e-ISSN: 2722-3558

Sriwijaya Journal of Surgery

[SJS]

https://sriwijayasurgery.com

Elevated Serum Lactate as an Indicator of Neurometabolic Derangement and its Independent Correlation with Clinical Outcomes in Traumatic Brain Injury

Satya Agusmansyah[1*], Anugerah Onie Widhiatmo[2], Theodorus[3]

[1]Department of General Surgery, Dr. Mohammad Hoesin General Hospital/Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

[2]Department of Neurosurgery, Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[3]Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

ARTICLE INFO

Keywords:
Biomarker
Neurometabolism
Prognosis
Serum lactate
Traumatic brain injury

***Corresponding author:**
Satya Agusmansyah

E-mail address:
rio.army13@gmail.com

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

https://doi.org/10.37275/sjs.v8i2.137

A B S T R A C T

Introduction: Traumatic brain injury (TBI) is a primary cause of global death and disability, where early and accurate prognostication is critical but remains a clinical challenge. Serum lactate is emerging as a biomarker of the complex neurometabolic derangement following TBI, extending beyond its traditional role as a marker of hypoxia. This study aimed to determine if serum lactate is an independent predictor of outcomes in TBI patients. **Methods:** We conducted a prospective, single-center observational study of 33 TBI patients at Dr. Mohammad Hoesin General Hospital. Serial venous serum lactate levels were measured at admission, 24, and 48 hours. The primary outcome was unfavorable functional status (Glasgow Outcome Scale [GOS] 1-3) at hospital discharge. Multivariate logistic regression was used to assess lactate as an independent predictor of unfavorable outcome, controlling for age and initial Glasgow Coma Scale (GCS) score. Survival was analyzed using Kaplan-Meier curves and a Cox proportional hazards model. **Results:** The cohort (N=33) was predominantly male (63.6%) with a mean age of 37.91 years. Higher admission lactate was strongly associated with worse GOS categories (p=0.002). After adjusting for age and initial GCS score, admission serum lactate remained a significant independent predictor of unfavorable outcome at discharge. For every 1 mmol/L increase in lactate, the odds of an unfavorable outcome increased by over twofold (Adjusted Odds Ratio: 2.15; 95% CI: 1.12-4.13; p=0.021). Similarly, lactate was an independent predictor of in-hospital mortality in the Cox proportional hazards model (Adjusted Hazard Ratio: 1.78; 95% CI: 1.05-3.01; p=0.032). **Conclusion:** Elevated admission serum lactate is a strong, independent predictor of unfavorable in-hospital functional outcome and mortality in TBI patients. As a readily available biomarker, it reflects the severity of the underlying neurometabolic crisis and provides crucial prognostic information beyond initial clinical and demographic assessments, aiding in early risk stratification.

1. Introduction

Traumatic brain injury (TBI) represents a silent epidemic and a formidable public health challenge, constituting a leading cause of mortality and profound long-term disability across all age groups globally.[1] The sheer scale of its impact is staggering, with estimates suggesting over 10 million cases annually that result in either hospitalization or death. Data from 2019 indicated approximately 27.16 million new cases of TBI worldwide, underscoring its pervasive threat.[2] The devastating consequences of TBI extend far beyond the immediate clinical crisis, imposing an immense socioeconomic burden through exorbitant healthcare costs, the necessity for prolonged and intensive rehabilitation, and the tragic loss of human potential and productivity for countless survivors and

their families. Within the acute setting, TBI is a quintessential neurosurgical emergency, where the rapid and precise application of medical and surgical interventions is paramount to mitigating damage, preserving neurological function, and ultimately, saving lives.[3] The pathophysiology of TBI is characterized by a biphasic cascade of injury. The primary injury is the direct, instantaneous, and irreversible mechanical damage inflicted upon the brain at the moment of impact. This includes parenchymal contusions, lacerations, tissue shearing leading to diffuse axonal injury (DAI), and intracranial hemorrhages. While this initial event sets the stage, the majority of the subsequent neurological devastation is driven by the secondary injury cascade. This is a complex, delayed, and potentially preventable series of deleterious biochemical, metabolic, and inflammatory processes that are triggered by the primary insult and evolve over the subsequent hours, days, and even weeks. This cascade is a vortex of interconnected pathologies, including glutamate-mediated excitotoxicity, neuroinflammation, the formation of cytotoxic and vasogenic cerebral edema, disruptions to the blood-brain barrier, cerebral ischemia and hypoxia, and mitochondrial dysfunction.[4] These processes converge on a final common pathway: a state of profound cerebral metabolic crisis, which elevates intracranial pressure (ICP), further compromises cerebral perfusion, and promotes widespread neuronal and glial cell death, thereby dictating the patient's ultimate functional outcome.

The complex and heterogeneous nature of TBI makes early and accurate prognostication a significant clinical challenge.[5] For decades, clinicians have relied on foundational tools like the Glasgow Coma Scale (GCS) and structural neuroimaging via Computed Tomography (CT) to gauge injury severity and predict patient trajectories. While indispensable, the limitations of these tools are well-recognized. The GCS, a cornerstone of neurological assessment, can be confounded by clinically necessary interventions like sedation and intubation, or by patient-specific factors such as intoxication or pre-existing conditions.[6] Cranial CT scans, while excellent at identifying macroscopic structural lesions like hematomas and fractures, often fail to capture the full extent of microscopic or metabolic damage, particularly in cases of DAI, where the initial scan can appear deceptively normal. This gap between structural appearance and functional reality has fueled a sustained search for objective, quantitative biological markers (biomarkers) that can provide a more precise and real-time assessment of the severity of brain injury and its metabolic consequences.[7] The ideal biomarker should be readily accessible, provide rapid results, and accurately reflect the underlying injury processes. Serum biomarkers, obtainable through minimally invasive blood draws, are particularly attractive for their practicality in the acute setting compared to the more invasive analysis of cerebrospinal fluid (CSF). While research into structural protein markers released from damaged brain cells—such as S100-beta, Glial Fibrillary Acidic Protein (GFAP), and Ubiquitin C-terminal Hydrolase L1 (UCH-L1)—has shown great promise, metabolic biomarkers offer a unique and complementary window into the functional state and energetic health of the brain. Among this class, serum lactate has emerged as a particularly compelling and widely available candidate.

Historically, hyperlactatemia in critically ill patients was almost exclusively interpreted as a sign of anaerobic metabolism resulting from systemic shock, hypoperfusion, or tissue hypoxia.[8] In TBI, this was often attributed to secondary insults like systemic hypotension or cerebral ischemia caused by critically elevated ICP. However, a more sophisticated, contemporary understanding of cerebral metabolism has unveiled a far more complex and nuanced role for lactate. Advanced research, including cerebral microdialysis studies, has conclusively demonstrated that significant lactate elevation can occur within the injured brain even in the presence of normal or elevated brain tissue oxygen levels—a phenomenon of "aerobic glycolysis" or a Warburg-like effect.[9] This is now understood to reflect a state of profound

neurometabolic derangement, where severe mitochondrial dysfunction prevents the efficient oxidative metabolism of pyruvate, forcing its conversion to lactate. Furthermore, the elegant metabolic coupling described by the astrocyte-neuron lactate shuttle (ANLS) hypothesis—whereby astrocytes provide lactate as a primary energy substrate for neurons—is catastrophically disrupted following severe TBI. Damaged neurons lose their ability to utilize this astrocyte-derived lactate, leading to its accumulation in the extracellular space and subsequent efflux into the systemic circulation. Despite a growing body of evidence linking hyperlactatemia to poor outcomes in TBI, its precise role as a dynamic, independent marker of this underlying metabolic crisis requires more rigorous validation.[10] Many studies have focused on single admission values without accounting for major confounders, and its interpretation as a direct reflection of cerebral metabolic distress needs to be solidified through more robust statistical modeling.

The primary aim of this study was to meticulously investigate the correlation between early, serially measured serum lactate levels and a spectrum of clinical outcomes in patients with TBI, and to determine if serum lactate serves as an independent predictor of unfavorable outcome and mortality after controlling for established prognostic factors. The novelty of this investigation lies in its rigorous, multivariate approach to validating lactate as a prognostic tool. We move beyond simple correlation by interpreting elevated lactate not merely as a surrogate for hypoxia, but as a quantifiable indicator of profound neurometabolic derangement. By employing multivariate regression models to adjust for the powerful confounding effects of initial injury severity (GCS) and age, this study seeks to isolate the independent predictive value of lactate. This approach provides a stronger pathophysiological and evidence-based rationale for its integration into routine clinical practice, framing it as a crucial biomarker that reflects the underlying cellular energy crisis in TBI.

2. Methods

This investigation was conducted as a prospective, single-center, observational cohort study. All patient recruitment and data collection took place at the Emergency Department and the integrated neurosurgical wards of Dr. Mohammad Hoesin General Hospital in Palembang, Indonesia. As a provincial tertiary referral center and the primary trauma hospital for the region, this institution manages a high volume and wide spectrum of TBI cases, providing a suitable environment for recruiting a representative cohort. The study enrollment period was conducted over four consecutive months, from May 1st, 2025, to August 31st, 2025. The single-center nature of the study, while ensuring uniformity in treatment protocols, is acknowledged as a factor that may influence the external validity of the findings. The study protocol, including all data collection instruments and consent forms, was submitted to and received full and unconditional approval from the Institutional Ethics Committee of Dr. Mohammad Hoesin General Hospital (Approval No. DP.04.03/D.XVIII.06.08/ETIK/208/2025). All procedures involving human participants were performed in strict adherence to the ethical principles outlined in the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) 2016 guidelines. Written informed consent was obtained from all participants or their legally authorized representatives prior to any study-related procedures. For patients who lacked the capacity to consent due to their altered level of consciousness, consent was obtained from their next of kin or a legally designated surrogate. The confidentiality and privacy of all patient data were rigorously maintained throughout the study; data were anonymized using unique study identifiers to prevent the disclosure of personal health information.

The study population consisted of all patients presenting to the emergency department with a suspected diagnosis of traumatic brain injury. A consecutive sampling strategy was employed, whereby all patients who met the eligibility criteria during the

study period were invited to participate to minimize selection bias. Patients were formally screened for eligibility based on the predefined inclusion and exclusion criteria. Inclusion Criteria: A definitive diagnosis of traumatic brain injury confirmed by a non-contrast cranial Computed Tomography (CT) scan performed within 48 hours of the traumatic event; Availability of complete laboratory data, including a serum lactate measurement upon admission to the emergency department; Provision of written informed consent by the patient or their legal representative. Exclusion Criteria: To isolate the effect of TBI-induced metabolic changes, the following conditions led to exclusion: A pre-existing history of a significant metabolic disease known to independently affect lactate metabolism, including but not limited to severe or uncontrolled diabetes mellitus, established liver failure (cirrhosis), or known mitochondrial disorders; The presence of concomitant severe multiple traumas, operationally defined as an Injury Severity Score (ISS) > 15 involving at least one extracranial body region (chest, abdomen, pelvis, or extremities with long bone fractures). This was done to minimize the confounding influence of hemorrhagic shock and peripheral tissue hypoperfusion on systemic lactate levels; A known history of pre-existing, significant intracranial pathology that could confound the clinical or biochemical picture, such as a primary or metastatic brain tumor, active central nervous system infection (meningitis, encephalitis), or a chronic neuroinflammatory condition.

Upon arrival at the emergency department, all enrolled patients underwent a standardized initial assessment according to Advanced Trauma Life Support (ATLS) protocols. A comprehensive neurological examination was performed, which included the determination of the Glasgow Coma Scale (GCS) score by trained emergency or neurosurgery personnel. This initial GCS score was used to classify the TBI severity as mild (GCS 14-15), moderate (GCS 9-13), or severe (GCS 3-8). Detailed demographic data (age, gender) and clinical information regarding the mechanism of injury and the time from injury to hospital arrival were meticulously recorded. The median time from injury to the first lactate measurement was 2.5 hours (Interquartile Range: 1.5 - 4.0 hours). Venous blood samples for serum lactate analysis were drawn from all patients at three standardized time points: at admission (time 0), and at 24 hours and 48 hours post-admission. The admission lactate level was used as the primary predictor variable for all analyses to assess its utility as an early prognostic marker. All samples were processed immediately in the hospital's central laboratory using a standard enzymatic colorimetric assay to determine the serum lactate concentration, expressed in mmol/L. Throughout their hospital stay, patients were managed according to standardized institutional neurotrauma care protocols, which are aligned with international guidelines from organizations like the Brain Trauma Foundation. This included therapies aimed at controlling ICP, maintaining adequate cerebral perfusion pressure, and preventing secondary systemic insults. Data on pre-hospital episodes of hypoxia or hypotension were collected but found to be inconsistently documented, and were therefore not included in the final regression models.

The primary dependent variable was the clinical outcome, assessed using the 5-point Glasgow Outcome Scale (GOS). The GOS provides a standardized measure of global functional recovery. The GOS was assessed at the time of patient discharge by a trained neurosurgery resident not directly involved in the patient's primary treatment decisions. The mean length of hospital stay for the cohort was 18.4 ± 12.1 days. It is explicitly acknowledged that this endpoint measures in-hospital outcomes and is subject to temporal bias, as it does not reflect long-term recovery, which evolves over months. For analytical purposes, the GOS was dichotomized into Favorable Outcome (GOS 4-5: Moderate Disability or Good Recovery) and Unfavorable Outcome (GOS 1-3: Dead, Persistent Vegetative State, or Severe Disability). In-hospital mortality (GOS 1) was also analyzed as a distinct endpoint for survival analysis.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software. Descriptive statistics were used to summarize cohort characteristics. The distribution of continuous data was assessed for normality using the One-Sample Kolmogorov-Smirnov test. As serum lactate levels were not normally distributed ($p < 0.05$), non-parametric tests were used for univariate comparisons. The Kruskal-Wallis H test was used to compare median lactate levels across the five GOS categories. To address the primary aim of the study, a multivariate logistic regression model was developed to determine if serum lactate was an independent predictor of unfavorable outcome (GOS 1-3). The admission lactate level (as a continuous variable), initial GCS score (continuous), and age (continuous) were entered as independent variables. Odds Ratios (OR) with 95% confidence intervals (CI) were calculated. For survival analysis, Kaplan-Meier curves were generated to visualize survival probability for dichotomized lactate groups, compared using the Log-Rank test. To determine the independent effect of lactate on mortality, a Cox proportional hazards model was employed, using the same independent variables as the logistic regression model. Hazard Ratios (HR) with 95% CIs were calculated. A two-tailed p-value of < 0.05 was considered statistically significant for all tests.

3. Results

Figure 1 provides a comprehensive and synthesized visualization of the key demographic and clinical characteristics of the 33 patients with Traumatic Brain Injury (TBI) enrolled in this prospective cohort study. The top-left quadrant serves as the anchor, prominently displaying the total cohort size of 33 patients. This fundamental metric underscores the sample from which all subsequent data are derived and is presented with clarity and emphasis to ground the reader. Adjacent to this, the top-right quadrant details the Gender Distribution within the cohort. This panel illustrates a notable male predominance, which is a well-established epidemiological feature of TBI worldwide. The data reveal that nearly two-thirds of the patients, specifically 63.6%, were male, while the remaining 36.4% were female. This distribution is consistent with higher-risk behaviors and occupational exposures typically observed in male populations, providing an important demographic context for the study's findings. Moving to the lower-left quadrant, the Age Distribution of the cohort is presented using a horizontal bar chart, which effectively stratifies the patients into three clinically relevant age categories. The data highlight that the vast majority of TBI cases occurred in the adult population, with 72.7% of patients falling within the 18 to 59-year age range. This represents the most economically productive years of life, underscoring the significant societal and personal impact of TBI. A smaller proportion of patients were in the older adult category (≥ 60 years), accounting for 18.2% of the cohort, while pediatric and adolescent patients (< 18 years) constituted the smallest group at 9.1%. This distribution provides critical insight into the age-related epidemiology of the TBI patients treated at the study center. Finally, the lower-right quadrant presents a compelling visual breakdown of the TBI Severity, as classified by the initial Glasgow Coma Scale (GCS) score upon admission. A donut chart elegantly depicts the distribution across the spectrum of injury severity. The largest segment of the cohort presented with Moderate TBI, accounting for 42.4% of all patients. This was followed closely by patients with Mild TBI, who made up 39.4% of the group. A significant minority of patients, 18.2%, presented with Severe TBI, representing the most critically injured subgroup. This distribution is crucial for interpreting the study's overall outcomes, as it demonstrates that the cohort comprised a heterogeneous mix of injury severities, making it a representative sample for investigating a prognostic biomarker like serum lactate.

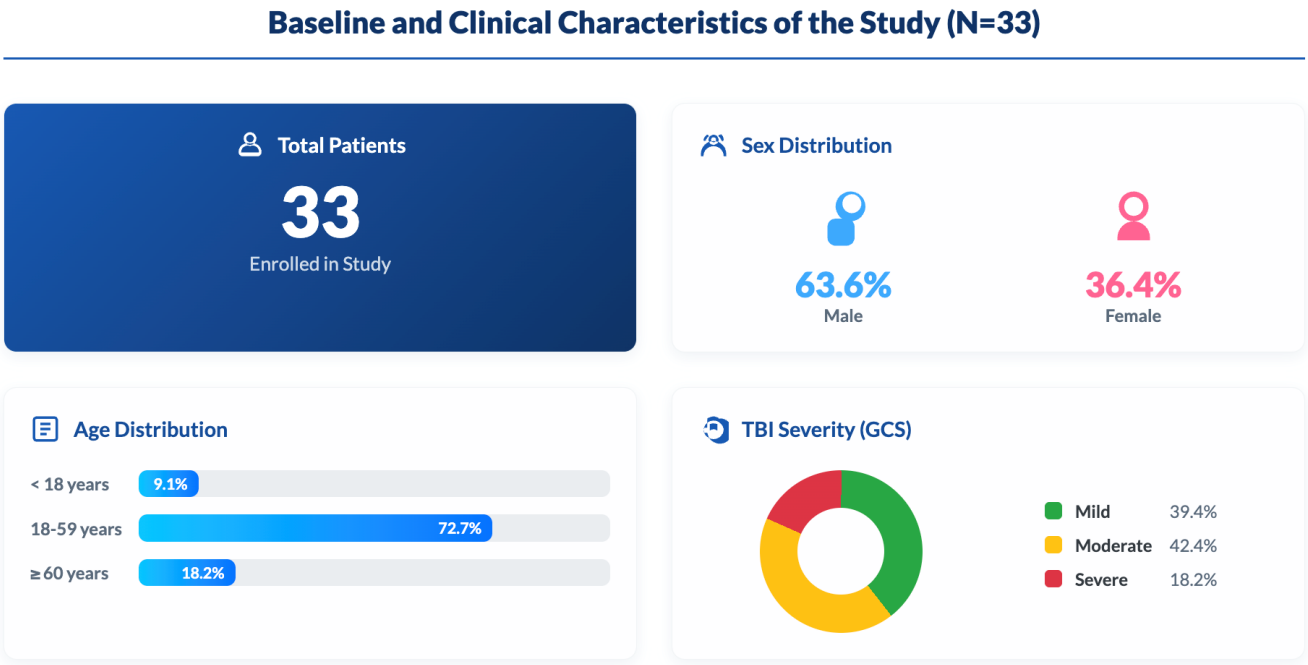

Figure 1. Baseline characteristics of the study.

Figure 2 presents a detailed and quantitative summary of the clinical outcomes observed in the cohort of 33 Traumatic Brain Injury (TBI) patients at the time of their hospital discharge. The data reveal a sobering reality: a significant majority of the patients, 60.6% (n=20), experienced an Unfavorable Outcome, defined as a GOS score of 1 to 3 (encompassing death, a persistent vegetative state, or severe disability requiring daily dependency). In contrast, a smaller proportion, 39.4% (n=13), achieved a Favorable Outcome, defined as a GOS score of 4 or 5 (indicating a return to independence with moderate disability or a good recovery). This primary stratification immediately highlights the profound burden of morbidity and mortality associated with TBI within this patient sample. The data illustrate a bimodal distribution at the extremes of the outcome scale. A substantial portion of the cohort, 24.2%, succumbed to their injuries, corresponding to a GOS score of 1 (Dead). Strikingly, an even larger group, 27.3%, survived but with the most severe form of neurological devastation, remaining in a Persistent Vegetative State (GOS 2). Together, these two worst-case scenarios account for over half of the entire cohort, underscoring the life-threatening and life-altering nature of the injuries sustained. The intermediate and favorable outcomes comprised the remainder of the group. A smaller segment, 9.1%, was discharged with a Severe Disability (GOS 3), conscious but dependent on others for daily care. The favorable outcomes were divided between patients who achieved a state of Moderate Disability (GOS 4), representing 15.2% of the cohort, and those who made a Good Recovery (GOS 5), representing 24.2%. Figure 2 delivers a powerful narrative about the clinical sequelae of TBI in this study. It demonstrates that while a return to a good quality of life is possible, the risk of death or profound, lifelong disability is substantial.

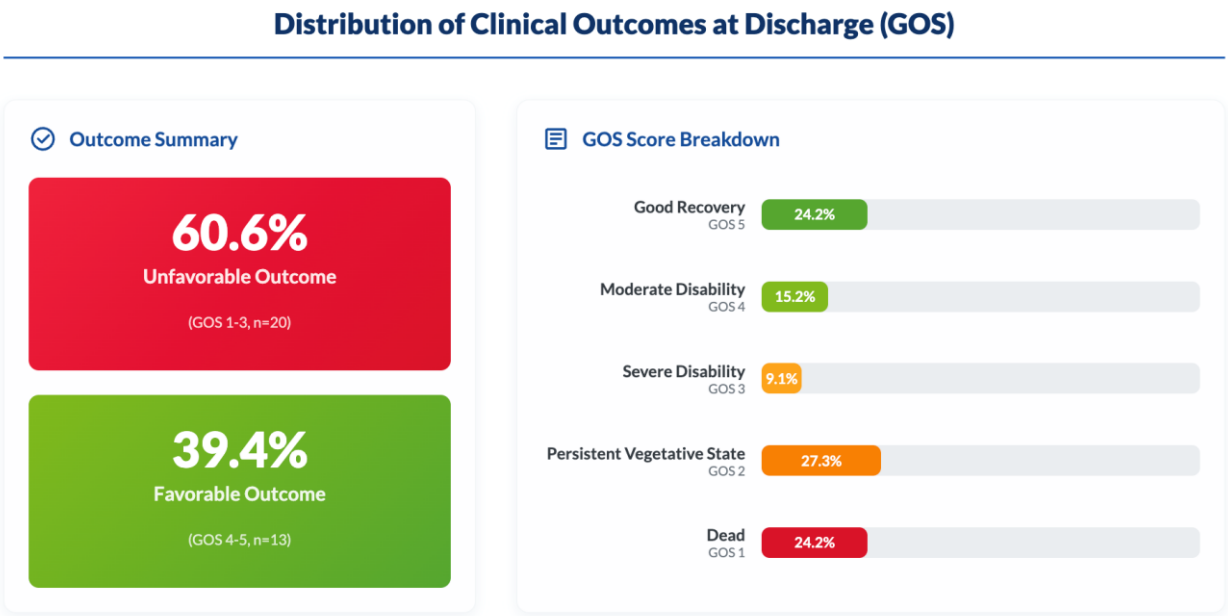

Figure 2. Clinical outcomes at discharge.

Figure 3 provides a compelling visual synthesis of the primary bivariate findings of the study, graphically illustrating the powerful and statistically significant relationship between admission serum lactate levels and the subsequent clinical course of patients with Traumatic Brain Injury (TBI). Figure 3 presents a schematic box plot that elegantly visualizes the core finding from the Kruskal-Wallis test ($p = 0.002$). This plot clearly demonstrates a strong, monotonic dose-response relationship between lactate concentration and the severity of the functional outcome at discharge. Each box represents the interquartile range (IQR) of lactate levels for a specific Glasgow Outcome Scale (GOS) category, with the bold internal line marking the median. The visualization strikingly reveals a progressive upward shift in the distribution of lactate levels as the clinical outcome worsens. Patients who achieved a "Good Recovery" (GOS 5) exhibited the lowest median lactate levels, clustered near the physiological baseline. As the outcome deteriorates through "Moderate Disability," "Severe Disability," and "Vegetative State," the corresponding box plots ascend systematically, indicating a clear trend of rising lactate concentrations. This culminates in the "Dead" (GOS 1) category, where the lactate levels are substantially elevated and occupy a distribution markedly distinct from the other groups. This graphical representation powerfully conveys that higher lactate is not just associated with a binary poor outcome, but that its concentration tracks closely with the entire spectrum of neurological recovery, reinforcing its role as a sensitive barometer of the underlying pathophysiological injury severity. Figure 3 transitions from functional outcome to the stark reality of mortality, presenting the results of the Log-Rank test ($p = 0.034$). This survival plot powerfully illustrates the impact of admission hyperlactatemia on the probability of survival over time. The two curves represent the cumulative survival of patients stratified into "Low Lactate" and "High Lactate" groups. The green line, representing the low-lactate group, remains high and stable, indicating a very high probability of survival throughout the observation period, with only a minimal, single drop. In dramatic contrast, the red line, representing the high-lactate group, exhibits a steep and rapid decline, particularly within the first 10

to 15 days following injury. This precipitous drop signifies a significantly increased risk of early mortality for patients presenting with elevated lactate. The clear and immediate separation between the two curves provides unambiguous visual evidence that a high admission lactate level is a potent and ominous predictor of death. Figure 3 offer a comprehensive and cohesive narrative. They demonstrate that serum lactate is not only a marker of mortality but also a graded indicator of morbidity across the full range of TBI outcomes. The robust statistical significance noted for both analyses, combined with the clear visual trends, solidifies the conclusion that serum lactate serves as a critical biomarker in the early assessment of TBI patients.

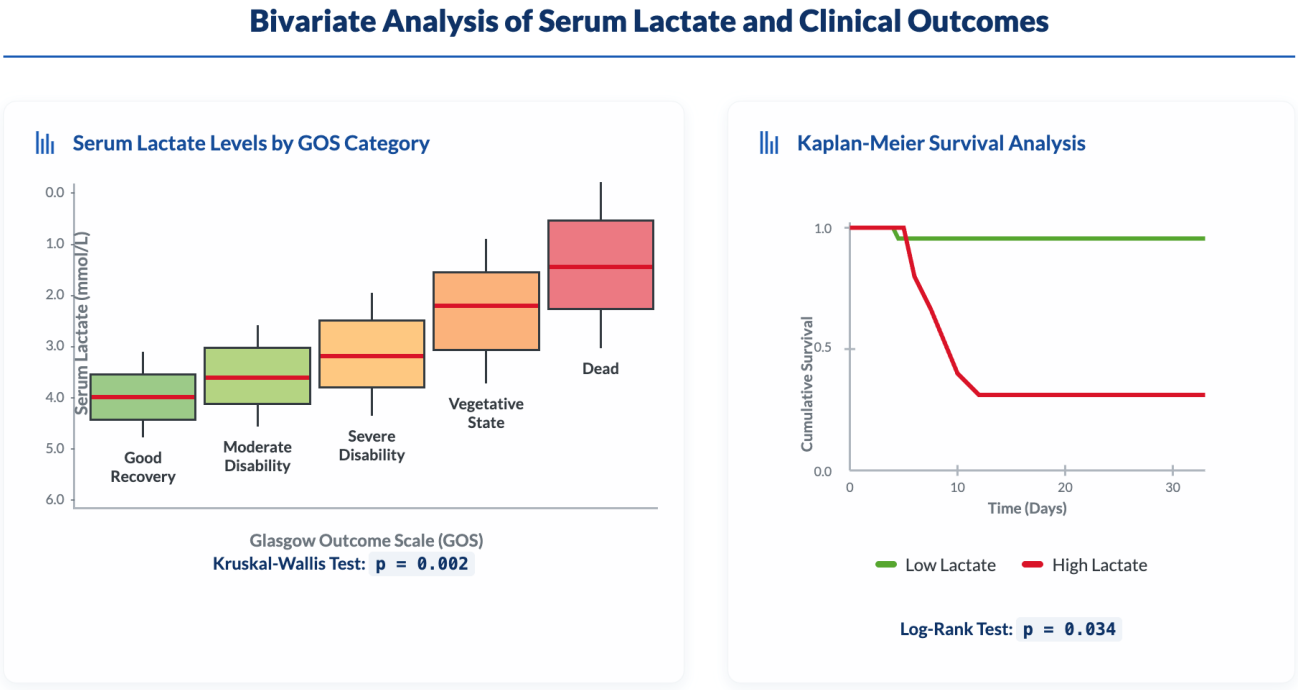

Figure 3. Bivariate analysis of lactate and outcome.

Figure 4 presents the central and most critical finding of this investigation: the results of the multivariate logistic regression analysis. This statistical model was designed to isolate the independent predictive value of key clinical variables on the likelihood of an unfavorable outcome at discharge (defined as a Glasgow Outcome Scale [GOS] score of 1-3). The analysis reveals two statistically significant independent predictors. The Initial Glasgow Coma Scale (GCS) score, a well-established prognostic marker, is confirmed to be a strong protective factor. For every one-point increase in a patient's GCS score at admission, the odds of having an unfavorable outcome decreased by 32% (aOR: 0.68; 95% CI: 0.51 - 0.91; p = 0.009). This is visually represented by the green point and its confidence interval, which lie entirely to the left of the line of no effect. Crucially, Admission Lactate emerges as a powerful and statistically significant risk factor, independent of the initial GCS and age. As depicted by the red point and its confidence interval lying entirely to the right of the line of no effect, higher lactate levels are independently associated with worse outcomes. The model quantifies this risk precisely: for every 1 mmol/L increase in a

patient's admission serum lactate, the odds of experiencing an unfavorable outcome increased by a substantial 115% (aOR: 2.15; 95% CI: 1.12 - 4.13; p = 0.021). In contrast, Age was not found to be a statistically significant independent predictor in this particular model (aOR: 1.02; 95% CI: 0.98 - 1.06; p = 0.345), as indicated by its grey confidence interval, which clearly crosses the line of no effect. Figure 4 provides definitive graphical evidence that even after accounting for the profound influence of the initial clinical severity of the brain injury, the admission lactate level provides significant, additional, and independent prognostic information. It moves beyond simple correlation to establish serum lactate as a key independent biomarker of risk in the acute phase of Traumatic Brain Injury.

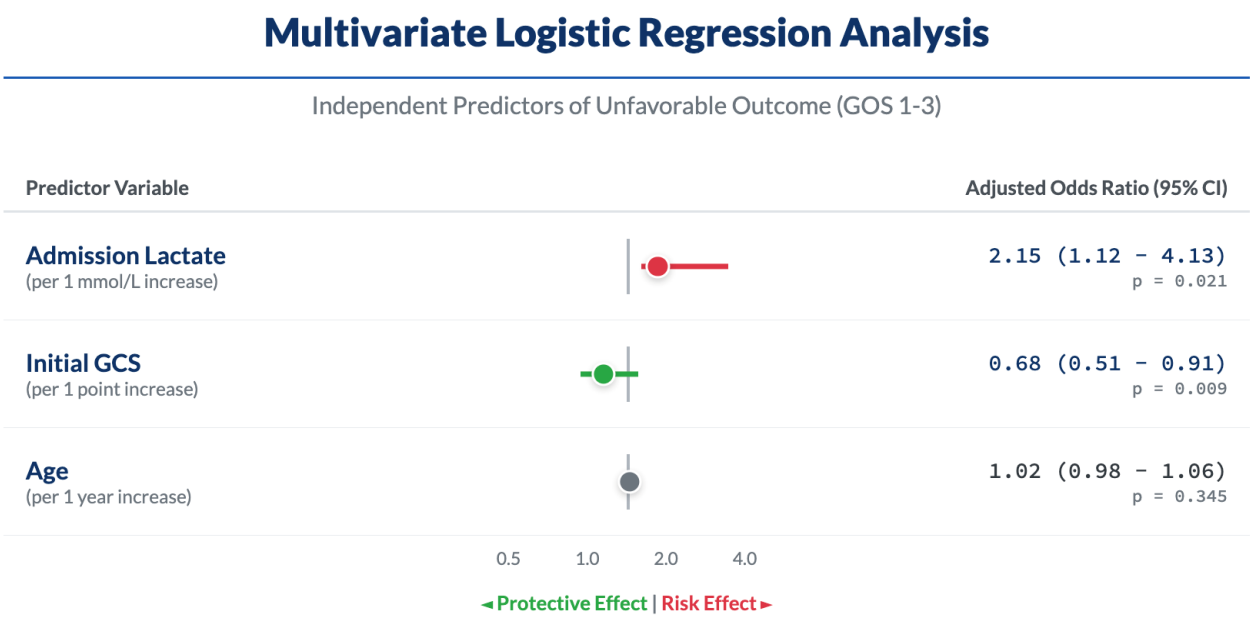

Figure 4. Multivariate analysis for predictors of unfavorable outcome.

Figure 5 provides a graphical summary of the multivariate survival analysis, which was conducted to identify the independent predictors of in-hospital mortality. This forest plot visualizes the results of the Cox proportional hazards model, a statistical method used to investigate the relationship between the survival time of patients and several predictor variables simultaneously. The plot is a standard and highly effective tool for communicating the results of survival analyses, as it clearly displays the hazard ratio for each variable, allowing for an immediate assessment of how each factor independently influences the risk of death over time. The central vertical line on the plot represents a hazard ratio (HR) of 1.0, which signifies no effect on the hazard of mortality. Each horizontal line corresponds to a predictor variable, showing its 95% confidence interval (CI), with the colored point representing the point estimate of the adjusted hazard ratio (aHR). A confidence interval that does not cross the line of no effect indicates that the predictor has a statistically significant impact on survival. An aHR greater than 1.0 signifies an increased hazard of death (a risk factor), while an aHR less than 1.0 signifies a reduced hazard (a protective factor). The analysis confirms the powerful and independent predictive capacity of both the initial clinical assessment and the admission metabolic state. The Initial Glasgow Coma Scale (GCS)

score is shown to be a significant protective factor. For every one-point increase in the admission GCS, the hazard of in-hospital mortality decreased by a substantial 28% (aHR: 0.72; 95% CI: 0.58 - 0.89; p = 0.003). This is represented by the green point and its confidence interval, which are located entirely to the left of the line of no effect. Most importantly, Admission Lactate is identified as a significant and independent risk factor for mortality. After adjusting for the influence of GCS and age, the model demonstrates that higher lactate levels are independently associated with a greater hazard of death. For every 1 mmol/L increase in admission serum lactate, the hazard of in-hospital mortality increased by 78% (aHR: 1.78; 95% CI: 1.05 - 3.01; p = 0.032). This critical finding is depicted by the red point and its confidence interval, which lie entirely to the right of the line of no effect. Consistent with the logistic regression model, Age was not found to be a statistically significant independent predictor of mortality in this specific cohort and model (aHR: 1.03; 95% CI: 0.99 - 1.07; p = 0.158), as its confidence interval crosses the line of no effect. Figure 5 provides clear, statistically adjusted evidence that the admission serum lactate level is not merely associated with mortality but is an independent predictor of a patient's risk of death during their hospital stay. It quantifies the increased hazard conferred by the state of metabolic derangement, even when the initial severity of the clinical injury is taken into account.

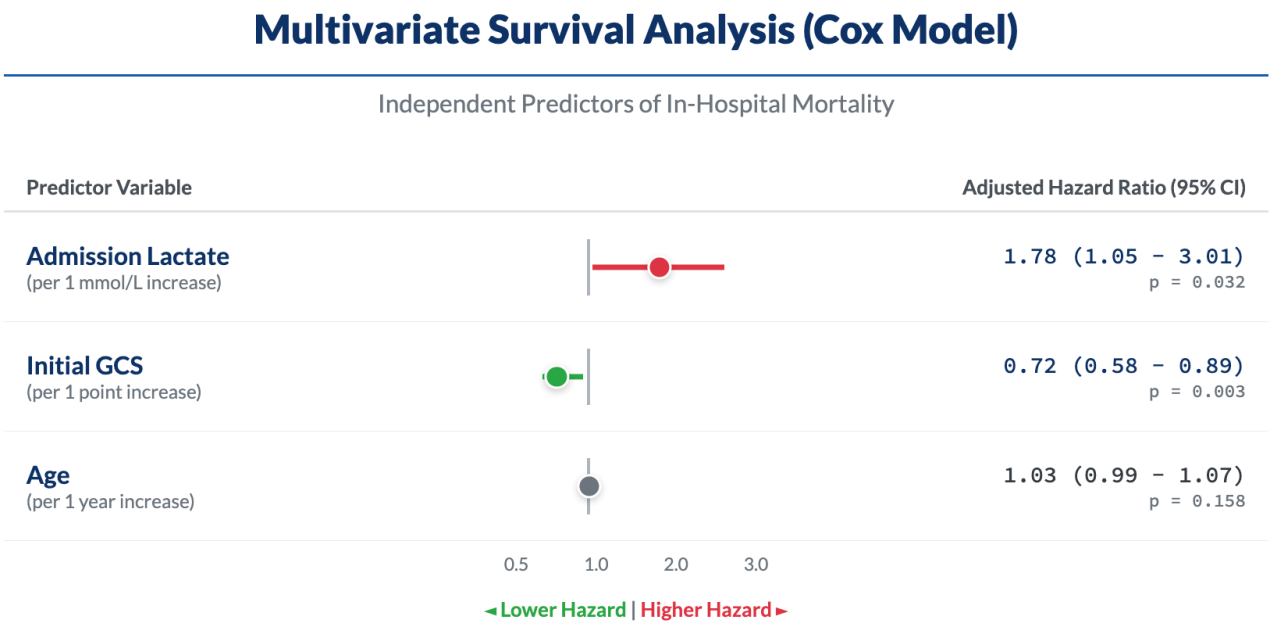

Figure 5. Multivariate survival analysis (Cox Model).

4. Discussion

This prospective study was designed to rigorously evaluate the prognostic utility of serum lactate in traumatic brain injury, moving beyond simple correlation to assess its value as an independent biomarker. The principal finding of this investigation is that elevated admission serum lactate is a strong and independent predictor of unfavorable in-hospital functional outcome and mortality in patients with TBI, even after accounting for the established prognostic influence of initial injury severity (GCS) and age.[11] Our multivariate analysis demonstrates that for each mmol/L increase in lactate, the odds of a poor outcome more than double, and the hazard of death increases

by nearly 80%. These results provide robust, statistically adjusted evidence to support the central thesis of this study: that serum lactate is not merely a bystander or a simple surrogate for injury severity, but rather a potent, quantitative biomarker reflecting the depth of a critical and often lethal cerebral neurometabolic derangement that drives secondary brain injury.[12] The interpretation of our findings hinges on understanding the complex role of lactate in cerebral energy metabolism, particularly under traumatic stress. The brain's exquisite vulnerability to any disruption in metabolic homeostasis makes lactate a uniquely sensitive reporter of its physiological state. Our results can be explained through the lens of several interconnected pathophysiological mechanisms that define the secondary injury cascade.

The cornerstone of cellular energy production is oxidative phosphorylation within the mitochondria. Following TBI, a confluence of factors conspires to cripple this vital machinery.[13] The secondary injury cascade unleashes a torrent of detrimental processes, including massive intracellular calcium influx and oxidative stress, which are profoundly toxic to mitochondria. This leads to a state of 'cytopathic hypoxia,' where cells cannot utilize oxygen effectively even when it is available, culminating in mitochondrial dysfunction. This is exacerbated by the opening of the mitochondrial permeability transition pore (mPTP), a catastrophic event that uncouples the electron transport chain, collapses the membrane potential, and halts ATP synthesis. A critical bottleneck forms at the pyruvate dehydrogenase (PDH) complex, which is inhibited by the post-traumatic biochemical environment. When pyruvate, the end-product of glycolysis, cannot enter the TCA cycle, it is shunted to lactate via lactate dehydrogenase (LDH). This reaction is crucial for regenerating NAD+, allowing the cell to continue generating at least a small amount of ATP through glycolysis.[14] Therefore, the hyperlactatemia observed in our patients with the worst outcomes is a direct biochemical manifestation of this mitochondrial failure and a quantifiable signal of profound bioenergetic collapse. The modern understanding of brain metabolism is framed by the Astrocyte-Neuron Lactate Shuttle (ANLS) hypothesis, a model of sophisticated metabolic coupling where astrocytes undergo glycolysis to produce lactate, which is then shuttled to neurons as their preferred energy fuel. In TBI, this elegant system is catastrophically disrupted. Activated astrocytes, responding to injury signals like glutamate, upregulate glucose transporters and glycolytic enzymes, ramping up glycolysis and producing even more lactate in a potentially compensatory response.[15] However, neurons suffering from excitotoxic damage and mitochondrial failure lose their ability to take up and utilize this lactate. This results in a 'supply-demand mismatch'. This decoupling leads to the accumulation of lactate in the brain's extracellular space, from where it diffuses into the systemic circulation. Consequently, high serum lactate levels signify a complete breakdown of the fundamental metabolic partnership between neurons and glia, a marker of physiological disintegration at the cellular level within the CNS. A hallmark of secondary brain injury is excitotoxicity, driven by the massive release of glutamate.[16] This leads to a sustained influx of calcium ions into neurons, activating degradative enzymes that dismantle the cell. From a metabolic standpoint, this is disastrous. Neurons must expend enormous amounts of ATP to power ion pumps in a frantic effort to restore ionic homeostasis. This surge in energy demand occurs at the very moment the cell's energy-producing capacity is compromised, forcing a maximal upregulation of glycolysis and shunting of pyruvate to lactate.[17] Therefore, the lactate level serves as a surrogate marker for the severity of ongoing excitotoxicity; the higher the lactate, the greater the excitotoxic burden and the more futile the cell's struggle, leading inevitably to cell death, reflected in the poor GOS scores of our patients. The brain's response to injury involves a robust inflammatory cascade, characterized by the activation of resident immune cells (microglia). These cells can adopt different phenotypes, including the pro-inflammatory "M1" state. M1 microglia are highly glycolytic, undergoing a metabolic

reprogramming similar to the Warburg effect, where they preferentially utilize glycolysis even in the presence of oxygen.[18] This "aerobic glycolysis" allows for the rapid production of biosynthetic intermediates needed for their inflammatory functions. The intense M1-skewed inflammatory infiltrate in the injured brain acts as a collection of localized lactate factories, further contributing to the lactate burden. The serum lactate level, therefore, can also reflect the intensity and character of the neuroinflammatory response, with higher levels suggesting a more damaging, pro-inflammatory state.

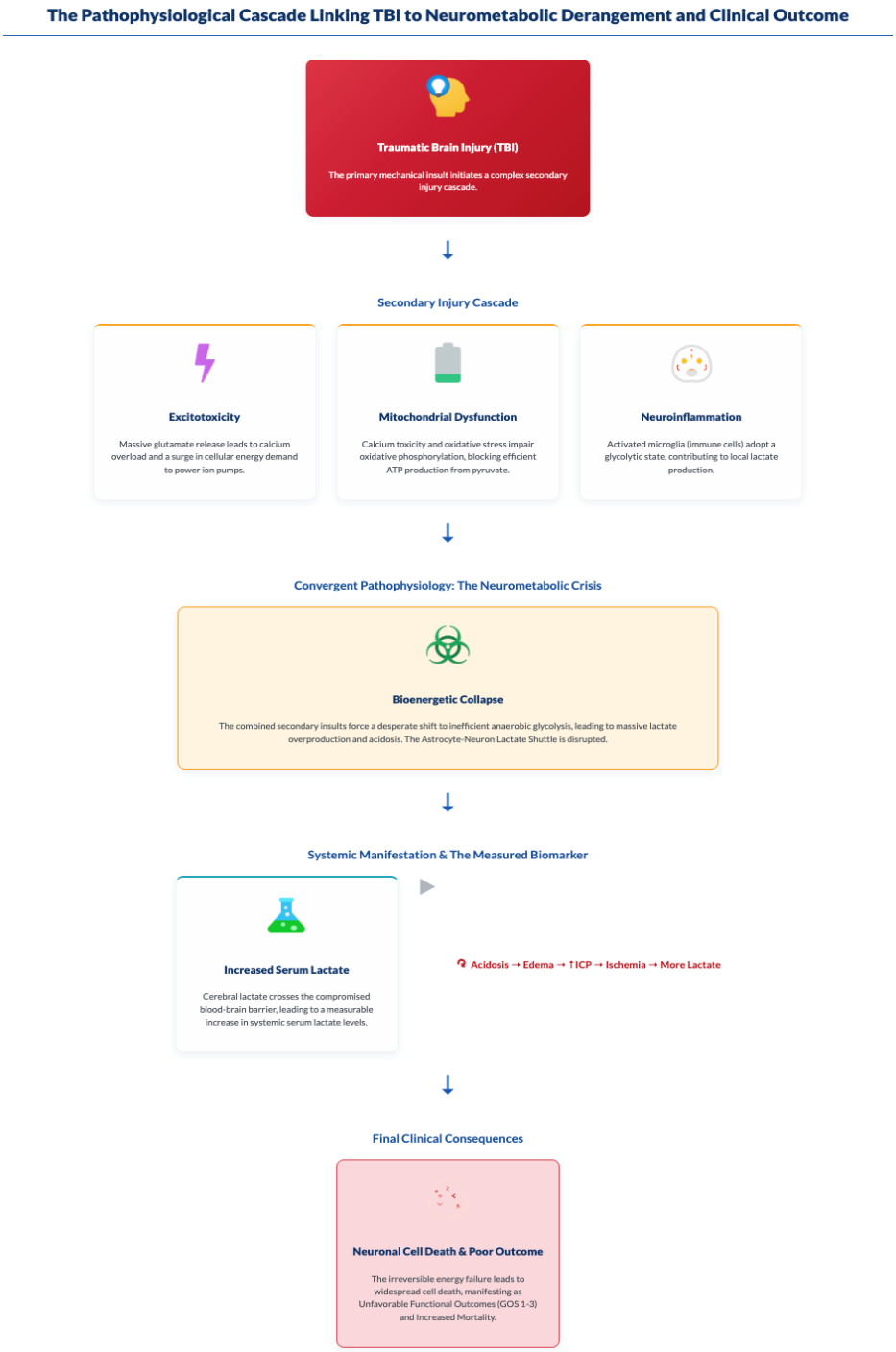

Figure 6. The pathophysiological cascade linking TBI to neurometabolic derangement and clinical outcome.

Figure 6 provides a comprehensive, multi-stage conceptual model that synthesizes the core pathophysiological processes linking the initial traumatic brain injury (TBI) to the ultimate clinical outcomes observed in this study, highlighting the central role of serum lactate as a key systemic biomarker. Stage 1: Traumatic Brain Injury (TBI) The entire pathological sequence is initiated by the primary mechanical insult to the brain. This event, depicted by a schematic of a dysfunctional and over-stimulated brain, encompasses the direct physical forces—acceleration, deceleration, and rotational stresses—that cause immediate structural damage to neurons, glia, and the cerebrovasculature. This primary impact results in parenchymal contusions, lacerations, and diffuse axonal injury. While this initial damage is largely irreversible, its most critical consequence is the immediate activation of a complex and multifaceted secondary injury cascade, a series of delayed and potentially preventable pathological processes that amplify the initial damage and ultimately determine the patient's long-term fate. Stage 2: The Secondary Injury Cascade This stage illustrates the three convergent pillars of secondary injury that drive the subsequent metabolic collapse. These processes do not occur in isolation but are deeply interconnected, creating a feed-forward cycle of damage. First, excitotoxicity, represented by a lightning bolt, signifies the massive, uncontrolled release of the neurotransmitter glutamate from damaged neurons. This leads to a catastrophic influx of calcium ions into surrounding neurons, creating an enormous and immediate demand for cellular energy (ATP) to power the ion pumps that frantically attempt to restore ionic homeostasis. Concurrently, this intracellular calcium overload, along with the associated oxidative stress from free radical production, triggers profound mitochondrial dysfunction, powerfully depicted by a low-battery icon. This cripples the cell’s primary energy-generating machinery, impairing the process of oxidative phosphorylation and preventing the efficient conversion of pyruvate to ATP. Finally, the brain mounts an intense neuroinflammatory response, represented by an icon of activated, amoeboid-shaped microglial cells within the brain's silhouette. These activated resident immune cells undergo a significant metabolic reprogramming, shifting to a highly glycolytic state that contributes to the local metabolic burden and lactate production while releasing cytotoxic inflammatory mediators. Stage 3: The Neurometabolic Crisis The convergent pressures of a surging energy demand (from excitotoxicity) and a collapsing energy supply (from mitochondrial failure) culminate in a state of profound bioenergetic collapse. This metabolic crisis, symbolized by a biohazard icon, forces a desperate and inefficient cellular shift to anaerobic glycolysis as the sole means of generating ATP. This results in the massive overproduction of lactate and the generation of intracellular acidosis. A key consequence of this state is the complete disruption of the elegant Astrocyte-Neuron Lactate Shuttle. In this pathological state, damaged neurons are unable to utilize the lactate provided by the now hyper-metabolic astrocytes, leading to its accumulation in the brain's interstitial fluid. Stage 4: Systemic Manifestation and the Measured Biomarker The lactate that accumulates within the brain’s extracellular space readily crosses the now-compromised blood-brain barrier, leading to a measurable increase in systemic serum lactate levels, as depicted by the test tube icon. This elevated serum lactate is therefore not merely a sign of peripheral hypoxia or shock, but a direct, quantifiable echo of the profound metabolic crisis occurring within the cranium. Furthermore, this process becomes dangerously self-amplifying; the resulting lactic acidosis worsens cerebral edema, which in turn increases intracranial pressure (ICP), reduces cerebral blood flow (leading to ischemia), and drives even more anaerobic glycolysis and lactate production. This devastating vicious cycle, illustrated in the schematic, accelerates the brain's descent into irreversible injury. Stage 5: Final Clinical Consequences The final, inexorable outcome of this irreversible energy failure and toxic intracellular environment is widespread neuronal cell death, powerfully visualized by a

schematic of a decaying neuron within the brain. This extensive loss of functional brain tissue is the ultimate biological substrate for the poor clinical outcomes observed in the study. It manifests clinically as an unfavorable functional outcome—classified as a Glasgow Outcome Scale score of 1 to 3—and a significantly increased risk of mortality, thereby closing the loop from the initial macroscopic injury to the systemic biomarker and, finally, to the patient's clinical fate.

The findings of this study have significant and practical implications for the clinical management of TBI patients. Serum lactate measurement is a rapid, inexpensive, and universally available test, making it an ideal biomarker for broad application.[19] Our results strongly advocate for its integration into the standard initial assessment of all TBI patients. An elevated lactate level, especially in the context of our multivariate analysis, should serve as a critical "red flag" for clinicians. For example, a patient with a moderate GCS score but a markedly high lactate level may be harboring a more severe underlying metabolic injury than is clinically apparent and should be prioritized for more intensive monitoring and aggressive management. This allows for a more nuanced risk stratification that moves beyond sole reliance on the GCS and structural imaging. A hypothetical "lactate alarm" protocol could be envisioned where a lactate level above a certain threshold (>2.5 mmol/L) in a moderate TBI patient could automatically trigger a neuro-intensivist consult, an earlier repeat CT scan, or consideration for invasive ICP monitoring. In resource-limited settings, where advanced neuromonitoring may be unavailable, lactate can serve as an invaluable tool for guiding resource allocation and providing objective prognostic information to families. While our primary analysis focused on the prognostic power of the admission lactate value, the collection of serial data highlights the importance of lactate kinetics. A single lactate value is a static snapshot, whereas the trend over time, or lactate clearance, reflects the patient's response to resuscitation and the evolution of the secondary injury.[20] A failure to clear lactate within the first 24-48 hours may signify a failure of initial resuscitation, inadequate control of ICP, or a relentlessly progressing secondary injury cascade, all of which portend an extremely poor prognosis. Although a formal analysis of lactate clearance was beyond the primary scope of this paper, our findings underscore the need for serial measurements. Future research should focus on lactate kinetics as a dynamic biomarker to guide ongoing therapeutic interventions, potentially identifying patients who require an escalation of care.

This study has several important limitations that must be acknowledged when interpreting its findings. First, the single-center design and small sample size (N=33) limit the statistical power and the external validity of our findings. The results require validation in larger, multi-center cohorts to ensure they are generalizable across different patient populations and healthcare systems. Second, the primary outcome of GOS at discharge is a significant limitation due to temporal bias. It reflects in-hospital outcome, which is influenced by length of stay and local discharge practices, rather than true long-term neurological recovery, which continues to evolve for months. Future studies must incorporate standardized, fixed-time point follow-up (at 6 or 12 months) to assess long-term outcomes. Third, while we controlled for major confounders, other unmeasured variables, such as pre-hospital hypoxia or hypotension and the specifics of resuscitation fluids, could have influenced the results. Finally, our study used venous lactate, and while strongly correlated with arterial lactate in many settings, arterial samples are considered the gold standard for assessing global metabolic state. These limitations highlight the need for further, more comprehensive research to build upon our findings.

5. Conclusion

This prospective, single-center study demonstrates that an elevated admission serum lactate level is a strong and independent predictor of unfavorable in-hospital functional outcome and mortality in patients with traumatic brain injury, even after adjusting for

initial injury severity and age. While the study's conclusions regarding long-term prognosis are limited by the use of a discharge-based endpoint, the findings powerfully reinforce the interpretation of lactate as a critical and accessible biomarker that reflects the severity of the underlying neurometabolic cascade involving mitochondrial failure, excitotoxicity, and neuroinflammation. Given its universal availability and low cost, serum lactate measurement should be integrated as a standard component in the early assessment and risk stratification of TBI patients, where it can provide invaluable prognostic information to enhance clinical decision-making and aid in the critical mission to mitigate the devastating consequences of secondary brain injury.

6. References

1. Crespy T, Durost M, Fricault P, Lemasson B, Bouzat P, Barbier EL, et al. Hypertonic sodium lactate to alleviate functional deficits following diffuse traumatic brain injury: an osmotic or a lactate-related effect? Neurocrit Care. 2021; 34(3): 795–803.
2. Wang Y-M, Zhu N, Zhou Y-M, Su R, Li H-L, Zhou J-X. The combination of arterial lactate level with GCS-pupils score to evaluate short term prognosis in traumatic brain injury: a retrospective study. BMC Neurol. 2022; 22(1): 430.
3. Wang R, He M, Qu F, Zhang J, Xu J. Lactate albumin ratio is associated with mortality in patients with moderate to severe traumatic brain injury. Front Neurol. 2022; 13: 662385.
4. Lee JH, Lee D, Lee BK, Cho YS, Kim DK, Jung YH, et al. The association between lactate to albumin ratio and outcomes at early phase in patients with traumatic brain injury. Ulus Travma Acil Cerrahi Derg. 2023; 29(7): 752–7.
5. Sharma B, Jiang W, Dhole Y, Agriantonis G, Bhatia ND, Shafaee Z, et al. Lactate is a strong predictor of poor outcomes in patients with severe traumatic brain injury. Biomedicines. 2024; 12(12).
6. Zhang K-Y, Li P-L, Yan P, Qin C-J, He H, Liao C-P. The significance of admission blood lactate and fibrinogen in pediatric traumatic brain injury: a single-center clinical study. Childs Nerv Syst. 2024; 40(4): 1207–12.
7. Plourde G, Ichai C, Quintard H. Cerebral lactate uptake after half-molar sodium lactate therapy in traumatic brain injury: a brief report. J Neurotrauma. 2024; 41(13–14): e1807–11.
8. Martin-Rodriguez F, Sanz-Garcia A, Lopez-Izquierdo R, Delgado Benito JF, Martínez Fernández FT, Otero de la Torre S, et al. Prehospital lactate levels obtained in the ambulance and prediction of 2-day in-hospital mortality in patients with traumatic brain injury. Neurology. 2024; 103(4): e209692.
9. Kusderci H, Oterkus M, Kayikci E, Akdeniz S, Genc C. Relationship between C-reactive protein/albumin ratio and lactate/albumin ratio and mortality in traumatic brain injury. Med Sci (Turkey). 2025; 14(3): 625.
10. Xie J, Zhang L, Gan N. Prognostic significance of D-dimer, neuron-specific enolase, and lactate dehydrogenase changes in patients with severe traumatic brain injury: a logistic regression analysis. J Pak Med Assoc. 2025; 75(1): 103–4.
11. Vespa P, Wolahan S, Buitrago-Blanco M, Real C, Ruiz-Tejeda J, McArthur DL, et al. Exogenous lactate infusion (ELI) in traumatic brain injury: higher dose is better? Crit Care. 2025; 29(1): 153.
12. Bu Z, Zhou Y, Xu F, Xu S. Single-cell RNA and transcriptome sequencing to analyze the role of lactate metabolism in traumatic brain injury astrocytes. Brain Behav. 2025; 15(5): e70428.
13. Jo YY, Kim JY, Choi JJ, Jung WS, Kim YB, Kwak HJ. Preoperative serum lactate cannot predict in-hospital mortality after decompressive craniectomy in traumatic brain injury. J Anesth. 2016; 30(4): 637–43.

14. Fu Y-Q, Bai K, Liu C-J. The impact of admission serum lactate on children with moderate to severe traumatic brain injury. PLoS One. 2019; 14(9): e0222591.
15. Hidayatulloh S. Dynamics of serum lactate and glucose level with coagulation factors in moderate and severe traumatic brain injury. Int J Surg Med. 2020; 1.
16. Wang R, Wang S, Zhang J, He M, Xu J. Serum lactate level in early stage is associated with acute kidney injury in traumatic brain injury patients. Front Surg. 2021; 8: 761166.
17. Liu Y, Yang P, Liu H-C, Sun S, Zhang J-L, Kang J. The significance of the detection of serum lactate dehydrogenase, hypersensitive C-reactive protein, and N-terminal pro-brain natriuretic peptide for the evaluation of the severity and progression of pediatric patients with traumatic brain injury. Curr Neurovasc Res. 2022; 19(2): 219–24.
18. Bender M, Friedrich M, Voigtmann H, Haferkorn K, Uhl E, Stein M. Impact of serum lactate as an early serum biomarker for cardiopulmonary parameters within the first 24 hours of intensive care unit treatment in patients with isolated traumatic brain injury. Diagnostics (Basel). 2023; 13(10).
19. Mahajan C, Goyal K, Shukla RK, Priya S. Serum lactate, base deficit, blood glucose levels and trauma scores as prognostic markers of isolated severe traumatic brain injury. Indian J Crit Care Med. 2024; 28(S1): S343–4.
20. Jiang H, Zeng W, Zhang X, Dong L, Pei Y, Peng A. Associations of blood pressure and serum lactate levels upon admission with one-week mortality in patients with severe traumatic brain injury: a multi-center retrospective study. Turk Neurosurg. 2025; 35(3): 492–502.