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Review

Biofluid-based Biomarkers in Traumatic Brain Injury: A Narrative Review

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HIGHLIGHTS

1. Traumatic brain injury (TBI) involves nerve damage, blood-brain barrier disruption, and immune response.
2. Biofluid-based biomarkers are promising tools in TBI research.
3. However, challenges remain in the development, measurement, and interpretation.

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Biofluid-based Biomarkers in Traumatic Brain Injury: A Narrative Review

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Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Traumatic brain injury (TBI) is a complex condition characterized by a multifaceted pathophysiology. It presents significant diagnostic and prognostic challenges in clinical settings. This narrative review explores the evolving role of biofluid biomarkers as essential tools in the diagnosis, prognosis, and treatment of TBI. In recent times, preclinical and clinical trials utilizing these biofluid biomarkers have been actively pursued internationally. Among the biomarkers for nerve tissue proteins are neuronal biomarkers like neuronal specific enolase and ubiquitin C-terminal hydrolase L1; astroglia injury biomarkers such as S100B and glial fibrillary acidic protein; axonal injury and demyelination biomarkers, including neurofilaments and myelin basic protein; new axonal injury and neurodegeneration biomarkers like total tau and phosphorylated tau; and others such as spectrin breakdown products and microtubule-associated protein 2. The interpretation of these biomarkers can be influenced by various factors, including secretion from organs other than the injury site and systemic conditions. This review highlights the potential of these biomarkers to transform TBI management and emphasizes the need for continued research to validate their efficacy, refine testing platforms, and ultimately improve patient care and outcomes.

Keywords: Traumatic Brain Injury; Biofluid Biomarkers; Neuronal Biomarkers; Astroglia Injury Biomarkers; Axonal Injury Biomarkers

INTRODUCTION

In the realm of brain diseases, discerning the pathophysiology of the brain extends beyond conventional brain imaging, especially when compared to diseases affecting other organs. Biofluid biomarkers are emerging as pivotal tools for the clinical diagnosis, prognosis, and treatment of brain diseases. These biomarkers offer a quantitative approach to measure conditions that are otherwise challenging to assess directly, leveraging biochemical and chemical methodologies [1,2]. Traumatic brain injury (TBI) stands out as a primary example, with ongoing research also encompassing stroke, amyotrophic lateral sclerosis, multiple sclerosis, and neurodegenerative diseases like Alzheimer's and Parkinson's [3-7]. A salient feature of TBI's pathophysiology is the diverse nature and severity of primary tissue injuries, often accompanied by a series of secondary pathophysiological events, such as

excitotoxicity, ionic dysregulation, metabolic crises, and neuroinflammation [8-10]. The widely recognized Glasgow Coma Scale (GCS) is employed bedside to diagnose (assess severity) and monitor (track disease progression and treatment response) these intricate disease progressions. However, its efficacy is compromised in severe patients due to factors like intubation, ventilator usage, sedative states, drug or alcohol intoxication, circadian rhythm disturbances, and pre-existing cognitive conditions [11-13]. Additionally, while brain computed tomography (CT) is the go-to for TBI patient triage, providing insights into intracranial hemorrhages, the necessity of surgical interventions, potential rebleeding post-surgery, and the outcomes of conservative treatments, it has its limitations. Severe TBI patients face risks during transfers to radiography rooms and during the imaging process itself. The dynamic nature of their condition, which can change multiple times within a day, makes continuous monitoring challenging. In the context of mild TBI, there's an observed trend of over-reliance on this imaging technique, often leading to redundant scans even in patients with minimal neurological symptoms. Moreover, detecting brain damages like diffuse axonal injury remains a challenge in CT scans for mild TBI cases [14,15]. This review aims to delve into biofluid biomarkers, reflecting the intricate and diverse pathophysiology of TBI, ensuring efficient and safe quantitative monitoring. With this foundation, the goal is to enhance the precision of prognostic models, monitor disease progression, and guide clinical management, ultimately tailoring rehabilitation treatments for TBI patients.

PATHOPHYSIOLOGY OF TBI RELATED TO BIOMARKER

Following an initial mechanical injury, there is an onset of acute nerve damage and disruption of the blood-brain barrier (BBB). Concurrently, cellular damage triggers the secretion of damage-associated molecular patterns and associated inflammatory mediators, including cytokines and chemokines (**Fig. 1**) [16]. These mediators activate myeloid cells, leading to the initial recruitment of neutrophils. Subsequently, as neutrophil levels decrease, there's an increased infiltration of monocytes and macrophages in the hours post-injury. The initial trauma also results in concurrent gliosis and glial cell injuries, persisting for several days, initiating necrotic and apoptotic cell death. Over time, axonal injuries associated with demyelination and white matter damage, neurodegeneration, and chronic traumatic encephalopathy evolve and can progress over months to years. Between 3–7 days post-injury, myeloid cells selectively recruit T and B cells, a response that can last weeks to months. Given these cellular and immune responses in TBI, early biomarkers primarily target neuronal injuries, BBB disruptions, and the presence of cytokines, as well as glial injuries and necrosis, to ascertain the extent of brain damage and determine TBI severity. In the subacute and chronic phases, biomarkers related to axonal injury, demyelination, neurodegeneration, and neuroinflammation become crucial for diagnosing secondary complications, monitoring therapeutic responses, and predicting prognosis.

OVERVIEW OF BIOFLUID-BASED BIOMARKERS

Biofluid-based biomarkers have garnered significant attention in the realm of TBI research due to their potential diagnostic and prognostic capabilities. In human studies, the predominant biofluids utilized for biomarker analysis are blood (comprising 75%, including serum, plasma, and whole blood) and the central nervous system (CNS, 22%, encompassing cerebrospinal fluid [CSF], microdialysis, and brain tissue). Other biofluids such as urine,

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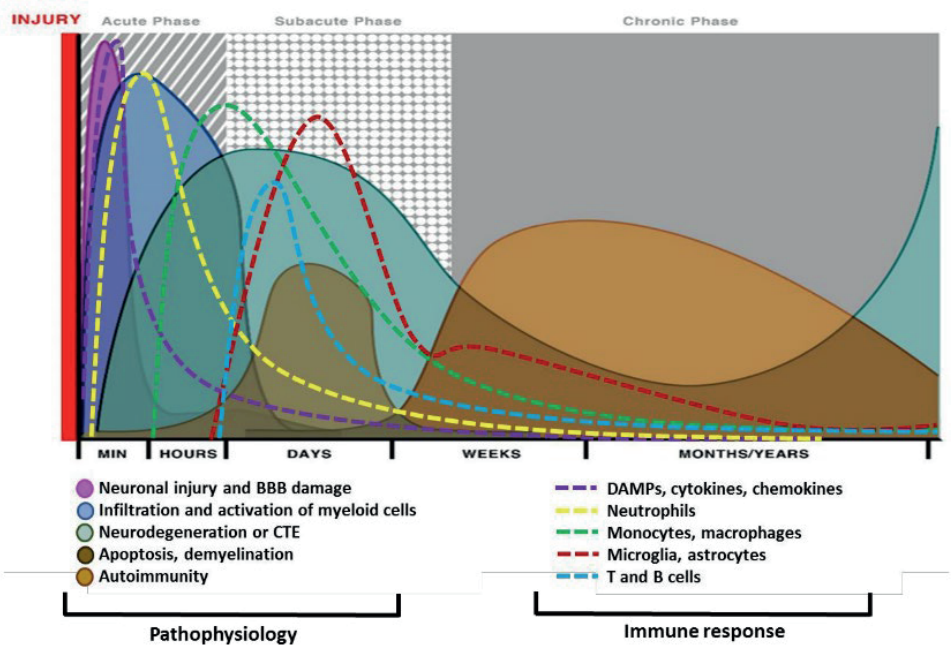

Fig. 1. Pathophysiology and immune response after traumatic brain injury (adapted from Jarrahi et al. [16]). BBB, blood-brain barrier; CTE, chronic traumatic encephalopathy; DAMP, damage-associated molecular pattern.

saliva, bronchoalveolar lavage fluid, buccal swabs, and gastric mucosa have also been explored [17]. Animal studies, primarily involving rats and mice, have reported the use of biofluids like brain tissue (69%), blood (24%), CSF (4%), and viscera (3%) [17]. In the context of TBI, nerve tissue proteins have been the most extensively assessed biomarkers. These proteins, originating from neuronal and neuroglia cells, play diverse biological roles ranging from structural functions to synaptic activity and CNS development. Following TBI, these brain-derived proteins are immediately elevated in biofluids due to damage to nerve and neuroglia cells. Biomarkers such as S100, neuronal specific enolase (NSE), glial fibrillary acidic protein (GFAP), and cytokines like interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-10 have been frequently reported. Coagulation tests, including platelet count and prothrombin time test/international normalized ratio, as well as hormone tests measuring cortisol levels, have also been highlighted in TBI research (**Fig. 2**) [17]. Emerging biomarkers in the field include ubiquitin C-terminal hydrolase L1 (UCH-L1), neurofilaments (NF), myelin basic protein (MBP), total tau (t-tau), phosphorylated tau (p-tau), and αII-spectrin breakdown products. For the practical application of these biomarkers, the development of robust analytical methods and platforms is paramount. Historically, the enzyme-linked immunosorbent assay has been the predominant method, followed by techniques like electrochemiluminescent immunoassay, radioimmunoassay, polymerase chain reaction, multiplex immunoassay, and mass spectrometry, among others.

In neuronal cell biomarkers, both NSE and UCH-L1 are included. NSE is a glycolytic enzyme originating from the neuronal cell body. Under normal conditions, it is not present in extracellular fluids. However, during neuronal destruction, its levels are upregulated [18,19]. With a half-life of less than 20 hours, measurements should be taken within 12–24 hours post-injury. In adults, levels exceeding 9 μg/L and in children, levels above 15 μg/L within 24 hours suggest poor prognosis when combined with CT scan abnormalities [20-23]. Its interpretation can be limited during polytrauma, hemolysis, hemorrhagic shock, and renal

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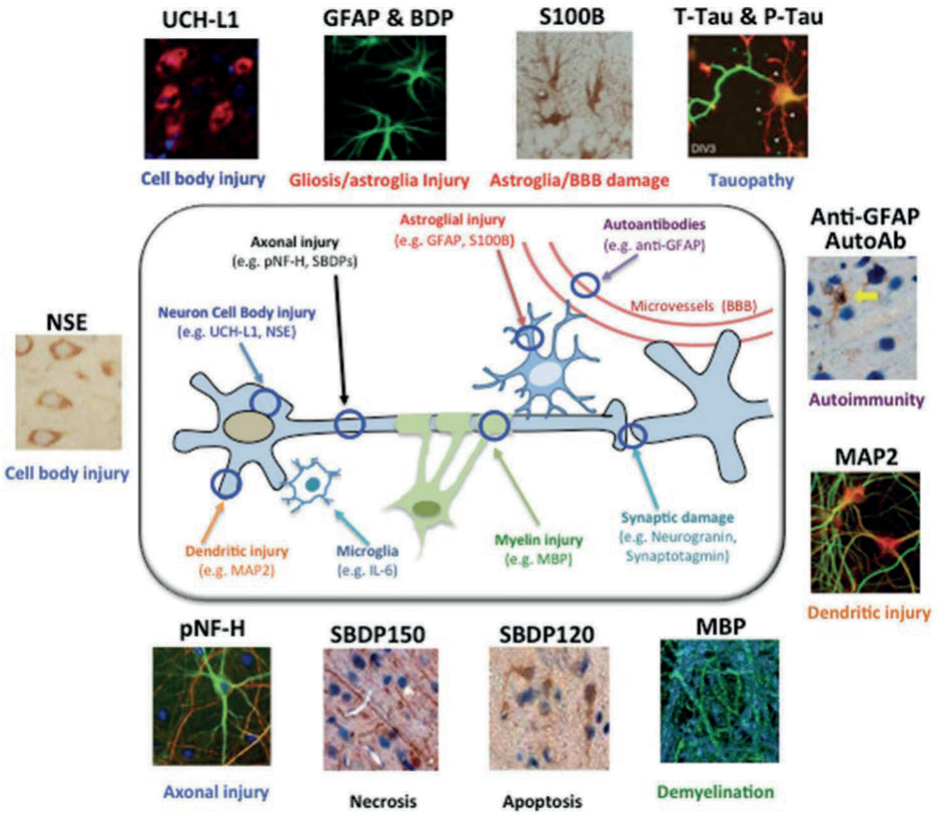

Fig. 2. Graphic representation of traumatic brain injury biomarkers based on the pathophysiology (adapted from Wang et al. [2]).
UCH-L1, ubiquitin C-terminal hydrolase L1; GFAP, glial fibrillary acidic protein; BDP, breakdown product; BBB, blood-brain barrier; t-tau, total tau; p-tau, phosphorylated tau; MAP, microtubule-associated protein; MBP, myelin basic protein; SBDP, spectrin breakdown product; NF, neurofilaments; NSE, neuronal specific enolase; IL, interleukin.

failure due to its presence in red blood cells and the extracranial compartment [24]. UCH-L1, an enzyme from neurons, plays a crucial role in normalizing excessive proteins by removing them [25]. Recently, it has garnered attention as a TBI biomarker alongside GFAP. Studies on severe TBI patients showed increased levels of UCH-L1 in both CSF and serum. Notably, significant differences were observed in serum UCH-L1 levels within 12 hours post-injury between groups with GCS 3–5 and GCS 5–8 [26]. Furthermore, non-survivor groups showed significant elevations in both CSF and serum UCH-L1 levels within 6 hours. In patients with mild and moderate TBI following blunt head trauma, UCH-L1 levels were significantly elevated compared to controls, and CT-positive groups had notably higher levels than CT-negative groups [27].

S100 and GFAP are 2 main biomarkers for glial cell biomarkers. S100, one of the most frequently reported biomarkers, originates from glial cells and is a calcium-binding protein. It increases during glial cell destruction and is known as a sensitive marker for BBB permeability. Systematic reviews and meta-analyses have reported associations between S100B levels and the presence of intracranial lesions in CT scans, TBI severity, and intracranial hypertension [28,29]. Specifically, in mild TBI patients, S100B levels exceeding 0.16 μg/L suggest the potential for positive lesions in CT scans [17]. The half-life of S100 is known to be 4–6 hours in mild TBI and up to 24 hours in severe TBI [22]. Guidelines suggest that in mild TBI patients, if

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S100B levels measured within 6 hours are below 0.1 μg/L, proceeding without a CT scan does not impact the patient's outcome [30]. However, its role as a predictor for post-concussion syndrome in mild TBI remains debated [31]. GFAP, an intermediate filament protein, serves as a structural unit in the cytoskeleton of astroglial cells and is a rising star among TBI biomarkers. With a half-life of 24–48 hours, which is relatively longer than S100B, GFAP can provide information about disease progression and secondary insults. Studies have shown that GFAP levels measured within 24 hours post-injury were significantly elevated in TBI patients, with CT-positive patients having levels about ten times higher than CT-negative patients [32]. Even in CT-negative patients, those with magnetic resonance imaging-observed axonal injuries had GFAP levels approximately 5 times higher [33]. Research comparing outcomes 6 months post-injury found correlations between serum GFAP levels measured within 5 days of injury and the Glasgow Outcome Scale (GOS) and mortality [34]. Co-measurement of UCH-L1 and GFAP could predict TBI severity, the presence of intracranial lesions in CT scans, and the need for neurosurgical intervention [35-38]. This combined measurement received Food and Drug Administration (FDA) approval in 2018.

Biomarkers for axon and myelin injury encompass both NF and MBP. NF, similar to GFAP, is an intermediate filament originating from axons. It forms the primary structure of the axonal cytoskeleton and plays a pivotal role in synapse formation and neurotransmission [2]. Comprising a trio of proteins—heavy, medium, and light—NF undergoes a transformation post-TBI. Due to calcium reflux, NF-H becomes phosphorylated, leading to a reduction in axonal integrity [39,40]. Additionally, NF-M levels have been reported to increase in the serum and CSF of severe TBI patients, while NF-L levels rise post-injury in patients with diffuse axonal injury [41,42]. MBP, a protein associated with the myelin surrounding axons, resides within oligodendrocytes. It becomes susceptible to proteases like calpain due to post-TBI axonal degeneration, leading to a delayed detection of MBP [43,44]. In the CSF, MBP levels rise a few days post-severe TBI, while in the serum, levels are elevated in patients with severe pediatric TBI or moderate-mild TBI with CT scan abnormalities [45,46].

t-tau and p-tau levels rise within 3 days post-severe TBI, with p-tau levels remaining elevated between 30–190 days [47]. In mild TBI patients, long-term increases in t-tau levels have been observed, especially in those with multiple TBIs. This elevation is associated with post-concussive symptoms [48]. New non-protein TBI biomarkers, including miRNA, exosomes, lipids, metabolomics, and DNA, have been reported. Notably, individuals with a high ε4 allele of the apolipoprotein E gene have a tenfold increased risk of dementia due to head injury and are associated with cognitive decline 30 days post-injury [49].

Produced from neuronal and glial cell injuries during initial trauma, cytokines are characterized by rapid expression, high peak concentration, and a short half-life. They are associated with the diagnosis and early prognosis of acute phase TBI. IL-6, a glycoprotein and prototypical cytokine, is upregulated during the TBI acute phase. It has been linked to initial mortality, poor health outcomes, elevated intracranial pressure, and in the chronic phase, persistent IL-6 elevation indicates secondary brain damage and is associated with functional & psychiatric outcomes [50,51]. IL-10 has shown significant associations with TBI severity, mortality, and unfavorable outcomes. In mild TBI, a chronic increase in IL-10 is linked to the occurrence of intracranial lesions in CT scans [50-52]. While TNF-α can increase due to neuroinflammation, it may also signify a therapeutic neurorestorative effect [53]. Thus, rather than a simple increase or decrease, the regulation of TNF-α might be linked to brain injury outcomes. However, its low brain specificity makes its usage still ambiguous.

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CONCLUSION

Biofluid biomarkers in TBI patients encapsulate a wealth of information and hold significant promise. However, aside from the clinically adopted S100B and the FDA-approved GFAP-UCH-L1 combination, many biomarkers still lack sufficient evidence and face various limitations. One of the major challenges is the development and commercialization of platforms that can efficiently and cost-effectively measure these biomarkers. Most biomarkers are not only secreted at the injury site but also from other organs. Their measurement, after filtration through the blood and potential increases due to systemic conditions, requires consideration of various confounding factors. As a result, many biomarkers have not consistently produced positive outcomes. Additionally, most biomarker studies have evaluated outcomes based on initial GCS, GOS, mortality, and brain CT scans. There's a noticeable absence of long-term prognostic evaluations, including assessments related to rehabilitation medicine, daily living activities, and cognitive evaluations. Future research should focus on bolstering clinical evidence, developing testing instruments, and comparing results with a broader range of assessment tools.

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Review

Biofluid-based Biomarkers in Traumatic Brain Injury: A Narrative Review

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HIGHLIGHTS

1. Traumatic brain injury (TBI) involves nerve damage, blood-brain barrier disruption, and immune response.
2. Biofluid-based biomarkers are promising tools in TBI research.
3. However, challenges remain in the development, measurement, and interpretation.

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Review

Biofluid-based Biomarkers in Traumatic Brain Injury: A Narrative Review

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Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Traumatic brain injury (TBI) is a complex condition characterized by a multifaceted pathophysiology. It presents significant diagnostic and prognostic challenges in clinical settings. This narrative review explores the evolving role of biofluid biomarkers as essential tools in the diagnosis, prognosis, and treatment of TBI. In recent times, preclinical and clinical trials utilizing these biofluid biomarkers have been actively pursued internationally. Among the biomarkers for nerve tissue proteins are neuronal biomarkers like neuronal specific enolase and ubiquitin C-terminal hydrolase L1; astroglia injury biomarkers such as S100B and glial fibrillary acidic protein; axonal injury and demyelination biomarkers, including neurofilaments and myelin basic protein; new axonal injury and neurodegeneration biomarkers like total tau and phosphorylated tau; and others such as spectrin breakdown products and microtubule-associated protein 2. The interpretation of these biomarkers can be influenced by various factors, including secretion from organs other than the injury site and systemic conditions. This review highlights the potential of these biomarkers to transform TBI management and emphasizes the need for continued research to validate their efficacy, refine testing platforms, and ultimately improve patient care and outcomes.

Keywords: Traumatic Brain Injury; Biofluid Biomarkers; Neuronal Biomarkers; Astroglia Injury Biomarkers; Axonal Injury Biomarkers

INTRODUCTION

In the realm of brain diseases, discerning the pathophysiology of the brain extends beyond conventional brain imaging, especially when compared to diseases affecting other organs. Biofluid biomarkers are emerging as pivotal tools for the clinical diagnosis, prognosis, and treatment of brain diseases. These biomarkers offer a quantitative approach to measure conditions that are otherwise challenging to assess directly, leveraging biochemical and chemical methodologies [1,2]. Traumatic brain injury (TBI) stands out as a primary example, with ongoing research also encompassing stroke, amyotrophic lateral sclerosis, multiple sclerosis, and neurodegenerative diseases like Alzheimer's and Parkinson's [3-7]. A salient feature of TBI's pathophysiology is the diverse nature and severity of primary tissue injuries, often accompanied by a series of secondary pathophysiological events, such as

excitotoxicity, ionic dysregulation, metabolic crises, and neuroinflammation [8-10]. The widely recognized Glasgow Coma Scale (GCS) is employed bedside to diagnose (assess severity) and monitor (track disease progression and treatment response) these intricate disease progressions. However, its efficacy is compromised in severe patients due to factors like intubation, ventilator usage, sedative states, drug or alcohol intoxication, circadian rhythm disturbances, and pre-existing cognitive conditions [11-13]. Additionally, while brain computed tomography (CT) is the go-to for TBI patient triage, providing insights into intracranial hemorrhages, the necessity of surgical interventions, potential rebleeding post-surgery, and the outcomes of conservative treatments, it has its limitations. Severe TBI patients face risks during transfers to radiography rooms and during the imaging process itself. The dynamic nature of their condition, which can change multiple times within a day, makes continuous monitoring challenging. In the context of mild TBI, there's an observed trend of over-reliance on this imaging technique, often leading to redundant scans even in patients with minimal neurological symptoms. Moreover, detecting brain damages like diffuse axonal injury remains a challenge in CT scans for mild TBI cases [14,15]. This review aims to delve into biofluid biomarkers, reflecting the intricate and diverse pathophysiology of TBI, ensuring efficient and safe quantitative monitoring. With this foundation, the goal is to enhance the precision of prognostic models, monitor disease progression, and guide clinical management, ultimately tailoring rehabilitation treatments for TBI patients.

PATHOPHYSIOLOGY OF TBI RELATED TO BIOMARKER

Following an initial mechanical injury, there is an onset of acute nerve damage and disruption of the blood-brain barrier (BBB). Concurrently, cellular damage triggers the secretion of damage-associated molecular patterns and associated inflammatory mediators, including cytokines and chemokines (**Fig. 1**) [16]. These mediators activate myeloid cells, leading to the initial recruitment of neutrophils. Subsequently, as neutrophil levels decrease, there's an increased infiltration of monocytes and macrophages in the hours post-injury. The initial trauma also results in concurrent gliosis and glial cell injuries, persisting for several days, initiating necrotic and apoptotic cell death. Over time, axonal injuries associated with demyelination and white matter damage, neurodegeneration, and chronic traumatic encephalopathy evolve and can progress over months to years. Between 3–7 days post-injury, myeloid cells selectively recruit T and B cells, a response that can last weeks to months. Given these cellular and immune responses in TBI, early biomarkers primarily target neuronal injuries, BBB disruptions, and the presence of cytokines, as well as glial injuries and necrosis, to ascertain the extent of brain damage and determine TBI severity. In the subacute and chronic phases, biomarkers related to axonal injury, demyelination, neurodegeneration, and neuroinflammation become crucial for diagnosing secondary complications, monitoring therapeutic responses, and predicting prognosis.

OVERVIEW OF BIOFLUID-BASED BIOMARKERS

Biofluid-based biomarkers have garnered significant attention in the realm of TBI research due to their potential diagnostic and prognostic capabilities. In human studies, the predominant biofluids utilized for biomarker analysis are blood (comprising 75%, including serum, plasma, and whole blood) and the central nervous system (CNS, 22%, encompassing cerebrospinal fluid [CSF], microdialysis, and brain tissue). Other biofluids such as urine,

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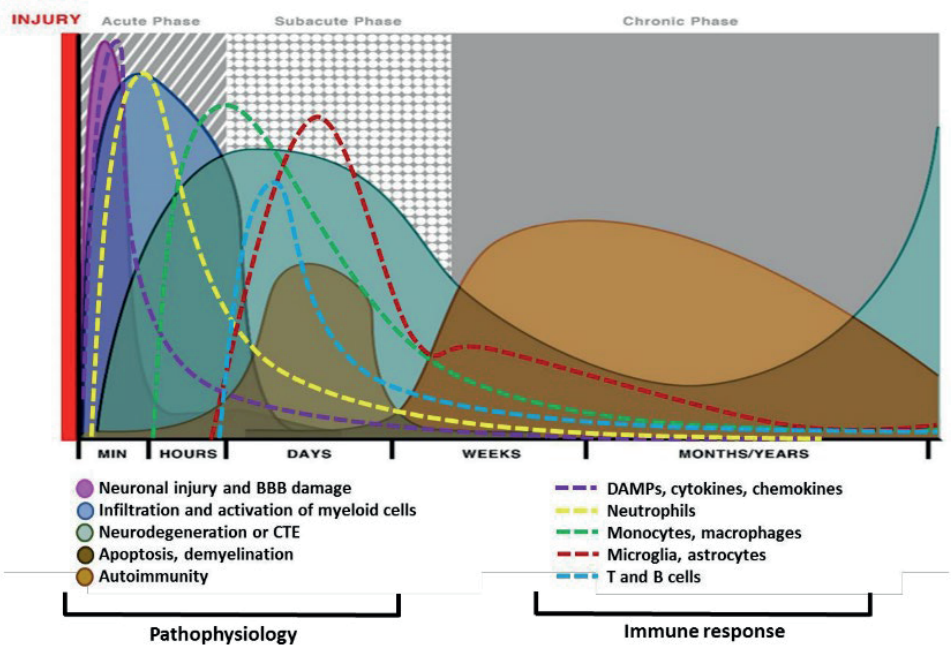

Fig. 1. Pathophysiology and immune response after traumatic brain injury (adapted from Jarrahi et al. [16]). BBB, blood-brain barrier; CTE, chronic traumatic encephalopathy; DAMP, damage-associated molecular pattern.

saliva, bronchoalveolar lavage fluid, buccal swabs, and gastric mucosa have also been explored [17]. Animal studies, primarily involving rats and mice, have reported the use of biofluids like brain tissue (69%), blood (24%), CSF (4%), and viscera (3%) [17]. In the context of TBI, nerve tissue proteins have been the most extensively assessed biomarkers. These proteins, originating from neuronal and neuroglia cells, play diverse biological roles ranging from structural functions to synaptic activity and CNS development. Following TBI, these brain-derived proteins are immediately elevated in biofluids due to damage to nerve and neuroglia cells. Biomarkers such as S100, neuronal specific enolase (NSE), glial fibrillary acidic protein (GFAP), and cytokines like interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-10 have been frequently reported. Coagulation tests, including platelet count and prothrombin time test/international normalized ratio, as well as hormone tests measuring cortisol levels, have also been highlighted in TBI research (**Fig. 2**) [17]. Emerging biomarkers in the field include ubiquitin C-terminal hydrolase L1 (UCH-L1), neurofilaments (NF), myelin basic protein (MBP), total tau (t-tau), phosphorylated tau (p-tau), and αII-spectrin breakdown products. For the practical application of these biomarkers, the development of robust analytical methods and platforms is paramount. Historically, the enzyme-linked immunosorbent assay has been the predominant method, followed by techniques like electrochemiluminescent immunoassay, radioimmunoassay, polymerase chain reaction, multiplex immunoassay, and mass spectrometry, among others.

In neuronal cell biomarkers, both NSE and UCH-L1 are included. NSE is a glycolytic enzyme originating from the neuronal cell body. Under normal conditions, it is not present in extracellular fluids. However, during neuronal destruction, its levels are upregulated [18,19]. With a half-life of less than 20 hours, measurements should be taken within 12–24 hours post-injury. In adults, levels exceeding 9 μg/L and in children, levels above 15 μg/L within 24 hours suggest poor prognosis when combined with CT scan abnormalities [20-23]. Its interpretation can be limited during polytrauma, hemolysis, hemorrhagic shock, and renal

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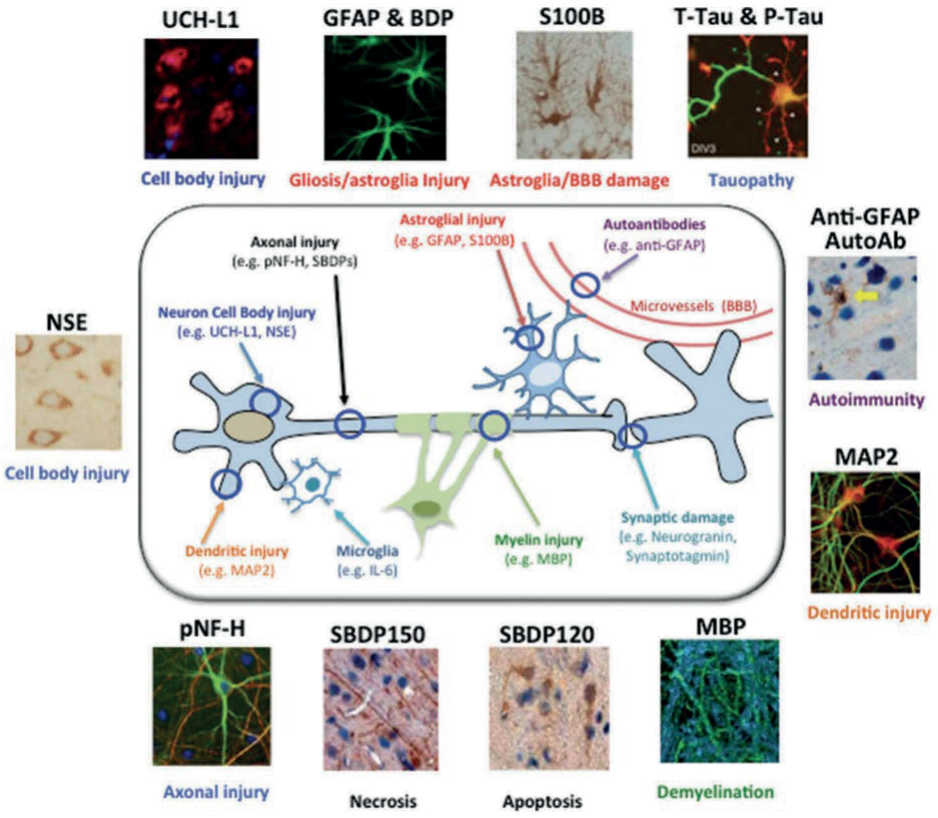

Fig. 2. Graphic representation of traumatic brain injury biomarkers based on the pathophysiology (adapted from Wang et al. [2]).
UCH-L1, ubiquitin C-terminal hydrolase L1; GFAP, glial fibrillary acidic protein; BDP, breakdown product; BBB, blood-brain barrier; t-tau, total tau; p-tau, phosphorylated tau; MAP, microtubule-associated protein; MBP, myelin basic protein; SBDP, spectrin breakdown product; NF, neurofilaments; NSE, neuronal specific enolase; IL, interleukin.

failure due to its presence in red blood cells and the extracranial compartment [24]. UCH-L1, an enzyme from neurons, plays a crucial role in normalizing excessive proteins by removing them [25]. Recently, it has garnered attention as a TBI biomarker alongside GFAP. Studies on severe TBI patients showed increased levels of UCH-L1 in both CSF and serum. Notably, significant differences were observed in serum UCH-L1 levels within 12 hours post-injury between groups with GCS 3–5 and GCS 5–8 [26]. Furthermore, non-survivor groups showed significant elevations in both CSF and serum UCH-L1 levels within 6 hours. In patients with mild and moderate TBI following blunt head trauma, UCH-L1 levels were significantly elevated compared to controls, and CT-positive groups had notably higher levels than CT-negative groups [27].

S100 and GFAP are 2 main biomarkers for glial cell biomarkers. S100, one of the most frequently reported biomarkers, originates from glial cells and is a calcium-binding protein. It increases during glial cell destruction and is known as a sensitive marker for BBB permeability. Systematic reviews and meta-analyses have reported associations between S100B levels and the presence of intracranial lesions in CT scans, TBI severity, and intracranial hypertension [28,29]. Specifically, in mild TBI patients, S100B levels exceeding 0.16 μg/L suggest the potential for positive lesions in CT scans [17]. The half-life of S100 is known to be 4–6 hours in mild TBI and up to 24 hours in severe TBI [22]. Guidelines suggest that in mild TBI patients, if

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S100B levels measured within 6 hours are below 0.1 μg/L, proceeding without a CT scan does not impact the patient's outcome [30]. However, its role as a predictor for post-concussion syndrome in mild TBI remains debated [31]. GFAP, an intermediate filament protein, serves as a structural unit in the cytoskeleton of astroglial cells and is a rising star among TBI biomarkers. With a half-life of 24–48 hours, which is relatively longer than S100B, GFAP can provide information about disease progression and secondary insults. Studies have shown that GFAP levels measured within 24 hours post-injury were significantly elevated in TBI patients, with CT-positive patients having levels about ten times higher than CT-negative patients [32]. Even in CT-negative patients, those with magnetic resonance imaging-observed axonal injuries had GFAP levels approximately 5 times higher [33]. Research comparing outcomes 6 months post-injury found correlations between serum GFAP levels measured within 5 days of injury and the Glasgow Outcome Scale (GOS) and mortality [34]. Co-measurement of UCH-L1 and GFAP could predict TBI severity, the presence of intracranial lesions in CT scans, and the need for neurosurgical intervention [35-38]. This combined measurement received Food and Drug Administration (FDA) approval in 2018.

Biomarkers for axon and myelin injury encompass both NF and MBP. NF, similar to GFAP, is an intermediate filament originating from axons. It forms the primary structure of the axonal cytoskeleton and plays a pivotal role in synapse formation and neurotransmission [2]. Comprising a trio of proteins—heavy, medium, and light—NF undergoes a transformation post-TBI. Due to calcium reflux, NF-H becomes phosphorylated, leading to a reduction in axonal integrity [39,40]. Additionally, NF-M levels have been reported to increase in the serum and CSF of severe TBI patients, while NF-L levels rise post-injury in patients with diffuse axonal injury [41,42]. MBP, a protein associated with the myelin surrounding axons, resides within oligodendrocytes. It becomes susceptible to proteases like calpain due to post-TBI axonal degeneration, leading to a delayed detection of MBP [43,44]. In the CSF, MBP levels rise a few days post-severe TBI, while in the serum, levels are elevated in patients with severe pediatric TBI or moderate-mild TBI with CT scan abnormalities [45,46].

t-tau and p-tau levels rise within 3 days post-severe TBI, with p-tau levels remaining elevated between 30–190 days [47]. In mild TBI patients, long-term increases in t-tau levels have been observed, especially in those with multiple TBIs. This elevation is associated with post-concussive symptoms [48]. New non-protein TBI biomarkers, including miRNA, exosomes, lipids, metabolomics, and DNA, have been reported. Notably, individuals with a high ε4 allele of the apolipoprotein E gene have a tenfold increased risk of dementia due to head injury and are associated with cognitive decline 30 days post-injury [49].

Produced from neuronal and glial cell injuries during initial trauma, cytokines are characterized by rapid expression, high peak concentration, and a short half-life. They are associated with the diagnosis and early prognosis of acute phase TBI. IL-6, a glycoprotein and prototypical cytokine, is upregulated during the TBI acute phase. It has been linked to initial mortality, poor health outcomes, elevated intracranial pressure, and in the chronic phase, persistent IL-6 elevation indicates secondary brain damage and is associated with functional & psychiatric outcomes [50,51]. IL-10 has shown significant associations with TBI severity, mortality, and unfavorable outcomes. In mild TBI, a chronic increase in IL-10 is linked to the occurrence of intracranial lesions in CT scans [50-52]. While TNF-α can increase due to neuroinflammation, it may also signify a therapeutic neurorestorative effect [53]. Thus, rather than a simple increase or decrease, the regulation of TNF-α might be linked to brain injury outcomes. However, its low brain specificity makes its usage still ambiguous.

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CONCLUSION

Biofluid biomarkers in TBI patients encapsulate a wealth of information and hold significant promise. However, aside from the clinically adopted S100B and the FDA-approved GFAP-UCH-L1 combination, many biomarkers still lack sufficient evidence and face various limitations. One of the major challenges is the development and commercialization of platforms that can efficiently and cost-effectively measure these biomarkers. Most biomarkers are not only secreted at the injury site but also from other organs. Their measurement, after filtration through the blood and potential increases due to systemic conditions, requires consideration of various confounding factors. As a result, many biomarkers have not consistently produced positive outcomes. Additionally, most biomarker studies have evaluated outcomes based on initial GCS, GOS, mortality, and brain CT scans. There's a noticeable absence of long-term prognostic evaluations, including assessments related to rehabilitation medicine, daily living activities, and cognitive evaluations. Future research should focus on bolstering clinical evidence, developing testing instruments, and comparing results with a broader range of assessment tools.

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