International Journal of
Life Sciences
International Peer Reviewed Open Access Refereed Journal

Int. J. of Life Sciences, 2024; 12 (3): 241-255
ISSN:2320-7817(p) | 2320-964X(o)

Review Article Open Access

Pediatric Traumatic Brain Injury: Chronic Neuropsychiatric Outcomes and Modern Therapeutic Interventions.

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Manuscript details:

Received: 18.08.2024
Accepted: 04.09.2024
Published: 30.09.2024

Cite this article as:
Jin Gary and Tawakol Omar (2024) Pediatric Traumatic Brain Injury: Chronic Neuropsychiatric Outcomes and Modern Therapeutic Interventions, *Int. J. of Life Sciences*, 12 (3): 241-255.
Available online on http://www.ijlsci.in
ISSN: 2320-964X (Online)
ISSN: 2320-7817 (Print)

ABSTRACT

Pediatric traumatic brain injury (TBI) is the primary cause of disability and mortality among children and adolescents. This review examines the pathophysiology of pediatric TBI and assesses current diagnostic techniques, treatment strategies, and rehabilita-tion measures. By focusing on primary and secondary injuries, the paper elucidates the processes induced by TBI that must be targeted for effective treatment and rehabilitation. The review is structured around three key aspects of comprehensive TBI management. First, it compares the different medical imaging modalities used in the diagnosis of TBI. Second, it evaluates surgical treatments, specifically decompressive craniotomy and decompressive craniectomy, and pharmacological treatments, including sedatives and analgesics, detailing their advantages and risks. Third, it addresses potential psychiatric consequences of TBI, such as ADHD and depression, and explores the role of neuroplasti-city in recovery, discussing therapeutic options that leverage this aspect of the developing brain. Due to the current challenges in managing long-term neurological deficits, this review emphasizes a holistic approach to pediatric TBI treatment. It proposes the implementation of personalized recovery plans, advanced MRI techniques, and neuroplasticity-driven rehabilitation strategies to enhance developmental trajectories and long-term outcomes.

Keywords: Pediatric TBI, neuroinflammation, CT, MRI, decompressive craniectomy, neuroplasticity.

INTRODUCTION

Traumatic brain injury (TBI) refers to damage to brain tissue caused by an external cranial impact. TBI often results from the head violently hitting an object or the penetration of an object through the skull and into brain tissue (National Academies of Sciences *et al.*, 2019). TBI severity is classified into three categories: mild, moderate, and severe.

While mild TBI is characterized by the absence of intracranial lesions and fully resolves within months, moderate and severe TBI cases involve prolonged loss of consciousness and result in long-term deficits in cognitive function (Christensen *et al*., 2021).

When identifying TBI, common immediate symptoms include headaches, dizziness, fatigue, cognitive and memory problems, and sensory sensitivities (Christensen *et al*., 2021). TBI can also lead to complications such as seizures, nerve damage, blood clots, stroke, and coma, though these become less likely over time (Christensen *et al*., 2021).

TBI imposes a significant economic burden on the United States and worldwide. In the United States alone, TBI results in the deaths of 53,000 individuals annually and has caused 5.3 million Americans to acquire long-term disabilities and mental deficits (Alali *et al*., 2015). The economic impact of TBI in 2010 was estimated to be around $76.5 billion, with the costs associated with disability and lost productivity far exceeding those for medical care and rehabilitation (Alali *et al*., 2015). Through examination of clinical study findings, strategies such as threshold-guided CT scanning and treatment in specialized care settings have been identified as economically beneficial for managing TBI patients (Alali *et al*., 2015).

Globally, TBI is substantially more prevalent in males than females, with the male-to-female TBI ratio ranging from 1.3 in China to >4 in South Africa (Bruns and Hauser, 2003). The consequences of acquiring a TBI between the ages of 0-5 are especially drastic: evidence indicates that the developing brains of younger children are highly susceptible to trauma and that TBI can severely diminish the developmental trajectories of these children, leading to long-term physical, cognitive, psychological, and emotional impairments (Goh *et al*., 2021).

Pediatric TBI is the leading cause of disability and death during childhood and impacts an estimated three million children each year globally (Jochems *et al*., 2021). Whereas motor vehicle accidents and falls are the most common causes of TBI in many countries, sports-related TBIs account for the greatest proportion of TBI among the adolescent populations of the United States and Australia (Christensen *et al*., 2021).

In this review, several critical aspects of pediatric TBI will be explored. The pathophysiological mechanisms behind primary and secondary injuries—the breaching of the blood-brain barrier, cerebral edema, and synaptic pruning—will be examined. Diagnostic techniques, such as CT and MRI, will be evaluated for their effectiveness in identifying TBI and guiding treatment strategies. Current surgical and pharmacological treatments will be assessed, with a focus on their efficacy and associated risks. Long-term cognitive, behavioral, and psychological impacts of TBI on children and recovery plans that leverage neuroplasticity to optimize developmental outcomes will also be discussed.

1 Pathophysiology

1.1 Acute Injury Mechanisms

The pathogenesis of TBI involves primary and secondary injuries that can combine to cause neurological deficits. The primary injury is the immediate result of the external force impacting the brain, causing direct structural damage to brain tissue. This damage initiates a series of secondary processes that have the potential to significantly exacerbate the injury (Ng and Lee, 2019).

Primary TBI injuries (shown in Table 1) can be classified into two categories: focal and diffuse. Focal injuries result from localized damage due to lacerations, compression, and concussive forces, typically occurring in closed head and penetrating TBIs. Such trauma is associated with skull fractures and localized contusions, often precipitating epidural, subdural, or subarachnoid hemorrhage and intracerebral hematoma (Ng and Lee, 2019). In contrast, diffuse brain injuries stem from non-contact forces like rapid deceleration and acceleration, which result in the shearing and stretching of brain tissues. This type of injury prominently features diffuse axonal injury (DAI), which predominantly affects axons in the subcortical and deep white matter regions such as the brain stem and corpus callosum (Ng and Lee, 2019).

Acute secondary changes in the brain post-TBI (shown in Table 1) include the rapid influx of calcium and neuroinflammation (Serpa *et al*., 2021). At the molecular level, TBI induces the depolarization of neurons, resulting in the excessive release of excitatory neurotransmitters such as glutamate and aspartate. The surge in neurotransmitters leads to an

influx of calcium ions into neurons, which triggers multiple intracellular pathways. Elevated intracellular calcium levels activate enzymes like caspase and calpain while also stimulating the generation of free radicals, all of which contribute to cellular degradation; this degradation can occur directly through necrosis or indirectly through apoptosis, a programmed cell death process (Galgano *et al*., 2017). The damage to neuronal cells then initiates a robust inflammatory response, further exacerbating neuronal injury and contributing to a breach in the blood-brain barrier (BBB) (Galgano *et al*., 2017).

The breach of the BBB allows for the influx of inflammatory cells and molecules into the brain parenchyma, leading to increased cerebral edema. The brain's homeostatic environment is tightly regulated, with intracranial volume comprising brain parenchyma, cerebrospinal fluid, and blood. When TBI causes an increase in intracranial volume—whether due to mass effect from hematomas, cytotoxic and vasogenic edema, or venous congestion—compensatory mechanisms are activated. Initially, cerebrospinal fluid is displaced to the spinal compartment, and subsequently, venous blood is extruded from the brain (Galgano *et al*., 2017). However, if these compensatory mechanisms are overwhelmed, pathological brain compression occurs, which can be fatal without timely intervention (Galgano *et al*., 2017).

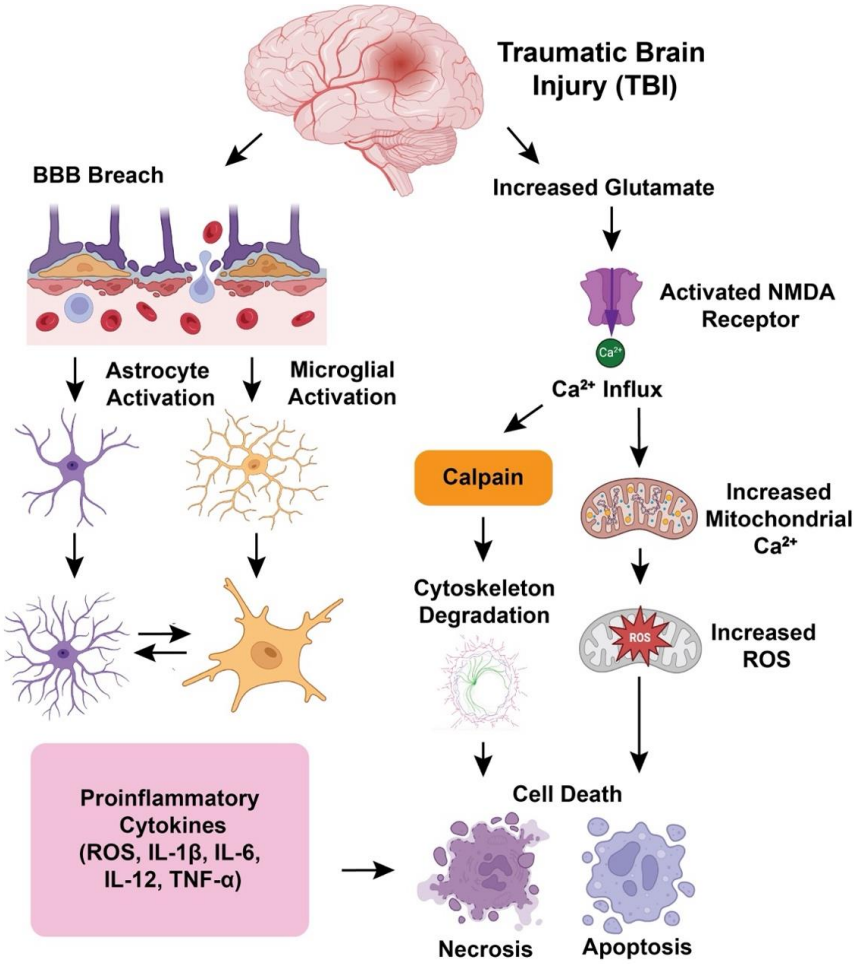

Fig. 1. Acute Injury Pathways. The initial trauma of TBI results in the breaching of the blood-brain barrier (BBB) and the release of glutamate from neurons. The BBB breach activates astrocytes and microglia and triggers the release of proinflammatory cytokines including ROS, IL-1β, IL-6, IL-12, and TNF-α, which upregulate the inflammatory response. This neuroinflammation subsequently induces cell death in the form of necrosis and apoptosis. The release of glutamate activates NMDA receptors, which leads to an influx of calcium. Increased intracellular calcium activates the calpain enzyme, catalyzing cytoskeleton degradation and leading to cell death. Calcium influx also elevates intramitochondrial calcium levels, increasing mitochondrial reactive oxygen species (ROS), which similarly triggers necrosis and apoptosis.

Table 1. Primary and Secondary Injury Mechanisms.

Type of Injury	Description
Primary Injuries	
Skull Fractures	Breaks in the cranial bones resulting from the impact.
Cortical Contusions	Bruises on the cortical surface of the brain.
Epidural Hemorrhage	Blood accumulation between the dura mater and the skull, often due to arterial bleeding and associated with skull fractures.
Subdural Hemorrhage	Blood accumulation between the dura and arachnoid membranes, typically resulting from venous bleeding.
Subarachnoid Hemorrhage	Blood accumulation in the subarachnoid space, where cerebrospinal fluid circulates, often due to tearing of small vessels.
Intracranial Hematoma	Bleeding within the brain tissue itself.
Diffuse Axonal Injury	Shearing damage to the brain's white matter tracts caused by rapid acceleration or deceleration forces.
Secondary Injuries	
Excitotoxicity	Nerve cell damage and death caused by excessive neurotransmitter stimulation.
Oxidative Stress	Cellular damage resulting from excess production of free radicals.
Apoptotic Cell Death	Programmed neuronal cell death triggered by elevated calcium levels and enzyme activation
Blood-Brain Barrier Disruption	Compromise of the BBB, allowing potentially harmful substances to enter the brain tissue.
Cerebral Edema	Brain swelling due to an accumulation of fluid, either intracellularly or extracellularly.
Neuroinflammation	Inflammatory response within the brain that elevates intracranial pressure and can potentially compress the brain.
Hypoxia	Inadequate oxygen supply to the brain.
Seizures	Abnormal electrical activity in the brain.

The secondary injury phase also involves various mediators that upregulate and downregulate the injury processes. Recovery from TBI requires the reorganization of brain structure and function at anatomical, molecular, and functional levels. This reorganization is essential for the restoration of neurological function and is influenced by the extent of the initial injury and the subsequent secondary injuries (Galgano *et al*., 2017).

1.2 Chronic Injury Mechanisms

Long-term pathophysiological effects of TBI include abnormal synaptic pruning and pituitary dysfunction. Synaptic pruning is a critical process for brain maturation, where active synapses are strengthened, and unused ones are eliminated. TBI can disrupt this process, leading to atypical pruning patterns associated with neurodevelopmental disorders such as schizophrenia and epilepsy (Serpa *et al*., 2021). In adolescents, TBI has been shown to cause abnormal increases in dendritic branching, spine density, and neuronal complexity, indicating disrupted synaptic pruning during a critical developmental window (Serpa *et al*., 2021).

Pituitary dysfunction is another significant long-term effect of TBI. The pituitary gland regulates various hormonal functions, and its disruption can lead to cognitive, affective, and somatic impairments. Hypopituitarism, a common consequence of TBI, affects growth hormone and gonadal axes, leading to issues such as delayed growth, altered pubertal development, and increased risk of cognitive and

behavioral deficits (Serpa *et al*., 2021). Despite the critical role of the pituitary gland in development, hypopituitarism often goes unrecognized and untreated in children following TBI. This underscores the need for improved screening and treatment protocols to address hormonal imbalances and support recovery and development in pediatric TBI patients (Serpa *et al*., 2021).

2 Diagnosis

2.1 Medical Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are the primary techniques currently used to assess TBI. CT refers to the generation of cross-sectional images using x-ray beams, whereas MRI creates images by subjecting the body to an external magnetic field.

CT is the primary imaging technique used in the acute diagnosis of TBI. Its rapid acquisition, cost-effectiveness, and high sensitivity to hemorrhagic injuries make it indispensable in emergency settings (Kim and Gean, 2011). CT imaging can quickly and accurately identify a range of intracranial injuries such as epidural, subdural, and subarachnoid hemorrhages, alongside cortical contusions and traumatic axonal injuries (Kim and Gean, 2011). These findings are critical for determining the need for urgent neurosurgical interventions.

In the context of TBI, CT is particularly effective in detecting acute hemorrhages that require immediate attention. Epidural hemorrhages, which are typically associated with skull fractures and arterial bleeding, appear as biconvex hyperdense areas on CT scans (Kim and Gean, 2011). Subdural hemorrhages, resulting from venous bleeding, present as crescent-shaped, dense collections that may cross suture lines but do not cross the midline (Kim and Gean, 2011). Subarachnoid hemorrhages are identified by the presence of blood in the basal cisterns and cerebral sulci, which can be indicative of severe brain injury (Kim and Gean, 2011).

CT also plays an important role in monitoring pathophysiological changes after the initial diagnosis. Serial CT scans are used to track the progression of hemorrhages, detect the development of secondary injuries such as cerebral edema and herniation, and assess the effectiveness of therapeutic interventions (Kim and Gean, 2011). Despite its strengths, CT has limitations, particularly in detecting non-hemorrhagic injuries and in providing detailed anatomical information about the brain's soft tissues (Kim and Gean, 2011).

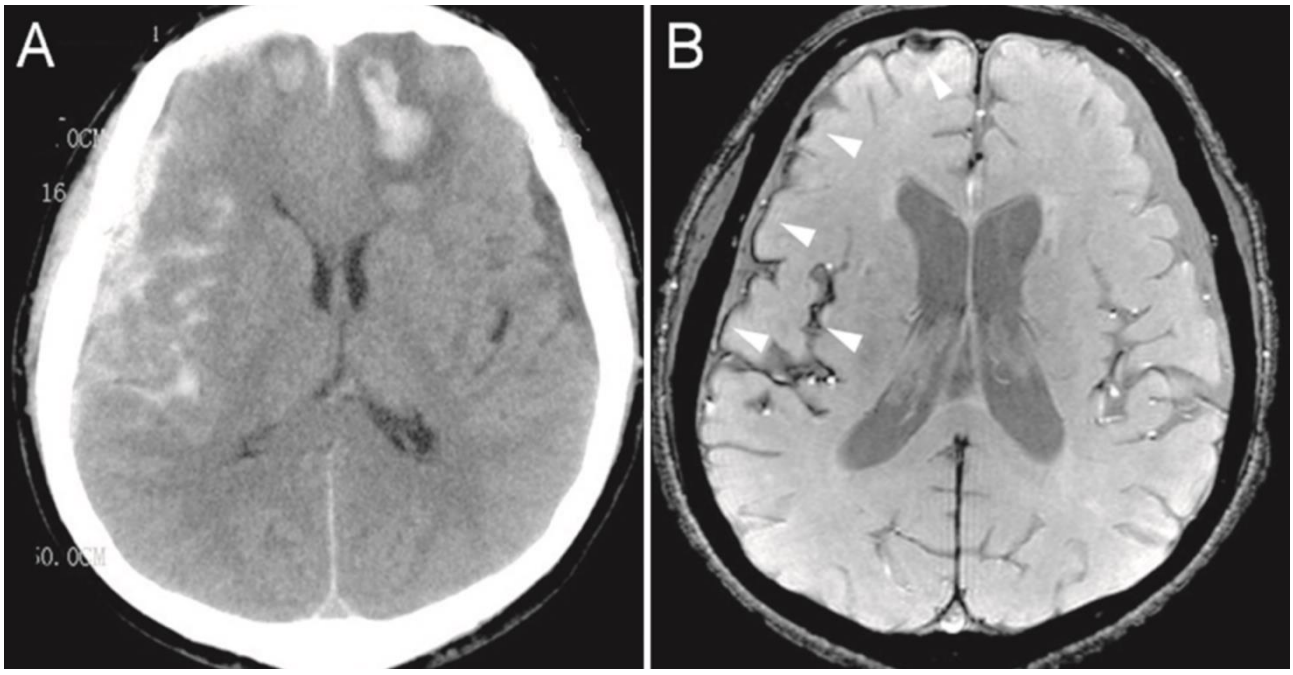

Fig. 2. Axial brain CT with acute intracerebral hemorrhage post-TBI (A). The 26-week follow-up MRI sample with subsequent hemosiderosis—the formation of iron deposits (B). Adapted from Zhao *et al*. (2015).

MRI offers enhanced sensitivity and specificity compared to CT in detecting non-hemorrhagic brain injuries. One key advantage of MRI is its ability to detect DAI, which is a common but often subtle consequence of TBI. DAI results from shearing forces that damage the brain's white matter tracts and can lead to significant cognitive and functional impairments (Kim and Gean, 2011). MRI, particularly using diffusion-weighted imaging (DWI) and susceptibility-weighted imaging (SWI), can reveal the microscopic damage associated with DAI (Kim and Gean, 2011). DWI can measure the movement of water molecules within the brain tissue, making it effective in identifying areas of cytotoxic edema and acute axonal injury (Kim and Gean, 2011). SWI enhances the detection of microhemorrhages and small blood products, providing a more detailed picture of the brain's microstructure (Kim and Gean, 2011).

Advanced MRI techniques—diffusion tensor imaging (DTI) and functional MRI (fMRI)—further enhance the diagnostic capabilities of TBI. DTI maps the orientation and integrity of white matter tracts, offering insights into the extent of axonal injury (Kim and Gean, 2011). This technique is useful in assessing the severity of brain injury and predicting long-term outcomes. fMRI localizes brain activity by monitoring changes in blood flow and oxygenation levels, facilitating the identification of functional impairments that may not be apparent on structural scans (Kim and Gean, 2011). Recent studies using fMRI in animal models, such as the pediatric porcine TBI model, have demonstrated its potential to detect disruptions in functional connectivity within the brain's networks. Specifically, resting-state and task-based fMRI were employed to reveal significant changes in network dynamics shortly after TBI. In the porcine model, fMRI detected significant decreases in functional connectivity within the executive control and sensorimotor networks just one day post-injury, highlighting its sensitivity to early functional disruptions (Simchick *et al*., 2021). These findings suggest that fMRI can effectively facilitate early prognosis, potentially identifying specific brain regions that are at risk for long-term deficits in motor, cognitive, and behavioral functions (Simchick *et al*., 2021).

2.2 Neuropsychological Assessment

The Glasgow Coma Scale (GCS) is the standard for assessing injury severity in the immediate aftermath of TBI. It scores patients' abilities to open their eyes, respond verbally, and move in response to stimuli (Matis and Birbilis, 2008). Scores range from 3 to 15: 3 to 8 corresponds to severe, 9 to 12 moderate, and 13 to 15 mild (Goh *et al*., 2021).

Table 2. Glasgow Coma Scale.

Response	Behavior	Score
Eye-Opening Response	Eyes open spontaneously	4
	Eyes open to speech	3
	Eyes open to pain	2
	No eye-opening response	1
Verbal Response	Orientated	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
Motor Response	Obeys command	6
	Localizes pain	5
	Flexes to withdraw from pain	4
	Abnormal flexion	3
	Abnormal extension	2
	No motor response	1

Table 3. Rancho Los Amigos Scale.

Level	Response
I	No response to sensory stimuli
II	Generalized response
III	Localized response
IV	Confused-agitated
V	Confused-inappropriate
VI	Confused-appropriate
VII	Automatic-inappropriate
VIII	Purposeful and appropriate (standby assistance)
IX	Purposeful and appropriate (standby assistance on request)
X	Purposeful and appropriate (modified independent)

In the long term, the Rancho Los Amigos Scale is widely used for the neuropsychological assessment of cognitive and behavioral changes post-TBI. The scale consists of 10 levels ranging from 1 to 10. Level 1 is characterized by no cognitive response and the need for total assistance; level 10 requires the patient to be purposeful and functionally independent (Patel *et al*., 2013).

3 Treatment

3.1 Surgical Intervention

In cases of severe TBI, neurosurgical intervention is often necessary to reduce intracranial pressure (ICP) and evacuate intracranial hemorrhage, typically through either decompressive craniotomy or decompressive craniectomy (Guo *et al*., 2022).

Decompressive craniotomy involves temporarily removing a section of the skull to access the brain for surgical treatment of injuries like hemorrhages and swelling, after which the bone flap is replaced (Guo *et al*., 2022). The procedure is used in the presence of intracranial hematomas and high ICP (Fong *et al*., 2017). Craniotomy allows surgeons to directly address the source of bleeding or injury while providing space for the brain to swell without being constrained by the skull (Guo *et al*., 2022). This approach is especially beneficial in scenarios where precise surgical intervention is required to remove blood clots and prevent further damage to brain tissues, thus facilitating better recovery and functional outcomes (Fong *et al*., 2017).

Meanwhile, decompressive craniectomy entails the removal of part of the skull without immediate replacement to relieve pressure caused by swollen brain tissue (Guo *et al*., 2022). This procedure is often performed when other medical management strategies fail to control elevated ICP (Fong *et al*., 2017). By removing part of the skull, craniectomy allows the swollen brain to expand outward, reducing the risk of further damage from ICP (Guo *et al*., 2022). Current literature supports the use of a large decompressive craniectomy technique, which typically involves removing a significant section of the skull, such as the fronto-temporoparietal region, either unilaterally or bilaterally, to allow maximum brain swelling (Patel *et al*., 2013).

Several studies have documented the effectiveness of decompressive craniectomy. For instance, a retrospective study conducted at St. Mary's Medical Center/ Palm Beach Children's Hospital examined pediatric patients who underwent decompressive craniectomy for TBI. This study found that patients treated with this surgical intervention showed favorable outcomes, as measured by the Rancho Los Amigos Scale at discharge and six months post-discharge. All seven patients in the study returned home with positive results, demonstrating the potential for excellent functional recovery (Patel *et al*., 2013). The DECRA trial, a large randomized controlled study conducted by Cooper *et al*., showed that decompressive craniectomy significantly reduced mean ICP levels in diffuse TBI patients. Post-randomization, the mean ICP was 14.4 mmHg in the surgical group compared to 19.1

mmHg in the standard care group. The study also determined that the number of hours with ICP greater than 20 mmHg was, on average, substantially lower in the surgical group (9.2 hours versus 30.0 hours) (Cooper *et al*., 2011).

Although this procedure is considered life-saving and can significantly lower ICP, it is associated with higher rates of complications and the need for subsequent surgical interventions, such as cranioplasty, to replace the removed bone flap (Guo *et al*., 2022). Despite these drawbacks, craniectomy is critical for patients with severe brain swelling and refractory intracranial hypertension, providing an immediate solution to prevent further brain damage and potential herniation (Fong *et al*., 2017).

Both decompressive craniotomy and craniectomy must be considered by doctors when treating severe TBI. The effectiveness of these procedures depends on various factors, including the nature and severity of the injury, the timing of the intervention, and the patient's overall health. Decompressive craniotomy is often preferred in cases where precise surgical intervention is needed to remove hematomas and repair brain tissue, leading to better cognitive and functional outcomes (Guo *et al*., 2022). In contrast, decompressive craniectomy should be used to control severe intracranial hypertension when other treatments have failed, as it provides a rapid and effective means of reducing ICP and preventing further brain injury (Fong *et al*., 2017).

3.2 Pharmacological Intervention

Pharmacological treatments for TBI primarily aim to manage secondary brain damage and improve patient outcomes for moderate and severe cases. This involves the use of sedatives, analgesics, osmotic agents, antiepileptic, and psychoactive drugs each playing a critical role in stabilizing the patient's condition and mitigating further brain injury (Losiniecki and Shutter, 2010).

Proper use of sedatives and analgesics is crucial for managing pain and agitation post-TBI (Kochanek *et al*., 2019). Propofol is the preferred sedative in neuro-intensive care because of its rapid onset and short half-life (Losiniecki and Shutter, 2010). It effectively reduces cerebral metabolism and ICP, though it may not decrease the chance of mortality. However, prolonged propofol use can lead to elevated lactic acid levels, making it unsuitable for extended sedation (Lui *et al*., 2022). Midazolam is also widely used for sedation but can cause retrograde amnesia, cardiac arrhythmias, and hypotension (Losiniecki and Shutter, 2010). Importantly, midazolam should be avoided during high ICP (> 20-25 mmHg) episodes due to the risk of cerebral hypoperfusion (Lui *et al*., 2022). Quetiapine fumarate and dexmedetomidine are newer agents; quetiapine is beneficial for managing agitation at lower doses, while dexmedetomidine provides sedation with minimal respiratory depression, making it suitable for patients undergoing ventilator weaning and extubation (Losiniecki and Shutter, 2010).

However, in pediatric patients, protocol is not recommendded because it can cause hypotension and excessively decrease cerebral perfusion pressure. Instead, etomidate is used for because it can lower ICP and enhance cerebral perfusion pressure (CPP). If etomidate is unavailable, ketamine is suggested as an alternative, though its effectiveness remains uncertain due to conflicting evidence about its impact on ICP (Lui *et al*., 2022).

Analgesics, especially opioids such as fentanyl and morphine, are widely used in the intensive care treatment of TBI due to their quick onset and short duration, which allow for frequent neurological evaluations (Losiniecki and Shutter, 2010). Fentanyl is generally preferred over morphine because of its higher effectiveness in managing pain in TBI patients (Lui *et al*., 2022).

When administering sedatives and analgesics over the long term, it is important to be aware of the risk of physiological dependence in pediatric patients. Research has shown that children and adolescents who have experienced TBI are more susceptible to substance abuse disorders. As a result, clinicians should expedite the weaning process of analgesic agents after the initial acute phase of the injury (Lui *et al*., 2022).

Mannitol, an osmotic agent, is used to quickly reduce ICP but must be administered carefully to avoid complications such as hypovolemia and renal failure. Hypertonic saline also provides rapid ICP reduction and is particularly useful during initial resuscitation (Losiniecki and Shutter, 2010). For managing intracranial hypertension, bolus administration of 3% hypertonic saline is recommended, with effective

doses ranging between 2 and 5 mL/kg (Lui *et al*., 2022).

Antiepileptic drugs are essential in preventing and managing seizures post-TBI. Phenytoin has been traditionally used for this purpose, requiring close monitoring of serum levels to avoid side effects like hypotension and cardiac arrhythmias. Levetiracetam is increasingly preferred due to its better side effect profile and the lack of need for regular serum level monitoring (Losiniecki and Shutter, 2010).

Chronic management of TBI, particularly in moderate and severe cases, similarly necessitates pharmacological treatment. In pediatric populations, long-term effects of TBI that can be treated using drugs include depression, agitation, and psychosis. Serotonin reuptake inhibitors (SSRIs), such as sertraline, citalopram, and fluoxetine, are used to treat post-TBI depression and have been proven effective at improving pathological laughing and crying (Tani *et al*., 2022). Beta-blockers, including propranolol and pindolol, help reduce post-TBI agitation (Tani *et al*., 2022). Rare cases of TBI-induced psychosis should be treated using atypical antipsychotics like quetiapine, clozapine, and ziprasidone due to their greater safety compared to typical antipsychotics (Tani *et al*., 2022).

4 Rehabilitation and Long-Term Management

4.1 Recovery Timeline in Children

The recovery timeline for pediatric TBI varies in length based on injury severity but, in most cases, consists of the same key steps. Immediate emergency care post-TBI is critical to stabilize the child and prevent further damage. In moderate and severe cases, a CT scan is necessary to assess whether the child requires hospitalization or even surgery to relieve brain pressure (Lui *et al*., 2022).

During the early recovery phase, which spans the subsequent days and weeks, medical follow-ups with specialists are essential. Ensuring both physical and cognitive rest during this period is also vital to facilitate healing. Long-term rehabilitation focuses on physical, occupational, speech, and cognitive therapies that aim to fully restore function (Lui *et al*., 2022). Furthermore, psychological support through counseling can address emotional and behavioral changes, while educational accommodations can promote reintegration into academic environments.

The duration of recovery from TBI will fluctuate significantly based on injury severity and the affected cognitive functions. Children with mild TBI typically regain full executive function within three months and learning and memory within two years and suffer no deficits in language, perceptual-motor function, or social cognition. Conversely, children with moderate to severe TBI often experience significant deficits in all categories beyond two years, making long-term rehabilitation therapies crucial for their recovery (Goh *et al*., 2021). Historically, mild TBI has constituted over 80 percent of brain injuries in the US. The remaining are divided between moderate TBI, non-classifiable brain injuries, penetrating brain injuries, and severe TBI, in descending order of prevalence (Leo and McCrea, 2016).

4.2 Neuroplasticity in Children and Recovery from TBI

Neuroplasticity refers to the brain's ability to reorganize itself by forming new neural connections and is particularly pronounced in children, making their brains more adaptable and resilient to injuries. The Kennard Principle, theorized by neurologist Margaret Kennard in 1942, dictates that there exists an inverse relationship between age at TBI and functional outcome (Giza and Prins, 2006). This principle is widely accepted in the field of neurology due to the consensus understanding that neuroplasticity, which is crucial for recovery from TBI, is greater in children.

At the cellular and synaptic levels, neuroplasticity involves long-term potentiation (LTP) and long-term depression (LTD). LTP strengthens synapses by increasing neurotransmitter release and synaptic strength, essential for memory and learning. Conversely, LTD weakens synapses by reducing receptor sensitivity, allowing for synaptic pruning and network refinement. These antagonistic processes facilitate recovery by enabling the brain to adapt and compensate for lost functions (Zotey *et al*., 2023).

Structural plasticity involves dynamic alterations in neuronal architecture, such as dendritic remodeling and axonal sprouting. Dendritic remodeling changes dendritic length, branching patterns, and spine density, promoting the growth of new synapses and reinforcing existing connections (Zotey *et al*., 2023). Axonal sprouting refers to the formation of new axonal branches from preexisting neurons, aiding recovery by

creating new connections around injured regions (Zotey *et al*., 2023).

Neuroplastic changes post-TBI can be immediate or delayed. Immediate changes occur within hours to days and involve cellular and synaptic modifications. Delayed changes span weeks to months and include axonal branching and dendritic remodeling, supporting functional recovery and compensation for lost functions (Zotey *et al*., 2023).

Rehabilitation strategies leveraging neuroplasticity aim to enhance brain reorganization and functional recovery. Constraint-induced movement therapy (CIMT) forces the use of the affected limb by restricting the unaffected one, promoting motor recovery and brain reorganization (Zotey *et al*., 2023). Repetitive task training (RTT) involves repeated practice of specific motor tasks to strengthen synaptic connections and encourage cortical reorganization (Zotey *et al*., 2023). Cognitive rehabilitation uses structured tasks to improve cognitive functions, often utilizing brain-computer interfaces (BCIs) for direct brain-to-device communication (Zotey *et al*., 2023). Virtual reality (VR) provides interactive environments that promote neural reorganization through engaging activities (Zotey *et al*., 2023).

Neuroplasticity also aids sensory recovery and cognitive enhancement. Techniques like sensory discrimination training enhance motor coordination and sensory perception (Zotey *et al*., 2023). Auditory rehabilitation, using cochlear implants and auditory training, capitalizes on neuroplasticity for improved speech and hearing (Zotey *et al*., 2023). Technological advancements in the field of robotics assist patients with controlled movements, facilitating neural relearning (Zotey *et al*., 2023). Noninvasive brain stimulation therapies, including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), promote neuroplastic changes by modulating neural activity (Zotey *et al*., 2023). Hameed *et al*. explored the application of TMS in various pediatric neuropathologies such as depression, Tourette syndrome, and autism spectrum disorder (ASD). The study highlighted that TMS has significant potential as both an experimental and therapeutic tool in pediatric populations, effectively modulating cortical excitability and promoting neuroplasticity, which can aid in the recovery of motor functions and other neurological outcomes in children (Hameed *et al*., 2017).

Customized neurorehabilitation approaches consider individual patient profiles, leveraging biomarkers like fMRI and genetic markers to predict neuroplastic responses and tailor therapies accordingly (Zotey *et al*., 2023). Tailoring rehabilitation programs to individual patient profiles enhances recovery outcomes by addressing specific impairments and effectively utilizing neuroplasticity. Integrating neuroplasticity insights into clinical practice will require continuous education and standardized evaluation methods. Exploring the synergistic effects of combination therapies, such as pairing brain stimulation with motor training, holds promise for enhanced neuroplasticity and recovery.

4.3 Psychiatric Consequences

TBI in children and adolescents can precipitate a variety of psychiatric consequences. Among these, attention problems, depression and mood disorders, anxiety, oppositional defiant disorder (ODD), and posttraumatic stress disorder (PTSD) are the most frequently studied (Emery *et al*., 2016).

Attention problems and hyperactivity are the most investigated outcomes of TBI in youth. Research consistently shows that children and adolescents hospitalized for TBI exhibit significantly higher rates of inattentiveness and hyperactivity compared to their non-hospitalized or healthy counterparts. Studies have found that hospitalized youth were over six times more likely to suffer from attention problems than healthy controls (Emery *et al*., 2016). Furthermore, children and adolescents with TBI are around three times more likely to display symptoms of secondary attention-deficit hyperactivity disorder (ADHD), though evidence suggests that all injuries, regardless of affected region, may increase the likelihood of ADHD (Emery *et al*., 2016).

Depression and mood disorders are also notably prevalent among youth post-TBI. Several studies indicate that children who have sustained TBI are at greater risk for developing mood disorders and experiencing elevated mood symptoms. For instance, Luis and Mittenberg found that children six months after TBI were 9.3 times more likely to be diagnosed with depression than the orthopedic injury control group (Emery *et al*., 2016). Mood swings, although not

necessarily translating into clinical depression, have also been observed more frequently among pediatric TBI patients (Emery *et al*., 2016).

Anxiety post-TBI tends to be more pronounced shortly after the initial injury, as children are significantly more likely to develop new-onset anxiety disorders. Luis and Mittenberg highlighted that children with TBI were over four times more likely to be diagnosed with an anxiety disorder compared to those with orthopedic injuries. However, longitudinal studies suggest that anxiety symptoms often do not persist at elevated levels in the long term, showing no significant difference in anxiety symptoms between children with TBI and controls at one- or two-years post-injury. Even so, young children who experience multiple TBIs are reported to have notably higher anxiety levels, indicating that repeated injuries compound the risk of enduring anxiety (Emery *et al*., 2016).

ODD and disruptive behavior are frequently diagnosed in children and adolescents post-TBI. Studies reveal that disruptive behaviors are often incited or exacerbated by pediatric TBI given findings indicating that adolescents hospitalized for TBI are more likely to be diagnosed with ODD and other disruptive behaviors than noninjured controls (Emery *et al*., 2016). Current research on disruptive behavior post-TBI primarily focuses on concerns with rage, emotional reactivity, or aggression, though conclusions are mixed due to external factors like preinjury behavior heavily influencing results (Emery *et al*., 2016).

The relationship between PTSD and pediatric TBI remains unclear. While some studies identified no significant difference in PTSD symptoms between children with TBI and those with orthopedic injuries, others reported higher self-reported PTSD symptoms among the TBI group (Emery *et al*., 2016).

Though less frequently studied, pediatric TBI has been associated with schizophrenia and substance abuse. For example, one study indicated that there is a potential connection between TBI and schizophrenia, particularly if the injury occurs before age 11 and if there is a familial predisposition (Emery *et al*., 2016). In addition, McKinlay *et al* reported that adolescents hospitalized for TBI are over three times more likely to develop substance abuse problems than uninjured controls (Emery *et al*., 2016).

4.4 Physical and Occupational Therapies

In the context of pediatric TBI, physical and occupational therapies can significantly improve long-term functional outcomes. Post-TBI physical therapy focuses on enhancing motor skills, improving coordination, and increasing strength and mobility. Techniques such as gait and balance training, constraint-induced movement therapy, and VR applications have all been shown to enhance patient motor function and overall physical recovery. For instance, a study by Biffi *et al*. found that VR-based treadmill exercises engage children in a multisensory environment, which not only promotes physical rehabilitation but also stimulates neural plasticity through enhanced engagement and motivation due to the activation of reward-related dopaminergic systems (Gmelig Meyling *et al*., 2022). Integrating these therapies into treatment plans would ensure comprehensive rehabilitation that addresses both physical and cognitive challenges to maximize recovery outcomes.

Occupational therapy for pediatric TBI often incorporates motor learning strategies (MLS) to enhance motor skill acquisition and facilitate reintegration into educational and social environments. MacWilliam *et al*. (2021) conducted a study examining the application of MLS by occupational therapists and concluded that common, effective strategies for improving patient executive function include promoting problem-solving, utilizing repetitive practice, and providing encouragement. Given the novelty of occupational therapy for pediatric TBI, these findings encourage further research into MLS and highlight the potential of occupational interventions to enhance patient outcomes.

5 Emerging Therapies and Clinical Trials

Recent clinical studies on pediatric TBI have investigated genetic factors, neurocognitive outcomes, and novel pharmacological and therapeutic interventions. Research has continued to examine the pathophysiological mechanisms that exacerbate or ameliorate secondary injuries and the potential of genetic markers to influence recovery trajectories (NCT01763892). Several clinical trials have begun evaluating the efficacy of different vitamins (NCT05958277) and pharmacological treatments (NCT04199247) to promote nerve regeneration and cognitive recovery. Advanced rehabilitation methods, such as robot-assisted therapy (NCT04768192) and

BMMNC infusion (NCT01851083), are starting to undergo testing for their effectiveness in improving muscle recovery and functional outcomes in pediatric patients. Early intervention strategies, including individually prescribed exercise programs (NCT04199247) and medications like ondansetron (NCT01815125), to prevent the development of persistent post-concussion symptoms have also become an area of interest (Gravel *et al*., 2017). These studies reflect the continued effort to enhance the understanding, management, and recovery of pediatric TBI and collectively aim to improve long-term outcomes for affected children.

Table 4. Clinical Trials.

Clinical Trial ID	Start Date	End Date	Condition	Inclusion Criteria	Description	Location
NCT00035139	2002	2005	TBI	6-16 years old and moderate to severe TBI	Evaluated the acute and long-term effects of early administration of methylphenidate on recovery	Philadelphia, PA
NCT01763892	2012	2015	TBI	0-15 years old and admitted to pediatric intensive care unit (PICU)	Investigated the connection between cerebral vasospasm, the apolipoprotein E allele, physiological symptoms, and neurocognitive outcomes.	Durham, NC
NCT01815125	2013	2014	TBI	8-17 years old and mild TBI	Analyzed the effect of ondansetron on post-concussion symptoms one-week post-mTBI in children	Montreal, Canada
NCT01851083	2020	2020	TBI	5-17 years old and severe TBI	Determined the effect of intravenous infusion of autologous BMMNCs on brain structure and neurocognitive outcomes after severe TBI in children	Houston, TX
NCT04199247	2020	2021	TBI	10-18 years old and mild TBI	Examined the effects of an exercise program on psychosocial and pain outcomes when initiated within 7 days post-injury and continued for two months	Aurora, CO
NCT04768192	2020	2021	TBI	5-18 years old and acquired brain lesion in the last 10 months before trial	Documented the effects of intensive rehabilitative programs with robotic-aided gait training (RAGT), in terms of kinematics and muscle metabolism	Bosisio Parini, Italy
NCT05958277	2021	2023	TBI	6-15 years old and severe TBI	Explored how vitamin B12 versus B3 therapy could support TBI recovery due to their positive effects on axon regrowth following nerve damage	Islamabad, Pakistan

DISCUSSION

Childhood TBI presents a significant challenge in pediatric healthcare due to its impact on cognitive development. Despite current advancements in diagnostic and therapeutic techniques, the variability in outcomes underscores the need for more individualized approaches to treatment and rehabilitation. Current practices, while effective to some extent, often fall short in addressing the long-term needs of pediatric TBI patients. The widespread reliance on traditional imaging techniques like CT and MRI, though invaluable, highlights the necessity for integrating advanced neuroimaging methods and biomarkers to predict outcomes more accurately and tailor interventions accordingly.

While the current management strategies for pediatric TBI encompass a range of pharmacological and surgical interventions, there is a notable gap in the comprehensive care required for optimal recovery. Pharmacological treatments primarily focus on immediate symptom management and ICP reduction but often neglect the long-term cognitive and psychological effects of TBI. The potential for physiological dependence and the risk of substance abuse disorders in patients receiving long-term analgesic and sedative treatments raise ethical concerns and highlight the need for careful monitoring and alternative therapeutic options.

Surgical interventions, such as decompressive craniectomy and craniotomy, while lifesaving, come with significant risks and complications. The high rates of subsequent surgeries and the potential for long-term neurocognitive deficits necessitate a more cautious approach. Post-operative care should be enhanced to effectively manage these complications and support recovery.

Although useful, current neuropsychological assessment tools, such as the Rancho Los Amigos Scale, may not capture the full spectrum of long-term cognitive and behavioral changes post-TBI. The evaluation of TBI requires more comprehensive and sensitive assessment instruments that can provide a detailed understanding of the impact on various cognitive functions and guide targeted rehabilitation.
Future research should center around developing personalized treatment plans based on genetic, neuroimaging, and neurophysiological biomarkers. Identifying specific biomarkers associated with better recovery outcomes can help tailor interventions to individual needs, enhancing the efficacy of treatment protocols.

Integrating advanced neuroimaging methods such as DTI and fMRI into routine clinical practice can provide deeper insights into the extent of brain injury and recovery processes. These techniques can help detect subtle brain changes that are not visible on traditional imaging and more accurately predict long-term cognitive outcomes.

Research into new pharmacological treatments that target the underlying mechanisms of TBI, such as neuroinflammation and synaptic dysfunction, can provide more effective and safer alternatives to most current medications. Exploring the potential of neuroprotective agents and drugs that enhance neuroplasticity could significantly improve recovery outcomes.

Leveraging the principles of neuroplasticity, future rehabilitation strategies should increasingly integrate innovative approaches such as BCIs, VR, and robotic-assisted therapies. These technologies can create engaging and adaptive rehabilitation environments that promote neural reorganization and functional recovery.

Establishing long-term monitoring programs for pediatric TBI patients is crucial to track their cognitive and psychological development over time. This includes regular follow-ups with neuropsychological assessments, specialized educational plans, and continuous psychological support to address emerging issues and adjust rehabilitation strategies as needed.
The application of artificial intelligence (AI) to tailor treatment plans holds promise for revolutionizing pediatric TBI recovery. AI algorithms can analyze data from genetic profiles, neuroimaging scans, and clinical histories to predict individual responses to various treatments. By continuously learning from new patient data, AI can help dynamically adjust treatment plans, ensuring that interventions remain optimal as the patient's condition evolves. This personalized approach both maximizes recovery potential and minimizes the risks associated with one-size-fits-all treatment strategies.

Pediatric TBI requires a forward-thinking approach to improve developmental outcomes. By implementing more personalized medicine, advanced diagnostic techniques, and innovative rehabilitation strategies, healthcare providers can enhance the recovery trajectory for pediatric TBI patients. Continuous research and the integration of new technologies and therapies will be essential to resolving current shortcomings and ensuring that children with TBI receive the most effective and comprehensive care possible.

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Conflict of interest: The authors declare that they have no conflict of interest.

Acknowledgements:
Figure 1 was created using BioRender.

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Peer review information
IJLSCI thanks the anonymous reviewers for their contribution to the peer review of this work. A peer review file is available.