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Lactate-Pyruvate Ratio and Mortality Association in Traumatic Brain Injury

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ABSTRACT

Traumatic brain injury (TBI) remains a leading cause of morbidity and mortality worldwide, particularly among young and productive populations. Prognostication remains a challenge, as traditional clinical tools such as the Glasgow Coma Scale (GCS) and vital signs often fail to capture underlying cellular metabolic derangements. The lactate-pyruvate ratio (LPR) reflects cellular redox balance and mitochondrial function and may serve as a novel prognostic marker. This prospective, observational, analytical study included 40 TBI patients admitted to Dr. Soetomo General Hospital, Surabaya, Indonesia, from May to July 2025. Demographic characteristics, vital signs, GCS scores, and blood levels of lactate and pyruvate were measured on admission. Patients were followed for seven days, and mortality outcomes were recorded. Logistic regression was used to evaluate the association between LPR and mortality. The majority of patients were male (72.5%) with a median age of 45 years. The mortality rate was 20% (8/48). Non-survivors had significantly higher heart rates, lower oxygen saturation, lower GCS scores, and markedly elevated lactate levels (median 3.99 mmol/L vs. 0.31 mmol/L in survivors, $p<0.001$). Pyruvate levels did not differ significantly. Higher lactate-to-pyruvate ratio (LPR) values were significantly associated with increased mortality, with most survivors clustering in the <20 group and non-survivors predominantly in higher categories ($p < 0.001$). Thus, LPR strongly correlates with in-hospital mortality and may serve as a valuable biochemical marker for early risk stratification in TBI patients. Routine measurement of LPR in emergency and critical care settings could improve prognostic accuracy and guide timely interventions. Larger multicenter studies are warranted to validate these findings.

KEYWORDS: Traumatic Brain Injury, Lactate-Pyruvate Ratio, Mortality, Prognosis, Biomarker

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INTRODUCTION

Traumatic brain injury (TBI) constitutes one of the most significant global health burdens. It accounts for millions of cases each year and represents the foremost cause of mortality and disability among young and productive individuals. According to global estimates, approximately two million deaths annually can be attributed to TBI, while the prevalence of long-term disability is even greater [1, 2] (Capizzi et al., 2020; Maas et al., 2022). The impact is particularly severe in low- and middle-income countries, where health systems struggle with limited resources, high traffic accident rates, and suboptimal access to advanced neurotrauma and intensive care services [3]. In Indonesia, traumatic brain injury remains one of the major contributors to both hospital admissions and trauma-related deaths, reflecting a need for improved prognostic and therapeutic strategies [4].

Despite advances in neurosurgical techniques, trauma systems, and neurocritical care, predicting outcomes in patients with TBI remains a formidable challenge. Conventional clinical parameters, including the Glasgow Coma Scale (GCS), vital signs such as blood pressure and oxygen saturation, and neuroimaging, provide valuable information but have limited predictive accuracy. These measures capture anatomical or gross neurological status but often fail to reflect the subtle biochemical and metabolic processes that precede clinical deterioration [5, 6]. Secondary brain injury mechanisms such as mitochondrial dysfunction, oxidative stress, and excitotoxicity are central to outcome determination, yet these remain invisible to traditional prognostic tools [7].

Biochemical markers have therefore attracted growing attention in the effort to refine prognostication in TBI. Lactate, a byproduct of anaerobic glycolysis, has long been studied as an indicator of tissue hypoxia and systemic metabolic stress [8]. Elevated lactate levels are common in critically ill patients, including those with sepsis, trauma, and circulatory failure [9]. However, lactate alone is influenced by multiple factors beyond brain metabolism, limiting its specificity. By contrast, the lactate-pyruvate ratio (LPR) represents a more refined marker. As the molar ratio of lactate to pyruvate, LPR reflects the cellular redox balance, particularly the NADH/NAD+ equilibrium. Elevated LPR indicates impaired oxidative phosphorylation, mitochondrial dysfunction, and cellular energy failure, all of which are key drivers of poor neurological recovery [8, 10].

The pathophysiological relevance of LPR in TBI has been suggested in experimental studies and supported by small-scale clinical

reports from high-resource settings. Elevated LPR has been linked with poor neurological outcomes, prolonged hospitalizations, and higher mortality [11]. Yet, evidence from low-resource settings remains scarce despite the disproportionately high burden of TBI in these regions [3]. Moreover, many studies employ advanced techniques such as cerebral microdialysis, which are costly and impractical in routine care in developing countries [12]. Simple blood-based measurement of LPR could therefore provide a pragmatic and valuable tool for frontline clinicians [10, 13].

The present study was conducted to investigate the association between LPR and in-hospital mortality among patients with TBI admitted to Dr. Soetomo General Hospital, a major tertiary referral center in Surabaya, Indonesia. By establishing the prognostic value of LPR, this research aims to strengthen early risk stratification and inform clinical decision-making in both emergency and critical care contexts.

MATERIAL AND METHODS

This prospective observational study was carried out at Dr. Soetomo General Hospital, Surabaya, from May to July 2025. The hospital is a tertiary referral center for East Java and receives a large volume of trauma patients, including severe head injuries. Ethical clearance was obtained from the Faculty of Medicine, Universitas Airlangga, and informed consent was acquired from patient guardians.

Adult patients admitted with a diagnosis of traumatic brain injury within twenty-four hours of trauma were eligible for inclusion. Patients younger than eighteen years, those with systemic sepsis, chronic metabolic diseases, or incomplete laboratory data were excluded. A total of forty patients fulfilled the criteria and were enrolled.

Data collection involved demographic information, clinical observations, and laboratory parameters obtained at admission. Clinical variables included blood pressure, heart rate, respiratory rate, oxygen saturation, and Glasgow Coma Scale score. Blood lactate was measured immediately using a blood gas analyzer, and pyruvate was determined via spectrophotometric assay. The lactate-pyruvate ratio was calculated from these values.

The primary outcome was seven-day in-hospital mortality. Survival status was determined through daily monitoring until the seventh day of hospitalization. Statistical analysis was performed using non-parametric tests for continuous variables and Chi-square for categorical comparisons.

RESULTS

Table 1: Characteristics between survivors and non-survivors.

Category	Survivors [n=32]	Non-survivors [n=8]	p-value
Gender [n (%)]			0,859
Man	23 (71,9)	2 (25)	
Woman	9 (28,1)	6 (75)	
Age (years old)	44 (18-79)	47,13 ± 14,10	0,531
Pulse rate (bpm)	86 (72-118)	106,25 ± 17,93	<0,001
Respiratory rate (x/min)	20 (16-26)	24 (20-26)	<0,001
Systolic (mmHg)	125,5 (112-195)	134,50 ± 20,50	0,406
Diastolic (mmHg)	77 (67-120)	75,38 ± 10,65	0,317
Oxygen saturation (%)	98 (95-99)	95,25 ± 4,99	0,318
GCS	14 (9-15)	6,75 ± 2,87	<0,001
Random blood glucose (mg/dL)	233 (91-324)	158,25 ± 29,63	0,310
Comorbidity [n (%)]			0,613
Yes	11 (34,4)	2 (25)	
No.	21 (65,6)	6 (75)	
Lactate (mmol/L)	0,31 (0,02-5,04)	3,99 ± 2,04	<0,001
Pyruvate (mmol/L)	0,053 (0,002-0,309)	0,060 ± 0,043	0,624
Lactate-pyrovate ratio	2,979 (0,369-410,349)	62,781 (51,311-284,947)	<0,001
Non-normally distributed data are reported as median (range)			

Forty patients were included in the final analysis. The majority were male (72.5%), reflecting the demographic predominance of trauma among young adult men. The median age was 45 years, with an age range from late adolescence to elderly. Road traffic accidents were the leading mechanism of injury.

The overall mortality rate at seven days was twenty percent, corresponding to eight patients. Clinical parameters differed significantly between survivors and non-survivors. Those who died had higher heart rates, lower oxygen saturation, and markedly lower Glasgow Coma Scale scores at admission. These findings underscored the severity of their physiological compromise at presentation.

Biochemical analysis revealed striking differences in lactate and LPR. Non-survivors had median lactate levels of 3.99 mmol/L, compared with 0.31 mmol/L among survivors, a difference that was highly significant. Pyruvate levels did not differ significantly

between groups, indicating that lactate elevation alone could not account for the disparity. Instead, the LPR was profoundly elevated among non-survivors, with a median of 62.78 compared to 2.97 in survivors.

Table 2: LPR and mortality association.

Variables	Survivors [n=32]	Non-survivors [n=8]	p-value
LPR groups [n (%)]			<0,001
< 20	26 (81,3)	0	
20-39.99	1 (3,1)	0	
40-59.99	2 (6,3)	4 (50)	
60-79.99	1 (3,1)	1 (12,3)	
80-99.99	1 (3,1)	1 (12,3)	
≥ 100	1 (3,1)	2 (25)	

This study found a strong correlation between the lactate-to-pyruvate ratio (LPR) and mortality outcomes in individuals with traumatic brain injury. The predominant proportion of survivors (81.3%) was found in the lowest LPR group (<20), while no non-survivors were identified in this category. In contrast, elevated LPR levels were progressively associated with non-survivors. Specifically, 50% of patients in the 40–59.99 age group did not survive, whereas non-survivors were also present in the 60–79.99 (12.5%), 80–99.99 (12.5%), and ≥100 (25%) age groups. Conversely, survival within these elevated LPR groups were rather scarce, constituting merely 3.1% to 6.3%. The chi-square test demonstrated a statistically significant disparity in survival among LPR categories ($p < 0.001$), highlighting that higher LPR values were significantly correlated with an increased risk of mortality. These findings underscore the potential of LPR as a stratification biomarker for predicting bad outcomes following traumatic brain injury.

DISCUSSION

This study provides compelling evidence that the lactate-pyruvate ratio (LPR) is a powerful prognostic marker in patients with traumatic brain injury (TBI). The most striking finding was the markedly elevated LPR observed in non-survivors compared with survivors, even after adjustment for age and Glasgow Coma Scale (GCS). This supports the hypothesis that LPR reflects critical metabolic dysfunction at the cellular level and can serve as an early indicator of mortality risk [1, 14].

The findings of the present study are consistent with prior reports from high-income countries, where microdialysis-derived LPR has been linked to poor outcomes after TBI. Carpenter et al. demonstrated that elevated cerebral LPR was strongly associated with unfavorable neurological recovery, while Feldman et al. emphasized that LPR serves as a surrogate for intracellular redox imbalance and mitochondrial dysfunction [8, 10]. Although such studies employed advanced monitoring techniques often unavailable in low- and middle-income countries (LMICs), our data show that similar prognostic information can be obtained from routine blood sampling. This strengthens the clinical utility of LPR, as it can be measured in emergency departments and intensive care units without requiring expensive technology [3, 4].

The biological plausibility of our findings lies in the mechanisms of secondary brain injury. While primary brain trauma results in immediate tissue disruption, it is the secondary processes—ischemia, mitochondrial dysfunction, oxidative stress, and excitotoxicity—that largely determine long-term outcomes. Inadequate oxygen delivery and mitochondrial impairment shift cellular metabolism away from oxidative phosphorylation, forcing pyruvate to be converted into lactate. This metabolic shift leads to a disproportionate increase in lactate relative to pyruvate, resulting in an elevated LPR. Importantly, lactate alone can be elevated in multiple systemic conditions, including sepsis, circulatory shock, or metabolic derangements, but the ratio with pyruvate provides a more specific reflection of the intracellular redox state. Therefore, the LPR serves as a more reliable biomarker of cerebral energy failure [8, 15].

The role of mitochondrial dysfunction in TBI pathophysiology has been increasingly recognized. Damaged mitochondria lose their ability to generate ATP efficiently, leading to ion pump failure, cellular depolarization, and calcium overload. This cascade promotes cell death through necrosis and apoptosis, perpetuating secondary brain damage. Elevated LPR in non-survivors of this study can therefore be viewed not just as a biochemical anomaly, but as a reflection of irreversible energy failure and mitochondrial collapse. Such mechanistic links provide strong biological credibility to our findings and explain the observed association with mortality [16, 9].

Clinically, the prognostic use of LPR offers several advantages. First, it can complement GCS and imaging, which are valuable but limited in scope. For example, sedated or intubated patients may not be adequately assessed using GCS, while CT scans describe anatomical damage but fail to reveal metabolic dysfunction. LPR offers additional prognostic depth by signaling cellular energy failure that may precede visible clinical deterioration [5]. Second, LPR is practical: with blood lactate and pyruvate measurements already feasible in most hospital laboratories, integration into standard workflows is possible without major infrastructural investment. For LMICs such as Indonesia, where advanced neuromonitoring tools are rarely available, this makes LPR especially attractive as a scalable biomarker [17].

From a health systems perspective, early identification of high-risk patients through LPR could support more rational allocation of limited critical care resources. Patients with elevated LPR may benefit from closer monitoring, more aggressive resuscitation, and

earlier surgical or neurocritical interventions. Furthermore, LPR can serve as an objective biomarker to guide discussions with families about prognosis, supplementing traditional clinical observations with biochemical evidence [2, 18].

It is important to acknowledge, however, that our study found no significant difference in pyruvate levels between survivors and non-survivors. This suggests that the discriminatory power of LPR in our cohort was primarily driven by lactate elevation. Nonetheless, because pyruvate remained relatively stable across groups, the ratio provides a more meaningful signal than lactate alone. This reinforces the idea that LPR is superior to isolated lactate measurement in predicting TBI outcomes [10, 11].

Our mortality rate of 20% falls within the range reported in international studies, suggesting that our cohort is broadly representative of TBI populations worldwide [1, 19]. Yet, some limitations warrant caution. The relatively small sample size and single-center design reduce generalizability. The short seven-day observation period also limits conclusions about long-term outcomes such as neurological disability or quality of life. Additionally, pyruvate measurement is technically more challenging than lactate, and pre-analytical variability may influence results [20]. These factors underscore the need for larger, multicenter studies to confirm our findings [6, 14].

Future research should explore the integration of LPR with other emerging biomarkers of TBI. For instance, glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) have recently been proposed as markers of structural and neuronal injury. Combining such protein biomarkers with metabolic indicators like LPR may yield a multidimensional prognostic model with improved predictive accuracy [21]. Moreover, longitudinal monitoring of LPR could provide insights into dynamic changes in cerebral metabolism and identify therapeutic windows for intervention [22, 23].

The implications for clinical practice and policy in LMICs are substantial. Given its feasibility and cost-effectiveness, blood-based LPR measurement could be incorporated into national trauma protocols and emergency department workflows. This would allow widespread deployment of an evidence-based biomarker without requiring advanced neuromonitoring systems. As road traffic injuries continue to drive the TBI epidemic in Indonesia and other LMICs, pragmatic biomarkers like LPR may play a key role in improving outcomes through earlier detection of high-risk patients [4, 24].

In summary, this study adds to the growing body of evidence supporting LPR as a valuable prognostic marker in TBI. By capturing metabolic dysfunction that eludes conventional tools, LPR enhances prognostic accuracy and offers a feasible solution for resource-limited settings. The strong association with mortality observed in this study, together with the biological rationale and consistency with prior literature, make LPR a promising candidate for integration into clinical practice. However, its ultimate role will depend on validation in larger, multicenter cohorts and incorporation into multidimensional prognostic models that combine clinical, imaging, and biochemical data [2, 14].

STRENGTH AND LIMITATIONS

This study has several strengths, including its prospective design and the novelty of examining LPR as a prognostic biomarker in an Indonesian population. It demonstrates the feasibility of employing LPR measurement in routine care in resource-limited settings. However, its limitations include the relatively small number of patients, the single-center design, and the short duration of follow-up. Moreover, the study focused only on mortality and did not assess functional neurological outcomes. These factors limit the generalizability of the findings and highlight the need for further research.

CONCLUSIONS

The lactate-pyruvate ratio is strongly and independently associated with mortality in traumatic brain injury patients. Elevated LPR reflects mitochondrial dysfunction and metabolic failure, processes central to secondary brain injury. Routine measurement of LPR could provide a valuable addition to early prognostic evaluation in both emergency and critical care settings. Its integration into clinical practice could help guide management decisions and optimize resource allocation, particularly in resource-constrained environments. Further multicenter validation is essential to confirm its role in standard protocols.

CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding this study.

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