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# Multi organ Dysfunction (MODS): A life-threatening aspect of Traumatic brain injury

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## ABSTRACT

Traumatic Brain Injury (TBI) is not only a leading cause of neurological impairment but also a critical trigger for systemic complications. Among these, Multiple Organ Dysfunction Syndrome (MODS) represents one of the most severe and life-threatening outcomes. Following a primary brain insult, secondary pathophysiological cascades—such as neuroinflammation, oxidative stress, autonomic dysregulation, and the release of damage-associated molecular patterns (DAMPs)—initiate a systemic inflammatory response that affects peripheral organs including the lungs, liver, kidneys, and heart. This brain–body cross-talk results in multi-organ dysfunction, which significantly worsens prognosis and increases mortality. Understanding the mechanisms linking TBI to MODS is essential for early diagnosis, targeted therapeutic interventions, and improved patient survival. This review highlights the underlying pathophysiology, affected organ systems, and emerging management strategies to mitigate the systemic consequences of traumatic brain injury.

## INTRODUCTION

Traumatic Brain Injury is a serious public health problem globally contributing to millions of deaths and disabilities annually.[1] It brings up damage to the brain caused by an instant trauma or injury to the head. This injury can result from a variety of incidents such as motor vehicle crashes, and other transportation related causes, falls (especially in elderly people and young children), physical attack and sports activities.[2] While TBI primarily have an impact on the brain, it can further lead to systemic manifestations that may impart development of Multiple Organ Dysfunction Syndrome (MODS) through various mechanisms including systemic inflammation, neurogenic pulmonary oedema, autonomic dysfunction, and coexisting injuries. Critically injured patients who survive the initial injury frequently develop multiple organ dysfunction syndrome (MODS), which can lead to poor outcomes. MODS is a severe and fatal condition mark by progressive dysfunction of more than two organ system following an acute injury or illness.[3] The severity of the injury and the necessity of surgical intervention are two factors that influence the number of cases of post-traumatic MODS. The unregulated immune reaction is foremost in the pathophysiology of traumatic MODS.[4]

TBI is a heterogenous neurological disorder that has been graded using injury severeness scores, typically used is the Glassglow Coma Scale (GCS). A GCS

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score of 8 or less measured an admission represents severe TBI, a GCS score of 9-12 traditionally has represented moderate TBI, and a GCS score of 13-15 shows mild TBI.

The majority of recognized TBIs are estimated to be mild, comprising approximately 70% - 90% of cases.[5] Comparatively mild, TBI frequently leads to chronic impairments that have long-term repercussions on patient health and quality of life.[6] Chronic TBI-induced abnormalities in motor and cognitive function and social behaviour, as well as the development of mood disorders, abnormal sleep cycles, and personality changes, all lead to a lower quality of life and a shorter total life expectancy, increasing the financial burden on health-care systems.[7] Severe TBI is a significant risk factor for Alzheimer's disease, dementia, stroke, and seizures, and it is associated with a higher long-term death risk than the rest of the population.[8] These neurodegenerative hazards can also appear in milder forms of TBI, particularly after repeated shocks. Therefore, TBI should not be viewed as a single static injury event, but rather as a chronic and progressive disease with severe long-term impacts. Therefore, the variety of TBI injury encompasses both the immediate mechanical harm caused by at the time of injury (primary injury) and the subsequent delayed molecular cascades (secondary injury).[9]

While several studies have focused on the effects of traumatic brain injury on the brain or individual organ systems, very few have explained how these systems interact to cause multiple organ dysfunction. This article is different from previous studies because it provides an integrated understanding of the mechanisms linking brain injury with systemic organ failure. It also discusses potential strategies for early diagnosis and management of MODS in TBI patients, which have not been well explored in earlier research.

TBI is a significant cause of mortality and morbidity across all age groups globally, with a greater burden in low and middle-income countries (LMICs) due to a large number of risk factors and the inadequacy of health systems to provide appropriate acute and long-term care.[10,11] The world's highest rate of TBIs is found in India. In India, about 1 million people suffer from serious TBIs, and over 100,000 people lose their lives each year.[12]

According to limited research, the incidence of systolic dysfunction in TBI can reach 22% when assessed with conventional echocardiograms and range from 10% to 38% when more sensitive measures of left ventricular function, like global longitudinal strain (GLS) are employed.[13] Prior research has demonstrated that TBI results in acute cardiac dysfunction. According to reports, TBI not only causes acute heart failure but also increases the risk of chronic heart failure, which is typified by progressive dysfunction within 30 days following TBI as well as a decrease in left ventricular ejection fraction and fractional shortening within 3 days.[14] Acute renal injury is a common complication following various critical illnesses, including TBI. The incidence of AKI following TBI has been found to range between 8% and 14%. Furthermore, the development of AKI has been consistently associated with poor clinical and functional outcomes during TBI.[15] After TBI, the SOFA score is used to assess multiorgan dysfunction. A composite score of five systems (cardiovascular, respiratory, coagulation, renal, and hepatic) is calculated. Using a cut point of 7, over 40% of patients with moderate to severe TBI experienced multiorgan dysfunction within the first 10 days of hospitalisation. Cardiopulmonary organ failures accounted for the majority of the dysfunction. Patients with multiorgan dysfunction had higher inpatient death rates.[16]

Multiple Organ Dysfunction Syndrome (MODS) in the context of Traumatic Brain Injury (TBI) represents a severe systemic response resulting

from primary neurological insult and secondary pathophysiological cascades. MODS is commonly defined using the Sequential Organ Failure Assessment (SOFA) score, which quantifies dysfunction across multiple organ systems. A dysfunction involving two or more organ systems with a SOFA score of ≥3 is generally considered indicative of MODS.[17] Based on the timing of onset, early MODS is defined as organ failure occurring within the first 72 hours after trauma, whereas late MODS develops after 72 hours of post-trauma.

The SOFA score serves as an essential prognostic tool to evaluate organ dysfunction and predict mortality in critically ill or trauma patients. It assesses six major organ systems — respiratory, coagulation, hepatic, cardiovascular, renal, and neurological — each scored according to the degree of functional impairment. The respiratory component is based on the $PAO_2/FIO_2$ ratio, coagulation is assessed through platelet count, hepatic function through serum bilirubin levels, cardiovascular performance by mean arterial pressure (MAP) or use of vasoactive agents, renal function by serum creatinine concentration, and neurological function by the Glasgow Coma Scale (GCS).

SOFA scoring is typically performed at admission and re-evaluated every 24 hours until discharge, using the most deranged values recorded during each 24-hour period to determine the degree of dysfunction.[18] This dynamic scoring system enables clinicians to monitor the progression of organ failure and stratify mortality risk in TBI patients, offering a valuable framework for both clinical management and research evaluation.

**Pathophysiology of MODS:**

TBI can have a number of systemic symptoms in addition to its brain manifestations, some of which can serve as independent markers of MODS. [19,20] The degree of brain damage mostly determines the nature and intensity of the systemic manifestations of TBI. While severe TBI can negatively impact the functioning of several organ systems, mild TBI induces systemic signs including fatigue and dizziness. Systemic complications include respiratory failure, renal failure, adrenal insufficiency, cardiac damage, and potentially multiple organ dysfunction.[21] While renal and hepatic symptoms are uncommon after severe TBI, endocrine dysfunction and electrolyte abnormalities are prevalent.

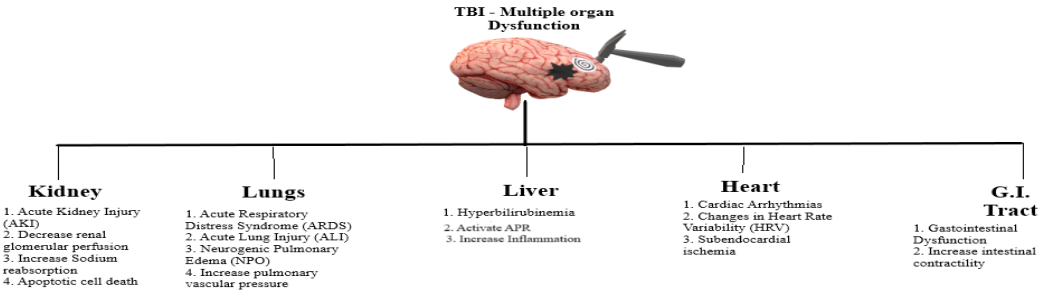


FIGURE 1. Devastating consequences of TBI on various organs (Through a series of autonomic and inflammatory reactions, traumatic brain injury (TBI) can cause multiple organ dysfunction (MODS), which can lead to organ damage and systemic adverse consequences)

**Heart:**

Neurogenic stunned myocardium (NSM) is a phenomenon in which acute neurological events, like TBI, cause circulatory abnormalities, including echocardiography (ECG) alterations, cardiac arrhythmias, a release of cardiac damage biomarkers, and left ventricular dysfunction (LVD).[22] The spleen responds to brain damage by transporting stationary leukocytes, secreting pro-inflammatory cytokines into the systemic circulation, and increasing the quantity of immune cells in the peripheral bloodstream. Immune cells and inflammatory substances promote collagen deposition, expansion of cardiac fibroblasts, and destruction of cardiomyocytes.[23] In the early stage of TBI (3 days post-TBI), infiltration of inflammatory cells into the heart and increased production of inflammatory markers can contribute to post-TBI acute and chronic cardiac dysfunction.[24]

Perfusion scans have revealed that, in along with myocardial damage, catecholamines cause vascular spasm in myocardial blood vessels, resulting in localized perfusion abnormalities and ischemia. Clinical symptoms include hypotension, cardiac arrhythmias, ventricular dysfunction, and alterations in the Electrocardiogram (ECG). Regional wall motion abnormalities, as well as systolic and diastolic dysfunction, may be detected using echocardiography. This cardiac dysfunction following neurogenic damage is frequently referred to as “neurogenic stunned myocardium or stress cardiomyopathy” (Takotsubo’s cardiomyopathy or broken heart syndrome.[25]

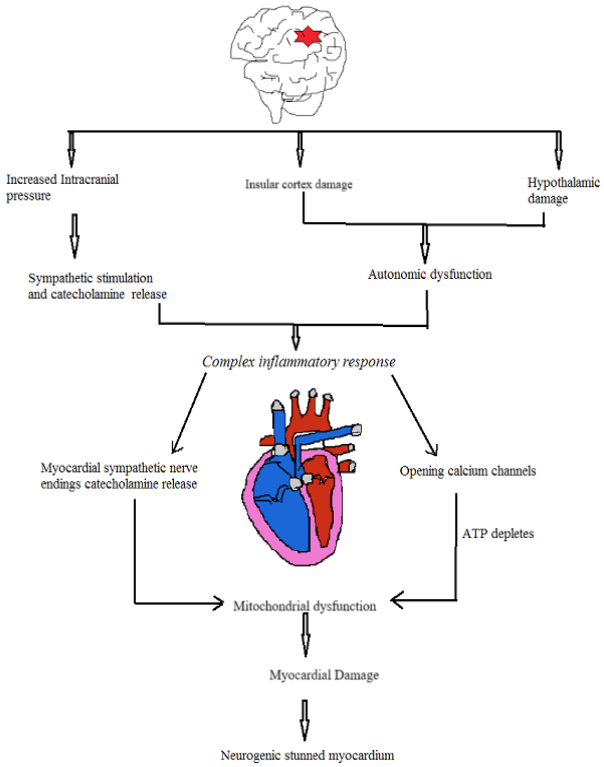


FIGURE. 2 Transient left ventricular failure, ECG abnormalities, and increased cardiac enzymes are the hallmarks of neurogenic stunned myocardium (NSM), a reversible cardiac malfunction that occurs after a neurological event such as traumatic brain injury (TBI).

**Lung:**

Lung complications and associated respiratory distress are thought to be one of the most frequent and life-threatening extracranial effects of TBI.[20,26] One third of moderate-severe TBI patients will develop acute lung injury (ALI), a condition characterized by bilateral opacities on lung imaging, with respiratory failure occurring within 7 days.[27]

TBI has long been associated with the development of acute respiratory distress syndrome (ARDS), which is a clinical syndrome characterized by acute, diffuse pulmonary injury.[25] Neurogenic pulmonary edema (NPE), ALI, ventilator-mediated lung injury, and increased risk for pneumonia are now seen as manifestations of a clinical spectrum of TBI-induced ALI.[28]

**Mechanism of developing ALI/ ARDS in TBI:**

**Systemic Inflammatory Response-** Severe TBI can trigger a systemic inflammatory response syndrome (SIRS), characterized by the release of pro-inflammatory cytokines and activation of inflammatory cascades throughout the body.[29]

**Primary lung Injury**- This systemic inflammation can lead to injury and increased permeability of the alveolar-capillary membrane in the lungs. Medullary injury may initiate anti-parasympathetic activity adding to inflammatory response in the lung and exaggeration of ALI. There is initial increase in airway resistance due to bronchoconstriction.[30,31] The disrupted barrier allows protein-rich fluid to leak into the alveoli, leading to pulmonary edema and impairing gas exchange.[32]

**Secondary Injury**- In addition to the primary injury, TBI patients may experience secondary insults such as hypoxia, and hypercapnia, which further exacerbate lung injury and contribute to the development of ALI. ALI worsens the neurological outcome in patients with TBI.[33] ARDS can lead to hippocampal injury, resulting in memory deficits and cognitive dysfunction.

**Neurogenic pulmonary edema** is the immediate buildup of proteinaceous pulmonary fluid after any neurological trauma.[34] NPE often develops in a bimodal distribution, possibly within minutes of injury or even in a delayed manner, 12-24 hours later.[28]

**Mechanism of developing NPE in TBI:**

**Sympathetic Hyperactivity**- TBI can lead to excessive sympathetic nervous system activation, resulting in systemic vasoconstriction, increased heart rate, and elevated blood pressure. This sympathetic surge is often characterized by an increase in circulating catecholamines (such as adrenaline and noradrenaline).[35]

**Increased Pulmonary Vascular Resistance**- Sympathetic activation causes vasoconstriction in the pulmonary vasculature, leading to increased pulmonary vascular resistance. This results in elevated pressure within the pulmonary circulation.[36]

**Fluid Transduction-**Elevated hydrostatic pressure in the pulmonary capillaries exceeds the oncotic pressure, leading to the transudation of fluid from the pulmonary vasculature into the interstitial space and alveoli.[37]

**Pulmonary Edema Formation-**The accumulation of fluid in the interstitial space and alveoli results in pulmonary edema. This edema compromises gas exchange, leading to hypoxemia and respiratory distress.

***Kidney:*** An essential mechanism to keep cerebral and kidney blood flow comparatively constant is autoregulation of blood flow, which is the vascular bed's innate ability to maintain constant perfusion despite variations in intracranial pressure (ICP) and arterial blood pressure (ABP). Due to their low vascular resistance and high perfusion, the kidney and brain are subjected to high

volumes of blood flow during the cardiac cycle.[38] Patients with traumatic brain injury (TBI) often suffer from impaired renal function and cerebrovascular autoregulation.[39] On the other hand, polyuria and elevated glomerular filtration rate with augmented renal clearance (ARC) are also commonly seen in TBI patient.[40] Following trauma, systemic inflammation, cytokine cascades driven on by brain lesions, vigorous fluid resuscitation, the use of hypertonic solutions, and vasopressor support may all contribute to disruptions in organ blood flow and excretory function.[41]

During TBI, serum urea and creatinine levels have been shown to rise within 24 hours of damage, which may indicate damaged renal function.[42] Acute renal injury, as evidenced by increases in serum creatinine and decreases in urine output, was found in 8-36% of severe TBI patients.[43]

AKI is likely to interfere with cerebral homeostasis both at the cellular level and via altering systemic cytokines, neurotransmitter concentrations, acid-base imbalance, haemostasis, and drug metabolism.

**Liver:**

The liver contains the highest number of resident macrophages of any other organ, and is the major contributor to the level of chemokines in serum after brain injury. Therefore, TBI has been shown to be directly associated with a systemic Acute phase response (APR). After acute brain injury, the chemokine expression by the liver results in neutrophil recruitment and hepatic damage, contributing to multi-organ dysfunction.[44] Along with a number of other inflammatory alterations in the body, TBI has been demonstrated to enhance mRNA expression in acute-phase response (APR), serum amyloid A1 (SAA1), and angiotensin II type 1 receptor (AT1R).[45]

The release of cytokines into the blood stream, particularly IL-6 and IL-1b, induces an acute phase response from the liver, which is hypothesised to be amplified by the release of norepinephrine as part of the sympathetic response. The acute-phase response is a biological defence against systemic or local tissue injury in which hepatocytes secrete acute-phase proteins such as serum amyloid A1, C-reactive protein, and fibrinogen into the bloodstream.[43] Inflammation, trauma, or stress cause increased SAA1 expression and synthesis, as well as its release into the bloodstream, which activates APR.[46] Clinical investigations have found elevated SAA1 levels in TBI patient's plasma, which correlates with acute inflammation and damage severity.[47] SAA1 is a pro-inflammatory mediator that induces gene expression of IL-1A, IL-1B, IL-8, IL-6, and TNFα in human macrophages that differentiate from peripheral monocytes.[48]

TNF-α, IL-1β, and IL-6 are inflammatory mediators linked to diminished cytochrome P450 (CYP450) activity, infection, and inflammation. Amplification in these cytokines have been observed in the cerebrospinal fluid (CSF) and serum of TBI patients.[44,49]

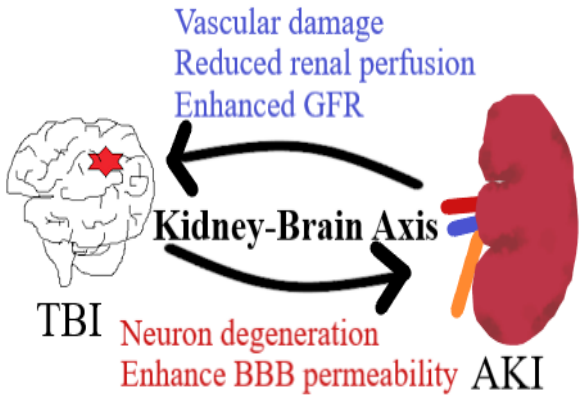


FIGURE. 3 **Acute kidney injury** (A variety of disorders can result from the kidney-brain axis, a bidirectional communication network that links the kidneys and the brain. It can be influenced by uremic toxin, inflammation, vascular damage, neuronal degeneration, and other factors)

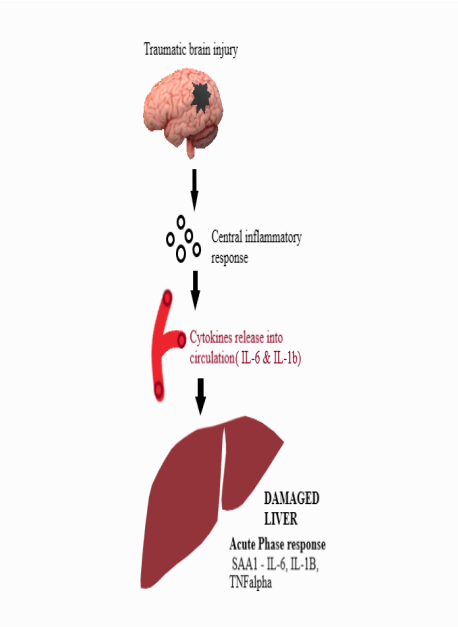


FIGURE. 4. Following the activation of the Hepatic APR (Acute Phase Response), TBI leads to a rise in IL-1β, IL-6, and TNF-α. Hepatic inflammation and increased bile acid release are triggered by the APR.

***GIT (Gastrointestinal Tract):***

TBI has a significant impact on various organ systems, particularly the GI tract,[50,51] which influences morbidity and mortality.[52] Approximately 50% of severe TBI patients develop feeding intolerance, particularly in the first week following injury, which is associated to injury severity.[53]

The brain-gut axis is a bidirectional pathway that is critical for central nervous system (CNS) and GI homeostasis and regulates diverse functions including visceral pain, intestinal barrier function, gut motility, and neurobehavior. TBI induces a stress response that impacts the well-documented autonomic nervous system (ANS) control of GI function.[54] Activation of the systemic immune system following TBI could play a major role in subsequent GI dysfunction, and the effects of TBI may be amplified further by psychological distress, which is known to exacerbate GI symptoms.[55] Gut-to brain communication is equally important, as sensory information arising from the gut lumen coordinates function across different regions of the gut. Changes in the gut microbiome are common in neurodegenerative disorders, spurring mechanistic studies on the role of specific microbiota and their microbial products.[56] There is also an expanding appreciation of the impact of secondary GI challenges on chronically injured TBI patients that worsen longterm morbidity and mortality.[9]

Experimental TBI has been documented to generate persistent changes in mucosal barrier activity and histopathology in the large intestine, which impact permeability.[57] TBI has been demonstrated to lower contraction and movement while increasing inflammation in gut smooth muscle, implying that small intestine motility is restricted as a result of secondary inflammatory damage produced by brain injury. The inflammatory response of the intestine following trauma is characterised by the mobilisation of neutrophils and monocytes into the intestine and the release of inflammatory cytokines, which can contribute to intestinal mucosal injury.[42] Systemic inflammation can last for months in persons suffering from mild[58] and severe TBI.[59,60] Prospective cohort studies found that TBI patients had higher serum levels of IL-1β, IL-6, IL-8, IL-10, and TNF-α than age-matched healthy controls in the first year following injury.[59]

TBI activates secondary damage pathways, including inflammation, leading to non-neurological dysfunctions in the cardiovascular, lungs, liver, gastrointestinal tract, kidneys, and endocrine systems. These findings indicate that non-neurological consequences of TBI should also be addressed in treatment.

**Limitations:** 1).Absence of Direct Clinical Correlation: There is little direct clinical validation in human populations for thr majority of the mechanistic knowledge linking TBI to MODS, which is taken from experimental and animal models. 2).The heterogeneity of TBI makes it difficult to develop consistent pathophysiological patterns and draw generalized conclusions because it includes a wide range of injury types, severities, and etiologies. 3).Variability in MODS Diagnostic Criteria: Despiter the widespread use of the Sequential Organ Failure Assessment (SOFA) score, many studies may reflect MODS incidence and severity differently due to variations in timing, scoring threshold, and interpretation.

**Future Directions:**

Large-scale, prospective, multi-center clinical studies should be the main focus of future research in order to confirm experimental results and determine the temporal correlations between the severity of TBI and systemic organ dysfunction. The creation of consistent scoring guidelines and standardized diagnostic

frameworks for neurotrauma-specific MODS would improve the reliability and comparability of study findings. Advanced molecular techniques like proteomics, metabolomics, and genomics can be used to identify early predictive biomarkers, which could lead to personalized treatment plans and early detection.

## CONCLUSION

TBI causes severe malfunction in extracranial organ systems, leading to subsequent brain damage and poor clinical outcomes. The majority of indications involve autonomic system activation or immune response suppression. Acute symptoms such as adrenal insufficiency, cardiac dysfunction, neurogenic pulmonary oedema, and GI dysmotility might be harmful. The most common factor of secondary injuries is the production of pro-inflammatory cytokines, which increases the severity of TBI and causes multiple organ dysfunction. Despite advancements in critical care, significant gaps remain in knowledge regarding the temporal evolution, inter-organ interactions, and molecular mediators underlying TBI-associated MODS. Expanding research efforts in low- and middle-income countries is also crucial to address regional disparities in epidemiology and care.

In conclusion, TBI should be recognized not merely as a cerebral insult but as a systemic disorder with the potential to culminate in MODS, a major determinant of poor outcomes and mortality. Understanding and managing this brain–body interplay are essential for improving survival, recovery, and long-term quality of life in patients with traumatic brain injury.

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