The Economist INTELLIGENCE UNIT

Exploring future possibilities to improve evaluation and management of traumatic brain injury

A report by The Economist Intelligence Unit

Key points:

- Current diagnostic tools for traumatic brain injury (TBI) have several limitations, such as unnecessary exposure to radiation, and poor sensitivity and specificity
- Lack of standard definitions and consistency in clinical management guidelines is a challenge in the diagnosis and management of mild TBI (mTBI)
- Patient and physician education is crucial to address the burden of TBI, especially mTBI
- Advancements in biomarker research have the potential to transform the assessment and care of mTBI patients
- Demonstrating clinical utility is the next step to advance the study and application of biomarkers for TBI

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Traumatic brain injury: the most common neurological disorder worldwide

Traumatic brain injury (TBI) is a sudden injury caused by a bump, blow, or jolt to the head, disrupting the normal function of the brain.[1,2] TBI is classified into mild, moderate and severe categories based on the extent and nature of the injury, duration of loss of consciousness, posttraumatic amnesia (loss of memory) and extent of confusion at initial assessment of the injury.[3] Often referred to as the "silent epidemic", TBI is the most common neurological disorder worldwide, contributing to more death and disability than any other traumatic injury.[2,4]

27 to 69 million annual TBI cases worldwide

Global economic burden estimated to be around US$400bn annually

Annually, the global incidence of TBI is variable but estimated to be 27 to 69 million.[5,6] TBI also places a substantial socioeconomic burden on individuals and their families, and on society as a whole. The global economic burden of TBI is estimated to be around US$400 billion annually.[7]

Mild TBI (mTBI) is the most common form of TBI, accounting for more than 80% of all TBI cases.[4] The World Health Organization Neurotrauma Task Force[8] defines mTBI as a blow to or jolting

of the head causing an acute disruption of brain function, manifested by a brief loss of consciousness (<30minutes), confusion, or posttraumatic amnesia (<24hours) not otherwise accounted for by factors such as psychological trauma or alcohol/drug intoxication. The highest rates of mTBI are observed in adults older than 75 years, children younger than 5 years and adolescents/young adults ages 15 to 24 years.[4] Though mTBI is the least severe of all brain injuries, diagnosis and management remains a key challenge, with mTBI often being mis- or underdiagnosed. Poor diagnosis and prognosis evaluation of mTBI can lead to serious neurological effects, including impairment of cognitive functions, movement coordination and social behavior and an overall decrease in quality of life.[9]

Current approaches for mTBI diagnosis and management

Diagnosis and management of mTBI often occurs in emergency departments (EDs). At present, typical approaches to identify and evaluate the severity of mTBI include

application of the Glasgow Coma Scale (GCS), neuropsychological assessments and neuroimaging to measure the damage caused by injury.

Glasgow Coma Scale (GCS)

The Glasgow Coma Scale (GCS) is the most common scoring system used to describe the level of consciousness in a person after a TBI and to gauge the severity of an acute brain injury. It measures visual, motor and verbal responses for a maximum total score of 15 points. A GCS score of 13-15 is classified as a mild brain injury, 9-12 is classified as moderate and 3-8 is classified as severe.[10] (See Table 1.)

While extremely useful in the clinical evaluation and management of TBIs, scientists are of the opinion that the GCS does not provide sufficient specific information about the pathophysiologic mechanisms of neurological deficits.[11] Apart from this, the GCS has other significant limitations since the results can be distorted by drug use, alcohol intoxication, shock and low blood oxygen levels.[12]

Neuropsychological assessments

A neuropsychological assessment consists of a variety of tests designed to measure the damage caused by a brain injury. The assessment primarily focuses on testing a patient's mental status, cranial nerves, sensory awareness, motor function and reflexes.[14]

Generally the neurological exam in trauma patients is done by the trauma team in consultation with a neurosurgeon or neurologist. In addition to this assessment, the team interviews the patient and patient's family members, evaluates the patient's hospital records and reviews any other information that might provide insight into the patient's health prior to the injury.

Table 1: Glasgow Coma Scale

	GCS (first 24 h)	Loss of Consciousness	Alteration of Consciousness	Imaging	PTA*
Mild	13 - 15	0 - 30 min	up to 24 h	Normal	0 - 1 d
Moderate	9 - 12	>30 min & <24 h	>24 h	Normal or abnormal	>1 d & <7 d
Severe	3 - 8	>24 h	>24 h	Normal or abnormal	>7 d

*Post-traumatic amnesia

Source: Capizzi et al., 2020[1]

However, these assessments have their own disadvantages. First, access is a major issue, particularly in remote areas, as not every hospital has a psychology department or a brain injury program, and assessments done by someone in private practice can be very expensive. Second, lack of standard guidelines often affect the results and consistency of such tests.[15]

Neuroimaging

Neuroimaging plays an important role in identifying a patient with a brain injury, both for acute injuries and injuries with persistent symptoms. Existing imaging modalities range from conventional computed tomography (CT) and magnetic resonance imaging (MRI) scans to more advanced techniques like perfusion CT scans (PCT), diffusion tensor imaging (DTI) techniques, and functional MRIs. A few of these novel modalities can also provide insight into metabolic abnormalities that may result from a TBI, thus aiding in the clinical management of patients.[16]

CT scan is the most commonly used neuroimaging technique and is usually the first test performed in an ED for a suspected TBI.[17] The advantages of low cost and greater convenience over other imaging techniques makes CT scans a preferred mode of imaging technology in diagnosing and evaluating acute head injuries.[18]

However, recent findings demonstrating poor outcomes of CT scans following mTBI have created controversy. A study conducted by Lannsjö and colleagues[19] involving 1,262 mTBI patients from Sweden found that, of all the patients examined for acute head injury by CT scans, only 4% had relevant or suspected pathological findings. No association was identified between CT scan pathology and self-reported symptoms. A growing concern about radiation exposure and increasing wait times further adds to this controversy. In a study by Rogg and colleagues[20], 8,312 patients in high-volume EDs who received a head CT reported a median wait time of 3 hours and 13 minutes (193 minutes) between the patient arrival and the CT preliminary report.[21]

MRIs and other advanced imaging techniques, by comparison, provide much more anatomical detail and are able to detect minute injuries that may escape CT scan detection. Additionally, unlike CT scans, MRIs work without radiation, thereby making them safe to use. Because of these advantages, MRIs have increasingly been used over the past few years for initial assessment of TBIs, especially in patients with unexplained neurological findings. However, limited availability in acute settings, longer imaging time and high costs raise concern about increased use of MRIs and have limited their adoption in diagnosis and management of TBIs.[22] As highlighted by Kevin Wang, "even though an MRI is more sensitive than a CT scan, it is not the standard of care in the US because it is expensive."

Other barriers affecting the identification and management of mTBI

Identification of mTBI remains a challenge, impacting the clinical management of patients. In spite of the increasing recognition of mTBI over the past few decades, there has been little progress in improving the diagnostic accuracy of such injuries. Andrew Maas noted, "mTBIs have been neglected in the past, and now we are coming to realize the tremendous burden that they produce." Timely and accurate diagnosis is crucial for patients with mTBI because a person who sustains a second injury before full recovery is at increased risk of prolonged or permanent neurological damage.[23] Besides the points made above about diagnostic tools, other factors limit identification and management of mTBI. While it is not possible to give just consideration to all the issues, two key barriers are discussed below:

1 Lack of standard definitions and consistency in clinical management guidelines

A significant barrier to accurate identification and management of mTBIs is the lack of a standard definition and inconsistency in diagnostic criteria and standardized assessment methods. A retrospective study comparing the mTBI definitions established by the American College of Rehabilitation Medicine (ACRM), Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) found that there is a lack of interdisciplinary consensus regarding what constitutes mTBI.[24] Adding to this challenge is the wide variation in clinical management of this condition. A study conducted by Foks and colleagues in EDs and hospital wards across Europe reported a lack of consistency in guidelines, with 49% of centres using national guidelines, 15% using local guidelines and 21% using no guidelines at all.[25] Evidence suggests that lack of standard guidelines on clinical management of mTBIs likely accounts for 50-90% of the mis- or underdiagnosed cases in the EDs, which in turn increases the patient's risk for a complicated or delayed recovery since they are not provided with any information regarding possible consequences of mTBIs and the expected recovery trajectory.[24]

Lack of standard definitions and inconsistency in clinical guidelines likely accounts for 50% - 90% of mis- or underdiagnosed mTBI cases in Emergency Departments

2 Lack of awareness and education

There is a general lack of awareness among patients and caregivers about how to identify and report mTBIs and how to manage symptoms once discharged from an ED. Since EDs are the first point of care for many TBI patients, it is imperative for the emergency physicians (EPs) to recognize and adequately counsel patients in order to improve outcomes and reduce the potential for life-long adverse effects. However, studies report that many EPs are uncomfortable

managing mTBIs and counseling patients on their injury, with the result that patients are often discharged without a follow-up plan for their care.[26] A study interviewing discharged mTBI patients found that none of them were provided discharge instructions for how to manage symptoms of mTBI.[27]

Awareness remains a substantial issue in TBI management. Patients, paramedics and other medical professionals need to be aware and educated.

Andrew I. R. Maas,
Emeritus professor of neurosurgery, Antwerp University Hospital, University of Antwerp; co-chairman, European Brain Injury Consortium, Belgium

A retrospective analysis of an observational study including 346 patients from level I EDs reported that despite the clinical guidelines available for physicians to identify patients with suspected mTBIs who require imaging tests, among physicians who did not adhere to these guidelines, CT scans were still overused by 10-35%.[28] Similar results were found in another study conducted in Canada that reported an overuse proportion of 26% in EDs.[29] All these care gaps and inconsistencies raise concerns about inadequate education and training programs for physicians, some of which have been traced back to medical schools.[26]

The potential of blood-based biomarkers to improve evaluation and management of TBI

A major focus of recent studies has been the application of biomarkers in the identification and clinical management of TBI. Evidence suggests biomarkers can have applications far beyond detecting brain injuries, including:[30]

- determining whether an mTBI patient presenting in the ED requires a CT scan for identification of intracranial pathology
- guiding personalized management by predicting outcomes following mTBI and helping direct resources for optimizing care
- guiding clinical research of targeted therapies for TBI by providing information about the underlying pathologies of the condition.

I see blood-based biomarkers as playing an important role in the future, not only for the identification of TBIs but also with some treatment plans or at least the diagnostic plans to determine the need for additional imaging in patients.

Geoffrey Manley,
Chief of neurosurgery, Zuckerberg San Francisco General Hospital; professor, vice chairman of neurological surgery, University of California, US

Attributes of an ideal biomarker

For a biomarker to be clinically useful, it should have the following attributes:[1]

- It should be readily measured in accessible bodily fluids such as cerebrospinal fluid or blood (serum/plasma).
- It should allow for repeated detections in one of the above mentioned bodily fluids up to 48 hours following the initial brain injury.
- The elevated levels of biomarkers (in native or modified form) should be a direct result of brain trauma and should correlate to the degree of severity of traumatic brain injury in the acute phase (within 24 hours after injury) as defined by the Glasgow Coma Scale, computed tomography scans and/or magnetic resonance imaging abnormality.

In selecting biomarkers for this review, we have targeted the following:

- biomarkers that can specifically improve the assessment of mTBI since these injuries account for the majority of the TBI burden
- blood-based biomarkers that can be readily measured and would be feasible in clinical settings (acknowledging the need for laboratory facilities)
- biomarkers in current use or that are being investigated in larger settings for use as surrogate markers for imaging to reduce cost and unnecessary exposure to radiation.

Glial markers

S100B

S100B—a calcium-binding protein located predominantly in the glial cells—is the most studied of all potential blood-based biomarkers in TBI. Under normal conditions, S100B is concentrated in the cerebrospinal fluid. At the onset of any cerebral lesions, the damaged cells immediately release S100B into the circulatory system, which is subsequently eliminated by the kidneys, having a short half-life of about 30-100 minutes.[1] However, S100B is not always specific to brain injuries. It is also released from extracranial sources such as fat, muscle and bone marrow, which often complicates its interpretation in clinical settings.[31] It is also present in melanocytes: Patients with darker skin can show higher levels of S100B compared to people with lighter skin, due to increased metabolic activity in melanocytes. When calculating outcomes from TBI patients with darker skin, higher serum levels may be falsely interpreted as elevated, resulting in unnecessary CT scans for mTBI.[32]

A meta-analysis of 22 studies comprising 7,754 patients suspected of mTBI evaluated the accuracy of S100B in detecting intracranial lesions on CT scans. The individual sensitivities and specificities were in the range of 72-100% and 5-77%, respectively, thus demonstrating wide variability in accuracy. Given the short half-life of the marker, the authors also stressed the importance of acquiring a sample within the first 6 hours after an mTBI.[30] The overall high sensitivity of S100B makes it an excellent candidate as a screening tool for physicians who might prefer avoiding overuse of CT scans. However, the poor specificity of the marker limits

its diagnostic value and makes it an unfavorable candidate for clinical applications.

In 2007, the S100B blood test was added to the clinical guidelines of the Scandinavian Neurotrauma Committee.[33] Additionally, as a Level C recommendation, the CDC advises conducting a S100B test in mTBI patients who have not suffered any significant extracranial injuries, but this biomarker has not received approval for clinical use by the US Food and Drug Administration (USFDA).[34] NICE concluded that there is low-quality clinical effectiveness data for S100B testing to rule out intracranial injuries and suggested additional investigation of S100B in patients with selected head injury patterns.[35]

GFAP

Glial fibrillary acidic protein (GFAP) is a well-established biomarker found in the astroglial cells of the central nervous system (CNS).[36] The potential use of GFAP as a marker for brain injuries has been reported in numerous studies. Unlike S100B, GFAP is not found outside the CNS, making it more brain specific. GFAP increases in the peripheral blood within hours following a brain injury, with some studies suggesting the elevation will peak at 20-24 hours post-injury.[34]

GFAP has the potential to identify patients with an intracranial injury after brain trauma, with some evidence demonstrating higher assessment accuracy than use of S100B.[35] A systematic review of 27 articles revealed that 89% of the studies (24 articles) reported a positive association between GFAP levels and acute trauma–related intracranial lesions on head CTs. The area under the receiver operating characteristic curve (ROC), which is a measure of test accuracy, ranged from 0.74 to 0.98, indicating good to excellent discrimination.[34] Moreover, in a recent prospective cohort study (TRACK-TBI) that included 450 patients, GFAP was shown to be more sensitive than CT scans for diagnosing.[37] In parallel, the European Commission–funded multicentre CENTER-TBI study, which included 2,867 patients less than 24 hours post-injury, found that GFAP achieved the highest discrimination for predicting CT abnormalities, with an accuracy measurement (AUC) value of 0.89.[38]

In addition to higher specificity than S100B, there is evidence suggesting that, because of its longer half-life, GFAP has high discriminatory ability to predict intracranial abnormalities on CT scans in TBI patients 24 hours post-injury, unlike S100B, which returns to baseline within 6 hours.[39]

Overall, recent findings regarding GFAP make it one of the best potential candidates for evaluation and management of mTBI. Experts we interviewed had the same opinion: "In our research, GFAP had the greatest discriminating ability. In fact, it performed better than other biomarkers, in isolation as well as in combination," said Andrew I. R. Maas.

Axonal markers

Tau proteins

Tau proteins are microtubule-linked phosphoproteins seen in normal neural axons. The tau protein becomes proteolytic after exposure to axonal damage and converts to cleaved tau protein (CTP), the level of which can be assessed to detect CNS damage. In an observational study including 86 patients who

had a CT scan approximately 10 hours after injury, CTP evaluation was performed using the ELISA method. The CTP has a sensitivity and specificity of 92% and 100%, respectively, in detecting intracranial trauma.[40] Another small study that evaluated the accuracy of CTP for evaluation of CT abnormalities in 50 patients reported a sensitivity and specificity of 50% and 75%, respectively.[12] Due to the limited number of studies, there is insufficient evidence to support the clinical validity of CTP for TBI assessment. Further investigation is required to determine the potential of CTP as a TBI biomarker.[30]

Neurofilaments

Neurofilaments (NFs) are also found in axons and are extremely sensitive to concussion-induced damage. They have the potential to be an excellent biomarker of mTBI-triggered axonal damage. NFs have three components—light, medium and heavy—the last of which can be phosphorylated neurofilament heavy subunit (pNfH) to protect it from degeneration. Evidence suggests these pNfHs might have the potential to be used as a biomarker for mTBI evaluation and clinical management, though further research is needed. A single study evaluating the potential of this biomarker found a rise in the pNfH levels of mTBI patients one and three days after injury, with sensitivity and specificity of >96% at both time points. These promising results of pNfHs warrant further research to explore their potential role in mTBI assessment.[35]

Neuronal markers

UCH-L1

Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is a protein that is primarily present in neurons. It is one of the most recent biomarkers to be studied. The evidence has been very promising as it shows increasing levels of UCH-L1 early on after both TBI and stroke. A systematic review that included 10 articles reported that serum UCH-L1 has high accuracy in predicting CT scan findings in mild to moderate TBIs.[41] Another prospective cohort study of 96 patients with mild (n=86) and moderate (n=10) TBIs showed that UCH-L1 was detectable in the serum within one hour of injury and was associated with the measures of injury severity, including GCS score, lesions seen during imaging, and the need for neurosurgical intervention.[42] Additionally, two recent studies[42,43] with 96 and 250 patients, respectively, that included mild to moderate adult TBI patients showed the same sensitivity, 100% (95% CI 88-100), and specificities of 21% (95 CI 12-32) and 39% (95% CI 33-46), respectively, reporting similar thresholds and assay.[30] However, clinical evidence also suggests that UCH-L1 may lack suitable specificity. Some findings have shown that the biomarker failed to differentiate between mTBI patients and orthopedic controls.[44] Further investigation needs to be done to determine the potential role of UCH L-1 in evaluation and management of mTBI.

Combination of GFAP and UCH-L1

GFAP and UCH-L1 have been evaluated in numerous studies for their potential role as surrogate markers for imaging and surgical

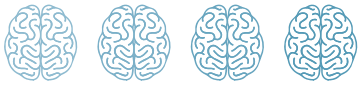
intervention in patients with suspected mTBI. In 2018, GFAP and UCH-L1 became the first biomarkers to be cleared by the USFDA to help determine the need for CT scans in mild to moderate TBI adult patients within 12 hours of injury.[45] This approval was based on the results from a large multicentre trial (ALERT-TBI; 2012-2014), which included 1,959 patients who demonstrated that UCH-L1 and GFAP measurements had a high sensitivity of 0.97 (95% CI) and an NPV of 0.99 (95% CI) with <1% patients reporting a positive result in a CT scan when the test was negative.[44] Similar findings were observed by another study that included a cohort of 206 patients with mTBIs enrolled in a multicentre observational study (TRACK-TBI) in which the individual AUC for GFAP and UCH-L1 were 0.91 and 0.87, respectively, but when combined, the AUC was reported to be 0.94 for discriminating between TBI patients and healthy controls.[46] Furthermore, Posti and colleagues[47] reported a strong correlation between the plasma levels of GFAP and UCH-L1 with severity of TBI in the first week post-injury, supporting the role of such biomarkers in acute settings.[48]

Future outlook

The combination of GFAP and UCH-L1 has been identified as a potential marker for improving the evaluation and clinical management of mTBI patients

Within the confines of this overview, the combination of GFAP and UCH-L1 seems to be a marker with potential for improving the evaluation and clinical management of mTBI patients. When used as a surrogate marker for imaging, this combination improved overall diagnostic accuracy, thereby reducing the number of unnecessary CT scans performed on patients with suspected mTBI. This evidence supports the argument that, for a complex and multifaceted condition such as TBI, a single biomarker might not be able to reflect the full spectrum of brain tissue's response to injury.

Though research is at an early stage, the approval of GFAP and UCH-L1 for mTBI testing marks a promising advance in the field of TBI and encourages continued research in this field. Many biomarkers can aid in management of TBIs by creating a more holistic view, and it is critical to continue this research to identify the ideal panel of biomarkers that may transform the way TBIs are managed.



It is a phenomenal thing that biomarker tests are finally getting over the finish line at the FDA. The more these are used in the real world, the more we will understand the value of these tests at various levels, and this will radically change the practice of medicine.

David Okonkwodo
Professor, neurological surgery, UPMC Presbyterian; director, Neurotrauma Clinical Trials Center, University of Pittsburgh, US

Conclusion

TBI is the most common neurological disorder worldwide, contributing to more death and disability than any other traumatic injury, and mTBI accounts for 80% of all TBI cases. Although common, identification and definition of specific criteria for mTBI has been a significant barrier in the clinical management of this condition. Experts agree that there is an unmet need for further research into biomarkers that can help to provide a comprehensive understanding of the pathological process. Such research will not only help in improving evaluation and management of TBIs but will also bridge the knowledge gap essential for new therapy development in this field.

Current diagnostic tools have several limitations.

Current diagnosis of TBI relies on CT scans (which involves exposure to radiation which in many cases is unnecessary), physiological and psychological assessments, and the GCS scoring system (the validity of which is often disputed due to poor sensitivity and specificity). These diagnostic tools are therefore often detrimental to patient wellbeing because patients who are mis- or undiagnosed frequently end up receiving suboptimal treatment that can ultimately lead to serious long-term neurological consequences impacting a patient's overall quality of life.

Lack of standard definitions and consistency in clinical management guidelines is a challenge in the diagnosis and management of mTBI.

Several organizations, such as the ACRM, WHO and CDC have published definitions of mTBI, but there is no consensus among these institutions regarding what constitutes an mTBI. Without clear guidelines, the evaluation and management of mTBI patients in acute settings becomes even more challenging for physicians. Evidence suggests that, due to the abovementioned factors, 50-90% of patients go undiagnosed in hospital EDs, putting them at higher risk of complicated recovery.

Patient and physician education is crucial to address the burden of TBI, especially mTBI.

There is a dearth of education and training programs for both patients and physicians on the identification and management of mTBI. While research has led to technological advances and more widely available and accurate diagnostic tools for TBI identification and clinical management, physicians without adequate training will be unable to make optimal use of these tools to manage TBI symptoms. As highlighted by Geoffrey Manley, "There is a greater awareness of the potential negative

impact of such injuries than there was 10-15 years ago, but there is still a long way to go."

Advancements in biomarker research have the potential to transform the evaluation and care of mTBI patients.

Researchers are now turning their attention to biomarkers as a tool for accurate identification and management of this condition. Numerous biomarkers that are being investigated currently (S100B, CTP, pNfH, GFAP and UCH-L1) have the potential to improve diagnostic accuracy, predict the rate and severity of injury progression, and guide a personalized approach to injury management. Of all the biomarkers that we reviewed, GFAP and UCH-L1, particularly when used in combination, demonstrated the highest accuracy in terms of AUC for discriminating between mTBI patients and healthy controls. The experts we spoke to were also positive about this combination. If real-world application shows these markers can improve decision-making and reduce the exposure to radiation inherent in CT scans, it could support their role in the clinical management of mTBI.

Demonstrating clinical utility is the next step to advance the study and application of biomarkers for TBI.

Interviewed experts were optimistic about the clinical utility of GFAP and UCH-L1. As explained by Manley, "With the FDA clearance, GFAP and UCH-L1 have become the lead biomarkers and have made room for research and development of additional biomarkers in TBI. The next thing that we should focus on is the clinical utility of these two markers that are already approved by the FDA." Physicians and regulatory authorities need to see real data based on clinical studies to fully justify the incorporation of biomarkers into clinical guidelines; currently there is just not enough data. Further study of these biomarkers and accumulated data will provide the proof necessary for regulatory groups to see biomarkers as the future of mTBI evaluation and care management.

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- **Andrew I. R. Maas,**
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- **David O. Okonkwo,**
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- **Gregory J. O'Shanick,**
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- **Kevin Wang,**
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