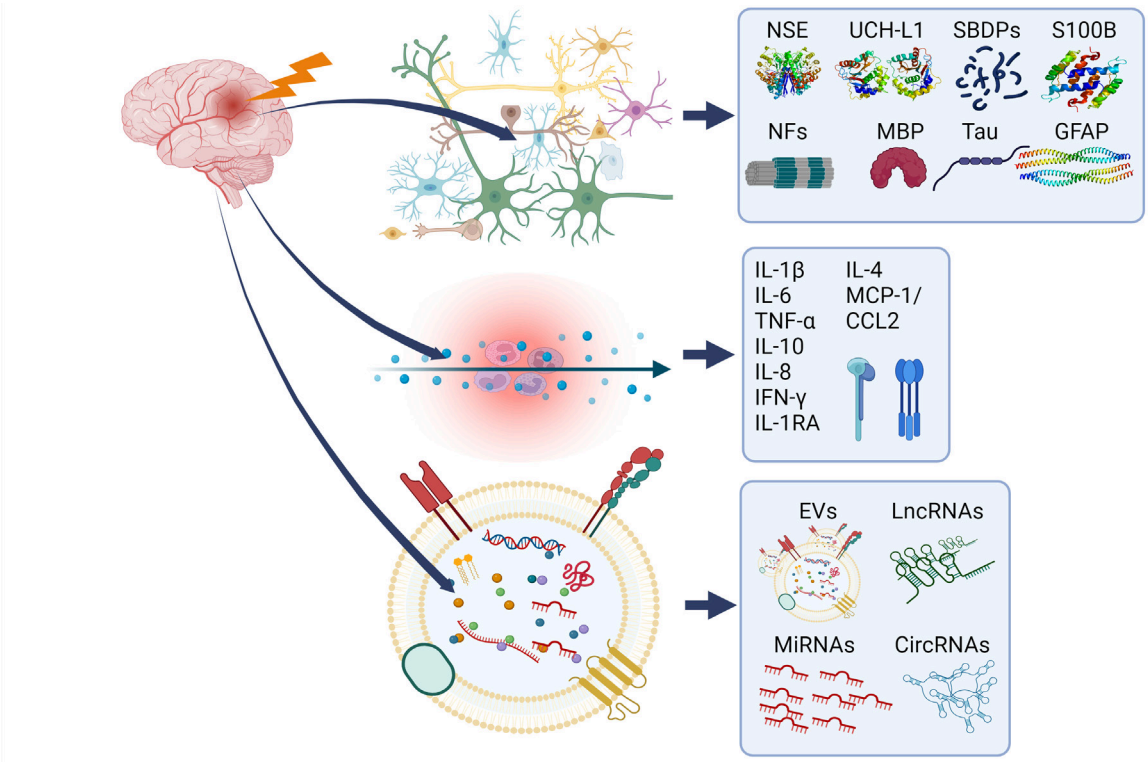

Fig. 1. Summary of the different types of TBI biomarkers that denote many processes such as neuronal injury, glial injury, axonal injury, inflammation, extracellular vesicles, and various non-coding RNAs.
NSE, Neuron-specifc enolase; UCH-L1, Ubiquitin C-terminal hydrolase-L1; SBDPs, α-II-spectrin breakdown products; NFs, Neurofilament proteins; MBP, Myelin basic protein; GFAP, Glial fibrillary acidic protein; S100B, S100B calcium binding protein B; LncRNA, Long non-coding RNA; MiRNA, MicroRNA; CircRNA, Circular RNA; EV, extracellular vesicle.

protein encoded by the MAPT gene, plays a crucial role in maintaining microtubule stability within the axonal cytoskeleton[25,26]. Recent research has focused on total Tau and phosphorylated Tau, noting their elevated levels following TBI and their correlation with injury severity and long-term outcomes, particularly within six months post-injury[27].

Inflammatory biomarkers in traumatic brain injury

TBI triggers neuronal inflammation, leading to alterations in neuronal function[72]. This process involves the release of chemical mediators, including cytokines, which are produced by various cells[73,74]. Cytokine production often occurs in a cascade, where one cytokine stimulates target cells to produce additional cytokines, amplifying the inflammatory response[75]. As intercellular messengers, cytokines bind to receptors on target cells and initiate specific responses[74]. Inflammatory responses play a complex role in recovery following TBI. While essential for removing damaged neurons and initiating repair processes, prolonged inflammation can lead to excessive neuronal damage, contributing to long-term neurological deficits[76,77]. Understanding the balance between beneficial and detrimental aspects of inflammation is crucial for developing interventions that minimize unfavorable outcomes for TBI patients.

Biomarkers offer insights into the biological processes activated by TBI. Neuroinflammation, characterized by both beneficial and detrimental effects, is a primary focus of biomarker research. Cytokines, primarily produced by immune cells like monocytes, lymphocytes, and macrophages, orchestrate the immune response and contribute to tissue repair[78]. They are categorized as pro-inflammatory (e.g., IL-1, IL-12, IL-18, IFN-γ, TNF-α) or anti-inflammatory (e.g., IL-4, IL-10, IL-13, IFN-α) based on their role in immune regulation[74]. Despite advancements, a significant gap remains in understanding the relationship between inflammatory cytokines and long-term outcomes following TBI. The persistent release of pro-inflammatory cytokines contributes to neurodegenerative diseases[79]. Activated microglia, a type of immune cell in the brain, are a chronic source of neurotoxic factors, including TNF-α, nitric oxide (NO), IL-1β, and reactive oxygen species (ROS), leading to progressive neuronal damage. Chronic activation of microglia, whether by a single stimulus like lipopolysaccharide or multiple exposures, leads to cumulative neuronal loss over time, implicating them in neurodegenerative conditions[80].

Previous research suggested a correlation between serum IL-1β levels and TBI severity, GCS score, and prognosis[81]. However, a recent meta-analysis of four studies involving 439 participants (263 with mTBI and 176 healthy controls) found no significant difference in blood IL-1β levels between cases and controls. Subgroup analysis revealed significantly elevated blood IL-1β levels in the acute phase (<7 days) after mTBI, indicating a role in the early inflammatory response. However, insufficient studies precluded a comprehensive analysis of chronic IL-

Table 1. Neuronal, axonal, myelin, and glial cell biomarkers in traumatic brain injury.

Biomarkers	Definition	Key features	Clinical Relevance	Ref.
Neuronal cell injury biomarkers				
NSE	A neuronal cytoplasmic enzyme involved in glycolysis.	– Predominantly found in neurons, released after acute neuronal damage; highly specific to the brain but limited by hemolysis interference	– Peaks within 12 hours post-TBI, declines within days. – High levels indicate severe injury, associated with poor neurological outcomes and increased mortality. – Limited utility due to potential false positives from hemolysis.	28–31
UCH-L1	Ubiquitin-related enzyme in the cytoplasm of neurons.	– Plays a critical role in the ubiquitin-proteasome system, regulating protein degradation. – Released into the bloodstream following TBI due to neuronal damage and blood-brain barrier disruption	– Levels increase within 6-24 hours post-TBI. Strongly correlates with injury severity, Glasgow Coma Scale (GCS) scores, and CT findings. – Early high levels predict poor outcomes within three months.	32–40
Axonal and myelin-related injury biomarkers				
NFs (NF-L, NF-M, NF-H)	Structural proteins essential for neuronal cytoskeleton integrity.	– Released following axonal damage. – Phosphorylation of NF-H enhances structural stability, making it a reliable marker of axonal injury. – NF-L is more sensitive for detecting diffuse axonal injury.	– Elevated levels persist for an extended period post-TBI, indicating ongoing axonal damage. – NF-L correlates with CT lesions and long-term neurological outcomes, particularly in sports-related concussions. – NF-H is associated with white matter injury and predicts both chronic disability and mortality.	40–46
MBP	Major structural protein crucial for myelin sheath integrity.	– Holds myelin layers together, essential for proper nerve conduction. – Released 1-3 days post-injury, reflecting delayed injury response.	– Elevated MBP levels correlate with severe outcomes, especially in cases of intracranial hemorrhage. – Biomarker levels can remain high for up to two weeks, providing insight into ongoing myelin damage. – Useful for assessing long-term prognosis but less effective for immediate diagnosis.	29,47–52
Tau Protein	Microtubule-associated protein involved in stabilizing neuronal structure.	– Stabilizes microtubules in neurons; hyperphosphorylation leads to neurofibrillary tangles seen in neurodegenerative diseases. Released into CSF and blood post-TBI.	– Elevated CSF tau levels correlate with TBI severity and poor neurological outcomes. – Serum tau may not always align with CT findings but is valuable for predicting long-term clinical outcomes and the risk of chronic traumatic encephalopathy (CTE).	53–57
SBDPs	Products of spectrin proteolysis by calpain and caspase.	– Serve as markers of necrosis (calpain) and apoptosis (caspase); specific to the central nervous system. – SBDP 145, a 145 kDa fragment, is particularly noteworthy as a marker of necrotic cell death activation.	– Increase rapidly after TBI, reflecting the extent of neuronal damage. – SBDP levels correlate with injury severity, lesion size on imaging, and are linked to outcomes like post-concussion syndrome and long-term cognitive impairment.	29,58–64

Table 1. *(Continued)*

Biomarkers	Definition	Key features	Clinical Relevance	Ref.
Glial cell injury biomarkers				
S100B Protein	Calcium-binding protein primarily found in astrocytes, Schwann cells, and myeloid-derived cells.	– Plays a key role in intracellular calcium homeostasis and astrocyte function. Released into the bloodstream following astrocytic injury.	– Elevated levels correlate with TBI severity, poor outcomes, and increased intracranial pressure. – Widely used in early TBI management protocols in Scandinavia. However, its specificity is reduced due to possible extracranial sources of S100B, such as adipose tissue and muscles.	6,10,40, 65–68
GFAP	Intermediate filament protein specific to astrocytes.	– Supports the structural integrity and function of astrocytes. – Highly specific to brain tissue and not typically found in blood.	– Levels rise significantly post-TBI, especially in moderate to severe cases. – Useful for assessing TBI severity, guiding neuroimaging decisions, and predicting long-term cognitive and psychiatric outcomes. – Elevated GFAP is also a strong predictor of poor neurological recovery.	10,40, 69–71

NSE, Neuron-specifc enolase; mTBI, Mild Traumatic Brain Injury; UCH-L1, Ubiquitin C-terminal hydrolase-L1; NFs, Neurofilament proteins; MBP, Myelin basic protein; GFAP, Glial fibrillary acidic protein; S100B, S100B calcium binding protein B; SBDPs, α-II-spectrin breakdown products.

1β levels[82]. Animal model studies have shown that early attenuation of IL-1β-dependent inflammatory signaling can prevent capillary damage by promoting pericyte coverage in the thalamus, highlighting the complex role of IL-1β in TBI recovery[83]. Further research is needed to fully understand the role of IL-1β and other cytokines in TBI progression and long-term outcomes.

IL-6 levels in the blood are elevated after TBI, potentially reflecting injury severity, though its predictive value for long-term outcomes remains unclear[84]. A recent meta-analysis by Malik et al.[82] indicated that a majority of studies (65%) showed significantly elevated IL-6 levels in mTBI patients compared to healthy controls[82], though some studies showed reduced or no significant differences[85-90]. Elevated IL-2 and IL-6 levels in the acute phase suggest a role in the early inflammatory response[91]. Elevated IL-6 levels at 6 hours post-mTBI have also been associated with the duration of symptoms[92-94]. Other cytokines, including IL-8, IL-10, and TNF-α, are also produced in excess after TBI, but their correlation with injury severity and long-term outcomes requires further investigation[10,84]. High serum IL-8 levels have been associated with moderate and severe cerebral hypoperfusion in TBI patients[95]. A meta-analysis of IL-8 levels in mTBI found variable results, with some studies showing elevated levels, others showing reduced levels, and some reporting no significant differences[82,96-98]. Elevated levels of IL-1RA, IL-8, and IFN-γ have been observed in mTBI patients, particularly within 24 hours, though the limited number of studies precluded a comprehensive meta-analysis[82].

The rapid and dynamic nature of biofluid biomarkers following TBI presents a significant challenge in identifying reliable indicators of injury severity and prognosis. Adiponectin, a marker of inflammation, has been found elevated in the plasma of TBI patients and identified as an independent predictor of poor outcomes and mortality. Similarly, high-mobility group box 1 (HMGB1), a cytokine and marker of inflammation, has emerged as a significant predictor of one-year mortality in TBI patients. HMGB1 translocates from the nucleus to the cytoplasm in the early stages of injury, followed by uptake by phagocytic microglia, suggesting HMGB1 may serve as both a valuable biomarker and a potential therapeutic target for TBI patients[40].

Extracellular vesicles and non-coding RNAs in traumatic brain injury

Following a TBI, a complex cascade of secondary events unfolds, including excitotoxicity, free radical generation, and a neuroinflammatory response. These processes, which begin within minutes and can persist for months, contribute significantly to neuronal, glial, and vascular damage[99]. Secondary injuries, particularly neuroinflammation, are major determinants of TBI outcomes[100]. The initial injury triggers the release of damage-associated molecular patterns (DAMPs), activating immune responses and triggering the release of pro-inflammatory mediators. This, coupled with the activation of microglia and astrocytes and the infiltration of peripheral immune cells, intensifies the inflammatory response[101]. This pro-inflammatory environment is strongly linked to tissue damage and poor neurological outcomes[102].

Extracellular vesicles

Extracellular vesicles (EVs), secreted by a variety of cells, are emerging as vital mediators of cell-to-cell communication, particularly in the central nervous system (CNS). Studies highlight their significant impact on neuronal differentiation, synaptic formation, glial interactions, and the regulation of homeostatic signaling and immune responses[103-105]. In the context of TBI, EVs play a crucial role in neuroimmune interactions, regulating neuroinflammation through their diverse cargo, which includes DNA fragments, RNA, lipids, and proteins[106,107]. Both the primary and secondary injuries following TBI influence the number and characteristics of EVs. For example, brain endothelial cells release EVs rich in occludin during vascular remodeling in response to mechanical injury[108]. Similarly, oxidative stress and reactive oxygen species (ROS) stimulate the release of EVs that regulate inflammation and vascular calcification[109-111]. Additionally, microglia activated by lipopolysaccharide (LPS), ATP, and pro-inflammatory cytokines (IL-1β, TNF-α, IFN-γ) release EVs with a distinct cargo profile, underscoring their critical role in neuroinflammation[112-114].

TBI and subsequent neuroinflammation also trigger the release of astrocyte-derived EVs containing neurotoxic proteins and miRNAs, such as elevated levels of miR-21 in neuron-derived EVs. EVs are not only released locally but are also found in other biological fluids after TBI (ref.[106]). For instance, serum EV concentrations increase rapidly in TBI patients[115,116], and cerebrovenous blood exhibits higher EV levels than arterial blood, suggesting an increased release from the brain[117]. In rodent studies, EVs positive for glial fibrillary acidic protein (GFAP+) and neuron-specific enolase (NSE+) peak at 3 hours post-TBI (ref.[118]), with GFAP+ EVs decreasing at 6 hours while NSE+ EVs remain elevated[118].

In the CSF, EVs concentrations double following brain injury[119]. TBI also induces inflammatory changes in salivary-derived EVs, which could play a role in intercellular communication. The ability of EVs to cross the BBB and their presence in both CSF and peripheral blood make them promising biomarkers for TBI, drawing significant research interest[120]. EVs carry information from their parent cells, which can be used to identify specific disease signatures. For example, elevated levels of Tau, amyloid-beta (Ab) 42, and IL-10 have been found in the EVs of military personnel with mild TBI, suggesting a link to chronic postconcussive symptoms and neuroinflammation[86]. Increased levels of phosphorylated Tau (p-Tau), neurofilament light (NfL), IL-6, and TNF-α in CNS-enriched EVs of older veterans correlate with cognitive impairment and inflammatory processes[121]. The molecular composition of circulating EVs changes significantly in individuals with mild TBI. Specific microRNAs (miRNAs) associated with inflammation and CNS disorders, such as hsa-miR-139-5p and hsa-miR-18a-5p, show marked differences[122]. Additionally, TBI alters the protein composition of EVs in the CSF, with elevated levels of αII-spectrin

breakdown products (BDPs), GFAP, and synaptophysin detectable in CSF-derived EVs (ref.[119]).

Research indicates that flotillin-1, associated with neuroregeneration, is uniquely present in the CSF after TBI. Moreover, the downregulation of ADP-ribosylation factor 6 (Arf6) and the delayed upregulation of Ras-related protein Rab7a (Rab7a) in the CSF post-TBI are linked to poor outcomes[123]. TBI-induced changes in gene expression within salivary-derived EVs also suggest their potential as biomarkers for assessing TBI severity[124]. These findings underscore the significant changes in EVs and their molecular cargo in response to TBI, both in the CNS and peripheral circulation. The presence of altered EVs in biological fluids holds great promise as a diagnostic and assessment tool for TBI.

non-coding RNAs

Diagnosing and predicting outcomes for TBI is challenging due to the varied nature of injuries and individual patient differences. Traditional diagnostic methods often fall short in addressing this complexity. Advances in EVs proteomics have shown promise in cancer research, particularly through liquid biopsies, and similar potential exists for TBI diagnostics[36,125]. However, a standardized and reliable evaluation system for this application is still needed.

Extracellular non-coding RNAs (ncRNAs) are notably resistant to degradation, making them promising candidates for stable and specific disease biomarkers[126]. Correlating these biomarkers with clinical parameters can provide valuable insights into TBI and recovery, enhancing diagnostic accuracy, risk stratification, treatment evaluation, prognostic prediction, and the development of personalized treatment strategies[126,127]. Extracellular microRNAs (miRNAs) are particularly appealing as TBI biomarkers due to their stability and ease of detection. Harrison et al.[106] showed that miR-21, miR-146, miR-7a, and miR-7b were upregulated, while miR-212 was downregulated in the brains of TBI model mice. Building on this, Ko et al.[128] developed a diagnostic method based on miRNA expression profiles (miR-129-5p, miR-212-5p, miR-9-5p, miR-152-5p, miR-21, miR-374b-5p, miR-664-3p), achieving 99% accuracy in distinguishing TBI from controls. Further research by Ko et al.[129] highlighted substantial overlap between miRNA biomarkers in preclinical models and clinical samples, validating their utility. Puffer et al.[130] identified 11 differentially expressed miRNAs in the plasma of TBI patients, linking these miRNAs to pathways related to injury and development. Additionally, extracellular circular RNAs (circRNAs) have been implicated in TBI, with studies showing significant differential expression in brain cells post-injury, with 155 upregulated and 76 downregulated circRNAs[131]. A controlled cortical impact (CCI) model in mice identified 191 differentially expressed circRNAs in the cortex, associated with inflammation, cell death, and repair[132]. While extracellular long non-coding RNAs (lncRNAs) are recognized as promising diagnostic markers in neuro-oncology, their potential in TBI diagnosis is still being explored[133]. Studies have indicated significant changes in lncRNA expression following TBI. For instance, Zhong et al.[134] reported significant alterations in the expression of 823 lncRNAs in the mouse cortex after CCI, with 667 upregulated and 156 downregulated. Similarly, Wang et al.[135] found 271 differentially expressed lncRNAs in the hippocampus of TBI rats. Functional analyses revealed that these lncRNAs are significantly enriched in categories related to inflammation, transcription, apoptosis, and necrosis. These findings suggest that extracellularly enriched lncRNAs and circRNAs hold significant potential as diagnostic biomarkers for TBI. Further exploration into their diagnostic utility is warranted[136].

Among ncRNAs, miRNAs are particularly significant in TBI pathogenesis[137,138]. Numerous studies have highlighted significant changes in miRNA expression post-TBI. Table 2 provides a detailed summary of these alterations in miRNA expression patterns, their functional roles, and potential mechanisms in TBI pathophysiology. MiRNAs have gained increasing research interest as novel mediators of neuroinflammation in brain trauma contexts[139,140]. During the acute phase of TBI, neuroinflammation is triggered in the brain, exacerbating damage and leading to neurological deficits[141]. It is widely recognized that curbing neuroinflammation can improve TBI prognosis. Several miRNAs have demonstrated potential in reducing neuroinflammation and improving outcomes for TBI patients[142,143]. For example, miR-873a-5p, which is upregulated in the brain lesion areas of TBI patients, has been shown to reduce microglia-mediated neuroinflammation by inhibiting ERK and NF-κB phosphorylation. Treatment of a TBI mouse model with miR-873a-5p resulted in reduced brain damage and edema[144]. Another study demonstrated that increasing miR-23a expression suppressed the secretion of inflammatory factors such as IL-6, IL-1β, and TNF-α, in a TBI cell model. In a mouse model, elevated miR-23a expression reactivated the PTEN/AKT/mTOR signaling pathway, improving prognosis in the injured brain[145].

Further research has demonstrated that the miRNA let-7 family member, let-7c-5p, is downregulated in mice with TBI. Overexpression of miR-let-7c-5p has been shown to mitigate neuroinflammation, decrease microglia/macrophage activation, reduce brain edema, and improve neurological function[146]. Additionally, let-7c-5p mimic treatments have been found to inhibit the release of inflammatory mediators in primary microglia exposed to oxygen-glucose deprivation. Another study identified elevated levels of miR-142 and miR-155 in immune and glial cells following TBI, indicating their involvement in astrocyte activation and the promotion of neuroinflammation in both human and rat models[147]. In a different TBI mouse model, increased levels of miR-146a were observed in the brain and serum. Overexpression of miR-146a through mimics was shown to inhibit the JNK and NF-κB pathways, thereby reducing neuroinflammation[148]. Furthermore, miR-21, which has been previously reported to be upregulated following TBI, plays a complex role in TBI pathology[149]. MiR-21 is secreted from neurons near the injury site and contributes to neuroinflammation by activating microglia[150]. These findings highlight the

Table 2. Non-coding RNAs involved in traumatic brain injury.

Non-coding RNA	Functions and associated mechanisms in brain injury	Ref.
LncRNAs		
lncRNA MALAT1	– Modulates inflammation targets in hASC-derived exosomes. – Downregulated in TBI models; correlates with edema. – Overexpression reduces edema and inflammatory markers. – Exosomes with MALAT1 lessen cortical damage and activate MAPK. – Inhibition suppresses angiogenesis by affecting endothelial health. – Regulates angiogenesis via EZH2/NOTCH1. – Knockdown increases NR2B levels, causing damage under OGD/R. – Binds and inhibits miR-125b-5p, promoting neuroinflammation.	151–157
lncRNA Meg3	– Decreased in TBI patients; negatively correlates with cytokines. – Regulates microglial inflammation via miR-7a-5p/Nlrp3.	158, 159
lncRNA Gm4419	– Promotes astrocyte apoptosis during TBI. – Acts as a sponge for miR-466l, upregulating TNF-α.	160
lncRNA HOTAIR	– Involved in microglial activation and inflammation. – Regulates MYD88 ubiquitination.	161
lncRNA Neat1	– Aggravates motor/cognitive functions post-TBI. – Inhibits apoptosis/inflammation in TBI cortex. – Knockdown elevates NR2B levels, causing OGD/R damage.	156,162
lncRNA Snhg1	– Its inhibition increases apoptosis. – Reduces HIF-1α/VEGF-A by binding miR-338.	163
lncRNA NKILA	– Decreases proliferation and inhibits apoptosis. – Binds to miR-195 and upregulates NLRX1 levels.	164
lncRNA ZFAS1	– Its inhibition reduces inflammation, apoptosis; recovers function.	165
lncRNA KCNQ1OT1	– Its downregulation has neuroprotective effects including the damage of brain microvascular and neuron loss in TBI mice. – Modulates the miR-873-5p-TRAF6-p38/NF-κB axis.	166
lncRNA PRR34-AS1	– Its downregulation has neuroprotective effects including reducing brain microvascular damage and neuron loss. – Targets miR-498.	167
lncRNA 4933431K23Rik	– Regulates microglial-induced neuroinflammation. – Inhibits microglial activation by elevating Smad7 expression.	168
lncRNA GAS5	– Levels are related to injury severity and inflammation. – Contributes to neuronal apoptosis during TBI. – Modulates the miR-335/Rasa1 axis.	169, 170
lncRNA VLDLR-AS1	– Levels lower in rmTBI vs. controls. – Correlates with depression symptoms.	171
lncRNA H19	– Increased in perilesional tissue after TBI; reverts over time. – Its knockdown aids recovery, preserves neuronal integrity. – Facilitates anti-inflammatory microglial/macrophage phenotypes. – Promotes activation of the Nrf2/HO-1 axis.	172
lncRNA TUBB6	– Key role in neuroprotection via TUBB6/Nrf2 pathway.	173
CircRNAS		
circMETTL9	– Downregulation improves neurological deficits and apoptosis. – Activates SND1 in astrocytes.	174
circScmh1	– Exosomes reduce hippocampal nerve damage. – Promotes microglial M2 polarization.	175
circIgfbp2	– Its inhibition relieves mitochondrial dysfunction. – Modulates miR-370–3p/BACH1/HO-1 axis.	176
circPtpn14	– Important for brain protection by melatonin. – Controls 5-LOX expression involved in ferroptosis.	177
circLphn3	– Improves BBB permeability upon TBI. – Regulates tight junction protein expression after TBI.	178
circ0116449	– Methylation-related; reduces neuronal loss. – Modulates miR-142–3p-NR1D2 axis as a miRNA sponge.	179
circRNA_009194	– Improves outcomes in rats with TBI. – Regulates the voltage-gated sodium channel Nav1.3 in TBI.	180

Table 2. *(Continued)*

Non-coding RNA	Functions and associated mechanisms in brain injury	Ref.
circHtra1	– Promotes neuronal loss and immune deficiency. – Controls miR-3960/GRB10 axis.	181
circLrp1b	– Inhibition reduces inflammation and autophagy in TBI. – Regulates miR-27a-3p/Dram2 signaling pathway.	182
circRNA-chr8	– Plays a pro-inflammatory role in TBI. – Involved in sequestering mmu-let-7a-5p.	183
Hsa_circ_0018401	– Potential biomarker; binds miR-127-5p, correlates with TBI severity.	184
MiRNAs		
miR-212-5p	– Protects against neuron death from iron toxicity. – Negatively regulates Ptgs2, impacts ferroptosis.	185
miR-212, miR-132	– Its overexpression in BMEC decreases barrier properties. – Potential targets: Cldn1, Jam3, Tjap1.	186
miR-132	– Its overexpression improves repair and clinical symptoms post-TBI. – Accelerates neurogenesis and tissue repair. – Enhances neuroblast migration, reduces microglia accumulation.	187
miR-146a	– Improves TBI outcomes, downregulates inflammatory cytokines. – MiR-146a inhibits the JNK and NF-κB signaling pathways.	148
miR-155	– Inhibition decreases neuroinflammation, enhances recovery. – Regulates NADPH oxidase 2 in microglia/macrophages. – Substantial decrease in TBI model; increased BACH1 expression.	188,189
miR-429	– Inhibition reduces inflammation, brain damage. – Targets DUSP1, inhibits pro-inflammatory release.	190
miR-124-3p	– Microglial exosomes improve cognition, reduce degeneration. – Targets the Rela/ApoE signaling pathway. – Elevated in blood and plasma at 2 d post-TBI vs. controls. – Higher levels correlate with larger chronic lesion areas. – Exosomes with high miR-124-3p levels reduce apoptosis and ER stress. – Binds to IRE1α, reducing its expression and inhibiting ER stress. – Transferred from microglia-derived exosomes to injured neurons, providing neuroprotection.	191–195
miR-93, miR-191, miR-499	– Elevated in TBI patients; higher in severe cases. – Strong predictive power for trauma cases.	196
miR-21-3p	– Increased in BMVECs post-TBI is detrimental to BBB restoration. – Its downregulation may aid BBB recovery.	197
miR-21	– Upregulation improves outcomes, reduces microvascular injury. – Overexpression of miR-21 activates the axis of Ang-1/Tie-2.	198–200
miR-21, miR-92, miR-16	– High predictive power for trauma diagnosis. – Potential biomarkers for survival.	201
miR-21, miR-92a, miR-874	– Involved in protective effects of exercise post-TBI.	202
miR-21, miR-124a, miR-107	– Increased at various times post-injury. – Linked to inflammatory proteins; inverse relationship with miRNA levels.	203
miR-107	– Participates in GRN expression regulation.	204
miR-23a	– Its overexpression inhibits neuroinflammation, aids prognosis. – Reactivates PTEN/AKT/mTOR pathway inhibited by TBI.	145
miR-23b	– Its overexpression has neuroprotective impact post-TBI. – Targets ATG12 to inhibit autophagy.	205
miR-27a	– Overexpression protects brain, suppresses neuroinflammation. – Targets FoxO3a, inhibiting its expression.	206
miR-136-3p, miR-9-3p	– Elevated levels distinguish mTBI from naïve rats. – Plasma levels higher in sTBI patients.	207
miR-219a-5p	– Discriminates sTBI/mTBI patients, regulates apoptosis. – Inhibits CCNA2 and CACUL1, affecting apoptotic pathways.	208
miR-145-3p	– Maintains Th17/Treg balance, reduces inflammation via the miR-145-3p/NFATc2/NF-κB axis.	209
miR-193a	– Its inhibition suppresses the NLRP3 expression and brain injury and neuroinflammation post-TBI.	210

Table 2. *(Continued)*

Non-coding RNA	Functions and associated mechanisms in brain injury	Ref.
miR-34b	– Trauma-induced anxiety was reduced by miR-34b, which targets CRHR1 to decrease HPA axis hyperactivity.	211
miR-433	– miR-433 expression was lower in patients with tibial fracture and craniocerebral injury compared to controls. – miR-433 regulates SPP1 mRNA and protein by binding to its 3'-UTR.	212
miR-711	– miR-711 levels increased in the cortex post-TBI and in vitro, due to rapid transcription (pri-miR-711) rather than catabolism. – Increases correlated with downregulation of Akt, activating FoxO3, GSK3α/β, pro-apoptotic PUMA, Bim, and mitochondrial release of cytochrome c and AIF. – Administration of miR-711 inhibitor post-TBI increased Akt, reduced apoptosis, and decreased cortical lesion volume and neuronal loss.	213
miR-302	– Pulsatile shear stress suppressed miR-302; exogenous miR-302 inhibited ERK1/2 and connexin43 phosphorylation. – Elevated miR-302 improved cognitive function and reduced brain damage by decreasing edema and contusion volume.	214
miR let-7c-5p	– Its overexpression suppresses inflammatory factor release and microglial activation. – Inhibits caspase-3 expression.	146
miR-9-5p	– Contributes to neurological recovery, reduces microvascular damage and neuroinflammation. – Activates the Hedgehog pathway and inhibits the NF-κB/MMP-9 pathway.	215
miR-17-92 cluster	– Exosomes enriched with miR-17-92 reduce neuroinflammation and enhance angiogenesis and neurogenesis, improving TBI recovery.	216
miR-22	– Provides neuroprotection by reducing damage and apoptosis in neuronal cells post-TBI. – Regulates apoptosis factors (BCL2, p-AKT1, BAX) and the PTEN/AKT signaling pathway.	217
miR-31	– Overexpression inhibits neuronal cell apoptosis in TBI in vitro. – Regulates the HIF-1A/VEGFA axis to reduce neuronal cell death.	218
miR-141–3p	– Ursolic acid regulates miR-141–3p to reduce TBI-induced apoptosis, oxidative damage, and inflammation. – In TBI mice, ursolic acid activates the PI3K/AKT pathway via miR-141–3p regulation.	219
miR-223–3p	– Influences sex-specific neuroinflammation post-TBI and inhibits neurite elongation. – Targets Armcx1 and is negatively correlated with its expression.	220, 221
miR-330–5p	– Reduces inflammatory cytokines and restores motor function in TBI rats. – Promotes anti-inflammatory microglia polarization via Ehmt2-mediated CXCL14 transcription.	222
miR-15a/16-1	– Intranasal delivery of the antagomir mimicked the protective effects of genetic deletion, improving sensorimotor and cognitive outcomes, enhancing white/gray matter integrity, and reducing inflammation compared to control antagomir-treated mice post-TBI.	223
miR-9a-5p	– Poorly expressed in the brain tissue of rats with TBI. – ELAVL1 is a downstream target of miR-9a-5p, negatively regulating its expression. – Increased miR-9a-5p expression protects against brain tissue damage in TBI rats by targeting ELAVL1.	224
miR-9-5p	– Expression decreased in biperiden-treated patients compared to placebo group. – Regulates stress response genes related to axonogenesis and neuronal death, relevant to PTE and TBI. – Biperiden may alter miR-9-5p expression in serum EVs, potentially aiding TBI resolution.	225
miR-206, miR-549a-3p	– Serum exosomes show good predictive value as biomarkers of TBI. – Correlate well with BDNF, NSE, and S100β, indicating potential as biomarkers in TBI patients.	226
miR-148a-3p	– MiR-148a-3p was highly expressed in TBI. – Significantly improved neurological scores and reduced brain injury in a rat TBI model by promoting microglial M1 to M2 transition. – Alleviated TBI by inhibiting the NF-κB pathway.	227
miR-127-5p	– Downregulated in patients with TBI. – Negative correlation with miR-423-3p confirmed binding to hsa_circ_0018401 via dual luciferase assay. – hsa_circ_0018401 and miR-127-5p, alone or in combination, have clinical value for TBI diagnosis, stratification, and outcome prediction.	184

critical role of miRNAs as key regulators of neuroinflammation in TBI, emphasizing their potential as therapeutic targets for managing this complex condition.

FUTURE PROSPECTIVE AND RECOMMENDATIONS

To enhance the clinical utility of inflammatory markers in diagnosing mTBI, addressing the significant variability in current study designs, analyses, and reporting is crucial. Improving the quality of evidence for these markers will involve enrolling representative and diverse study cohorts. Large-scale, multicenter initiatives like the CENTER-TBI and TRACK-TBI studies present an excellent opportunity to achieve this goal. By including participants from varied populations, these studies can generate findings that are more broadly applicable to mTBI cases[228]. The substantial sample sizes provided by such multicenter studies allow for more accurate statistical analysis, accounting for various confounding factors such as age, gender, previous head injuries, and extent of extracranial damage. These methodological advancements will contribute to a more reliable understanding of how inflammatory markers can be used in mTBI diagnosis and treatment.

A key challenge is distinguishing neuroinflammation from systemic inflammation due to extracranial injuries. Several strategies are being explored to tackle this issue: (I) Statistical Corrections and Control Groups: Using statistical methods to adjust for extracranial injuries or including patients with orthopedic injuries alongside healthy controls can help isolate neuroinflammation[229,230]. (II) Cranial EVs: Analyzing inflammatory markers within cranially derived EVs may offer a direct measure of the cranial inflammatory response, potentially providing a clearer indication of neuroinflammation[130,231]. (III) MicroRNA Analysis: Assessing microRNAs as biochemical markers of inflammation could help identify signals specific to neuroinflammation[230,232]. (IV) Proteomic Techniques: Employing proteomics might uncover biomarkers uniquely associated with the neuroinflammatory response[233].

Looking ahead, there is a shift expected from traditional analytical methods, such as ELISA Immunoplex, and SIMOA, to Point-of-Care (POC) platforms that use electrochemical biosensors[234,235]. POC platforms offer the advantage of quickly identifying biomarker concentrations at the site of injury or in emergency settings without the need for extensive laboratory processing[236]. Recent developments show that POC tests combining UCH-L1 and GFAP can match the sensitivity of traditional lab-based methods. Given that some inflammatory markers rise rapidly after injury, integrating them into POC platforms could be beneficial for early mTBI assessment. However, solid evidence is needed before incorporating these markers into routine clinical practice.

Research involving EVs in TBI faces several hurdles, such as the need for standardized isolation protocols and dealing with the inherent heterogeneity of EVs[237]. This variability in size, shape, and content, along with the diverse origins of EVs, complicates the use of a single profiling approach[237]. Moreover, exosome toxicity adds another layer of complexity, highlighting the need for further research to develop safe and effective exosome-based treatments for TBI. Establishing standardized methods for EV isolation and analysis will be crucial for ensuring consistent and comparable results across studies[238]. The application of machine learning to analyze EV cargo data shows promise for developing predictive models for disease diagnosis and treatment. By integrating various omics data types, machine learning can identify patterns and relationships, leading to personalized treatment recommendations based on individual patient profiles[239,240].

Emerging research indicates that mTBI may elevate the risk of neurodegenerative diseases if proper recovery time is not allowed[241]. Such injuries are common among athletes and military personnel but are often underreported. Therefore, finding objective markers that go beyond traditional assessments – like symptom evaluations, cognitive tests, and balance assessments – is critical[242,243]. Exosomal biomarkers, acting as a "liquid biopsy," could provide valuable insights into brain-specific changes following Mtbi (ref.[244]). Further research on these biomarkers could illuminate the long-term effects of mTBI, including the potential development of conditions like Alzheimer's disease or chronic traumatic encephalopathy. Expanding testing protocols and further investigating exosomal biomarkers will be essential for improving long-term outcomes for individuals with mTBI (ref.[238]). Building a strong interdisciplinary research community will be key to advancing TBI management and prevention[238].

CONCLUSIONS

The diverse etiology, pathology, and clinical progression of TBI present substantial challenges for the use of traditional biomarkers in both clinical practice and research. Neuroimaging methods such as CT and MRI are effective for detecting major head injuries but fall short in identifying subtle neural damage or structural changes, and their high costs restrict their widespread application. Fluid biomarkers, although potentially useful for correlating with neuronal, axonal, or glial cell injuries, often suffer from low abundance and require highly sensitive assays, which can result in undetectable levels. EVs and non-coding RNAs, particularly miRNAs, offer promising alternatives. Elevated levels of these biomarkers in TBI patients compared to healthy individuals have been observed. Research indicates that EVs and miRNAs can provide high diagnostic accuracy for TBI, especially in cases with diffuse injuries, where increased levels of exosomal GFAP and neurofilament light chains are noted. Moreover, miRNA profiles in CSF and serum plasma show distinct variations following TBI, reflecting injury severity and aiding in both diagnosis and severity assessment. Despite the advantages of isolating exosomes and miRNAs over traditional fluid proteins, challenges remain due to the variability in miRNA expression among in-

dividuals, particularly those with altered consciousness. Identifying the most effective miRNAs and establishing reliable cutoff values for TBI diagnosis and prognosis continue to be complex issues that need to be addressed.

Search strategy and selection criteria

The search strategy for this review involved systematically querying electronic databases, including PubMed, Scopus, and Web of Science, for articles published up to August 1, 2024. Keywords such as "traumatic brain injury," "biomarkers," "extracellular vesicles," "non-coding RNAs," and "clinical outcomes" were used in various combinations. Selection criteria included peer-reviewed original research or review articles focusing on biomarker applications in TBI prognosis or diagnosis. Exclusion criteria encompassed studies with insufficient methodological details or non-human data. References were screened based on relevance, quality, and recency to ensure comprehensive coverage of the topic.

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REFERENCES

1. Greve MW, Zink BJ. Pathophysiology of traumatic brain injury. Mt Sinai J Med 2009;76:97-104.
2. Maas AI, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, Aries M, Bashford T, Bell MJ, Bodien YG. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. Lancet Neurol 2022;21:1004-60.
3. Guan B, Anderson DB, Chen L, Feng S, Zhou H. Global, regional and national burden of traumatic brain injury and spinal cord injury, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. BMJ Open 2023;13:e075049. doi: 10.1136/bmjopen-2023-075049
4. James SL, Theadom A, Ellenbogen RG, Bannick MS, Montjoy-Venning W, Lucchesi LR, Abbasi N, Abdulkader R, Abraha HN, Adsuar JC. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:56-87.
5. Wilson L, Stewart W, Dams-O'Connor K, Diaz-Arrastia R, Horton L, Menon DK, Polinder S. The chronic and evolving neurological consequences of traumatic brain injury. Lancet Neurol 2017;16:813-25.
6. Wang KK, Yang Z, Zhu T, Shi Y, Rubenstein R, Tyndall JA, Manley GT. An update on diagnostic and prognostic biomarkers for traumatic brain injury. Expert Rev Mol Diagn 2018;18:165-80.
7. Stein SC, Spettell C, Young G, Ross SE. Limitations of neurological assessment in mild head injury. Brain Inj 1993;7:425-30. doi: 10.3109/02699059309029685
8. Tong KA, Oyoyo UE, Holshouser BA, Ashwal S, Medina LS. Traumatic Brain Injury: Evidence-Based Neuroimaging. In: Medina LS, Sanelli PC, Jarvik JG, eds. Evidence-Based Neuroimaging Diagnosis and Treatment: Improving the Quality of Neuroimaging in Patient Care. Springer New York; 2013:357-84.
9. Behzadi F, Luy DD, Schaible PA, Zywiciel JF, Puccio AM, Germanwala AV. A systematic review and meta-analysis of major blood protein biomarkers that predict unfavorable outcomes in severe traumatic brain injury. Clin Neurol Neurosurg 2024;242:108312. doi: 10.1016/j.clineuro.2024.108312
10. Azar S, Hasan A, Younes R, Najdi F, Baki L, Ghazale H, Kobeissy FH, Zibara K, Mondello S. Biofluid proteomics and biomarkers in traumatic brain injury. Methods Mol Biol. 2017;1598:45-63. doi: 10.1007/978-1-4939-6952-4_3
11. McCrory P, Meeuwisse W, Dvorak J, Aubry M, Bailes J, Broglio S, Cantu RC, Cassidy D, Echemendia RJ, Castellani RJ. Consensus statement on concussion in sport – the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med 2017;51:838-47.
12. Røe C, Sveen U, Alvsåker K, Bautz-Holter E. Post-concussion symptoms after mild traumatic brain injury: influence of demographic factors and injury severity in a 1-year cohort study. Disabil Rehabil 2009;31:1235-43.
13. Williams WH, Potter S, Ryland H. Mild traumatic brain injury and postconcussion syndrome: a neuropsychological perspective. J Neurol Neurosurg Psychiatr 2010;81:1116-22.
14. Ahmed F, Plantman S, Cernak I, Agoston DV. The temporal pattern of changes in serum biomarker levels reveals complex and dynamically changing pathologies after exposure to a single low-intensity blast in mice. Front Neurol 2015;6:114.
15. Newcombe VF, Correia MM, Ledig C, Abate MG, Outtrim JG, Chatfield D, Geeraerts T, Manktelow AE, Garyfallidis E, Pickard JD. Dynamic changes in white matter abnormalities correlate with late improvement and deterioration following TBI: a diffusion tensor imaging study. Neurorehabil Neural Repair 2016;30(1):49-62.
16. Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. Nat Rev Neurosci 2013;14(2):128-42.
17. Gilmer LK, Roberts KN, Joy K, Sullivan PG, Scheff SW. Early mitochondrial dysfunction after cortical contusion injury. J Neurotrauma 2009;26:1271-80.
18. Arun P, Abu-Taleb R, Oguntayo S, Wang Y, Valiyaveettil M, Long JB, Nambiar MP. Acute mitochondrial dysfunction after blast exposure: potential role of mitochondrial glutamate oxaloacetate transaminase. J Neurotrauma 2013;30:1645-51.
19. Alluri H, Wiggins-Dohlvik K, Davis ML, Huang JH, Tharakan B. Blood–brain barrier dysfunction following traumatic brain injury. Metab Brain Dis 2015;30:1093-104.
20. Shlosberg D, Benifla M, Kaufer D, Friedman A. Blood–brain barrier breakdown as a therapeutic target in traumatic brain injury. Nat Rev Neurol 2010;6:393-403.
21. Bramlett HM, Dietrich WD. Pathophysiology of cerebral ischemia and brain trauma: similarities and differences. J Cereb Blood Flow Metab 2004;24(2):133-50.
22. Jeter CB, Hergenroeder GW, Ward III NH, Moore AN, Dash PK. Human mild traumatic brain injury decreases circulating branched-chain amino acids and their metabolite levels. J Neurotrauma 2013;30:671-9.
23. Nielson JL, Cooper SR, Yue JK, Sorani MD, Inoue T, Yuh EL, Mukherjee P, Petrossian TC, Paquette J, Lum PY. Uncovering precision phenotype-biomarker associations in traumatic brain injury using topological data analysis. PloS One 2017;12:e0169490.
24. Jha RM, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. Neuropharmacology 2019;145:230-46.
25. Gabbita SP, Scheff SW, Menard RM, Roberts K, Fugaccia I, Zemlan FP. Cleaved-tau: a biomarker of neuronal damage after traumatic brain injury. J Neurotrauma 2005;22(1):83-94.
26. Anderson J, Hampton D, Patani R, Pryce G, Crowther R, Reynolds R, Franklin R, Giovannoni G, Compston D, Baker D. Abnormally phosphorylated tau is associated with neuronal and axonal loss in experimental autoimmune encephalomyelitis and multiple sclerosis. Brain 2008;131(7):1736-48.
27. Bogoslovsky T, Wilson D, Chen Y, Hanlon D, Gill J, Jeromin A, Song L, Moore C, Gong Y, Kenney K. Increases of plasma levels of glial fibrillary acidic protein, tau, and amyloid β up to 90 days after traumatic brain injury. J Neurotrauma 2017;34(1):66-73.
28. Babkina AS, Lyubomudrov MA, Golubev MA, Pisarev MV, Golubev AM. Neuron-Specific Enolase-What Are We Measuring? Int J Mol Sci 2024;25(9):5040. doi: 10.3390/ijms25095040
29. Mehta T, Fayyaz M, Giler GE, Kaur H, Raikwar SP, Kempuraj D, Selvakumar GP, Ahmed ME, Thangavel R, Zaheer S. Current trends in biomarkers for traumatic brain injury. Open Access J Neurol Neurosurg 2020;12:86.
30. Cheng F, Yuan Q, Yang J, Wang W, Liu H. The prognostic value of serum neuron-specific enolase in traumatic brain injury: systematic review and meta-analysis. PloS One 2014;9:e106680.
31. Mercier E, Boutin A, Shemilt M, Lauzier F, Zarychanski R, Fergusson DA, Moore L, McIntyre LA, Archambault P, Légaré F. Predictive value of neuron-specific enolase for prognosis in patients with moder-

ate or severe traumatic brain injury: a systematic review and meta-analysis. Can Med Assoc J 2016;4(3):E371-E382.
32. Lorton F, Lagares A, de la Cruz J, Méjan O, Pavlov V, Sapin V, Poca MA, Lehner M, Biberthaler P, Chauviré-Drouard A, Gras-Le-Guen C, Scherdel P. Performance of glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) biomarkers in predicting CT scan results and neurological outcomes in children with traumatic brain injury (BRAINI-2 paediatric study): protocol of a European prospective multicentre study. BMJ Open 2024;14:e083531. doi:10.1136/bmjopen-2023-083531
33. Gong B, Leznik E. The role of ubiquitin C-terminal hydrolase L1 in neurodegenerative disorders. Drug News Perspect 2007;20:365-70.
34. Mondello S, Linnet A, Buki A, Robicsek S, Gabrielli A, Tepas J, Papa L, Brophy GM, Tortella F, Hayes RL. Clinical utility of serum levels of ubiquitin C-terminal hydrolase as a biomarker for severe traumatic brain injury. Neurosurgery 2012;70:666-75.
35. Li J, Yu C, Sun Y, Li Y. Serum ubiquitin C-terminal hydrolase L1 as a biomarker for traumatic brain injury: a systematic review and meta-analysis. Am J Emerg Med 2015;33:1191-6.
36. Mondello S, Thelin EP, Shaw G, Salzet M, Visalli C, Cizkova D, Kobeissy F, Buki A. Extracellular vesicles: pathogenetic, diagnostic and therapeutic value in traumatic brain injury. Expert Rev Proteom 2018;15(5):451-61.
37. Liu MC, Akinyi L, Scharf D, Mo J, Larner SF, Muller U, Oli MW, Zheng W, Kobeissy F, Papa L. Ubiquitin C-terminal hydrolase-L1 as a biomarker for ischemic and traumatic brain injury in rats. Eur J Neurosci 2010;31(4):722-32.
38. Papa L, Akinyi L, Liu MC, Pineda JA, Tepas III JJ, Oli MW, Zheng W, Robinson G, Robicsek SA, Gabrielli A. Ubiquitin C-terminal hydrolase is a novel biomarker in humans for severe traumatic brain injury. Crit Care Med 2010;38:138-44.
39. Mondello S, Muller U, Jeromin A, Streeter J, Hayes RL, Wang KK. Blood-based diagnostics of traumatic brain injuries. Expert Rev Mol Diagn 2011;11:65-78.
40. Ghaith HS, Nawar AA, Gabra MD, Abdelrahman ME, Nafady MH, Bahbah EI, Ebada MA, Ashraf GM, Negida A, Barreto GE. A literature review of traumatic brain injury biomarkers. Mol Neurobiol 2022;59:4141-58.
41. Trifilio E, Bottari S, McQuillan LE, Barton DJ, Lamb DG, Robertson C, Rubenstein R, Wang KK, Wagner AK, Williamson JB. Temporal Profile of Serum Neurofilament Light (NF-L) and Heavy (pNF-H) Level Associations With 6-Month Cognitive Performance in Patients With Moderate-Severe Traumatic Brain Injury. J Head Trauma Rehabil 2024;39(6):E470-E480. doi: 10.1097/HTR.0000000000000932
42. Park Y, KC N, Paneque A, Cole PD. Tau, Glial Fibrillary Acidic Protein, and Neurofilament Light Chain as Brain Protein Biomarkers in Cerebrospinal Fluid and Blood for Diagnosis of Neurobiological Diseases. Int J Mol Sci 2024;25:6295.
43. Tomar GS, Singh GP, Lahkar D, Sengar K, Nigam R, Mohan M, Anindya R. New biomarkers in brain trauma. Clinica Chimica Acta 2018;487:325-9.
44. Yuan A, Rao MV, Nixon RA. Neurofilaments and neurofilament proteins in health and disease. Cold Spring Harb Perspect Biol 2017;9(4):a018309.
45. Siedler DG, Chuah MI, Kirkcaldie MT, Vickers JC, King AE. Diffuse axonal injury in brain trauma: insights from alterations in neurofilaments. Front Cell Neurosci 2014;8:429.
46. Shahim P, Gren M, Liman V, Andreasson U, Norgren N, Tegner Y, Mattsson N, Andreasen N, Öst M, Zetterberg H. Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. Sci Rep 2016;6(1):36791.
47. Zhan H, Cheng L, Wang X, Jin H, Liu Y, Li H, Liu D, Zhang X, Zheng W, Hao H. Myelin basic protein and index for neuro-Behçet's disease. Clin Immunol 2023;250:109286.
48. Boggs JM. Myelin basic protein: a multifunctional protein. Cell Mol Life Sci 2006;63:1945-61. doi: 10.1007/s00018-006-6094-7
49. Kim HJ, Tsao JW, Stanfill AG. The current state of biomarkers of mild traumatic brain injury. JCI Insight 2018;3(1):e97105. doi: 10.1172/jci.insight.97105
50. Berger RP, Adelson PD, Pierce MC, Dulani T, Cassidy LD, Kochanek PM. Serum neuron-specific enolase, S100B, and myelin basic protein concentrations after inflicted and noninflicted traumatic brain injury in children. J Neurosurg 2005;103(1 Suppl):61-8. doi: 10.3171/ped.2005.103.1.0061
51. Yamazaki Y, Ohtaka H, Morii S, Kitahara T, Ohwada T, Yada K. Diagnostic significance of serum neuron-specific enolase and myelin basic protein assay in patients with acute head injury. Surg Neurol 1995;43(3):267-70; discussion 270-1. doi: 10.1007/978-4-431-68231-8_86
52. Thomas D, Palfreyman J, Ratcliffe J. Serum-myelin-basic-protein assay in diagnosis and prognosis of patients with head injury. Lancet 1978;311:113-15.
53. Lantero-Rodriguez J, Camporesi E, Montoliu-Gaya L, Gobom J, Piotrowska D, Olsson M, Burmann IM, Becker B, Brinkmalm A, Burmann BM. Tau protein profiling in tauopathies: a human brain study. Mol Neurodegener 2024;19(1):54.
54. Wang J, Li J, Han L, Guo S, Wang L, Xiong Z, Chen Z, Chen W, Liang J. Serum τ protein as a potential biomarker in the assessment of traumatic brain injury. Exp Ther Med 2016;11(3):1147-51.
55. Papa L, Ramia MM, Edwards D, Johnson BD, Slobounov SM. Systematic review of clinical studies examining biomarkers of brain injury in athletes after sports-related concussion. J Neurotrauma 2015;32:661-73.
56. Ost M, Nylen K, Csajbok L, Ohrfelt AO, Tullberg M, Wikkelso C, Nellgard P, Rosengren L, Blennow K, Nellgard B. Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury. Neurology 2006;67:1600-4.
57. Franz G, Beer R, Kampfl A, Engelhardt K, Schmutzhard E, Ulmer H, Deisenhammer F. Amyloid beta 1-42 and tau in cerebrospinal fluid after severe traumatic brain injury. Neurology 2003;60:1457-61.
58. Liu Y, Yao X, Lv X, Qian J. The role of spectrin breakdown products in patients with traumatic brain injury: a systematic review and meta-analysis. Neurol Sci 2023;44:1171-83.
59. Chen S, Shi Q, Zheng S, Luo L, Yuan S, Wang X, Cheng Z, Zhang W. Role of α-II-spectrin breakdown products in the prediction of the severity and clinical outcome of acute traumatic brain injury. Exp Ther Med 2016;11:2049-53.
60. McGinn MJ, Kelley BJ, Akinyi L, Oli MW, Liu MC, Hayes RL, Wang KK, Povlishock JT. Biochemical, structural, and biomarker evidence for calpain-mediated cytoskeletal change after diffuse brain injury uncomplicated by contusion. J Neuropathol Exp Neurol 2009;68:241-9.
61. Angileri F, Aguennouz MH, Giusa M, DE DIVITIIS O, Calisto A, Cardali SM, Conti A, LA TORRE D, Grasso G, Vita G. Detection of αII-Spectrin and Breakdown Products in Humans After Severe Traumatic Brain Injury. IRIS. 2005. Available from: https://iris.unime.it/handle/11570/1429795
62. Pineda JA, Lewis SB, Valadka AB, Papa L, Hannay HJ, Heaton SC, Demery JA, Liu MC, Aikman JM, Akle V. Clinical significance of α II-spectrin breakdown products in cerebrospinal fluid after severe traumatic brain injury. J Neurotrauma 2007;24:354-66.
63. Pike BR, Flint J, Dave JR, Lu X-CM, Wang KK, Tortella FC, Hayes RL. Accumulation of calpain and caspase-3 proteolytic fragments of brain-derived αII-spectrin in cerebral spinal fluid after middle cerebral artery occlusion in rats. J Cereb Blood Flow Metab 2004;24:98-106.
64. Ringger NC, O'steen B, Brabham J, Silver X, Pineda J, Wang K, Hayes R, Papa L. A novel marker for traumatic brain injury: CSF αII-spectrin breakdown product levels. J Neurotrauma 2004;21:1443-56.
65. Zarei H, Roshdi Dizaji S, Toloui A, Yousefifard M, Esmaeili A. Diagnostic and Prognostic Values of S100B versus Neuron Specific Enolase for Traumatic Brain Injury; a Systematic Review and Meta-analysis. Arch Acad Emerg Med 2024;12:e29. doi: 10.22037/aaem.v12i1.2222
66. Kleindienst A, Schmidt C, Parsch H, Emtmann I, Xu Y, Buchfelder M. The passage of S100B from brain to blood is not specifically related to the blood-brain barrier integrity. Cardiovasc Psychiatry Neurol 2010;2010:801295.
67. Pfortmueller CA, Drexel C, Krähenmann-Müller S, Leichtle AB, Fiedler GM, Lindner G, Exadaktylos AK. S-100 B concentrations are a predictor of decreased survival in patients with major trauma, independently of head injury. PLoS One 2016;11:e0152822.
68. Undén J, Ingebrigtsen T, Romner B, Committee SN. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med 2013;11:1-14.
69. Trung Nguyen K, Dinh Le T, Dang Le M, Viet Tran T, Van Pham C, Van Dang B, Tien Nguyen S, Chi Nguyen T, Quang Nguyen H, The Vu A. Changes in the levels of serum glial fibrillary acidic protein and the correlation with outcomes in severe traumatic brain injury patients. SAGE Open Med 2024;12:20503121241260006.

70. Davidoff MS, Middendorff R, Köfüncü E, Müller D, Ježek D, Holstein A-F. Leydig cells of the human testis possess astrocyte and oligodendrocyte marker molecules. Acta Histochem 2002;104:39-49.
71. Zhang Z, Zoltewicz JS, Mondello S, Newsom KJ, Yang Z, Yang B, Kobeissy F, Guingab J, Glushakova O, Robicsek S. Human traumatic brain injury induces autoantibody response against glial fibrillary acidic protein and its breakdown products. PloS One 2014;9:e92698.
72. Yue JK, Kobeissy FH, Jain S, Sun X, Phelps RR, Korley FK, Gardner RC, Ferguson AR, Huie JR, Schneider AL. Neuroinflammatory biomarkers for traumatic brain injury diagnosis and prognosis: A TRACK-TBI pilot study. Neurotrauma Rep 2023;4:171-83.
73. Tsitsipanis C, Miliaraki M, Paflioti E, Lazarioti S, Moustakis N, Ntotsikas K, Theofanopoulos A, Ilia S, Vakis A, Simos P. Inflammation biomarkers IL-6 and IL-10 may improve the diagnostic and prognostic accuracy of currently authorized traumatic brain injury tools. Experimental and Ther Med 2023;26:1-14.
74. Rodney T, Osier N, Gill J. Pro-and anti-inflammatory biomarkers and traumatic brain injury outcomes: a review. Cytokine 2018;110:248-56.
75. Kattan D, Barsa C, Mekhijian S, Shakkour Z, Jammoul M, Doumit M, Zabala MCP, Darwiche N, Eid AH, Mechref Y. Inflammasomes as biomarkers and therapeutic targets in traumatic brain injury and related-neurodegenerative diseases: A comprehensive overview. Neurosci Biobehav Rev 2023;144:104969.
76. Postolache TT, Wadhawan A, Can A, Lowry CA, Woodbury M, Makkar H, Hoisington AJ, Scott AJ, Potocki E, Benros ME. Inflammation in traumatic brain injury. J Alzheimers Dis 2020;74:1-28.
77. Hanscom M, Loane DJ, Aubretch T, Leser J, Molesworth K, Hedgekar N, Ritzel RM, Abulwerdi G, Shea-Donohue T, Faden AI. Acute colitis during chronic experimental traumatic brain injury in mice induces dysautonomia and persistent extraintestinal, systemic, and CNS inflammation with exacerbated neurological deficits. J Neuroinflamm 2021;18:1-31.
78. Zhang J-M, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007;45:27-37.
79. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. Signal transduction and targeted therapy. Signal Transduct Target Ther 2023;8:267.
80. Ruchika F, Shah S, Neupane D, Vijay R, Mehkri Y, Lucke-Wold B. Understanding the Molecular Progression of Chronic Traumatic Encephalopathy in Traumatic Brain Injury, Aging and Neurodegenerative Disease. Int J Mol Sci 2023;24(3):1847. doi: 10.3390/ijms24031847
81. Taşçı A, Okay Ö, Gezici AR, Ergün R, Ergüngör F. Prognostic value of interleukin-1 beta levels after acute brain injury. Neurol Res 2003;25:871-4.
82. Malik S, Alnaji O, Malik M, Gambale T, Farrokhyar F, Rathbone MP. Inflammatory cytokines associated with mild traumatic brain injury and clinical outcomes: a systematic review and meta-analysis. Front Neurol 2023;14:1123407.
83. Özen I, Clausen F, Flygt J, Marklund N, Paul G. Neutralization of Interleukin 1-beta is associated with preservation of thalamic capillaries after experimental traumatic brain injury. Front Neurol 2024;15:1378203. doi: 10.3389/fneur.2024.1378203
84. Woodcock T, Morganti-Kossmann MC. The role of markers of inflammation in traumatic brain injury. Front Neurol 2013;4:18. doi: 10.3389/fneur.2013.00018
85. Brett BL, Savitz J, Nitta M, Espana L, Teague TK, Nelson LD, McCrea MA, Meier TB. Systemic inflammation moderates the association of prior concussion with hippocampal volume and episodic memory in high school and collegiate athletes. Brain Behav Immun 2020;89:380-8.
86. Gill J, Mustapic M, Diaz-Arrastia R, Lange R, Gulyani S, Diehl T, Motamedi V, Osier N, Stern RA, Kapogiannis D. Higher exosomal tau, amyloid-beta 42 and IL-10 are associated with mild TBIs and chronic symptoms in military personnel. Brain Inj 2018;32:1359-66.
87. Guedes VA, Kenney K, Shahim P, Qu B-X, Lai C, Devoto C, Walker WC, Nolen T, Diaz-Arrastia R, Gill JM. Exosomal neurofilament light: A prognostic biomarker for remote symptoms after mild traumatic brain injury? Neurology 2020;94:e2412-e2423.
88. Di Battista AP, Rhind SG, Richards D, Hutchison MG. An investigation of plasma interleukin-6 in sport-related concussion. PLoS One 2020;15:e0232053.
89. Powell JR, Boltz AJ, DeCicco JP, Chandran A, DeLellis SM, Healy ML, Kane SF, Lynch JH, Means GE, Hackney AC. Neuroinflammatory biomarkers associated with mild traumatic brain injury history in special operations forces combat soldiers. J Head Trauma Rehabil 2020;35(5):300-7.
90. Rusiecki J, Levin LI, Wang L, Byrne C, Krishnamurthy J, Chen L, Galdzicki Z, French LM. Blast traumatic brain injury and serum inflammatory cytokines: a repeated measures case-control study among US military service members. J Neuroinflamm 2020;17:1-12.
91. Vedantam A, Brennan J, Levin HS, McCarthy JJ, Dash PK, Redell JB, Yamal J-M, Robertson CS. Early versus late profiles of inflammatory cytokines after mild traumatic brain injury and their association with neuropsychological outcomes. J Neurotrauma 2021;38(1):53-62.
92. Meier TB, Huber DL, Bohorquez-Montoya L, Nitta ME, Savitz J, Teague TK, Bazarian JJ, Hayes RL, Nelson LD, McCrea MA. A prospective study of acute blood-based biomarkers for sport-related concussion. Ann Neurol 2020;87(6):907-20.
93. Nitta ME, Savitz J, Nelson LD, Teague TK, Hoelzle JB, McCrea MA, Meier TB. Acute elevation of serum inflammatory markers predicts symptom recovery after concussion. Neurology 2019;93:e497-e507.
94. Meier TB, Guedes VA, Smith EG, Sass D, Mithani S, Vorn R, Savitz J, Teague TK, McCrea MA, Gill JM. Extracellular vesicle-associated cytokines in sport-related concussion. Brain Behav Immun 2022;100:83-7.
95. Stein DM, Lindell AL, Murdock KR, Kufera JA, Menaker J, Bochicchio GV, Aarabi B, Scalea TM. Use of serum biomarkers to predict cerebral hypoxia after severe traumatic brain injury. J Neurotrauma 2012;29:1140-9.
96. Thompson HJ, Martha SR, Wang J, Becker KJ. Impact of age on plasma inflammatory biomarkers in the 6 months following mild traumatic brain injury. J Head Trauma Rehabil 2020;35:324-31.
97. Chaban V, Clarke GJ, Skandsen T, Islam R, Einarsen CE, Vik A, Damås JK, Mollnes TE, Håberg AK, Pischke SE. Systemic inflammation persists the first year after mild traumatic brain injury: results from the prospective trondheim mild traumatic brain injury study. J Neurotrauma 2020;37:2120-30.
98. Tylicka M, Matuszczak E, Hermanowicz A, Dębek W, Karpińska M, Kamińska J, Koper-Lenkiewicz OM. BDNF and IL-8, but not UCHL-1 and IL-11, are markers of brain injury in children caused by mild head trauma. Brain Sci 2020;10:665.
99. Liu X, Zhang L, Cao Y, Jia H, Li X, Li F, Zhang S, Zhang J. Neuroinflammation of traumatic brain injury: Roles of extracellular vesicles. Front Immunol 2023;13:1088827.
100. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, Jane JA, Marmarou A, Foulkes MA. The role of secondary brain injury in determining outcome from severe head injury. 50 Landmark Papers every Trauma Surgeon Should Know. J Trauma 1993;34(2):216-22. doi: 10.1097/00005373-199302000-00006
101. Jassam YN, Izzy S, Whalen M, McGavern DB, El Khoury J. Neuroimmunology of traumatic brain injury: time for a paradigm shift. Neuron 2017;95:1246-65.
102. Yates AG, Anthony DC, Ruitenberg MJ, Couch Y. Systemic immune response to traumatic CNS injuries–are extracellular vesicles the missing link? Front Immunol 2019;10:2723.
103. Filannino FM, Panaro MA, Benameur T, Pizzolorusso I, Porro C. Extracellular Vesicles in the Central Nervous System: A Novel Mechanism of Neuronal Cell Communication. Int J Mol Sci 2024;25:1629.
104. Antoniou A, Auderset L, Kaurani L, Sebastian E, Zeng Y, Allahham M, Cases-Cunillera S, Schoch S, Gründemann J, Fischer A. Neuronal extracellular vesicles and associated microRNAs induce circuit connectivity downstream BDNF. Cell Rep 2023;42(2):112063. doi: 10.1016/j.celrep.2023.112063
105. Cabrera-Pastor A. Extracellular Vesicles as Mediators of Neuroinflammation in Intercellular and Inter-Organ Crosstalk. Int J Mol Sci 2024;25:7041.
106. Harrison EB, Hochfelder CG, Lamberty BG, Meays BM, Morsey BM, Kelso ML, Fox HS, Yelamanchili SV. Traumatic brain injury increases levels of miR-21 in extracellular vesicles: implications for neuroinflammation. FEBS Open Bio 2016;6:835-46.
107. Ruan J, Miao X, Schlüter D, Lin L, Wang X. Extracellular vesicles in neuroinflammation: Pathogenesis, diagnosis, and therapy. Mol Ther 2021;29:1946-57.
108. Andrews AM, Lutton EM, Merkel SF, Razmpour R, Ramirez SH. Mechanical injury induces brain endothelial-derived microvesicle

release: implications for cerebral vascular injury during traumatic brain injury. Front Cell Neurosci 2016;10:43.
109. Furmanik M, Chatrou M, van Gorp R, Akbulut A, Willems B, Schmidt H, van Eys G, Bochaton-Piallat M-L, Proudfoot D, Biessen E. Reactive oxygen-forming Nox5 links vascular smooth muscle cell phenotypic switching and extracellular vesicle-mediated vascular calcification. Circ Res 2020;127:911-27.
110. Li G, Huang D, Li N, Ritter JK, Li PL. Regulation of TRPML1 channel activity and inflammatory exosome release by endogenously produced reactive oxygen species in mouse podocytes. Redox Biol 2021;43:102013.
111. Collett GP, Redman CW, Sargent IL, Vatish M. Endoplasmic reticulum stress stimulates the release of extracellular vesicles carrying danger-associated molecular pattern (DAMP) molecules. Oncotarget 2018;9(6):6707.
112. Yang Y, Boza-Serrano A, Dunning CJ, Clausen BH, Lambertsen KL, Deierborg T. Inflammation leads to distinct populations of extracellular vesicles from microglia. J Neuroinflamma 2018;15:1-19.
113. Lombardi M, Gabrielli M, Adinolfi E, Verderio C. Role of ATP in extracellular vesicle biogenesis and dynamics. Front Pharmacol 2021;12:654023.
114. Holm MM, Kaiser J, Schwab ME. Extracellular vesicles: multimodal envoys in neural maintenance and repair. Trend Neurosci 2018;41(6):360-72.
115. Hazelton I, Yates A, Dale A, Roodselaar J, Akbar N, Ruitenberg MJ, Anthony DC, Couch Y. Exacerbation of acute traumatic brain injury by circulating extracellular vesicles. J Neurotrauma 2018;35:639-51.
116. Kerr NA, de Rivero Vaccari JP, Umland O, Bullock MR, Conner GE, Dietrich WD, Keane RW. Human lung cell pyroptosis following traumatic brain injury. Cells 2019;8(1):69.
117. Nekludov M, Mobarrez F, Gryth D, Bellander B-M, Wallen H. Formation of microparticles in the injured brain of patients with severe isolated traumatic brain injury. J Neurotrauma 2014;31:1927-33.
118. Tian Y, Salsbery B, Wang M, Yuan H, Yang J, Zhao Z, Wu X, Zhang Y, Konkle BA, Thiagarajan P. Brain-derived microparticles induce systemic coagulation in a murine model of traumatic brain injury. Blood 2015;125:2151-9.
119. Manek R, Moghieb A, Yang Z, Kumar D, Kobessiy F, Sarkis GA, Raghavan V, Wang KK. Protein biomarkers and neuroproteomics characterization of microvesicles/exosomes from human cerebrospinal fluid following traumatic brain injury. Mol Neurobiol 2018;55:6112-28.
120. Beard K, Meaney DF, Issadore D. Clinical applications of extracellular vesicles in the diagnosis and treatment of traumatic brain injury. J Neurotrauma 2020;37:2045-56.
121. Peltz CB, Kenney K, Gill J, Diaz-Arrastia R, Gardner RC, Yaffe K. Blood biomarkers of traumatic brain injury and cognitive impairment in older veterans. Neurology 2020;95(9):e1126-e1133.
122. Devoto C, Lai C, Qu B-X, Guedes VA, Leete J, Wilde E, Walker WC, Diaz-Arrastia R, Kenney K, Gill J. Exosomal microRNAs in military personnel with mild traumatic brain injury: preliminary results from the chronic effects of neurotrauma consortium biomarker discovery project. J Neurotrauma 2020;37:2482-92.
123. Kuharić J, Grabušić K, Tokmadžić VS, Štifter S, Tulić K, Shevchuk O, Lučin P, Šustić A. Severe traumatic brain injury induces early changes in the physical properties and protein composition of intracranial extracellular vesicles. J Neurotrauma 2019;36:190-200.
124. Cheng Y, Pereira M, Raukar NP, Reagan JL, Quesenberry M, Goldberg L, Borgovan T, LaFrance Jr WC, Dooner M, Deregibus M. Inflammation-related gene expression profiles of salivary extracellular vesicles in patients with head trauma. Neural Regen Res 2020;15:676-81.
125. Beylerli O, Tamrazov R, Gareev I, Ilyasova T, Shumadalova A, Bai Y, Yang B. Role of exosomal ncRNAs in traumatic brain injury. Noncoding RNA Res 2023;8:686-92.
126. Taylor DD, Gercel-Taylor C. Exosome platform for diagnosis and monitoring of traumatic brain injury. Philos Trans R Soc B Biol Sci 2014;369:20130503.
127. Goetzl L, Merabova N, Darbinian N, Martirosyan D, Poletto E, Fugarolas K, Menkiti O. Diagnostic potential of neural exosome cargo as biomarkers for acute brain injury. Ann Clin Transl Neurol 2018;5:4-10.
128. Ko J, Hemphill M, Yang Z, Sewell E, Na Y, Sandsmark D, Haber M, Fisher S, Torre E, Svane KC. Diagnosis of traumatic brain injury using miRNA signatures in nanomagnetically isolated brain-derived extracellular vesicles. Lab on a Chip 2018;18:3617-30.
129. Ko J, Hemphill M, Yang Z, Beard K, Sewell E, Shallcross J, Schweizer M, Sandsmark DK, Diaz-Arrastia R, Kim J. Multi-dimensional mapping of brain-derived extracellular vesicle microRNA biomarker for traumatic brain injury diagnostics. J Neurotrauma 2020;37:2424-34.
130. Puffer RC, Garcia LMC, Himes BT, Jung MY, Meyer FB, Okonkwo DO, Parney IF. Plasma extracellular vesicles as a source of biomarkers in traumatic brain injury. J Neurosurg 2020;134:1921-8.
131. Zhao RT, Zhou J, Dong XL, Bi CW, Jiang RC, Dong JF, Tian Y, Yuan HJ, Zhang JN. Circular Ribonucleic Acid Expression Alteration in Exosomes from the Brain Extracellular Space after Traumatic Brain Injury in Mice. J Neurotrauma 2018;35(17):2056-66. doi: 10.1089/neu.2017.5502
132. Jiang YJ, Cao SQ, Gao LB, Wang YY, Zhou B, Hu X, Pu Y, Li ZL, Wang Q, Xiao X, Zhao L, Wang S, Liang WB, Zhang L. Circular Ribonucleic Acid Expression Profile in Mouse Cortex after Traumatic Brain Injury. J Neurotrauma 2019;36(7):1018-28. doi: 10.1089/neu.2018.5647
133. Fan Q, Yang L, Zhang X, Peng X, Wei S, Su D, Zhai Z, Hua X, Li H. The emerging role of exosome-derived non-coding RNAs in cancer biology. Cancer Lett 2018;414:107-15.
134. Zhong J, Jiang L, Cheng C, Huang Z, Zhang H, Liu H, He J, Cao F, Peng J, Jiang Y. Altered expression of long non-coding RNA and mRNA in mouse cortex after traumatic brain injury. Brain Res 2016;1646:589-600.
135. Wang CF, Zhao CC, Weng WJ, Lei J, Lin Y, Mao Q, Gao GY, Feng JF, Jiang JY. Alteration in Long Non-Coding RNA Expression after Traumatic Brain Injury in Rats. J Neurotrauma 2017;34(13):2100-8. doi: 10.1089/neu.2016.4642
136. Yang H, Fu H, Xu W, Zhang X. Exosomal non-coding RNAs: a promising cancer biomarker. Clin Chem Lab Med 2016;54(12):1871-9.
137. Sun P, Liu DZ, Jickling GC, Sharp FR, Yin KJ. MicroRNA-based therapeutics in central nervous system injuries. J Cereb Blood Flow Metab 2018;38:1125-48.
138. Sun P, Hamblin MH, Yin K-J. Non-coding RNAs in the regulation of blood–brain barrier functions in central nervous system disorders. Fluids Barriers CNS 2022;19:27.
139. Gaudet AD, Fonken LK, Watkins LR, Nelson RJ, Popovich PG. MicroRNAs: roles in regulating neuroinflammation. Neuroscientist 2018;24:221-45.
140. Zhang J, Li A, Gu R, Tong Y, Cheng J. Role and regulatory mechanism of microRNA mediated neuroinflammation in neuronal system diseases. Front Immunol 2023;14:1238930.
141. Chen X, Zhang KL, Yang SY, Dong JF, Zhang JN. Glucocorticoids aggravate retrograde memory deficiency associated with traumatic brain injury in rats. J Neurotrauma 2009;26:253-60.
142. Brogan RJ, Kontojannis V, Garara B, Marcus HJ, Wilson MH. Near-infrared spectroscopy (NIRS) to detect traumatic intracranial haematoma: A systematic review and meta-analysis. Brain Inj 2017;31:581-8. doi: 10.1080/02699052.2017.1287956
143. Wei HL, Ma SQ, Li CX. Deficiency of unc-51 like kinase 1 (Ulk1) protects against mice traumatic brain injury (TBI) by suppression of p38 and JNK pathway. Biochem Biophys Res Commun 2018;503:467-73. doi: 10.1016/j.bbrc.2018.04.154
144. Long X, Yao X, Jiang Q, Yang Y, He X, Tian W, Zhao K, Zhang H. Astrocyte-derived exosomes enriched with miR-873a-5p inhibit neuroinflammation via microglia phenotype modulation after traumatic brain injury. J Neuroinflammation 2020;17(1):89. doi: 10.1186/s12974-020-01761-0
145. Li Z, Xu R, Zhu X, Li Y, Wang Y, Xu W. MicroRNA-23a-3p improves traumatic brain injury through modulating the neurological apoptosis and inflammation response in mice. Cell Cycle 2020;19:24-38. doi: 10.1080/15384101.2019.1691763
146. Lv J, Zeng Y, Qian Y, Dong J, Zhang Z, Zhang J. MicroRNA let-7c-5p improves neurological outcomes in a murine model of traumatic brain injury by suppressing neuroinflammation and regulating microglial activation. Brain Res 2018;1685:91-104. doi: 10.1016/j.brainres.2018.01.032
147. Korotkov A, Puhakka N, Gupta SD, Vuokila N, Broekaart DWM, Anink JJ, Heiskanen M, Karttunen J, van Scheppingen J, Huitinga I, Mills JD, van Vliet EA, Pitkänen A, Aronica E. Increased expression of miR142 and miR155 in glial and immune cells after traumatic brain injury may contribute to neuroinflammation via astrocyte activation. Brain Pathol 2020;30:897-912. doi: 10.1111/bpa.12865

148. Zhang L, Zhao L, Zhu W, Ding Y, Chen H, Chi N. miR-146a Mimics Ameliorates Traumatic Brain Injury Involving JNK and NF-κB Signaling Pathway. Neuromolecular Med 2020;22:484-92. doi: 10.1007/s12017-020-08599-y
149. Li S, Qiu N, Ni A, Hamblin MH, Yin KJ. Role of regulatory non-coding RNAs in traumatic brain injury. Neurochem Int 2024;172:105643. doi: 10.1016/j.neuint.2023.105643
150. Harrison EB, Hochfelder CG, Lamberty BG, Meays BM, Morsey BM, Kelso ML, Fox HS, Yelamanchili SV. Traumatic brain injury increases levels of miR-21 in extracellular vesicles: implications for neuroinflammation. FEBS Open Bio 2016;6:835-46. doi: 10.1002/2211-5463.12092
151. Patel NA, Moss LD, Lee JY, Tajiri N, Acosta S, Hudson C, Parag S, Cooper DR, Borlongan CV, Bickford PC. Long noncoding RNA MALAT1 in exosomes drives regenerative function and modulates inflammation-linked networks following traumatic brain injury. J Neuroinflammation 2018;15:204. doi: 10.1186/s12974-018-1240-3
152. Zhang Y, Wang J, Zhang Y, Wei J, Wu R, Cai H. Overexpression of long noncoding RNA Malat1 ameliorates traumatic brain injury induced brain edema by inhibiting AQP4 and the NF-κB/IL-6 pathway. J Cell Biochem 2019;120:17584-92. doi: 10.1002/jcb.29025
153. Moss LD, Sode D, Patel R, Lui A, Hudson C, Patel NA, Bickford PC. Intranasal delivery of exosomes from human adipose derived stem cells at forty-eight hours post injury reduces motor and cognitive impairments following traumatic brain injury. Neurochem Int 2021;150:105173. doi: 10.1016/j.neuint.2021.105173
154. Liu H, Wei Z, Sun X, Wang Z. MALAT1 improves functional recovery after traumatic brain injury through promoting angiogenesis in experimental mice. Brain Res 2022;1775:147731. doi: 10.1016/j.brainres.2021.147731
155. Wu N, Cheng CJ, Zhong JJ, He JC, Zhang ZS, Wang ZG, Sun XC, Liu H. Essential role of MALAT1 in reducing traumatic brain injury. Neural Regen Res 2022;17(8):1776-84. doi: 10.4103/1673-5374.332156
156. Wang L, Fu G, Han R, Fan P, Yang J, Gong K, Zhao Z, Zhang C, Sun K, Shao G. MALAT1 and NEAT1 Are Neuroprotective During Hypoxic Preconditioning in the Mouse Hippocampus Possibly by Regulation of NR2B. High Alt Med Biol 2024 May 29. doi: 10.1089/ham.2023.0135 Epub ahead of print.
157. Li Y, Fan H, Han X, Sun J, Ni M, Hou X, Fang F, Zhang W, Ma P. Long Non-Coding RNA MALAT1 Protects Against Spinal Cord Injury via Suppressing microRNA-125b-5p Mediated Microglial M1 Polarization, Neuroinflammation, and Neural Apoptosis. Mol Neurobiol 2024;61:2136-50. doi: 10.1007/s12035-023-03664-6
158. Shao HF, Li ZZ, Zheng XF, Wang HJ, Wang YG, Ma ZL, Liu ZB, Han QY. Research on the correlation of changes in plasma lncRNA MEG3 with change in inflammatory factors and prognosis in patients with traumatic brain injury. Eur Rev Med Pharmacol Sci 2019;23:4341-7. doi: 10.26355/eurrev_201905_17940
159. Meng J, Ding T, Chen Y, Long T, Xu Q, Lian W, Liu W. LncRNA-Meg3 promotes Nlrp3-mediated microglial inflammation by targeting miR-7a-5p. Int Immunopharmacol 2021;90:107141. doi: 10.1016/j.intimp.2020.107141
160. Yu Y, Cao F, Ran Q, Wang F. Long non-coding RNA Gm4419 promotes trauma-induced astrocyte apoptosis by targeting tumor necrosis factor α. Biochem Biophys Res Commun 2017;491:478-85. doi: 10.1016/j.bbrc.2017.07.021
161. Cheng S, Zhang Y, Chen S, Zhou Y. LncRNA HOTAIR Participates in Microglia Activation and Inflammatory Factor Release by Regulating the Ubiquitination of MYD88 in Traumatic Brain Injury. J Mol Neurosci 2021;71:169-77. doi: 10.1007/s12031-020-01623-7
162. Zhong J, Jiang L, Huang Z, Zhang H, Cheng C, Liu H, He J, Wu J, Darwazeh R, Wu Y, Sun X. The long non-coding RNA Neat1 is an important mediator of the therapeutic effect of bexarotene on traumatic brain injury in mice. Brain Behav Immun 2017;65:183-94. doi: 10.1016/j.bbi.2017.05.001
163. Yang X, Zi XH. LncRNA SNHG1 alleviates OGD induced injury in BMEC via miR-338/HIF-1α axis. Brain Res 2019;1714:174-81. doi: 10.1016/j.brainres.2018.11.003
164. He B, Chen W, Zeng J, Tong W, Zheng P. Long noncoding RNA NKILA transferred by astrocyte-derived extracellular vesicles protects against neuronal injury by upregulating NLRX1 through binding to mir-195 in traumatic brain injury. Aging 2021;13(6):8127-45. doi: 10.18632/aging.202618
165. Feng J, Zhou Z, Feng R, Zeng C, Wei M, Hong T. Silencing long noncoding RNA zinc finger antisense 1 restricts secondary cerebral edema and neuron injuries after traumatic brain injury. Neurosci Lett 2021;756:135958. doi: 10.1016/j.neulet.2021.135958
166. Liu N, Sun H, Li X, Cao W, Peng A, Dong S, Yu Z. Downregulation of lncRNA KCNQ1OT1 relieves traumatic brain injury induced neurological deficits via promoting „M2" microglia polarization. Brain Res Bull 2021;171:91-102. doi: 10.1016/j.brainresbull.2021.03.004
167. Jin Y, Jiang L, Wang Y, Huang Y, Yu W, Ma X. lncRNA PRR34-AS1 knockdown represses neuroinflammation and neuronal death in traumatic brain injury by inhibiting microRNA-498 expression. Brain Inj 2023;37611-20. doi: 10.1080/02699052.2023.2192524
168. He X, Huang Y, Liu Y, Zhang X, Wang Q, Liu Y, Ma X, Long X, Ruan Y, Lei H, Gan C, Wang X, Zou X, Xiong B, Shu K, Lei T, Zhang H. Astrocyte-derived exosomal lncRNA 4933431K23Rik modulates microglial phenotype and improves post-traumatic recovery via SMAD7 regulation. Mol Ther 2023;31:1313-31. doi: 10.1016/j.ymthe.2023.01.031
169. Dai X, Yi M, Wang D, Chen Y, Xu X. Changqin NO. 1 inhibits neuronal apoptosis via suppressing GAS5 expression in a traumatic brain injury mice model. Biol Chem 2019;400:753-63. doi: 10.1515/hsz-2018-0340
170. Lei J, Zhang X, Tan R, Li Y, Zhao K, Niu H. Levels of lncRNA GAS5 in Plasma of Patients with Severe Traumatic Brain Injury: Correlation with Systemic Inflammation and Early Outcome. J Clin Med 2022;11(12):3319. doi: 10.3390/jcm11123319
171. Patel RS, Krause-Hauch M, Kenney K, Miles S, Nakase-Richardson R, Patel NA. Long Noncoding RNA VLDLR-AS1 Levels in Serum Correlate with Combat-Related Chronic Mild Traumatic Brain Injury and Depression Symptoms in US Veterans. Int J Mol Sci 2024;25(3):1473. doi: 10.3390/ijms25031473
172. Chen Q, Wu B, Shi Z, Wang Y, Yuan Y, Chen X, Wang Y, Hu J, Mao L, Gao Y, Wu G. LncRNA H19 knockdown promotes neuropathologic and functional recovery via the Nrf2/HO-1 axis after traumatic brain injury. CNS Neurosci Ther 2024;30(7):e14870. doi: 10.1111/cns.14870
173. Zhang L, Bai W, Peng Y, Lin Y, Tian M. Human umbilical cord mesenchymal stem cell-derived exosomes provide neuroprotection in traumatic brain injury through the lncRNA TUBB6/Nrf2 pathway. Brain Res 2024;1824:148689. doi: 10.1016/j.brainres.2023.148689
174. Huang C, Sun L, Xiao C, You W, Sun L, Wang S, Zhang Z, Liu S. Circular RNA METTL9 contributes to neuroinflammation following traumatic brain injury by complexing with astrocytic SND1. J Neuroinflammation 2023;20:39. doi: 10.1186/s12974-023-02716-x
175. Chen S, Wang X, Qian Z, Wang M, Zhang F, Zeng T, Li L, Gao L. Exosomes from ADSCs ameliorate nerve damage in the hippocampus caused by post traumatic brain injury via the delivery of circ-Scmh1 promoting microglial M2 polarization. Injury 2023;54:110927. doi: 10.1016/j.injury.2023.110927
176. Du M, Wu C, Yu R, Cheng Y, Tang Z, Wu B, Fu J, Tan W, Zhou Q, Zhu Z, Balawi E, Huang X, Ma J, Liao ZB. A novel circular RNA, circIgfbp2, links neural plasticity and anxiety through targeting mitochondrial dysfunction and oxidative stress-induced synapse dysfunction after traumatic brain injury. Mol Psychiatry 2022;27:4575-89. doi: 10.1038/s41380-022-01711-7
177. Wu C, Du M, Yu R, Cheng Y, Wu B, Fu J, Tan W, Zhou Q, Balawi E, Liao ZB. A novel mechanism linking ferroptosis and endoplasmic reticulum stress via the circPtpn14/miR-351-5p/5-LOX signaling in melatonin-mediated treatment of traumatic brain injury. Free Radic Biol Med 2022;178:271-94. doi: 10.1016/j.freeradbiomed.2021.12.007
178. Cheng YQ, Wu CR, Du MR, Zhou Q, Wu BY, Fu JY, Balawi E, Tan WL, Liao ZB. CircLphn3 protects the blood-brain barrier in traumatic brain injury. Neural Regen Res 2022;17(4):812-18. doi: 10.4103/1673-5374.322467
179. Zheng P, Ren D, Yu C, Zhang X, Zhang Y. DNA Methylation-Related circRNA_0116449 Is Involved in Lipid Peroxidation in Traumatic Brain Injury. Front Mol Neurosci 2022;15:904913. doi: 10.3389/fnmol.2022.904913
180. Huang XJ, Su GJ, Wu CW, Sha XS, Zou JF, Liu XS, Li M, He Y. Knockdown of rno_circRNA_009194 Improves Outcomes in Traumatic Brain Injury Rats through Inhibiting Voltage-Gated Sodium Channel Nav1.3. J Neurotrauma 2022;39:196-210. doi: 10.1089/neu.2020.7520
181. Zheng P, Shu L, Ren D, Kuang Z, Zhang Y, Wan J. circHtra1/miR-3960/GRB10 Axis Promotes Neuronal Loss and Immune Deficiency in

Traumatic Brain Injury. Oxid Med Cell Longev 2022;2022:3522492. doi: 10.1155/2022/3522492
182. Li H, Lu C, Yao W, Xu L, Zhou J, Zheng B. Dexmedetomidine inhibits inflammatory response and autophagy through the circLrp1b/miR-27a-3p/Dram2 pathway in a rat model of traumatic brain injury. Aging 2020;12:21687-705. doi: 10.18632/aging.103975
183. Chen Z, Wang H, Zhong J, Yang J, Darwazeh R, Tian X, Huang Z, Jiang L, Cheng C, Wu Y, Guo Z, Sun X. Significant changes in circular RNA in the mouse cerebral cortex around an injury site after traumatic brain injury. Exp Neurol 2019;313:37-48. doi: 10.1016/j.expneurol.2018.12.003
184. Ma X, Wang H, Ye G, Zheng X, Wang Y. Hsa_circ_0018401 and miR-127-5p Expressions Are Diagnostic and Prognostic Markers for Traumatic Brain Injury (TBI) in Trauma Patients. Neuroscience 2024;545:59-68. doi: 10.1016/j.neuroscience.2024.03.010
185. Xiao X, Jiang Y, Liang W, Wang Y, Cao S, Yan H, Gao L, Zhang L. miR-212-5p attenuates ferroptotic neuronal death after traumatic brain injury by targeting Ptgs2. Mol Brain 2019;12:78. doi: 10.1186/s13041-019-0501-0
186. Burek M, König A, Lang M, Fiedler J, Oerter S, Roewer N, Bohnert M, Thal SC, Blecharz-Lang KG, Woitzik J, Thum T, Förster CY. Hypoxia-Induced MicroRNA-212/132 Alter Blood-Brain Barrier Integrity Through Inhibition of Tight Junction-Associated Proteins in Human and Mouse Brain Microvascular Endothelial Cells. Transl Stroke Res 2019;10:672-83. doi: 10.1007/s12975-018-0683-2
187. Jia M, Guo X, Liu R, Sun L, Wang Q, Wu J. Overexpress miR-132 in the Brain Parenchyma by a Non-invasive Way Improves Tissue Repairment and Releases Memory Impairment After Traumatic Brain Injury. Cell Mol Neurobiol 2023;44:5. doi: 10.1007/s10571-023-01435-4
188. Henry RJ, Doran SJ, Barrett JP, Meadows VE, Sabirzhanov B, Stoica BA, Loane DJ, Faden AI. Inhibition of miR-155 Limits Neuroinflammation and Improves Functional Recovery After Experimental Traumatic Brain Injury in Mice. Neurotherapeutics 2019;16:216-30. doi: 10.1007/s13311-018-0665-9
189. Li Z, Wang Y, Zeng G, Zheng X, Wang W, Ling Y, Tang H, Zhang J. Increased miR-155 and heme oxygenase-1 expression is involved in the protective effects of formononetin in traumatic brain injury in rats. Am J Transl Res 2017;9:5653-5661.
190. Qi R, Wang X. Inhibition of miR-429 improves neurological recovery of traumatic brain injury mice and attenuates microglial neuroinflammation. Int Immunopharmacol 2020;79:106091. doi: 10.1016/j.intimp.2019.106091
191. Vuokila N, Das Gupta S, Huusko R, Tohka J, Puhakka N, Pitkänen A. Elevated Acute Plasma miR-124-3p Level Relates to Evolution of Larger Cortical Lesion Area after Traumatic Brain Injury. Neuroscience 2020;433:21-35. doi: 10.1016/j.neuroscience.2020.02.045
192. Vuokila N, Aronica E, Korotkov A, van Vliet EA, Nuzhat S, Puhakka N, Pitkänen A. Chronic Regulation of miR-124-3p in the Perilesional Cortex after Experimental and Human TBI. Int J Mol Sci 2020;21(7):2418. doi: 10.3390/ijms21072418
193. Ge X, Guo M, Hu T, Li W, Huang S, Yin Z, Li Y, Chen F, Zhu L, Kang C, Jiang R, Lei P, Zhang J. Increased Microglial Exosomal miR-124-3p Alleviates Neurodegeneration and Improves Cognitive Outcome after rmTBI. Mol Ther 2020;28:503-22. doi: 10.1016/j.ymthe.2019.11.017
194. Zhao J, Wang Y, Wang D, Yan W, Zhang S, Li D, Han Z, Chen F, Lei P. MiR-124-3p attenuates brain microvascular endothelial cell injury in vitro by promoting autophagy. Histol Histopathol 2022;37:159-68. doi: 10.14670/hh-18-406
195. Wang Y, Li D, Zhang L, Yin Z, Han Z, Ge X, Li M, Zhao J, Zhang S, Zuo Y, Xiong X, Gao H, Liu Q, Chen F, Lei P. Exosomes derived from microglia overexpressing miR-124-3p alleviate neuronal endoplasmic reticulum stress damage after repetitive mild traumatic brain injury. Neural Regen Res 2024;19:2010-18. doi: 10.4103/1673-5374.391189
196. Yang T, Song J, Bu X, Wang C, Wu J, Cai J, Wan S, Fan C, Zhang C, Wang J. Elevated serum miR-93, miR-191, and miR-499 are noninvasive biomarkers for the presence and progression of traumatic brain injury. J Neurochem 2016;137:122-9. doi: 10.1111/jnc.13534
197. Ge X, Li W, Huang S, Yin Z, Yang M, Han Z, Han Z, Chen F, Wang H, Lei P, Zhang J. Increased miR-21-3p in Injured Brain Microvascular Endothelial Cells after Traumatic Brain Injury Aggravates Blood-Brain Barrier Damage by Promoting Cellular Apoptosis and Inflammation through Targeting MAT2B. J Neurotrauma 2019;36:1291-305. doi: 10.1089/neu.2018.5728
198. Ge X, Han Z, Chen F, Wang H, Zhang B, Jiang R, Lei P, Zhang J. MiR-21 alleviates secondary blood-brain barrier damage after traumatic brain injury in rats. Brain Res 2015;1603:150-7. doi: 10.1016/j.brainres.2015.01.009
199. Ge XT, Lei P, Wang HC, Zhang AL, Han ZL, Chen X, Li SH, Jiang RC, Kang CS, Zhang JN. miR-21 improves the neurological outcome after traumatic brain injury in rats. Sci Rep 2014;4:6718. doi: 10.1038/srep06718
200. Wang L, Zhao C, Wu S, Xiao G, Zhuge X, Lei P, Xie K. Hydrogen Gas Treatment Improves the Neurological Outcome After Traumatic Brain Injury Via Increasing miR-21 Expression. Shock Sep 2018;50:308-15. doi: 10.1097/shk.0000000000001018
201. Pinchi E, Frati A, Cipolloni L, Aromatario M, Gatto V, La Russa R, Pesce A, Santurro A, Fraschetti F, Frati P, Fineschi V. Clinical-pathological study on β-APP, IL-1β, GFAP, NFL, Spectrin II, 8OHdG, TUNEL, miR-21, miR-16, miR-92 expressions to verify DAI-diagnosis, grade and prognosis. Sci Rep 2018;8:2387. doi: 10.1038/s41598-018-20699-1
202. Miao W, Bao TH, Han JH, Yin M, Yan Y, Wang WW, Zhu YH. Voluntary exercise prior to traumatic brain injury alters miRNA expression in the injured mouse cerebral cortex. Braz J Med Biol Res 2015;48:433-9. doi: 10.1590/1414-431x20144012
203. Johnson D, Cartagena CM, Tortella FC, Dave JR, Schmid KE, Boutté AM. Acute and subacute microRNA dysregulation is associated with cytokine responses in the rodent model of penetrating ballistic-like brain injury. J Trauma Acute Care Surg 2017;83(1Suppl1):S145-S149. doi: 10.1097/ta.0000000000001475
204. Wang WX, Wilfred BR, Madathil SK, Tang G, Hu Y, Dimayuga J, Stromberg AJ, Huang Q, Saatman KE, Nelson PT. miR-107 regulates granulin/progranulin with implications for traumatic brain injury and neurodegenerative disease. Am J Pathol 2010;177:334-45. doi: 10.2353/ajpath.2010.091202
205. Sun L, Liu A, Zhang J, Ji W, Li Y, Yang X, Wu Z, Guo J. miR-23b improves cognitive impairments in traumatic brain injury by targeting ATG12-mediated neuronal autophagy. Behav Brain Res 2018;340:126-36. doi: 10.1016/j.bbr.2016.09.020
206. Sun L, Zhao M, Wang Y, Liu A, Lv M, Li Y, Yang X, Wu Z. Neuroprotective effects of miR-27a against traumatic brain injury via suppressing FoxO3a-mediated neuronal autophagy. Biochem Biophys Res Commun 22 2017;482:1141-1147. doi: 10.1016/j.bbrc.2016.12.001
207. Das Gupta S, Ciszek R, Heiskanen M, Lapinlampi N, Kukkonen J, Leinonen V, Puhakka N, Pitkänen A. Plasma miR-9-3p and miR-136-3p as Potential Novel Diagnostic Biomarkers for Experimental and Human Mild Traumatic Brain Injury. Int J Mol Sci 2021;22(4):1563. doi: 10.3390/ijms22041563
208. Yan J, Bu X, Li Z, Wu J, Wang C, Li D, Song J, Wang J. Screening the expression of several miRNAs from TaqMan Low Density Array in traumatic brain injury: miR-219a-5p regulates neuronal apoptosis by modulating CCNA2 and CACUL1. J Neurochem 2019;150:202-17. doi: 10.1111/jnc.14717
209. Cui C, Zhang D, Sun K, Li H, Xu L, Lin G, Guo Y, Hu J, Chen J, Nong L, Cai Y, Yu D, Yang W, Wang P, Sun Y. Propofol maintains Th17/Treg cell balance and reduces inflammation in rats with traumatic brain injury via the miR-145-3p/NFATc2/NF-κB axis. Int J Mol Med 2021;48(1):135. doi: 10.3892/ijmm.2021.4968
210. Si L, Wang H, Wang L. Suppression of miR-193a alleviates neuroinflammation and improves neurological function recovery after traumatic brain injury (TBI) in mice. Biochem Biophys Res 2020;523:527-34. doi: 10.1016/j.bbrc.2019.11.095
211. Zhu J, Chen Z, Tian J, Meng Z, Ju M, Wu G, Tian Z. miR-34b attenuates trauma-induced anxiety-like behavior by targeting CRHR1. Int J Mol Med 2017;40(1):90-100. doi: 10.3892/ijmm.2017.2981
212. Han Z, Shi F, Chen Y, Dong X, Zhang B, Li M. Relationship between miRNA-433 and SPP1 in the presence of fracture and traumatic brain injury. Exp Ther Med Sep 2021;22(3):928. doi: 10.3892/etm.2021.10360
213. Sabirzhanov B, Stoica BA, Zhao Z, Loane DJ, Wu J, Dorsey SG, Faden AI. miR-711 upregulation induces neuronal cell death after traumatic brain injury. Cell Death Differ 2016;23:654-68. doi: 10.1038/cdd.2015.132
214. Chen W, Zhao L, Zhang J, Wang B, Xu G, Lin C, Liu N. Elevated expression of miR-302 cluster improves traumatic brain injury by in-

hibiting phosphorylation of connexin43 via ERK signaling. J Chem Neuroanat 2019;99:1-8. doi: 10.1016/j.jchemneu.2019.05.003
215. Wu J, He J, Tian X, Luo Y, Zhong J, Zhang H, Li H, Cen B, Jiang T, Sun X. microRNA-9-5p alleviates blood-brain barrier damage and neuroinflammation after traumatic brain injury. J Neurochem 2020;153:710-26. doi: 10.1111/jnc.14963
216. Zhang Y, Zhang Y, Chopp M, Pang H, Zhang ZG, Mahmood A, Xiong Y. MiR-17-92 Cluster-Enriched Exosomes Derived from Human Bone Marrow Mesenchymal Stromal Cells Improve Tissue and Functional Recovery in Rats after Traumatic Brain Injury. J Neurotrauma 2021;38(11):1535-50. doi: 10.1089/neu.2020.7575
217. Ma J, Shui S, Han X, Guo D, Li T, Yan L. microRNA-22 attenuates neuronal cell apoptosis in a cell model of traumatic brain injury. Am J Transl Res 2016;8(4):1895-902.
218. Qian Y, Li X, Fan R, Li Q, Zhang Y, He X, Yang W, Sun W, Lv S. MicroRNA-31 inhibits traumatic brain injury-triggered neuronal cell apoptosis by regulating hypoxia-inducible factor-1A/vascular endothelial growth factor A axis. Neuroreport 2022;33:1-12. doi: 10.1097/wnr.0000000000001741
219. Zhang H, Xing Z, Zheng J, Shi J, Cui C. Ursolic acid ameliorates traumatic brain injury in mice by regulating microRNA-141-mediated PDCD4/PI3K/AKT signaling pathway. Int Immunopharmacol 2023;120:110258. doi: 10.1016/j.intimp.2023.110258
220. Lu D, Wang Y, Liu G, Wang S, Duan A, Wang Z, Wang J, Sun X, Wu Y, Wang Z. Armcx1 attenuates secondary brain injury in an experimental traumatic brain injury model in male mice by alleviating mitochondrial dysfunction and neuronal cell death. Neurobiol Dis 2023;184:106228. doi: 10.1016/j.nbd.2023.106228
221. Prajapati P, Wang WX, Pesina SA, Geleta U, Springer JE. Sex-Specific Alterations in Inflammatory MicroRNAs in Mouse Brain and Bone Marrow CD11b+ Cells Following Traumatic Brain Injury. Cell Mol Neurobiol 2023;43:423-29. doi: 10.1007/s10571-021-01164-6
222. Li Y, Sun M, Wang X, Cao X, Li N, Pei D, Li A. Dental stem cell-derived extracellular vesicles transfer miR-330-5p to treat traumatic brain injury by regulating microglia polarization. Int J Oral Sci 2022;14:44. doi: 10.1038/s41368-022-00191-3
223. Zhou C, Li S, Qiu N, Sun P, Hamblin MH, Dixon CE, Chen J, Yin KJ. Loss of microRNA-15a/16-1 function promotes neuropathological and functional recovery in experimental traumatic brain injury. JCI Insight 2024;9(12):e178650. doi: 10.1172/jci.insight.178650
224. Feng C, Tian Q, Tang X, Yu J, Li H, Geng C, Xu L. microRNA-9a-5p disrupts the ELAVL1/VEGF axis to alleviate traumatic brain injury. Exp Neurol 2024;375:114721. doi: 10.1016/j.expneurol.2024.114721
225. Villena-Rueda BE, Kajitani GS, Ota VK, Honorato-Mauer J, Santoro ML, Bugiga AVG, Rosa JS, Asprino PF, Meneghetti P, Torrecilhas AC, Intasqui P, Bertolla RP, Foresti ML, da Graça Naffah-Mazzacoratti M, de Moraes Mello LEA, Belangero SI. miR-9-5p is Downregulated in Serum Extracellular Vesicles of Patients Treated with Biperiden After Traumatic Brain Injury. Mol Neurobiol 2024;61(11):9595-607. doi: 10.1007/s12035-024-04194-5
226. Yang Y, Wang Y, Li P, Bai F, Liu C, Huang X. Serum exosomes miR-206 and miR-549a-3p as potential biomarkers of traumatic brain injury. Sci Rep 2024;14(1):10082. doi: 10.1038/s41598-024-60827-8
227. Qian Y, Li X, Li G, Liu H, Li Q, Liu X, Zhang Y, He Z, Zhao Y, Fan H. Astrocyte-Derived Exosomal miR-148a-3p Suppresses Neuroinflammation and Restores Neurological Function in Traumatic Brain Injury by Regulating the Microglial Phenotype. eNeuro 2024;11(2):ENEURO.0336-23.2024. doi: 10.1523/ENEURO.0336-23.2024
228. Mercier E, Tardif PA, Emond M, Ouellet MC, de Guise É, Mitra B, Cameron P, Le Sage N. Characteristics of patients included and enrolled in studies on the prognostic value of serum biomarkers for prediction of postconcussion symptoms following a mild traumatic brain injury: a systematic review. BMJ Open 2017;7:e017848. doi: 10.1136/bmjopen-2017-017848
229. Wilde EA, Ware AL, Li X, Wu TC, McCauley SR, Barnes A, Newsome MR, Biekman BD, Hunter JV, Chu ZD, Levin HS. Orthopedic Injured versus Uninjured Comparison Groups for Neuroimaging Research in Mild Traumatic Brain Injury. J Neurotrauma 2019;36:239-49. doi: 10.1089/neu.2017.5513
230. Visser K, Koggel M, Blaauw J, van der Horn HJ, Jacobs B, van der Naalt J. Blood-based biomarkers of inflammation in mild traumatic brain injury: A systematic review. Neurosci Biobehav Rev 2022;132:154-68. doi: 10.1016/j.neubiorev.2021.11.036
231. Beard K, Yang Z, Haber M, Flamholz M, Diaz-Arrastia R, Sandsmark D, Meaney DF, Issadore D. Extracellular vesicles as distinct biomarker reservoirs for mild traumatic brain injury diagnosis. Brain Commun 2021;3:fcab151. doi: 10.1093/braincomms/fcab151
232. Zhou Q, Yin J, Wang Y, Zhuang X, He Z, Chen Z, Yang X. MicroRNAs as potential biomarkers for the diagnosis of Traumatic Brain Injury: A systematic review and meta-analysis. Int J Med Sci 2021;18:128-36. doi: 10.7150/ijms.48214
233. Lindblad C, Pin E, Just D, Al Nimer F, Nilsson P, Bellander BM, Svensson M, Piehl F, Thelin EP. Fluid proteomics of CSF and serum reveal important neuroinflammatory proteins in blood-brain barrier disruption and outcome prediction following severe traumatic brain injury: a prospective, observational study. Crit Care 2021;25:103. doi: 10.1186/s13054-021-03503-x
234. Bazarian JJ, Welch RD, Caudle K, Jeffrey CA, Chen JY, Chandran R, McCaw T, Datwyler SA, Zhang H, McQuiston B. Accuracy of a rapid glial fibrillary acidic protein/ubiquitin carboxyl-terminal hydrolase L1 test for the prediction of intracranial injuries on head computed tomography after mild traumatic brain injury. Acad Emerg Med 2021;28:1308-17. doi: 10.1111/acem.14366
235. Okonkwo DO, Puffer RC, Puccio AM, Yuh EL, Yue JK, Diaz-Arrastia R, Korley FK, Wang KKW, Sun X, Taylor SR, Mukherjee P, Markowitz AJ, Jain S, Manley GT. Point-of-Care Platform Blood Biomarker Testing of Glial Fibrillary Acidic Protein versus S100 Calcium-Binding Protein B for Prediction of Traumatic Brain Injuries: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury Study. J Neurotrauma 2020;37(23):2460-7. doi: 10.1089/neu.2020.7140
236. Pankratova N, Jović M, Pfeifer ME. Electrochemical sensing of blood proteins for mild traumatic brain injury (mTBI) diagnostics and prognostics: towards a point-of-care application. RSC Adv 2021;11:17301-19. doi: 10.1039/d1ra00589h
237. Zaborowski MP, Balaj L, Breakefield XO, Lai CP. Extracellular Vesicles: Composition, Biological Relevance, and Methods of Study. Bioscience 2015;65(8):783-97. doi: 10.1093/biosci/biv084
238. Dey A, Ghosh S, Bhuniya T, Koley M, Bera A, Guha S, Chakraborty K, Muthu S, Gorai S, Vorn R. Clinical theragnostic signature of extracellular vesicles in traumatic brain injury (TBI). ACS Chem Neurosci 2023;14(17):2981-94.
239. Kharb S, Joshi A. Multi-omics and machine learning for the prevention and management of female reproductive health. Front Endocrinol 2023;14:1081667. doi: 10.3389/fendo.2023.1081667
240. Liu Y, Li Y, Zeng T. Multi-omics of extracellular vesicles: An integrative representation of functional mediators and perspectives on lung disease study. Front Bioinform 2023;3:1117271.
241. Bramley H, Hong J, Zacko C, Royer C, Silvis M. Mild traumatic brain injury and post-concussion syndrome: treatment and related sequela for persistent symptomatic disease. Sports Med Arthrosc Rev 2016;24:123-9.
242. Akin FW, Murnane OD, Hall CD, Riska KM. Vestibular consequences of mild traumatic brain injury and blast exposure: a review. Brain Inj 2017;31:1188-94.
243. Vaughn MN, Winston CN, Levin N, Rissman RA, Risbrough VB. Developing biomarkers of mild traumatic brain injury: promise and progress of CNS-derived exosomes. Front Neurol 2022;12:698206.
244. Agoston DV, Shutes-David A, Peskind ER. Biofluid biomarkers of traumatic brain injury. Brain Inj 2017;31(9):1195-203.