# Research Report

Synthesis of Recent Research on Traumatic Brain Injury (TBI)

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## **Content Outline**

#### I. Abstract

- Overview of TBI as a significant public health issue with cognitive, behavioral, and physiological impacts.
- Research focuses on mechanisms, outcomes, and interventions related to TBI.
- Highlights influence of age, sex, and care type on long-term outcomes.
- Importance of consolidating literature on TBI, emphasizing novel insights from population statistics, neuroimaging, and machine learning.
- Traditional assessment tools remain relevant; newer methodologies show predictive capabilities for recovery.
- Emphasizes tailored interventions to improve clinical outcomes and the need for ongoing research into TBI neurobiology.

#### II. Introduction

#### Background

- TBI is a major global cause of morbidity and mortality from incidents such as falls and accidents.
- Involves immediate cellular injury followed by secondary processes exacerbating damage.
- Age, sex, and care type significantly influence outcomes, necessitating comprehensive assessment approaches.

#### Objective

- Aim to synthesize recent findings on TBI mechanisms, recovery predictors, and treatment effectiveness.
- Specific objectives include evaluating machine learning in predicting consciousness disorders and the impact of neuroscience ICU care on outcomes.

#### Literature Review

- Evidence supports advanced neuroimaging and machine learning as predictive tools for TBI outcomes.
- Specialized neuroscience intensive care improves mortality rates, highlighting the need for targeted interventions.
- Research focuses on glial cells, neuroinflammation, and regenerative capabilities in lower vertebrates like zebrafish.

#### **III. Research Method**

#### **Experimental Method**

- Animal Models: Use of mice and zebrafish to study TBI mechanisms; protocols developed for varying injury severities.
- Clinical Trials: Randomized trials assessing EEG biomarkers for predicting outcomes in severe TBI patients.

#### **Processing Method**

- Neuroimaging Analysis: Diffusion tensor imaging (DTI) to assess white matter changes related to lipidomic alterations.
- Transcriptomic Analysis: RNA sequencing to characterize glial responses, revealing agedependent patterns.

#### **Data Analysis Methods**

- Machine Learning Models: Meta-analysis of machine learning models predicting consciousness disorders, measuring effectiveness via receiver operating characteristic curves.
- Statistical Analysis: Multivariable regression models to assess care type impact on patient outcomes.

#### Key Tools/Software

- Statistical Software: R or Python for statistical analysis of neuroimaging and machine learning data.
- Neuroimaging Tools: FSL or SPM for processing DTI data.

#### **IV. Research Result**

- Mortality Rates: Lower in-hospital mortality in NSUs compared to non-NSUs (10% vs. 11%).
- Neuroimaging Biomarkers: Serum lipid profile changes correlate with white matter microstructural alterations.
- Machine Learning Accuracy: Pooled accuracy of 0.83 in predicting consciousness disorders; pediatric models show higher accuracy.
- Age-Dependent Responses: Glial responses to TBI vary with age, indicating the need for agespecific strategies.
- Functional Connectivity: Increased physical activity enhances connectivity in the frontoparietal control network post-TBI.
- Regenerative Mechanisms: Zebrafish studies provide insights into brain regeneration mechanisms post-TBI.

#### V. Conclusion

- The research highlights the complexity of TBI and the need for improved understanding of its pathophysiology and treatment strategies.
- Integrating machine learning and neuroimaging offers potential for enhancing patient prognoses.
- Future studies should elucidate biological mechanisms of TBI, optimize treatments, and address diverse patient needs for improved recovery outcomes.

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## Abstract

Traumatic brain injury (TBI) is a major public health concern affecting millions globally, leading to a wide range of cognitive, behavioral, and physiological impairments that can significantly impact quality of life. This report synthesizes findings from recent research focused on elucidating the mechanisms, outcomes, and potential interventions associated with TBI, drawing from various studies to provide a comprehensive overview of the current state of knowledge in this rapidly evolving field. The background indicates that TBI can result in long-lasting neurological dysfunction, with factors such as age, sex, and the type of care received playing crucial roles in determining patient outcomes. The primary objective of this report is to consolidate the extant literature on TBI, emphasizing novel insights garnered from population-based statistics, advanced neuroimaging techniques, and machine learning models that aim to predict recovery trajectories and functional outcomes in affected individuals. The literature review reveals that while traditional assessment tools such as the Glasgow Coma Scale (GCS) remain integral to evaluating TBI severity, emerging methodologies utilizing machine learning algorithms and neuroimaging biomarkers are proving to be valuable in enhancing predictive accuracy regarding mortality and recovery in TBI patients. For instance, the incorporation of quantitative electroencephalogram (EEG) biomarkers has shown promise in forecasting clinical outcomes by monitoring abnormal brain activity patterns that correlate with inflammatory markers, thus facilitating personalized therapeutic interventions. Furthermore, research indicates that admission to dedicated Neuroscience Intensive Care Units (NSUs) is associated with improved clinical outcomes, as evidenced by lower in-hospital mortality rates compared to non-NSU settings. Additional studies underscore the significance of age-dependent glial responses in TBI, highlighting the distinct roles of various glial cell types across different life stages, which may influence recovery and neuroinflammation. The synthesis of findings from animal models, including non-human primates and zebrafish, provides insights into the molecular mechanisms governing TBI pathology and potential regenerative processes. Importantly, this synthesis not only enhances our understanding of TBI but also informs clinical practices by identifying potential targets for therapeutic interventions. The findings advocate for continued research into the neurobiological processes underpinning TBI, emphasizing the necessity of developing tailored interventions to improve clinical outcomes for patients. This report ultimately aims to guide future research trajectories and clinical practices, fostering advancements in the management and treatment of TBI.

## Introduction

#### Background

Traumatic brain injury (TBI) represents a significant global health crisis, being one of the leading causes of morbidity and mortality across various demographics. The mechanisms leading to TBI are multifaceted, encompassing falls, vehicular accidents, and assaults, with each contributing uniquely to the injury profiles observed in affected populations[1]. The pathophysiology of TBI is intricate; it begins with immediate cellular injury due to mechanical forces, followed by a cascade of secondary injury processes that can further exacerbate neuronal damage and functional impairment[2]. Recent advancements in the understanding of TBI have underscored the importance of various factors that influence recovery outcomes. Age and sex have been identified as critical determinants, with older adults and males generally exhibiting poorer prognoses[3]. Moreover, the type of care received, particularly in specialized neuroscience intensive care units, has been linked to improved patient outcomes, reinforcing the necessity for targeted interventions and comprehensive management strategies[4][5]. Understanding the complex interplay of these factors is essential for developing effective treatment protocols for TBI patients.

#### Objective

This report aims to synthesize recent research findings on traumatic brain injury, focusing on three primary objectives. First, it will investigate the mechanisms of injury that lead to TBI, emphasizing the biological and biochemical cascades that contribute to secondary damage. Second, the report will evaluate predictive factors for recovery, including the efficacy of machine learning models in forecasting disorders of consciousness and the role of age, sex, and care type in recovery trajectories. Lastly, the report will assess the effectiveness of various treatment modalities, such as the application of advanced neuroimaging techniques and emerging therapies designed to mitigate neuroinflammation and promote recovery[6]. By addressing these objectives, the research intends to enhance the understanding of TBI and contribute to the ongoing discourse regarding best practices in the assessment and treatment of affected individuals. This study seeks not only to clarify existing gaps in knowledge but also to propose actionable insights that can inform clinical practice and improve patient outcomes.

#### **Literature Review**

The literature surrounding traumatic brain injury is rapidly expanding, with a particular focus on advanced neuroimaging techniques and the integration of machine learning algorithms for predicting outcomes. Studies have demonstrated that specialized care in neuroscience units can lead to significantly improved mortality rates and functional recovery, highlighting the critical role of tailored interventions [5][3]. Recent investigations have also illuminated the role of glial cells and neuroinflammation in the aftermath of TBI. For instance, research indicates that microglial activation is a double-edged sword, contributing both to neuroprotection and neurodegeneration, depending on the context and timing of the inflammatory response<sup>[7]</sup>. Additionally, the exploration of regenerative mechanisms seen in lower vertebrates, such as zebrafish, has provided valuable insights into potential therapeutic strategies for enhancing recovery in mammals<sup>[8]</sup>. Furthermore, the application of machine learning models has shown promise in predicting disorders of consciousness, offering new avenues for early intervention and personalized treatment plans<sup>[9]</sup>. The convergence of these findings underscores the need for a multidisciplinary approach to TBI management, integrating insights from neurobiology, clinical practice, and technological innovation to address the complexities of this condition. In summary, the literature emphasizes a significant trend towards utilizing advanced methodologies and interdisciplinary strategies in the study and treatment of TBI. This report aims to delve deeper into these facets, ultimately contributing to a more comprehensive understanding of TBI and its implications for clinical practice

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## **Research Methods**

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#### **Experimental Methods**

Animal models serve as a crucial component in studying the mechanisms underlying traumatic brain injury (TBI) and the subsequent recovery processes. Various species, notably mice and zebrafish, have been employed due to their unique physiological attributes that allow for the exploration of TBI pathophysiology. In the case of mice, a standardized protocol utilizing a closedhead weight-drop model has been developed to induce different severities of TBI. This model allows researchers to precisely control the impact force and assess the resultant neurological deficits using a Neurological Severity Score (NSS) to evaluate motor and cognitive functions post-injury. Furthermore, zebrafish have emerged as a valuable model for TBI research due to their remarkable capacity for brain regeneration, which is not seen in mammals. Protocols for inducing TBI in zebrafish typically involve physical injury methods, such as the use of a micromanipulator to deliver a controlled impact. This model not only facilitates the study of immediate cellular responses to injury but also enables longitudinal investigations into the regeneration capabilities of the fish brain. Clinical trials represent another vital experimental approach, particularly in assessing the effectiveness of various interventions in human populations. A randomized clinical trial has been initiated to explore the predictive capabilities of quantitative electroencephalogram (EEG) biomarkers in determining mortality and functional recovery outcomes in patients suffering from severe TBI. This trial protocol includes continuous monitoring of EEG patterns, which allows for realtime analysis of abnormal brain activity linked to cognitive outcomes. Participants are followed through various stages of recovery, utilizing validated assessment scales to evaluate neurological function and quality of life. This dual approach of animal models and clinical trials provides a comprehensive

framework for understanding TBI and developing potential therapeutic strategies.



#### **Processing Methods**

Data processing methodologies are essential for translating raw experimental data into meaningful insights. Neuroimaging analysis, particularly through diffusion tensor imaging (DTI), has been employed extensively to assess microstructural changes in white matter associated with TBI. DTI allows for the visualization of water diffusion in brain tissue, revealing alterations in microstructural integrity that may correspond with clinical outcomes. In this context, advanced analysis techniques, such as tract-based spatial statistics, are utilized to derive quantitative metrics like fractional anisotropy (FA) and mean diffusivity (MD). These metrics provide insights into the extent of white matter damage and are correlated with lipidomic changes observed in TBI patients, suggesting a potential biomarker for injury severity and recovery. Transcriptomic analysis further enhances understanding of the molecular responses to TBI. RNA sequencing has been applied to characterize the responses of glial cells, which play crucial roles in the central nervous system's response to injury. This highthroughput sequencing technique enables the identification of age-dependent expression patterns and the molecular pathways activated in response to TBI. By analyzing gene expression profiles across different developmental stages, researchers can elucidate the complex interplay between age and injury response, leading to targeted therapeutic strategies that consider the unique biological characteristics of different age groups.



#### **Data Analysis Methods**

Data analysis in TBI research often employs sophisticated statistical methodologies to derive meaningful conclusions from complex datasets. Machine learning models have gained traction for their capacity to predict clinical outcomes based on diverse data inputs. A recent metaanalysis evaluated the predictive accuracy of these models in determining disorders of consciousness (DOC) following TBI. By employing receiver operating characteristic (ROC) curves, the study assessed the effectiveness of various machine learning algorithms in distinguishing between different states of consciousness. The findings indicated a pooled area under the curve (AUC) of 0.83, reflecting the significant potential of machine learning in clinical prognostication. Statistical analysis also plays a pivotal role in understanding the impact of different care types on patient outcomes. Multivariable regression models are employed to examine the relationship between the type of intensive care unit—specifically, Neuroscience Intensive Units (NSU) versus non-NSU—and various patient outcomes, such as mortality and length of stay. These models are adjusted for known predictors of poor outcomes, providing a robust framework for understanding how specialized care environments influence recovery trajectories in braininjured patients.



#### Key Tools/Software

A variety of key tools and software are employed throughout the research process to facilitate data analysis and processing. Statistical software packages such as R and Python are widely utilized for their flexibility and capability to handle complex statistical analyses. These platforms enable the execution of machine learning algorithms, statistical modeling, and data visualization, making them indispensable for researchers in the field of TBI. In terms of neuroimaging data analysis, specialized tools like FSL (FMRIB Software Library) and SPM (Statistical Parametric Mapping) are commonly used for processing DTI data. These software packages provide frameworks for preprocessing, analyzing, and visualizing neuroimaging data, allowing researchers to derive insights into the structural changes associated with TBI. In addition, advanced quantitative analysis tools are utilized for lipidomic profiling, such as ultra-high-performance liquid chromatography coupled with mass spectrometry (UHPLC-MS). This technology facilitates the detailed analysis of lipidomic changes in serum

samples, providing insights into the biochemical alterations associated with TBI. Collectively, these tools and methodologies not only enhance the rigor and reliability of research findings but also contribute to the broader understanding of TBI mechanisms and recovery processes. The integration of experimental methods, processing techniques, data analysis strategies, and advanced software tools fosters a comprehensive approach to tackling the complexities of traumatic brain injury research.

## **Research Results**

The findings from the reviewed studies yield several critical insights into Traumatic Brain Injury (TBI), each contributing to a more nuanced understanding of its pathology and potential therapeutic avenues.

1. Mortality Rates: The analysis of in-hospital mortality rates reveals that admission to dedicated Neuroscience Intensive Care Units (NSUs) significantly correlates with improved clinical outcomes. Specifically, patients with TBI admitted to NSUs exhibited an in-hospital mortality rate of 10%, compared to a 11% mortality rate for those in nonNSUs. This difference, although seemingly marginal, highlights the potential benefits of specialized care environments that are tailored for brain-injured individuals. The multivariable regression analysis further substantiated this finding, indicating that after adjusting for known predictors of poor outcomes, the odds ratio for in-hospital mortality in NSUs remained significantly lower (OR 0.8; 95% CI 0.7-0.9). These findings underscore the critical role of specialized units in improving survival rates for patients with acute brain injuries.

2. Neuroimaging Biomarkers: Another pivotal discovery centers on the relationship between serum lipid profiles and neuroimaging features indicative of TBI severity. An investigation of lipidomic changes in a cohort of TBI patients revealed significant associations between alterations in serum lipid compositions and microstructural changes in cerebral white matter as measured by diffusion tensor imaging. Specifically, increasing TBI severity was linked to higher mean diffusivity (MD) and lower fractional anisotropy (FA) values, with distinct lipidomic signatures corresponding to these neuroimaging alterations. This correlation suggests that lipidomic profiling could serve as a noninvasive biomarker for assessing the severity of TBI and may provide insights into the underlying pathophysiological processes.

**3. Machine Learning Accuracy**: The application of machine learning models in predicting disorders of consciousness (DOC) following TBI has shown remarkable promise. A meta-analysis indicated a pooled accuracy of 0.83 in predicting DOC, with pediatric models demonstrating even higher accuracy (0.88). This suggests that machine learning algorithms can effectively leverage clinical data to enhance prognostic capabilities, providing valuable information for treatment planning and patient management. The implications of this accuracy are profound, as they can lead to more informed decisions regarding rehabilitation strategies and resource allocation in TBI care.

**4. Age-Dependent Responses**: The study of glial cell responses to TBI underscores the complexity of neuroinflammatory processes and their age dependence. Research involving zebrafish models highlighted distinct patterns of glial activation and response to injury across different life stages. Age-specific glial dynamics were observed, with younger organisms exhibiting a different response to TBI compared to adults. The identification of specific signaling pathways involved in these age-dependent responses points to the necessity for tailored therapeutic strategies that consider the age of the patient, suggesting that interventions may need to be adapted to optimize recovery outcomes across different age groups.

**5. Functional Connectivity**: Investigating functional connectivity within the frontoparietal control network (FPCN) has revealed a positive association between physical activity and enhanced connectivity in individuals with a history of TBI. The analysis demonstrated that increased physical activity correlates with improved functional connectivity, which may mitigate some of the cognitive deficits associated with TBI. This finding supports the notion that engaging in physical activity can play a crucial role in rehabilitation, potentially serving as an adjunct to traditional therapeutic approaches aimed at improving cognitive and functional outcomes.

6. Regenerative Mechanisms: Insights gained from studies using zebrafish models have elucidated the cellular and molecular mechanisms underlying brain regeneration following TBI. Unlike mammals, zebrafish exhibit significant regenerative capabilities, which can inform therapeutic strategies for human conditions. The research has identified key pathways involved in neuroprotection and repair, offering potential targets for future interventions aimed at promoting recovery in mammalian models. This line of investigation emphasizes the importance of understanding regenerative processes as a foundation for developing novel treatments for TBI and related neurodegenerative conditions.

The collective findings from these studies not only enhance our understanding of TBI and its implications but also pave the way for future research aimed at improving diagnosis, treatment, and rehabilitation strategies for individuals affected by this pervasive condition. The integration of specialized care, advanced biomarker identification, machine learning applications, and age-appropriate therapeutic approaches represents a multifaceted strategy that could significantly alter the landscape of TBI management and recovery.

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## Conclusion

This synthesis of recent research underscores the multifaceted nature of traumatic brain injury (TBI) and emphasizes the critical need to advance our understanding of its pathophysiology, outcomes, and treatment strategies. The findings from various studies illustrate that TBI is not a singular event but rather a complex interplay of biological processes that vary significantly among individuals. The integration of advanced methodologies such as machine learning and neuroimaging into clinical practice holds immense promise for improving patient prognoses. For instance, machine learning models have demonstrated high accuracy in predicting disorders of consciousness, offering a valuable tool for clinicians to tailor interventions based on individual patient profiles and potential recovery trajectories. Moreover, the insights derived from animal models, particularly with zebrafish and nonhuman primates, provide foundational knowledge about the underlying mechanisms of brain injury and the regenerative processes that could inform future therapeutic approaches. The identification of specific signaling pathways and glial responses to injury, as observed in various animal studies, highlights the potential for developing novel interventions that could mitigate the effects of TBI and promote recovery. The impact of age on TBI outcomes is another crucial aspect revealed by recent research, indicating that younger and older patients exhibit different responses to brain injury. Understanding these age-dependent variations is essential for optimizing treatment protocols that cater to the unique needs of diverse patient populations. Furthermore, the findings suggest that dedicated care environments, such as Neuroscience Intensive Care Units, significantly improve survival rates for brain-injured patients, underscoring the importance of specialized care in enhancing recovery outcomes. As we look to the future, several key areas warrant further research. First, elucidating the biological mechanisms underlying TBI remains paramount. Investigating the roles of specific cellular responses, signaling pathways, and inflammatory processes will deepen our understanding of TBI's pathophysiology and potentially unveil new therapeutic targets. Furthermore, optimizing treatment protocols that consider individual patient variability, including age, sex, and comorbidities, will be critical for improving clinical outcomes. Lastly, addressing the long-term effects of TBI on guality of life is essential, particularly in populations such as military veterans who exhibit unique challenges postinjury. Future studies should focus on longitudinal assessments that track cognitive, emotional, and physical recovery, helping to identify predictors of successful rehabilitation. By bridging the gaps in our current understanding and utilizing innovative research methodologies, we can pave

the way for more effective interventions that enhance recovery and improve the quality of life for individuals affected by traumatic brain injury.



# **Recent Research List**

	['Xi Zhu', 'Li Gao', 'Jun Luo']	['Youstina Metry', 'Christel McMullan', 'Rachel Upthegrove', 'Antonio Belli', 'Renata S M Gomes', 'Richard J Elanch', 'Zubair Ahmed']	-		~	['Emma M Tinney', 'Meishan Ai', 'Goretti España-Irla', 'Charles H Hillman', 'Timothy P Morris']	['Abby E Beatty', 'Tara M Barnes-Tompkins', 'Kira M Long', 'Daniel J Tobiansky']	['Javier Allende Labastida', 'Massoud Motamedi', 'Ping Wu', 'Bartosz Szczesny']	['Aldrich Chan', 'Jason Ouyang', 'Kristina Wguyen', 'Aaliyah Jones', 'Sophia Basso', 'Ryan Karasik']	['Friyanka P Srivastava', 'Sidharth Bhasin', 'Sunita S Shankaran', 'Catherine Roger', 'Rajesh Ramachandran', 'Shilpi Minocha']	['Tingting Li', 'Wenwen Shi', 'Margaret S Ho', 'Yong Q Zhang']	['Cheng-Hao Lin', 'Bei-Yao Gao', 'Rui-Dong Ge', 'Rui Cui', 'Wen Han', 'Shan Jiang']	['Adam James Wells', 'Peter Lawrence Reilly']	['Walter Gomes da Silva Filho', 'Layza Julhia do Mascimento Moura', 'Arthur Barcelos Masariol Mascimento', 'Gabrielle Cristina Tessmann', 'Fabricia Silva Miranda', 'Vitòria Caroline Reinoso de Almeida', 'Bérbara Vargens Broedel', 'Miller Lucas de Faria', 'Fernando Zanela da Silva Aréas']	['Brendan J Johnson', 'Rachel W Andrews', 'John D Olson', 'J Mark Cline']	['Huiwen Qin', 'Shuguang Yu', 'Ruyi Han', 'Jie	['Angel J Cadena-Tejada', 'Shaista Alam', 'Varoon Thavapalan', 'Sara Habib', 'Fred Rincon']	Authors ['G Smith', 'C Santana-Gomez', 'R J Staba', 'N G Harris']
Consciousness After Traumatic Brain Injury by Machine Learning Models.	A Meta-analysis of Predicting Disorders of	Understanding how traumatic brain injury-related changes in fluid biomarkers affect quality of life outcomes in veterans: a prospective observational trial protocol (UNTANCLE).	Adverse impact of female reproductive signaling on age-dependent neurodegeneration after mild head trauma in .	Osteocalcin-expressing neutrophils from skull bone marrow exert inmunosuppressive and neuroprotective effects after TBI.	Serum lipidome associates with neuroimaging features in patients with traumatic brain injury.	Physical activity and frontoparietal network connectivity in traumatic brain injury.	Comparative analysis of meningeal transcriptomes in birds: Potential pathways of resilience to repeated impacts.	Protocol for inducing varying TBI severity in a mouse model using a closed-head, weight-drop, impact-induced acceleration mechanism.	Traumatic brain injuries: a neuropsychological review.	A reproducible method to study traumatic injury- induced zebrafish brain regeneration.	A Pvr-AP-1-Mmp1 signaling pathway is activated in astrocytes upon traumatic brain injury.	The application of optogenetics in traumatic brain injury research: A narrative review.	50 Years of the Glasgow Coma Scale: A historical perspective.	Electroencephalogram biomarkers as predictors of mortality and functional recovery in patients with severe traumatic brain injury: Protocol study.	Radiation-induced Brain Injury and the Radiation Late Effects Cohort (KLEC) of Rhesus Macaques (Macaca mulatta).	Age-dependent glial heterogeneity and traumatic	In-hospital Mortality is Lower in Erain-Injured Patients After Admission to a Neuroscience Intensive Care Unit: A Multi-Center Cohort Study.	Title Unbiased Population-Based Statistics to Obtain Pathologic Burden of Injury after Experimental TBL.
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