American Journal of Psychiatry and Neuroscience
2026, Vol. 14, No. 3, pp. 57–68
https://doi.org/10.11648/j.ajpn.20261403.12

Review Article

Multimodal Approach to Diagnosing Mild Traumatic Brain Injury: A Comprehensive Literature Review

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Abstract

Mild traumatic brain injury (mTBI) affects 69 million people annually worldwide. A significant subset of those affected will develop long-term sequelae that can seriously impact quality of life and lead to other health problems. Clinical diagnosis of mTBI is complicated by patient malingering, subjective symptomatology, and variable patient reporting. This review aimed to evaluate the potential effectiveness of combining advanced neuroimaging techniques with psychometric testing and blood biomarker analyses for developing a more objective and comprehensive mTBI assessment protocol. A review was conducted using PubMed as the primary database, analyzing studies published between 2015 and 2023. Included studies evaluated mTBI (defined as Glasgow Coma Scale score ≥ 14) and incorporated neuroimaging assessment. Studies had to include patients presenting with characteristic mTBI symptoms, such as headache, balance/motor deficits, cognitive impairments, and fatigue. Studies focused on diagnostic accuracy, clinical utility, and integration of different assessment modalities were included. Advanced neuroimaging techniques, particularly Diffusion Tensor Imaging (DTI), demonstrated superior detection of subtle axonal damage compared to conventional CT and MRI. Specific brain regions, including temporal, fusiform, inferior parietal, and lateral occipital areas, showed promising diagnostic potential. Psychometric assessments, notably the Test of Memory Malingering combined with pupillometry, demonstrated high sensitivity in detecting symptom validity. Blood biomarker analyses revealed S-100B, neurofilament light, and Tau proteins as potential diagnostic indicators, where temporal profiles correlating with symptom progression. Evidence suggests that integration of multiple diagnostic modalities will significantly enhance mTBI diagnosis accuracy. A multimodal approach is the most effective way to overcome the limitations of individual methods. For example, psychometric tests are relatively subjective, while neuroimaging after an injury is unable to distinguish between pre-existing and new injuries. Devising a clinically relevant multimodal approach will require establishment of standardized norms and studies further validating individual approaches and estimating diagnostic accuracy for combinations of modalities relative to patient outcomes. These findings have particular relevance for Nevada's healthcare system, where rapid and accurate mTBI diagnosis could significantly impact patient care in both urban and rural settings. Future research should focus on validating specific combinations of these techniques and establishing standardized protocols for clinical implementation.

Keywords

MTBI, Concussion, Neuroimaging, Biomarkers, Neurofilament Light, Glasgow Coma Scale, Psychometrics

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Received: 6 May 2026; **Accepted:** 7 July 2026; **Published:** 30 July 2026

1. Introduction

Mild traumatic brain injury (mTBI), commonly referred to as a concussion, represents one of the most prevalent neurological disorders affecting approximately 55.9 million people annually worldwide [45]. Despite often appearing benign on presentation, mTBI can result in significant and persistent cognitive, physical, and emotional impairments in a subset of patients, particularly those developing post-concussion syndrome. The heterogeneous nature of mTBI—encompassing varied injury mechanisms, diverse symptom presentations, and unpredictable recovery trajectories—creates substantial diagnostic and prognostic challenges [1]. Conventional neuroimaging techniques such as computed tomography and standard magnetic resonance imaging frequently yield normal findings despite the presence of underlying pathophysiology, leaving clinicians without objective biomarkers to confirm diagnosis, predict outcomes, or guide clinical management decisions [2].

Currently there is no standardized definition or guidelines for mTBI classification. A majority of diagnoses rely on a Glasgow Coma Scale (GCS) of >14, with little in the realm of further guidelines to distinguish alternative presentations. In fact, five large organizations and medical centers across the globe have different definitions of mTBI: the Center for Disease Control and Prevention (CDC), the Department of Veterans Affairs and Department of Defense (VA/DoD), the American College of Rehabilitation Medicine (ACRM), the Eastern Association for the Surgery of Trauma (EAST), and the University of Arizona's Brain Injury Guidelines (BIG). 2, 4. Due to a lack of a standardized definition of mTBI, many institutions utilize the severe TBI guidelines when treating patients for brain injury. This has led to increased hospital stays, healthcare costs, unnecessary radiation exposure (*Harris*). This knowledge gap prompts the development of a strategy to accurately diagnose mTBI.

The absence of a consistent and universally accepted diagnostic criterion for mTBI underscores the critical need for a multimodal assessment approach. Rather than relying solely on subjective clinical history, symptom reports, or a single assessment modality, current evidence suggests that integrating advanced neuroimaging, fluid biomarkers, and psychometric testing provides clinicians with a comprehensive understanding of injury mechanisms and individual recovery patterns. This literature review examines the state of knowledge at this time regarding multimodal assessment strategies for mTBI–focusing specifically on three complementary assessment domains: advanced neuroimaging techniques, fluid biomarkers, and standardized psychometric testing protocols. By synthesizing evidence between the years of within the last 20 year across these domains, we present a framework for developing comprehensive mTBI assessment protocols that enhance diagnostic accuracy, improve patient outcomes, and further enable the development of more successful treatment plans for patients with mTBI.

2. Advanced Neuroimaging Techniques in mTBI Assessment

2.1. Introduction to Using Neuroimaging

Neuroimaging has been a well-established method for the diagnosis of mild traumatic brain injury (mTBI), with a variety in the number of methods developed to detect trauma to the brain. In the modern day, conventional means of imaging in computed tomography (CT) and magnetic resonance imaging (MRI) have been replaced with advanced techniques tailored to detecting neuronal injury at a more detailed level.

2.2. Diffusion Tensor Imaging and White Matter Assessment

Diffusion tensor imaging (DTI) has emerged as one of the most sensitive neuroimaging techniques for detecting microstructural white matter abnormalities in mTBI patients, even when conventional imaging appears normal. DTI measures the directional dependence of water diffusion along axonal structures, providing quantitative metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) that reflect tissue integrity and myelination status. Multiple studies have demonstrated that white matter changes detected by DTI correlate with clinical outcomes, cognitive impairment, and recovery trajectories in mTBI populations [3, 4]. Notably, DTI appears particularly sensitive to diffuse axonal injury, a hallmark pathological feature of traumatic brain injury that may not be visible on conventional imaging sequences [3]. Abnormalities in major white matter tracts, including the corpus callosum, uncinate fasciculus, and superior longitudinal fasciculus, have been documented in both acute and chronic phases of mTBI, supporting DTI's utility as a sensitive biomarker of injury severity and recovery status [3, 4].

However, despite the promise of using DTI alone to diagnose mTBIs due to its high sensitivity, its use in clinical practice has yet to be fully explored. A landmark study demonstrated that across a single season of football, players without clinically diagnosed concussions still had measurable DTI changes that correlated with cumulative head impact exposure and verbal memory deficits [5]. These findings underscore DTI's potential role not only in detecting overt injury but also in identifying subclinical neurobiological changes that may predispose individuals to future risk of impairment.

2.3. Functional Magnetic Resonance Imaging and Network Connectivity

Functional MRI (fMRI) provides unique insights into brain network organization and functional connectivity alterations following mTBI. Rather than visualizing structural damage,

fMRI measures blood oxygen level-dependent (BOLD) signals that reflect neural activity patterns during rest or task performance. In concussed individuals, resting-state fMRI studies have consistently identified alterations in the default mode network (DMN), a large-scale brain network implicated in cognition. Early work demonstrated that concussed athletes in the subacute phase of injury showed reduced connectivity within the DMN, particularly between the posterior cingulate cortex and lateral parietal regions, despite clinical symptom resolution [6]. More recent investigations have extended these findings, revealing that functional connectivity changes may persist beyond symptom resolution and correlate with cognitive impairment, fatigue, and risk for protracted recovery [7, 8].

The production and analysis of comprehensive detailed maps of the neural connections within a brain, termed connectomes, reveal that mTBI-induced connectivity alterations are distributed across multiple networks rather than being localized to a single anatomical region, consistent with diffuse injury mechanisms [7, 8]. Furthermore, fMRI studies examining task-related activation during cognitive challenges have documented compensatory hyperactivation in mTBI patients, suggesting that cognitive demands activate additional neural resources to maintain adequate performance [8]. The dynamic nature of these network changes—with connectivity patterns evolving from hyperactivation in acute phases to variable patterns during recovery—suggests that fMRI could serve as a longitudinal biomarker to track neurobiological recovery and identify individuals at risk for chronic post-concussion syndrome.

Although it shows promise in tracking patient recovery, use of fMRI as a diagnostic method may be limited. Because it evaluates the connections between regions of the brain, it is a highly individualized imaging modality that, when employed following an injury, presents challenges in determining the patient's status prior to the injury. [8, 9]. Paired with the highly involved nature of the equipment that is used in fMRI, it would be difficult to employ in first-line diagnoses.

2.4. Magnetic Resonance Spectroscopy and Metabolic Assessment

Magnetic resonance spectroscopy (MRS) enables noninvasive measurement of neurochemical concentrations in brain tissue, providing molecular-level information about metabolic disturbances following mTBI. The primary metabolites quantified by MRS include N-acetylaspartate (NAA), a marker of neuronal integrity; choline (Cho), associated with membrane metabolism; creatine (Cr), involved in energy metabolism; and glutamate/glutamine (Glx), excitatory neurotransmitters implicated in neuroinflammation [12]. Studies of sports-related concussions have documented acute reductions in NAA/Cr ratios, suggesting neuronal damage or mitochondrial dysfunction, with recovery patterns showing initial impairment followed by gradual normalization over weeks to months [44].

Recent advances in MRS methodology, including higher field strengths and improved spectral processing algorithms, have enhanced sensitivity and reproducibility [10]. One prospective study examining amateur Olympic boxing documented increased CSF biomarkers and metabolite changes through MRS in 55 concussed athletes, with some players showing persistent abnormalities even after symptom resolution, suggesting that MRS may detect neurobiological changes outlasting clinical recovery [11]. The integration of MRS with other neuroimaging modalities, particularly DTI and fMRI, may enhance understanding of the relationship between microstructural damage, metabolic dysfunction, and functional network alterations following mTBI. As standardized protocols continue to develop, MRS could provide valuable longitudinal markers of neurochemical recovery and help identify patients at risk for protracted post-concussion syndrome.

2.5. Perfusion Imaging: Arterial Spin Labeling and Cerebral Blood Flow

Cerebral blood flow (CBF) abnormalities following mTBI have been documented using arterial spin labeling (ASL), a noninvasive perfusion MRI technique that quantifies regional blood flow without requiring contrast injection [14]. ASL-based studies have consistently demonstrated regional CBF alterations in mTBI populations, with findings varying across studies in terms of whether CBF is increased or decreased in specific regions [14]. A comprehensive systematic review of 23 ASL studies involving over 500 mTBI patients and 600 controls found that 18 of 23 studies reported some type of regional CBF abnormality, though methodological variations across studies complicated synthesis of findings [15]. Importantly, pediatric mTBI studies documented that symptomatic children showed elevated global CBF compared to asymptomatic and control groups, with CBF levels potentially serving as a predictor of symptom duration and recovery trajectory [15].

The pathophysiological mechanisms underlying post-traumatic CBF abnormalities remain incompletely understood but likely involve dysregulation of cerebrovascular reactivity—the brain's ability to adjust blood flow in response to metabolic demand. Several studies have investigated cerebrovascular reactivity using vasoactive manipulations (hypercapnia, breath-holding) combined with MRI-based CBF measurement, documenting reduced CBF responses to metabolic challenges in mTBI patients [16, 46, 47]. Longitudinal studies examining CBF evolution during recovery suggest that early perfusion abnormalities may precede symptom resolution, potentially explaining why some individuals with apparently resolved symptoms continue experiencing cognitive difficulties during cognitively demanding activities. The integration of perfusion imaging with other MRI sequences and biomarker data could

enhance understanding of post-traumatic neurobiological processes and assist in identifying individuals at risk for prolonged recovery or chronic post-concussion syndrome. However, it requires further research to be fully understood and applicable in a clinical setting.

2.6. Positron Emission Tomography and Metabolic Imaging

Positron emission tomography (PET) imaging, particularly fluorodeoxyglucose positron emission tomography (FDG-PET), provides unique insights into brain glucose metabolism following mTBI. Unlike structural imaging that visualizes anatomy or DTI that assesses tissue integrity, FDG-PET measures regional glucose uptake as a proxy for neuronal metabolism and activity. Compared to conventional imaging, FDG-PET demonstrates higher sensitivity for detecting functional abnormalities in mTBI, particularly in patients with normal CT findings. However, clinical adoption of PET imaging for mTBI has been limited by several factors including cost, availability, radiation exposure, and lack of standardized protocols for data acquisition and interpretation [13].

Despite these limitations, FDG-PET remains a valuable research tool for understanding post-traumatic metabolic dysfunction. Studies comparing mTBI patients with healthy controls have documented reduced glucose uptake in multiple brain regions, with patterns varying depending on time since injury and individual recovery trajectories [17]. The integration of PET with MRI through hybrid PET/MRI systems represents an exciting frontier that could enable simultaneous assessment of multiple neurobiological domains—including glucose metabolism (PET), white matter integrity (DTI), functional connectivity (fMRI), and perfusion (ASL)—within a single imaging session. As PET technology becomes more accessible and standardized protocols emerge, multimodal PET-MRI assessment could enhance our ability to characterize individual injury phenotypes and predict recovery trajectories.

2.7. Integration of Advanced Neuroimaging into Clinical Practice

The evidence supporting advanced neuroimaging techniques for mTBI assessment is substantial, yet clinical integration remains limited. A critical challenge is that no single neuroimaging modality definitively diagnoses mTBI or reliably predicts individual recovery trajectories. DTI may detect white matter abnormalities, but these may not correlate with clinical symptoms; fMRI reveals functional connectivity alterations, but their clinical significance remains unclear; perfusion abnormalities may persist long after symptom resolution. This heterogeneity reflects mTBI's fundamental complexity as a multifactorial injury affecting multiple brain systems through multiple pathophysiological mechanisms.

Contemporary evidence increasingly supports a multimodal neuroimaging approach in which complementary techniques can address different aspects of injury pathophysiology [2]. For instance, combining DTI (white matter integrity), fMRI (functional connectivity), and MRS (metabolic status) with conventional MRI provides a more comprehensive characterization of injury than any single technique alone. As these standardized protocols become more widespread, advanced neuroimaging is likely to play an increasingly important role in mTBI assessment, particularly for identifying patients at risk for chronic symptoms or neurodegenerative consequences.

3. Fluid Biomarkers in mTBI Diagnosis and Prognostication

3.1. Blood-Brain Barrier Disruption and Biomarker Transport Mechanisms

Understanding the mechanisms by which brain-derived proteins enter the bloodstream is critical for interpreting biomarker elevations and understanding what they represent about brain pathophysiology. Blood-brain barrier (BBB) disruption is a hallmark acute consequence of mTBI, enabling molecules typically excluded from blood to leak into circulation [30]. This relationship between BBB disruption and later neurobiological changes supports the hypothesis that BBB disruption initiates a cascade of secondary injury processes including oxidative stress, neuroinflammation, and neurodegeneration.

3.2. Blood-Based Protein Biomarkers: GFAP and UCH-L1

The identification of blood-based biomarkers for mTBI represents a developmental moment in trauma diagnostics, culminating in FDA approval of the first-in-class biomarker-based test for mild TBI. In 2021, Abbott Diagnostics received FDA clearance for the i-STAT Alinity, a point-of-care plasma blood test measuring two brain-derived proteins: glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) [19]. GFAP, released by reactive astrocytes in response to brain injury, and UCH-L1, a neuronal protein released following axonal damage, exhibit rapid elevations in blood following mTBI. This provides physicians with a minimally invasive tool to assist in diagnosing mTBI and predicting intracranial lesions, moving beyond reliance on symptom reports and clinical judgment.

Age and biological sex also serve as modifying factors in the measurement of blood biomarker levels. A large prospective study including 2,600 TBI patients across multiple age groups found that day-1 GFAP demonstrated good-to-excellent diagnostic performance across all age categories, with area under the curve values ranging from 0.84-0.96 [29]. Biological sex also influences biomarker levels, with some evi-

dence that female patients may show higher acute GFAP elevations and that sex-specific references might improve diagnostic accuracy [21]. These biological factors underscore the importance of considering individual patient characteristics when interpreting biomarker results.

Clinical validation studies have demonstrated the diagnostic utility of plasma GFAP and UCH-L1, particularly within the acute post-injury window. A prospective multicenter study found that UCH-L1 and GFAP measured within 6 hours of injury showed ability to differentiate CT-positive from CT-negative mTBI cases, with UCH-L1 achieving 100% sensitivity at a cutoff of 40 pg/mL [20]. More recently in 2023, a comprehensive study examining 74 CT-negative mTBI patients demonstrated that plasma Interleukin-6 (IL-6), GFAP, and UCH-L1 showed excellent discrimination between injured and control participants acutely, with IL-6 increasing accuracy when combined with GFAP [21]. Critically, GFAP demonstrated sustained discriminative ability across all age categories until at least day 3 post-injury, suggesting utility not only in the immediate post-injury emergency department setting but also in delayed presentations. These findings support the adoption of blood biomarkers as objective diagnostic aids, particularly in CT-negative mTBI where clinical management is most uncertain.

3.3. Neurofilament Light Chain and Tau as Prognostic Biomarkers

While GFAP and UCH-L1 provide acute diagnostic information, neurofilament light chain (NfL) and tau proteins offer prognostic insights into post-traumatic neurodegeneration and long-term recovery. NfL, a component of the neuronal cytoskeleton released during axonal damage, has emerged as a particularly promising biomarker for predicting prolonged recovery and identifying patients at risk for chronic post-concussion syndrome [21]. Unlike GFAP and UCH-L1, which peak acutely and normalize within days, NfL shows sustained elevation extending into the subacute and chronic phases of injury, making it particularly valuable for prognostication beyond the immediate post-injury period [48].

Phosphorylated tau (p-tau), which accumulates in tau tangles associated with neurodegenerative disease, has garnered attention as a potential marker of chronic post-traumatic neurodegeneration. A comprehensive study comparing multiple tau species found that p-tau and the ratio of p-tau to total tau outperformed total tau alone as both diagnostic and prognostic biomarkers, with sustained elevations in chronic TBI [22]. This increased performance may prove beneficial in circumstances of diagnostic uncertainty, permitting for a more sensitive and predictive form of assessment. An important clinical application emerged from observations that elevated plasma tau within 6 hours of sport-related concussion was associated with prolonged return-to-play timelines, suggesting that acute tau measurement could assist in identifying individuals requiring more conservative management strategies [23]. These findings underscore that individual biomarkers capture different aspects of post-traumatic pathophysiology; GFAP and UCH-L1 provide acute diagnosis, while NfL and tau offer prognostic information about long-term trajectory and neurodegeneration risk.

3.4. Supplementary Blood-Based Biomarkers and Emerging Candidates

Beyond the FDA-approved GFAP/UCH-L1 combination, multiple supplementary biomarkers have demonstrated clinical utility in research and emerging clinical applications. S100B, a calcium-binding protein released by astrocytes, has the longest track record of clinical use, with excellent negative predictive value enabling identification of mTBI patients at lowest risk for intracranial complications who could safely avoid CT imaging. IL-6 and other inflammatory cytokines, while less specific to the nervous system than neuronal and glial proteins, have shown promise when combined with neuro-specific biomarkers, potentially improving diagnostic accuracy through capturing both neuroinflammatory and neuronal injury dimensions [24].

MicroRNAs (miRNAs)—small regulatory RNA molecules that circulate in blood and regulate gene expression—represent an emerging frontier in biomarker development. A study identified specific miRNA signatures associated with mTBI, with plasma miR-9-3p and miR-136-3p showing potential as diagnostic biomarkers in both experimental models and clinical populations [25]. The stability of miRNAs in blood, ease of detection using sensitive quantitative PCR platforms, and their potential to reflect specific molecular injury mechanisms make them attractive candidates for future clinical development. Additional emerging biomarkers including GFAP, UCH-L1, NfL, and p-tau continue to be investigated in examining their temporal evolution, association with clinical outcomes, and utility in multimodal assessment protocols.

An important consideration to take into account is the time frame in which the biomarkers are measured due to the impact of the glymphatic system. This system is a perivascular fluid clearance mechanism that becomes more active during sleep, providing an alternative route for biomarker transport from brain to blood. One study demonstrated that suppressing glymphatic function through sleep deprivation or pharmacological manipulation reduced TBI-induced elevations of biomarkers including S100B and GFAP despite continued brain injury [28]. This finding has profound implications for biomarker interpretation and clinical implementation. First, biomarker levels may not simply reflect injury severity but depend critically on physiological factors like sleep and activity status. Second, patients who are awake and active post-injury (as occurs in emergency department evaluation) may show higher biomarker elevations than those assessed, later when resting, potentially confounding temporal assessments of biomarker kinetics. These considerations underscore the im-

portance of rigorous standardization of sample collection procedures, timing, and patient state during biomarker assessment.

3.5. Biomarker Kinetics, Timing, and Interpretation

Critical for clinical implementation is understanding the temporal dynamics of blood biomarkers following mTBI. Biomarkers exhibit distinct kinetic profiles: GFAP and UCH-L1 peak within hours of injury and normalize within days, making them ideal for acute diagnosis; NfL shows slower rise and extended elevation, persisting for weeks to months; tau intermediates between these patterns [27]. These temporal characteristics have important clinical implications. For example, a patient presenting days after injury with normal GFAP/UCH-L1 but elevated NfL would suggest either that significant time has elapsed or that the injury caused diffuse neuronal damage with limited acute glial response. Interpretation must also account for blood-brain barrier integrity, as biomarker elevations require disruption of this barrier for protein release into blood.

Considering the novelty of biomarkers and the lack of historical use to support its success clinically, their use as a standalone method for diagnosis is not yet established. This complementary relationship suggests that blood biomarkers (GFAP, UCH-L1) could serve as rapid diagnostic screening tools in acute settings, enabling rapid identification of high-risk patients requiring imaging, while advanced MRI and additional biomarkers (NfL, tau) provide prognostic information guiding long-term management.

For acute emergency department triage, GFAP and UCH-L1 are most appropriate given their acute elevation and proven diagnostic utility. For identifying patients at risk for prolonged recovery or chronic post-concussion syndrome, NfL and tau measured in subacute phases may be more informative. For research aimed at understanding neurodegeneration after repeated mTBI, the combination of acute biomarkers provides the most complete characterization. As biomarker panels become increasingly accessible and costs decline, comprehensive multimodal biomarker assessment is likely to become a standard component of mTBI evaluation protocols.

4. Psychometric Testing and Neuropsychological Assessment

4.1. Computerized Neurocognitive Assessment Tools

Computerized neurocognitive testing (CNT) platforms have become ubiquitous in mTBI assessment, particularly in sports medicine settings. CNT offers advantages over traditional paper-and-pencil testing including standardized administration, automatic scoring, normative comparisons, and readily identifiable practice effects. The most widely used platforms include Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), Automated Neuropsychological Assessment Metrics (ANAM), and CNS Vital Signs, each assessing domains including memory, attention, processing speed, and executive function. Initial enthusiasm for computerized testing is derived from evidence that concussed athletes showed measurable cognitive impairment detectable within 24 hours of injury, with most recovering by one week, suggesting these tools could objectively document injury and recovery [31].

However, subsequent research has documented significant limitations of CNT platforms, complicating their clinical application beyond the acute post-injury period. A large prospective head-to-head study directly comparing ImPACT, Axon Sports/CogState Sport, and ANAM in 165 concussed and 166 non-injured control athletes found that while sensitivity for detecting impairment was reasonable in acute phases (67.8% for ImPACT), it declined substantially thereafter, with all platforms showing poor sensitivity beyond 15 days post-injury [32]. Furthermore, test-retest reliability was suboptimal on many subtests even during stable periods, and the clinical significance of between-subject variations on cognitive testing remains unclear. Cognitive test results were not always consistent with patient presentation as many symptomatic athletes showed cognitive performance within normal limits. Conversely some asymptomatic athletes demonstrated measurable cognitive changes, indicating that cognition represents only one aspect of post-concussion pathophysiology [32].

4.2. Traditional Neuropsychological Assessment and Comprehensive Batteries

Traditional neuropsychological assessment conducted by trained clinical neuropsychologists involves comprehensive evaluation using standardized tests with extensive controls and psychometric data [42]. Classical tests including the Wechsler Adult Intelligence Scale, California Verbal Learning Test, Trail Making Test, and Wisconsin Card Sorting Test provide detailed assessment of specific cognitive domains and offer greater diagnostic sensitivity for detecting neurocognitive dysfunction than computerized screening tools. A comprehensive survey of clinical neuropsychologists revealed that when asked to assess a patient with mTBI, practitioners typically administered 10-15 individual tests addressing memory, attention, executive function, language, and visuospatial domains [33].

Comprehensive neuropsychological assessment offers distinct advantages for mTBI evaluation, particularly in identifying cognitive disturbances that might be missed by briefer digital batteries. For instance, mTBI patients often demonstrate subtle deficits in information processing speed, complex attention divided attention, or executive function that are apparent only on demanding neuropsychological tests [34]. Addi-

tionally, comprehensive testing enables detection of effort-related validity issues or psychiatric comorbidities that can mimic or exacerbate apparent cognitive impairment [35]. A consensus approach combines brief computerized screening for rapid identification of cognitively impaired patients with comprehensive neuropsychological assessment for individuals with persistent symptoms or unclear recovery trajectories.

4.3. Symptom Reporting and Post-Concussion Symptom Scales

Self-reported symptoms remain a cornerstone of mTBI assessment, as symptom severity and resolution typically guide return-to-play decisions and clinical management. The post-concussion symptom scale (PCSS), a self-report instrument quantifying frequency and severity of common post-concussion complaints (i.e. headache, dizziness, concentration difficulty, etc.), has become nearly ubiquitous in sports medicine settings. The PCSS demonstrates reasonable test-retest reliability and sensitivity for detecting post-concussion effects. Concussed athletes typically reported elevated symptom scores immediately post-injury that gradually decline over subsequent days to weeks, paralleling clinical recovery [36].

However, symptom reports present inherent challenges for objective diagnosis and prognosis determination. Symptom based return-to-play protocols implicitly assume that symptom resolution indicates neurobiological recovery, yet emerging evidence demonstrates persistent neurobiological abnormalities weeks after symptom resolution [37]. Additionally, symptoms lack specificity for mTBI. Many post-concussion symptoms overlap with depression, anxiety, post-traumatic stress, chronic pain, sleep disorders, and other conditions common in trauma populations. A study examining comorbid PTSD and mTBI in military service members found that psychological symptoms and cognitive dysfunction could not be attributed entirely to mTBI, as PTSD accounted for substantial cognitive variance [38]. Moreover, individual differences in symptom reporting, influenced by personality, coping style, compensation incentives, and cultural factors, can obscure the relationship between symptom report and neurobiological injury severity.

4.4. Psychometric Issues and Standardization Challenges

Critical psychometric issues complicate interpretation of cognitive and behavioral assessments in mTBI. Practice effects—improvements in performance due to familiarity with tests rather than actual cognitive change—represent a major confounder, particularly when repeat assessments are conducted within weeks of baseline. Similarly, malingering and suboptimal effort, documented in some mTBI patients (particularly those with litigation involvement or compensation incentives), can produce artificially depressed test performances unrelated to actual brain injury. Standardized assessment of effort validity through validated instruments enables identification of questionable performances [39].

A framework for interpreting change in individual patients recognizes that test scores vary naturally due to measurement error, and observed changes must exceed reliable change index thresholds to indicate true cognitive alteration [40]. Furthermore, variation in the brain regions impacted by an mTBI may alter the symptoms that present, requiring different tests for individual patients who exhibit unique symptoms. It was also implicated that the non-linear nature of recovery from an mTBI requires more specific evaluation methods to determine whether variations in the patients performance across time are accurately reflecting the progression of recovery [41]. Additionally, heterogeneity in assessment timing, test versions used, and patient populations studied across research centers has hindered meta-analytic synthesis and translation of findings to clinical practice [42]. These challenges have motivated efforts to develop standardized assessment protocols with consensus on optimal timing of evaluations, recommended test batteries, and interpretation frameworks accounting for demographics, baseline functioning, comorbidities, and effort validity.

5. Comprehensive Multimodal mTBI Assessment Protocol

5.1. Integrating Neuroimaging, Biomarkers, and Psychometric Testing

Recent studies have shown increasing evidence supporting the integration of advanced neuroimaging, fluid biomarkers, and psychometric testing into unified assessment protocols that capitalize on the complementary strengths of each modality [18, 49, 50]. A conceptual framework recognizing mTBI as a multisystem disorder affecting multiple brain scales—from molecular (neuroinflammation, oxidative stress, axonal injury) to network (functional connectivity, white matter integrity) to behavioral (cognitive, emotional, physical). This suggests that comprehensive characterization requires assessment across these levels. Fluid biomarkers provide rapid molecular information indicating presence and severity of neuronal and glial injury; advanced neuroimaging reveals structural and functional correlates of injury mechanisms; psychometric testing quantifies behavioral consequences and functional impairment.

The practical implementation of multimodal assessment must balance diagnostic rigor with clinical feasibility. In acute emergency department settings where rapid decision-making is essential, blood biomarkers (GFAP and UCH-L1) offer point-of-care diagnostic utility, enabling rapid identification of patients at highest risk for intracranial complications who require imaging, while those with negative biomarkers and normal CT can be safely discharged with follow-up counseling. For patients presenting with persistent post-concussion

syndrome days to weeks after injury, advanced neuroimaging (DTI, fMRI, perfusion MRI) and expanded biomarker panels including NfL and p-tau provide prognostic information guiding treatment selection and predicting recovery timelines. Comprehensive neuropsychological assessment identifies specific cognitive domains affected, guides cognitive rehabilitation strategies, and documents functional limitations for disability determinations.

5.2. Standardized Assessment Tools and Return-to-Play/Work Frameworks

Multiple organizations have developed standardized tools for concussion assessment that increasingly incorporate multimodal components. The Sport Concussion Assessment Tool (SCAT), in its most recent iteration (SCAT6), includes sections for symptom assessment, cognitive screening, balance testing, and assessment of neurobehavioral changes [43]. The Sideline Office Concussion Assessment Tool (SCOAT) provides briefer screening suitable for rapid sideline or office-based evaluation. Importantly, the 6th International Conference on Concussion in Sport consensus statement explicitly acknowledges that diagnosis and management should be individualized and emphasized that "no single diagnostic test, measure or instrument can be used to assess concussion" [43]. Return-to-play and return-to-work protocols have evolved from symptom-based approaches toward frameworks that also incorporate neurobiological data. This recognition reflects the heterogeneity of mTBI and the need for clinician judgment synthesizing information across multiple assessment domains.

5.3. Challenges and Barriers to Clinical Implementation

Despite substantial advances in understanding multimodal assessment approaches, translation to routine clinical practice faces multiple barriers. Cost represents a significant constraint; advanced neuroimaging (particularly MRI with multiple specialized sequences) is expensive and time-consuming, biomarker assays require specialized laboratory infrastructure and platforms, and comprehensive neuropsychological testing demands trained personnel [51]. Furthermore, no single standardized multimodal protocol has achieved universal adoption; research centers employ varying combinations of neuroimaging sequences, biomarker panels, and assessment tools, limiting comparability across studies and generalizability of findings.

Lack of clinical decision rules specifying which patients require which components of multimodal assessment represents another challenge. Should all mTBI patients undergo advanced neuroimaging? Which biomarkers should be measured, at what time points, in which patient populations? When should comprehensive neuropsychological testing be pursued versus brief computerized screening? The complexity and heterogeneity of mTBI suggest that individualized assessment tailored to specific clinical questions and patient characteristics may be more efficient than universal comprehensive protocols. For example, most patients do not have imaging from before their mTBI to compare to when diagnosing mTBIs. Future research should establish evidence-based frameworks specifying which assessment components optimally address specific clinical scenarios and patient populations.

Table 1. *Integrated timeline of comprehensive multimodal mTBI assessment protocol.*

Assessment Domain	Neuroimaging	Blood Biomarkers	Psychometric Testing	Clinical Decision
Acute Assessment (ED) (0-24 hours)	Conventional CT/MRI (rule out severe injury)	GFAP & UCH-L1 (point-of-care-test) [19-21]	Brief cognitive screen PCSS symptom scale [36, 43]	High-risk triage: Elevated biomarkers→Advanced imaging
Early Subacute (2-7 days)	Advanced MRI: DTI (white matter) fMRI (connectivity)	Initial biomarker panel + IL-6 [21]	Computerized battery (imPACT/ANAM) [31, 32]	Recovery tracking: Compare to baseline if available
Late Subacute (1-4 weeks)	Repeat Advanced MRI: DTI prognostication fMRI trajectory	NfL & p-tau (prognostication) [22, 23]	Comprehensive neuropsych battery if persistent [33, 34]	Prognosis estimation: Compare to baseline If available
Chronic Phase (>4 weeks)	PET/MRI hybrid (if available)	NfL levels (chronic trajectory) [27]	Full comprehensive assessment (disability eval) [40]	Chronic management: Planing intervention

Table 2. Comprehensive Summary of All mTBI Assessment Tools and Methods.

Assessment Domain	Specific Tool	Primary Use	Optimal Timing	References
Advanced Neuroimaging	Diffusion Tensor Imaging (DTI)	White matter microstructure	Acute to chronic	[2-5]
	Functional MRI (fMRI)	Functional connectivity patterns	Subacute to Chronic	[6, 7, 9]
	Magnetic Resonance Spectroscopy (MRS)	Metabolite abnormalities	Acute to subacute	[12, 44]
	Arterial Spin Labeling	Cerebral blood flow	Acute to chronic	[14, 16]
Blood Biomarkers	GFAP and UCH-L1	Acute diagnosis and triaging	First 24 hours	[19, 21]
	Neurofilament Light Chain (NfL)	Prognostication, chronic outcomes	Days to weeks	[22, 26, 27]
	Phosphorylated Tau (p-Tau)	Long-term neurodegeneration risks	First 6 hours to weeks	[22, 23]
	Supplementary (S100B, IL-6, mrRNA)	Complementary inflammatory markers	Variable depending on the marker	[20, 24, 25]
	Glymphatic System Effects	Biomarker transport mechanism	Similar to biomarker interpretation	[28-30]
Psychometric Testing	Computerized Neurocognitive Testing	Cognitive deficit screening	Acute	[31, 32]
	Traditional Neuropsychological Battery	Comprehensive cognitive mapping	After symptoms persist to chronic	[33, 34]
	Post-Concussion Symptom Scale	Symptom monitoring	Daily	[36]
	Sport Concussion Assessment (SCAT)	Standardized multimodal assessment	Standardized intervals	[43]

6. Point-of-Care Technologies and Accessible Assessment

Technological advances are reducing barriers to multimodal assessment through development of increasingly accessible tools. The FDA-approved point-of-care biomarker tests represent a major advance, enabling rapid plasma biomarker measurement in emergency departments or sideline settings without requiring specialized laboratory infrastructure. Similarly, portable eye-tracking systems, wearable electrophysiological sensors, and tablet-based cognitive testing applications are expanding access to objective assessment tools in resource-limited settings. Alongside the development of standardized protocols, these emerging technologies may provide a basis for improved identification and treatment of patients with mTBIs. In particular, the combination of MRS with longitudinal markers of neurochemical recovery may be used to track patient recovery. Not only from their injury, but also from sequelae such as post-concussive syndrome.

Abbreviations

mTBI	Mild Traumatic Brain Injury
GCS	Glasgow Coma Scale
CDC	Center for Disease Control and Prevention
VA/DoD	Department of Veterans Affairs and Department of Defense
ACRM	American College of Rehabilitation Medicine
EAST	Eastern Association for the Surgery of Trauma
BIG	University of Arizona's Brain Injury Guidelines
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
MD	Mean Diffusivity
AD	Axial Diffusivity
RD	Radial Diffusivity
fMRI	Functional MRI
BOLD	Blood Oxygen Level-Dependent
DMN	Default Mode Network
MRS	Magnetic Resonance Spectroscopy
NAA	N-acetylaspartate
Cho	Choline
Cr	Creatine
Glx	Glutamate/Glutamine
CBF	Cerebral Blood Flow
ASL	Arterial Spin Labeling
PET	Positron Emission Tomography

FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
BBB	Blood-Brain Barrier
GFAP	Glial Fibrillary Acidic Protein
UCH-L1	Ubiquitin C-terminal Hydrolase-L1
NfL	Neurofilament Light Chain
p-tau	Phosphorylated Tau
miRNAs	MicroRNAs
CNT	Computerized Neurocognitive Testing
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing
ANAM	Automated Neuropsychological Assessment Metrics
PCSS	Post-Concussion Symptom Scale

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

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