ISSN 1669-9106 MEDICINA (Buenos Aires) 2026: 86 (Suppl. IV): 1-21

Supplement

INITIAL MANAGEMENT OF MILD TRAUMATIC BRAIN INJURY IN EMERGENCY DEPARTMENTS AND WALK-IN CLINICS IN ARGENTINA. PROPOSAL BY THE EMERGENCY COUNCIL OF THE ARGENTINE MEDICAL SOCIETY (SAM) AND THE ARGENTINE SCIENTIFIC SOCIETY OF EMERGENCY MEDICINE (SCEA)

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Abstract

Mild traumatic brain injury (MTBI) has traditionally been defined by a Glasgow Coma Scale (GCS) score between 13 and 15 points. It accounts for 80–90% of head injuries treated in emergency departments. While most patients have a favorable outcome, up to 16% have intracranial injuries, although less than 1% will require critical interventions, justifying systematized diagnostic strategies. The overuse of computed tomography (CT) scans leads to unnecessary exposure to ionizing radiation, avoidable costs, and overcrowding in emergency departments.

Clinical decision rules standardize the use of neuroimaging with high sensitivity for relevant lesions; however, their limited specificity and low adherence limit their impact on daily practice. Serum biomarkers have demonstrated sensitivity of 96–100% and negative predictive values of 95–100% for ruling out intracranial lesions within 12 hours after trauma, thereby reducing the number of unnecessary CT scans.

This review proposes an update focused on a stepwise diagnostic model that integrates structured clinical assessment, warning signs, decision rules, and biomarkers, adapted to different levels of complexity, including centers without access to CT scans—a common reality in our setting. New paradigms in follow-up after mild traumatic brain injury (MTBI) are also analyzed: early identification of persistent symptoms, patient education, and telemedicine.

Key words: mild traumatic brain injury, computed tomography, clinical decision rules, biomarkers, glial fibrillary acidic protein, persistent symptoms after concussion

KEY POINTS
Current knowledge

- Mild traumatic brain injury (mTBI) accounts for 80–90% of head injuries treated in emergency departments. Clinical decision rules (Canadian CT Head Rule, New Orleans Criteria, NEXUS II) help identify patients who require neuroimaging, although their low specificity remains a limitation. When used in combination within 12 hours of a mild TBI, the serum biomarkers GFAP and UCH-L1 have demonstrated a negative predictive value (NPV) greater than 99% for ruling out traumatic intracranial injury requiring intervention.

Contribution of the article to current knowledge

- This review updates the management of mild traumatic brain injury (mTBI) and proposes an integrated decision algorithm that combines clinical evaluation, red flags, decision rules, and biomarkers, tailored to the reality of emergency departments in Argentina and Latin America, including a specific algorithm for centers without access to CT. It incorporates updated evidence on the management of persistent post-concussion symptoms and the identification of high-risk groups for persistent symptoms.

Mild traumatic brain injury (mTBI) accounts for approximately 80–90% of all traumatic brain injuries (TBI) treated in emergency departments and constitutes a major public health problem requiring an interdisciplinary approach[1-3]. It affects more than 42 million people annually worldwide[4]. In Argentina, information is limited. A prospective study conducted in the City of Buenos Aires (CABA) reported an incidence rate of 322 TBI cases per 100 000 inhabitants. Of these, 93% were mTBI, 4% were moderate, and 3% were severe[5] —representing approximately 9345 mTBI cases annually in this jurisdiction. Another prospective study conducted at a referral hospital in Salta city recorded a total of 1,496 head injuries, 84% of which were mTBI. This represents 1257 cases treated at that referral center in Salta capital city alone[6].

mTBI presents a particularly challenging clinical scenario due to the need to identify a small subgroup of patients with potentially serious intracranial injuries among a large population, the majority of whom will have a favorable initial course and normal imaging findings. It is estimated that 16% of mTBI cases will have some type of intracranial injury[7], but <1% will require some form of active neurosurgical and/or neurointensive care intervention[8].

The American Congress of Rehabilitation Medicine (ACRM) proposed expanded diagnostic criteria for mTBI that broaden its definition to a "physiological alteration of brain function resulting from an external mechanical force," requiring the following criteria: 1- a plausible traumatic mechanism, 2- at least one acute clinical sign, 3- at least two acute symptoms, 4- at least one objective finding on physical examination or in biomarkers, and 5- imaging findings (if a CT scan was indicated)[9].

For decades, head CT has been the primary diagnostic method for ruling out acute intracranial injuries. However, the increasing use of this imaging modality has also highlighted important considerations, including overuse of the test in very low-risk patients, cumulative exposure to ionizing radiation, rising healthcare costs, and overburdening of emergency departments[10-12]. This overuse can vary widely—from 7.8% to 80.2%[13].

In response to this problem, clinical decision rules have been developed over the past twenty years, including the Canadian CT Head Rule[14], the New Orleans Criteria[15], and the NEXUS II Head CT Decision Instrument[16], which aim to identify, with high sensitivity, patients who require immediate neuroimaging. These tools have made possible to standardize initial decision-making and reduce clinical variability; however, their limited specificity continues to lead to a considerable number of CT scans being performed on patients with positive findings on the decision rule, but who ultimately do not have clinically relevant intracranial lesions[17,18]. Furthermore, even the Canadian Rule is associated with an estimated 30% rate of CT scan overuse[7], underscoring the need for complementary tools to optimize decision-making.

Review methodology

A narrative literature review was conducted to identify the most relevant and up-to-date evidence on the evaluation, diagnosis, initial management, and follow-up of mild traumatic brain injury (mTBI) in adults.

The literature search was conducted primarily in the PubMed/MEDLINE, SciELO, and Latindex databases and was supplemented by a review of clinical practice guidelines, consensus documents, and references from the selected articles. The following terms were used,

both individually and in combination using the Boolean operators AND and OR: "mild traumatic brain injury," "mTBI," "minor head injury," "concussion," "head trauma," "computed tomography," "clinical decision rules," "Canadian CT Head Rule," "New Orleans Criteria," "NEXUS Head CT," "biomarkers," "GFAP," "UCH-L1," "neuroimaging," "emergency department," "follow-up," and "telemedicine." Additional searches were conducted targeting specific aspects addressed in the manuscript.

Priority was given to guidelines and consensus statements, systematic reviews and meta-analyses, prospective and diagnostic validation studies, and clinically relevant cohort studies. Classic studies considered fundamental to the development or validation of clinical decision rules, as well as studies of local relevance, were also included. The selection process considered methodological quality, recency, clinical relevance, and applicability of the evidence. The search was updated during the preparation of the manuscript to incorporate publications available through July 2026.

The manuscript was drafted through an iterative process involving all three authors. After agreeing on the objectives, scope, and thematic areas, successive rounds of review were conducted to evaluate the selected evidence, its alignment with the text's statements and recommendations, conceptual clarity, and clinical relevance. Discrepancies were resolved by consensus. In the final review, references were updated, redundancies were removed, and the terminology and structure of the manuscript were harmonized. The final version was approved by all three authors.

Concept and definition

From a practical perspective, the terms "concussion" and "mild traumatic brain injury (mTBI)" refer to the same clinical entity and are interchangeable provided that neuroimaging was normal or not clinically indicated. A theoretical distinction suggests that while all concussions are mTBI, not all mTBI cases are concussions if they do not meet the criteria of the American Congress of Rehabilitation Medicine[19].

The classification of TBI was based almost exclusively on the Glasgow Coma Scale (GCS—Table 1), with a score between 13 and 15 considered mild TBI, 9 to 12 moderate, and ≤ 8 severe. This classification remains a valid tool for initial assessment due to its simplicity, reproducibility, and prognostic value.

However, clinical experience and accumulated evidence have shown that the level of consciousness measured by the GCS alone is insufficient to describe the complexity of mTBI, and the integration of the other components of the neurological evaluation is required.

It should be noted that the guidelines of the American College of Emergency Physicians (ACEP) do not classify a GCS score of 13 as a mild, considering only patients with GCS scores of 14 and 15 to have mTBI—provided they return to a GCS score of 15 within two hours of the injury[10].

There is a significant gap in training regarding the application of GCS; it is also important to record its individual components separately, as they have different prognostic implications[20]. It should also be noted that confounding factors such as delirium, alcohol intoxication, use of sedative medications, metabolic abnormalities, hypoxia, or concomitant injuries may limit the GCS's specificity in estimating the risk of traumatic brain injury[21,22,11].

Medical history and mechanism of injury

Medical history is the first step in the evaluation and should be obtained, whenever possible, from the patient, accompanying persons, and prehospital personnel. Assessing the mechanism of injury allows for an estimation of the energy transferred to the skull and identifies situations associated with a higher risk of intracranial injury, such as ejection from a vehicle, falls from a height, high-energy direct trauma, and mechanisms involving significant acceleration-deceleration[10,11] as well as the use of personal protective equipment recommended for occupational or sports activities.

The presence and duration of loss of consciousness, post-traumatic amnesia, episodes of vomiting, the presence of headache and/or seizures and their characteristics, as well as behavioral changes and any new neurological deficits—including vestibular and oculomotor signs—should be documented. The inability to stand due to orthostatic intolerance may be re-

Table 1 | Glasgow Coma Scale used to assess the level of consciousness in patients with traumatic brain injury

Glasgow Coma Scale (GCS)		
Component	*Response*	*Score*
Eye opening	Spontaneous	4
	To voice	3
	In response to pain	2
	None	1
Verbal response	Oriented	5
	Confused	4
	Inappropriate words	3
	Unintelligible sounds	2
	None	1
Motor response	Follows commands	6
	Locates pain	5
	Withdraws from pain	4
	Abnormal flexion (decortication)	3
	Abnormal extension (decerebration)	2
	None	1

Adapted from Teasdale and Jennett *Lancet* 1974; 2:81-4

lated to baroreceptor dysfunction; however, in selected cases, it could be the first manifestation of potentially serious extracranial injuries—such as hypovolemia or sepsis—as the cause of the trauma. These findings not only guide the initial diagnosis but also form the basis upon which clinical decision-making rules will subsequently be applied. It is important to note that if the patient was engaged in sports or work activities, these must be suspended immediately, as a new injury could worsen the patient's condition and prolong recovery.

There are a number of warning signs or red flags in mTBI (Table 2), such as the presence of seizures, diplopia, loss of consciousness (especially if lasting longer than one minute), weakness or paresthesia in the arms or legs (consider spinal cord injury), progressive deterioration of the level of consciousness or lucid intervals, persistent vomiting, a headache that is worsening or very severe, agitation, aggression, or a combative state, and a persistently low GCS <15[1]. In addition, visible anatomical injuries, such as skull deformity or penetrating trauma, require urgent neurosurgical evaluation regardless of the GCS score. Initial risk stratification is based on a multidimensional assessment that includes: the characteristics of the trauma mechanism, the patient's medical history and underlying conditions, and the findings obtained during clinical evaluation.

Physical examination and neurological assessment

The initial approach will follow the XABCDE trauma protocol (recognition and management of life-threatening external bleeding, airway, ventilation and oxygenation, circulation, neurological deficit, and exposure with protection from environmental factors), ruling out life-threatening injuries requiring immediate treatment[23]. This systematic evaluation must always be performed to avoid overlooking high-risk situations. For example, older adults may present with concomitant skeletal injuries such as hip fractures in up to 3% of mild TBI cases; however, since attention is often focused on managing the fracture, TBI may be underdiagnosed. The coexistence of a hip fracture—and even other skeletal injuries—drastically increases mortality, worsens functional outcomes, and significantly prolongs the hospital stay[24].

Following initial stabilization, care focuses on neurological evaluation, which includes determining the GCS score, examining the pupils, screening for cognitive, motor, or sensory deficits, and assessing speech, coordination, gait, etc.

In addition, a thorough examination of the scalp and craniofacial region must be performed to look for hematomas, penetrating wounds, depressed fractures, or signs suggestive of a skull base fracture, such as periorbital ecchymosis, retroauricular ecchymosis, hemotympanum, rhinorrhea/rhinorrachia, otorrhea/otorrachia, or cranial nerve abnormalities. Although these findings are rare in mild TBI, their identification substantially alters the diagnostic and therapeutic approach by raising red flags.

Clinical decision rules

Since the late 1990s, several clinical decision rules have been developed with the aim of systematically identifying patients with mTBI who are at higher risk for intracranial injury and require urgent intervention. These tools generally exhibit high sensitivity and high negative predictive value (NPV). Although they were not designed to replace clinical judgment, they help make it more reproducible and standardized and improve equity in access across different populations by optimizing the use of neuroimaging[10-11]. Table 3 summarizes the most relevant characteristics of the three most commonly used rules in adult patients.

The Canadian CT Head Rule (CCHR) (Table 4) is the tool most widely recommended by international guidelines for adult patients with mild TBI. Its use has been shown to reduce the number of CT scans by approximately 20–30% [25]without increasing the risk of missing clinically relevant injuries, which is why it is currently the standard strategy in most emergency departments[14, 10]. The *New* Orleans criteria (Table 5) have high sensitivity for detecting intracranial injuries; however, this comes at the expense of lower specificity. Nevertheless, in a recent study conducted in resource-limited settings, no statistically significant differences were observed between the two clinical rules for predicting clinically significant brain injuries or the need for neurosurgical intervention, suggesting that either rule is useful for determining whether neuroimaging should be performed[26]. The NEXUS II Head CT Decision Instrument (Table 6) incorporates a more heterogeneous population and uses simpler clinical criteria, with the aim of facilitating its implementation in daily practice. Like the previous rules, it prioritizes diagnostic sensitivity over specificity, accepting a higher number of negative results as the trade-off for minimizing the risk of missing clinically significant intracranial lesions[16].

Although contemporary guidelines agree on recommending the systematic use of clinical decision rules as part of the initial evaluation of patients with mTBI, adherence is suboptimal[10,11]. Recent studies report that only 45% of emergen-

Table 2 | Red flags associated with an increased risk of clinically significant intracranial injury in patients with mild traumatic brain injury

Red flags in mild traumatic brain injury	
Red Flag	*Description*
Seizures	Immediate seizure (at the time of impact or within minutes afterward)
Prolonged loss of consciousness	Loss of consciousness lasting longer than a brief period (>1 minute)
Severe or progressive headache	Severe headache or one that progressively worsens
Persistent or recurrent vomiting	Repeated episodes of vomiting
Neurological deterioration	Impaired level of consciousness, increased lethargy, or confusion
Persistent focal neurological deficit	Weakness, paresthesias in the extremities, diplopia
Combative behavior	Aggressive or combative behavior
Cervical spine injury	Neck pain, tenderness, limited range of motion, or deformity

Adapted from Leddy *N Engl J Med 2025*; 392:483-93

Table 3 | Comparison of the main clinical decision rules for indicating head CT in patients with mild traumatic brain injury

Comparison of Clinical Decision Rules						
Decision Rule	Year / Author	Target Population	Primary criteria	Sensitivity	Specificity	Key Limitations
Canadian CT Head Rule (CCHR)	Stiell et al. 2001 Canada	GCS 13–15, >16 years of age, no anticoagulation. Age as a risk factor: ≥65 years.	High risk: · GCS <15 at 2 h >65 years · Open or depressed fracture · Signs of a base fracture · Amnesia lasting >30 min · Vomiting ≥2 episodes · High-risk mechanism of injury	83-100%	36-79%	Excludes: <16 years of age, patients on anticoagulants, post-traumatic seizure, GCS <15. Less accurate for GCS 13.
New Orleans Criteria (NOC)	Haydel et al. 2000 U.S.	GCS 15, fully alert Adults (without anticoagulation) Age as a risk factor: ≥60 years.	CT scan indicated if ≥1 criterion: · Headache · Vomiting · Age >60 years · Alcohol consumption · Post-traumatic seizure · Evidence of trauma above the clavicles · Short-term amnesia	93-100%	12-25%	Applies only to GCS 15. Very low specificity: leads to overuse. Does not include the mechanism or trauma-related energy.
NEXUS II Head CT	Mower et al. 2005 U.S.	GCS 13–15, >18 years Heterogeneous population	CT scan if ≥1 criterion: · Evidence of skull fracture (signs of fracture on examination) · Scalp hematoma · Focal neurological deficit · Abnormal level of consciousness · Abnormal behavior · Persistent vomiting · Coagulopathy · Age ≥65 years	98.3%	13-25%	Low specificity compared to CCHR. Does not assess amnesia or duration of loss of consciousness. Less reduction in CT scans.

CCHR: Canadian CT Head Rule; CT: computed tomography; GCS: Glasgow Coma Scale; NEXUS II: National Emergency X-Radiography Utilization Study II; NOC: New Orleans Criteria; min: minutes; h: hours

Adapted by the authors from Stiell et al. *Lancet* 2001; 357:1391–6; Haydel et al. *N Engl J Med* 2000; 343:100–5; and Mower et al. *J Trauma* 2005; 59:954–9.

Table 4 | Risk criteria of the Canadian CT Head Rule for patients with mild traumatic brain injury

Canadian CT Head Rule	
Category	Criteria
High-risk criteria	• GCS <15 within 2 hours of injury • Suspected open or depressed skull fracture • Any sign of a skull base fracture (hemotympanum, raccoon eyes, Battle's sign, CSF otorrhea, or rhinorrhea) • ≥2 episodes of vomiting • Age ≥65 years
Moderate-risk criteria	• Retrograde amnesia ≥30 minutes prior to the impact • Hazardous mechanism: pedestrian struck by a vehicle, occupant ejected from a motor vehicle, or fall from a height of >3 feet (>91 cm) or >5 steps
Interpretation	The absence of all criteria is associated with a very low probability of clinically significant intracranial injury. The presence of at least one high- or moderate-risk criterion requires further evaluation.

Adapted from Stiell et al *Lancet* 2001; 357:1391-6

Table 5 | New Orleans Criteria for the indication of cranial computed tomography in patients with mild traumatic brain injury and a GCS of 15

Criteria	Definition
Headache	Presence of headache following trauma
Vomiting	One or more episodes of vomiting
Age >60 years	Patients over 60 years of age
Drug or alcohol intoxication	Clinical evidence of intoxication at the time of evaluation
Short-term memory impairment	Anterograde amnesia or impairment of recent memory
Physical evidence of trauma above the clavicles	Visible injuries to the head, face, or neck
Post-traumatic seizure	Seizure occurring after the trauma

Adapted from Haydel et al. *N Engl J Med* 2000; 343:100-5

Table 6 | Low-risk criteria from the NEXUS II rule for indicating cranial CT scanning in patients with mild traumatic brain injury

Low-risk criteria	Definition
Absence of significant skull fracture	No clinical evidence of open, depressed, or skull base fracture
Absence of focal neurological deficit	No motor, sensory, or cranial nerve deficits
Absence of altered level of consciousness	Normal level of consciousness during evaluation
No abnormal behavior	No agitation, disorientation, or inappropriate behavior attributable to the trauma
No coagulopathy	No coagulation disorders or anticoagulant therapy associated with an increased risk of bleeding
No persistent vomiting	No repeated episodes of vomiting following the trauma
Age <65 years	Patients younger than 65 years

Adapted from Mower et al. *J Trauma* 2005; 59:954-9

cy physicians use them routinely[27], with adherence rates ranging from 62.1% to 87.8% depending on the center[28,13]. This gap between evidence and practice represents a significant opportunity for improvement: correct application of the Canadian Rule may reduce CT scans by up to 70%[29]. Various educational and operational strategies have been implemented to improve adherence; among them, combining feedback to the treating team with data on costs and radiation exposure halved the number of inappropriate CT scans without any loss of sensitivity[30].

Biomarkers in mild traumatic brain injury

The inherent limitations of clinical decision rules have driven the search for new tools to increase the specificity of the diagnostic process. In this context, serum biomarkers of brain injury have emerged as a complement to clinical rules, promoting an even more appropriate use of CT scans. Table 7 summarizes the ideal characteristics that a biomarker for mild TBI should meet.

A growing number of biomarkers measurable in peripheral blood are being identified, each with distinct characteristics (Table 8) regarding their kinetics (time from injury to sample collection), confounding factors (age, concomitant extracranial trauma), preanalytical technical issues (ability to be measured in whole blood versus plasma, sample storage), and analytical aspects (point-of-care or automated laboratory systems). Regarding post-analytical considerations, one of the most common errors in interpreting biomarker performance is focusing exclusively on sensitivity or specificity. While both parameters are relevant for describing their diagnostic behavior, the primary practical utility of biomarkers in mild TBI lies in the negative predictive value (NPV). Table 9 presents common errors in the use of biomarkers for mild TBI.

In a setting where the prevalence of clinically relevant intracranial injuries is relatively low, a biomarker with very high sensitivity and an NPV close to 100% makes it possible to identify those patients whose probability of having a significant traumatic injury is low. From this perspective, the greatest clinical benefit of biomarkers is not to confirm an intracranial injury, but to provide additional evidence that helps avoid unnecessary CT scans[17,12,18].

This interpretation of biomarkers brings their use closer to a concept already familiar in relation to another biomarker: D-dimer in venous thromboembolism. In both cases, a positive result does not, by itself, establish a definitive diagnosis, whereas a negative result—interpreted in the appropriate clinical context—significantly reduces the probability of disease and allows for a modification of the diagnostic approach.

Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is currently one of the biomarkers of choice in the

Tabla 7 | Desirable characteristics of an ideal biomarker for mild traumatic brain injury (mTBI)

What characteristics should the ideal biomarker for mild TBI have	
1	High sensitivity
2	NPV close to 100%
3	Quick results (<30–60 minutes)
4	Easy availability and integration with common automated systems
5	Low cost
6	Reproducibility
7	Minimal influence of extracranial lesions
8	Multicenter validation
9	Integration with clinical guidelines and emergency department workflows

This table lists the properties a biomarker should possess to optimize its clinical utility in the initial evaluation of mTBI, including high diagnostic performance, rapid processing, feasibility of implementation, and adequate integration with clinical decision rules and emergency care pathways.
Source: Author's own work

Table 8 | . Characteristics, advantages, and limitations of the main biomarkers used in the evaluation of mild traumatic brain injury (mTBI)

Biomarker	Cellular origin	Time window	Advantage	Disadvantages	Clinical consideration
S100B	Calcium-binding protein primarily found in glial cells (astrocytes)	Within 3–6 hours after trauma	Most extensively studied biomarker Excellent sensitivity (91% at 0.1 µg/L) 30% reduction in CT in Scandinavian guidelines Commercially available	Very short half-life (requires rapid sampling) Lack of neurospecificity (elevated in extracranial trauma) Low specificity (30% at 0.1 µg/L)	Conventional cutoff value: 0.1 µg/L Optimal cutoff value: 0.72 µg/L Included in the 2013 Scandinavian and French guidelines
GFAP (glial fibrillary acidic protein)	Structural protein of astrocytes (glial cells)	Within 12 hours after trauma	High cerebral specificity Wider time window than S100B Approved by the FDA (2018) Best diagnostic marker for mild TBI Sensitivity of 93% at 22 pg/mL	Lower prognostic value than other biomarkers Requires combination with UCH-L1 for clinical use	Optimal cutoff: 626 pg/mL (sensitivity 71%, specificity 71%) High-sensitivity cutoff: 22 pg/mL Included in the 2022 French guidelines Available on point-of-care devices
UCH-L1 (C-terminal ubiquitin hydrolase L-1)	Neuronal protein (neuron cell bodies)	Within 12 hours after trauma	Neuron-specific FDA-approved in combination with GFAP (2018) Higher incremental prognostic value Available at the point of care	Moderate/ acceptable diagnostic performance as a standalone marker Limited data for meta-analysis	Used in combination with GFAP Best predictor of functional outcome in moderate-to-severe TBI Devices available with results in 15–18 minutes
NfL (Light Neurofilament)	Axonal structural protein (axons)	Subacute: 7 days post-trauma (late peak)	Excellent subacute diagnostic accuracy (AUC 0.81 at 7 days) Comparable to acute GFAP Best predictor of incomplete recovery in mild TBI Significant prognostic value	Not useful in the acute phase Requires waiting several days for elevation Prolonged elevation (weeks)	Useful for late-onset cases Indicator of ongoing axonal injury Subgroups with extreme elevation (7.4%) have prolonged recovery May remain elevated for 12 weeks

AUC: area under the curve; CT: computed tomography; FDA: U.S. Food and Drug Administration; GFAP: glial fibrillary acidic protein; NfL: neurofilament light chain; S100B: S100 Calcium-Binding Protein B; TBI: traumatic brain injury; UCH-L1: Ubiquitin C-Terminal Hydrolase L1; µg/L: micrograms per liter; pg/mL: picograms per milliliter
Adapted from Oris et al. *Clin Chem 2024; 70:1023-36*

evaluation of mild traumatic brain injury (mTBI). It is a structural protein of astrocytes that is rapidly released into circulation following a traumatic brain injury. Several prospective studies and systematic reviews have demonstrated high sensitivity for detecting intracranial lesions visible on CT and, in particular, a negative predictive value close to 100% for ruling out clinically relevant lesions[17,2]. A negative GFAP result, obtained within the validated time window (<12 h) in appropriately selected patients, identifies a group with a very low prob-

Table 9 | Common errors in the interpretation and use of serum biomarkers in mild traumatic brain injury (mTBI)

Common mistakes in the interpretation and use of serum biomarkers	
1	Assuming that a positive biomarker confirms bleeding.
2	Believing that it replaces clinical evaluation.
3	Ordering it outside the validated time window for each one.
4	Interpreting it without considering the pretest probability.
5	Use it as a substitute for clinical guidelines.

The main potential errors associated with the clinical use of biomarkers are described, including their isolated interpretation, use outside validated time windows, and use as a substitute for clinical evaluation or clinical decision rules. Source: author's own work

ability of significant intracranial injury, thereby reducing the need for CT scans without compromising diagnostic accuracy.

C-terminal ubiquitin hydrolase-L1 (UCH-L1)

Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is a specific enzyme whose release reflects early neuronal damage. Its combined use with GFAP has been shown to improve diagnostic performance compared to the isolated use of either biomarker, taking advantage of their different release kinetics and the complementary nature of glial and neuronal injury. This combination currently constitutes a robust strategy for determining the need for CT scanning in patients with mild TBI[17]. Evidence supporting the combined use of GFAP and UCH-L1 continues to grow; a recent prospective study conducted at 20 centers demonstrated a sensitivity and NPV of over 96% using a point-of-care test performed on whole blood (without centrifugation) with results available in 15 minutes[31].

Other biomarkers

S100B is an astrocyte-specific protein. It was one of the first biomarkers evaluated in mTBI and continues to be included in some European guidelines. However, its limited specificity—due to its presence in extracerebral tissues—as well as its short half-life in plasma (the sample must be collected within 3 hours of the injury) has progressively reduced its relevance compared to more specific biomarkers such as GFAP[32]. Meanwhile, light chain neurofilaments (NfL) represent one of the most promising lines of research for assessing axonal damage and functional prognosis; their kinetics differ significantly from those of the other markers discussed, with levels that may peak up to three days after the injury and remain elevated for weeks, aiding in retrospective diagnosis, although they may yield false positives in neurodegenerative diseases. Their incorporation into clinical practice still requires further validation and greater analytical standardization[12,18].

Diagnostic performance of biomarkers in clinical practice

Recent studies confirm the performance of the GFAP/UCH-L1 combination in ruling out intracranial injuries in mild TBI. Multiple prospective cohorts have consistently demonstrated sensitivities of 96–100% and negative predictive values of 95–100% when samples are collected within the first 12 hours after trauma[33-37]. In an Italian cohort of 130 patients with mild TBI (GCS 13–15), the combination of biomarkers achieved 100% sensitivity and NPV for detecting lesions visible on CT scans[33].

The specificity of the biomarkers is relatively low (19–67%), resulting in a significant proportion of false positives[36,38]. An analysis of more than 1,000 patients identified factors associated with false positives: age over 80 years and neurodegenerative diseases for GFAP; age over 80 years, hemolysis, and extracranial fractures for UCH-L1[38]. The implementation of age-adjusted thresholds in patients over 80 years of age improved specifically from 27% to 33% [38,39]. Given that their primary role is to prevent unnecessary CT scans in cases of mild TBI thanks to their

NPV, this low specificity does not have a negative impact in this scenario.

Integration of biomarkers into clinical practice

Even in the era of biomarkers, clinical evaluation remains the first step in risk stratification; clinical decision rules help standardize this evaluation, and biomarkers provide additional biological information that reduces uncertainty in the decision to order an imaging study or not.

Despite these advances, the routine use of biomarkers in mTBI faces significant challenges. These include (for the time being) limited availability, the need to validate cutoff values in different populations, standardization across analytical platforms, and the evaluation of their cost-effectiveness in different healthcare systems. However, these same challenges have been present to a greater or lesser extent with the introduction of other markers, such as high-sensitivity troponin, into emergency departments[40]. To attempt to address some of these questions in routine clinical practice, the IMPACTS-BRAINI study is evaluating an automated laboratory assay for GFAP and UCH-L1 in adult patients with mild TBI, including those with neurological comorbidities, to determine its impact on CT scan utilization (where it is estimated that it could reduce inappropriate use by 30–40%) and patient flow in the emergency department[41]. Finally, its technical simplicity, compatibility with standard point-of-care or automated equipment, and integration into workflows could facilitate its implementation even in Latin American settings where CT scanner availability is limited, often requiring inter-institutional transfers or longer hospital stays for observation.

Economic considerations

Cost-benefit analyses of biomarkers exist. A study on GFAP/UCH-L1 found that, despite the cost of the test, the potential reduction in unnecessary CT scans could be cost-effective for the healthcare system[42]. However, the cost-benefit ratio depends critically on the local prevalence of intracranial lesions and the cost of CT scans. In Latin American settings with limited resources, implementation must carefully consider these economic factors, as well as the availability of CT scans and the logistics and costs associated with inter-institutional transfers or bed occupancy for observation.

Appropriate use of CT: integration of clinical evaluation, decision rules, and biomarkers

CT scan is typically the gold standard for diagnosing acute intracranial injuries in patients with mild TBI. Its high sensitivity for detecting traumatic hemorrhages, skull fractures, and injuries requiring neurosurgical treatment makes it an important tool in the initial evaluation.

The information obtained during the medical history and physical examination allows for an initial estimate of the probability of an intracranial injury; subsequently, clinical decision rules reduce variability in the diagnostic process through standardized criteria, and, if available, biomarkers would provide additional objective evidence that helps reduce uncertainty before ordering (or refraining from ordering) neuroimaging.

As mentioned, when discussing red flags, not all patients benefit from this stepwise strategy. Patients presenting with severe impairment of consciousness, focal neurological deficits, signs of skull base fracture, open or depressed skull fractures, post-traumatic seizures, progressive neurological deterioration, or any other condition consistent with a high probability of intracranial injury require an immediate CT scan. In these scenarios, the indication for neuroimaging arises from the clinical evaluation and should not be delayed by the performance of additional tests[10,11].

It is important to note that the incorporation of biomarkers does not alter the central role of CT in the diagnosis of traumatic injuries. Currently, no biomarker can anatomically localize a hemorrhage, determine its volume, identify associated injuries, or guide neurosurgical management. Even the presence of an intracranial injury does not necessarily warrant active neurosurgical intervention or indicate a worsening of clinical outcomes; therefore, a CT scan remains necessary when there is a well-founded suspicion of an intracranial injury or when the scan results will determine the therapeutic ap-

proach. Figure 1 summarizes the stepwise approach using a clinical decision algorithm that incorporates biomarkers.

Management in centers without a CT scanner

Given the reality in Argentina and Latin America, where CT scan availability can vary, healthcare teams often face the decision of either clinically monitoring patients with mTBI or arranging their transfer—with the associated risks, burden on the healthcare system, and occupation of a critical care bed or shock room that allows for continuous neurological and hemodynamic monitoring, as well as immediate intervention in case of deterioration. At this point, it is important to clarify that skull X-rays should not be used in patients with mTBI, even in low-resource settings, since they fail to detect intracranial injuries and have low sensitivity for detecting skull fractures, potentially giving the healthcare team a false sense of security while exposing the patient to unnecessary radiation[43].

In this context, biomarkers used in conjunction with the initial clinical evaluation and decision rules allow for more accurate decisions when determining the need for transfer and, when appropriate, avoiding it. In centers without CT scan availability, after the initial evaluation to identify red flags and the application of a clinical rule, biomarkers can be used to classify the case. In appropriately selected patients, a negative biomarker result—when integrated with clinical evaluation and decision rules—can help rule out the need for neuroimaging and, consequently, avoid unnecessary transfers or prolonged observation. A positive biomarker result will necessitate referral to a center with a CT scanner and neurosurgical services available; although a positive result does not confirm the presence of an intracranial lesion or, ultimately, the need for surgery, the goal is to minimize the need for subsequent transfers[18]. Figure 2 presents the clinical algorithm for centers without CT scanning capabilities.

Special populations

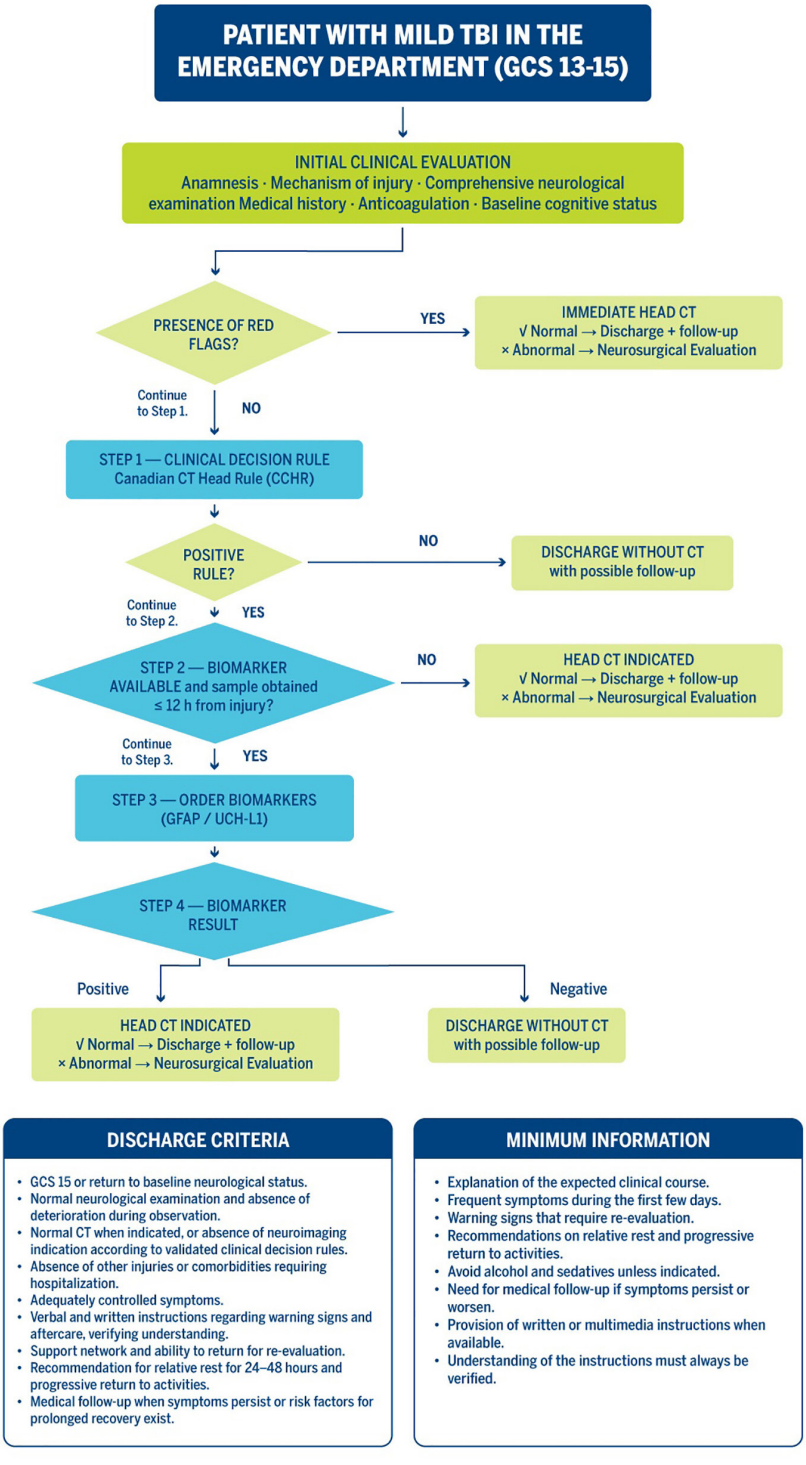
The likelihood of an intracranial injury depends not only on the trauma but also on the patient's characteristics. Advanced age has been one of the risk factors most consistently associated with intracranial hemorrhage, even following seemingly minor trauma. Similarly, treatment with anticoagulants or antiplatelet agents, a history of neurosurgery, the presence of other coagulation disorders, alcohol or drug use, and the inability to perform a reliable neurological examination substantially modify the diagnostic strategy and the threshold for ordering additional tests[10,11]. Repeat CT scans in patients with mild TBI following an initial normal CT scan are not indicated unless there is clinical deterioration[44].

Older adults require special consideration. Age-related cerebral atrophy allows intracranial hemorrhages to reach a considerable volume before producing obvious clinical manifestations. Concomitant injuries to mild TBI may go unnoticed and have a very significant negative impact[24]. Furthermore, the frequent coexistence of antithrombotic therapy increases the risk of bleeding and may contribute to the development of delayed complications. As noted, some biomarkers may yield false positives in individuals over 80 years of age, likely due to underlying neurodegenerative diseases[38].

Intimate partner violence (IPV) is a public health crisis affecting at least one in three women worldwide[45]. In this context, mild TBI may be a visible manifestation of IPV[46]. In this context, pathophysiology can be particularly complex, as it combines repeated head trauma with repeated non-fatal strangulation (which causes cerebral ischemic injury), worsening the prognosis[47], compounded by the possibility of other concomitant injuries and the psychological, familial, and social impact. Persistent symptoms may be more severe in this population and may be interrelated with post-traumatic stress, anxiety, and depression[48]. The professional team must be prepared to conduct a rapid assessment, ideally using validated tools. Understanding the interpersonal nature and the social, family, and economic impact of a domestic violence scenario requires addressing the issue from a broad perspective, considering the victim's specific preferences and circumstances while offering all available medical, mental hearlt, legal and social interventions.

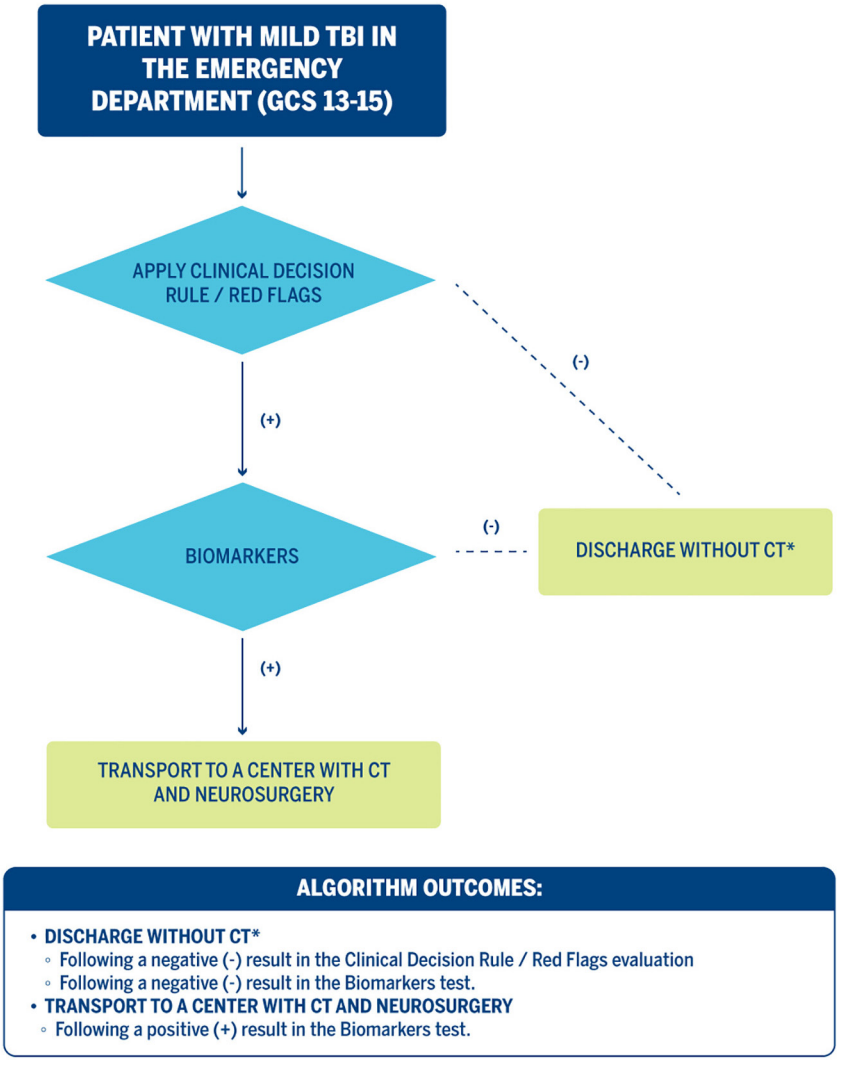
Finally, among athletes, variations are observed based on sex (concussions are more common in women), type of sport (more common during games than during practices), position

Figure 1 | Algorithm for hospitals with CT scanning capabilities. Proposed algorithm for the initial evaluation of mild traumatic brain injury (mTBI) in the emergency department. The algorithm integrates the identification of red flags, the application of validated clinical decision rules, and the complementary use of serum biomarkers (GFAP and UCH-L1) when available



MTBI: mild traumatic brain injury; GCS: Glasgow Coma Scale; CT: computed tomography; GFAP: gliofibrillary acid protein; UCH-L1: carboxy-terminal ubiquitin hydrolase L1
Source: author's own work

Figure 2 | Algorithm for hospitals without CT scanning. Proposed diagnostic strategy for the evaluation of patients with mild traumatic brain injury (mTBI) in centers without immediate access to computed tomography (CT). Clinical decision rules and serum biomarkers (GFAP and UCH-L1) are used to determine the need for transfer to a center with CT and neurosurgery services to complete the diagnostic evaluation and determine the course of treatment.



MTBI: mild traumatic brain injury; GCS: Glasgow Coma Scale; CT: computed tomography; GFAP: gliofibrillary acid protein; UCH-L1: C-terminal ubiquitin hydrolase L1
Source: author's own work

(more common in goalkeepers than in field players), as well as other personal factors such as a previous concussion, prior attention disorders, adolescence, a family history of migraine[1]

Role of advanced neuroimaging

Although CT scans identify macroscopic structural abnormalities with great precision, they have low sensitivity for detecting microscopic lesions or functional abnormalities that may explain the persistence of symptoms following an apparently mild trauma.

In recent years, various magnetic resonance imaging (MRI) modalities and even positron emission tomography (PET) have shown a greater ability to identify subtle brain lesions that remain hidden on conventional CT scans. Magnetic susceptibility (SWI) sequences in MRI are

particularly useful for detecting traumatic microhemorrhages; diffusion imaging—and particularly diffusion tensor imaging (DTI)—allows for the evaluation of white matter abnormalities consistent with diffuse axonal injury; and functional MRI, which focuses on studying changes in brain connectivity associated with persistent cognitive disorders[49,18].

These findings have contributed to a better understanding why some patients continue to experience headaches, cognitive impairments, balance disturbances, difficulty concentrating, or emotional symptoms despite an initial normal CT scan. However, it is important to note that the identification of these abnormalities using advanced techniques does not necessarily imply a change in therapeutic management and, in many cases, their prognostic significance remains under investigation; it could even be a source of clinical uncertainty and anxiety for the patient and the treating team.

Consequently, advanced neuroimaging techniques are not part of the routine evaluation of mTBI. Their use should be reserved for specific situations, such as patients with persistent or progressive symptoms, discrepancies between clinical course and conventional neuroimaging findings, suspected diffuse axonal injury, or research protocols.

Persistent post-concussion symptoms

A significant proportion of patients continue to experience physical, cognitive, emotional, or behavioral symptoms for days, weeks, or even months after the injury, even when the initial evaluation was apparently normal[3,1]. Consequently, discharge from the emergency department no longer marks the end of the diagnostic process but rather the beginning of a new phase aimed at early detection of persistent symptoms, preventing complications, and promoting adequate functional recovery and a return to sports or work.

There are multiple mechanisms potentially responsible for persistent post-concussion symptoms, including genetic and inflammatory factors, neuronal dysfunction (with functional alterations in ion pumps and ATP utilization), neurotransmitter release, and even altered cerebral blood flow with neuronal death. Some of these alterations may persist even thirty days after the trauma and be exacerbated by repeated trauma, especially within very short time frames[49].

Definition, prevalence, and risk factors

Most patients experience a full recovery during the first few weeks following the injury. However, between 10% and 30% may develop persistent symptoms. Although these conditions were traditionally grouped under the term "persistent post-concussion symptoms," it is now recognized that their pathophysiology is complex and likely multifactorial, involving biological, psychological, and social mechanisms[3]. Rather than a single entity, persistent symptoms represent a heterogeneous set of manifestations whose course depends on multiple factors, such as repeated head injuries, age, personal and even family history (e.g., migraine and psychiatric disorders), and female gender. The severity of initial symptoms has been associated with a higher risk of persistence, although no single factor can reliably predict the clinical course.

It is important to explain to patients the expected course of the condition, the most common temporary symptoms, self-care measures, and warning signs that require a follow-up visit. This reduces uncertainty, improves adherence to follow-up care, and decreases unnecessary visits. There are written materials produced by various scientific societies and organizations, such as the Centers for Disease Control and Prevention (CDC), that are easy to understand and informative; they serve as a tool for reassurance and are recommended in various clinical practice guidelines as a means of ensuring quality care[3]. There are also online resources for patients created by various organizations, but their quality is generally limited[50]; therefore, it is recommended to at least provide written instructions that include clear guidelines on the gradual return to normal activities (including work, sports, and school). These recommendations should be tailored to each patient's clinical course and individual characteristics, avoiding both excessive restriction and premature return to activities that could exacerbate symptoms or expose the patient to new injuries.

Prolonged bed rest is not considered beneficial and may even be associated with a slower recovery. The evidence supports a brief period of relative rest, generally 24–48 hours, including screen time restrictions, followed by a gradual return to physical and cognitive activities, provided they do not cause a significant worsening of symptoms[1]. Providing documentation and supporting evidence for work and school will help the patient adhere to the guidelines for their recovery.

Follow-up approach

Although most patients can be managed on an outpatient basis by their primary care physician, certain subgroups are at higher risk for an unfavorable outcome and may benefit from structured follow-up or evaluation by specialized teams. These include patients with symptoms persisting beyond the first few weeks, those with a history of multiple concussions, high-performance athletes, or workers in high-risk professions such as pilots, older adults, individuals with pre-existing neurological or psychiatric disorders, and those with significant limitations in resuming their usual activities.

Telemedicine is a viable tool for monitoring patients following a mild TBI. Although randomized studies are not currently available, this tool allows for follow-up after an initial in-person evaluation, with high rates of satisfaction among both patients and healthcare professionals[51].

Finally, an interdisciplinary approach—including sleep hygiene, headache management, and interventions for anxiety and depression—can help optimize functional recovery and improve quality of life.

Discharge criteria from the emergency department

Hospital discharge for patients with mild TBI should be based on a comprehensive clinical evaluation and not exclusively on the CT scan results or the decision not to perform a CT scan if it is not indicated.

Patients may be discharged from the emergency department if they have a normal neurological examination with a GCS score of 15 (or a return to baseline), no clinical deterioration, and no other traumatic injuries or medical conditions requiring hospitalization. In addition to clinical stability, it is essential that the patient understand the recommendations provided at discharge, receive written instructions regarding the expected course of recovery and warning signs, and, ideally, have a support network for at least the first 24 hours and access to a follow-up medical evaluation in case of deterioration. As previously mentioned, routine hospitalization or the routine repetition of normal CT scans is not recommended for patients on anticoagulants or antiplatelet therapy with a normal neurological examination, provided they remain clinically and neurologically stable.

Future perspectives

Although the GCS remains the gold standard for the initial assessment and classification of TBI, there is a growing consensus that its ability to reflect the biological complexity of brain injury and predict clinical outcomes is limited[52,53]. The mTBI category encompasses a highly heterogeneous population, in which patients with the same GCS score may present markedly different pathophysiological mechanisms, imaging findings, risks of deterioration, and functional prognoses[54,55]. Moving beyond this initial classification and recognizing the different phenotypes facilitates a new conceptualization of mild TBI[56,57] as well as the development and validation of multimodal models capable of integrating clinical variables with serum biomarkers, advanced neuroimaging techniques, noninvasive brain monitoring methods, and artificial intelligence tools[52,56-58,10] thereby promoting truly individualized diagnostic and therapeutic strategies[54,56].

Another emerging line of research is the systematic incorporation of noninvasive brain monitoring techniques into integrated prognostic models. Methods such as quantitative pupillometry[59], transcranial Doppler, ultrasound measurement of the optic nerve sheath diameter [60] and assessment of intracranial compliance using specific devices could provide dynamic information on brain function that complements that obtained through biomarkers and structural imaging. The integration of these parameters would allow for the characterization not only of the presence of brain injury but also of its physiological impact and its progression over time, further reducing the use of radiation; however,

the specific utility of these interventions in mild TBI still requires validation through prospective studies.

At the same time, major international consortia, such as TRACK-TBI[61] and CENTER-TBI[62], are driving an even more profound conceptual shift through the development of models based on brain injury endotypes and biotypes[54,56,57]. While endotypes seek to identify underlying biological mechanisms such as predominant axonal damage, persistent neuroinflammation, vascular dysfunction, or neurodegenerative processes, biotypes integrate clinical information, biomarkers, advanced neuroimaging, physiological monitoring, and neurocognitive assessment to define subgroups with different courses of disease and potential therapeutic responses[56,57]. This approach recognizes that mild TBI is not a single disease but a biologically heterogeneous syndrome, and it represents one of the pillars of future precision medicine in neurotrauma.

Artificial intelligence and machine learning models could play a significant role. The ability to simultaneously integrate large volumes of clinical, biochemical, imaging, and physiological data will enable the development of predictive models with greater diagnostic and prognostic accuracy than currently available tools[56, 57, 10]. These algorithms could assist in decision-making during initial care in emergency departments and optimize resource allocation by helping the healthcare team more accurately select which patients require hospitalization, specialized follow-up, or specific interventions.

All of these new strategies require validation through prospective, multicenter studies that determine not only their diagnostic accuracy but also their impact on clinically relevant outcomes, including the detection of clinically significant intracranial lesions, early neurological deterioration, the need for neurosurgery, functional progression, neurocognitive recovery, quality of life, and the cost-effectiveness of their implementation in different healthcare systems[54-58].

This paradigm shift will make it possible to move away from a one-size-fits-all approach and adopt precision medicine, in which diagnostic, therapeutic, and follow-up decisions are tailored to each patient's biological characteristics and specific risk.

Conclusions

Mild TBI is a very common reason for presentation to emergency departments and one of the greatest diagnostic challenges in emergency medicine. The low prevalence of clinically relevant intracranial injuries, coupled with the potential consequences of missing a severe injury, has for decades shaped a strategy based on the widespread use of CT as the primary diagnostic tool.

The overuse of neuroimaging, variability in clinical practice, and the identification of patients with persistent symptoms despite a normal CT scan have driven the development of a tiered diagnostic model that integrates initial evaluation with the use of decision rules. In this context, biomarkers represent a significant advance. Their high negative NPV offers the possibility of more reliably identifying patients with a very low probability of a significant intracranial lesion and promoting a more appropriate use of neuroimaging, always integrated with the clinical context and decision rules.

In patients with a high pretest probability and/or positive biomarkers, a CT scan will allow for the exclusion of an intracranial lesion or its confirmation and stratification if present, as well as the planning of any necessary surgical and neurointensive care. However, the routine incorporation of biomarkers still requires cost-effectiveness validation across different healthcare systems, especially in Latin America, and therefore their availability remains limited.

The recognition that some patients may develop persistent symptoms or functional limitations even in the absence of visible lesions on CT scans necessitates looking beyond the acute phase and incorporating strategies for patient education, follow-up, and rehabilitation when appropriate.

Future priorities include efficiently validating and incorporating these new tools, increasing access, and standardizing care, given that, even with validated clinical guidelines, adherence remains variable and training is insufficient.

Strategies and algorithms should aim to optimize the use of diagnostic resources and the length of stay in emergency departments without compromising patient safety and while enabling appropriate management of healthcare costs, with the goal of moving toward a more

personalized, precise, efficient, and evidence-based approach to emergency medicine.

Conflict of interest: Pascual Valdez, Adolfo Savia, and Leandro Aguilar received honoraria from bioMérieux Argentina for their authorship of this publication.

Statement on the use of artificial intelligence tools: In preparing this manuscript, the authors used ChatGPT and Claude to improve the text's readability, writing style, and translation quality. After using these tools, the authors critically reviewed and edited the generated content and assume full responsibility for the final content of the publication.

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