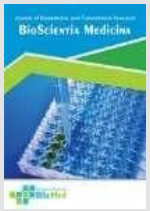
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Metabolic and Inflammatory Signatures of Neurotrauma: Correlating Early Glycemic and Leukocytic Shifts with Glasgow Coma Scale Scores

Ni Wayan Lisa Suasti[1*], Roland Sidabutar[2], Agung Budi Sutiono[3], Guata Naibaho[3]

[1]Neurosurgery Resident, Department of Neurosurgery, Faculty of Medicine, Universitas Padjajaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

[2]Chief of Skullbase Division, Department of Neurosurgery, Faculty of Medicine, Universitas Padjajaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

[3]Staff of Skullbase Division, Department of Neurosurgery, Faculty of Medicine, Universitas Padjajaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

ARTICLE INFO

Keywords:
Glasgow coma scale
Leukocytosis
Neuroinflammation
Stress-induced hyperglycemia
Traumatic brain injury

***Corresponding author:**
Ni Wayan Lisa Suasti

E-mail address:
wayan21002@mail.unpad.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i2.1519

A B S T R A C T

Background: Traumatic brain injury (TBI) precipitates a profound systemic physiological stress response, often termed the sympathetic storm, characterized by neuroendocrine dysregulation and widespread inflammation. While admission biomarkers such as White Blood Cell (WBC) count and Blood Glucose levels are routinely measured, their comparative utility in stratifying injury severity—particularly in distinguishing between moderate and severe phenotypes—remains under-characterized. This study aimed to evaluate the discriminatory power of these markers, hypothesizing that metabolic and immune responses exhibit distinct saturation kinetics relative to the Glasgow Coma Scale (GCS). **Methods:** We conducted a retrospective analytical observational study at Dr. Hasan Sadikin General Hospital (RSHS), a level I trauma center in Bandung, Indonesia. From an annual pool of admitted neurotrauma patients (January–December 2021), a stratified sample of 238 patients aged 18-60 years was analyzed. Strict exclusion criteria were applied to minimize confounders, including a history of metabolic disease and alcohol intoxication. TBI severity was stratified into mild (GCS 13-15), moderate (GCS 9-12), and severe (GCS 3-8). Statistical analysis utilized the Kruskal-Wallis and Mann-Whitney tests to assess non-parametric relationships. **Results:** The cohort was predominantly male (82.8%) and young (18-40 years, 68.9%). Both biomarkers correlated with overall severity; however, their trajectories diverged significantly. WBC counts exhibited a threshold effect, rising significantly from Mild (17.50 ± 6.56 $x10^3/\mu L$) to Moderate (18.81 ± 5.27 $x10^3/\mu L$) severity, but plateauing between moderate and severe groups ($p>0.05$), suggesting a saturation of the demargination response. Conversely, blood glucose displayed a graded linear escalation: Mild (133.11 ± 34.53 mg/dL), moderate (158.35 ± 49.59 mg/dL), and severe (226.14 ± 105.61 mg/dL) ($p<0.001$), with significant discrimination across all severity pairings. **Conclusion:** Admission hyperglycemia serves as a superior, graded biomarker for stratifying TBI severity compared to leukocytosis, which functions primarily as a binary threshold marker. The observed immune plateau contrasts with the linear metabolic scaling, highlighting stress-induced hyperglycemia as a critical indicator of severe neuro-metabolic derangement.

1. Introduction

Traumatic brain injury (TBI) remains a formidable public health challenge, representing a leading cause of mortality and long-term disability worldwide.[1] The pathophysiology of TBI is biphasic: the primary insult occurs at the moment of impact, causing immediate structural damage, while the secondary insult follows minutes to days later.[2] This secondary cascade is

driven by a complex interplay of ischemic, cytotoxic, and inflammatory processes that can exacerbate neuronal death and worsen clinical outcomes. It is within this window of secondary injury that clinicians have the greatest opportunity to intervene, yet accurate prognostication and severity stratification remain challenging, particularly when the Glasgow Coma Scale (GCS) is obscured by sedation or intubation.[3] A central component of the secondary cascade is the systemic physiological stress response, often referred to as the sympathetic storm. This involves a massive, unchecked release of catecholamines (epinephrine and norepinephrine) and corticosteroids (cortisol) mediated by the hypothalamic-pituitary-adrenal (HPA) axis. This neuroendocrine surge profoundly alters the body's homeostatic balance, manifesting notably in two distinct physiological domains: the immune system and the metabolic system.[4]

In the immune domain, the stress response triggers rapid demargination of neutrophils from the vascular endothelium and the release of bone marrow reserves, leading to peripheral leukocytosis. Previous research has established leukocytosis as a marker of trauma.[5] However, the utility of total white blood cell (WBC) count as a granular severity indicator is debated. While some studies suggest a correlation with outcome, others propose that the immune response may be biphasic or subject to saturation.[6] Specifically, the phenomenon of leukocyte trafficking—where neutrophils migrate out of the periphery and into injured tissues—may complicate the interpretation of peripheral blood counts in the most severe cases. Simultaneously, the metabolic axis undergoes significant dysregulation. The brain, an obligate glucose consumer, signals for increased energy availability during stress.[7] The hyperadrenergic state stimulates hepatic glycogenolysis and gluconeogenesis while concurrently inducing peripheral insulin resistance via inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). This condition, stress-induced hyperglycemia (SIH), is distinct from diabetic hyperglycemia and is theoretically proportional to the magnitude of the injury.[8] Unlike the immune response, which is limited by the finite pool of marginated leukocytes, the metabolic response is driven by hepatic output, which may possess a higher physiological ceiling, potentially allowing glucose to scale linearly with extreme physiological stress.[9]

Despite the existence of literature linking these biomarkers to TBI outcomes independently, there remains a paucity of data rigorously comparing their discriminatory capacity side-by-side within the specific demographic context of a developing nation's tertiary trauma system. Furthermore, existing studies often group moderate and severe TBI together, obscuring potential nuances in how the body responds to escalating degrees of neurotrauma.[10] The novelty of this study lies in its specific investigation into the saturation point of these biological markers. We posit the divergent trajectory hypothesis: that while the immune response (WBC) reaches a saturation plateau in moderate injuries, the metabolic response (Glucose) maintains linearity into severe stages. Therefore, this study aimed to determine the relationship between admission WBC count and blood glucose levels with the degree of head injury at Dr. Hasan Sadikin General Hospital (RSHS), Bandung, specifically seeking to identify which marker offers superior stratification value for the most critically injured patients.

2. Methods

This research utilized a retrospective analytical observational design to investigate the correlation between biological markers and clinical severity in TBI patients. The study was conducted at the Department of Neurosurgery, Dr. Hasan Sadikin General Hospital (RSHS), Bandung, West Java, Indonesia. As a Level I trauma referral center, RSHS manages a high volume of complex neurotrauma cases, providing a robust dataset for analysis. The data collection period spanned one full calendar year, from January 1st, 2021, to December 31st, 2021. The target population comprised all patients admitted to the RSHS

Emergency Unit with a primary diagnosis of head injury. To ensure a representative cohort within the timeframe, a stratified sampling technique was employed based on the Isaac and Michael table formula with an error tolerance of 5%, resulting in a final sample size of 238 patients.

Inclusion and exclusion criteria strict eligibility criteria were applied to isolate the effects of neurotrauma from chronic systemic conditions and pre-hospital confounders: Inclusion: Patients aged 18 to 60 years (to exclude pediatric physiological variations and geriatric immunosenescence); confirmed diagnosis of traumatic brain injury; documented Glasgow Coma Scale (GCS) score upon admission; and documented laboratory values for WBC count and random blood glucose (RBG) obtained at the time of admission. Exclusion: Patients were excluded if they had pre-existing systemic diseases capable of altering inflammatory or metabolic baselines (Diabetes Mellitus, Chronic Renal Failure, Hypertension). Additionally, patients with clinical evidence of alcohol intoxication or drug influence were excluded to ensure the GCS score accurately reflected structural brain injury. Crucially, patients with major extracranial polytrauma were excluded to ensure biomarkers reflected neuro-centric stress. Operational definitions the degree of head injury was stratified by the admission Glasgow Coma Scale (GCS) score: Mild TBI (GCS 13–15), Moderate TBI (GCS 9–12), and Severe TBI (GCS 3–8). Leukocytosis was defined as a WBC count > 10.00 x $10^3/\mu L$. Hyperglycemia was defined as a random blood glucose (RBG) level > 200 mg/dL.

Data were tabulated and analyzed using standard statistical software. Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to characterize the demographic profile. Due to the non-parametric nature of the data (skewed distribution of biological markers in severe trauma), the Kruskal-Wallis test was utilized to determine overall differences across the three severity groups. Post-hoc pairwise comparisons were conducted using the Mann-Whitney test to identify specific differences between groups (Mild vs. Moderate, Mild vs. Severe, Moderate vs. Severe). A p-value of < 0.05 was considered statistically significant.

3. Results

Figure 1 provides a comprehensive visual synthesis of the baseline demographic and clinical characteristics of the 238 patients included in this retrospective observational study, conducted at Dr. Hasan Sadikin General Hospital (RSHS) in Bandung, Indonesia, throughout 2021. This figure serves not merely as a recounting of population statistics but as foundational evidence of the study's external validity, demonstrating that the cohort is highly representative of the typical epidemiological patterns observed in trauma centers across developing nations. The data presented here contextualizes the subsequent biomarker analyses within a specific, high-risk population subset. The upper-left panel displays the gender distribution, revealing a pronounced male predominance. Nearly 83% (n=195) of the admitted TBI patients were male, outnumbering female patients by a factor of nearly five to one. This stark disparity is consistent with global trauma literature and is sociologically attributed to higher rates of participation in high-risk activities among males in this region, particularly occupational hazards and motorcycle-based transportation, which are the primary mechanisms of injury in Southeast Asia. This finding underscores that neurotrauma in this setting is largely a disease burden carried by the male population. Adjacent to the gender distribution is the age stratification analysis. The data indicate that TBI is overwhelmingly a pathology of the young and economically productive demographic. Over two-thirds of the cohort (68.9%, n=164) fell within the 18 to 40-year age bracket. This concentration of injuries among young adults highlights the profound socioeconomic impact of TBI, as it disproportionately affects individuals at the peak of their workforce participation and family responsibilities. The smaller proportion of patients aged 41–60 years (31.1%) suggests a gradual tapering of risk exposure with age

in this inclusion criteria range. The lower panel of Figure 1 illustrates the distribution of injury severity based on admission Glasgow Coma Scale (GCS) scores, visualizing the classic trauma pyramid. The majority of cases were classified as Mild TBI (GCS 13–15), accounting for 70.2% (n=167) of presentations. This is followed by Moderate TBI (GCS 9–12) at 20.6% (n=49), and finally, the most critically injured subset, Severe TBI (GCS 3–8), comprising 9.2% (n=22) of the cohort. This distribution is critical for interpreting the subsequent biomarker data; it confirms that the study captured the full spectrum of neurotrauma presentations, from the walking wounded to the comatose patient requiring immediate neurocritical intervention. The relative rarity of severe cases, while statistically challenging, makes the distinct physiological signals observed in that subgroup even more salient. the cohort reflects recognized patterns of age, sex, and severity distribution, it provides confidence that the metabolic and inflammatory signatures derived from this patient group are applicable to the broader context of acute neurotrauma management in similar tertiary care settings.

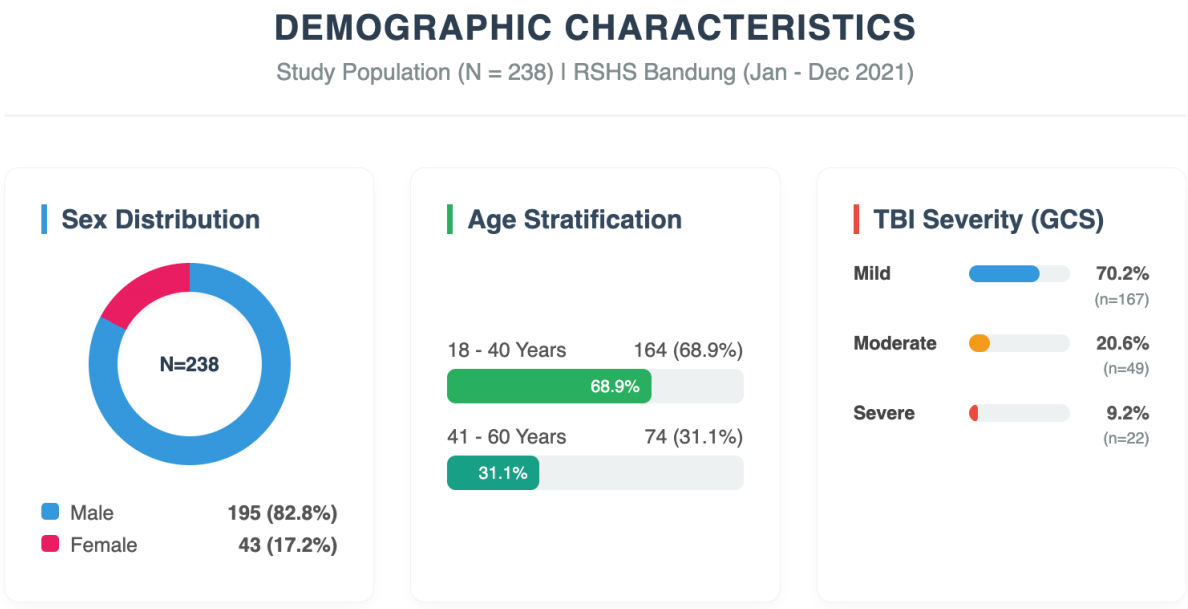


Figure 1. Demographic and clinical characteristics.

Figure 2 presents a detailed graphical analysis of the acute inflammatory response to traumatic brain injury, as quantified by admission white blood cell (WBC) counts across stratifications of the Glasgow Coma Scale (GCS). This figure is pivotal to the study's hypothesis, as it visually demonstrates the phenomenon of physiological saturation within the immune axis of the sympathetic stress response. The data reveals a clear progressive trend in raw numbers, yet a critical flattening of statistical significance at the higher end of injury severity.

The bar chart illustrates stepwise increases in mean WBC counts as the clinical condition worsens. Patients with Mild TBI presented with a substantial mean elevation of 17.50 x 10^3/µL. This escalates to 18.81 x 10^3/µL in Moderate TBI, and peaks at 21.33 x 10^3/µL in Severe TBI. The prevalence data embedded below each bar further emphasizes the ubiquity of this

response: clinical leukocytosis (defined as >10,000/μL) was present in nearly 90% of mild cases and reached a striking 100% penetrance in the severe group. This confirms that virtually every patient sustaining significant neurotrauma manifests an immediate systemic inflammatory reaction.

However, the most scientifically significant element of Figure 2 is the schematic statistical bridge connecting the Moderate and Severe groups. While the statistical analysis confirmed significant differences between Mild and Moderate groups ($p<0.05$) and Mild and Severe groups ($p<0.05$), the comparison between Moderate and Severe TBI yielded a non-significant result ($p > 0.05$). This indicates a plateau effect. Despite the clinical condition advancing from a comatose state (Moderate) to a critical state (Severe), the peripheral immune marker failed to show a corresponding statistically significant escalation.

Pathophysiologically, this plateau is interpreted as the saturation of the acute demargination response. The initial surge in WBCs following trauma is driven by the massive release of catecholamines (epinephrine), which causes the immediate detachment of the marginated pool of neutrophils from the vascular endothelium. This pool is finite. The data suggest that the physiological stress of a Moderate TBI is sufficient to near-maximally deplete this marginated reservoir. Consequently, even with increased injury severity, there are few remaining marginated cells to recruit into the circulation in the acute phase. Further increases would require bone marrow release driven by cortisol, a slower process that may not be fully reflected in admission blood draws.

Furthermore, the error bars, representing standard deviation, widen notably in the severe group (± 8.92), indicating increased heterogeneity in the immune response among the most critically ill. Some patients may exhibit extreme leukemoid reactions, while others may show blunted responses due to leukocyte trafficking—the migration of activated white blood cells out of the periphery and into injured tissues like the brain and lungs.

In conclusion, Figure 2 characterizes total WBC count as a sensitive threshold marker that reliably identifies the presence of significant trauma but lacks the granularity to discriminate between moderate and critical injury grades due to biological saturation of the demargination mechanism.

Figure 3 provides a striking visual contrast to the immune kinetics observed in the previous figure, detailing the admission blood glucose profile across TBI severity groups. The bar chart demonstrates a sharp, progressive rise in mean blood glucose levels. Mild TBI patients presented with a mean glucose of 133.11 mg/dL, already elevated above typical fasting norms. This rises significantly to 158.35 mg/dL in the Moderate group. The most dramatic escalation occurs in the Severe TBI group, where the mean glucose spikes to 226.14 mg/dL. The prevalence data highlight the clinical urgency of this finding: while only 5.7% of mild cases exhibited hyperglycemia (>200 mg/dL), this exploded to over 57% in the severe cohort, identifying admission hyperglycemia as a hallmark feature of critical neurotrauma. Crucially, the schematic statistical connector overlaying the Moderate and Severe bars indicates a statistically significant difference ($p < 0.05$). Unlike WBC counts, which plateaued, blood glucose levels continue to rise significantly even as injury severity progresses from moderate to severe. This indicates that the metabolic response is highly sensitive to the magnitude of the insult and does not saturate within the physiological ranges observed. This linearity is explained by the pathophysiology of Stress-Induced Hyperglycemia (SIH), which involves a synergistic uncoupling of glucose production and disposal. On the supply side, the catecholamine storm drives hepatic gluconeogenesis and glycogenolysis with a near-infinite capacity in the acute setting; the more severe the brain injury, the more intense the sympathetic drive, and the greater the hepatic glucose output.

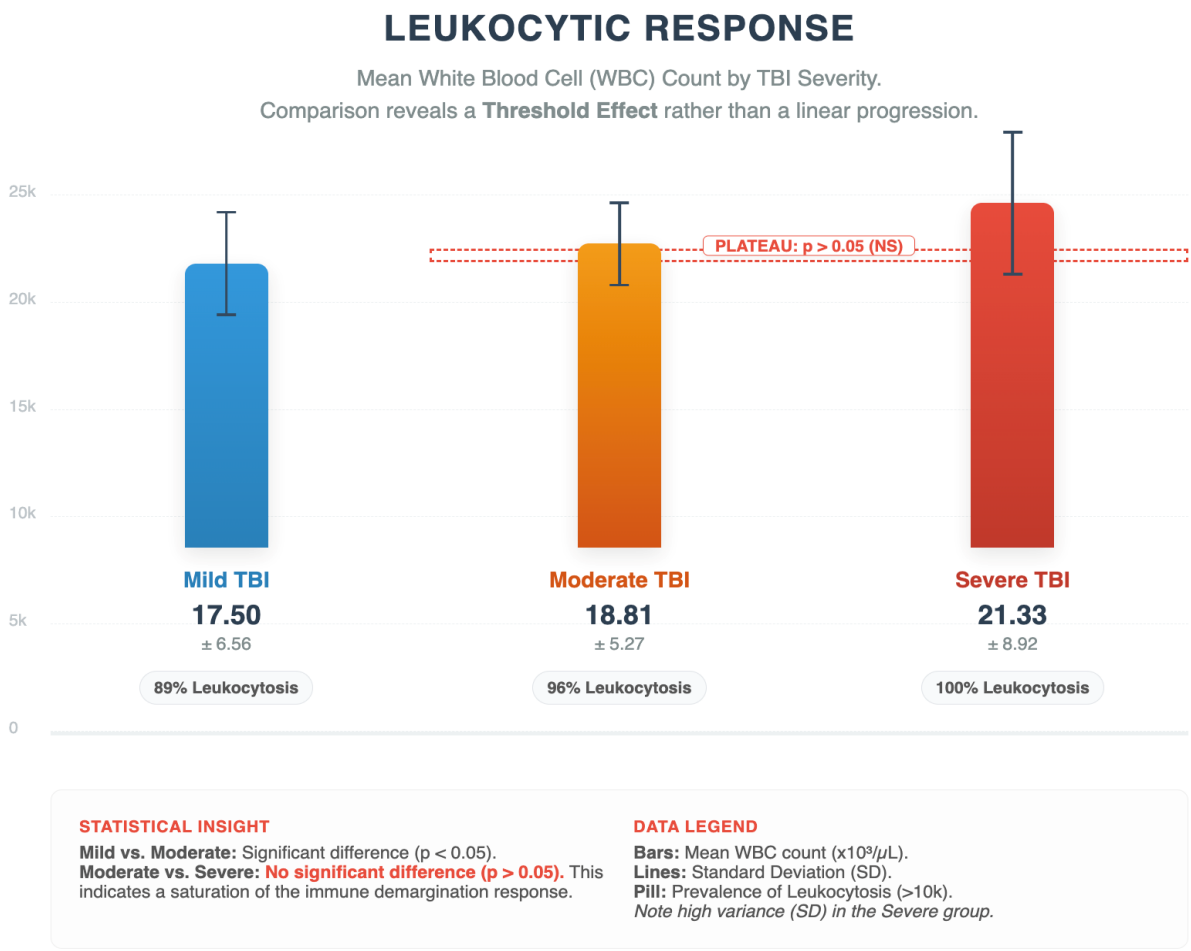


Figure 2. Leukocytic (WBC) response.

Simultaneously, on the demand side, the release of pro-inflammatory cytokines induces acute peripheral insulin resistance, preventing glucose uptake by tissues. This perfect storm of overproduction and underutilization results in a skyrocketing glucose level that proportionally reflects the total neuro-endocrine stress burden. Another critical feature of Figure 3 is the massive error bar on the Severe group, representing a standard deviation of ±105.61 mg/dL. This indicates extreme variance among critically ill patients. While the mean is high, the distribution includes patients with extreme hyperglycemic excursions (potentially >400 mg/dL). This subset of patients is at the highest risk for secondary metabolic brain injury, as severe hyperglycemia drives anaerobic metabolism, lactic acidosis, and subsequent blood-brain barrier disruption and cerebral edema. Figure 3 establishes admission blood glucose as a graded marker of TBI severity. Its ability to linearly track physiological stress without saturation makes it an indispensable tool for identifying patients in the throes of a severe neuro-metabolic crisis.

Figure 4 serves as the conceptual apex of the study, crystallizing the complex statistical and physiological data presented in previous figures into a unified schematic model. It offers a direct, side-by-side comparison of the diagnostic utility of leukocytosis (the immune response) versus hyperglycemia (the metabolic response). The left panel, dedicated to leukocytosis (WBC), features a schematic trend line that rises steeply initially but flattens out into a distinct plateau as severity increases.

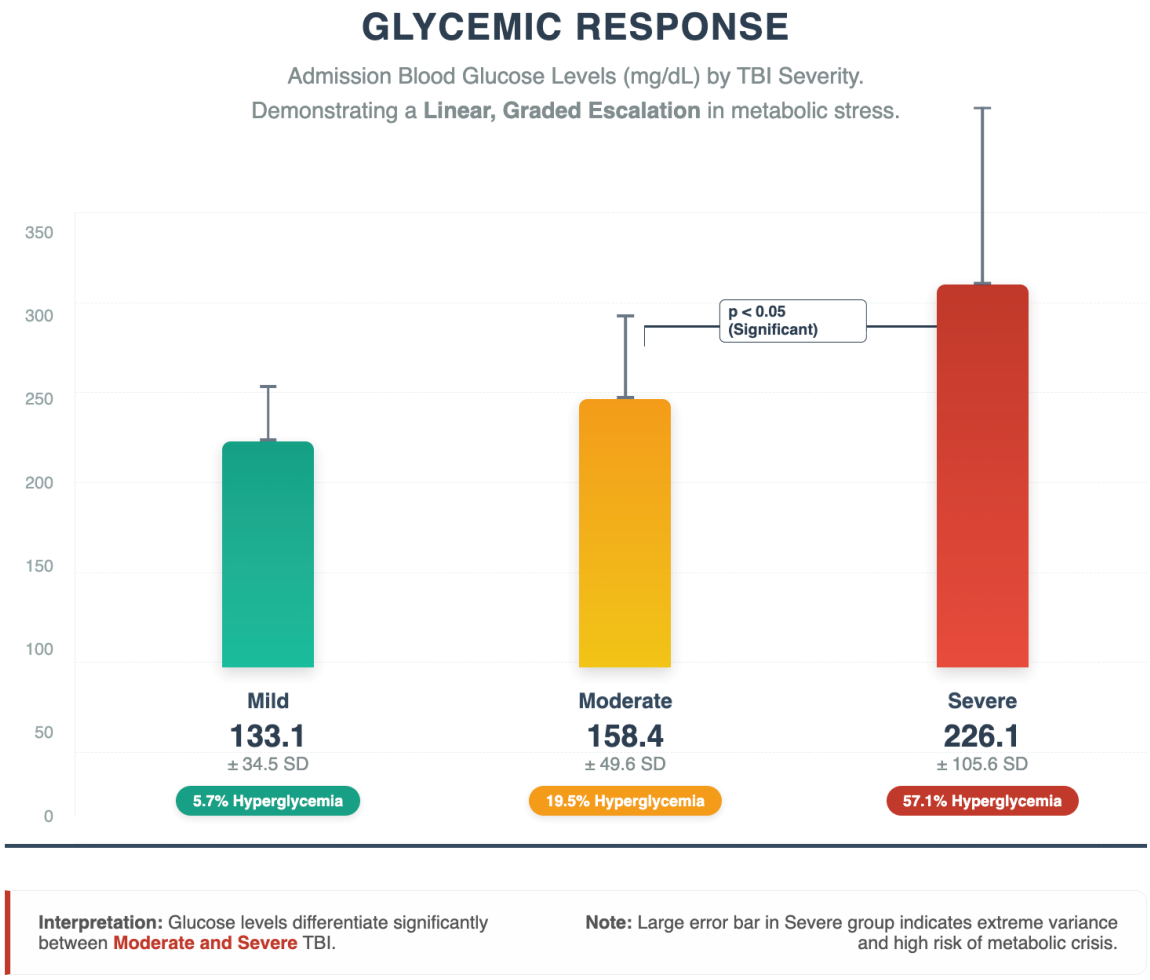


Figure 3. Glycemic response.

This visualization corresponds to the statistical findings where WBC counts successfully differentiated mild from significant injury but failed to distinguish moderate from severe cases. The status badges below confirm this pattern: a green distinguishes for mild vs. moderate, but a red fails for moderate vs. severe. The accompanying text categorizes WBC as a threshold/saturating marker. Its clinical role is defined as a binary alarm—highly effective at confirming the presence of a systemic inflammatory insult, but limited by the biological ceiling of neutrophil demargination, rendering it incapable of grading the highest extremes of injury intensity. Conversely, the right panel, illustrating hyperglycemia (Glucose), shows a trend line with a continuous, uninterrupted upward trajectory, indicating a linear or graded escalation relative to severity. This reflects the study's finding that glucose levels continue to rise significantly across all GCS stratifications. The status badges for Glucose are universally positive, showing green distinguishes for both mild vs. moderate and the critical moderate vs. severe comparison. This marker is categorized as graded/linear. Its clinical role is described as a severity barometer, capable of providing a proportional readout of the neuro-endocrine stress burden. The text emphasizes that high levels, specifically those exceeding the 200mg/dL threshold, are specific red flags for severe injury phenotypes. The

bottom section unites these concepts, stating that while leukocytosis is useful for confirming injury, admission hyperglycemia provides superior granularity for stratifying the most critically injured patients. This figure ultimately highlights the importance of looking beyond individual lab values and understanding the underlying physiological kinetics. It suggests that in the acute phase, the metabolic axis provides a more reliable window into the magnitude of the sympathetic storm than the immune axis, which is constrained by finite cellular reservoirs. Figure 4 advocates for a nuanced, multi-marker approach where glucose is prioritized for acute risk stratification in high-acuity neurotrauma presentations.

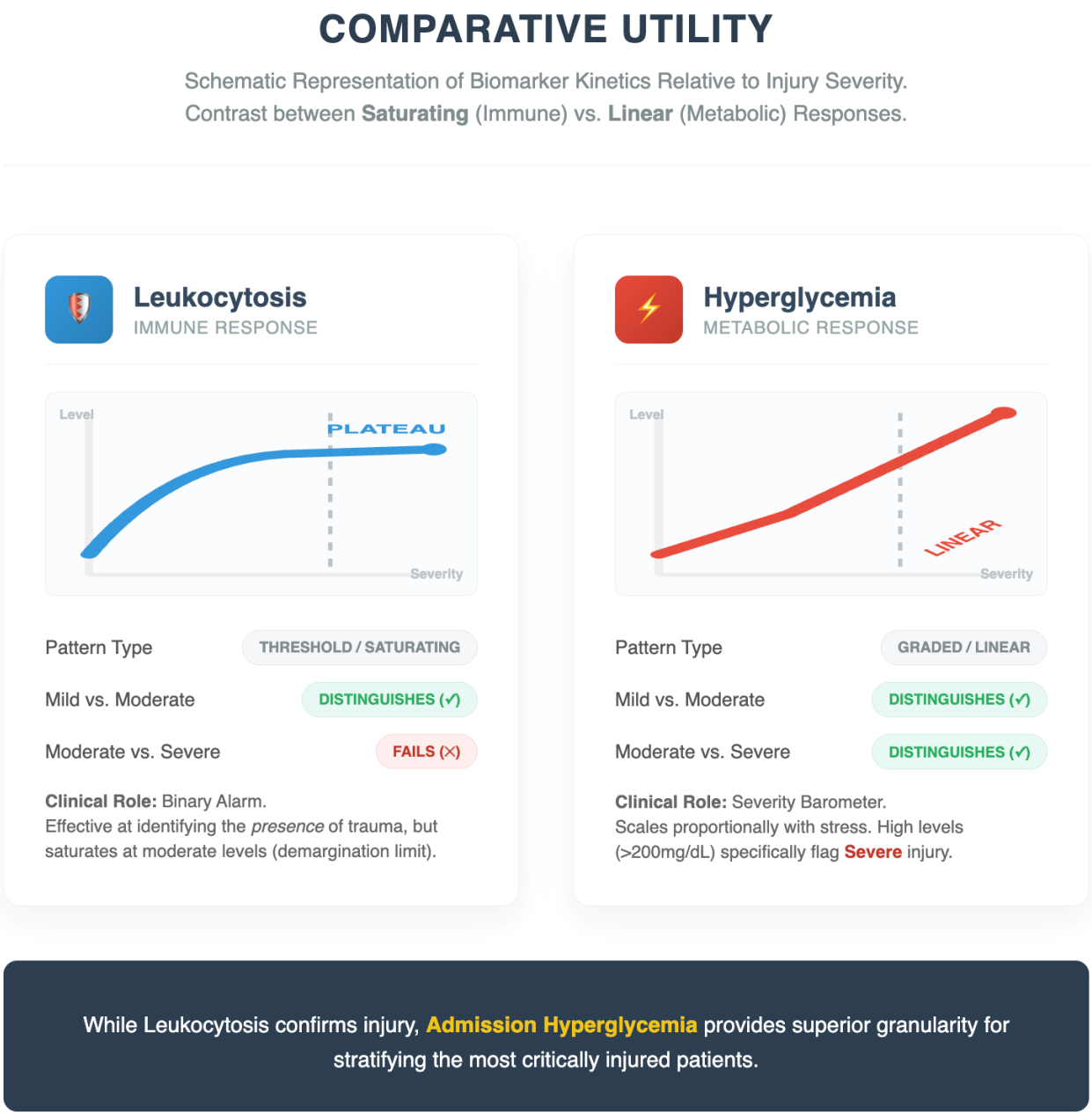


Figure 4. Comparative utility.

4. Discussion

The cardinal finding of this study is the divergence in the prognostic utility of WBC count versus blood glucose levels in the acute phase of neurotrauma.[11] While both markers serve as indicators of the systemic stress response, they exhibit distinct kinetic profiles relative to injury severity. Specifically, we identified a leukocytic plateau where inflammatory markers saturate at moderate injury levels, contrasted with a glycemic linearity where metabolic markers continue to scale proportionally with increasing severity. This divergence necessitates a detailed exploration of the underlying pathophysiological mechanisms governing the neuro-immune-metabolic axis. Figure 5 serves as the definitive mechanistic synthesis of this study, translating the statistical correlations observed in the clinical data into a coherent pathophysiological framework. It provides a schematic roadmap detailing how a singular, catastrophic event—Traumatic brain injury (TBI)—initiates a unified neuro-endocrine cascade that subsequently bifurcates into two distinct physiological trajectories with divergently kinetic profiles. This figure visually articulates the divergence hypothesis, explaining why the immune response (leukocytosis) saturates at moderate injury levels while the metabolic response (hyperglycemia) continues to scale linearly with increasing trauma severity. The schematic begins at the apex with the central trigger: the primary insult of TBI itself. The immediate consequence of significant brain injury is the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, precipitating a sympathetic storm.[12] This is characterized by a massive, systemic efflux of catecholamines (primarily epinephrine and norepinephrine) and corticosteroids (cortisol). This neuroadrenergic surge is the common progenitor for both the immune and metabolic alterations observed in the acute phase, acting as a generalized alarm signal to the body to mobilize resources for survival. Below this central trigger, the pathway forks, visualizing the uncoupling phenomenon. The left pathway details the Immune Axis, leading to the observed leukocytic plateau. The first step in this cascade is driven by the acute epinephrine surge. Under normal physiological conditions, approximately half of the body's neutrophils are marginated, loosely adherent to the vascular endothelium in the lung and spleen, rather than circulating freely.[13] The sudden spike in epinephrine stimulates beta-adrenergic receptors, causing these cells to instantly detach—a process known as demargination. This results in the rapid doubling or tripling of the circulating white blood cell (WBC) count typically seen in trauma admission bays.[14] However, Figure 5 illustrates why this response is finite, leading to the plateau kinetic. The marginated pool is a limited reservoir. The data suggest that the physiological stress of a moderate TBI is sufficient to deplete this pool near-maximally.[15] Once depleted, immediate further increases in peripheral WBC count must rely on bone marrow release of immature cells, a slower process driven by cortisol that lags behind the acute sympathetic phase. Furthermore, the figure introduces the critical concept of tissue sequestration or leukocyte trafficking. In the most severe injuries, activated leukocytes do not merely circulate; they aggressively migrate out of the vasculature and infiltrate injured organs—most notably, crossing the disrupted blood-brain barrier into the cerebral parenchyma to mediate secondary neuroinflammation.[16] In severe TBI, the rate at which leukocytes leave the blood to enter damaged tissue may equal or exceed their rate of entry into the circulation, causing the peripheral count to level off even as total-body inflammation skyrockets. Consequently, Figure 5 categorizes the immune response as a threshold marker—excellent for detecting the presence of a significant insult, but biologically constrained from grading its upper extremes. Conversely, the right pathway details the metabolic axis, explaining the observed glycemic linearity. Unlike the immune response, the mechanisms driving stress-induced hyperglycemia lack an easily reachable biological ceiling in the acute setting. The first step involves hepatic overdrive. The injured brain acts as an obligate glucose sink,

signaling for massive energy substrate release. The catecholamine storm, augmented by glucagon, stimulates hepatic gluconeogenesis (creating new glucose from non-carbohydrate precursors) and glycogenolysis (breaking down stored glycogen) at rates directly proportional to the intensity of the sympathetic drive. In severe TBI, this drive is maximal. Crucially, this surge in supply is met with a pathological blockade in demand, labeled as step two: insulin resistance. The acute inflammatory response releases a storm of cytokines, including TNF-α and IL-6, which interfere with insulin signaling pathways in skeletal muscle and adipose tissue, preventing peripheral glucose uptake. Step three, Uncoupling, describes the resulting metabolic crisis: a synergistic combination of unchecked hepatic glucose production and paralyzed peripheral glucose clearance. This creates a stepwise, linear escalation in blood glucose levels that mirrors the severity of the neurological insult without saturation. Therefore, Figure 5 categorizes the metabolic response as a graded marker, acting as a highly sensitive barometer of total neuro-endocrine stress. The schematic converges at the bottom to illustrate the clinical consequence of this divergence. It emphasizes that the linear scaling of glucose is not merely a biomarker phenomenon but a pathogenic driver. The severe hyperglycemia (>200 mg/dL) observed in the most critical patients fuels anaerobic metabolism within the ischemic injured brain. This results in the excessive accumulation of lactic acid. The ensuing localized acidosis is highly neurotoxic; it further degrades tight junction proteins in the blood-brain barrier, exacerbates vasogenic and cytotoxic cerebral edema, and raises intracranial pressure. Ultimately, Figure 5 provides the mechanistic rationale for why admission glucose, due to its linear kinetics and direct contribution to secondary injury cascades, is a superior tool for stratifying the highest risk neurotrauma patients compared to the saturable WBC count.[17]

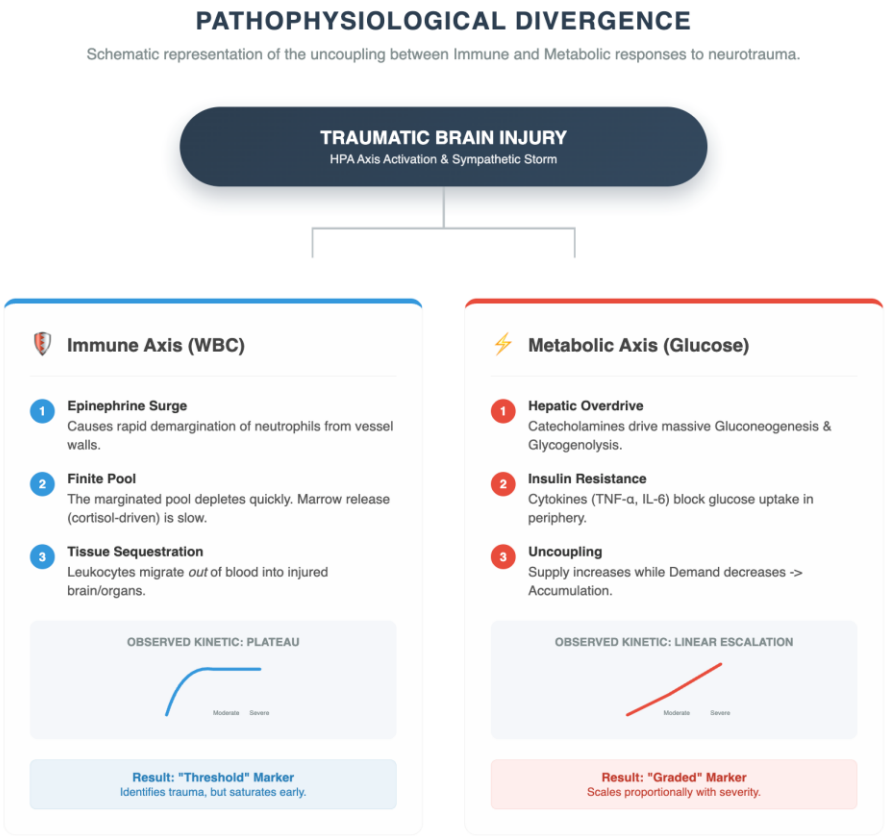


Figure 5. Pathophysiological divergence.

The observation that WBC counts do not significantly differ between Moderate and Severe TBI groups suggests a biological ceiling to the acute demargination response. The initial leukocytosis seen in trauma is primarily driven by the sympathetic surge. Upon impact, the massive release of epinephrine stimulates Beta-2 adrenergic receptors on the vascular endothelium. This causes the immediate detachment of the marginated pool of neutrophils—a reserve of white blood cells loosely adherent to vessel walls. This process is rapid and results in a near-instantaneous doubling of the circulating WBC count. However, the marginated pool is finite. Our data suggests that the physiological stress associated with moderate TBI (GCS 9-12) is sufficient to induce near-maximal demargination. Consequently, when injury severity escalates to severe TBI (GCS 3-8), there are few remaining marginated neutrophils to recruit. The secondary phase of leukocytosis, which involves the release of immature neutrophils (bands) from the bone marrow driven by cortisol and granulocyte-colony stimulating factor (G-CSF), is a slower process taking hours to days. In the acute admission window, this marrow release may not yet be substantial enough to create a statistical difference between moderate and severe groups.[18]

An alternative and clinically critical explanation for the WBC plateau is the phenomenon of leukocyte trafficking. In the most severe brain injuries, the systemic inflammatory response syndrome (SIRS) is not merely characterized by high circulating cell counts but by the activation and migration of these cells into tissues. Up-regulation of adhesion molecules (ICAM-1, VCAM-1) on the endothelium of the brain, lungs, and liver facilitates the transmigration of leukocytes out of the vasculature and into the parenchyma. In severe TBI, the breakdown of the blood-brain barrier (BBB) allows massive infiltration of neutrophils into the cerebral tissue, where they release matrix metalloproteinases (MMP-9) and reactive oxygen species (ROS), contributing to secondary injury. It is theoretically plausible that in our severe group, the peripheral WBC count plateaued because a significant fraction of the mobilized leukocytes had already sequestered into the injured brain and other end-organs.[19] Thus, the peripheral blood count underestimates the true magnitude of the total body inflammatory state in the most critical patients.

In stark contrast to the saturable immune response, blood glucose levels exhibited a robust linear correlation with decreasing GCS. The mechanism of stress-induced hyperglycemia (SIH) appears to lack the ceiling effect observed in demargination. This linearity is driven by the synergistic uncoupling of glucose production and disposal. The liver functions as a near-infinite glucose engine during acute stress. The magnitude of hepatic glucose output is directly proportional to the intensity of the sympathetic drive (epinephrine) and the HPA axis activation (glucagon and cortisol). In severe TBI, the catecholamine storm is significantly more intense than in moderate TBI, driving hepatic gluconeogenesis to extreme levels to fuel the perceived energy demand of the injured brain. Concurrently, the release of pro-inflammatory cytokines, particularly TNF-alpha and IL-6, disrupts insulin signaling pathways in skeletal muscle and adipose tissue. This induces a state of acute, transient insulin resistance. The severity of this resistance correlates with the total inflammatory burden. As injury severity worsens, the liver produces more glucose (driven by catecholamines) while the peripheral tissues consume less (driven by insulin resistance). This uncoupling creates a stepwise escalation in blood glucose that mirrors the GCS score, making it a superior discriminator for severe injury. The presence of hyperglycemia in Severe TBI (Mean: 226.14 mg/dL) is not merely a bystander biomarker but a potential driver of secondary neuropathology. Under normal physiological conditions, the brain relies on aerobic glycolysis. However, in the acute phase of severe neurotrauma, Cerebral Perfusion Pressure (CPP) is often compromised, and mitochondrial function is impaired, forcing the brain to shift toward anaerobic metabolism.

In the presence of abundant substrate (hyperglycemia), this anaerobic shift leads to the excessive accumulation of lactic acid (lactate) within the cerebral parenchyma. This phenomenon, known as the lactate-edema spiral, creates a localized acidosis that is highly neurotoxic. Acidosis further disrupts the tight junctions of the BBB, increases membrane permeability, and exacerbates cytotoxic edema. This swelling raises Intracranial Pressure (ICP), further reducing perfusion and perpetuating the cycle. Our finding that 57.14% of severe patients presented with significant hyperglycemia identifies this subgroup as being at extreme risk for this metabolic cascade. The practical application of these findings lies in early risk stratification. The leukocytic plateau implies that while a high WBC count confirms the presence of trauma, it should not be relied upon to grade severity in the upper extremes. Conversely, the glycemic gradient suggests that admission glucose is a quantitative barometer of neuro-metabolic stress.[20]

Clinicians should interpret admission hyperglycemia >200 mg/dL as an alarming sign of severe physiological derangement, indicative of a patient whose neuro-endocrine compensatory mechanisms are operating at maximum capacity. However, treatment strategies must be nuanced. While hyperglycemia drives acidosis, aggressive insulin therapy to achieve normoglycemia (80-110 mg/dL) carries the risk of iatrogenic hypoglycemia, which is equally devastating to the metabolic-starved injured brain. Therefore, the goal should be the avoidance of severe hyperglycemia rather than strict normalization, using the glucose level primarily as a severity indicator to guide the urgency of neuro-critical care interventions.

5. Conclusion

This study elucidates the distinct metabolic and inflammatory signatures of neurotrauma, revealing that the body's immune and metabolic systems respond to injury with different kinetic profiles. Leukocytosis is a highly sensitive indicator for the presence of significant trauma but lacks the specificity to distinguish between moderate and severe TBI, likely due to a saturation of the demargination response and leukocyte trafficking. Admission blood glucose levels correlate linearly with GCS scores, offering superior discriminatory power across all severity levels. The magnitude of hyperglycemia directly reflects the intensity of the neuro-endocrine stress response. A specific profile of admission hyperglycemia (>200 mg/dL) combined with plateaued leukocytosis is strongly indicative of Severe TBI. These findings advocate for the prioritization of glycemic status as a nuanced prognostic tool, distinguishing the most critical patients who require vigilant monitoring to prevent secondary metabolic brain injury.

6. References

1. Mukherjee S, Sivakumar G, Goodden J, Tyagi A, Chumas PD. Prognostic value of leucocytosis in paediatric traumatic brain injury. Neurosurgery. 2019; 66(Suppl 1): 310–43.
2. Vijian K, Teo EG, Kanesen D, Wong ASH. Initial leucocytosis and other significant indicators of poor outcome in severe traumatic brain injury: an observational study. Chin Neurosurg J. 2020; 6(1).
3. Nagata K, Suto Y, Cognetti J, Browne KD, Kumasaka K, Johnson VE, et al. Early low-anticoagulant desulfated heparin after traumatic brain injury: Reduced brain edema and leukocyte mobilization is associated with improved water maze learning ability weeks after injury. J Trauma Acute Care Surg. 2018; 84(5): 727–35.
4. Hubbard WB, Banerjee M, Vekaria H, Prakhya KS, Joshi S, Wang QJ, et al. Differential leukocyte and platelet profiles in distinct models of traumatic brain injury. Cells. 2021; 10(3): 500.
5. Lopez AJ, ElSaadani M, Culkin MC, Jacovides CL, Georges AP, Song H, et al. Persistent blunting of penumbral leukocyte mobilization

by beta blockade administered for two weeks after traumatic brain injury. J Surg Res. 2022; 280: 196–203.
6. Shi M, Mi L, Li F, Li Y, Zhou Y, Chen F, et al. Fluvoxamine confers neuroprotection via inhibiting infiltration of peripheral leukocytes and M1 polarization of microglia/macrophages in a mouse model of traumatic brain injury. J Neurotrauma. 2022; 39(17–18): 1240–61.
7. Wang R, Xu J, He M. Blood leukocyte-based clusters in patients with traumatic brain injury. Front Immunol. 2024; 15: 1504668.
8. Culkin MC, Bele P, Georges AP, Santos P, Niziolek G, Kaplan LJ, et al. Dose-dependent tranexamic acid blunting of penumbral leukocyte mobilization and blood-brain barrier permeability following traumatic brain injury: an in vivo Murine study. Neurocrit Care. 2024; 41(2): 469–78.
9. Saikia BB, Bhowmick S, Malat A, Preetha Rani MR, Thaha A, Abdul-Muneer PM. ICAM-1 deletion using CRISPR/Cas9 protects the brain from traumatic brain injury-induced inflammatory leukocyte adhesion and transmigration cascades by attenuating the paxillin/FAK-dependent Rho GTPase pathway. J Neurosci. 2024; 44(11): e1742232024.
10. Tsai Y-C, Wu S-C, Hsieh T-M, Liu H-T, Huang C-Y, Chou S-E, et al. Association of stress-induced hyperglycemia and diabetic hyperglycemia with mortality in patients with traumatic brain injury: Analysis of a propensity score-matched population. Int J Environ Res Public Health. 2020; 17(12): 4266.
11. Matovu P, Kirya M, Galukande M, Kiryabwire J, Mukisa J, Ocen W, et al. Hyperglycemia in severe traumatic brain injury patients and its association with thirty-day mortality: a prospective observational cohort study in Uganda. PeerJ. 2021; 9(e10589): e10589.
12. Abu el-Kheir MM, Attia SM, Ahmed ME-S, Ahmed AAA. Hyperglycemia as prognostic factor in pediatric traumatic brain injury in emergency hospital Mansoura University. Egypt J Hosp Med. 2022; 87(1): 2139–46.
13. Parenrengi MA, Suryaningtyas W, Destiansyah RA. Hyperglycemia as a predictor of outcome in paediatric severe traumatic Brain Injury patients underwent surgery: a single center experience from eastern Indonesia from 2017-2022. Wiad Lek. 2023; 76(6): 1342–6.
14. Tseng C-C, Huang Y-C, Tu P-H, Yip PK, Chang T-W, Lee C-C, et al. Impact of diabetic hyperglycemia on clinical outcomes in patients with diabetes mellitus following traumatic brain injury. Turk Neurosurg. 2023; 33(4): 548–55.
15. Zhou M, Du M, Tang R, Liu H-Y, Gao Z, Wang Y, et al. Central GLP-1 resistance induced by severe traumatic brain injury was associated with persistent hyperglycemia in humans. Neuroendocrinology. 2023; 113(6): 625–40.
16. Ali R, Memon KN, Soomro F, Shah IA. Role of hyperglycemia on outcomes of traumatic brain injury among patients admitted in tertiary level hospital. Pak BioMed J. 2024; 20–4.
17. Madhusoodanan G, Praseetha. Intraoperative hyperglycemia in patients undergoing emergency craniotomy for traumatic brain injury. Int J Sci Res (Raipur). 2024; 13(6): 8–10.
18. Melo JRT, de Brito Tischer CM, Rodrigues FPA, Giordano JC, de Oliveira LFG, Bodra SM, et al. Accuracy of acute hyperglycemia as a biomarker of severe brain damage in children with traumatic brain injury. Childs Nerv Syst. 2024; 40(9): 2781–7.
19. Yin X, Xia Y, Shen L, Zhu X, Lu L, Meng X. Postoperative hyperglycemia in patients with traumatic brain injury: development of a

prediction model. Arch Med Sci. 2025; 21(1): 131–7.

20. Cui S, Xu D, Xiong H, Zhuang Y, He Z. Stress-induced hyperglycemia and mortality in patients with traumatic brain injury without preexisting diabetes: a meta-analysis. Biomol Biomed. 2025; 25(2): 291–303.