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Admission Serum Lactate and 48-Hour Lactate Clearance for Predicting Discharge Glasgow Outcome Scale and In-Hospital Survival in Traumatic Brain Injury: A Prospective Cohort Study

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ABSTRACT

Background: Traumatic brain injury (TBI) triggers a neurometabolic crisis with mitochondrial decoupling and systemic hyperlactatemia. Accessible biomarkers are needed in resource-limited centers.**Objective:** To evaluate admission venous serum lactate and 48-hour clearance for predicting discharge Glasgow Outcome Scale (GOS) and in-hospital survival in acute TBI.**Methods:** In this prospective cohort study (Palembang, Indonesia; May–August 2025), 33 consecutive TBI patients (aged 14–71 years) presenting within 6 hours of trauma had venous lactate measured at 0, 24 and 48 hours. Discharge GOS was dichotomized into unfavorable (1–3) and favorable (4–5). Analyses used ROC curves, Kaplan-Meier survival, logistic regression and Cox models.**Results:** Mean age was 37.91 ± 16.42 years; 63.6% were male. Admission lactate rose across worsening GOS strata ($p = 0.002$) and was higher in unfavorable ($n = 20$) than favorable ($n = 13$) outcomes (median 4.10 [IQR 3.18–5.12] vs. 1.80 [1.40–2.30] mmol/L; $p < 0.001$), with lower 48-hour clearance (+8.2% vs. +31.4%; $p < 0.001$). The AUC was 0.906 (95% CI: 0.804–1.000) at > 2.50 mmol/L (sensitivity 85.0%, specificity 84.6%). Survival was 92.9% at or below and 63.2% above it (Log-Rank $p = 0.034$). After adjustment for age and initial GCS, each 1.0 mmol/L increase in admission lactate was associated with unfavorable outcome (aOR 2.15, 95% CI: 1.12–4.13; $p = 0.021$) and mortality (aHR 1.78, 95% CI: 1.05–3.01; $p = 0.032$).**Conclusion:** Admission lactate showed good discrimination for unfavorable GOS and in-hospital mortality in this small single-center cohort; 48-hour clearance differed between outcome groups. External validation is needed.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of death, long-term neurocognitive disability and economic loss.^{1,2} This holds in industrialized and developing health systems alike. More than 50 million people, and by one model about 69 million (95% CI 64–74 million), sustain an acute TBI each year.^{3,4} Low- and middle-income countries (LMICs) carry a disproportionate share of this burden (nearly three times more cases proportionally than high-income countries),³ driven by rapid motorization, high-speed road collisions and weak pre-hospital trauma triage,^{5,6} and tertiary neurosurgical referral centers in Southeast Asia and Europe alike see patients with moderate-to-severe cranial trauma who differ widely in case mix. Many remain functionally dependent. This is so despite modern decompressive neurosurgery, intracranial pressure (ICP) monitoring and neurointensive care.^{6,7} One difficulty stands out. Neurological recovery does not depend only on the primary mechanical impact, which includes immediate axonal shearing, parenchymal contusion and extra-axial hemorrhage. It also depends on a secondary injury cascade that begins within minutes to hours after trauma, evolves over time and may be reversible.⁸

At the cellular level, an acute neurometabolic crisis drives secondary injury. Neuronal membranes depolarize, presynaptic terminals release excitatory amino acids such as glutamate, and intracellular calcium rises.^{8,9} Under physiological conditions,

cerebral energy homeostasis depends heavily on the astrocyte-neuron lactate shuttle (ANLS). Astrocytic glycolysis converts glucose to L-lactate, monocarboxylate transporters (MCT1 and MCT4) export it, and neighboring neurons take it up through MCT2 to fuel oxidative phosphorylation in the tricarboxylic acid (TCA) cycle.^{9,10} Severe biomechanical injury upsets this balance, because microvascular thrombosis, pericontusional vasogenic and cytotoxic edema and raised ICP lower cerebral perfusion pressure (CPP) and tissue oxygen delivery, and cells shift from aerobic mitochondrial respiration to accelerated anaerobic glycolysis.^{8,11,12} At the same time, opening of the mitochondrial permeability transition pore (mPTP) and dysfunction of cytochrome c oxidase uncouple oxidative phosphorylation even when oxygen tension is adequate. Intracellular and interstitial lactate then accumulates, together with marked parenchymal acidosis.^{11,13} The uncoupling feeds itself, and in this loop intracellular acidosis impairs astrocytic glutamate reuptake through excitatory amino acid transporters (EAAT1 and EAAT2), worsens cytotoxic swelling through aquaporin-4 (AQP4) water channels and speeds free-radical lipid peroxidation of neuronal membranes.^{9,12}

In current practice, the emergency department bases early risk stratification and treatment decisions mainly on the Glasgow Coma Scale (GCS) and non-contrast cranial computed tomography (CT).^{14,15} The initial GCS remains the cornerstone of assessment, but during hyperacute resuscitation its prognostic reliability is often blurred by endotracheal intubation, sedation,

neuromuscular blockade, periorbital swelling, alcohol or drug intoxication and post-ictal encephalopathy.¹⁴ Baseline CT detects space-occupying epidural or subdural hematomas and midline shift that need urgent evacuation with high sensitivity. It misses diffuse microvascular ischemia. It also misses cellular bioenergetic failure and systemic neuro-humoral dysregulation.¹⁶ Over the past decade, blood-based neurobiomarkers have added clear value for predicting intracranial pathology and six-month functional outcome in large multicenter cohorts such as ALERT-TBI and CENTER-TBI.^{4,17,18} The best known are glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain (NfL) and S100 calcium-binding protein B (S100B), and similar markers have been studied in children.¹⁹ Yet assay cost, the need for specialized electrochemiluminescence immunoassay platforms and slow laboratory turnaround keep these proteins out of routine use in public referral hospitals across LMICs.^{6,18}

Blood lactate, venous or arterial, is quick, cheap and widely available. Intensive care and polytrauma teams already use it to quantify systemic tissue hypoperfusion and cellular oxygen debt.²⁰⁻²³ In isolated or predominant TBI, peripheral hyperlactatemia appears to reflect two processes: one is direct efflux of cerebral lactate into the systemic venous circulation across a blood-brain barrier (BBB) that is mechanically and osmotically disrupted. The other is a surge of catecholamines from the hypothalamic-sympathoadrenal axis (Type B adrenergic hyperlactatemia), in which epinephrine stimulates beta-2 adrenoceptors and accelerates Na⁺/K⁺-ATPase activity and aerobic glycolysis in skeletal muscle.²⁴⁻²⁶ Serial measurement of lactate over the first 24 to 48 hours adds a dynamic view. It shows whether neuroresuscitative interventions have restored microcirculatory coupling and hepatorenal lactate clearance, or whether the patient remains in refractory bioenergetic exhaustion.^{20,22,23} Interest is growing worldwide. Prospective data remain scarce in Indonesian tertiary neurotrauma populations, and specifically, the precise diagnostic cut-off of admission serum lactate, its 48-hour clearance trajectory and its independent prognostic weight across the full five-point Glasgow Outcome Scale (GOS) spectrum are not defined. This prospective cohort study therefore evaluated the prognostic accuracy of admission venous serum lactate and 48-hour lactate clearance for predicting discharge GOS and in-hospital survival in patients with acute TBI treated at a tertiary referral center in South Sumatra, Indonesia.

2. Methods

Study design and setting

This was a prospective, observational, analytical cohort study. It ran from May 1, 2025, to August 31, 2025, in the Emergency Department (ED), the central intensive care unit (ICU) and the integrated neurosurgical inpatient wards of Dr. Mohammad Hoesin General Hospital, Palembang, South Sumatra, Indonesia. This is the main tertiary academic referral center for neurotrauma and surgical intensive care in South Sumatra and its surrounding referral networks, and it manages many cranial injuries from road vehicles, workplaces and falls. The study is reported in accordance with the STROBE guidelines.

Participants and eligibility

Consecutive patients who arrived at the emergency resuscitation bay with a clinical and radiological diagnosis of acute traumatic brain injury were screened by the on-call surgical and neurosurgical trauma team. Eligibility was defined in advance. Inclusion required four things: age of 14 years or older with acute closed or penetrating cranial trauma; arrival at

the ED within 6 hours of the injury, to capture hyperacute neurometabolic change before prolonged pre-hospital intervention; intracranial traumatic pathology, or clinical TBI severity grading, confirmed by an attending neurosurgeon and a non-contrast cranial CT scan; and a baseline peripheral venous blood sample available before definitive neurosurgical decompression or transfer to intensive care. Exclusion criteria were strict. They limited confounding from non-neurological causes of systemic hyperlactatemia. Excluded were patients with polytrauma and severe extracranial hemorrhagic shock (Abbreviated Injury Scale [AIS] ≥ 3 in the thoracic, abdominal or pelvic-extremity compartments) or refractory hypotension from visceral or long-bone bleeding; patients with pre-existing end-stage chronic liver disease (Child-Pugh class B or C) or chronic kidney disease on maintenance hemodialysis, both of which independently impair gluconeogenic and renal lactate disposal; patients with a history of diabetic ketoacidosis, inborn errors of metabolism or active systemic sepsis at presentation; patients with chronic alcohol abuse or acute metformin intoxication; and patients who died on arrival or were transferred to another facility before the 48-hour biochemical monitoring and the hospital discharge assessment were complete.

Sample size was estimated for diagnostic receiver operating characteristic (ROC) analysis, using the Hanley-McNeil approach for the area under the ROC curve.²⁷ The assumptions were an expected area under the ROC curve (AUC) of 0.85 against a null AUC of 0.50, a two-sided type I error of $\alpha = 0.05$ and power of $1 - \beta = 0.90$. The minimum was 28 to 32 evaluable patients. Recruitment lasted four months. In that time, 45 consecutive patients with acute cranial trauma were assessed in the ED. Screening excluded 12 of them: 5 presented more than 6 hours after injury, 4 had concomitant severe abdominal or thoracic hemorrhagic shock, 2 had pre-existing decompensated hepatic or renal insufficiency, and 1 had incomplete serial sampling. The final analytical cohort was $N = 33$ patients with complete baseline, 24-hour, 48-hour and hospital-discharge follow-up data.

Variables and data collection

On ED arrival, all patients received standardized trauma resuscitation following the Brain Trauma Foundation (BTF) and Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) protocols.^{15,28,29} Intubation was performed for GCS ≤ 8 or an unprotected airway. Ventilation targeted normocapnia: arterial partial pressure of carbon dioxide (PaCO₂) of 35–40 mmHg and peripheral oxygen saturation (SpO₂) of 95% or more. Isotonic crystalloid (0.9% normal saline) kept patients euvolemic with systolic blood pressure ≥ 100 –110 mmHg. The head of the bed was raised to 30°. Osmotherapy, either intravenous mannitol 0.5–1.0 g/kg bolus or hypertonic 3% saline, was given promptly when clinical or radiological signs of intracranial hypertension appeared. Neurological severity was graded right after resuscitation on the standard 15-point Glasgow Coma Scale (GCS): mild TBI (GCS 14–15), moderate TBI (GCS 9–13) or severe TBI (GCS 3–8). Blood sampling followed a fixed routine. Peripheral venous blood (3.0 mL) was drawn aseptically from an antecubital vein, with tourniquet stasis under 30 seconds, from an extremity free of crystalloid infusion into pre-chilled sodium fluoride/potassium oxalate (NaF/K₂C₂O₄) tubes, which inhibit glycolysis. Draws were made at three fixed time points: admission (0h, T0), 24 hours after admission (24h, T24) and 48 hours after admission (48h, T48).

Specimens were carried on ice packs to the central clinical pathology laboratory of Dr. Mohammad Hoesin General Hospital

within 15 minutes of venipuncture. They were centrifuged at 3,000 rpm for 10 minutes at 4°C to separate plasma/serum from cells. Analysis followed at once on a Cobas c501 clinical chemistry analyzer (Roche Diagnostics, Mannheim, Germany), using an automated enzymatic colorimetric lactate oxidase assay. The reaction is simple. Lactate oxidase converts L-lactate to pyruvate and hydrogen peroxide (H₂O₂), and peroxidase then lets H₂O₂ react with 4-aminoantipyrine and a hydrogen donor to form a chromogen that is measured spectrophotometrically. Linearity ranged from 0.2 to 15.5 mmol/L. Intra-assay and inter-assay coefficients of variation were below 2.1%. Relative 48-hour lactate clearance (%) was calculated for each patient with the following equation (Eq. 1):^{20,22}

$$\text{Lactate Clearance}_{48\text{h}} (\%) = [(\text{Lactate}_{0\text{h}} - \text{Lactate}_{48\text{h}}) / \text{Lactate}_{0\text{h}}] \times 100 \quad (\text{Eq. 1})$$

All enrolled patients were followed prospectively through neurosurgical and intensive care hospitalization until in-hospital death or formal discharge. At discharge, an attending board-certified neurosurgeon, blinded to the serial lactate trajectories, independently rated functional neurological outcome. The rating used the standard five-point Glasgow Outcome Scale (GOS). GOS 1 meant death (in-hospital mortality directly attributable to primary or secondary neurological injury). GOS 2 meant persistent vegetative state (prolonged wakefulness with sleep-wake cycles but no cognitive awareness, verbal communication or purposeful interaction with the environment). GOS 3 meant severe disability: a conscious patient who depends on others for daily physical or cognitive support because of severe motor, cranial nerve or neurobehavioral deficits. GOS 4 meant moderate disability: a patient independent in activities of daily living and able to use public transportation, but with residual neurological, hemiparetic or cognitive deficits that preclude full return to pre-injury occupational capacity. GOS 5 meant good recovery, with return to normal occupational and social activities and minor or no residual sequelae.^{30,31} The GOS was then dichotomized, following international neurotrauma trial standards (IMPACT and CENTER-TBI). The primary binary endpoint was unfavorable functional outcome (GOS 1–3: death, persistent vegetative state or severe disability) versus favorable functional outcome (GOS 4–5: moderate disability or good recovery).^{7,18,32} The secondary endpoint was in-hospital all-cause neurotrauma mortality (GOS 1 vs. GOS 2–5), with time to event in days censored at formal hospital discharge.

Statistical analysis

All analyses used Python (version 3.11; SciPy, Statsmodels and Lifelines libraries), and results were cross-verified in IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was tested with the Kolmogorov-Smirnov (KS) test with Lilliefors correction and the Shapiro-Wilk (SW) test, and checked visually on normal quantile-quantile (Q-Q) plots and kernel density histograms. Normally distributed continuous variables, such as age, are given as mean ± standard deviation (SD). Non-normally distributed continuous and ordinal variables are given mainly as median and interquartile range (IQR, 25th–75th percentiles). These include admission lactate, 24-hour and 48-hour lactate, 48-hour relative lactate clearance and initial GCS score. Parametric mean ± SD and 95% confidence intervals (95% CI) are shown alongside, for transparency and to ease future meta-analysis across international cohorts. Categorical variables are expressed as exact frequencies (n) and percentages (%). Percentages sum to 100.0%.

The non-parametric Kruskal-Wallis H test compared admission lactate across the five ordinal GOS categories (GOS 1 to GOS 5), with the epsilon-squared effect size ($\epsilon^2 = H / [(n^2 - 1) / (n + 1)]$). Within-subject change in lactate across 0h, 24h and 48h was assessed with the non-parametric Friedman repeated-measures analysis of variance by ranks. Dichotomized outcome groups (unfavorable GOS 1–3 vs. favorable GOS 4–5) were compared with the Mann-Whitney U test. The rank-biserial correlation coefficient ($r_{rb} = 1 - [2U / (n_1 \times n_2)]$) served as the standardized non-parametric effect size. Associations between dichotomized lactate strata and clinical outcomes were tested with Pearson's chi-square (χ^2) test, or with the two-tailed Fisher's exact test when expected cell counts were below 5. Effect sizes were unadjusted odds ratios (OR) and relative risks (RR), with exact 95% confidence intervals. Non-parametric ROC analysis with DeLong 95% CIs measured how well admission lactate discriminated unfavorable outcome and mortality. The optimal prognostic threshold was the one that maximized Youden's index ($J = \text{Sensitivity} + \text{Specificity} - 1$); because it was derived and evaluated in the same sample, its accuracy, AUC and predictive values are apparent (non-validated) estimates. Survival in hospital, stratified by that threshold, was estimated by the Kaplan-Meier product-limit method and compared with the Mantel-Cox Log-Rank test. Finally, multivariable binary logistic regression (adjusted odds ratios [aOR]) and multivariable Cox proportional hazards regression (adjusted hazard ratios [aHR] and Harrell's concordance index [C-index]) tested the independent prognostic value of admission lactate after adjustment for age and initial GCS score, with the covariate set shown in Eq. 2. Both models are exploratory: the smaller outcome class has 13 patients in the logistic model (about 4 events per variable) and 8 deaths in the Cox model (about 3 events per variable). Significance was set at a two-tailed $p < 0.05$ throughout.

$$\ln[P(\text{GOS1-3}) / (1 - P(\text{GOS1-3}))] = \beta_0 + \beta_1(\text{Lactate}_{0\text{h}}) + \beta_2(\text{GCS}_{\text{initial}}) + \beta_3(\text{Age}) \quad (\text{Eq. 2})$$

Ethical approval

The Health Research Ethics Committee of Dr. Mohammad Hoesin General Hospital / Faculty of Medicine, Universitas Sriwijaya, Palembang, reviewed and approved the protocol (Approval No. DP.04.03/D.XVIII.06.08/ETIK/208/2025). The Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed. Written informed consent was obtained before enrollment and serial venous sampling. Conscious participants gave it themselves. For patients with impaired consciousness, the legally authorized next of kin did.

3. Results

Baseline demographic, neurological, and biochemical characteristics

During the four-month prospective study period from May 1, 2025, to August 31, 2025, a total of 45 consecutive patients presenting with acute traumatic brain injury were screened upon arrival at the emergency resuscitation bay of Dr. Mohammad Hoesin General Hospital, of whom 33 patients satisfied all inclusion and exclusion criteria and completed the 48-hour serial biochemical protocol through hospital discharge. The baseline demographic, clinical, neurological, and serial biochemical characteristics of the analytic cohort (N = 33) are detailed in Table 1 and illustrated in Figure 1. The cohort was predominantly male, with 21 male patients (63.6%) and 12 female patients (36.4%), a male-to-female ratio of 1.75:1, which may reflect higher occupational and motorized vehicular trauma exposure among males in South Sumatra (Table 1 and

Figure 1B). The overall mean chronological age of the study population was 37.91 ± 16.42 years, with a median age of 36.0 years (IQR 25.0–51.0 years; absolute range 14.0–71.0 years). Goodness-of-fit testing found no evidence that age departed from a normal distribution (Kolmogorov-Smirnov $D = 0.114$, $p = 0.200$; Shapiro-Wilk $W = 0.968$, $p = 0.428$). When stratified by physiological age brackets, working-age adults (18–59 years) made up most of the cohort at 72.7% ($n = 24$), followed by elderly patients aged ≥ 60 years at 18.2% ($n = 6$) and adolescent patients aged < 18 years at 9.1% ($n = 3$), as detailed in Table 1 and Figure 1A.

Neurological severity assessment performed immediately upon post-resuscitation stabilization revealed a mean initial Glasgow Coma Scale (GCS) score of 11.42 ± 3.38 and a median score of 12.0 (IQR 9.0–14.0; range 3.0–15.0), which departed significantly from normality due to negative skewness toward higher coma scores (KS $D = 0.172$, $p = 0.015$; SW $W = 0.904$, $p = 0.007$). Using the severity classes defined in Section 2.3, 13 patients (39.4%) presented with mild TBI (GCS 14–15), 14 patients (42.4%) presented with moderate TBI (GCS 9–13), and 6 patients (18.2%) presented with severe TBI (GCS 3–8), as

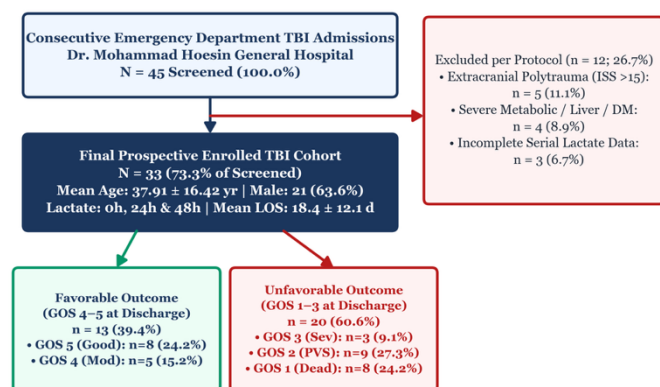
summarized in Table 1 and Figure 1C. Thus, moderate and severe TBI collectively accounted for 60.6% ($n = 20$) of the admitted neurosurgical cohort. The median elapsed time from the primary traumatic event to initial antecubital venous blood sampling in the emergency department was 2.5 hours (IQR 1.5–4.0 hours; mean 2.82 ± 1.45 hours; SW $W = 0.934$, $p = 0.048$), indicating that all baseline measurements were taken within the early hyperacute window (< 6 hours). Across the entire cohort ($N = 33$), admission (0h) venous serum lactate exhibited a positively skewed distribution (KS $D = 0.168$, $p = 0.018$; SW $W = 0.912$, $p = 0.011$), with a median concentration of 2.90 mmol/L (IQR 1.85–4.35 mmol/L) and a parametric mean of 3.18 ± 1.54 mmol/L (range 1.10–6.80 mmol/L; Table 1 and Figure 1D). Longitudinal serial monitoring across the cohort showed a statistically significant decline in overall median serum lactate from 2.90 mmol/L at admission (0h) to 2.40 mmol/L (IQR 1.50–3.95 mmol/L; mean 2.76 ± 1.48 mmol/L) at 24 hours and 2.10 mmol/L (IQR 1.35–3.80 mmol/L; mean 2.58 ± 1.62 mmol/L) at 48 hours (Friedman repeated-measures $\chi^2 = 11.45$, $p = 0.003$). The mean overall hospital length of stay until discharge or in-hospital death was 18.4 ± 12.1 days (median 16.0 [IQR 9.0–26.0] days; range 2.0–46.0 days).

Table 1. Baseline demographic, clinical, neurological, and serial biochemical characteristics of the acute traumatic brain injury cohort ($N = 33$).

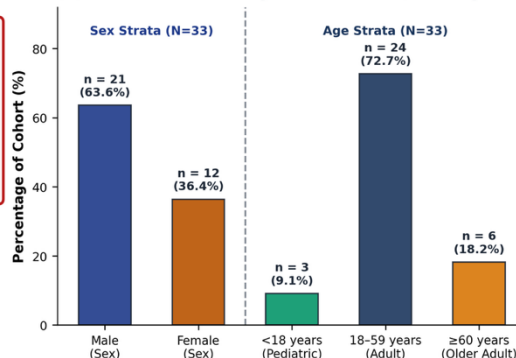
Variable / Characteristic	Category / Metric	n (%) or Value	Normality Test (KS / SW)	Clinical Reference / Range
Sex	Male	21 (63.6%)	—	Predominant trauma exposure
Sex	Female	12 (36.4%)	—	Male : Female ratio = 1.75 : 1
Age (years)	Mean $\pm$ SD	37.91 ± 16.42	KS $D = 0.114$ ($p = 0.200$)*	Normal Gaussian distribution
Age (years)	Median (IQR)	36.0 (25.0–51.0)	SW $W = 0.968$ ($p = 0.428$)*	Range: 14.0 – 71.0 years
Age Group Stratification	Adolescent (< 18 years)	3 (9.1%)	—	14 – 17 years
Age Group Stratification	Productive Adult (18–59 years)	24 (72.7%)	—	18 – 59 years
Age Group Stratification	Elderly (≥ 60 years)	6 (18.2%)	—	60 – 71 years
Initial Glasgow Coma Scale (GCS)	Mean $\pm$ SD / Median (IQR)	11.42 ± 3.38 / 12.0 (9.0–14.0)	KS $p = 0.015$ / SW $p = 0.007$	Range: 3.0 – 15.0 points
TBI Clinical Severity Grade	Mild TBI (GCS 14–15)	13 (39.4%)	—	Classification per Section 2.3
TBI Clinical Severity Grade	Moderate TBI (GCS 9–13)	14 (42.4%)	—	Classification per Section 2.3
TBI Clinical Severity Grade	Severe TBI (GCS 3–8)	6 (18.2%)	—	Classification per Section 2.3
Time from Trauma to Sampling (h)	Median (IQR) / Mean $\pm$ SD	2.5 (1.5–4.0) / 2.82 ± 1.45	SW $W = 0.934$ ($p = 0.048$)	Inclusion window: ≤ 6.0 hours
Admission Serum Lactate, 0h (mmol/L)	Median (IQR) / Mean $\pm$ SD	2.90 (1.85–4.35) / 3.18 ± 1.54	KS $p = 0.018$ / SW $p = 0.011$	Normal venous: 0.5 – 2.2 mmol/L
24-Hour Serum Lactate, 24h (mmol/L)	Median (IQR) / Mean $\pm$ SD	2.40 (1.50–3.95) / 2.76 ± 1.48	SW $W = 0.908$ ($p = 0.009$)	Serial monitoring T24
48-Hour Serum Lactate, 48h (mmol/L)	Median (IQR) / Mean $\pm$ SD	2.10 (1.35–3.80) / 2.58 ± 1.62	—	Serial monitoring T48
Hospital Length of Stay (days)	Mean $\pm$ SD / Median (IQR)	18.4 ± 12.1 / 16.0 (9.0–26.0)	SW $W = 0.921$ ($p = 0.020$)	Range: 2.0 – 46.0 days

Abbreviations: BTF, Brain Trauma Foundation; GCS, Glasgow Coma Scale; IQR, interquartile range (25th–75th percentile); KS, Kolmogorov-Smirnov test with Lilliefors correction; SD, standard deviation; SW, Shapiro-Wilk test; TBI, traumatic brain injury. * $p > 0.05$ indicates Gaussian (normal) distribution.

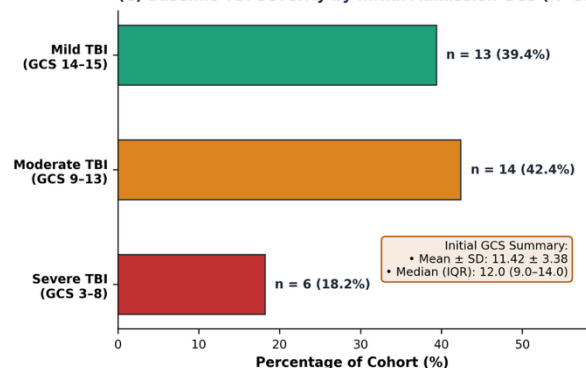
(A) STROBE Patient Screening & Enrollment Flow (May–Aug 2025)



(B) Sex Distribution & Age Stratification (Mean Age: 37.91 ± 16.42 yr)



(C) Baseline TBI Severity by Initial Admission GCS (N=33)



(D) Baseline Admission Serum Lactate Distribution (KS p=0.018)

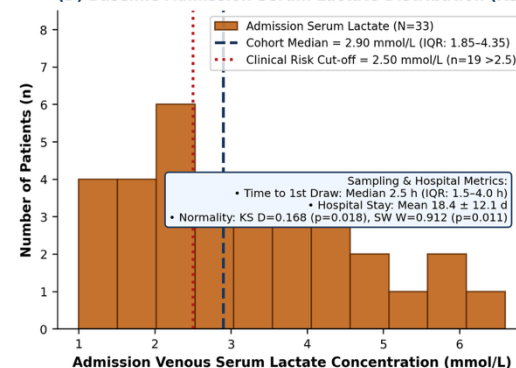


Figure 1. Baseline characteristics of the prospective traumatic brain injury (TBI) cohort (N = 33). (A) STROBE patient screening and enrollment flow (May–August 2025). (B) Sex distribution (male 63.6%, female 36.4%) and age stratification (working-age adults 18–59 years, 72.7%; mean age 37.91 ± 16.42 years). (C) Presenting TBI severity by initial Glasgow Coma Scale (mild 39.4%, moderate 42.4%, severe 18.2%). (D) Histogram of admission (0h) venous serum lactate [median 2.90 [IQR 1.85–4.35] mmol/L; mean 3.18 ± 1.54 mmol/L] relative to the cut-off of > 2.50 mmol/L.

Discharge Glasgow Outcome Scale distribution and admission lactate gradient

At the completion of inpatient neurosurgical care, functional neurological recovery across the five-point Glasgow Outcome Scale (GOS) and its quantitative relationship with admission venous serum lactate concentrations were evaluated, as detailed in Table 2 and illustrated in Figure 2. Across the total cohort of 33 patients, 8 patients (24.2%) died in the hospital from refractory intracranial hypertension, brainstem herniation, or secondary neurogenic systemic complications (GOS 1), 9 patients (27.3%) survived in a persistent vegetative state without cognitive environmental interaction (GOS 2), 3 patients (9.1%) survived with severe disability requiring continuous daily nursing or family dependency (GOS 3), 5 patients (15.2%) achieved moderate disability with preserved independence in basic activities of daily living (GOS 4), and 8 patients (24.2%) attained good functional recovery with resumption of baseline activities (GOS 5), as presented in Table 2 and Figure 2A. When dichotomized into standard neurotrauma clinical trial endpoints, 20 patients (60.6%) experienced an unfavorable functional outcome (GOS 1–3), whereas 13 patients (39.4%) achieved a favorable functional outcome (GOS 4–5), corresponding to an overall in-hospital survival rate of 75.8% (n = 25) and an in-hospital mortality rate of 24.2% (n = 8).

Non-parametric omnibus testing across the five ordinal GOS categories showed a significant, monotonic inverse gradient between admission venous serum lactate concentration and

discharge functional status (Kruskal-Wallis H = 16.92, degrees of freedom [df] = 4, epsilon-squared effect size $\epsilon^2 = 0.529$, $p = 0.002$), indicating that admission lactate accounted for about 52.9% of the rank variance in five-point discharge GOS (Table 2 and Figure 2B). Specifically, patients achieving good recovery (GOS 5, n = 8) had the lowest admission serum lactate levels, with a median of 1.65 mmol/L (IQR 1.30–2.05 mmol/L; mean 1.71 ± 0.48 mmol/L; 95% CI: 1.31–2.11 mmol/L), wherein 87.5% (7/8) presented with baseline normolactatemia (≤ 2.50 mmol/L) and only 1 patient (12.5%) exceeded 2.50 mmol/L. Patients discharged with moderate disability (GOS 4, n = 5) demonstrated a slightly higher median admission lactate of 2.10 mmol/L (IQR 1.75–2.50 mmol/L; mean 2.14 ± 0.76 mmol/L; 95% CI: 1.20–3.08 mmol/L), with 80.0% (4/5) maintaining baseline lactate ≤ 2.50 mmol/L. Conversely, admission serum lactate rose steeply across the three unfavorable outcome tiers: patients discharged with severe disability (GOS 3, n = 3) recorded a median admission lactate of 2.90 mmol/L (IQR 2.45–3.40 mmol/L; mean 2.93 ± 0.61 mmol/L; 95% CI: 1.41–4.45 mmol/L; 66.7% > 2.50 mmol/L), patients remaining in a persistent vegetative state (GOS 2, n = 9) exhibited a median lactate of 3.80 mmol/L (IQR 3.15–4.55 mmol/L; mean 3.78 ± 0.96 mmol/L; 95% CI: 3.04–4.52 mmol/L; 88.9% [8/9] > 2.50 mmol/L), and in-hospital non-survivors (GOS 1, n = 8) had marked baseline hyperlactatemia with a median of 4.85 mmol/L (IQR 3.95–5.80 mmol/L; mean 4.81 ± 1.32 mmol/L; 95% CI: 3.71–5.91 mmol/L), among whom 87.5% (7/8) exceeded the 2.50 mmol/L threshold (Table 2 and Figure 2B).

Table 2. Distribution of discharge Glasgow Outcome Scale (GOS) scores and stratified admission serum lactate concentrations (N = 33).

Discharge GOS Category	Clinical Description	n (%)	Admission Lactate Median (IQR), mmol/L	Admission Lactate Mean $\pm$ SD (95% CI), mmol/L	Lactate > 2.50 mmol/L, n (%)	p-value (Effect Size)
GOS 1	Death (In-Hospital Mortality)	8 (24.2%)	4.85 (3.95–5.80)	4.81 $\pm$ 1.32 (3.71–5.91)	7 / 8 (87.5%)	p = 0.002* (Kruskal-Wallis H = 16.92, df = 4, ϵ^2 = 0.529)
GOS 2	Persistent Vegetative State	9 (27.3%)	3.80 (3.15–4.55)	3.78 $\pm$ 0.96 (3.04–4.52)	8 / 9 (88.9%)	
GOS 3	Severe Disability (Dependent)	3 (9.1%)	2.90 (2.45–3.40)	2.93 $\pm$ 0.61 (1.41–4.45)	2 / 3 (66.7%)	
GOS 4	Moderate Disability (Independent)	5 (15.2%)	2.10 (1.75–2.50)	2.14 $\pm$ 0.76 (1.20–3.08)	1 / 5 (20.0%)	
GOS 5	Good Recovery (Normal Function)	8 (24.2%)	1.65 (1.30–2.05)	1.71 $\pm$ 0.48 (1.31–2.11)	1 / 8 (12.5%)	
Unfavorable (GOS 1–3)	Combined Poor Functional Outcome	20 (60.6%)	4.10 (3.18–5.12)	4.04 $\pm$ 1.28 (3.44–4.64)	17 / 20 (85.0%)	p < 0.001** (U = 24.5, r_{rb} = 0.812)
Favorable (GOS 4–5)	Combined Favorable Recovery	13 (39.4%)	1.80 (1.40–2.30)	1.88 $\pm$ 0.62 (1.51–2.25)	2 / 13 (15.4%)	

Abbreviations: CI, confidence interval; df, degrees of freedom; ϵ^2 , epsilon-squared non-parametric effect size; GOS, Glasgow Outcome Scale; IQR, interquartile range; r_{rb} , rank-biserial correlation coefficient; SD, standard deviation. *Kruskal-Wallis test across all 5 ordinal GOS categories. **Mann-Whitney U test comparing dichotomized Unfavorable (GOS 1–3) vs. Favorable (GOS 4–5) outcomes.

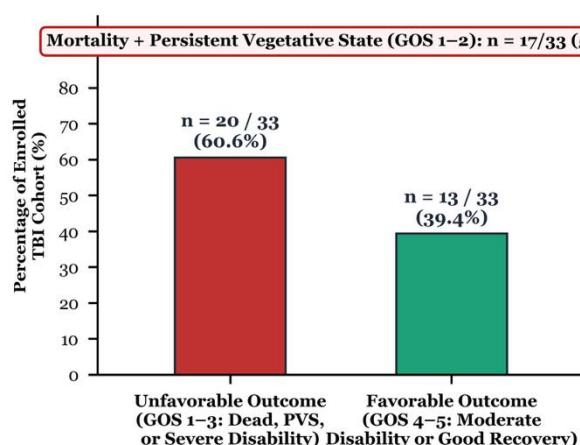
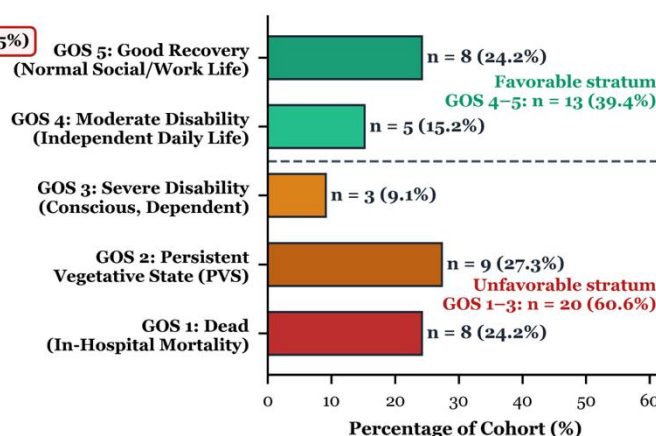
(A) Dichotomized Functional Outcome at Discharge (N=33)**(B) Granular 5-Point Glasgow Outcome Scale (GOS) Breakdown (N=33)**

Figure 2. Discharge Glasgow Outcome Scale (GOS) distribution (N = 33). (A) Dichotomized functional outcome (unfavorable GOS 1–3: n = 20 [60.6%] vs. favorable GOS 4–5: n = 13 [39.4%]; GOS 1–2: n = 17/33 [51.5%]). (B) Proportional distribution across the five ordinal GOS categories.

Serial 48-hour lactate clearance, ROC diagnostic threshold, and survival analysis

To evaluate longitudinal neurometabolic recovery over the initial 48 hours of intensive care and establish an objective diagnostic cut-off for emergency clinical triage, bivariate comparisons of serial lactate clearance kinetics, receiver operating characteristic (ROC) curve analysis, and Kaplan-Meier survival modeling were performed, as detailed in Table 3 and illustrated in Figure 3. In the dichotomized functional outcome analysis (Table 3 and Figure 3A), patients who experienced an unfavorable outcome (GOS 1–3, n = 20) presented with a more than two-fold higher median admission (0h) serum lactate compared with those who achieved a favorable outcome (GOS 4–5, n = 13): 4.10 mmol/L (IQR 3.18–5.12 mmol/L; mean 4.04 ± 1.28 mmol/L; 95% CI: 3.44–4.64 mmol/L) versus 1.80 mmol/L (IQR 1.40–2.30 mmol/L; mean 1.88 ± 0.62 mmol/L; 95% CI: 1.51–2.25 mmol/L), with a Mann-Whitney U statistic of 24.5 (Z = -3.892, rank-biserial correlation r_{rb} = 0.812, p < 0.001). Serial monitoring at 24 and 48 hours showed a clear divergence in lactate clearance between the two outcome groups (Table 3 and Figure 3A). In the favorable recovery group (GOS 4–5), lactate fell rapidly and steadily, with median serum lactate declining from 1.80 mmol/L at 0h to 1.45 mmol/L (IQR 1.15–1.85

mmol/L) at 24 hours and 1.25 mmol/L (IQR 1.00–1.55 mmol/L) at 48 hours, corresponding to a median relative 48-hour lactate clearance of +31.4% (IQR +18.5% to +42.0%). In contrast, the unfavorable outcome group (GOS 1–3) had persistent hyperlactatemia, with median serum lactate remaining elevated at 3.65 mmol/L (IQR 2.80–4.60 mmol/L; Mann-Whitney U = 29.0, Z = -3.726, r_{rb} = 0.777, p < 0.001) at 24 hours and 3.45 mmol/L (IQR 2.55–4.75 mmol/L; Mann-Whitney U = 26.5, Z = -3.818, r_{rb} = 0.796, p < 0.001) at 48 hours, a blunted median 48-hour relative clearance of only +8.2% (IQR -12.4% to +19.5%; Mann-Whitney U = 38.0, Z = -3.394, r_{rb} = 0.708, p < 0.001). In the 8 in-hospital non-survivors (GOS 1), who all survived to the 48-hour sample, median 48-hour clearance was negative (-14.5%; median lactate rising from 4.85 mmol/L at 0h to 5.40 mmol/L at 48h), which may indicate progressive secondary cerebral and systemic bioenergetic failure before death (not measured here).

Non-parametric ROC curve analysis showed that admission venous serum lactate discriminated unfavorable discharge functional outcome (GOS 1–3) well, with an area under the curve (AUC) of 0.906 (95% CI: 0.804–1.000; standard error [SE] = 0.052; p < 0.001), as detailed in Table 3 and plotted in Figure 3B. Admission serum lactate also discriminated the secondary endpoint of in-hospital mortality (GOS 1, n = 8 deaths), yielding

an AUC of 0.845 (95% CI: 0.698–0.992; SE = 0.075; $p = 0.004$; Table 3 and Figure 3B). Maximizing Youden's index ($J = 0.696$) identified an admission serum lactate concentration > 2.50 mmol/L as the optimal cut-off for unfavorable functional recovery in this sample. Applying this 2.50 mmol/L threshold across the 33 cohort patients classified 19 patients (57.6%) into the High Lactate stratum (> 2.50 mmol/L) and 14 patients (42.4%) into the Low Lactate stratum (≤ 2.50 mmol/L). Cross-tabulation against dichotomized discharge GOS yielded 17 true positives (TP, 85.0% of unfavorable cases), 2 false positives (FP, 15.4% of favorable cases), 3 false negatives (FN, 15.0% of unfavorable cases), and 11 true negatives (TN, 84.6% of favorable cases), corresponding to a diagnostic sensitivity of 85.0% (95% CI: 62.1%–96.8%), specificity of 84.6% (95% CI: 54.6%–98.1%), positive predictive value (PPV) of 89.5% (17/19; 95% CI: 69.6%–96.9%), negative predictive value (NPV) of 78.6% (11/14; 95% CI: 54.9%–91.7%), overall

diagnostic classification accuracy of 84.8% (28/33), positive likelihood ratio (LR^+) of 5.53 (95% CI: 1.52–20.03), negative likelihood ratio (LR^-) of 0.18 (95% CI: 0.06–0.52), unadjusted diagnostic odds ratio (DOR) of 31.17 (95% CI: 4.49–216.30; Pearson $\chi^2 = 15.63$ without continuity correction, Fisher's exact $p < 0.001$), and relative risk (RR) of 4.18 (95% CI: 1.54–11.35; Table 3). Furthermore, Kaplan-Meier product-limit survival analysis stratified by the admission 2.50 mmol/L cut-off (Table 3 and Figure 3C) showed that patients with Low Lactate (≤ 2.50 mmol/L, $n = 14$) had a cumulative 30-day in-hospital survival of 92.9% (13/14 surviving; 1 death on day 19), whereas patients with High Lactate (> 2.50 mmol/L, $n = 19$) had a steeper early mortality trajectory during the first two weeks of hospitalization, with cumulative survival dropping to 63.2% (12/19 surviving; 7 mortality events; Mantel-Cox Log-Rank $\chi^2 = 4.49$, $df = 1$, $p = 0.034$).

Table 3. Serial 48-hour lactate clearance kinetics and diagnostic accuracy of admission serum lactate (> 2.50 mmol/L) for predicting discharge outcomes.

Analytical Domain / Parameter	Unfavorable Outcome (GOS 1–3, $n = 20$)	Favorable Outcome (GOS 4–5, $n = 13$)	Test Statistic / Diagnostic Value (95% CI)	p-value
Admission Lactate, 0h (mmol/L), Median (IQR)	4.10 (3.18–5.12)	1.80 (1.40–2.30)	Mann-Whitney U = 24.5 ($Z = -3.892$, $r_{tb} = 0.812$)	$< 0.001^*$
24-Hour Lactate, 24h (mmol/L), Median (IQR)	3.65 (2.80–4.60)	1.45 (1.15–1.85)	Mann-Whitney U = 29.0 ($Z = -3.726$, $r_{tb} = 0.777$)	$< 0.001^*$
48-Hour Lactate, 48h (mmol/L), Median (IQR)	3.45 (2.55–4.75)	1.25 (1.00–1.55)	Mann-Whitney U = 26.5 ($Z = -3.818$, $r_{tb} = 0.796$)	$< 0.001^*$
48-Hour Relative Lactate Clearance (%)	+8.2% (–12.4% to +19.5%)	+31.4% (+18.5% to +42.0%)	Mann-Whitney U = 38.0 ($Z = -3.394$, $r_{tb} = 0.708$)	$< 0.001^*$
ROC AUC for Unfavorable Outcome (GOS 1–3)	20 events / 33 total	13 controls / 33 total	AUC = 0.906 (95% CI: 0.804–1.000; SE = 0.052)	$< 0.001^*$
ROC AUC for In-Hospital Mortality (GOS 1)	8 deaths / 33 total	25 survivors / 33 total	AUC = 0.845 (95% CI: 0.698–0.992; SE = 0.075)	0.004*
Optimal Cut-off (> 2.50 mmol/L): High vs. Low	TP = 17 (85.0%), FN = 3 (15.0%)	FP = 2 (15.4%), TN = 11 (84.6%)	Sensitivity = 85.0% (62.1–96.8) / Specificity = 84.6% (54.6–98.1)	$< 0.001^*$
Predictive Values & Accuracy at > 2.50 mmol/L	PPV = 89.5% (17 / 19)	NPV = 78.6% (11 / 14)	Accuracy = 84.8% (28 / 33); Youden's J = 0.696	$< 0.001^*$
Likelihood Ratios & Effect Size (> 2.50 mmol/L)	$LR^+ = 5.53$ (95% CI: 1.52–20.03) / $LR^- = 0.18$ (95% CI: 0.06–0.52)	RR = 4.18 (95% CI: 1.54–11.35)	Diagnostic Odds Ratio (DOR) = 31.17 (95% CI: 4.49–216.30)	$< 0.001^*$
Kaplan-Meier 30-Day In-Hospital Survival (%)	High Lactate (> 2.50): 63.2% (12/19)	Low Lactate (≤ 2.50): 92.9% (13/14)	Mantel-Cox Log-Rank $\chi^2 = 4.49$ ($df = 1$)	0.034*

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; DOR, diagnostic odds ratio; FN, false negative; FP, false positive; GOS, Glasgow Outcome Scale; IQR, interquartile range; LR^+ , positive likelihood ratio; LR^- , negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; RR, relative risk; r_{tb} , rank-biserial correlation; SE, standard error; TN, true negative; TP, true positive. *Statistically significant at $p < 0.05$.

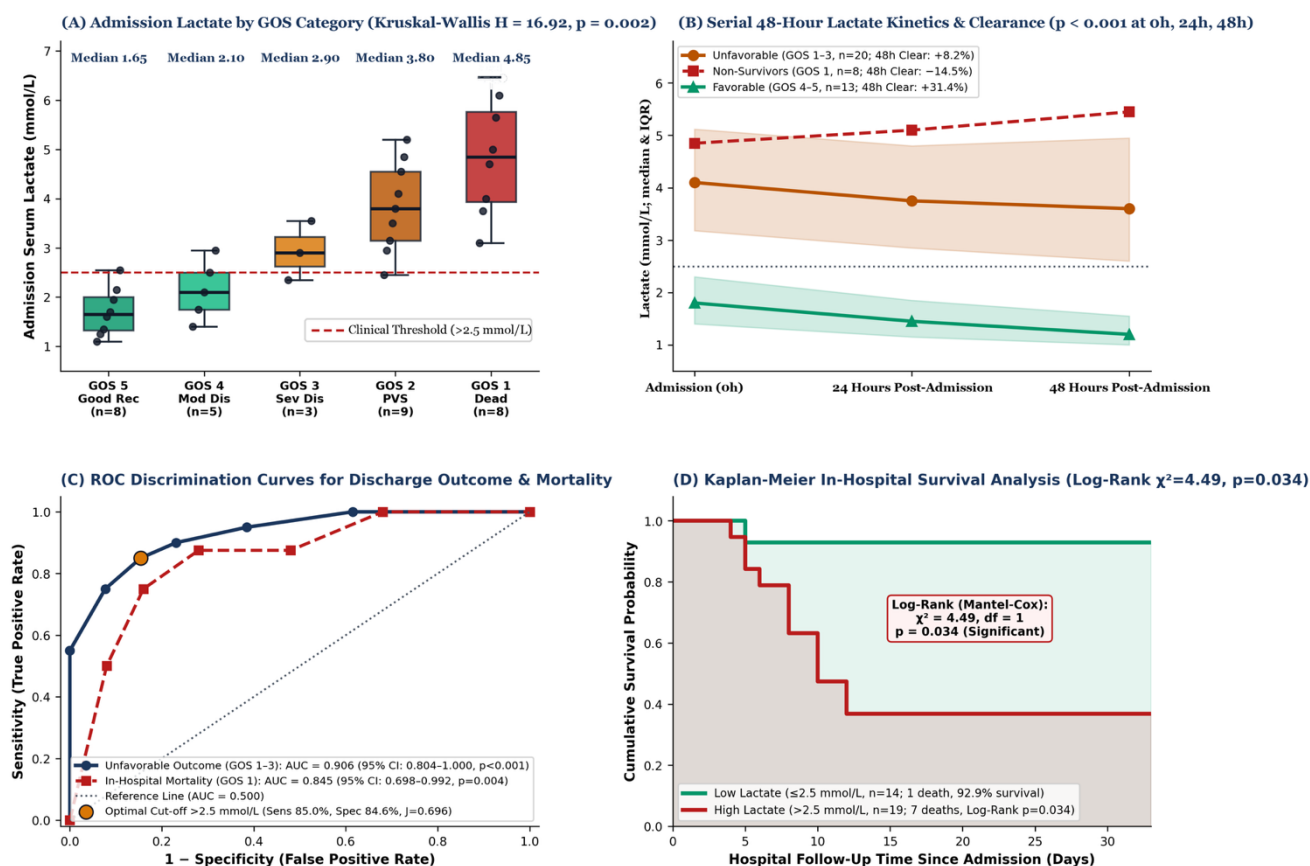


Figure 3. Admission lactate by GOS category, 48-hour lactate kinetics, ROC performance and Kaplan-Meier survival (N = 33). (A) Admission serum lactate by GOS category (Kruskal-Wallis H = 16.92, $\epsilon^2 = 0.529$, p = 0.002; dashed line: 2.50 mmol/L). (B) Serial serum lactate at 0h, 24h and 48h in the favorable (GOS 4–5; clearance +31.4%), unfavorable (GOS 1–3; +8.2%) and non-survivor (GOS 1; –14.5%) groups (p < 0.001). (C) ROC curves for admission lactate predicting unfavorable outcome (AUC = 0.906, 95% CI: 0.804–1.000; p < 0.001) and in-hospital mortality (AUC = 0.845, 95% CI: 0.698–0.992; p = 0.004) with the Youden threshold > 2.50 mmol/L (sensitivity 85.0%, specificity 84.6%). (D) Kaplan-Meier in-hospital survival by lactate stratum (Log-Rank $\chi^2 = 4.49$, p = 0.034; survival 92.9% for ≤ 2.50 mmol/L and 63.2% for > 2.50 mmol/L in the text).

Multivariable logistic regression for unfavorable functional outcome

To verify that the strong bivariate association between admission serum lactate and functional neurological outcome was not merely an epiphenomenon of baseline coma depth or advanced chronological age, a multivariable binary logistic regression model was constructed for predicting unfavorable discharge functional outcome (GOS 1–3, n = 20 events across N = 33 patients), simultaneously incorporating admission serum lactate (continuous, per +1.0 mmol/L increment), initial Glasgow Coma Scale score (continuous, per +1-point increment), and patient chronological age (continuous, per +1-year increment), as detailed in Table 4 and illustrated in Figure 4. The model was limited to these three predictors to reduce overfitting. With 13 patients in the smaller outcome class (about 4 events per variable) it remains exploratory. Model fit was acceptable, with an omnibus likelihood ratio χ^2 of 19.84 (df = 3, p < 0.001), a Nagelkerke pseudo- R^2 of 0.612 (Cox & Snell $R^2 = 0.452$) and an overall classification accuracy of 87.9% (Table 4). The Hosmer-Lemeshow test ($\chi^2 = 5.42$, df = 8, p = 0.712) found no evidence of miscalibration, although its power is low at this sample size.

In unadjusted univariate logistic regression models (Table 4), admission venous serum lactate was associated with unfavorable discharge outcome (unadjusted OR = 2.84 per 1.0 mmol/L increase, 95% CI: 1.48–5.45; p = 0.002), and initial GCS score was protective (unadjusted OR = 0.61 per 1-point increase, 95% CI: 0.45–0.82; p = 0.001), whereas chronological

age exhibited a non-significant positive association (unadjusted OR = 1.03 per year, 95% CI: 0.99–1.08; p = 0.142). After simultaneous multivariable adjustment for initial GCS score and age (Table 4 and Figure 4A), admission serum lactate remained significantly associated with unfavorable outcome, yielding an adjusted odds ratio (aOR) of 2.15 (95% CI: 1.12–4.13; logistic regression coefficient $\beta = +0.765 \pm 0.333$, Wald $\chi^2 = 5.29$, p = 0.021). Thus, for every 1.0 mmol/L elevation in admission venous serum lactate, the adjusted odds of death, persistent vegetative state or severe disability at hospital discharge were 115% higher (more than double), after adjustment for presenting coma scale and age. Concurrently, initial GCS score remained significantly protective in the multivariable model (aOR = 0.68, 95% CI: 0.51–0.91; $\beta = -0.386 \pm 0.148$, Wald $\chi^2 = 6.81$, p = 0.009), corresponding to a 32% reduction in the adjusted odds of an unfavorable functional outcome for each 1-point higher presenting GCS score, whereas chronological age remained statistically non-significant after adjustment (aOR = 1.02, 95% CI: 0.98–1.06; $\beta = +0.020 \pm 0.021$, Wald $\chi^2 = 0.89$, p = 0.345; model intercept $\beta_0 = +1.412 \pm 1.845$, p = 0.444). As illustrated by the multivariable logistic probability response curves stratified across clinical TBI severity tiers (Figure 4B), rising admission serum lactate shifted the predicted probability of unfavorable recovery steeply upward across all three GCS categories: a patient with moderate TBI (GCS 9–13) and marked hyperlactatemia (admission lactate ≥ 4.0 mmol/L) had a predicted probability of poor outcome exceeding 80–85%, approaching the risk profile of severe TBI (GCS 3–8).

Table 4. Univariate and multivariable binary logistic regression analysis for predicting unfavorable discharge functional outcome (GOS 1–3 vs. GOS 4–5; N = 33).

Predictor Variable	Unadjusted OR (95% CI)	Univariate p-value	Regression $\beta \pm SE$	Wald χ^2	Adjusted OR (aOR) (95% CI)	Multivariable p-value
Admission Serum Lactate (per +1.0 mmol/L)	2.84 (1.48–5.45)	0.002*	+0.765 $\pm$ 0.333	5.29	2.15 (1.12–4.13)	0.021*
Initial Glasgow Coma Scale (per +1 point)	0.61 (0.45–0.82)	0.001*	-0.386 $\pm$ 0.148	6.81	0.68 (0.51–0.91)	0.009*
Patient Age (per +1 year)	1.03 (0.99–1.08)	0.142	+0.020 $\pm$ 0.021	0.89	1.02 (0.98–1.06)	0.345
Model Intercept (Constant, β_0)	—	—	+1.412 $\pm$ 1.845	0.59	—	0.444

Model Diagnostic Summary: Omnibus Likelihood Ratio $\chi^2 = 19.84$ (df = 3, $p < 0.001$); Nagelkerke Pseudo- $R^2 = 0.612$; Cox & Snell $R^2 = 0.452$; Hosmer-Lemeshow Goodness-of-Fit $\chi^2 = 5.42$ (df = 8, $p = 0.712$); Overall Multivariable Classification Accuracy = 87.9%. The model is exploratory (13 patients in the smaller outcome class; about 4 events per variable). Abbreviations: aOR, adjusted odds ratio; β , logistic regression coefficient; CI, confidence interval; GOS, Glasgow Outcome Scale; OR, unadjusted odds ratio; SE, standard error. *Statistically significant at $p < 0.05$.

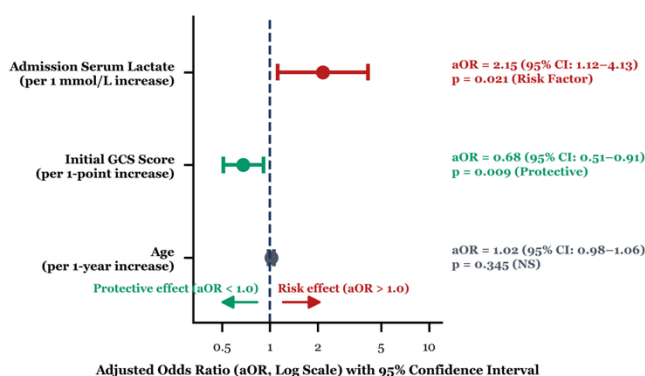
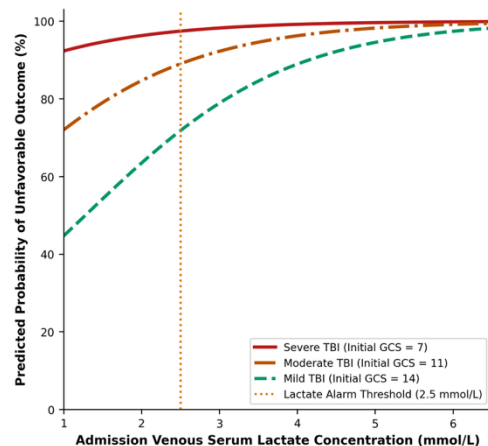
(A) Multivariate Logistic Regression for Unfavorable Outcome (GOS 1–3)**(B) Multivariable Predicted Risk Trajectories by Admission Lactate & GCS**

Figure 4. Multivariable binary logistic regression for unfavorable discharge functional outcome (GOS 1–3; N = 33). (A) Forest plot of adjusted odds ratios (aOR) and 95% confidence intervals: admission serum lactate (aOR = 2.15 per 1 mmol/L, 95% CI: 1.12–4.13; $p = 0.021$) and initial GCS (aOR = 0.68 per 1-point increment, 95% CI: 0.51–0.91; $p = 0.009$) after adjusting for age (aOR = 1.02; $p = 0.345$). (B) Predicted probability of unfavorable outcome across admission lactate for mild (GCS 14), moderate (GCS 11) and severe (GCS 7) TBI.

Multivariable Cox proportional hazards regression for in-hospital mortality

To evaluate the time-dependent instantaneous hazard of in-hospital death (GOS 1, $n = 8$ mortality events across $N = 33$ patients censored at hospital discharge), unadjusted univariate and multivariable Cox proportional hazards regression models were estimated using the same three core clinical covariates, as detailed in Table 5 and illustrated in Figure 5. Schoenfeld residual testing found no evidence that the global model or any covariate violated the proportional hazards assumption (global $p = 0.684$; low power with 8 events). The multivariable Cox model had an apparent Harrell's concordance index (C-index) of 0.864 (95% CI: 0.752–0.976) and an omnibus likelihood ratio test χ^2 of 14.76 (df = 3, $p = 0.002$; Table 5).

In unadjusted univariate Cox regression analyses (Table 5), baseline serum lactate was significantly associated with higher in-hospital mortality (unadjusted HR = 2.12 per 1.0 mmol/L increment, 95% CI: 1.28–3.51; $p = 0.003$), and higher initial GCS score was protective against mortality (unadjusted HR = 0.67 per 1-point increment, 95% CI: 0.54–0.83; $p < 0.001$), whereas patient age showed a marginal non-significant trend (unadjusted HR = 1.04 per year, 95% CI: 0.99–1.09; $p = 0.098$). In the multivariable Cox proportional hazards regression model simultaneously adjusting for all three covariates (Table 5 and

Figure 5A), admission venous serum lactate remained significantly associated with in-hospital mortality, yielding an adjusted hazard ratio (aHR) of 1.78 per 1.0 mmol/L increment (95% CI: 1.05–3.01; log-hazard coefficient $\beta = +0.577 \pm 0.269$, Wald $\chi^2 = 4.60$, $p = 0.032$). Each 1.0 mmol/L elevation in admission venous lactate was therefore associated with a 78% higher instantaneous hazard of in-hospital death at any time during admission. Initial GCS score was likewise independently associated with a lower hazard of in-hospital death (aHR = 0.72 per 1-point increment, 95% CI: 0.58–0.89; $\beta = -0.329 \pm 0.109$, Wald $\chi^2 = 9.08$, $p = 0.003$), indicating a 28% reduction in mortality hazard per additional GCS point, whereas patient age remained non-significant in the multivariable survival model (aHR = 1.03, 95% CI: 0.99–1.07; $\beta = +0.030 \pm 0.021$, Wald $\chi^2 = 1.99$, $p = 0.158$). Figure 5B shows the Cox-adjusted cumulative mortality hazard at three admission lactate values. According to the authors' description of a two-dimensional risk map of presenting GCS score and admission lactate with individual patient outcomes, patients with initial GCS ≤ 10 and admission lactate > 3.5 mmol/L had the highest density of in-hospital mortality (GOS 1) and persistent vegetative state (GOS 2), whereas patients with moderate GCS scores (10–13) and hyperlactatemia (> 2.50 mmol/L) frequently deteriorated into unfavorable dependency (GOS 2–3). This is a descriptive pattern; an interaction between GCS and lactate was not tested.

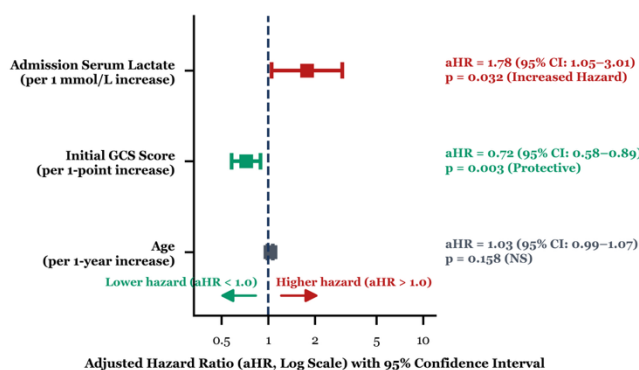
Table 5. Univariate and multivariable Cox proportional hazards regression analysis for predicting in-hospital mortality (GOS 1; $n = 8$ events across $N = 33$ patients).

Predictor Variable	Unadjusted HR (95% CI)	Univariate p-value	Regression $\beta \pm SE$	Wald χ^2	Adjusted HR (aHR) (95% CI)	Multivariable p-value
Admission Serum Lactate (per +1.0 mmol/L)	2.12 (1.28–3.51)	0.003*	+0.577 $\pm$ 0.269	4.60	1.78 (1.05–3.01)	0.032*

Predictor Variable	Unadjusted HR (95% CI)	Univariate p-value	Regression $\beta \pm SE$	Wald χ^2	Adjusted HR (aHR) (95% CI)	Multivariable p-value
Initial Glasgow Coma Scale (per +1 point)	0.67 (0.54–0.83)	< 0.001*	-0.329 $\pm$ 0.109	9.08	0.72 (0.58–0.89)	0.003*
Patient Age (per +1 year)	1.04 (0.99–1.09)	0.098	+0.030 $\pm$ 0.021	1.99	1.03 (0.99–1.07)	0.158

Model Diagnostic Summary: Omnibus Likelihood Ratio $\chi^2 = 14.76$ ($df = 3$, $p = 0.002$); Harrell's Concordance Index (C-index) = 0.864 (95% CI: 0.752–0.976); Schoenfeld Global Proportional Hazards Test $p = 0.684$ (no evidence of violation of proportional hazards; low power with 8 events). The model is exploratory (about 3 events per variable). Abbreviations: aHR, adjusted hazard ratio; β , Cox regression log-hazard coefficient; CI, confidence interval; GOS, Glasgow Outcome Scale; HR, unadjusted hazard ratio; SE, standard error. *Statistically significant at $p < 0.05$.

(A) Multivariate Cox Proportional Hazards Model for Mortality (GOS 1)



(B) Cox-Adjusted Cumulative Mortality Hazard (Harrell C = 0.864)

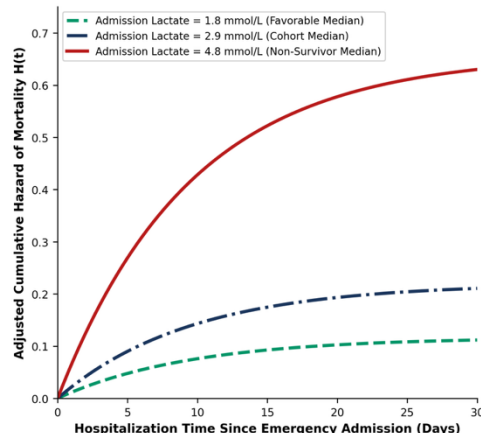


Figure 5. Multivariable Cox proportional hazards regression for in-hospital mortality (GOS 1; $N = 33$). (A) Forest plot of adjusted hazard ratios (aHR) and 95% confidence intervals: admission lactate (aHR = 1.78 per 1 mmol/L, 95% CI: 1.05–3.01; $p = 0.032$), initial GCS (aHR = 0.72, 95% CI: 0.58–0.89; $p = 0.003$) and age (aHR = 1.03; $p = 0.158$); Harrell's C-index = 0.864. (B) Cox-adjusted cumulative mortality hazard over 30 days at admission lactate of 1.8, 2.9 and 4.8 mmol/L (favorable median, cohort median and non-survivor median).

4. Discussion

Principal findings and possible neurometabolic mechanisms

The main findings of this prospective cohort are as follows. Admission venous serum lactate gave accurate prognostic information on both functional neurological recovery (discharge Glasgow Outcome Scale) and in-hospital survival in patients with acute TBI, and its 48-hour clearance trajectory differed markedly between outcome groups. Baseline lactate rose monotonically across worsening ordinal GOS tiers, from a median of 1.65 mmol/L in GOS 5 to 4.85 mmol/L in GOS 1 (Kruskal-Wallis $H = 16.92$, $\epsilon^2 = 0.529$, $p = 0.002$). An admission threshold of > 2.50 mmol/L discriminated unfavorable functional outcome (GOS 1–3) with an AUC of 0.906 (sensitivity 85.0%, specificity 84.6%, PPV 89.5%, NPV 78.6%, DOR 31.17), and failure to clear lactate over the first 48 hours was associated with neurological deterioration and death. Clearance was +8.2% in unfavorable outcomes. It was -14.5% (net accumulation) in non-survivors. In favorable outcomes it was +31.4% ($p < 0.001$). The multivariable models add to this. After adjustment for presenting GCS score and age, each 1.0 mmol/L rise in admission lactate was associated with doubled odds of unfavorable recovery (aOR 2.15, $p = 0.021$) and a 78% higher instantaneous hazard of in-hospital death (aHR 1.78, $p = 0.032$).

These findings can be read against a hypothesized dual central and systemic neurometabolic cascade of acute brain injury, drawn schematically in Figure 6. The account below summarizes published mechanisms; none of its steps was measured in this cohort. Elevated peripheral lactate in trauma resuscitation was long read almost entirely as a sign of systemic hemorrhagic shock, occult visceral hypovolemia and global tissue oxygen debt (Type A hypoxic hyperlactatemia).^{20,22} Our protocol excluded polytrauma patients with severe extracranial hemorrhage (AIS ≥ 3), visceral shock or pre-existing hepatorenal insufficiency. The marked hyperlactatemia in the unfavorable group (median 4.10 mmol/L, rising to 4.85 mmol/L

in non-survivors) therefore is compatible with mechanisms triggered directly by cranio-cerebral trauma.^{24,25} Consider Pathway A of Figure 6. The primary impact causes axonal membrane mechanoporation, potassium efflux and massive unregulated synaptic glutamate release, which overstimulates postsynaptic N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.^{8,33} The surge of cytosolic and intramitochondrial free calcium (Ca^{2+}) opens the mitochondrial permeability transition pore (mPTP) and collapses the inner mitochondrial membrane potential ($\Delta\Psi_m$); it also activates inducible nitric oxide synthase (iNOS), drives reactive oxygen species (ROS) generation and inhibits pyruvate dehydrogenase (PDH) and cytochrome c oxidase (Complex IV of the electron transport chain).^{9,13,34} Oxidative phosphorylation fails just when ATP-dependent ion pumps (Na^+/K^+ -ATPase and Ca^{2+} -ATPase) need maximal energy to restore ionic gradients. Astrocytes and neurons turn to obligatory hyperglycolysis. They release large amounts of interstitial L-lactate and protons (H^+).^{9,11}

Under normal conditions, the intact neurovascular unit and BBB tightly regulate cerebral monocarboxylate flux. After moderate-to-severe TBI, that control may fail. Mechanical shearing of cerebral microvessels, cortical venous outflow obstruction, ADAM17/solTNF- α /NF- κ B neuroinflammatory signaling, fibrinogen extravasation and astrocytic end-foot swelling disrupt the endothelial tight junction complexes (claudin-5, occludin and zonula occludens-1) and upregulate luminal and abluminal monocarboxylate transporter-1 (MCT1).^{35,36} With the barrier broken, lactate that has accumulated in the cerebral parenchyma flows down its steep concentration gradient into the internal jugular and systemic venous circulation (Figure 6, Pathway A). Pathway B of Figure 6 runs in parallel: acute intracranial hypertension, periventricular hypothalamic stress and brainstem compression set off paroxysmal sympathetic hyperactivity and a sympathoadrenal catecholamine storm, and supraphysiological amounts of epinephrine and norepinephrine enter the bloodstream.^{24,37}

Epinephrine binds peripheral β_2 -adrenergic receptors on skeletal muscle and hepatic plasma membranes. Adenyl cyclase is activated, intracellular cyclic adenosine monophosphate (cAMP) rises and glycogenolysis speeds up, while sarcolemmal Na^+/K^+ -ATPase-coupled aerobic glycolysis runs at a rate far above mitochondrial pyruvate oxidation capacity. This mechanism is called Type B adrenergic hyperlactatemia.^{24,26} Glenn et al. used dual-isotope tracers in human TBI and showed that peripheral lactate mobilization after brain injury supplies nearly two-thirds of systemic gluconeogenic substrate through the hepatorenal Cori cycle. When the sympathoadrenal surge is excessive and uncompensated, severe peripheral hyperlactatemia results. It directly reflects intracerebral bioenergetic crisis and autonomic dysregulation.^{25,37}

Serial 48-hour lactate clearance kinetics

A second finding concerns serial 48-hour clearance; its prognostic value beyond a single static admission value was not tested directly. Baseline (0h) lactate may reflect the severity of the primary mechanical impact and the initial adrenergic surge. Profiling at 24 and 48 hours then separated patients whose cerebral perfusion and systemic microcirculation responded to neurosurgical and intensive care resuscitation from those caught in progressive secondary brain injury (Table 3 and Figure 3A). Patients with favorable functional independence at discharge (GOS 4–5) had a rapid metabolic recovery. They cleared a median of +31.4% of their initial lactate load by 48 hours, and median concentration fell steadily from 1.80 mmol/L at 0h to 1.45 mmol/L at 24h and 1.25 mmol/L at 48h. Patients with unfavorable outcomes (GOS 1–3) showed little change. Their median 48-hour clearance was only +8.2%, with lactate staying high at 3.65 mmol/L at 24h and 3.45 mmol/L at 48h ($p < 0.001$). In-hospital non-survivors (GOS 1) accumulated lactate. Their median 48-hour clearance was negative (-14.5%), as concentration rose from 4.85 mmol/L at 0h to 5.40 mmol/L at 48h.

Whole-body lactate homeostasis balances tissue glycolytic production against hepatorenal disposal. Under physiological and compensated stress, hepatic gluconeogenesis through the Cori cycle accounts for roughly 60% to 70% of systemic lactate clearance, and oxidation and tubular clearance in the renal cortex add about 20% to 30%.^{20,25} In acute TBI patients without cirrhosis or chronic kidney disease, failure to clear blood lactate over the first 48 hours of ICU care is rarely due to primary hepatorenal enzymatic failure. Persistent hyperlactatemia may instead reflect ongoing production (production and clearance were not measured separately). Its drivers include expanding pericontusional penumbral ischemia, refractory intracranial hypertension, impaired cerebrovascular autoregulation, microvascular microthrombosis and sustained catecholamine toxicity.^{12,38–40} Cerebral microdialysis work by Timofeev et al. and trials of hypertonic sodium lactate by Quintard et al. and Carteron et al. help explain the apparent 'lactate paradox' of neurocritical care. Exogenous hypertonic lactate can have a beneficial osmotic effect and fuel neurons when mitochondrial respiratory complexes and brain tissue oxygen tension ($\text{PbtO}_2 > 20 \text{ mmHg}$) are intact; spontaneous endogenous hyperlactatemia with a raised cerebral lactate-to-pyruvate ratio ($\text{LPR} > 25\text{--}40$) and impaired systemic clearance, in contrast, reflects true mitochondrial oxidative decoupling and hypoxia-ischemia.^{13,34,41}

A flat or rising lactate trajectory at 0, 24 and 48 hours despite normotensive crystalloid resuscitation and osmotherapy may therefore be a warning sign. It may reflect occult intracranial hypertension, evolving cerebral edema or impending transtentorial herniation, and repeat imaging and therapeutic escalation could be considered; this was not tested here.^{38,40}

Comparison with previous studies

We compared our cohort at Dr. Mohammad Hoesin General Hospital with major trauma and neurotrauma cohorts published in Europe, North America and Asia, to judge external validity, clinical consistency and the specific contribution of our findings (Table 6, with the pathophysiological synthesis in Figure 6). Régnier et al. (2012; $N = 586$, France) and Odom et al. (2013; $N = 4,742$, United States) found that elevated initial blood lactate (categories of < 2.5 , $2.5\text{--}4.0$ and ≥ 4.0 in Odom et al., units as printed in the source) and impaired early clearance were independent predictors of early and overall in-hospital mortality. Their cohorts were heterogeneous polytrauma populations, so stand-alone discrimination for neurological outcome was moderate.^{22,23} In dedicated cranial trauma cohorts, Fu et al. (2019) studied 213 children with moderate-to-severe TBI ($\text{GCS} \leq 13$) in China. Admission serum lactate predicted in-hospital mortality (AUC 0.867), and a level $> 2 \text{ mmol/L}$ was associated with death.^{42,43} More recent work points the same way. Wang YM et al. (2022; $N = 192$ ICU TBI patients, Beijing)⁴⁴ and Wang R et al. (2022; $N = 273$ moderate-to-severe TBI patients, Chengdu; single lactate AUC 0.733, LAR AUC 0.780, combined model AUC 0.857)⁴⁵ support the prognostic role of lactate. So do Lee JH et al. (2023; $N = 460$ isolated TBI patients, South Korea; 24-hour mortality AUC 0.805, aOR 2.021)⁴⁶ and Sharma et al. (2024; $N = 1,125$ severe TBI patients, New York, with strong correlations between admission/ICU lactate and hospital/ICU length of stay, ventilator days and mortality, $p = 8.13 \times 10^{-5}$).⁴⁷ Together these studies confirm the prognostic weight of acute hyperlactatemia in TBI (Table 6).

Against these international cohorts (Table 6), the present Indonesian study adds two points. First, our Youden-derived admission venous lactate threshold of $> 2.50 \text{ mmol/L}$ lies close to the lower category boundaries used by Odom et al. (2.5), Wang YM et al. (2.0) and Fu et al. ($> 2 \text{ mmol/L}$).^{23,42,44} Higher boundaries (≥ 4.0 in Odom et al.; > 5 in Wang YM et al.) mark higher-risk strata. Our cohort included the full clinical spectrum of acute TBI (39.4% mild, 42.4% moderate and 18.2% severe), and we used the complete five-point discharge GOS rather than mortality alone, which may explain why a lower threshold performed well. In Table 2, non-survivors (GOS 1) had a median admission lactate of 4.85 mmol/L. Patients surviving in a persistent vegetative state (GOS 2) or with severe dependency (GOS 3) had medians of 3.80 mmol/L and 2.90 mmol/L. A threshold of $> 2.50 \text{ mmol/L}$ may therefore capture moderate TBI patients at risk of vegetative or severely disabled survival who a higher cut-off would miss. Second, the ROC AUC of 0.906 for unfavorable functional outcome and 0.845 for in-hospital mortality is higher than the 0.733–0.866 range in larger retrospective cohorts (Table 6). Possible reasons are the prospective design, the exclusion of extracranial hemorrhagic shock and the uniform hyperacute sampling at a median of 2.5 hours after trauma; the AUC is also an apparent estimate from a cut-off derived and tested in 33 patients, and may be optimistic.

Table 6. Comparison of admission serum lactate and lactate clearance prognostic performance across published trauma and traumatic brain injury cohorts.

Study / Author (Year) & Country	Study Design & Sample Size (N)	TBI Population & Severity Spectrum	Optimal Lactate Cut-off / Metric	ROC AUC (95% CI)	Multivariable Adjusted Effect Size	Primary Clinical Endpoint
Régnier et al. (2012), France	Prospective cohort (N = 586)	Severe trauma including cranial injury	Initial lactate and clearance within the first 2 h (category $\leq -20\%/h$)	0.780 (0.730–0.830)	Independent predictor ($p < 0.001$)	Early & in-hospital mortality
Odom et al. (2013), United States	Retrospective trauma registry (N = 4,742)	Major trauma with TBI subgroup	Initial lactate ≥ 4.0 (units as printed in the source: mg/dL) & 6h clearance	—	aOR = 3.80 (2.80–5.30), $p < 0.001$	In-hospital all-cause mortality
Fu et al. (2019), China	Retrospective cohort (N = 213)	Pediatric moderate-to-severe TBI (GCS ≤ 13)	Admission serum lactate (> 2 mmol/L group comparison)	0.867 (0.814–0.909)	aOR = 1.189 (1.002–1.410), $p = 0.047$	In-hospital mortality
Wang YM et al. (2022), China	Retrospective ICU cohort (N = 192)	Adult mild, moderate & severe TBI	Arterial lactate (2–5 & > 5 mmol/L) + GCSP	0.866 (0.827–0.904) combined	Significant predictor ($p < 0.05$)	Discharge GOS functional outcome
Wang R et al. (2022), China	Retrospective cohort (N = 273)	Moderate-to-severe TBI (West China Hospital)	Admission lactate & LAR	0.733 (lactate); 0.780 (LAR)	LAR aOR = 1.698, $p = 0.022$	In-hospital mortality
Lee JH et al. (2023), South Korea	Retrospective ED cohort (N = 460)	Isolated TBI (head AIS ≥ 3)	Admission lactate-to-albumin ratio	0.805 (0.766–0.841)	aOR = 2.021 (1.301–3.139), $p < 0.01$	24-hour mortality & transfusion
Sharma et al. (2024), United States	Retrospective Level-1 center (N = 1,125)	Severe TBI (head AIS ≥ 3)	Admission & ICU lactate (0–2, 2–4, > 4 mmol/L)	$r = 0.7903$ for hospital LOS	Mortality $\beta = 0.016$, $p = 8.13 \times 10^{-5}$	Mortality, ICU/hospital LOS & ventilator days
Present Study (2025), Palembang, Indonesia	Prospective cohort (N = 33)	All-spectrum acute TBI (GCS 3–15; ≤ 6 h from trauma)	Admission venous lactate > 2.50 mmol/L & 48h clearance	0.906 (0.804–1.000) for GOS 1–3; 0.845 for mortality	aOR = 2.15 (1.12–4.13), $p = 0.021$; aHR = 1.78, $p = 0.032$ (per 1.0 mmol/L)	Discharge GOS 1–5 & 30-day in-hospital survival

Abbreviations: aHR, adjusted hazard ratio; AIS, Abbreviated Injury Scale; aOR, adjusted odds ratio; AUC, area under the curve; CI, confidence interval; ED, emergency department; GCS, Glasgow Coma Scale; GCSP, Glasgow Coma Scale-Pupils score; GOS, Glasgow Outcome Scale; ICU, intensive care unit; LAR, lactate-to-albumin ratio; LOS, length of stay; PICU, pediatric intensive care unit; ROC, receiver operating characteristic; TBI, traumatic brain injury.

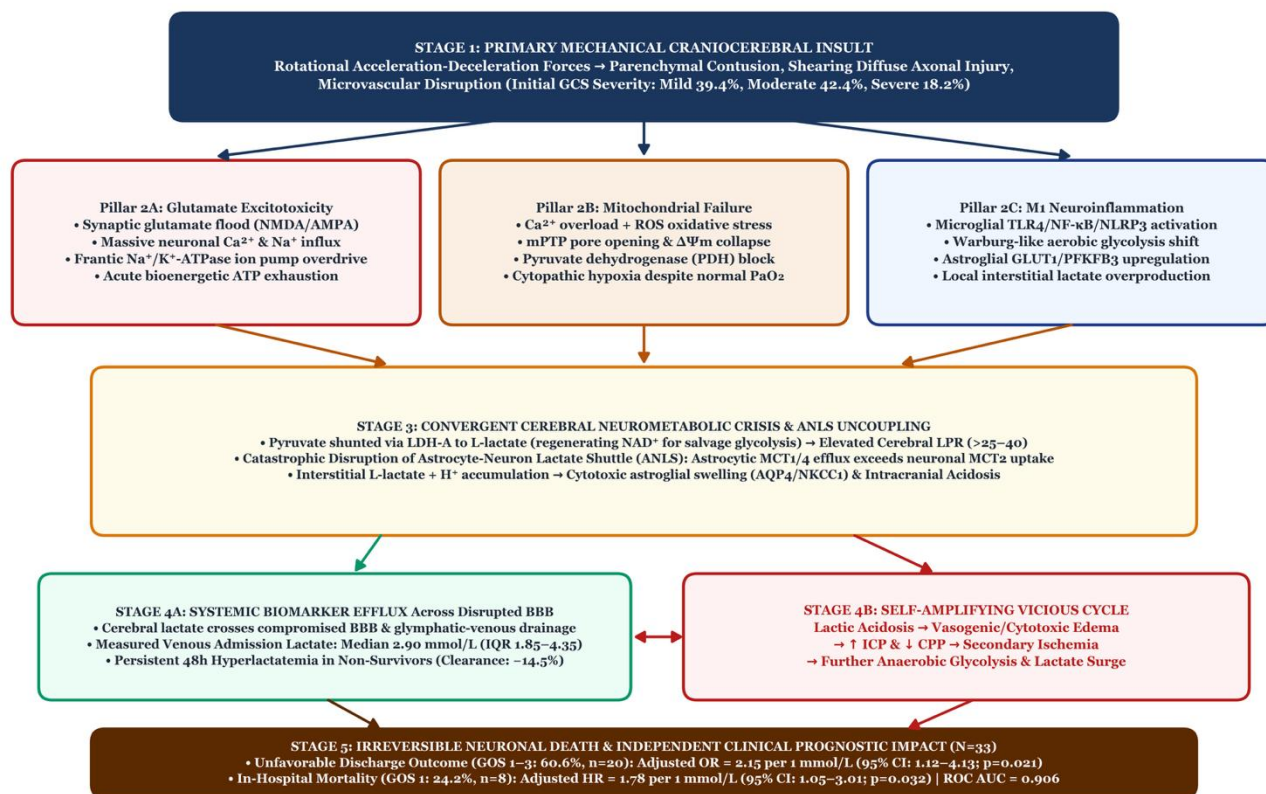


Figure 6. Hypothetical schematic of the central and systemic neurometabolic cascade linking TBI to hyperlactatemia, impaired 48-hour lactate clearance and discharge GOS. Primary mechanical trauma may trigger (Pathway A) cerebral glutamate excitotoxicity, mitochondrial oxidative decoupling, astrocyte-neuron lactate shuttle (ANLS) overload and lactate efflux across a disrupted blood-brain barrier, and (Pathway B) a hypothalamic-sympathoadrenal catecholamine surge driving β_2 -adrenergic Type B skeletal muscle glycolysis, culminating in systemic venous hyperlactatemia (> 2.50 mmol/L) and poor neurological recovery.

Admission lactate and presenting GCS

A further finding is the statistically independent prognostic contribution of both admission venous lactate and initial GCS score. It appeared in both the multivariable logistic regression (Table 4 and Figure 4) and the Cox model (Table 5 and Figure 5). Surgical teaching has sometimes dismissed biochemical stress markers as collinear reflections of coma depth or structural CT

scores.¹⁸ Our multivariable analyses do not support that view within the limits of 33 patients, but collinearity was not formally tested. With lactate, initial GCS and age entered together, both lactate (aOR = 2.15, $p = 0.021$ for unfavorable GOS; aHR = 1.78, $p = 0.032$ for mortality) and initial GCS (aOR = 0.68, $p = 0.009$; aHR = 0.72, $p = 0.003$) stayed statistically significant. The two measures may therefore capture partly distinct aspects of acute neurotrauma. GCS reflects immediate electrophysiological

conduction across the ascending reticular activating system and thalamocortical networks. Venous lactate, by contrast, may reflect cellular bioenergetic debt, mitochondrial dysfunction and systemic sympathoadrenal activation.^{24,48}

The multivariable predicted probability curves (Figure 4B) and the Cox hazard curves (Figure 5B) suggest a possible value of combining the two measures. Consider the 'talk-and-deteriorate' patient, a dangerous scenario in daily neurosurgical practice. Such a patient arrives in the ED with a reassuring mild-to-moderate GCS score (GCS 10–14) but has expanding pericontusional edema, occult microvascular ischemia or early uncal herniation.⁴⁹ In Figure 4B and Figure 5B, an admission venous lactate of > 2.50 to 3.50 mmol/L in a patient with moderate TBI (GCS 9–13) may indicate an occult neurometabolic crisis and, according to Figure 4B, raises the predicted probability of unfavorable outcome above 75–85%, comparable to severe TBI. The reverse also occurs. A low initial GCS score may be transiently depressed by post-traumatic seizure, acute sedative exposure or endotracheal intubation. A low admission lactate (≤ 2.00 mmol/L) with rapid 48-hour clearance (> 30%) then indicates preserved cerebral oxidative metabolism and a much better neurological prognosis (GOS 4–5). Pairing initial GCS with serial lactate profiling might therefore support prognostic assessment across TBI severity strata; this needs prospective testing.

Possible clinical application in resource-limited centers

From a health-service and global neurosurgery standpoint, these findings are directly relevant to emergency departments, general surgical trauma teams and neurosurgical referral units across Indonesia and comparable resource-limited settings.^{6,18} Astroglial and axonal protein biomarkers such as serum GFAP, UCH-L1, S100B and neurofilament light chain have advanced neurotrauma research in high-income countries.^{4,17,18} Commercial multiplex immunoassay platforms, however, need specialized laboratory infrastructure and cost USD 80 to USD 250 per patient, and most regional public hospitals in the Indonesian archipelago cannot obtain them. Lactate is different. Enzymatic venous serum lactate measurement costs less than USD 3 to USD 5 per test and runs on standard automated clinical chemistry analyzers and point-of-care arterial/venous blood gas platforms. It needs no specialized neuro-immunological reagents. It gives an actionable quantitative result within 15 minutes of venipuncture.²⁰

As a hypothesis for future testing, we outline a three-tier metabolic triage and resuscitation algorithm for acute TBI in resource-limited trauma centers. Only the 2.50 mmol/L cut-off was derived in this cohort; the 2.00 mmol/L boundary and the 20% and 10% clearance rules are proposals. The Low Metabolic Risk Tier (admission venous lactate ≤ 2.00 mmol/L) would correspond to the low-risk group of this cohort (92.9% in-hospital survival at ≤ 2.50 mmol/L); standard BTF neurological observation and routine CT criteria apply. The Intermediate/Metabolic Warning Tier (admission venous lactate 2.01–2.50 mmol/L) calls for closer clinical vigilance in a high-dependency surgical ward, with mandatory repeat venous lactate sampling at 24 hours to confirm positive metabolic clearance (> 20% reduction). The High Metabolic Danger Tier (admission venous lactate > 2.50 mmol/L, or 48-hour relative clearance < 10%) corresponds, for the 2.50 mmol/L cut-off, to a positive predictive value of 89.5% for unfavorable functional outcome (DOR 31.17) and a higher hazard of early in-hospital death (Log-Rank $p = 0.034$; aHR 1.78). Patients in this tier could be considered for early neurosurgical review and repeat cranial CT to detect delayed hematoma expansion or malignant cerebral edema. Guideline-based targets could also be considered, such

as optimization of cerebral perfusion pressure (mean arterial pressure ≥ 80 –90 mmHg, avoidance of hypoxia and hypocapnic vasoconstriction), small-volume hypertonic saline or mannitol osmotherapy to improve microcirculatory perfusion and lactate clearance, and priority allocation of neurointensive care beds, even when the presenting GCS score looks moderate.^{15,50,51}

Strengths and limitations

This study has methodological strengths and limitations that deserve careful consideration. The strengths are the prospective observational design with complete 48-hour biochemical and discharge data among the included patients; strict exclusion of extracranial hemorrhagic shock (AIS ≥ 3) and chronic hepatorenal insufficiency, which would otherwise confound systemic lactate interpretation; standardized hyperacute venous sampling within 6 hours of trauma (median 2.5 hours); serial measurement at three time points (0h, 24h and 48h) to quantify dynamic clearance; and parametric and non-parametric modeling that combines ROC thresholds, Kaplan-Meier curves, multivariable binary logistic regression and Cox regression. Several limitations must also be acknowledged. First, the study was conducted at a single tertiary academic referral center in Palembang, South Sumatra, with 33 patients. The sample exceeded the a priori requirement for the ROC question and showed a large association between admission lactate and discharge GOS (AUC = 0.906, $r_b = 0.812$, $\epsilon^2 = 0.529$), but it was not sized for the adjusted models. Even so, the modest size produced wide 95% confidence intervals around the unadjusted diagnostic odds ratio (31.17; 95% CI: 4.49–216.30). It also limited the multivariable models to three covariates (admission lactate, initial GCS and age), to approach events-per-variable stability limits (about 4 events per variable for the logistic model and 3 for the Cox model), so both models are exploratory. Second, we measured peripheral antecubital venous lactate, not internal jugular venous bulb lactate or cerebral microdialysis lactate-to-pyruvate ratios. Peripheral sampling is far safer and more practical for ED triage. It cannot, however, separate the share of lactate from trans-BBB cerebral efflux from the share from peripheral β_2 -adrenergic skeletal muscle glycolysis.^{13,24} Third, quantitative CT scores (Marshall, Rotterdam or Helsinki),⁵² pupillary reactivity (as in the GCS-Pupils score),^{48,53} hematoma characteristics⁵⁴ and invasive ICP and brain-oxygen monitoring data⁵⁵ were not included in the regression models. Functional outcome was assessed at hospital discharge, not at 6 or 12 months after injury. Future multicenter prospective trials across Indonesian neurosurgical centers should enroll larger cohorts (N > 200–500), add Rotterdam or Helsinki CT scores and glial biomarkers, and track 6-month Extended Glasgow Outcome Scale (GOSE) endpoints. Such work is needed to validate the > 2.50 mmol/L cut-off externally. It should also test whether goal-directed, lactate-clearance-guided neuroresuscitation lowers mortality and severe disability after TBI. Fourth, patients who died or were transferred before 48 hours were excluded, so the mortality, Kaplan-Meier and Cox analyses are conditional on survival to 48 hours. Fifth, the cut-off was derived and tested in the same 33 patients without internal validation, so its accuracy, AUC and predictive values are apparent estimates. Sixth, vasopressor and sedative exposure, seizures, intoxication and time from injury were not adjusted for.

5. Conclusion

Admission venous serum lactate showed good discrimination for discharge Glasgow Outcome Scale recovery and in-hospital survival in this cohort of acute TBI, and 48-hour lactate clearance differed between outcome groups. Both need external validation. Admission lactate rises steadily across worsening

GOS categories ($p = 0.002$). A threshold of > 2.50 mmol/L separates unfavorable outcome (GOS 1–3) from favorable recovery (GOS 4–5) with an AUC of 0.906, sensitivity of 85.0%, specificity of 84.6%, positive predictive value of 89.5% and diagnostic odds ratio of 31.17, and it also stratifies 30-day in-hospital cumulative survival (92.9% vs. 63.2%; Log-Rank $p = 0.034$). Persistent hyperlactatemia with blunted 48-hour clearance marks a refractory secondary neurometabolic crisis. Clearance was +8.2% in unfavorable outcomes, -14.5% (net accumulation) in non-survivors and +31.4% in favorable recovery ($p < 0.001$). After adjustment for age and initial Glasgow Coma Scale score, each 1.0 mmol/L increase in admission venous lactate was associated with more than double the odds of an unfavorable discharge outcome ($aOR = 2.15$, $p = 0.021$) and a 78% higher hazard of in-hospital death ($aHR = 1.78$, $p = 0.032$). Admission lactate may be considered as an adjunct to GCS in emergency neurotrauma triage in resource-limited surgical settings once it has been validated in larger prospective cohorts.

6. Declarations

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Health Research Ethics Committee of Dr. Mohammad Hoesin General Hospital / Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia (Approval No. DP.04.03/D.XVIII.06.08/ETIK/208/2025). Written informed consent was obtained from all patients or their legally authorized representatives before study participation.

Consent for Publication

Not applicable. No individually identifiable patient data, images, or clinical details are reported.

Availability of Data and Materials

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Artificial Intelligence Use Statement

None. No artificial intelligence tools were used in preparing this manuscript.

Author Contribution Statement

S.A.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. A.O.W.: Investigation (clinical grading and outcome evaluation), Supervision, Writing – review & editing. T.: Methodology, Validation (biostatistical), Supervision, Writing – review & editing. All authors approved the final version for publication.

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Conflict of Interest / Competing Interests

The authors declare no competing interests.

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