Mild Traumatic Brain Injury: Reviewing Current Trends in Neuroimaging & Biomarkers

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Abstract

Traumatic brain injury (TBI) is a major public health concern affecting millions of individuals each year, with severity ranging from mild concussions to life-threatening neurological damage. While moderate and severe TBIs often receive prompt clinical attention, mild TBI (mTBI) presents challenges due to its subtle symptoms and frequent underdiagnosis. This review examines current advances in neuroimaging and biofluid biomarkers for the detection and monitoring of mTBI. Neuroimaging techniques such as functional MRI (fMRI), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS) are assessed for their ability to detect functional changes that are not visible on conventional imaging. Biofluid biomarkers, including glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), tau proteins, cytokines, and exosomes, are evaluated as minimally invasive indicators of neuronal injury, neuroinflammation, and blood-brain barrier disruption. Practical factors such as accessibility, cost, diagnostic windows, and technological feasibility are also discussed. Lastly, emerging tools such as digital phenotyping, wearable biosensors, and implantable devices are explored as part of a shift toward individualized and continuous monitoring. By synthesizing these developments, this review concludes that the future of mTBI care lies in a multi-modal diagnostic approach that integrates functional imaging with targeted biomarker panels, paving the way for more personalized and effective patient management.

Introduction

Traumatic brain injury (TBI) results from an external physical force—such as a blow, jolt, or penetrating injury—that causes the brain to accelerate and decelerate within the skull, leading to potential bruising, bleeding, and axonal tearing. TBI is classified by severity: mild TBI (mTBI), or concussion, involves brief symptoms like headache and confusion with minimal or no loss of consciousness (≤30 minutes); moderate TBI presents with more persistent symptoms and unconsciousness lasting up to 24 hours; and severe TBI is characterized by unconsciousness exceeding 24 hours and significant, often permanent, cognitive or physical impairments. While distinct in clinical presentation, all forms of TBI can impact a person's cognitive, physical, and emotional functions.

TBIs affect millions of people every year, with incidence rates continuing to rise due to increased participation in contact sports, military combat, higher rates of road traffic accidents, and falls among older populations (Leo & McCrea, 2016). The global incidence of TBI is estimated to range between 27 and 69 million cases per year (Williamson & Rajajee, 2023). In the United States alone, approximately 214,110 TBI-related hospitalizations were reported in 2020, with 69,473 TBI-related deaths recorded in 2021 (CDC, 2024). That said, these figures likely underestimate the impact of TBI, as many cases — particularly mTBIs with their less severe symptoms — remain undiagnosed or unreported.

While moderate and severe TBIs often receive more clinical attention due to their more severe consequences, long-term impacts, and life-threatening nature, mTBIs are far more common and often overlooked due to the fact that most individuals recover from their injury within a few weeks. However, even mTBIs can have severe, long-term consequences if they are poorly managed or occur repeatedly: concussions have been linked to increased risk of developing neurodegenerative diseases such as chronic traumatic encephalopathy (CTE),

Alzheimer's disease, Parkinson's disease, and long-term cognitive and psychological sequelae (Ladak et al., 2019).

Despite the importance of mTBIs, effective, efficient, and reliable diagnosis remains a challenge. Unlike moderate or severe TBIs, mTBIs often do not show up on standard imaging methods like magnetic resonance imaging (MRI) or computed tomography (CT) as these methods are limited in their ability to detect subtle structural and functional damage (Carlson et al., 2009). Imaging techniques can also be very costly, require specific conditions to function, and may not be available in more rural or less privileged areas due to cost. Instead, diagnosis often relies on patient-reported symptoms and clinical exams which are often subjective and inconsistent across clinical settings. Additionally, there's no single biomarker or test that can confirm mTBIs. As a result, many cases of mTBI go undiagnosed, misclassified, or neglected, leading to inadequate management, which ultimately results in an increased risk of long term effects (Amyot et al., 2015).

Fortunately, recent advances in neuroimaging techniques are helping to improve mTBI diagnosis. Imaging modalities such as functional near-infrared spectroscopy (fNIRS), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG), for example, have demonstrated significant promise. fNIRS allows for noninvasive monitoring of cerebral hemodynamics, providing insights into regional changes in brain activity (Skau et al., 2019). fNIRS also allows for increased mobility, broadening the potential for diverse, monitored stimuli. fMRI, on the other hand, can reveal functional connectivity alterations and allows for signal detection deeper in the cortex, which is crucial for understanding potential long-term sequelae (Hayes et al., 2016). Lastly, EEG can aid in early detection of mTBIs by detecting subtle electrophysiological abnormalities in brain wave patterns that conventional imaging often misses (Ianof & Anghinah, 2017). These tools can all help improve early detection, enable more precise monitoring of recovery, and guide treatment strategies for individuals affected by mTBI.

Likewise, research into biofluid biomarkers has shown promise in improving mTBI diagnosis. A biofluid biomarker is a measurable indicator found in biological fluids, such as blood, that provides insight into an organism's state or condition; in this case, biomarkers would be indicating brain damage representative of the impact of mTBIs including axonal injury, neuroinflammation, and blood-brain barrier (BBB) disruption, which can then contribute to secondary injury (Ghaith et al., 2022; Ladak et al., 2019). Biofluid biomarkers are valuable because they are released into the body's fluids quickly after injury, allowing for rapid detection during the acute phase of injury, ultimately leading to timely diagnoses and effective management of the injury (Papa et al., 2016; Middleton, 2022; Reyes et al., 2023). Additionally, assessing the presence of biofluid biomarkers is generally much easier and more accessible than other methods. For example, unlike neuroimaging, which often requires expensive equipment and specialized facilities, biomarker testing can be done through a simple blood draw. This makes it far more practical in real-world settings — especially in emergency care, rural areas, or for patients with limited access to advanced medical resources.

This review provides a comprehensive analysis of current tools for diagnosing and monitoring mTBI, focusing on advanced neuroimaging modalities (fMRI, EEG, fNIRS) and key biofluid biomarkers (GFAP, UCH-L1, tau, IL-6, and exosomes). By evaluating not only their diagnostic accuracy but also their real-world feasibility, this paper synthesizes current knowledge to identify the most promising paths toward improving clinical outcomes for individuals affected by mTBI.

Neuroimaging

Traditionally, CT scans and standard MRI have been used to detect TBIs, each having their own strengths for diagnoses and tracking. CT scans are fast, widely available, and are ideal for ruling out critical issues such as skull fractures or bleeding. MRI provides better contrast between brain tissues and can catch small contusions and edema that CT might miss (Amyot et al., 2015). However, both CT and conventional MRI often miss the microscopic damage linked to mTBI that would be valuable to know in order to effectively diagnose and manage the injury (Hayes et al., 2016).

Currently, one of the most popular techniques for identifying and monitoring mTBIs is fMRI, which has remarkable spatial resolution. fMRI is similar to an MRI in the sense that they both use the same core technology (strong magnetic fields and radio waves) to capture images of the brain. The difference between the two lies in the fact that MRI shows what the brain looks like, while fMRI shows what it's doing. fMRI works by mapping neural activity by measuring blood oxygenation levels, allowing it to detect functional networks (e.g. a person who has mTBI may show unusual connectivity between the frontal cortex and the default mode network (DMN) — correlating to cognitive impairment — which can be picked up by fMRI scans (Mayer et al., 2011).

This said, fMRI does have its drawbacks. For one, it can be very costly depending on the clinic and insurance of the patient. The price for one hour of fMRI scanning ranges from $500 to $2000 (*Functional MRI (FMRI)*, 2019). For another, it requires participants to remain stationary and there are additional various restrictive specifications (i.e. ferromagnetic materials are not safe in an fMRI machine due to the strong magnetic field required for function), preventing scientists from gathering data in more naturalistic environments and from looking at patients with absolute contraindications such as cardiac implantable electronic devices (Ghadimi & Sapra, 2023). Lastly, fMRI machines are primarily only found in large medical centers, university hospitals, and specialized hospitals due to their expensive assembly (around $3 million, generally speaking), limiting the accessibility of this technique for many individuals (Amyot et al., 2015). Given these limitations, the presence of other, effective neuroimaging modalities is valuable in detecting and monitoring mTBI.

Another promising, though less effective option is electroencephalography (EEG) which provides excellent temporal resolution and a non-invasive approach. EEG records brain activity via electrodes arranged on the patient's scalp which capture voltage fluctuations generated by neuronal activity. These signals are then represented as oscillatory brain waves across frequency bands. This tool can detect TBIs by picking up changes in the brain's normal rhythmic activity (e.g. slowed brain waves or irregular spikes), providing valuable information about functional impairment — this tends to become particularly useful in monitoring people with moderate to severe TBI (Amyot et al., 2015; Rabinowitz & Levin, 2014). However, for people with mTBI, the correspondence is inconsistent and unreliable. That, and EEG generally has poor spatial resolution, especially when compared to fMRI. While less expensive than fMRI, EEG still presents cost and accessibility challenges. While there are certain affordable options when it comes to the cap itself, the channels are often limited (5-14). The gold standard for EEG (typically 32-64 or more channels) can range anywhere from $25,000 to $100,000, and more in some cases (Farnsworth, 2019). Oftentimes, a single session ranges from $200 to $700 without insurance, and extended or ambulatory monitoring can exceed $2,000 (*How Much Does an EEG Cost?*, 2013). Thus, a demand for an alternative technique presents itself.

Functional near-infrared spectroscopy (fNIRS) is a more modern technology (invented in the early 1990s but gained more popularity in the 2000s). It works by applying light sources to the scalp that are caught by nearby detectors as the light scatters and diffuses through brain tissues, measuring changes in absorption corresponding to oxyhemoglobin and deoxyhemoglobin levels, which, in turn, relate to brain activity. This is a non-invasive and portable technique with good temporal and spatial resolution (Plenger et al., 2015; Chang et al., 2022). While neither the temporal nor spatial resolution of fNIRS beats out EEG or fMRI respectively, it serves as a medium and is less costly to create than fMRI (one of the most frequently used fNIRS is the Kernel Flow 2 which costs $117,000 (*Kernel | Products*, 2025)). Additionally, fNIRS has already proved itself to be helpful in monitoring patients during the acute phase of TBI, and may prove to be useful in tracking residual psychiatric symptoms months after TBI (Skau et al., 2019; Chang et al., 2022).

This said, the majority of existing research only shows an associative link between mTBI and HbO changes rather than a casual connection. In other words, while fNIRS can detect changes in oxygenation, a decrease in HbO isn't indicative of mTBI, as other conditions or factors could cause similar shifts, calling into question its definitive diagnostic ability (Chang et al., 2022). Nevertheless, fNIRS holds significant value for its unique potential in mobile and accessible neuroimaging, allowing for data to be collected in more naturalistic environments (Skau et al., 2019). This is important because naturalistic settings offer richer, more dynamic, and varying stimuli that more closely resemble everyday experiences. By developing such brain imaging technology, scientists would be able to observe the effects of stimuli on the brain that was not possible before due to the restrictive nature of many neuroimaging modalities (Figure 1), which could in turn lead to more accessible and comfortable diagnoses for mTBI. Additionally, great efforts are currently being made to develop its motion correction to create a clearer image, which will be crucial for more real-world applications. So, while fNIRS is not definitive for the diagnosis and monitoring of mTBI, requires further research into its causational connections, and necessitates improvements in its motion correction software, the technology reserves plenty of promise as a diagnostic tool in the future for its qualities as a non-invasive and portable technique with quality resolution.

Ultimately, the choice of neuroimaging modality represents a strategic trade-off: fMRI offers unmatched spatial detail for research, EEG provides the temporal precision needed for seizure monitoring, and fNIRS presents a scalable option for real-time, naturalistic assessment. The clinical challenge, therefore, is not to find a single superior method, but to intelligently deploy these tools based on the specific diagnostic question at hand (Figure 1).

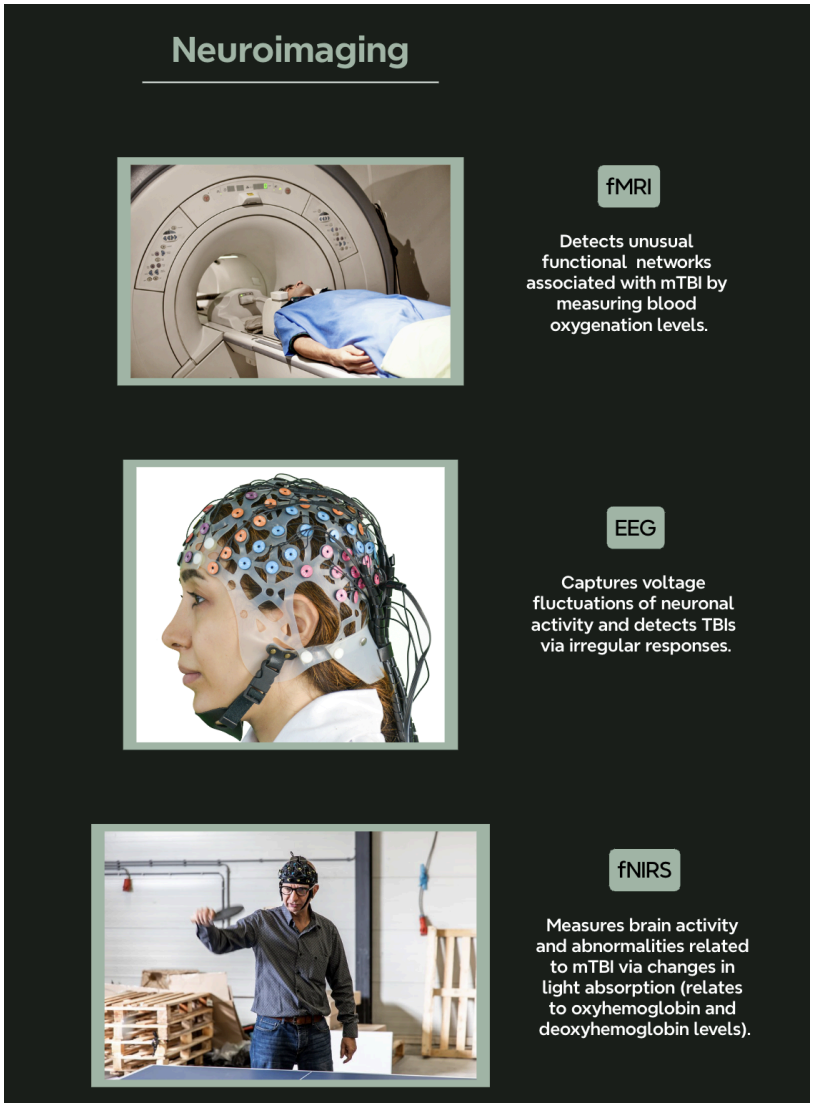

Figure 1: Comparison of neuroimaging modalities used to investigate TBI: fMRI (Reitz, 2014), EEG (Seo, 2024), and fNIRS (*Artinis Medical Systems | (F)NIRS Devices*, 2024).

Biofluid Biomarkers

The reason certain biomarkers appear in the bloodstream after a mTBI is due to disruption of the blood-brain barrier (BBB). Under normal conditions, the BBB acts as a protective filter, tightly controlling which substances can pass between the blood and the brain. However, even mild head trauma can weaken this barrier, allowing things that are normally kept out—such as immune cells and inflammatory molecules—to enter the brain (Ladak et al., 2019). This can set off a cascade of secondary injury processes, including neuroinflammation and oxidative stress, which can worsen the effects of the initial trauma (de Jager et al., 2009; Leo & McCrea, 2016). At the same time, damage to the BBB allows brain-specific proteins like GFAP, UCH-L1, and exosomes (biomarkers for neuronal and astroglial injury), or IL-6 (neuroinflammatory markers) and tau proteins (indicators of neuronal damage and long-term

cognitive decline) to leak into the bloodstream (Papa et al., 2016; Middleton, 2022; Hossain et al., 2022; Goetzl et al., 2019; Kenney et al., 2018; Ayala-Mar et al., 2019). Because these proteins are normally confined to the brain, their presence in blood samples serves as a strong indicator that a brain injury has occurred, and, depending on the specific proteins detected, the nature of the underlying damage. Key examples of these informative biomarkers include exosomes, GFAP, IL-6, and tau proteins.

One of the more promising fluid biomarkers are exosomes. Exosomes are tiny, membrane-bound extracellular vesicles which are released by many different cell types and contain a diverse cargo of proteins, lipids, and nucleic acids. The contents of each exosome reflects the state of their parent cells, which, in the context of mTBI, can provide insights into neuroinflammatory responses, neuronal damage, and synaptic dysfunction. Research has shown that exosomal cargo, such as microRNAs, may serve as reliable indicators of TBI (microRNA can reflect changes in gene expression and cellular processes that occur after injury, offering a window into the brain's response to trauma) (Goetzl et al., 2019). However, while exosomes hold significant promise, challenges remain regarding the standardization of isolation techniques, the speed at which results can be obtained in clinical settings, and the accessibility of equipment. For example, differential ultracentrifugation, a commonly used method, yields variable recovery and purity (depending on rotor, spin time, and sample properties), can take 2-10 hours, and requires specialized equipment that can cost between $50,000 and $100,000, with annual maintenance costing around $3,000, making the method less accessible (particularly in resource-limited settings) (Ayala-Mar et al., 2019; Liga et al., 2015).

Glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) are promising blood-based biomarkers for diagnosing mTBI, reflecting astrocytic and neuronal injury, respectively. GFAP is an intermediate filament protein primarily found in astrocytes, typically released into the bloodstream following TBI, indicating astroglial injury. UCH-L1, on the other hand, is a neuronal cytoplasmic enzyme which serves as a sensitive indicator of neuronal injury. These biomarkers can be analyzed with tests like i-STAT TBI Plasma, which provides results within 3–4 hours, costs about $16 per test, and requires less expensive equipment (~$10,000) (Middleton, 2022). Such rapid results is valuable given that GFAP and UCH-L1 can be detectable within one hour of injury — GFAP peaks around 20 hours and remains elevated for up to 72 hours, while UCH-L1 peaks around 8 hours and declines by 48 hours (Papa et al., 2016). This makes GFAP and UCH-L1 particularly useful for early detection of mTBI, when clinical symptoms may be subtle or nonspecific. However, their utility declines outside this window, and their levels can be additionally influenced by age, comorbid conditions, or extracranial injuries, which may limit diagnostic specificity. Thus, these biomarkers are valuable, but are not sufficient as stand-alone diagnostic tools.

Neuroinflammation is characterized by microglia, astrocytes, and peripheral leukocytes penetrating a weakened blood–brain barrier (BBB) and releasing inflammatory mediators that interfere with neural repair processes, therefore exacerbating neuronal damage and contributing to neurological deficits. In TBIs, even mild ones, the BBB becomes increasingly permeable, thereby increasing the risk and severity of neuroinflammation. Markers of neuroinflammation such as cytokines, chemokines, and acute phase proteins (e.g. IL-6 or TNF-alpha) are useful in gauging the extent of this inflammatory response, which helps both diagnose and identify the severity of the TBI. For example, interleukin-6 (IL-6) is significantly elevated within 6 hours of mild TBI (even in patients with normal head CT scans), enabling discrimination between

imaging-negative mTBI and healthy controls, outperforming GFAP and UCH-L1 in early detection (Reyes et al., 2023). Additionally, higher IL-6 concentrations generally indicate a more severe or sustained neuroinflammatory process following mTBI. In terms of accessibility, many hospitals and specialized centers have access to equipment for measuring IL-6 (e.g. ELISA readers and multiplex immunoassay platforms), though these instruments may be less common in smaller or resource-limited clinics and take around 3-6 hours to be processed.

Tau proteins bind to and regulate microtubules, promoting their assembly and preventing their disassembly. This ensures the structural integrity of neurons and facilitates the transport of materials down the axon vital for neuronal function and communication. As a biomarker, its release into biofluids following TBIs can signal axonal damage and cytoskeleton disruption, offering insights into the progression of neuropathological changes and the risk of long-term cognitive impairments. For example, a study involving combat veterans with a history of repetitive mild TBIs found that concentrations of exosomal total tau and phosphorylated tau were significantly higher in those who had sustained three or more injuries, which correlated with affective, cognitive, and somatic post-concussive symptoms (Kenney et al., 2018). That said, measuring and analyzing tau proteins has its limitations. For example, plasma tau proteins are often released in relatively low concentrations after mTBI compared to moderate or severe TBI, meaning standard assays (like ELISA) may be just barely or not sensitive enough to detect the subtle elevations, limiting early diagnostic utility without ultra-sensitive platforms like Simoa (Hossain et al., 2022). Additionally, elevated tau levels can occur in a range of neurological conditions, such as Alzheimer's disease, chronic traumatic encephalopathy (CTE), stroke, or aging, where neuronal injury or degeneration also occurs. This limits tau proteins' specificity for mTBI, as elevated levels may result from other neurological conditions. Lastly, high-sensitivity assays (e.g. Simoas) required to detect tau in mTBI are costly (for example, the Quanterix Simoa HD-1 Analyzer costs around $150,000 to $250,000), and are not widely available outside major research or academic centers (*HD-X Analyzer™ Fully Automated Simoa Bead-Based Immunoassay Platform*, 2025).

Overall, biofluid biomarkers provide a powerful and minimally invasive window into the molecular aftermath of mTBI, offering insights that complement imaging by capturing dynamic biological processes like inflammation, neuronal injury, and axonal disruption, advancing the field toward more precise and timely diagnosis (Figure 2).

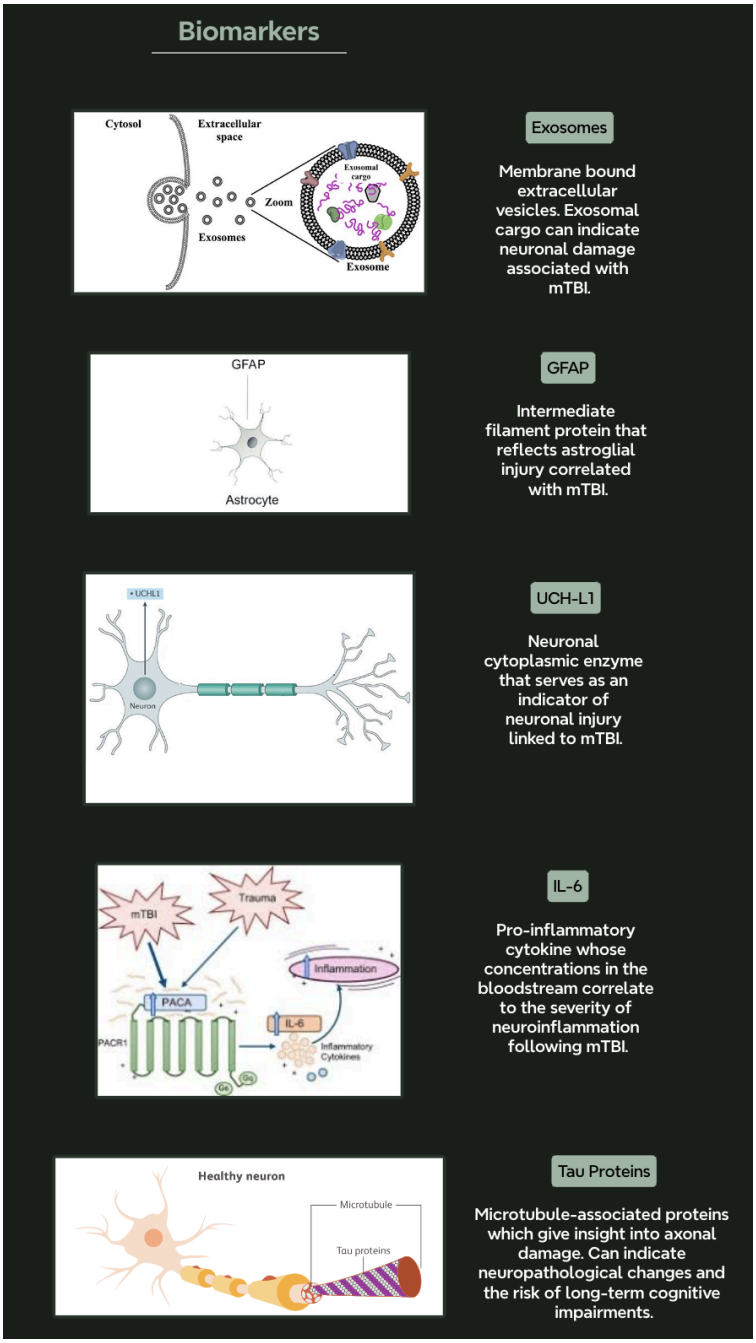

Figure 2: Summary of TBI-related biomarkers: Exosomes (de la Torre Gomez et al., 2018), GFAP (Hepner et al., 2019), UCH-L1 (Zetterberg & Blennow, 2016), IL-6 (Adams et al., 2025), tau proteins (*Tau in Alzheimer's Disease Fact Sheet – Bristol Myers Squibb*, 2024).

Discussion

The diagnosis and management of mTBI remains a clinical challenge despite its widespread occurrence and potential for long-term consequences. Standard imaging techniques often fail to detect subtle structural or functional brain changes, and symptoms can appear deceptively mild in the acute phase of injury. However, even mTBI can trigger complex

neurophysiological cascades such as BBB disruption, neuroinflammation, and neuronal/glial injury that increase the risk of chronic neurological dysfunction (Ladak et al., 2019). This highlights the need for diagnostic tools that are not only sensitive and accurate but also accessible and efficient across clinical settings.

To meet this need, advanced imaging techniques such as fMRI, fNIRS, and EEG are being refined to enhance spatial and temporal resolution, enable real-time data acquisitions, and integrate machine learning models to identify subtle connectivity changes. Multimodal approaches (e.g. combining fMRI with EEG) are gaining traction for providing a more holistic view of structural and functional brain connectivity following injury (Mayer et al., 2011).

Simultaneously, biomarker technologies are evolving to enhance diagnostic precision and utility. Multiplex assays now allow for the simultaneous detection of key biomarkers like GFAP, UCH-L1, IL-6, tau proteins, and exosomes, each reflecting distinct aspects of neuronal or glial damage and neuroinflammation. Ultra-sensitive platforms such as single-molecule arrays (Simoa) have lowered detection thresholds, enabling the measurement of low-abundance proteins.

Looking ahead, next-generation neurotechnologies may further transform mTBI diagnosis and treatment. Digital phenotyping, which passively gathers data from smartphones, wearables, and voice analysis, shows promise for continuously monitoring post-injury symptoms such as sleep disturbances and mood fluctuations, potentially flagging deterioration before it becomes clinically evident (Schultz et al., 2025; Rubaiat et al., 2025). Biosensors, including implantable and wearable microfluidic devices, are being developed to track inflammatory biomarkers in sweat or interstitial fluid, offering an alternative approach to blood sampling (Kim et al., 2019). Additionally, neural dust — ultra small, wireless, implantable sensors capable of monitoring electrophysiological activity — may eventually allow for chronic, deep-brain monitoring of neural disruptions following mTBI (Seo et al., 2016). While these technologies are still in early development and remain largely experimental, they signal a shift from static, episodic diagnostics toward continuous, individualized neuro-monitoring.

Synthesizing these findings, a tiered diagnostic framework for mTBI appears most promising. This approach would begin with rapid, cost-effective biofluid assays (e.g., GFAP/UCH-L1) in acute care settings to rule in or rule out intracranial injury. Positive or equivocal results could then trigger targeted functional assessments with portable neuroimaging like fNIRS or EEG to evaluate cognitive or electrophysiological deficits. Costly and less accessible modalities like fMRI would be reserved for complex cases or longitudinal research studies tracking neural network recovery. Such a framework would optimize resource allocation while moving mTBI diagnosis from a subjective art toward a data-driven science.

Table 1: The papers referenced in this review, the population size of the studies, and their relevance to mTBI.

Study	Population size	Relevance to mTBI
Rubaiat et al., 2025	239 (97 concussed and 94 age-matched healthy controls, 29 parkinson disease and 15 healthy controls for the PaTaKa test;	Explored machine learning techniques applied to speech data as a potential digital tracker for TBI and neurodegeneration,

	91 concussed and 104 healthy controls, 29 parkinson disease and 15 healthy controls for the Sustained Vowel (/ah/) test)	identifying speech alterations that may assist in mTBI detection.
Schultz et al., 2025	15 (military population with a history of traumatic brain injury and co-occurring psychological and cognitive symptoms)	Showed feasibility of collecting passive smartphone data to support digital phenotyping as a low-burden approach to track psychological symptoms, which can be applied to mTBI.
Reyes et al., 2023	118 (participants with mTBI recruited from The Alfred Hospital Level 1 Emergency & Trauma Center and uninjured control)	GFAP and UCH-L1 detected mTBI in patients with normal CT scans, supporting the biomarkers as effective diagnostic tools that can out-compete some neuroimaging techniques.
Ghadimi & Sapra, 2023	N/A, review	Reviewed contraindications to MRI and safety issues in receiving imaging which contextualized the limitations of fMRI accessibility for mTBI patients.
Dennis et al., 2023	N/A, review	Outlined emerging neuroimaging trends for TBI research and care, emphasizing the clinical potential of advanced imaging in diagnosing subtle mTBI-related changes.
Middleton, 2022	N/A, review	Described the use of UCH-L1 and GFAP as biomarkers in emergency care settings to detect intracranial injuries in mTBI patients.
Hossain et al., 2022	N/A, review	Reviewed tau proteins as biomarkers for mTBI and

		neurodegeneration, linking tau to long-term effects of mTBI, including cognitive decline.
Ghaith et al., 2022	N/A, review	Reviewed a wide spectrum of biomarkers, including exosomal proteins and tau, for diagnosing and monitoring mTBI across acute and chronic phases.
Chang et al., 2022	97 (37 patients with neurocognitive disorders after TBI and 60 healthy controls)	Demonstrated utility of fNIRS for detecting neurocognitive impairments post-TBI and supported fNIRS as a portable, cost-effective tool for assessing mTBI effects.
Wang et al., 2021	N/A, review	Outlines GFAP and UCH-L1 as biomarkers recently approved by the FDA and their diagnostic performance, timing of elevation, and role in reducing unnecessary CT scans
Skau et al., 2019	40 (20 with TBI-MF at least 5 months after injury, and 20 age-matched healthy controls)	Used fNIRS to measure cognitive fatigue and performance deficits post-mTBI.
Ladak et al., 2019	N/A, review	Covered molecular mechanisms, secondary, and long-term sequelae behind TBI.
Kim et al., 2019	N/A, review	Highlighted wearable biosensor applications for health monitoring, including the potential to track mTBI symptoms.
Goetzl et al., 2019	53 (18–26 year olds: 18 one week after a sports-related mild traumatic brain injury	Found altered levels of neuronal exosomes and proteins in mTBI patients,

	(acute mTBI), 14 three months or longer after the last of 2–4 mTBIs (chronic mTBI), and 21 with no recent history of TBI)	demonstrating diagnostic value of exosomes and protein cargo for acute mTBI.
Functional MRI, 2019	N/A, review	Discussed procedural overview, costs, and patient factors associated with fMRI use, emphasizing limited accessibility for routine mTBI evaluation.
Ayala-Mar et al., 2019	N/A, review	Outlined technological advances and isolation challenges in exosomes, revealing the limitations of the biomarker in diagnosing mTBI.
Kenney et al., 2018	195 (Veterans enrolled in the Chronic Effects of Neurotrauma Consortium Multicenter Observational Study)	Correlates elevated tau levels with affective, cognitive, and somatic post-concussive symptoms in mTBI patients.
Ianof & Anghinah, 2017	N/A, review	EEG can reveal electrophysiological changes following traumatic brain injury, highlighting its potential in detecting and monitoring mTBI.
Seo et al., 2016	N/A, review	Presented neural dust as a wireless recording technology for the nervous system, highlighting a future direction for biosensing that could enhance mTBI monitoring through neural activity tracking.
Papa et al., 2016	584 (adult trauma patients seen at the ED of a level I trauma center in Orlando Regional Medical Center)	GFAP and UCH-L1 biomarkers accurately identified mTBI soon after injury.

Leo & McCrea, 2016	N/A, review	Provided a comprehensive epidemiological overview of mTBI, including incidence, demographics, and risk factors.
Hayes et al., 2016	N/A, review	Examined connectivity in TBI patients and MRI/fMRI as a valuable tool in uncovering abnormalities.
Plenger et al., 2015	27 (13 healthy controls and 14 patients with moderate to severe TBI)	fNIRS revealed reduced prefrontal activation during Stroop task in TBI patients, indicating impaired cognitive control after mTBI.
Liga et al., 2015	N/A, review	Reviewed microfluidic approaches for isolating exosomes, a key source of mTBI biomarkers, emphasizing the need for efficient, scalable exosome processing in clinical research.
Faul & Coronado, 2015	N/A, review	Described TBI epidemiology in the US which reinforced the need for improved mTBI detection.
Amyot et al., 2015	N/A, review	Highlights strengths and limitations of imaging tools in detecting subtle mTBI damage.
Rabinowitz & Levin, 2014	N/A, review	mTBI often leads to lasting issues with attention, memory, and executive function.
Mayer et al., 2011	53 (27 semiacute mTBI patients and 26 gender, age and education-matched controls)	Found abnormal brain connectivity in mTBI patients via fMRI, validating use for detecting subtle functional disruptions.

de Jager et al., 2009	4 (healthy volunteers)	Studied the impact of various factors on the reproducibility and reliability of cytokine detection and outlined the value and limiations of cytokines as a potential mTBI biomarker.
Carlson et al., 2009	N/A, review	Compared clinical and diagnostic profiles across mild, moderate, and severe TBI and touched on mTBI diagnostic difficulties.
Bruns & Hauser, 2003	N/A, review	Epidemiological data on TBI incidence across severity levels, establishing mTBI as a significant health concern warranting diagnostic improvement.
Mayfield Brain & Spine, n.d.	N/A, review	Provided an overview of mTBI, including common symptoms, recovery timelines, and when to seek medical care.

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