TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is an alteration in brain function, or other evidence of brain pathology, caused by an external force.[1] The majority of TBI cases are of mild severity (mild TBI).[2]

TRAUMATIC BRAIN INJURY

- **Traumatic brain injury (TBI)** is caused by a bump, blow, or jolt to the head or a penetrating head injury that results in the disruption of normal brain function.[3]
- TBI may have immediate complications and be life-threatening. It is a **medical emergency**, requiring evaluation by a healthcare professional and **admission to the hospital in many cases**.
- The main danger is **post-traumatic intracranial complications** (lesions) which may lead to compression of vital centers in the brain stem, that regulate respiratory and cardiovascular functions. This may ultimately result in the unconscious state of the patient, a persistent vegetative state, coma or even death.
- TBI of so-called **mild severity (mTBI)** represents 70-90% of cases.[2]

BURDEN OF TBI

- **TBI is a major public health issue.** Annual incidence of TBI is estimated at 27 to 69 million globally (**Figure 1**).[4]
- TBI also represents a high social and economic burden.[4]
- It is a major source of health loss and disability worldwide with far-reaching physical, emotional, and economic consequences for patients, families, and society at large.[5]
- TBIs were estimated to result in 8.1 million years of living with disability worldwide in 2016.[5]
- **Table 1** shows the socio-economic burden of mild TBI (most frequent form) in the US. Moderate and severe TBIs are however more serious and costly. Fatal TBIs and TBIs requiring hospitalization account for ~90% of total TBI medical costs.[6-9]

Figure 1. Worldwide TBI burden according to WHO Region.[4,10]

Adapted from Dewan MC, *et al. J Neurosurg.* 130:1080–1097, 2019 ; Wikipedia List of WHO Regions

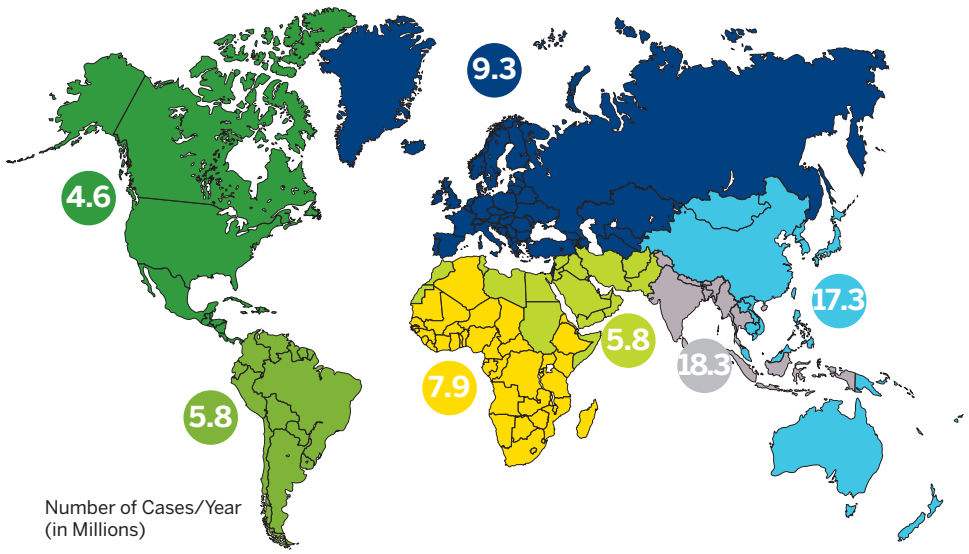


Table 1. Mild TBI Health System & Socio-economic Burden (US example).[7-9]

Adapted from Alali AS, *et al. Value Health.* 2015;18:721-734; Humphreys I, *et al. ClinicoEcon Outcomes Res*. 2013;5:281–287; Nelson LD, *et al*. *JAMA Neurol.* 2019;76(9):1049-1059

USE OF HOSPITAL FACILITIES AND RESOURCES	COSTS
• > 1.5 million ED visits per year	• Direct cost per case $33k - $36k
• > 300,000 admissions per year	• Direct cost per year $100-300 million
• > 80% GP visits at 3-month	• Indirect cost per year $100-300 million
• Use of rehabilitation programs	• Productivity loss per year $521 million

CAUSES OF TBI

Table 2. Main causes of TBI according to age group.[2,11]

Adapted from Peterson B, *et al.* CDC Surveillance Report 2017; Maas AIR, *et al. Lancet Neurol.* 2017;16(12):987-1048

Infants/children (0-4 y.o.)	Young adults	Elderly (> 65 y.o.)
Falls	Car crash	Falls
	Assault	
	Blast injuries	
	Sport injuries	

External forces responsible for TBI

- Direct impact
- Acceleration/deceleration
- Penetrating

A greater proportion of elderly TBI patients with falls as the main cause of injury is observed in high-income countries, compared with younger patients and traffic accidents as the primary cause of injury in lower-income countries.

INITIAL EVALUATION, SEVERITY ASSESSMENT AND CLASSIFICATION OF TBI

- Initial evaluation, severity assessment and classification of TBI often takes place on arrival of medical, paramedical staff or other emergency services at the site of injury, followed by initial care measures.
- Reevaluation is also constantly performed, including on arrival at healthcare facilities, to monitor the patient's state and potential deterioration.

Glasgow Coma Scale (GCS)

- Based on clinical presentation and assessment of severity using the **Glasgow Coma Scale (GCS)**, TBI is classified as **Mild, Moderate and Severe** (**Figure 2, Table 3**).[12]
- The GCS score is based on 3 evaluations: **Eyes, Verbal and Motor.**
- In addition, the **Head Injury Severity Score** (HISS) identifies patients with minimal head injury, based on a GCS score of 15 and no risk factors.[13]

Figure 2. GCS assessment of TBI[12]

Adapted from www.glasgowcomascale.org

GLASGOW COMA SCALE

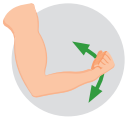
EYE OPENING RESPONSE

Spontaneous ____ 4
To sound ____ 3
To pressure ____ 2
None ____ 1

VERBAL RESPONSE

Orientated ____ 5
Confused ____ 4
Words ____ 3
Sounds ____ 2
None ____ 1

MOTOR RESPONSE



Obey commands ____ 6
Localising ____ 5
Normal flexion ____ 4
Abnormal flexion ____ 3
Extension ____ 2
None ____ 1

NOTE: The Modified Glasgow Coma Scale for Infants and Children is called the **Pediatric Glasgow Coma Scale** (pGCS).[14] https://www.mdcalc.com/calc/3702/pediatric-glasgow-coma-scale-pgcs. It is mainly used for children 2 years and younger. For older children, the standard GCS scale is normally used.

Table 3. Classification of TBI.[2,12,15-17]

Adapted from Peterson B, *et al*. CDC Surveillance Report 2017; www.glasgowcomascale.org; Greenberg M.S. Handbook of Neurosurgery. 2016; Levin SL, Diaz-Arrastia RR. *Lancet Neurol.* 2015;14: 506–17; VA/DoD Clinical Practice Guideline for the Management of Concussion-mild Traumatic Brain Injury. 2016.

Stage	Mild TBI	Moderate TBI	Severe TBI
GCS Score	13-15 or 14-15*	9-12	3-8
Clinical Examination	Headache Slightly impaired vigilance Confusion Short and mild alteration of brain function	Clearly impaired consciousness and vigilance Lasting confusion Physical/psychological changes	Unconscious state (coma) Threat to vital functions Severe physical/psychological changes Epilepsy and other neural disorders
Loss of consciousness (LOC)	0-30 minutes	>30 minutes and <24 hours	>24 hours
Alteration of consciousness/ mental state (AOC)	Up to 24 hours	>24 hours; severity based on other criteria	
Post-traumatic amnesia (PTA)	0-1 day	>1 day	>7 days
Frequency	70-90%	5-15%	5-10%

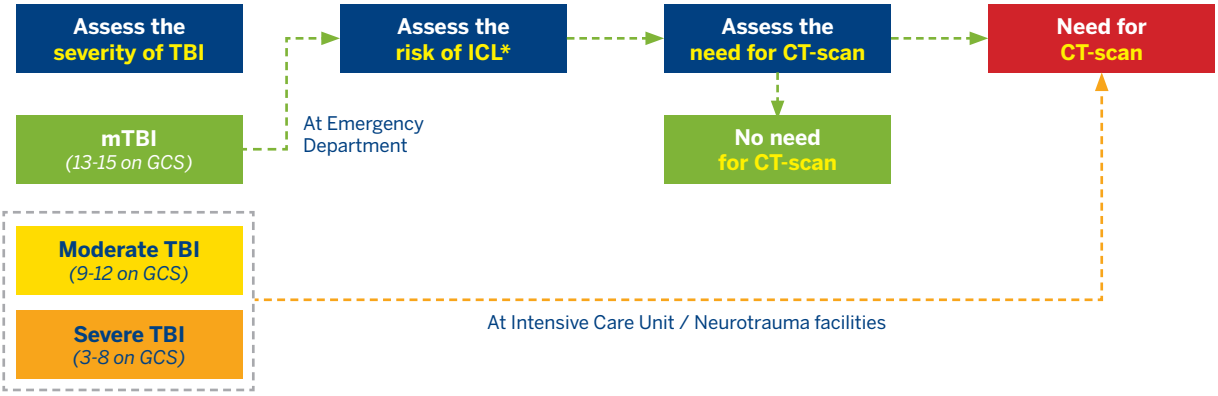
*** IMPORTANT:** The lower threshold level for mild TBI may vary between a GCS score of 13 or 14, depending on settings and countries.[16]

Table 4. Direct consequences of severity assessment and evaluation.[15]
Adapted from Greenberg MS. Handbook of Neurosurgery. 2016

Stage	Mild TBI	Moderate TBI	Severe TBI
Initial management	ED	ED or ICU	ICU or specialized Neuro-ICU
Risk of intracranial lesions and degradation	Low	Medium	High
Imagine requirement	May be required	MANDATORY	MANDATORY
Type of imaging	CT	CT	CT
Imaging delay	1-12h post-arrival depending on risk factors	Urgent	Urgent
Surgery	May be needed in very rare cases	May be required	Often required in emergency

* ED: Emergency Department; ICU: Intensive Care Unit; CT: Computed Tomography

Figure 3. Assessment of risk of intracranial lesions and need for CT-scan.[15]
Adapted from Greenberg MS. Handbook of Neurosurgery. 2016.



* ICL: intracranial lesion

CONSEQUENCES AND COMPLICATIONS OF TBI

In addition to signs and symptoms at presentation, TBI may have other consequences and complications. Among them, the presence of **intracranial lesions (ICL)** reflects structural damage following a traumatic event (**Figure 4**). Intracranial lesions may be life-threatening and may require emergency surgery with subsequent complex intensive care.

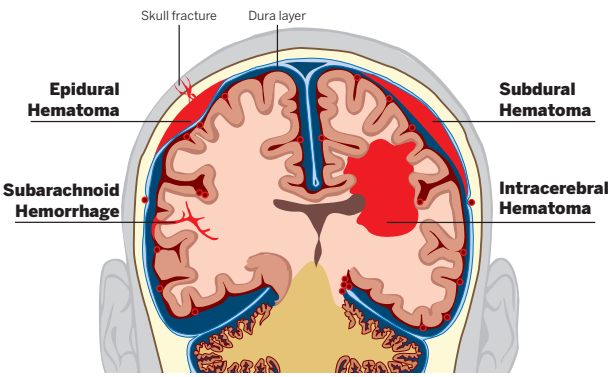
Intracranial lesions (ICL)

An **ICL** is a pathologic area inside the skull or brain, which may lead to brain tissue damage, compression or irritation.

The main types include:

- **Intracranial hemorrhage (ICH), most common form of ICL**
- **Fractures**
- **Brain edema, seen more often in moderate-to-severe TBI cases**

Figure 4. Main types of intracranial lesions (ICL).[18]
Adapted from Wikimedia Commons. Category: Intracranial hemorrhage



Radiological Evaluation

Head computed tomography (CT) is the reference method to detect post-traumatic intracranial lesions (ICL), which may sometimes require surgical management, or may cause further clinical deterioration (**Figure 5**).[19]

IMPORTANT! The use of CT is associated with radiation exposure. There are reports of increased cancer risks from CT scans, estimated at 1 in 5,000 to 10,000 for a single head CT scan in young adults.[20]

Such incidence and risks are much **higher in infants and children**. Excess relative risk of new brain tumor averaged 1.29 (95% confidence interval, 0.66–1.93) for pediatric patients exposed to one or more head CTs.[21]

Figure 5. Head CT of diffuse brain edema following TBI.[19]
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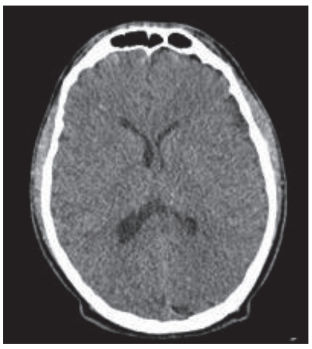


MANAGEMENT AND TREATMENT OF TBI

After initial evaluation and observation, the patient may be either admitted to hospital or discharged:[11,22]

- **Admission:** if patient has moderate or severe TBI with intracranial abnormalities/lesions or associated medical (chronic disease) or social (isolation) issues.
- **Discharge:** main criteria to send a patient home, with oral and written instructions, are:
  - uncomplicated mild TBI with normal head CT or negligible risk of ICLs,
  - no serious associated comorbidities.

Management of **admitted patients** will depend on the type of ICL and associated risk factors:

NON-THREATENING ICL	THREATENING ICL	THREATENING AND SPECIFIC ICL
Monitoring using CT scan may be needed	Specific measures to prevent worsening, such as discontinuation/reversion of blood thinners, admission to ICU, and CT monitoring	Surgery and/or symptomatic treatment measures to combat consequences of ICL (bleeding and associated complications)

Medication to prevent nerve damage or promote nerve healing after TBI is currently not available.[22]

MILD TRAUMATIC BRAIN INJURY

This section will focus on some specificities and challenges of mild TBI.

- **Mild TBI is by far the most frequent presentation of TBI,** with 70 to 90% of TBI being mild. In practice, this number could be underestimated and could even represent more than 90%.[2]
- Clinical signs may not be observed in all cases of mild TBI. **Symptoms are essential for diagnosis**. Reliance on recall of the event and subjective reporting of loss of consciousness, post-traumatic amnesia, and symptoms all affect the diagnostic accuracy/precision of mild TBI (**Table 5**).[16] Accurate diagnosis and defining criteria for mild TBI and its clinical consequences have been problematic.[23]
- In patients with mild TBI, the prevalence of CT-detected intracranial injury is typically **less than 10%**.[16] This brings into question the widespread use of head CT scanning, which generates potential adverse effects of radiation exposure, unnecessary emergency department (ED) resource use, and cost.[24]
- Whether a patient with mild TBI should get a head CT depends on assessment of the **overall risk of having intracranial lesions (ICL)** following a traumatic event (**Figure 6**).

Table 5. Mild TBI Initial Presentation – most frequent signs and symptoms.[16]

Adapted from Levin SL, Diaz-Arrastia RR. *Lancet Neurol.* 2015;14: 506–17

SYMPTOMS (apparent and reported by PATIENT)	SIGNS (objectively perceived by HEALTHCARE PROFESSIONAL)
Loss of consciousness	Confusion
Amnesia	Disorientation
Headache	(Transient) Muscle weakness (hand, leg)
Nausea	Speech disturbances
Vomiting	Seizures
Dizziness	Vision disorders (nystagmus)
Fatigue	
Attention impairment	
Light & sound sensitivity	

Mild TBI and Concussion

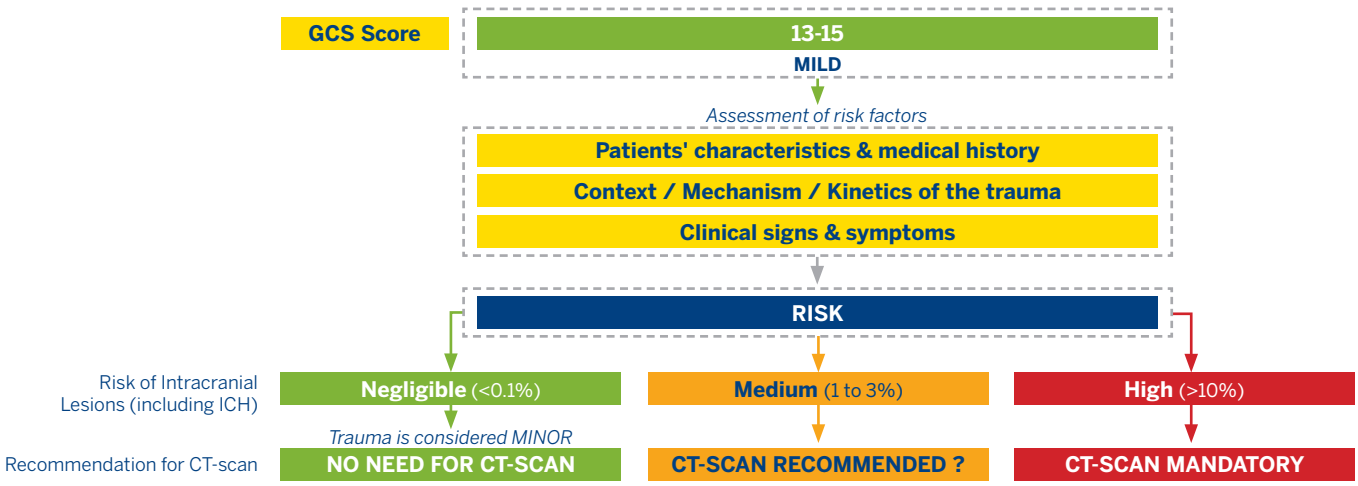
There is no consensus definition of concussion. Most mTBIs with a negative CT-scan can be considered to be **concussions**[15], and in this case mild TBI and concussion are interchangeable terms, whereas mTBI with a lesion cannot be considered as concussion. Sports concussion is considered to be a subtype of mild TBI.[16]

Post-concussion Syndrome

Mild TBI may also have some delayed effects. The most common is **Post-concussion Syndrome (PCS)**, which may affect up to 15% of mTBI patients. **PCS** is the **persistence of concussion symptoms** beyond the normal course of the brain recovery (generally 3 months or more after a concussion).[25]

Figure 6. Risk assessment of mild TBI.[16,26,27]

Adapted from Levin SL, Diaz-Arrastia RR. *Lancet Neurol.* 2015;14: 506–17; Unden J, *et al. BMC Med.* 2013;11:50; Gil-Jardiné, 2022



MILD TBI GUIDELINES AND CLINICAL DECISION RULES

Attempts exist to harmonize approaches to mTBI management, including CT decision-making.[28] In routine practice, clinicians may rely more on national guidelines or specific clinical decision rules.[29]

Some examples of national guidelines for mild TBI management include :

- American College of Emergency Physicians[30]
- National Institute for Health and Care Excellence (NICE) in the UK[31]
- Scandinavian guidelines[26]
- Joint Guidelines of French Societies of Emergency Physicians & Intensive Care Medicine[27]

Using these guidelines, **over 90% of head CTs in the mild TBI population are normal.**

Clinical decision rules (CDRs), such as the Canadian CT head Rule, have been developed with the goal of reducing unnecessary head CT scans, but have had limited impact on CT use.[32]

ROLE OF BLOOD-BASED BIOMARKERS IN TBI

Several proteins, released from brain tissue, can be detected in the blood (**Figure 7**).[33]

Some of them, including **S100B**, **GFAP and UCH-L1**, have been extensively studied, mainly for **prediction of absence of intracranial injuries** on head CT-scan in moderate and mild TBI,[34,35] and are recommended in some national guidelines for mTBI patient management.[26,27]

Measurement of blood-based brain biomarkers following suspected mTBI provides clinicians with an additional objective tool to predict absence of immediate intracranial complications (**Figure 8**), and may be an aid in optimizing the use of head CTs. By potentially reducing excessive CTs in selected patients, associated harmful radiation exposure, waiting times and costs may be avoided.[34]

Figure 7. Protein biomarkers in brain tissue.[36]

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UCH-L1: ubiquitin C-terminal hydrolase -L1
NSE: neuron-specific enolase
PDS95: postsynaptic density protein 95
Aß42: amyloid beta 42
BDNF: brain derived neurotrophic factor
GFAP: glial fibrillary acidic protein
MAP2: microtubule-associated protein 2
MBP: myelin basic protein
S100B: S100 calcium-binding protein B

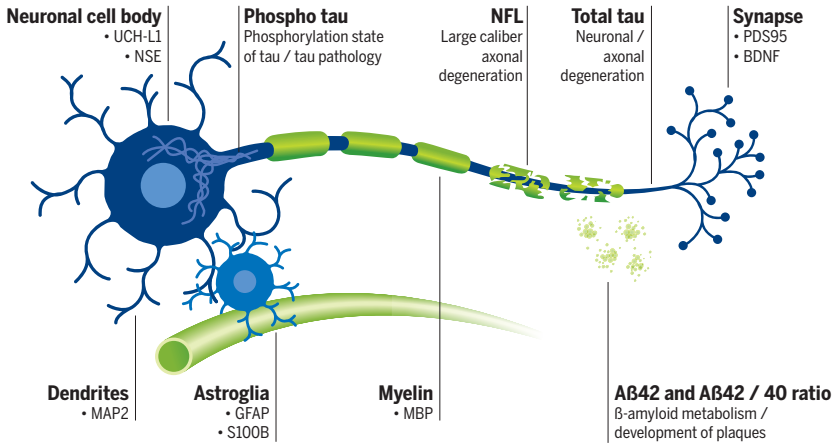
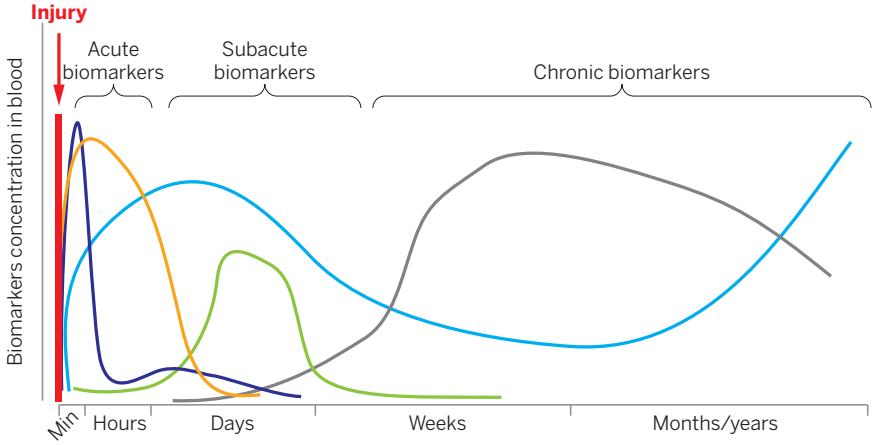


Figure 8. Kinetics of blood-based brain biomarkers.[11]

Adapted from Maas AIR, *et al. Lancet Neurol*. 2017;16(12):987-1048

- **Neuronal or axonal injury** (eg, UCH-L1), **blood-brain barrier damage** (eg, S100B)
- **Gliosis or glial injury** (eg, GFAP)
- **Neurodegeneration or CTE** (eg, P-tau)
- **Apoptosis** (eg, SBDP120), **demyelination** (eg, MBP)
- **Autoimmunity** (eg, autoAb-[GFAP])

CTE: chronic traumatic encephalopathy
SBDP120: spectrin breakdown product 120



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