Chapter 23

TRAUMATIC BRAIN INJURY

Louissa Srama Rosner Cidral
Marina Corrêa Freitas
Maria Angélica Otero de Melo dos Reis
Julia Correia Lemos
Isabella Denardi
Marina Rosa Martins
Victoria Arrais Maia
Suellen Maroco Cruzeiro Lombello
Victória Góis De Moraes Rodrigues
Maíra Taliberti
Kevin Amorim Alves
Gabriela Fonseca Nascimento

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Data de aceite: 02/09/2024

Louissa Srama Rosner Cidral
Universidade Positivo (UP)
Curitiba - PR

Marina Corrêa Freitas
Faculty of Biomedical Sciences of the Austral University (FCB UA)
Pilar - Buenos Aires

Maria Angélica Otero de Melo dos Reis
Universidad Nacional de Rosario (UNR)
Rosario - Argentina

Julia Correia Lemos
Centro Universitário FAMINAS - Muriaé
Muriaé - MG

Isabella Denardi
Universidade de Medicina Santo Amaro (UNISA)
São Paulo - SP

Marina Rosa Martins
Faculdade Multivix - Vitória ES
Vitória - ES

Victoria Arrais Maia
Universidade Nove de Julho (UNINOVE)
Osasco - SP

Suellen Maroco Cruzeiro Lombello
Universidade Federal de Juiz de Fora - Campus Governador Valadares (UFJF-GV)
Governador Valadares - MG

Victória Góis De Moraes Rodrigues
Faculdade Ciências Médicas de Minas Gerais (FCMMG)
Belo Horizonte - MG

Maíra Taliberti
Universidade do Oeste Paulista (UNOESTE)
Jaú - SP

Kevin Amorim Alves
Universidad Nacional de Rosário (UNR)
Rosario - Argentina

Gabriela Fonseca Nascimento
Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM)
Vitória - ES

Traumatic brain injury (TBI) is a critical medical condition often resulting from direct impacts or acceleration-deceleration forces, which can cause temporary or permanent damage to the brain. It is one of the leading causes of morbidity and mortality worldwide, especially among young and adult individuals. Due to its multifaceted nature, TBI can lead to a wide range of neurological, cognitive, and behavioral deficits, significantly affecting the quality of life of patients (McGinn; Povlishock, 2016).

Within the spectrum of medical emergencies, TBI represents a significant challenge for both diagnosis and treatment. Studies indicate that hemorrhagic progression in the pericontusional zones of the brain, initially attributed to coagulopathy, involves several other causal factors. Additionally, the severity of brain contusions is closely related to the size, location, and potential for bilateral involvement of the brain (McGinn; Povlishock, 2016).

TBI is the most common cause of death and disability in individuals under 40 years old in the United Kingdom. In low- and middle-income countries, mortality and morbidity rates are even higher (Khellaf; Khan and Helmy, 2019). Globally, it is estimated that millions of cases of TBI occur each year, with a substantial impact on public health and healthcare systems.

Demographic data on TBI show a higher prevalence among males, particularly in younger ages, due to factors such as traffic accidents, falls, and sports activities. The incidence of TBI varies geographically, being higher in regions with poor safety infrastructure and less access to specialized medical care (Khellaf; Khan and Helmy, 2019).

Historically, the approach to TBI has evolved significantly with the advancement of imaging technologies and neurological monitoring. The implementation of specialized neurointensive care and legislation on the use of protective equipment, such as seat belts and helmets, have contributed to reducing the incidence and improving outcomes in TBI patients (Khellaf; Khan and Helmy, 2019).

Risk factors for TBI include young age, male sex, participation in contact sports, traffic accidents, falls, and interpersonal violence. Additionally, exposure to hazardous work environments and the absence of adequate safety measures significantly increase the risk of TBI. Statistics indicate that patients with severe TBI have a high hospital mortality rate. Studies show that accurately defining the severity of TBI is crucial for the uniformity and precision in patient classification, improving clinical practice and epidemiological research (Savitsky *et al*., 2016). Prevention strategies for TBI include the use of protective equipment, awareness campaigns on traffic and workplace safety, and strengthening safety regulations. Early screening programs and rapid response protocols are essential for the effective identification and treatment of TBI, minimizing long-term impact (Dennis *et al*., 2022).

EPIDEMIOLOGY

Traumatic brain injury (TBI) is a severe public health issue occurring in various contexts worldwide, affecting a broad age range and showing significant global prevalence. The condition is often classified into degrees of severity (mild, moderate, and severe) based on the Glasgow Coma Scale, with most reported cases considered mild, representing about 75% to 90% of cases (Haarbauer-Krupa *et al*., 2021; Toccalino; Colantonio; Chan, 2021; Williams *et al*., 2020).

Historically, TBI was more prevalent among the young population, particularly due to traffic accidents and high-impact sports activities. However, with the increasing aging of the global population, there has been a significant shift, with a rise in the incidence of TBI among the elderly, especially in developed countries. This demographic change requires new approaches and techniques for the appropriate management of TBI in the elderly, reflecting the need for the development of specific prevention and treatment strategies (Giner *et al*., 2022; Pugh *et al*., 2020; Brazinova *et al*., 2020).

The main risk factors for TBI include falls from a standing height, injuries during sports activities, and violence, such as fights and assaults, in addition to traffic accidents. Vulnerable populations, such as the elderly, people with neurodegenerative disorders (Alzheimer›s disease and Parkinson›s disease), individuals experiencing intimate partner violence, and high-impact sports athletes, are more susceptible to TBI. Additionally, genetic factors and pre-existing medical conditions, such as neurodegenerative diseases, also significantly contribute to the risk of developing TBI (Williams *et al*., 2018; Toccalino; Colantonio and Chan, 2021; Mollayeva; Mollayev and Colantonio, 2018; Giner *et al*., 2020; Baggiani *et al*., 2020).

Globally, it is estimated that approximately 69 million people suffer from TBI each year. The distribution of TBI shows a male predominance, with a ratio of 16:1 between men and women suffering severe TBI. In the United States, recent studies indicate that TBI is one of the most prevalent causes of emergency room visits, totaling about 2.87 million cases, with the main causes being collisions with objects, falls, and motor vehicle accidents (Toccalino; Colantonio; Chan, 2021; Haarbauer-Krupa *et al*., 2021; Mollayeva; Mollayeva and Colantonio, 2018; Kennedy *et al*., 2020; Majdan *et al*., 2020).

DIAGNOSIS

The pathophysiology of traumatic brain injury (TBI) is not just an acute event but also a progressive and delayed neurodegenerative process composed of multiple, parallel, interactive, and interdependent cascades of biological reactions at the tissue, cellular, and subcellular levels. Axons are particularly vulnerable to physical trauma, and axonal injury is a common occurrence in both focal and diffuse brain trauma and can be found in TBI regardless of its severity. Not only are neurons at risk of injury, but also astroglial cells and oligodendrocytes (Wang *et al*., 2018).

A comprehensive understanding of the pathological processes at the cellular and subcellular levels is fundamental for developing precise diagnostic and prognostic molecular biomarkers for TBI (Beard; Meaney; Issadore, 2020; Wang et al., 2018; Najen et al., 2018). The absence of validated diagnostic biomarkers leads to a reliance on subjective clinical symptoms for the diagnosis of TBI. Neuroimaging biomarkers are clinically established for moderate to severe TBI, but other imaging modalities are still at recommendation levels II-III (Wilde *et al*., 2022).

Computed tomography (CT) scans are crucial for identifying life-threatening conditions post-TBI, while magnetic resonance imaging (MRI) provides detailed anatomical information for diagnostic clarity (Wilde *et al.*, 2022). CT, the initial modality used during TBI diagnosis, only assesses macroscopic anatomical changes characteristic of severe TBI, such as hemorrhages and brain lesions, but does not evaluate other features like inflammation, gliosis, and diffuse axonal injury (Beard; Meaney and Issadore, 2020; Wang et al., 2018). MRI can be used to assess regions of increased brain activity, altered cerebral blood flow, axonal, and microvascular pathology, but its high cost and inaccessibility limit its use for repeated monitoring of TBI progression (Beard; Meaney and Issadore, 2020). In selected cases, MRI can also provide important information due to its better tissue contrast and increased sensitivity compared to CT (Albano *et al.*, 2023).

Electroencephalogram (EEG) and imaging exams are standard clinical measures for TBI assessment. Molecular biomarkers derived from cerebrospinal fluid (CSF) or serum biopsy overcome many limitations associated with these measures (Najen et al., 2018) and have been used to evaluate inflammation, oxidative stress, excitotoxicity, and other pathophysiological mechanisms occurring within days to weeks after the injury (Beard; Meaney and Issadore, 2020; Wang *et al.*, 2018; Najen *et al.*, 2018).

As biomarkers indicative of neuronal cellular injury, Neuron-Specific Enolase (NSE), a homodimer found in mature neurons and neuroendocrine cells, and Ubiquitin C-terminal Hydrolase-L1 (UCH-L1), a neuronal cytosolic protein, are evaluated (Wang et al., 2018; Najen et al., 2018). Elevations of NSE have been observed in the blood compartment (Wang et al., 2018) and UCH-L1 in the cerebrospinal fluid and serum of patients with severe TBI (Wang *et al.*, 2018; Najen *et al.*, 2018). The general concept is that injured neurons release such molecules into the interstitial fluid, where they gain access to the CSF and systemic circulation (Najen et al., 2018). A major disadvantage of using NSE as a specific marker for TBI is its abundance in red blood cells, requiring consideration of hemolytic processes in the blood measurement of NSE (Wang *et al.*, 2018). UCH-L1 is not specific to the central nervous system (CNS) and is expressed by peripheral nervous system cells, some tumor cells, endocrine system cells, and smooth muscle cells (Najen *et al.*, 2018).

The S100B protein, a calcium-binding astroglial protein (Wang et al., 2018), and glial fibrillary acidic protein (GFAP) have been analyzed as astroglial biomarkers. S100B is also released by adipose tissue and cardiac/skeletal muscles, and its levels are elevated in orthopedic trauma without TBI. Nevertheless, it is a sensitive marker as a predictor of CT abnormalities and the development of post-concussion syndromes. GFAP biomarker levels are elevated within 3 to 34 hours in CSF and serum after severe TBI and in serum samples after moderate TBI, with this increase being trauma severity-dependent (Wang *et al.*, 2018; Najen *et al.*, 2018).

Neurofilament (NF) proteins and myelin basic protein (MBP) are markers of late axonal injury and demyelination (Wang *et al.*, 2018). NFs exist as bundles known as

neurofibrils, which are an important component of the cytoskeleton, primarily functioning to provide structural support to the axon. They can be dissociated from the cytoskeleton into the cytosol or possibly the extracellular fluid if cell membrane integrity is compromised (Wang *et al*., 2018). MBP degradation results from axon and myelin sheath deterioration and can be released into biofluids (CSF and/or serum) after TBI (Wang *et al*., 2018).

MicroRNAs (miRNAs) have been evaluated as emerging biomarkers in TBI diagnosis based on their roles in regulating various cellular functions in the brain. miRNA-targeted genes are involved in a wide range of processes such as neurogenesis and brain development, differentiation of neural cells like oligodendrocytes, myelination and axon guidance, regulation of synaptic plasticity, and inflammatory genes (Albano *et al*., 2023; Wang *et al*., 2018; Najen *et al*., 2018). These biomarkers can be detected early in the blood, establishing themselves as a rapid diagnostic tool essential in emergency and urgent care contexts. This early detection capability is vital for initiating effective treatment and mitigating severe complications (Albano *et al*., 2023). miRNAs are short, non-coding regulatory RNA molecules composed of 20 to 24 nucleotides usually located within introns, playing important roles in regulating gene/protein expression. Several microRNAs have indeed been identified at elevated levels in the biofluids (CSF, serum, or plasma) of TBI patients (Wang *et al*., 2018; Najen *et al*, 2018), such as miR-16 and miR-92a (Wang *et al*., 2018; Najen *et al*., 2018) in moderate TBI patients, and miR-93, miR-191 (Wang *et al*., 2018; Najen *et al*., 2018), and miR-499 (Najen et al., 2018) in the serum of patients with mild, moderate, and severe TBI. The levels of all three miRNAs were related to injury severity and clinical outcomes several months later (Wang *et al*., 2018; Najen *et al*., 2018). The downregulation of miR-425-5p and miR-502 shortly after injury characterized moderate TBI patients, while the upregulation of miR-21 and miR-335 was observed in the serum of patients after severe TBI (Najen *et al*., 2018).

Notably, miRNA sample collection involves non-invasive methods, which is advantageous in emergency settings where patients may be in debilitating or critical conditions. The technology for detecting miRNAs, including microarrays, next-generation sequencing (NGS), and quantitative real-time PCR (qRT-PCR), can be adapted depending on the need for broad screening or targeted analysis of specific miRNAs. Additionally, the use of bioinformatics systems to identify target genes of dysregulated miRNAs and their related signaling pathways could also link severe TBI with neurodegenerative conditions, acting as a prognostic marker for this condition (Albano *et al*., 2023).

Exosomes (EVs) are membranous vesicles released from all types of neural cells, varying in size and origin, and possessing specific surface markers, RNA, and proteins (Beard; Meaney and Issadore, 2020). Studies on the use of exosomes as diagnostic biomarkers for TBI have focused on traditionally evaluated proteins, such as UCHL1, Tau, and β-amyloid (Beard; Meaney and Issadore, 2020). Exosomes derived from neurofunctional proteins, such as UCHL1 and occludin, showed transient elevations in their levels after

the acute event, while elevated levels of exosomes composed of Tau and β-amyloid were exhibited in both acute and chronic events (Beard; Meaney and Issadore, 2020).

Most biomarker studies for TBI lack validation in large cohorts and do not meet Level 1 Evidence standards, hindering their clinical use (Wilde *et al.*, 2022). However, diagnostic biomarkers have the potential to differentiate TBI endophenotypes, aiding in identifying patients who may benefit most from specific interventions. Combining digital biomarkers with neuroimaging and biofluid markers would enhance TBI assessment and patient stratification for better clinical decision-making, given the current limitations of these methods due to the heterogeneity of injuries. Predictive biomarkers offer insights into treatment responses and clinical outcomes (Wilde *et al.*, 2022). The use of machine learning algorithms to analyze multimodal biomarker data could provide a comprehensive understanding of TBI pathophysiology and patient outcomes.

TREATMENT

The primary goal in the treatment of Traumatic Brain Injury (TBI) is to minimize or prevent the progression to secondary injury, primarily ischemia and intracranial hypertension, highlighting the need for early intervention. Thus, patient management strategies aim to reduce edema and intracranial pressure, as well as to preserve cerebral perfusion and oxygen delivery to brain tissue (Jinadasa; Boone, 2016).

The treatment plan varies according to the severity of the TBI, classified as mild, moderate, or severe using the Glasgow Coma Scale. However, regardless of the severity, the therapeutic approach is always focused on preventing possible secondary injury. In the initial management, hemodynamic stabilization, monitoring and maintenance of intracranial pressure and cerebral perfusion, ventilatory and oxygenation support if necessary, administration of hyperosmolar saline solution and/or sedatives, seizure prophylaxis, and nutritional support form the basis of patient care. In more severe cases, surgical options such as decompressive craniotomy or cerebrospinal fluid drainage via ventricular drain are emphasized. Additionally, therapeutic adjustments are made as needed and based on the patient›s individualized response (Yan *et al.*, 2024).

Another important aspect of TBI treatment is providing information and guidance to both the patient and their family regarding medical follow-up after the event. Even in mild cases, it is essential that the patient and/or their companion be advised to return to the healthcare service if warning signs or severe symptoms, such as altered consciousness and seizures, occur. Therefore, implementing educational strategies by the healthcare team is crucial in preventing and managing post-TBI sequelae (Seabury *et al.*, 2018).

Severely injured patients require immediate care and rapid stabilization to prevent worsening. Monitoring and maintaining systemic blood pressure is critical, with the need to recognize both hypotension and hypertension. A systolic pressure of up to 100 mmHg is

recommended for patients aged 49 to 69 years, and up to 110 mmHg for patients aged 15 to 49 years or over 70 years. Intravenous saline solutions should be administered as needed. After hemodynamic normalization, an urgent non-contrast head computed tomography (CT) scan should be performed, as it is the standard initial examination for moderate to severe TBI. In children, radiation exposure should be considered before deciding to obtain a CT scan (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

Intracranial pressure (ICP) monitoring should be performed via an intraventricular catheter, considered the gold standard for being the most accurate and measuring global ICP. Guidelines recommend maintaining ICP below 22 mmHg and a target cerebral perfusion pressure (CPP) between 60 to 70 mmHg. Reduction of ICP to adequate levels is achieved through sedation, induced hyperventilation, hyperosmolar therapy (use of mannitol), hypothermia, and appropriate surgical treatment (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

Hyperosmolar therapy or osmotherapy is administered when sedation, intubation, and postural repositioning are not effective in reducing ICP. Osmotherapy is often administered with mannitol at the standard dose of 0.25 - 1g/Kg every 6 hours to reduce ICP (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

Mechanical ventilation is frequently used, and guidelines recommend hyperventilation as a temporary measure to reduce ICP, which should be avoided in the first 24 hours and used with moderation and for a limited time (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

TBI patients with elevated levels of fibrinogen degradation products may benefit from early administration, within 3 hours, of tranexamic acid (TXA) to reduce the likelihood of death due to extracranial bleeding (Yan *et al.*, 2024; Jinadasa *et al.*, 2016).

Hypothermia has been used as a prophylactic neuroprotector, serving as a resource to control increased ICP by reducing cerebral blood flow and volume (Yan *et al.*, 2024; Jinadasa *et al.*, 2016). Studies indicate that treating fever can decrease brain damage in patients with severe brain injuries and reduce shivering through therapeutic interventions such as buspirone, meperidine, or neuromuscular blocking agents.

After implementing general measures, the surgical resection of lesion masses and CSF drainage should be considered. According to the 2017 guidelines for severe TBI, initial surgical evacuation of an epidural hematoma is recommended if the patient has a Glasgow Coma Scale (GCS) score less than 9, clot thickness greater than 15mm, and midline shift greater than 5mm, or a focal neurological deficit. Additionally, surgical evacuation can also be considered if the subdural hematoma (SDH) is greater than 1 cm, with a midline shift greater than or equal to 5mm, GCS less than 8, and ICP greater than 20 mmHg or rapid neurological decline. Surgery for eligible patients shows significant mortality benefit if evacuation is performed within less than 4 hours (Yan *et al.*, 2024).

Decompressive craniectomy is a surgical method that can be used as a treatment option for severe refractory cases of intracranial hypertension. This method involves removing part of the skull where the dura mater is opened to increase the volume of the

cranial cavity and thereby reduce ICP. While effective, it includes risks such as wound infection, meningitis, brain abscess, CSF leakage, hematoma, and cerebral infarction (Jinadasa *et al*., 2016).

Moderate to severe TBI is often associated with physical and mental sequelae or disabilities. These deficits can be challenging to detect due to their silent epidemiology. Sequelae can range from mild deficits to comatose states and have significant implications for both short-term management and long-term care of individuals with TBI. Delirium after TBI is one of the most frequent manifestations, typically lasting an average of 43 days in patients with severe TBI (de Guzman *et al*., 2017).

The standard treatment consists of addressing other contributing medical factors such as infection, dehydration, electrolyte disturbances, severe anemia, hypoxia, and hypotension, among others. A review of the patient›s medications should be conducted to eliminate those that may contribute to delirium, such as benzodiazepines, highly anticholinergic drugs, and excess or inappropriate administration of opioids. Psychosocial measures are essential for this type of treatment, including sleep-wake cycle regulation, reorientation, sensory aids, and early mobilization with physical therapy and getting out of bed. Antipsychotics are used for delirium in the general hospital and ICU, and anticonvulsants are also used to treat different neuropsychiatric sequelae, particularly if they present with seizure disorders, mood lability, mania, impulsivity, and aggression (de Guzman *et al*., 2017).

In addition to the common therapies mentioned above, new medications are being tested to enhance TBI treatment, such as Amantadine Hydrochloride, a drug traditionally used to control dyskinesia in Parkinson›s disease and for prophylaxis against certain viruses. Amantadine acts as an NMDA receptor antagonist and dopaminergic agonist, thus being useful in controlling cognitive deficits observed in TBI due to dopaminergic and glutamatergic dysregulation. The medication was well-tolerated and showed medium-term cognitive benefits; however, its long-term effects have not been fully elucidated, and its efficacy in cognitive recovery was only proven for four weeks of treatment, with a loss of effectiveness by the sixth week. Therefore, further studies on the application of Amantadine in controlling post-TBI cognitive deficits are essential to confirm the reliability of this drug (Loggini *et al*., 2020).

Non-invasive monitoring methods are also being developed, such as Near-Infrared Spectroscopy (NIRS), which assesses cerebral perfusion by analyzing the absorption of infrared light by tissue. This works because, between wavelengths of 700 nm and 1000 nm, the absorption of radiation by oxygenated and deoxygenated hemoglobins is maximized, while that of other components is minimized. Thus, it is possible to obtain information on the supply and consumption of oxygen by brain tissue, enabling non-invasive monitoring of patients who have suffered TBI (Roldán; Kyriacou, 2021).

Currently, the methods used to monitor patients are more invasive and complex, such as subdural, parenchymal, or intraventricular catheters for monitoring intracranial pressure

(ICP), as well as imaging exams (computed tomography and magnetic resonance imaging). Since these methods can require more time to perform in certain scenarios, combining them with less invasive forms like NIRS, which can be used both in hospital beds and ambulances, can be beneficial for the early detection of changes in pressure and cerebral perfusion (Roldán; Kyriacou, 2021).

REFERENCES

ALBANO, Giuseppe Davide, *et al.* An Overview on the Use of miRNAs as Possible Forensic Biomarkers for the Diagnosis of Traumatic Brain Injury. **International Journal of Molecular Sciences**, v. 24, n. 7, p. 6503, 2023.

BAGGIANI, Marta; GUGLIELMI, Angelo; CITERIO, Giuseppe. Acute traumatic brain injury in frail patients: the next pandemic. **Current opinion in critical care**, v. 28, n. 2, p. 166-175, 2022.

BEARD, Kryshawna; MEANEY, David F.; ISSADORE, David. Clinical applications of extracellular vesicles in the diagnosis and treatment of traumatic brain injury. **Journal of neurotrauma**, v. 37, n. 19, p. 2045-2056, 2020.

BRAZINOVA, Alexandra, *et al*. Epidemiology of traumatic brain injury in Europe: a living systematic review. **Journal of neurotrauma**, v. 38, n. 10, p. 1411-1440, 2021.

DE GUZMAN, Earl; AMENT, Andrea. Neurobehavioral management of traumatic brain injury in the critical care setting: an update. **Critical care clinics**, v. 33, n. 3, p. 423-440, 2017.

DENNIS, Emily L., *et al*. ENIGMA brain injury: Framework, challenges, and opportunities. **Human brain mapping**, v. 43, n. 1, p. 149-166, 2022.

GINER, J., *et al*. Traumatic brain injury in the new millennium: new population and new management. **Neurología (English Edition)**, v. 37, n. 5, p. 383-389, 2022.

HAARBAUER-KRUPA, Juliet, *et al*. Epidemiology of chronic effects of traumatic brain injury. **Journal of neurotrauma**, v. 38, n. 23, p. 3235-3247, 2021.

JINADASA, Sayuri; BOONE, M. Dustin. Controversies in the management of traumatic brain injury. **Anesthesiology clinics**, v. 34, n. 3, p. 557-575, 2016.

KHELLAF, Abdelhakim; KHAN, Danyal Zaman; HELMY, Adel. Recent advances in traumatic brain injury. **Journal of neurology**, v. 266, n. 11, p. 2878-2889, 2019.

LOGGINI, Andrea, *et al.* The role of amantadine in cognitive recovery early after traumatic brain injury: a systematic review. **Clinical Neurology and Neurosurgery,** v. 194, p. 105815, 2020.

MCGINN, Melissa J.; POVLISHOCK, John T. Pathophysiology of traumatic brain injury. **Neurosurgery Clinics**, v. 27, n. 4, p. 397-407, 2016.

MOLLAYEVA, Tatyana; MOLLAYEVA, Shirin; COLANTONIO, Angela. Traumatic brain injury: sex, gender and intersecting vulnerabilities. **Nature Reviews Neurology**, v. 14, n. 12, p. 711-722, 2018.

PUGH, Mary Jo, *et al*. Phenotyping the spectrum of traumatic brain injury: a review and pathway to standardization. **Journal of neurotrauma**, v. 38, n. 23, p. 3222-3234, 2021.

ROLDÁN, María; KYRIACOU, Panayiotis A. Near-infrared spectroscopy (NIRS) in traumatic brain injury (TBI). **Sensors**, v. 21, n. 5, p. 1586, 2021.

SAVITSKY, B., et al. Traumatic brain injury: it is all about definition. Brain injury, v. 30, n. 10, p. 1194-1200, 2016.

SEABURY, Seth A., *et al*. Assessment of follow-up care after emergency department presentation for mild traumatic brain injury and concussion: results from the TRACK-TBI study. **JAMA network open**, v. 1, n. 1, p. e180210-e180210, 2018.

TOCCALINO, Danielle; COLANTONIO, Angela; CHAN, Vincy. Update on the epidemiology of work-related traumatic brain injury: a systematic review and meta-analysis. **Occupational and environmental medicine**, v. 78, n. 10, p. 769-776, 2021.

WANG, Kevin K., *et al.* An update on diagnostic and prognostic biomarkers for traumatic brain injury. **Expert review of molecular diagnostics**, v. 18, n. 2, p. 165-180, 2018.

WILDE, Elisabeth A., *et al.* A framework to advance biomarker development in the diagnosis, outcome prediction, and treatment of traumatic brain injury. **Journal of neurotrauma**, v. 39, n. 7-8, p. 436-457, 2022.

WILLIAMS, W. Huw, *et al.* Traumatic brain injury: a potential cause of violent crime?. **The Lancet Psychiatry**, v. 5, n. 10, p. 836-844, 2018.

YAN, Amy, *et al*. Clinical Management in Traumatic Brain Injury. **Biomedicines**, v. 12, n. 4, p. 781, 2024.