A new characterisation of acute traumatic brain injury: the NIH-NINDS TBI Classification and Nomenclature Initiative

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The clinical severity of traumatic brain injury (TBI) is commonly classified according to the Glasgow Coma Scale (GCS) sum score as mild (13–15), moderate (9–12), or severe (3–8). A new approach is needed for characterising TBI more accurately. In 2022, the US National Institutes of Health–National Institute of Neurological Disorders and Stroke launched an international initiative to address this need, with a focus on the acute phase of injury. Six working groups of TBI experts, implementation scientists, people with lived experience, and federal partners were established, involving 94 participants from 14 countries. The proposed new framework for the characterisation of acute TBI incorporates four pillars: a clinical pillar (full GCS and pupillary reactivity); a biomarker pillar (blood-based measures); an imaging pillar (pathoanatomical measures); and a modifier pillar (features influencing clinical presentation and outcome; CBI-M). The CBI-M framework provides a multidimensional characterisation of TBI to inform individualised clinical management and to improve scientific rigor. Research priorities include validation of the CBI-M framework, evaluation of its applicability beyond the acute phase of TBI, and strategies for clinical implementation.

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability worldwide.[1] Nearly 50 million people sustain a TBI annually at an estimated cost to the international economy of US$ 400 billion.[1] TBI is commonly classified according to the Glasgow Coma Scale (GCS) sum score, which has a range of 3–15.[2,3] Mild TBI is defined in patients with a score of 13–15, moderate TBI is applied to those with a score of 9–12, and severe TBI corresponds to a score of 3–8. The GCS was introduced in 1974 as a clinical instrument for the structured assessment of the level of consciousness in individual patients. Although the GCS remains highly relevant to clinical practice, using it to group patients with TBI into three broad categories has substantial limitations. First, this tripartite categorisation results in loss of crucial information regarding the severity of the injury, which cannot be categorical but is on a continuum.

***Panel 1*: Observations from people with lived experience of traumatic brain injury expressed during the National Institute of Neurological Disorders and Stroke workshop in January, 2024 (Bethesda, MD, USA)**

- "Having been diagnosed with a mild traumatic brain injury [TBI] has created substantial challenges in my recovery. I've constantly had to fight to [have my symptoms] be taken seriously."
- "Mine was categorised as mild TBI, and it worked against me. That label evokes a passive detrimental attitude in care providers and patients."
- "Most doctors and nurses who diagnosed my TBI as severe could not imagine I'd be alive, let alone walking and talking on the stage today."
- "Severe TBI is a term that reinforces resignation."

Second, the current approach is unimodal–that is, based on a single clinical parameter–and ignores other diagnostic modalities, such as imaging or blood-based biomarkers that might contribute to a detailed pathophysiological characterisation. Third, this categorisation does not allow for meaningful selection of patients for therapeutic interventions or clinical trials. Fourth, stigma and bias are invoked by the nomenclature mild, moderate, and severe. Patients characterised as having mild TBI are assumed to recover quickly and so they often experience barriers to follow-up care. For some patients characterised as having severe TBI, a perceived poor prognosis and consequent nihilism might affect treatment decisions, possibly leading to premature withdrawal of life-sustaining treatment.[4] People with lived experience of TBI express serious concerns over the use of the terms mild, moderate, and severe (panel 1). These labels, which were intended to describe an acute injury, are commonly misapplied as expected outcomes, with unintended and lasting consequences that negatively affect people with lived experience.

The development of an updated and broadly applicable classification system for TBI was one of the main recommendations of the 2022 Roadmap for Accelerating Progress in TBI report from the US National Academies of Science, Engineering, and Medicine (NASEM).[5] Hence, in this Policy Review, we describe the development of a novel framework for comprehensive TBI classification and precise nomenclature, and identify gaps in knowledge and research priorities that could inform refinement and updating of this new framework.

Previous approaches to improve characterisation of acute TBI

Efforts to redefine the classification of acute TBI have included machine learning and clustering approaches.[6]

Unsupervised, hypothesis-free methods have been used to identify clusters, mainly defined by injury mechanism, major extracranial injury, and the GCS.[7] Analysis of data from the COBRIT drug trial,[8] with external validation in the TRACK-TBI pilot dataset, identified three patient clusters based on six baseline features: haematology measures, coagulation measures, blood glucose concentration, blood pressure, heart rate, and midline shift. Qiu and colleagues[9] used latent class analysis to identify five stable endotypes characterised by specific acute comorbidity profiles. Other efforts, which have focused on subpopulations (eg, people with mild TBI, as defined by the GCS,[10] or people in the intensive care unit[11]), used time-series data[12] or focused on one dimension, such as imaging[13–18] or analysis of EEG recordings.[19] To our knowledge, no comprehensive approaches have been undertaken to develop a multidimensional approach to TBI characterisation, applicable across the spectrum of injury severity. In response to the call for action by NASEM, and in recognition of the needs of patients, clinicians, researchers, caregivers, and advocates, the US National Institutes of Health-National Institute of Neurological Disorders and Stroke (NIH-NINDS) launched an international initiative in 2022 to develop a multidimensional approach to characterisation and to establish a specific nomenclature for the characterisation of patients with TBI.

The NIH-NINDS initiative and our consensus process

The NIH-NINDS initiative is primarily based on a process of multidisciplinary expert consensus, informed by a literature review, and participation of many international experts, working under the premise that any novel approach to characterisation should be applicable worldwide. In total, the initiative involved 94 experts from 14 countries. The design and timeframe of our initiative are described in panel 2.

The NIH-NINDS initiative builds on recommendations from a 2007 NINDS workshop on TBI classification[1,26] in the context of clinical trials. These recommendations included: establishment of large databases; introduction of common data elements to standardise reporting and facilitate analyses across studies, broadening the focus to include patients with less severe TBI; and the introduction of advanced statistical and bioinformatics approaches. Over the past two decades, many of these goals have been accomplished, and large observational TBI studies have generated detailed data that can now inform the development of a new framework for TBI characterisation.

The aims of the current NIH-NINDS initiative were to develop a comprehensive TBI classification and precise nomenclature, and to identify gaps in knowledge and research priorities that could inform refinement and updating of the new TBI classification and its nomenclature.

Our proposed framework is for the characterisation of patients with TBI in the acute phase. The working groups of the initiative fully recognise, however, that the characterisation of TBI should be a dynamic process that evolves over time.

Proposed framework for acute TBI characterisation

Our proposed framework incorporates four pillars: the clinical, the biomarker, the imaging, and the modifier pillar, that together constitute the CBI-M framework. The pillars have basic components (for use in all patients) and expanded components (relevant to subpopulations, settings, or to provide further characterisation). The

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Panel 2: Design and timeframes of the National Institute of Neurological Disorders and Stroke Traumatic Brain Injury Classification and Nomenclature Initiative

March, 2022

Launch of the Initiative with nomination of a steering committee, consisting of four clinical and traumatic brain injury (TBI) experts and three representatives from the US National Institutes of Health and the National Institute of Neurological Disorders and Stroke.

May, 2023

Implementation of six working groups on:

- The role of clinical assessment on days 1–14
- Blood-based biomarkers
- Neuroimaging
- Psychosocial and environmental modifiers
- Retrospective identification and characterisation
- Knowledge to practice: translating TBI classification into policy and practice

These working groups were tasked with developing recommendations for improved characterisation of TBI and identifying research priorities within their specific domain. The Retrospective Classification working group addressed challenges faced by clinicians and researchers in characterising the severity of TBI when patients presented for evaluation during the chronic phase. The Knowledge-to-Practice working group provided advice on optimising implementation of a new TBI characterisation framework and conducted a survey that helped to identify and prioritise the framework and develop strategies to address perceived barriers and facilitators to implementation.

June, 2023–December, 2023

Working groups met on a regular basis via web conferences and started drafting recommendations.

January, 2024

Plenary workshop involving all working group participants, steering committee, people with lived experience, and federal partners. People with lived experience of TBI with diverse injury characteristics and care trajectories were involved in the planning and presentations of the plenary workshop to share their expertise and perspectives with the steering committee and the working groups. This meeting was livestreamed to invite public interaction and feedback. Based on feedback from the working groups, a decision was made to initially focus on adults with TBI in the acute phase, defined as the first 24 h after injury.

February, 2024–January, 2025

Incorporation of feedback received, finalisation of recommendations and submission of manuscripts on the clinical, biomarker, imaging, and molecular framework (main output of the initiative), and detailed reports of each working group.[20–25]

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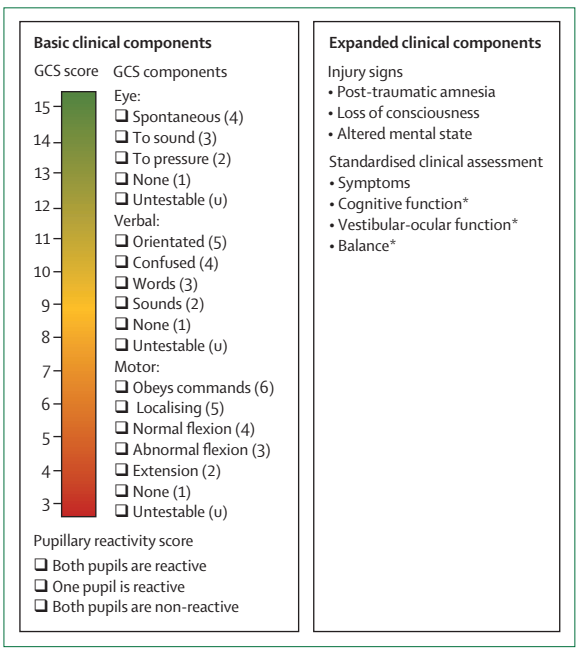


Figure 1: **Clinical pillar of the CBI-M framework**
Recommended basic and expanded clinical components for the characterisation of acute traumatic brain injury. Confounders to the GCS assessment include intoxication, sedation, intubation, and eye swelling or occular trauma. Untestable components due to confounding factors (eg, orbital swelling, sedation, intubation, or aphasia) should be specifically annotated as V(u).[35] *Although these components have achieved common use in some contexts, further work is needed before they can be widely recommended. CBI-M=clinical, biomarker, imaging, and modifier. GCS=Glasgow Coma Scale.

clinical pillar incorporates the GCS and the pupillary reactivity score; the biomarker pillar includes blood-based measures; the imaging pillar includes imaging measures that describe pathoanatomical features; and the modifier pillar incorporates factors known to influence clinical presentation and outcome after TBI (eg, pre-morbid conditions, injury mechanism and circumstances, systemic injuries, and psychosocial and environmental factors). In combination, the four pillars can provide a multidimensional characterisation of TBI.

The clinical pillar

Based on current best practice and available evidence, we considered two basic components for the clinical pillar: the GCS and pupillary reactivity. Previous studies have shown a clear association of these components with both injury severity and clinical outcome.[3,27] Additional documentation of the GCS components (eye, verbal, and motor scores) is recommended, as these components offer more detailed information on patient responses and provide complementary prognostic information.[28,29]

We recommend the use of automated pupillometry, if feasible. We propose three possible pupillary reactivity responses: both pupils are reactive, one pupil is reactive, or both are non-reactive. We considered the GCS-P score (1–15) as previously proposed by Brennan and Teasdale; [30] however, the summary GCS-P score does not fully capture the prognostic value that the GCS and pupillary reactivity have when used as separate components for predicting mortality and other unfavourable outcomes.[31] Moreover, we foresaw potential implementation problems that could result from the modification of the GCS, an instrument that has now been embedded into clinical practice and research for 50 years.[32]

Documentation of post-traumatic amnesia is a strong predictor of TBI outcome.[33,34] Accordingly, the clinical pillar includes the assessment of post-traumatic amnesia as an expanded clinical component in the CBI-M framework. An additional expanded component is the assessment of signs and symptoms (eg, headache, dizziness, and sensitivity to noise), ideally with validated rating scales, to refine prognosis and recommendations for follow-up care (figure 1).

The biomarker pillar

Blood-based biomarkers have rapidly evolved from being research tools to become measures for clinical use, providing objective indicators of tissue damage at both the macrostructural and microstructural level. Increased concentrations of biomarkers of astrocytic and neuronal injury are associated with lesion burden[36] and worse outcomes.[37–49] Blood-based biomarkers have the potential to inform triage, diagnosis,[50] and treatment,[51–53] and to overcome some of the limitations of clinical assessment that can be confounded by a host of subjective (eg, symptoms) and non-injury (eg, intoxication) factors.[54]

Although biomarker assays for TBI are not yet in wider clinical use, we consider that they have great potential. Among the many potential biomarkers, [55] we recommend acute (<24 h) post-TBI measurement of one or more of the following three biomarkers: glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase L1 (UCH-L1), or S100 calcium-binding protein B (S100B). This recommendation was based on the diagnostic and prognostic utility of these biomarkers in acute care settings. Low concentrations of each of the three biomarkers accurately indicate a very low risk of traumatic intracranial injury on head CT scans. Two of these biomarkers (GFAP and UCH-L1) are now cleared by the US Food and Drug Administration (FDA) and all are CE certified for clinical use in Europe.[56] These biomarkers add value for predicting CT abnormalities in patients presenting with a GCS score of 13–15, compared with clinical characteristics[38] and clinical decision rules.[1,57]

These biomarkers are now included in Scandinavian and French guidelines[58,59] to select patients with a GCS score of 13–15 for CT scanning, and their use has been reported to reduce the need for CT scanning by about 30%.[60] Overuse of CT scanning in patients with a GCS of 13–15 has been estimated at 27%, resulting in unnecessary radiation exposure and increased health-care costs.[61] Incorporation of S100B in the Scandinavian guidelines[58] for the intial management of head injuries in adults has

been reported to save €39 per patient, based on data collected between 2007 and 2013.[62] Reduction of health-care costs has also been reported for the use of the combination of GFAP and UCH-L1.[63] With established reference ranges in healthy individuals, blood-based biomarkers also have the potential to aid in the diagnosis of TBI by signifying microstructural damage in patients with a normal CT scan on presentation, and in identifying patients who might benefit from MRI to detect CT-occult injury at both ends of the severity spectrum.[64–66]

Rigorous studies, including inferential statistical approaches, are needed to definitively establish cost-effectiveness and clinical utility of blood-based biomarkers beyond their use for selection of patients for CT scanning,[67] particularly in paediatric and older populations.[68] Further work is also needed to standardise cross-platform reference ranges and cutoff values,[69] and to better understand biomarker kinetics and effects of sample processing. Although the three recommended biomarkers in the CBI-M framework have regulatory clearance to rule-out the need for CT imaging and do not require informed consent, some validation studies of the framework and expanded indications for biomarker use might require informed consent. We also recognise the importance of modifiers for blood-based biomarkers, such as sampling time from injury,[70] patient age, and extracranial injuries (for S100B).[71,72] Warranted by evolving evidence, additional biomarkers, such as neurofilament light, might be included in the CBI-M framework in the future (figure 2).

The imaging pillar

Neuroimaging provides a great source of information about the type and extent of a brain injury. The introduction of radiological common data elements for TBI in 2010,[79] including definitions and data dictionaries, has enhanced communications among research and clinical settings. The imaging pillar builds upon these common data elements to incorporate new research findings regarding specific lesions. This pillar focuses on CT, the most widely used imaging modality within the first 24 h of injury. The imaging working group recognises that MRI is more sensitive than CT, and can provide additional information (eg, diffusion metrics),[1,80] but the practicalities around the use of MRI in the acute phase is logistically challenging, time consuming, and is generally reserved for specific indications—ie, for paediatric patients, for whom radiation exposure should be restricted as much as possible. The use of MRI is increasingly relevant in the post-acute and chronic phases after TBI, particularly in patients with persisting symptoms or worse-than-expected outcome.

The frequency of occurrence and relevance of imaging abnormalities to management and prognosis were prime considerations for their inclusion as basic imaging components. Research based on an extensive analysis of data from large studies of acute TBI in the USA and Europe[13,81] has shown that subarachnoid haemorrhage, skull fractures, contusions, and acute subdural haematomas are the most frequently detected neuro-imaging abnormalities across all injury severities. Taking a pragmatic approach, the imaging pillar includes these four most frequently occurring findings as basic imaging components, along with epidural haematoma, intraventricular haemorrhage, intracerebral haematoma, and—the newly refined descriptor—traumatic axonal or microvascular injury (both can co-occur). The term traumatic axonal or microvascular injury was proposed by the imaging working group to replace traumatic axonal injury and diffuse axonal injury, which are typically seen on acute CT or MRI scans.[25] This change in nomenclature is based on the finding that axonal and microvascular lesions often occur in the same locations, and might be difficult or impossible to distinguish on an acute brain CT scan.[82] Although already published in a pictorial review of common data elements in radiological

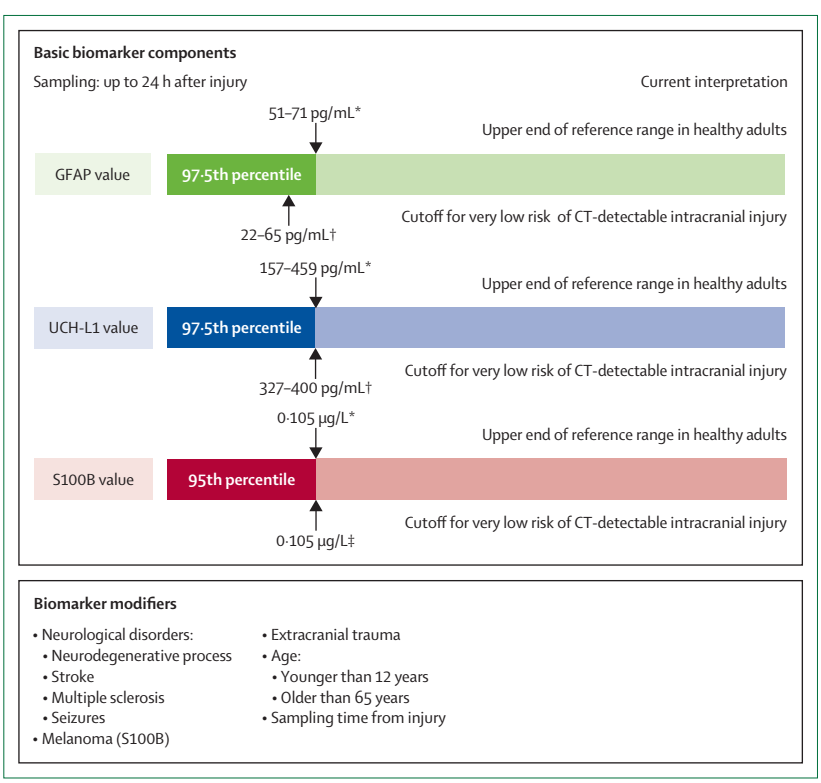


Figure 2: **Biomarker pillar of the CBI-M framework**
Recommended blood-based biomarkers for the characterisation of acute traumatic brain injury (TBI). For the acute (<24 h) phase of TBI, we recommend measuring one or more of the three biomarkers presented. CBI-M=clinical, biomarker, imaging, and modifier. GFAP=glial fibrillary acidic protein. S100B=S100 calcium-binding protein B. TBI=traumatic brain injury. UCH-L1=ubiquitin C-terminal hydrolase L1. *97·5th and 95th percentile values in healthy adults are based on regulatory information from Abbott,[73-76] Roche,[77] and bioMeriéux.[78] Reference ranges vary depending on assay type, age, and gender. †Based on regulatory information from Abbott [73-76] and bioMeriéux.[78] Cutoff values vary depending on assay. GFAP and UCH-L1 cutoffs within this range were measured with Abbott[73-76] and bioMeriéux[78] assays, which have been approved by the US Food and Drug Administration to assist in determining the need for head CT scans within 12–24 h for patients with suspected TBI (GCS score of 13–15). ‡S100B at this cutoff was measured with Roche Elecsys S100 assay, which has CE certification in Europe to assist in determining the need for head CT scans within 3 h for patients with suspected TBI (GCS score of 13–15).

imaging,[81] the general adoption of this new terminology might require endorsement by neuroradiological societies. An additional recommendation is the documentation of lesions with a total volume of 25 mL or more, CT signs of mass effect, and other chronic or incidental lesions. Expanded imaging components can provide further detailed information on lesion size and location, vascular lesions, and other imaging abnormalities (figure 3).

The proposed imaging recommendations have the potential to facilitate integration of standardised neuroradiological reporting into electronic medical records. An imaging tool incorporating a well organised drop-down menu of relevant common data elements could be incorporated into radiology-reading software, similar to programmes currently available for other imaging contexts, such as in mammography.[83]

The modifier pillar

In patients with TBI, their presentation, recovery, and outcome are influenced not only by the biomechanical and physiological features of their brain injury event, but also by the multitude of factors described in the biological, psychological, sociological, and ecological model of TBI, as described in the 2022 NASEM report.[5] These factors can be conceptualised as psychosocial and environmental modifiers that might affect the disease course across the entire continuum of injury severity, ranging from influencing risk for experiencing TBI and other types of trauma, acute post-injury presentation, clinical course, and long-term outcomes.

The modifier pillar incorporates three classes of basic components: injury-related factors, patient-related factors, and community and society-related factors (figure 4). Various patient-related and injury-related factors are included in the modifier pillar because we think that they can be more accurately characterised as modulators of TBI than as features that express the severity of the brain injury itself. The relevance of modifiers varies by type of outcome, and might also vary by subpopulation (eg, gender).[84] The role of patient-related, community-related, and society-related factors on clinical outcomes has been particularly well established in patients with a GCS score of 13–15,[5,85] as well as in paediatric populations.[86] Social factors—eg, geographical location, cultural-linguistic background, and pre-injury mental health—are also important determinants of outcome in patients with a GCS score of 3–12, with implications for the intensity and quality of rehabilitation that these patients will be able to access.[87–90] Social factors might also contribute to health disparities in clinical outcomes.[84,91,92] Some of the proposed modifiers have early effects (eg, hypotension), whereas others (eg, mental health[93] or substance misuse[94]) can influence the course of recovery. To our knowledge, no previous attempts have been made to include a structured assessment of psychosocial and environmental modifiers in the standard characterisation of acute TBI. We recognise the practical challenges in using these modifiers in the acute setting and the need to improve standard tools for measuring them.

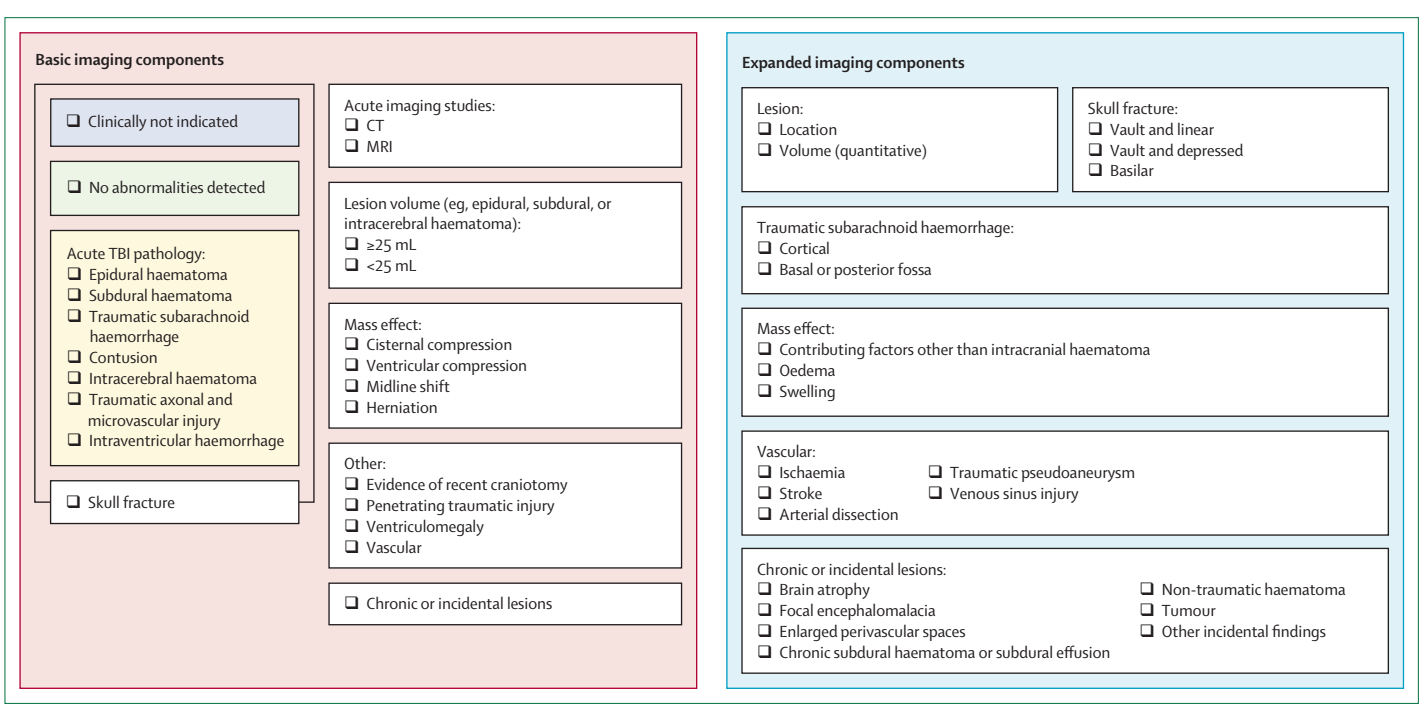


Figure 3: **Imaging pillar of the CBI-M framework**
Basic and expanded imaging components for the characterisation of acute traumatic brain injury. CBI-M=clinical, biomarker, imaging, and modifier. TBI=traumatic brain injury.

Basic modifier components

Injury factors	• Mechanism of injury • Comorbid extracranial injury • Secondary insults • Early post-traumatic seizure • Stressful circumstances
Patient factors	• Age • Sex • Medical history and medication • Mental health condition • Developmental history • TBI history • Language or communication barrier
Community and society factors	• Social disadvantage or deprivation • No or partial health-care insurance

Expanded modifier components

Extracranial injury
- Abbreviated Injury Scale*
  - Head
  - Face
  - Neck
  - Thorax
  - Abdomen and pelvis
  - Spine
  - Upper extremities
  - Lower extremities
  - External
- Spinal cord injury

Patient factors
- Medications (eg, anticoagulation)
- Frailty and fall risk
- Alcohol and substance misuse
- Mental health history
- Cognitive impairment
- Previous disability
- Language or communication barrier
- Employment status

Living circumstances
- Living with partner or family
- Living alone
- Sheltered housing
- Residential care
- Homelessness
- Incarceration

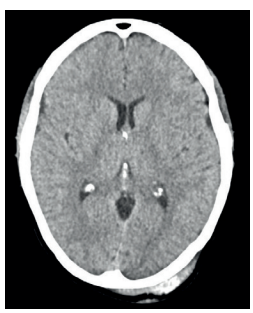
Mechanism of injury
- Motor vehicle crash
- Fall from ground-level
- Fall from height
- Sports injury
- Non-accidental injury
- Other trauma event

Secondary insults
- Hypoxia
- Hypotension

Stressful circumstances
- Perceived life threat
- Death or serious injury to another person
- Reported or suspected non-accidental injury by self
- Reported or suspected non-accidental injury by another person

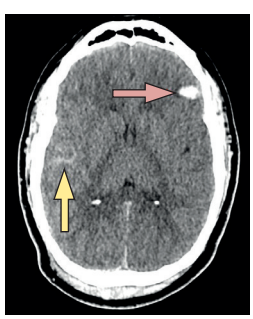
Social barriers
- Financial concerns
- Transportation barriers
- Food insecurity
- Health insurance

Figure 4: **Modifier pillar of the CBI-M framework**
Basic and expanded modifier components for the characterisation of acute traumatic brain injury. These components are not considered hierarchical and should be recorded, if present, to inform about the overall burden of injury, patient history, and community and society factors that can affect injury presentation and patient's outcome. *Each body region is scored on a scale from 1 (minor) to 6 (fatal). CBI-M=clinical, biomarker, imaging, and modifier. TBI=traumatic brain injury.



A

Clinical
GCS score: 15 (eyes=4; verbal=5; motor=6)
Biomarker
GFAP: 140 pg/mL
Imaging
CT: no acute structural abnormalities
Modifier
None



B

Clinical
GCS score: 10 (eyes=2; verbal=3; motor=5)
Biomarker
GFAP: 1200 pg/mL
Imaging
CT: subarachnoid haemorrhage (yellow arrow) and contusion (red arrow)
Modifier
Patient is unemployed, has a history of TBI, and has bipolar disorder

Figure 5: **Application of the CBI-M framework in patients with traumatic brain injury**
(A) CT scan of a male aged 28 years, injured by a bicycle crash. The patient is currently classified as having mild TBI based on their GCS score alone. The patient presented with a brief period of post-traumatic amnesia, and the CT scan showed no acute abnormalities. Headache, dizziness, and nausea were reported. At this stage, using the current terminology of mild TBI, the patient would likely be discharged without arrangements for follow-up care. However, with the CBI-M framework, the additional information of the biomarker concentration being more than the 51–71 pg/mL reference range in healthy adults (hence, indicative of brain injury) and in the presence of multiple acute symptoms, the patient would be referred for follow-up and symptom-targeted treatment. (B) CT scan of a female aged 48 years, injured by a ground-level fall. This patient is currently classified as having moderate TBI on the basis of their GCS score alone. The patient presented with loss of consciousness, and the biomarker concentration and CT scan were abnormal. Because of the presence of traumatic intracranial abnormalities and modifiers, the patient had a high risk for persisting disability. Follow-up care to support the patient's recovery is indicated, and referral to additional services—eg, mental health services, social services, and care coordination programmes—might help the patient to manage modifiable risk factors for poor outcome, such as mental health. Application of the CBI-M framework provides a more detailed characterisation that informs decision making and could influence patient outcome. CBI-M=clinical, biomarker, imaging, and modifier. GCS=Glasgow Coma Scale. TBI=traumatic brain injury.

The CBI-M framework in practice

The CBI-M framework is intended for use in patients with TBI of all severities (GCS score 3–15). The sequence of assessment of the different pillars, however, depends on the clinical condition of the patient and available resources. The clinical pillar should be assessed as the first priority in all patients. For patients in whom a definite clinical indication for urgent imaging exists, the imaging pillar takes precedence over the biomarker pillar. Nevertheless, the biomarker pillar remains relevant from a prognostic perspective. In patients without, or uncertain, indication for imaging, the biomarker pillar with greater relevance for providing evidence of brain injury, and to inform the need for CT scanning. Some components of the modifier pillar might be assessed acutely, whereas other components, being more relevant to the recovery phase, might be assessed at later stages after injury.

We provide case examples to illustrate how the CBI-M framework might enhance the characterisation of TBI and guide the delivery of acute care (figure 5). Additional cases, describing patients with low GCS scores, are

included in the appendix (p 3). We have explored the potential correlations between components within, and across, the four pillars of the CBI-M framework (appendix pp 4–6). The clinical, biomarker, and imaging pillars as brain injury-related pillars (ie, reflecting the effect of the injury on the patient), show strong correlations with each other, as well as with clinical decision-making and outcome. Most components of the modifier pillar mainly reflect a different construct (ie, the effect of patient-related and socioeconomic factors on the disease course).

Characterisation of patients after the acute injury phase

The characterisation of TBI is dynamic and can change over time, hence the recommendation for repeated assessments. However, uncertainty exists about the applicability of the CBI-M framework beyond the acute stage. Further research is required to determine the relative importance of pillars and their components in the subacute and chronic stages after injury. For instance, the clinical characterisation might be primarily based on symptoms and function, and the biomarker selected might include a protein that is known to be increased weeks after the injury, such as neurofilament light.[95] MRI is logistically easier to perform at later stages after injury, and can provide a much more detailed insight into the nature and extent of structural brain damage. Modifiers, including mental health, living circumstances, and social circumstances, are highly relevant to the recovery phase, and might need to be captured in more detail following the acute injury.

A particular challenge exists when patients present late after injury and no objective data are available to subsequently characterise the injury. In community samples, it was reported that up to 42% of people with a TBI did not seek medical care at the time of injury,[96] and that chronic symptoms do not differ between those who seek care and those who do not.[97] Care for patients with enduring or worsening symptoms in the post-acute or chronic stages needs to be informed by carefully ascertained retrospective injury-severity characterisation. We consider that self-reporting or proxy-reporting—which provides information that cannot be obtained via other methods—is essential. Sufficient evidence supports a recommendation for clinicians and researchers to use validated tools and protocols (eg, the Boston Assessment of Traumatic Brain Injury-Lifetime,[98] Ohio State University TBI Identification Method,[99] and Brain Injury Screening Questionnaire[100]), which use contextual recall cues for capturing previous history of TBI. We consider the extraction of medical records relevant, although the quality of medical record documentation needs to improve. We offer no recommendations for the use of imaging methods, blood-based biomarkers, and performance-based methods, such as neuropsychological assessments, to detect previous history of TBI, due to the relative paucity of evidence. Self-reporting remains the primary method for characterising exposure to repetitive head impacts in sport, the military, and occupational environments, but consensus on definition and validation of elicitation methods is needed. We identified the need for research on clinical and biological indices that are both sensitive and specific to previous TBI and repetitive head impacts.

Implementation of the CBI-M framework into research and clinical settings

The development of our CBI-M framework was guided from inception of this initiative by the knowledge-to-practice working group. A fundamental approach underpinning our work was integrated knowledge transfer, defined as "a model of collaborative research, where researchers work with knowledge users who identify a problem and have the authority to implement the research recommendations".[101] Key discussions included articulating potential barriers and facilitators to implementation of a new TBI classification system, determination of target audiences for implementation actions, and identification of so-called change champions—ie, individuals or groups that would be instrumental in facilitating uptake of the proposed recommendations into policy and practice.

The successful implementation of the CBI-M framework into research, and ultimately into clinical practice, will require substantial efforts. Challenges to implementation include ensuring that outreach and engagement builds awareness of the proposed new framework across a diverse array of sectors and settings, such as community-based organisations, clinical settings across the care continuum, lay and professional communication channels, policy makers, and professional societies. Further challenges include the initiation of dedicated knowledge-translation research to explore attitudes and beliefs regarding TBI classification in specific settings and populations; the development and provision of information and training materials; and identification of infrastructure and financial needs (eg, changes to electronic medical records). Tailoring recommendations to resource-limited settings where access to imaging and biomarkers is low, or to settings with varying local policies and practices, will also prove difficult. These challenges and strategies to address them are well documented in knowledge-translation literature.[102,103]

Challenges and applicability in resource-limited settings

Considering how the proposed CBI-M framework might be used is important, especially when some or most of the information needed to define a pillar is missing or not yet available in routine clinical practice. At present, blood-based biomarker assessments are not widely available. Furthermore, obtaining neuroimaging data will be largely determined by clinical need and availability of resources. A strength of our multidimensional approach, however, is that appropriate characterisation remains possible even when some components of a pillar, or even an entire pillar, are not available. We recognise that some recommendations might be difficult

to implement in resource-limited settings. The clinical pillar remains of primary and central importance in these contexts. Documentation of components within the modifier pillar is feasible in resource-limited settings, and increased awareness of the relevance of modifiers to the recovery process and to social reintegration can inform follow-up care, thus improving outcome. Ultimately, the multidimensional approach of CBI-M framework allows flexibility to enable the implementation across the full range of settings and resources.

Conclusions and future directions

We have developed a CBI-M framework as a novel multidimensional instrument for the improved characterisation of TBI in response to calls from the community and recommendations of the 2022 NASEM report.[5] We do not present this framework as a finished product. The framework will require refinement and validation in large contemporary studies before being considered for implementation into general clinical practice. This validation is ongoing, with some preliminary results being reported that show strong correlations of injury-related components with CBI-M pillars. The modifier pillar provides context for clinical interpretation of the other pillars, adding an important dimension to the characterisation and management of TBI. Extensive field-testing across diverse settings is required, and the applicability of the CBI-M framework for characterisation of TBI beyond the acute phase needs to be established. Analyses of large TBI cohorts will allow for probability weighting of individual pillar components, and will facilitate the development of a CBI-M severity score and prognostic risk calculator. Effective strategies towards optimising knowledge transfer will be crucial to maximise implementation of the CBI-M framework into research and clinical practice worldwide. With development of the framework, current gaps in knowledge and research priorities were identified by the working groups to inform refinement of the new TBI classification and nomenclature (panel 3).

Case examples using the basic components of the CBI-M show how this approach provides a better guide for acute care and follow up, as well as more detailed characterisation of TBI beyond the GCS scoring of mild, moderate, and severe. The CBI-M framework can facilitate the design of clinical trials, and components of the framework are already being used as enrolment criteria for recently initiated clinical trials.[104] The CBI-M framework should only be piloted for research purposes of acute TBI characterisation. The expanded components are useful, if appropriate, to further characterise the injury and identify subpopulations for more specific research and clinical care. The CBI-M framework should not over-ride current protocols and guidelines for TBI management and patient care, nor should it yet be used as a clinical prognostic tool. The next phase of this effort, with continued contributions from international stakeholders and people with lived experience, will further refine the proposed CBI-M framework, offering a foundation for future research and eventual clinical implementation to improve TBI characterisation, care, and outcomes.

Strengths of the proposed CBI-M framework include its multidimensional structure, and its development with input from international experts across a wide range of disciplines, also with the engagement of implementation scientists and the involvement of people with lived experience. Enlisting a dedicated implementation working group from the outset enabled real-time identification and discussion of implementation issues. This approach differs from many others, in which implementation is only considered at the conclusion of primary research. A limitation of our framework is that the recommendations are mainly based on a process of consensus and expert opinion. However, this limitation is offset by a systematic literature search and additional targeted literature searches guided by experts in the working groups. We acknowledge that the recommendations were primarily developed for use in the acute stage (<24 h after injury), and that further work is required to determine their applicability for later stages.

***Panel 3*: Research priorities to improve the characterisation of traumatic brain injury**

- Update common data elements of traumatic brain injury (TBI) based on empirical evidence
- Assess the relative weighting of the pillars and their components, differentiated for the adult population, the paediatric population, and older people, while exploring how this weighting might change along the disease course
- Determine the applicability of the Clinical, Biomarker, Imaging, and Modifier (CBI-M) framework for dynamic assessments across the continuum of the disease course after TBI, including its use for post-acute and chronic TBI characterisation
- Explore the clinical utility of the pillar components in paediatric and older patients, and refine the framework for use in these subpopulations
- Determine the predictive effectiveness of the CBI-M framework for other outcomes than the Glasgow Outcome Scale Extended (eg, post-concussion symptoms or cognitive function)
- Determine clinical indicators that warrant blood biomarker assessment and neuroimaging
- Develop cross-platform harmonisation of biomarkers (ie, standardised assay methods and materials)
- Establish appropriate biomarker reference ranges for clinical decision making
- Develop an interactive neuroimaging tool to facilitate structured reporting, clinical decision making, and data aggregation for research
- Devise neuroimaging feature clusters with diagnostic, prognostic, and therapeutic implications
- Develop and validate culturally relevant assessments of psychosocial and environmental modifiers in diverse cultures and settings
- Refine modifiers for use in infants, young adults, and older adults
- Validate standardised two-tier assessments of self-reported TBI across languages and cultures
- Audit, measure, and monitor implementation strategies across cases, settings, and contexts

Search strategy and selection criteria

We searched Ovid MEDLINE and Ovid Evidence-Based Medicine Reviews for reviews published between Jan 1, 2020, and Dec 19, 2024, pertaining to TBI classification using terms relating to the CBI-M framework. The search strategy was: (exp Brain Injuries/ or exp Craniocerebral Trauma/) AND (*Diagnosis/ or *Classification/ or *Diagnostic Imaging/ or *Biomarkers/ or *Psychosocial Functioning/ or *Psychosocial Support Systems/ or social environmental protective factors. mp or "social environmental risk and protective factors".mp or exp Trauma Severity Indices/) AND review.ti,pt. We also searched Google Scholar for articles published between Jan 1, 2020, and Dec 19, 2024, using the search strategy: ("brain injury"|"traumatic brain injury"|"craniocerebral trauma" AND diagnosis|classification|"diagnostic imaging"|biomarkers|"psychosocial functioning" AND review). All searches were restricted to English language publications. 100 articles from Google Scholar were selected by relevance and 122 articles were selected from OVID databases. After removal of eight duplicates, the remaining 214 articles were screened by PB. Of these, 84 were determined to not be relevant to the CBI-M framework. The remaining 130 articles and abstracts were exported into a reference list for review by the authors with TBI clinical expertise to determine relevance to the CBI-M framework. Of these publications, we deemed 60 as relevant to our CBI-M framework.

Validation research will be necessary to understand how well the CBI-M framework applies across the lifespan in paediatric and older populations with TBI. Finally, participation from low-income and middle-income countries was under-represented in the initiative, therefore, some recommendations might be difficult to implement in these countries or other resource-limited settings.

Contributors

GTM, AIRM, and MAM contributed to the data analysis, data interpretation, writing, literature search, and figures. JJB, KD-O'C, JDC, and ARF contributed to data analysis, data interpretation, and writing. PB, DKM, and NDS contributed to data analysis, writing, and literature search. CLMD, LDN, LW, and ELY contributed to data analysis, writing, and figures. MLA, HOA, AD, MMM, JvdN, DP, NU, and HZ contributed to data analysis and writing.

Declaration of interests

GTM received research funding from NINDS, the US Department of Defense, Abbott Laboratories, the National Football League Scientific Advisory Board, and is a member of the NIH-NINDS steering committee initiative for improved characterisation and nomenclature of TBI. KD-O'C received research funding from the National Institute on Disability, Independent Living, and Rehabilitation Research and the US Department of Defense; consulting fees from Tampa VA Research Foundation; and travel support to attend meetings from National Neurotrauma Society. MA received research support from NIH and Life Molecular Imaging. JJB received consulting fees from Abbott Laboratories. PB and JC received travel support from NINDS. AF received research funding from NINDS, the US Department of Defense, the US Department of Veterans Affairs, Wings for Life Foundation, Craig H Neilsen Foundation, and Noyce Foundation. CLMD received research support from NIH and the US Department of Defense and travel support from NIH. DM received research funding from UK Research and Innovation, the National Institute for Health and Care Research, the Ministry of Defence (UK), and Alzheimer's Research UK and consulting fees from Neurotrauma Sciences, Lantmannen, GlaxoSmithKline, PressuraNeuro, CSL Behring, and Invex. MMM received research funding from the National Institute on Aging, the US Department of Defense, the Patient Centered Outcomes Research Institute, and Dexcom and royalites from Elsevier. JvdN received travel support from NIH. LDN received research support from NINDS and consulting fees from Resolys Bio. DP received research funding from the European Commission Seventh Framework Program, the Hannelore Kohl Stiftung, OneMind, Integra LifeSciences, and NeuroTrauma Sciences. NDS received research funding from NIH, Canadian Institutes of Health Research, Canada Foundation for Innovation, WorkSafeBC, Ontario Brain Institute, and the US Department of Defense. LW received consulting fees from Neurotrauma Sciences, Novartis, Mass General Brigham, and Medical College of Wisconsin, and travel support from NIH. ELY received research grants from NIH and the US Department of Defense. HZ received research funding from the Swedish Research Council, the EU's Horizon Europe Research and Innovation Programme, Swedish State Support for Clinical Research, Alzheimer Drug Discovery Foundation, and the EU Joint Programme. AIRM received research funding from the European Commission Seventh Framework Program and consulting fees from NeuroTrauma Sciences, GryphonBio, and PressuraNeuro. MAM received research funding from NINDS, the US Department of Defense, Abbott Laboratories, National Football League Scientific Advisory Board, National Collegiate Athletic Association, and is a member of the NIH-NINDS steering committee initiative for improved characterisation and nomenclature of TBI. All other authors declare no competing interests.

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