Consensus paper on the assessment of adult patients with traumatic brain injury with Glasgow Coma Scale 13–15 at the emergency department: A multidisciplinary overview

Barbra E. Backus[a,b], Farès Moustafa[c], Karoline Skogen[d], Vincent Sapin[e], Neil Rane[f], Francisco Moya-Torrecilla[g,h], Peter Biberthaler[i] and Olli Tenovuo[j]

Traumatic brain injury (TBI) is a common reason for presenting to emergency departments (EDs). The assessment of these patients is frequently hampered by various confounders, and diagnostics is still often based on nonspecific clinical signs. Throughout Europe, there is wide variation in clinical practices, including the follow-up of those discharged from the ED. The objective is to present a practical recommendation for the assessment of adult patients with an acute TBI, focusing on milder cases not requiring in-hospital care. The aim is to advise on and harmonize practices for European settings.
A multiprofessional expert panel, giving consensus recommendations based on recent scientific literature and clinical practices, is employed. The focus is on patients with a preserved consciousness (Glasgow Coma Scale 13–15) not requiring in-hospital care after ED assessment. The main results of this paper contain practical, clinically usable recommendations for acute clinical assessment, decision-making on acute head computerized tomography (CT), use of biomarkers, discharge options, and needs for follow-up, as well as a discussion of the main features and risk factors for prolonged recovery. In conclusion, this consensus paper provides a practical stepwise approach for the clinical assessment of patients with an acute TBI at the ED. Recommendations are given for the performance of acute head CT, use of brain biomarkers and disposition after ED care including careful patient information and organization of follow-up for those discharged. ***European Journal of Emergency Medicine*** **31: 240–249**

European Journal of Emergency Medicine 2024, **31**:240–249

Keywords: biomarkers, computed tomography scan, diagnostics, emergency department, postconcussion symptoms, traumatic brain injury

[a]Emergency Department, Franciscus Gasthuis and Vlietland, Rotterdam, [b]Emergency Department, Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands, [c]Emergency Department, University Hospital Clermont Auvergne, Clermont-Ferrand, France, [d]Department of Radiology and Nuclear Medicine, Oslo University Hospitals, Oslo, Norway, [e]Biochemistry and Molecular Genetics Department, University Hospital Clermont Auvergne, Clermont-Ferrand, France, [f]Department of Neuroradiology, St Marys Hospital Major Trauma Centre, Imperial College London NHS Trust, London, UK, [g]Physical Therapy Department, School of Health Sciences, University of Malaga, Spain, [h]International Medical Services, Vithas Xanit International Hospital, Malaga, Spain, [i]Department of Trauma Surgery, Klinikum rechts der Isar Technische Universität, Munich, Germany and [j]Department of Clinical Medicine, University of Turku, Turku, Finland

Correspondence to Barbra E. Backus, MD, PhD, Franciscus Gasthuis and Vlietland, Kleiweg 500, 3045 PM, Rotterdam, The Netherlands
Tel: +31 64 794 4555; e-mail: barbrabackus@hotmail.com

Received 10 January 2024 **Accepted** 15 April 2024.

Introduction

An estimated >5 million people with acute head injuries visit European emergency departments (EDs) annually [1]. There has been a major shift in the epidemiology of TBI in Europe, with an increasing number of falls and elderly people as victims [2,3]. ED physicians must assess if a head injury has caused a traumatic brain injury (TBI), and if yes, what kind of actions this requires. TBI is a complex disease and is probably best regarded as a group of pathophysiologies, triggered by the trauma event. TBI is defined as 'an alteration in brain function, or other evidence of brain pathology, caused by an external force' [4]. Up to 90% of patients with a TBI visiting an ED have injuries that do not require immediate actions or hospital admission, often classified as mild TBIs (mTBIs) [5].

There are several definitions for an mTBI [5,6], describing the vague nature of this concept. The severity of a TBI is a continuum, without obvious pathophysiological boundaries. Most current classifications categorize TBIs based on the level of consciousness, duration of posttraumatic amnesia and findings in brain imaging. The adjectives 'mild', 'moderate' and 'severe' may be misleading, and an international reclassification of TBIs is being developed (https://www.ninds.nih.gov/news-events/events/ninds-tbi-classification-and-nomenclature-workshop). The recent American Congress of Rehabilitation Medicine Task Force recommendation covers the various aspects of early diagnostics [6]. The clinical signs of a TBI are nonspecific, and their assessment is frequently hampered by various confounders [7,8].

A recent study showed that there is substantial variation in the acute assessments and practices for an mTBI in Europe [9]. This consensus paper aims to advise on and harmonize the diagnostic workup of (suspected) TBIs

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.euro-emergencymed.com).

 DOI: 10.1097/MEJ.0000000000001140

in adults (≥16 years of age) throughout European EDs. There is little hard scientific evidence for many aspects of the acute evaluation of these patients, but a strong clinical experience and consensus [10]. There is still insufficient evidence to show how some existing recommendations (such as using head computed tomography [CT] rules or biomarkers) apply for elderly people [11–14], frequently presenting with comorbidities and polypharmacy, including drugs affecting bleeding risk. We focus on a practical everyday approach to acute TBIs not in obvious need of immediate in-hospital care, without delineating these injuries as 'mild' or 'moderate', which is often impossible in the ED.

Management of traumatic brain injury presenting to the emergency department, a European perspective

Throughout Europe, there is wide variation in the management of patients with TBI at the ED [9]. Although the need for a CT scan is defined by the use of validated guidelines, discharge considerations and follow-up guidance are less well defined. We try to provide ED physicians with a comprehensive summary of the management of patients with TBI, based on cumulated scientific evidence.

When assessing a patient ≥16 years of age with a blunt (penetrating head injuries are not covered by this recommendation) head trauma at the ED (including acceleration/deceleration mechanisms), the physician's priority is to ensure that the vital functions are fine, based on the ABCDE approach (Fig. 1). Abnormal vital parameters such as hypoxia, hypotension and tachycardia should be corrected to preserve cerebral function and before assessing neurologic function. Vital functions should be regularly monitored during the ED stay, half-hourly for 2 h, then 1 hourly for 4 h and 2 hourly thereafter [15]. This is because patients with intracranial bleeding often deteriorate during the first hours after the injury [16,17]. Monitoring is especially important in intoxicated and elderly patients. The following steps apply for patients with a Glasgow Coma Scale (GCS) of 13–15 after correction of vital functions.

Check the history of the patient with respect to injury mechanisms, pre-existing neurological problems and medications (especially anticoagulants). Check and document the history including trauma mechanism, presence and duration of loss of consciousness (LOC), amnesia, vomiting or seizures (Table 1). Check and document clinical signs and symptoms, including focal neurological deficits, headache, impaired balance, disorientation, mental slowness, altered mental status, aggressivity, cognitive/ behavioral symptoms and suspicion of skull fracture (Table 2). Determine the level of intoxication. If the patient is using a vitamin K antagonist, determine the international normalised ratio [19,20]. Routine laboratory tests, including blood count + thrombocytes, creatinine and electrolytes, should be performed according to local policies.

Criteria for brain imaging

Determination of the need for a head CT should be performed either using a validated decision rule (see below) or based on the level of biomarkers (see section 'Use of blood biomarkers') [21–23]. If CT is not necessary or when the result of the head CT is negative, a decision should be made on whether the patient can be discharged (see next section). When the need for a CT has been determined, it is recommended to be performed within 1 h for those with GCS < 15, suspicion of open/ depressed or basal skull fracture, posttraumatic seizure, focal neurologic deficit or repeated vomiting [24,25]. For the others, it should be done within 8 h but in practice, a preferred option is to perform the CT as soon as the radiology department is able to.

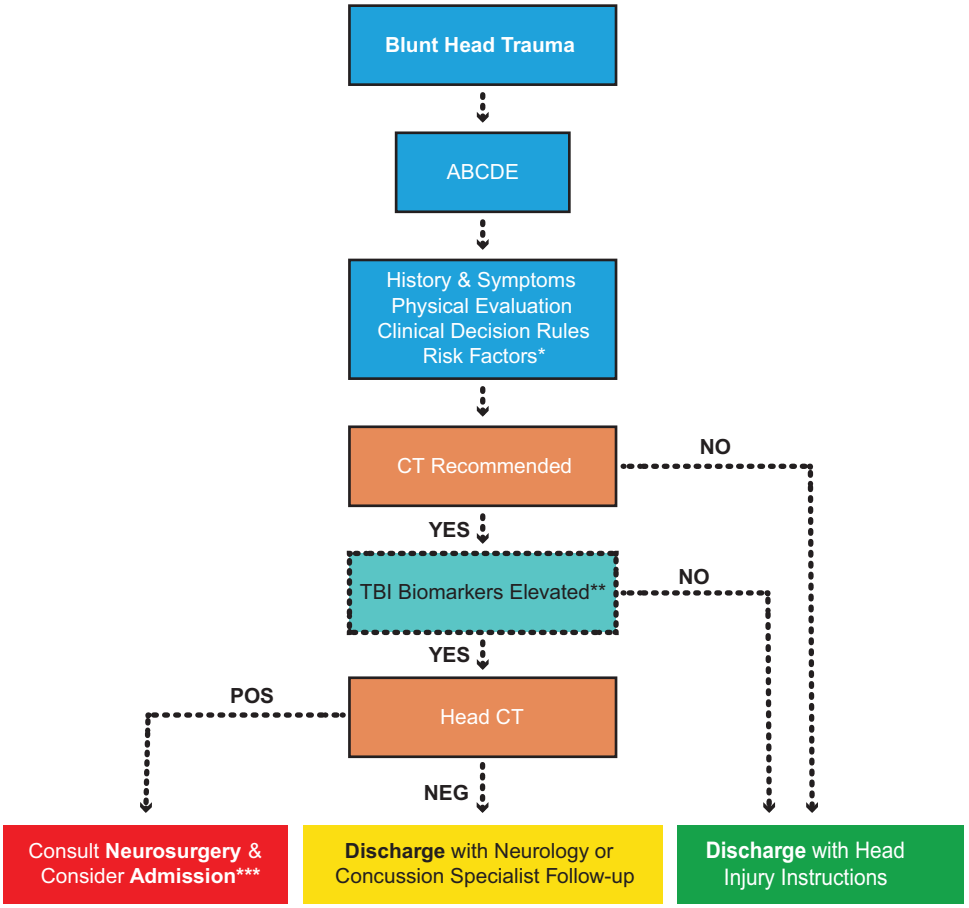
Noncontrast head CT is the gold standard to assess head injury in the acute setting. CT is a rapid, cheap and accessible tool that provides a high sensitivity for detecting intracranial injury requiring acute measures. The incidence of intracranial hemorrhage (ICH) in TBI patients with GCS 13–15 is low, less than 10% [26,27], while only than 1–2% of these individuals will require neurosurgical intervention [28]. Due to the advances in CT technology, the smallest of traumatic subarachnoid hemorrhages can now be identified, making this the most common finding, followed by acute subdural hematoma, brain contusion, epidural (extradural) hematoma and intraventricular hemorrhage [29]. Access to CT has increased over the past decades contributing to a rapid increase in its use. Technological advances, when applied, can reduce the exposure to ionizing radiation, resulting in a reduced risk of radiation-induced neoplasia [30].

Use of clinical decision rules

Numerous clinical decision rules have been established to assist in deciding the need for a head CT [24,31–37]. Several key clinical features are used as predictors (GCS, LOC, vomiting, neurological deficits, age, high-energy trauma, anticoagulation, etc.), but each rule differs slightly regarding inclusion and exclusion criteria, thus only being valid in patients meeting these criteria. In regard to this, many are valid only for those presenting within 24 h of injury, but it is not uncommon that patients seek medical attention later [38,39], for a variety of reasons. How different rules perform for those with a late presentation has not been well studied, but at least the NICE Head CT rule has been reported to lose its sensitivity after the first day [39]. Many of these rules can be used from a web-based tool [40–42], which is often a more simple and rapid way to apply them.

In general, the high sensitivity and negative predictive value of these rules are well recognized (Table 3).

Fig. 1



TBI algorithm in the ED for patients with GCS 13-15. ED, emergency department; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

The cost of higher sensitivity is the loss of specificity, which results in an increased number of CTs performed [43]. All clinical decision rules identify patients requiring neurosurgical intervention, which would have resulted in a fatal outcome, with 100% accuracy. Currently, the Scandinavian Neurotrauma Committee [32] and the new French Emergency Medicine Society [25] guidelines are the only guidelines incorporating a blood biomarker (S100B and/or GFAP/UCH-L1), which when used correctly can reduce the number of scans [44,45].

Adherence to clinical decision rules is often poor, particularly in the context of milder cases [46]. One evaluation of the Canadian CT Head Rule (CCHR) demonstrated overuse of CT for mTBI of 11% for the entire population rising to 37% for patients under 65 years [47]. This is not the only reason for the exponential increase in CT use in patients with TBI. Additional factors include increasing elderly populations, increasing availability of CT scanners and patients not meeting the inclusion criteria for the decision rules, such as late presentation beyond 24 h of injury. Nonetheless, this adds to the already exhausted

capacity of radiology departments. Immediate artificial intelligence (AI)-assisted 'flagging' of CTs with ICH can efficiently increase the turnover of patients, which is feasible with the introduction of established and validated machine learning and AI tools and algorithms (further information in the Supplementary Material 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A437*) [48].

Repeated imaging

In the ED setting, after a normal head CT there is no need for routine repeated CT, not even in patients with anticoagulants [49,50]. Patients with intracranial abnormalities on CT are usually observed or admitted to a ward or ICU, where a local protocol is followed, but routine repeated CT in mTBI is not recommended without clinical deterioration [51]. In those who have been discharged after a normal head CT, a repeated CT is always indicated if the patient returns to ED due to worsening symptoms.

Table 1 Essential features of history taking in patients with acute traumatic brain injury

Injury history	Symptom history[a]	Preinjury health
Trauma energy Speeds, falling height, material damage, weight of an object	Loss of consciousness[b] Eye-witnessed, estimated duration	Pre-existing chronic illnesses Including epilepsy, Alzheimer's disease, MS, psychiatric history
Trauma impact Site of impact, serial impacts, contact surfaces	Amnesia Preceding or following the trauma event	Current medications Anticoagulants, CNS-active drugs
Direction of trauma energy Linear, lateral, rotational	Serious symptoms[c] Seizures, confusion, disorientation, slowness, agitation, somnolence, motor incoordination or tonic posturing, vomiting (once or repeated)	Earlier traumatic brain injuries
Protective equipment Use and their damage		Current alcohol/drug abuse
Time factors Delays in receiving assessment or care		

CNS, central nervous system; MS, multiple sclerosis.
[a]Acutely reported or recorded symptoms (before admission).
[b]Loss of consciousness (LOC) can sometimes be deduced without an eyewitness if the first memory suggests that the patient would not have been there without an LOC.
[c]By eyewitnesses (recommended to interview whenever possible) or prehospital care personnel.

Computed tomography in patients on antithrombotics

Along with aging populations, the use of antithrombotic drugs is increasing. Two of the main CT rules, CCHR [33] and New Orleans Criteria [34], exclude patients with antithrombotic therapy. Most rules consider anticoagulant use an indication for CT. Recent reviews have not found antiplatelet monotherapy increasing the risk of mortality, hospital stay or neurosurgical intervention in patients with TBI, but dual therapy (e.g. acetylsalicylic acid + clopidogrel) is associated with ICH progression and need for neurosurgery [52]. The evidence regarding newer direct oral anticoagulants is still lacking [53] – there is limited evidence that they may be safer than vitamin K antagonists [54,55], but currently, all anticoagulant drugs are considered an important risk factor [52–56].

The role of MRI

While MRI is typically more sensitive than CT in detecting intracranial lesions, it adds little to that provided by CT in the acute setting in adult patients with TBI (further information in the Supplementary Material 2, Supplemental digital content 1, *http://links.lww.com/EJEM/A437*) [57].

Decisions of discharge from the emergency department

The flow chart (Fig. 1) provides criteria for recommended hospital admission of which a more detailed description can be found in Table 4. Although not based on research evidence, factors such as high-energy trauma, presence of diagnostic confounders or living alone are often considered to indicate admission to a hospital ward for observation [58]. These decisions partly depend on

Table 2 Clinical signs to be observed in patients with acute traumatic brain injury

Physical examination and external signs	Neurological signs and symptoms[a]	Cognitive signs and behavior symptoms[a]
Scalp[b] and face wounds Lacerations, bruises, hematomas	Oculomotor signs Pupillary reactions and symmetry, empty gaze, nystagmus, dysconjugate gaze, slow or asymmetric saccades	Disorientation Time, place, situation
Signs of skull fracture Skull impressions, Brittle's sign, Battle's sign	Motor/sensory symptoms Motor/sensory asymmetry on face or extremities, clumsiness, impaired coordination (dysmetria, diadochokinesis), impaired balance, tingling, paraesthesias, numbness, weakness	Altered mental state Slowness, somnolence, confusion, feeling foggy, difficulty concentrating
Signs of facial fractures Deformities, local tenderness		Inappropriate behavior Agitation, aggressivity
Cervical spine/neck injury Midline tenderness[d], restricted neck movements, neck stiffness		Unable to follow commands
Clinical symptoms Headache, nausea, vomiting, vertigo, dizziness	Speech and swallowing Slurred, slowed, dysphagia	Memory problems[c] Retrograde or posttraumatic amnesia, memory complaints
	Visual or hearing problems Double vision, sensitivity to light or noise, tinnitus	Emotional symptoms Irritated, anxious, depressed

[a]If neurological or cognitive signs can better be explained by inebriation/intoxication, observe that they get normalized as expected.
[b]Scalp covered by hair should be examined visually and palpated.
[c]We recommend using a structured assessment tool for monitoring the presence/clearance of posttraumatic amnesia (PTA), such as the Abbreviated Westmead PTA Test [18].
[d]In case of midline tenderness or other clinical suspicions of cervical fractures, do not test neck movements before cervical imaging.

Table 3 Clinical decision rules and their diagnostic accuracy for detecting intracranial bleeds in patients with traumatic brain injury

	Sensitivity	Specificity	NPV	PPV
NOC	97%	4%	95%	5%
CCHR	87%	35%	98%	7%
NEXUS-II	85%	35%	98%	7%
NICE	76%	58%	98%	9%
SNC	89%	50%	99%	9%

CCHR, Canadian CT Head Rule; NEXUS-II, National Emergency X-Radiography Utilization Study; NICE, National Institute for Clinical Excellence; NOC, New Orleans Criteria; NPV, negative predictive value; PPV, positive predictive value; SNC, Scandinavian Neurotrauma Committee.

Table 4 Recommended indications for hospital admission

(1) GCS < 13 at 30 min from the injury or later, not accountable to inebriation or drugs (= 'moderate to severe TBI').
(2) Head CT shows any of the following less than 24 h. from the injury: subdural hematoma (SDH), epidural hematoma (EDH), intracerebral hemorrhage (ICH), traumatic subarachnoid hemorrhage (tSAH), brain contusion, or diffuse edema. Consult a neurosurgeon on-call whenever the head CT shows acute intracranial abnormalities.
(3) Seizure at the time of injury or later.
(4) Patients with multitrauma.
(5) The patient has severe symptoms, such as severe headache, repeated vomiting, difficulties with speech, impaired balance, repeated questioning of already discussed issues, mental slowness and restlessness/agitation.
(6) Worsening symptoms during the ED stay.
(7) The patient does not reach GCS 15 during the ED follow-up (disorientation, somnolence).
(8) Any other cause, which according to the treating ED physician, indicates that other options do not sufficiently guarantee patient safety, such as anticoagulation therapy, social aspects and preinjury dementia.

CT, computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

local practices and resources, such as availability of hospital beds or an acute observation facility. Finally, these are always individual decisions by the treating physician, considering all aspects of an individual case.

A discharge home can be considered safe if all the following are met [58]:

(1) No indication for head CT based on a validated CT rule and/or biomarker assay under validated clinical decision cutoff, or a normal head CT.
(2) The patient has reached GCS 15 with full orientation.
(3) No severe symptoms present (severe headache, repeated vomiting, difficulties with speech, impaired balance, mental slowness).
(4) The clinical assessment has been done without significant confounders.

It is recommended that the patient is accompanied by a reliable adult person for the next 24 h.

Patients who do not meet all the above-listed features for a safe discharge home usually require either a hospital admission or prolonged follow-up at a healthcare facility until they fulfill the requirements for a safe discharge. When discharge from the ED is considered safe, detailed written discharge instructions (Supplementary Material 2, Supplemental digital content 1, *http://links.lww.com/EJEM/A437*) should be provided to the patient, including a list of concerning symptoms when reassessment at the ED is indicated. Risk factors for prolonged symptoms should be taken into consideration as an indication for planned outpatient follow-up, as discussed later in 'Management after emergency department evaluation'.

Use of blood biomarkers

In TBI, metabolically or structurally damaged brain cells release their complex molecular content in the extracellular compartment. By direct extracellular interstitial transport (glymphatic pathway) and via cerebrospinal fluid transitory passage, these molecules cross the blood-brain barrier and become measurable as blood biomarkers of TBI. Two major cellular origins can be defined: astroglial cells, releasing for example S100B and glial fibrillary acidic protein (GFAP), and the soma of the neuronal cells, releasing, for example, ubiquitin carboxy terminal hydrolase L1 (UCH-L1) [59]. None of these biomarkers is exclusively present in the brain, and all can be found in the spinal cord and peripheral nervous system. S100B (and UCH-L1 in a lesser degree) has significant potential sources outside the nervous system, complicating the use in TBI diagnostics [59]. The blood levels of these biomarkers are often also age-related, affecting their clinical use in elderly patients [60]. The levels of S100B are clearly correlated with skin pigmentation, leading to the need for specific decisional cutoffs, to offer sufficient specificity [61].

All these biomarkers show various kinetic profiles after a TBI [62]. Three kinetic groups are usually defined: early responders (minutes to hours: UCH-L1 and S100B), mid-late ones (hours to days: GFAP) and late ones (days to weeks: neurofilament light chain [NF-L], P-Tau) [62]. Consequently, the late biomarkers are of little use for acute diagnostics but may be very useful for prognostics and monitoring. To be compatible with the timing of acute TBI diagnostics, only early and mid-late biomarkers have been retained by the in vitro diagnostics companies to develop commercial kits. Up to date, clinically approved blood determinations with a short turnaround time are only available for S100B (about 1 h using a central laboratory analyzer) and GFAP + UCH-L1 (about 1 h using a central laboratory analyzer and 15 min using a point-of-care device but see below). The validated diagnosis window is within 3 h (in France) or 6 h (in Scandinavian countries) after trauma for S100B and within 12 h after trauma for GFAP/UCH-L1 [25,32].

To define the precise recommendations about how to use GFAP + UCH-L1 or S100B, the clinicians must be aware of some important properties described in Supplementary Material 3, Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A437*, particularly

the inclusion window after the traumatic event and exclusion criteria. When using S100B in the assessment of TBI, it is important to have a strict and timely clinical workflow upon arrival in the ED because of the timeframe.

There is strong scientific evidence that both S100B and GFAP/UCH-L1 can be used for assessing the need for a head CT and that their use diminishes the number of unnecessary CTs [63–66]. Currently, their use requires either an analysis at the hospital laboratory (S100B, GFAP/UCH-L1) or centrifugation of the blood sample to plasma before making a point-of-care assay (GFAP/UCH-L1). The practical value of these biomarkers for CT indication depends on how soon the results are locally available. Determining the level of these biomarkers, however, is also of overall clinical value, reflecting the degree of brain damage irrespective of imaging – providing that the age-related values and confounders (especially for S100B) are considered. This is fully comparable to the clinical routine for assessing liver or kidney function at the ED using laboratory tests. The new TBI classification beyond 'mild, moderate, severe' agreed upon in a large international workshop in January 2024 (https://www.ninds.nih.gov/news-events/events/ninds-tbi-classification-and-nomenclature-workshop) will include blood biomarkers of TBI. Therefore, we recommend their implementation and use for ED clinical practices. Although studies have shown that levels of brain biomarkers are predictive of TBI outcomes, they have not yet been able to predict incomplete outcomes in patients with GCS 13–15 [67,68]. At least NF-L as a slowly increasing late biomarker may turn out to be useful in finding out those patients whose slow or incomplete recovery is due to axonal pathology [69,70].

Management after emergency department evaluation

All patients with a TBI or suspected TBI, who have been deemed safe for discharge home from the ED, require both oral and written information before discharge (Supplementary Material 2, Supplemental digital content 1, *http://links.lww.com/EJEM/A437*). This will inform patients of normal expected symptoms, average recovery time and warning signs. Adequate discharge information has been proposed to improve recovery [71,72]. Nonetheless, there is a substantial percentage of patients who will suffer from prolonged or persistent symptoms after a TBI needing further medical care. According to recent studies in the United States and Europe, among those who have had a head CT and were discharged home, about 50% had not reached full recovery at 6–12 months from the injury [73,74]. Research suggests that ED physicians tend to underestimate the time needed for recovery in patients with TBI discharged from the ED [75]. Therefore, it is important to take adequate time to communicate with the patient regarding imaging findings, the recovery process and when to revisit a healthcare provider.

Supplementary Material 2, Supplemental digital content 1, *http://links.lww.com/EJEM/A437* provides a suggestion for an information sheet to be given before discharge from the ED. Such a document should describe anticipated symptoms and their course, warning signs, recommendations for activities to avoid or encourage and whom to contact regarding warning signs or prolonged recovery. The latter will depend on local practices and resources. After discharge, patients are advised to initially restrict activities and gradually increase daily physical and work activities depending on their symptoms [76]. Return to school, work and sports are subject to symptoms and should be carefully considered. No strict time frame should be given in order not to hamper natural recovery.

Common symptoms include headache, dizziness, photophobia, phonophobia, fatigue and a sluggish or hazy feeling [77,78]. In many patients, these symptoms will resolve within days or weeks [79], yet a significant percentage will suffer from these symptoms for months or even permanently. After a TBI considered to be mild, 10–50% – depending on the study population – develop a pattern of symptoms including somatic complaints, such as headaches, dizziness, blurred vision, fatigue and sleep disturbances; cognitive symptoms, such as poor memory, reduced concentration and focus, mental slowness; behavioral/psychological symptoms, such as depression, irritability, anxiety and emotional lability [77]. These symptoms do not differ from those experienced with more severe injuries and significantly lower the quality of life and prevent a normal return to work or daily activities, causing a great economic impact [80].

Several risk factors for prolonged recovery after a 'mild' TBI have been identified in various studies [81]. These can be assessed at the ED and include:

(1) Pre-existing psychiatric history
(2) Pre-existing sleeping problems
(3) Female sex
(4) CT abnormalities
(5) Headache at the ED
(6) Neck pain at the ED
(7) Neurological symptoms at the ED (including cognitive problems, dizziness, LOC, posttraumatic amnesia, a GCS <15, nausea, numbness and photophobia).

Additional risk factors have been reported, such as mechanism of injury (motor vehicle collisions, assaults), age, preinjury health status, earlier TBIs and intoxication at the time of injury. Despite the recognized risk factors, the existing models predicting prolonged recovery or persistent symptoms acutely after the injury have performed poorly [82]. Several studies have shown that a more reliable prediction of prolonged recovery and persisting

symptoms can be done when certain symptoms are present between 1 and 2 weeks postinjury [83,84].

The more abovementioned risk factors an individual patient shows, the more likely a scheduled follow-up assessment is needed when discharged from the ED, but these decisions depend also on local resources and practices. Some patients come to the ED first at this point or return after an acute visit because of lingering symptoms and inability to return to work. These patients should be referred at the earliest opportunity to outpatient care specializing in treating post-TBI problems.

Future studies and analyses will probably produce a risk scoring, which aids in recognizing those who should be directed to follow-up assessments. This scoring will probably consist of demographic features, injury details, symptoms and biomarkers.

There is a great unmet need in the medical assessment and timely professional care of patients with prolonged symptoms [85,86]. We recognize that existing systems to address this are largely lacking [87], but strongly recommend that such systems should be established. Within a population of one million people, an estimated 2000 people annually need specialized follow-up, based on epidemiological and outcome studies. These same outpatient services – 'Brain Injury Clinics' – could also be utilized by those who are discharged from hospital wards after a TBI, thus guaranteeing good expertise in dealing with subacute diagnostic problems and care after a TBI.

The outpatient follow-up and care for patients with prolonged symptoms are out of the scope of this paper, but often need great expertise and multiprofessional evaluation, including but not limited to neurological, neuropsychological, psychiatric and physiotherapeutic approaches. Questions such as return to work, return to sport, driving ability and rehabilitation needs must be frequently addressed, and as these injuries are often covered by insurance, medical statements are demanding. By taking care of these, as well as all aspects of care, will in due course greatly diminish later burden and costs for the patient and their closest ones, healthcare, social security and society.

Gaps in knowledge

Due to the extreme complexity and variability of TBIs, few issues in TBI medicine are based on strong scientific evidence. On the other hand, there is a general trend toward personalized medicine, the need for which is especially pronounced in TBIs. Yet, clinical decision-making must be based on available evidence, completed by clinical experience. We have listed in Supplementary Material 3, Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/EJEM/A437*, three major gaps in knowledge for each section of this paper. With this, we aim to highlight the existing clinical uncertainties and priorities for further research. Understandably, this is not a comprehensive list, and priorities may vary depending on the beholder.

Conclusion

In this paper, we present a concise recommendation for the workflow needed when facing patients with a TBI of 13–15 at the ED, based on accumulated research and multiprofessional clinical experience. Some aspects of this paper, such as features of history taking and clinical examination, decisions of discharge, as well as a list of various risk factors for incomplete recovery, are hard to find in the existing scientific literature. We also provide a practical update on the use of currently available blood biomarkers for TBI. We do hope that this paper helps to harmonize the assessment of these patients and avoid deleterious consequences these patients may face if important aspects in their acute clinical evaluation have been missed.

Acknowledgements

The work of the expert panel group was supported by Abbott Inc., United States.

This paper does not contain nor discuss any new study results but was meant as an expert-driven, pragmatic approach to the diagnostics and treatment of patients with mild traumatic brain injury at the emergency department.

All authors contributed evenly to constructing the paper, and all authors had final acceptance and responsibility for the decision to submit for publication.

Conflicts of interest

F. Moustafa has served as a consultant for Bayer HealthCare Pharmaceuticals and Sanofi, been a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo, Leo-pharma, Pfizer, Sanofi and Abbott and received grants from Sanofi, Bayer HealthCare and LFB. V.S. has served as a consultant for Roche Diagnostics, Abbott Diagnostics, Biomérieux, Diasorin and Snibe. O.T. has received consultation fees from NeuroTraumaSciences Ltd. P.B. has served as a speaker for Abbott and Bonesupport and is surgical OR trainer on several hands on courses for ZimmerBiomet, DepuySynthes and Smith&Nephew. B.E.B. has served as a speaker for Abbott, AstraZeneca and QuidelOrtho, served as a consultant for AstraZeneca and received a grant from QuidelOrtho. K.S. has served as a speaker for Abbott. F. Moya has served as a speaker for Abbott, Medtronic, Bayer and Boehringer Ingelheim. N.R. has no conflicts of interest.

References

1 Traumatic brain injury. https://www.cdc.gov/traumaticbraininjury/data/tbi-edvisits_1_1.html. [Accessed January 2024]

2 Brazinova A, Rehorcikova V, Taylor MS, Buckova V, Majdan M, Psota M, *et al*. Epidemiology of traumatic brain injury in Europe: a living systematic review. *J Neurotrauma* 2021; **38**:1411–1440.

3 Kannus P, Niemi S, Parkkari J, Mattila V, Sievänen H. Fall-induced hospital-treated traumatic brain injuries among elderly Finns in 1970-2017. *Arch Gerontol Geriatr* 2020; **86**:103958.
4 Menon DK, Schwab K, Wright DW, Maas AI; Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil* 2010; **91**:1637–1640.
5 Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, *et al.*; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehab Med* 2004(43 Suppl):28–60.
6 Silverberg ND, Iverson GL, Cogan A, Dams-O-Connor K, Delmonico R, Graf MJP, *et al.*; ACRM Brain Injury Special Interest Group Mild TBI Task Force members. The American Congress of rehabilitation medicine diagnostic criteria for mild traumatic brain injury. *Arch Phys Med Rehabil* 2023; **104**:1343–1355.
7 Levin HS, Diaz-Arrastia RR. Diagnosis, prognosis, and clinical management of mild traumatic brain injury. *Lancet Neurol* 2015; **14**:506–517.
8 Tenovuo O, Diaz-Arrastia R, Goldstein LE, Sharp DJ, van der Naalt J, Zasler ND. Assessing the severity of traumatic brain injury – time for a change? *J Clin Med* 2021; **10**:148.
9 Foks KA, Cnossen MC, Dippel DWJ, Maas AIR, Menon D, van der Naalt J, *et al.* Management of mild traumatic brain injury at the emergency department and hospital admission in Europe: a survey of 71 neurotrauma centers participating in the CENTER-TBI study. *J Neurotrauma* 2017; **34**:2529–2535.
10 Marshall S, Bayley M, McCullagh S, Velikonja D, Berrigan L, Ouchterlony D, *et al.*; mTBI Expert Consensus Group. Updated clinical practice guidelines for concussion/mild traumatic brain injury and persistent symptoms. *Brain Inj* 2015; **29**:688–700.
11 Oris C, Bouillon-Minois JB, Pinguet J, Kahouadji S, Durif J, Meslé V, *et al.* Predictive performance of blood S100B in the management of patients over 65 years old with mild traumatic brain injury. *J Gerontol A Biol Sci Med Sci* 2021; **76**:1471–1479.
12 Ward MD, Weber A, Merrill VD, Welch RD, Bazarian JJ, Christenson RH. Predictive performance of traumatic brain injury biomarkers in high-risk elderly patients. *J Appl Lab Med* 2020; **5**:608.
13 Santing JAL, Hopman JH, Verheul RJ, van der Naalt J, van den Brand CL, Jellema K. Clinical value of S100B in detecting intracranial injury in elderly patients with mild traumatic brain injury. *Injury* 2024; **55**:111313.
14 Lagares A, Payen JF, Biberthaler P, Poca MA, Méjan O, Pavlov V, *et al.*; Braini2_elderly_investigators Collaborative group. Study protocol for investigating the clinical performance of an automated blood test for glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1 blood concentrations in elderly patients with mild traumatic BRAIN Injury and reference values (BRAINI-2 Elderly European study): a prospective multicentre observational study. *BMJ Open* 2023; **13**:e071467.
15 Head injury. Triage, assessment, investigation and early management of head injury in children, young people and adults. https://www.ncbi.nlm.nih.gov/books/NBK248061/pdf/Bookshelf_NBK248061.pdf. [Accessed January 2024]
16 Matsumura K, Yamamoto R, Namiki J, Takemura R, Sasaki J. Cushing index based on Cushing signs to predict in-hospital death and early intervention for minor head injury. *J Neurotrauma* 2023; **40**:2110–2117.
17 Davis DP, Kene M, Vilke GM, Sise MJ, Kennedy F, Eastman AB, *et al.* Head-injured patients who 'talk and die': the San Diego perspective. *J Trauma* 2007; **62**:277–281.
18 Meares S, Shores EA, Taylor AJ, Lammél A, Batchelor J. Validation of the Abbreviated Westmead Post-traumatic Amnesia Scale: a brief measure to identify acute cognitive impairment in mild traumatic brain injury. *Brain Inj* 2011; **25**:1198–1205.
19 Barbosa RR, Jawa R, Watters JM, Knight JC, Kerwin AJ, Winston ES, *et al.*; Eastern Association for the Surgery of Trauma. Evaluation and management of mild traumatic brain injury: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg* 2012; **73**:S307–S314.
20 Head injury: assessment and early management. https://www.nice.org.uk/guidance/ng232/chapter/Recommendations#admission-and-observation. [Accessed January 2024]
21 Papa L, Ladde JG, O'Brien JF, Thundiyil JG, Tesar J, Leech S, *et al.* Evaluation of glial and neuronal blood biomarkers compared with clinical decision rules in assessing the need for computed tomography in patients with mild traumatic brain injury. *JAMA Netw Open* 2022; **5**:e221302.
22 Czeiter E, Amrein K, Gravesteijn BY, Lecky F, Menon DK, Mondello S, *et al.*; CENTER-TBI Participants and Investigators. Blood biomarkers on admission in acute traumatic brain injury: relations to severity, CT findings and care path in the CENTER-TBI study. *EBioMedicine* 2020; **56**:102785.
23 Jones CMC, Harmon C, McCann M, Gunyan H, Bazarian JJ. S100B outperforms clinical decision rules for the identification of intracranial injury on head CT scan after mild traumatic brain injury. *Brain Inj* 2020; **34**:407–414.
24 https://www.nice.org.uk/guidance/ng232/chapter/recommendations#criteria-for-doing-a-ct-head-scan. [Accessed January 2024]
25 Gil-Jardiné C, Payen JF, Bernard R, Bobbia X, Bouzat B, Catoire P, *et al.* Management of patients suffering from mild traumatic brain injury 2023. *Anaesth Crit Care Pain Med* 2023; **42**:101260.
26 Korley FK, Kelen GD, Jones CM, Diaz-Arrastia R. Emergency department evaluation of traumatic brain injury in the United States, 2009–2010. *J Head Trauma Rehabil* 2016; **31**:379–387.
27 Foks KA, Van Den Brand CL, Lingsma HF, van der Naalt J, Jacobs B, de Jong E, *et al.* External validation of computed tomography decision rules for minor head injury: prospective, multicentre cohort study in the Netherlands. *BMJ* 2018; **362**:k3527.
28 Sweeney TE, Salles A, Harris OA, Spain DA, Staudenmayer KL. Prediction of neurosurgical intervention after mild traumatic brain injury using the national trauma data bank. *World J Emerg Surg* 2015; **10**:23.
29 Yuh EL, Jain S, Sun X, Pisica D, Harris MH, Taylor SR, *et al.*; TRACK-TBI Investigators for the CENTER-TBI Investigators. Pathological computed tomography features associated with adverse outcomes after mild traumatic brain injury: a TRACK-TBI study with external validation in CENTER-TBI. *JAMA Neurol* 2021; **78**:1137–1148.
30 Yabuuchi H, Kamitani T, Sagiyama K, Yamasaki Y, Matsuura Y, Hino T, *et al.* Clinical application of radiation dose reduction for head and neck CT. *Eur J Radiol* 2018; **107**:209–215.
31 Mower WR, Hoffman JR, Herbert M, Wolfson AB, Pollack CV, Jr, Zucker MI, *et al.* Developing a decision instrument to guide computed tomographic imaging of blunt head injury patients. *J Trauma* 2005; **59**:954–959.
32 Undén J, Ingebrigtsen T, Romner B; Scandinavian Neurotrauma Committee (SNC). Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. *BMC Med* 2013; **11**:50.
33 Stiell IG, Wells GA, Vandemheen K, Clement C, Lesiuk H, Laupacis A, *et al.* The Canadian CT Head Rule for patients with minor head injury. *Lancet* 2001; **357**:1391–1396.
34 Haydel MJ, Preston CA, Mills TJ, Luber S, Blaudeau E, DeBlieux BM. Indications for computed tomography in patients with minor head injury. *N Engl J Med* 2000; **343**:100–105.
35 Jagoda AS, Bazarian JJ, Bruns JJ, Jr, Cantrill SV, Gean AD, Howard PK, *et al.*; American College of Emergency Physicians. Clinical policy: neuroimaging and decisionmaking in adult mild traumatic brain injury in the acute setting. *Ann Emerg Med* 2008; **52**:714–748.
36 Joseph B, Friese RS, Sadoun M, Aziz H, Kulvatunyou N, Pandit V, *et al.* The BIG (brain injury guidelines) project: defining the management of traumatic brain injury by acute care surgeons. *J Trauma Acute Care Surg* 2014; **76**:965–969.
37 van den Brand CL, Foks KA, Lingsma HF, van der Naalt J, Jacobs B, de Jong E, *et al.* Update of the CHIP (CT in Head Injury Patients) decision rule for patients with minor head injury based on a multicenter consecutive case series. *Injury* 2022; **53**:2979–2987.
38 Borland ML, Dalziel SR, Phillips N, Lyttle MD, Bressan S, Oakley E, *et al.*; Paediatric Research in Emergency Department International Collaborative (PREDICT) Group. Delayed presentations to emergency departments of children with head injury: a PREDICT study. *Ann Emerg Med* 2019; **74**:1–10.
39 Khan MS, Alam MS, Ismail S, Ghafoor B, Sajjad N, Khan N, *et al.* Use of National Institute for Health and Care Excellence head injury guidelines among patients with delayed presentation after head trauma can lead to missed traumatic brain injury: a 5-year institutional review. *Ann Med Surg (Lond)* 2023; **85**:4268–4271.
40 Canadian CT Head Injury/Trauma Rule. https://www.mdcalc.com/calc/608/canadian-ct-head-injury-trauma-rule. [Accessed January 2024]
41 NEXUS Head CT Instrument. https://www.mdcalc.com/calc/10423/nexus-head-ct-instrument. [Accessed January 2024]
42 CHIP (CT in Head Injury Patients) Prediction Rule. https://www.mdcalc.com/calc/3952/chip-ct-head-injury-patients-prediction-rule. [Accessed January 2024]
43 Svensson S, Vedin T, Clausen L, Larsson P-A, Edelhamre M. Application of NICE and SNC guidelines may reduce the need for CT in patients with

mild TBI: a retrospective chart review and theoretical application of five guidelines. *Scand J Trauma Resusc Emerg Med* 2019; **27**:99.
44 Undén L, Calcagnile O, Undén J, Reinstrup P, Bazarian J. Validation of the Scandinavian guidelines for initial management of minimal, mild and moderate traumatic brain injury in adults. *BMC Med* 2015; **13**:292.
45 Minkkinen M, Iverson GL, Kotilainen AK, Pauniaho SL, Mattila VM, Lehtimäki T, *et al*. Prospective validation of the Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries in adults. *J Neurotrauma* 2019; **36**:2904–2912.
46 Lagares A, Castaño-Leon AM, Richard M, Tsitsopoulos PP, Morales J, Pavlov V, *et al*. Variability in the indication of brain CT scan after mild traumatic brain injury. A transnational survey. *Eur J Trauma Emerg Surg* 2023; **49**:1189–1198.
47 Al Omran B, Patil JD, Anala A, Menezes P, Ahmed N, Cheffi I, *et al*. Prevalence of computed tomography overuse for mild head injury in adults. *Cureus* 2023; **15**:e35551.
48 Hibi A, Jaberipour M, Cusimano MD, Bilbily A, Krishnan RG, Aviv RI, *et al*. Automated identification and quantification of traumatic brain injury from CT scans: are we there yet? *Medicine (Baltim)* 2022; **101**:e31848.
49 Wang S, Meagher M, Mullin E, Brown C, Skicki EJ. Routine repeat imaging is unnecessary for coagulopathic patients sustaining head trauma. *Am Surg* 2022; **88**:1754–1759.
50 Hadwe SE, Assamadi M, Barrit S, Giannis D, Haidich AB, Goulis DG, *et al*. Delayed intracranial hemorrhage of patients with mild traumatic brain injury under antithrombotics on routine repeat CT scan: a systematic review and meta-analysis. *Brain Inj* 2022; **36**:703–713.
51 Rosen CB, Luy DD, Deane MR, Scalea TM, Stein DM. Routine repeat head CT may not be necessary for patients with mild TBI. *Trauma Surg Acute Care Open* 2018; **3**:e000129.
52 Fiorelli EM, Bozzano V, Bonzi M, Rossi SV, Colombo G, Radici G, *et al*. Incremental risk of intracranial hemorrhage after mild traumatic brain injury in patients on antiplatelet therapy: systematic review and meta-analysis. *J Emerg Med* 2020; **59**:843–855.
53 Rønning P, Helseth E, Skaansar O, Tverdal C, Andelic N, Bhatnagar R, *et al*. Impact of preinjury antithrombotic therapy on 30-day mortality in older patients hospitalized with traumatic brain injury (TBI). *Front Neurol* 2021; **12**:650695.
54 Antoni A, Wedrich L, Schauperl M, Höchtl-Lee L, Sigmund IK, Gregori M, *et al*. Management of traumatic brain injury in patients with DOAC therapy-are the 'new' oral anticoagulants really safer? *J Clin Med* 2022; **11**:6268.
55 Botros D, Gautam D, Hamrick FA, Nguyen S, Cortez J, Young JB, *et al*. Impact of premorbid oral anticoagulant use on survival in patients with traumatic intracranial hemorrhage. *Neurosurg Focus* 2023; **55**:E2.
56 Mathieu F, Güting H, Gravesteijn B, Monteiro M, Glocker B, Kornaropoulos EN, *et al*.; Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Investigators and Participants. Impact of antithrombotic agents on radiological lesion progression in acute traumatic brain injury: a center-TBI propensity-matched cohort analysis. *J Neurotrauma* 2020; **37**:2069–2080.
57 Amyot F, Arciniegas DB, Brazaitis MP, Curley KC, Diaz-Arrastia R, Gandjibakhche A, *et al*. A review of the effectiveness of neuroimaging modalities for the detection of traumatic brain injury. *J Neurotrauma* 2015; **32**:1693–1721.
58 Head injury: assessment and early management. https://www.nice.org.uk/guidance/ng232/chapter/Recommendations#discharge-and-follow-up. [Accessed January 2024]
59 Sapin V, Gaulmin R, Aubin R, Walrand S, Coste A, Abbott M. Blood biomarkers of mild traumatic brain injury: state of art. *Neurochirurgie* 2021; **67**:249–254.
60 Ward MD, Weber A, Merrill VD, Welch RD, Bazarian JJ, Christenson RH. Predictive performance of traumatic brain injury biomarkers in high-risk elderly patients. *J Appl Lab Med* 2020; **5**:91–100.
61 Janigro D, Mondello S, Posti JP, Unden J. GFAP and S100B: what you always wanted to know and never dared to ask. *Front Neurol* 2022; **13**:835597.
62 Azizi S, Hier DB, Allen B, Obafemi-Ajayi T, Olbricht GR, Thimgan MS, Wunsch DC 2nd. A kinetic model for blood biomarker levels after mild traumatic brain injury. *Front Neurol* 2021; **12**:668606.
63 Biberthaler P, Linsenmeier U, Pfeifer KJ, Kroetz M, Mussack T, Kanz K-G, *et al*. Serum S-100B concentration provides additional information for the indication of computed tomography in patients after minor head injury: a prospective multicenter study. *Shock* 2006; **25**:446–453.
64 Bazarian JJ, Biberthaler P, Welch RD, Lewis LM, Barzo P, Bogner-Flatz V, *et al*. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. *Lancet Neurol* 2018; **17**:782–789.
65 Chayoua W, Visser K, de Koning ME, Beishuizen A, IJmker R, van der Naalt J, *et al*. Evaluation of glial fibrillary acidic protein and ubiquitin c-terminal hydrolase-L1 using a rapid point of care test for predicting head computed tomography lesions after mild traumatic brain injury in a Dutch multi-center cohort. *J Neurotrauma* 2024. doi: 10.1089/neu.2023.0491. [Epub ahead of print]
66 Trivedi D, Forssten MP, Cao Y, Ismail AM, Czeiter E, Amrein K, *et al*. Screening performance of S100 calcium-binding protein B, glial fibrillary acidic protein, and ubiquitin C-terminal hydrolase L1 for intracranial injury within six hours of injury and beyond. *J Neurotrauma* 2024; **41**:349–358.
67 Korley FK, Jain S, Sun X, Puccio AM, Yue JK, Gardner RC, *et al*.; TRACK-TBI Study Investigators. Prognostic value of day-of-injury plasma GFAP and UCH-L1 concentrations for predicting functional recovery after traumatic brain injury in patients from the US TRACK-TBI cohort: an observational cohort study. *Lancet Neurol* 2022; **21**:803–813.
68 Mikolić A, Steyerberg EW, Polinder S, Wilson L, Zeldovich M, von Steinbuechel N, *et al*. Prognostic models for global functional outcome and post-concussion symptoms following mild traumatic brain injury: a Collaborative European Neurotrauma Effectiveness Research In Traumatic Brain Injury (CENTER-TBI) study. *J Neurotrauma* 2023; **40**:1651–1670.
69 Shahim P, Politis A, van der Merwe A, Moore B, Chou YY, Pham DL, *et al*. Neurofilament light as a biomarker in traumatic brain injury. *Neurology* 2020; **95**:e610–e622.
70 Hossain I, Mohammadian M, Maanpää HR, Takala RSK, Tenovuo O, van Gils M, *et al*. Plasma neurofilament light admission levels and development of axonal pathology in mild traumatic brain injury. *BMC Neurol* 2023; **23**:304.
71 Eliyahu L, Kirkland S, Campbell S, Rowe BH. The effectiveness of early educational interventions in the emergency department to reduce incidence or severity of postconcussion syndrome following a concussion: a systematic review. *Acad Emerg Med* 2016; **23**:531–542.
72 Rytter HM, Graff HJ, Henriksen HK, Aaen N, Hartvigsen J, Hoegh M, *et al*. Nonpharmacological treatment of persistent postconcussion symptoms in adults: a systematic review and meta-analysis and guideline recommendation. *JAMA Netw Open* 2021; **4**:e2132221.
73 Nelson LD, Temkin NR, Dikmen S, Barber J, Giacino JT, Yuh E, *et al*.; and the TRACK-TBI Investigators. Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers: a transforming research and clinical knowledge in traumatic brain injury (TRACK-TBI) study. *JAMA Neurol* 2019; **76**:1049–1059.
74 Steyerberg EW, Wiegers E, Sewalt C, Büki A, Citerio G, De Keyser V, *et al*.; CENTER-TBI Participants and Investigators. The contemporary landscape of traumatic brain injury in Europe: case-mix, care pathways, and outcomes from the CENTER-TBI study. *Lancet Neurol* 2019; **18**:923–934.
75 Korley FK, Peacock WF, Eckner JT, Maio R, Levin S, Bechtold KT, *et al*. Clinical gestalt for early prediction of delayed functional and symptomatic recovery from mild traumatic brain injury is inadequate. *Acad Emerg Med* 2019; **26**:1384–1387.
76 McLeod TC, Lewis JH, Whelihan K, Bacon CE. Rest and return to activity after sport-related concussion: a systematic review of the literature. *J Athl Train* 2017; **52**:262–287.
77 Voormolen DC, Cnossen MC, Polinder S, von Steinbuechel N, Vos PE, Haagsma JA. Divergent classification methods of post-concussion syndrome after mild traumatic brain injury: prevalence rates, risk factors, and functional outcome. *J Neurotrauma* 2018; **35**:1233–1241.
78 Keatley E, Bechtold K, Psoter K, Peters ME, Everett A, Rao V, *et al*. Longitudinal trajectories of post-concussive symptoms following mild traumatic brain injury. *Brain Inj* 2023; **37**:737–745.
79 Voormolen DC, Zeldovich M, Haagsma JA, Polinder S, Friedrich S, Maas AIR, *et al*. Post-concussion symptoms in complicated vs. uncomplicated mild traumatic brain injury patients at three and six months post-injury: results from the CENTER-TBI study. *J Clin Med* 2019; **8**:1921.
80 van der Vlegel M, Polinder S, Mikolic A, Kaplan R, von Steinbuechel N, Plass AM, Zeldovich M, van Praag D, Bockhop F, Cunitz K, Mueller I, Haagsma JA, The Center-Tbi Participants And Investigators. The association of post-concussion and post-traumatic stress disorder symptoms with health-related quality of life, health care use and return-to-work after mild traumatic brain injury. *J Clin Med* 2021; **10**:2473.
81 Lubbers VF, van den Hoven DJ, van der Naalt J, Jellema K, van den Brand C, Backus B. Emergency department risk factors for post-concussion syndrome after mild traumatic brain injury: a systematic review. *J Neurotrauma* 2024. doi: 10.1089/neu.2023.0302. [Epub ahead of print]
82 Cnossen MC, van der Naalt J, Spikman JM, Nieboer D, Yue JK, Winkler EA, *et al*. Prediction of persistent post-concussion symptoms after mild traumatic brain injury. *J Neurotrauma* 2018; **35**:2691–2698.
83 van der Naalt J, Timmerman ME, de Koning ME, van der Horn HJ, Scheenen ME, Jacobs B, *et al*. Early predictors of outcome after mild traumatic brain

injury (UPFRONT): an observational cohort study. *Lancet Neurol* 2017; **16**:532–540.
84 Mikolić A, Polinder S, Steyerberg EW, Retel Helmrich IRA, Giacino JT, Maas AIR, *et al*. Prediction of global functional outcome and post-concussive symptoms after mild traumatic brain injury: external validation of prognostic models in the CENTER-TBI study. *J Neurotrauma* 2021; **38**:196–209.
85 Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, *et al*.; InTBIR Participants and Investigators. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *Lancet Neurol* 2022; **21**:1004–1060.
86 Wienhoven M, Piercy J. Towards further progress in traumatic brain injury. *Lancet Neurol* 2023; **22**:109.
87 Seabury SA, Gaudette E, Goldman DP, Markowitz AJ, Brooks J, McCrea MA, *et al*.; TRACK-TBI Investigators. Assessment of follow-up care after emergency department presentation for mild traumatic brain injury and concussion: results from the TRACK-TBI study. *JAMA Netw Open* 2018; **1**:e180210.