Prognostic Indicators of Severe Traumatic Brain Injury in Patients Admitted in ICU: A ProspectiveObservational Study

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Abstract:

Background: Traumatic brain injury (TBI) is a major public health issue worldwide, with high rates of mortality and morbidity despite advances in medical and surgical management. Lactate and hypocalcaemia are emerging as potential prognostic factors in severe TBI, with several studies suggesting that their measurement may help predict outcomes and guide management strategies. Further research is needed to confirm these associations and elucidate the underlying mechanisms.
Methods: This observational cohort study was conducted in the Departments of Anesthesiology & Critical Care Medicine at the Sheri-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, from March 2021 to February 2022. Around 70 patients with severe traumatic brain injury (TBI), Glasgow Coma Scale (GCS) scores of 3-8, and abnormal computed tomography (CT) scans upon admission to the ICU were included in the study. Considering that critical patients die within 12 hours of hospital admission, we had decided to use patients having TBI of 24 hrs as an arbitrary cutoff point. Patients were then stratified according to two clinical outcomes: Group I, with GOS score ≤ 3, and Group II, including patients with GOS score > 3.
Results: The mean age of patients in Group I was 49.7±10.52 years, while in Group II, it was 35.8±9.43 years. The P-value for the age difference between the two groups was <0.001, indicating a statistically significant difference. The lactate levels on Day 3 were found significantly higher in patients having GOS≤3 and also there was a significant correlation (r=0.415) between lactate on Day 0 and lactate on Day 3. At Day 3, the ionized and non-ionized Ca levels were significantly lower in Group I compared to Group II.
Conclusion: The present study has demonstrated that prognostic markers such as age, gender, pupil reactivity, and laboratory markers like calcium and lactate have a significant impact on the outcome of traumatic brain injury (TBI).These markers can be utilized to triage, prognosticate, and evaluate the severity of TBI patients, especially in resource-limited settings where these markers are readily available. Timely intervention may enhance the prognosis.

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Introduction

Traumatic brain injury (TBI) is a major public health issue worldwide, with high rates of mortality and morbidity despite advances in medical and surgical management. The identification of prognostic factors is critical in determining appropriate management strategies and predicting outcomes in TBI patients. Recently, there has been growing interest in the role of lactate and hypocalcaemia as potential prognostic factors in severe TBI. Lactate is a metabolic byproduct of anaerobic respiration, which is known to occur in brain tissue following injury. Elevated lactate levels have been associated with poor outcomes in TBI patients, including increased mortality and disability (1). Additionally, lactate levels have been shown to correlate with injury severity, as measured by the Glasgow Coma Scale (GCS) (2). Furthermore, persistent elevation of lactate levels in the first 24 hours following injury has been associated with poorer outcomes, including increased mortality and longer hospital stays (3).Hypocalcaemia, defined as a serum calcium level less than 8.5 mg/dL, is a common electrolyte abnormality following TBI, occurring in up to 40% of cases (4). Hypocalcaemia has been shown to be associated with increased mortality and morbidity in TBI patients, with one study reporting a 4-fold increased risk of mortality in patients with severe hypocalcaemia (5). Furthermore, hypocalcaemia has been associated with an increased risk of seizures, cerebral edema, and delayed recovery (6).While the exact mechanisms underlying the associations between lactate and hypocalcaemia and poor outcomes in TBI remain unclear, several hypotheses have been proposed. These include the possibility that elevated lactate levels may reflect ongoing tissue hypoxia, inflammation, or cellular damage, while hypocalcaemia may exacerbate cerebral edema, increase seizure activity, and impair cerebral auto regulation (7). It is imperative that lactate and hypocalcaemia are emerging as potential prognostic factors in severe TBI, with several studies suggesting that their measurement may help predict outcomes and guide management strategies. Further research is needed to confirm these associations and elucidate the underlying mechanisms.

Methods

This observational cohort study, entitled "Lactate and Hypocalcaemia as Possible Prognostic Factors of Mortality and Morbidity in Severe Traumatic Brain Injury," was conducted in the Departments of Anesthesiology & Critical Care Medicine at the Sheri-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, from March 2021 to February 2022. Institutional Ethical Committee approval was obtained, and written informed consent was obtained from patients' family members prior to participation in the study.

All patients with severe traumatic brain injury (TBI) admitted to the ICU of the institution between December 2020 and October 2022 were included in the study. A cohort study was conducted with 70 consecutive patients with severe TBI, Glasgow Coma Scale (GCS) scores of 3-8, and abnormal computed tomography (CT) scans upon admission to the ICU. All patients were managed according to institutional protocols consistent with recent traumatic brain injury guidelines. SKIMS provided the highest level of care for neuro-trauma patients and corresponded to the comprehensive service (level 3) in the Kashmir valley. Due to the observational nature of the study, written informed consent was waived by the SKIMS Institutional Ethics Committee in accordance with Indian Law for Health Research in patients.

Inclusion Criteria: Patients with isolated severe TBI admitted within 24 hours of injury, age over 18 years, GCS scores of 3-8, and no prior history of inflammatory, metabolic, or neuro-psychiatric disorders that could influence biomarker concentrations and clinical outcomes were included in the study.

Exclusion Criteria: Patients undergoing repeat surgical procedures, CSF shunt procedures, and those with co-morbid conditions predisposing them to an intraoperative increase in serum lactate, such as liver disease, kidney disease, shock, and sepsis, were excluded from the study. Other exclusions were diabetes mellitus history, hemodynamic instability, chronic severe neurological disturbance, active neurologic conditions such as stroke, TBI beyond 24 hours, intake of medication or diseases affecting calcium metabolism, hyperphosphatemia> 1.32 mmol/L, hypomagnesemia< 0.61 mmol/L, alcoholism, hypoalbuminemia, preexisting hyperlactatemia, and pregnancy at the time of injury.

During the study period, all neuro-trauma patients over 18 years old admitted to the ICU were included. For each patient admitted, the following data was recorded by an ICU physician during the pre-ICU phase: age, sex, trauma characteristics, systolic arterial blood pressure, heart rate, respiratory rate, Glasgow Coma Scale, blood gas analysis with lactate/Ca2+ levels, and oxygen saturation. Injury severity was classified as per injury severity score (ISS). The details of the care provided during the pre-ICU phase were also recorded. On arrival at the ICU, hemodynamic, neurological, and respiratory status was re-evaluated and recorded. Considering that critical patients die within 12 hours of hospital admission, we had decided to use patients having TBI of 24 hrs as an arbitrary cutoff point. Patients were then stratified according to two clinical outcomes: Group I, with GOS score ≤ 3, and Group II, including patients with GOS score > 3.Patients with severe traumatic brain injury who were scheduled for operative procedures underwent a comprehensive preoperative neurological assessment using the Glasgow Coma Scale (GCS) to record their score. Airway assessment was also performed to ensure adequate ventilation support. Baseline investigations, including CBC, KFT, LFT, blood glucose, serum electrolytes, ECG, chest X-ray, and baseline lactate levels, were recorded for each study subject. Other patient information, such as age, gender, weight, type of surgery and anesthesia, anesthesia and surgery time, pH level, lactate levels on the day of admission and subsequently on a daily basis, and calcium levels (both ionized and non-ionized), were also documented.At the end of the study, lactate and calcium levels in patients who developed fresh-onset neuro-deficits in the postoperative period were compared statistically with the lactate and calcium levels of patients who did not develop any new-onset neuro-deficits during this period. Additionally, lactate and calcium levels in patients with TBI were compared statistically between two groups of patients with a GOS score less than 3 and those with a GOS score greater than 3. Severe brain injury was defined as closed injury with a post-resuscitation Glasgow Coma Score (GCS) of 8 or less, or a deterioration to a GCS score of 8 or less within 24 hours of admission.

Statistical Analysis: SPSS and Graph Pad Prism (Version 9) was used to perform statistical analysis on the data. Mean values with standard deviations were calculated and the significance of differences between different experimental variables was tested using the Student's t-test and one-way analysis of variance (ANOVA), wherever applicable. A p-value of less than or equal to 0.05 was considered statistically significant. Pearson's coefficient of correlation was also calculated using R software, version 4.2.2, to estimate the strength of the relationship between different variables.

Results

This study included 70 patients diagnosed with moderate to severe traumatic brain injury, who were then classified into two distinct groups based on their Glasgow Outcome Scale (GOS) scores. Group I consisted of patients with GOS

scores of three or lower (≤ 3), while Group II included patients with GOS scores higher than three (> 3). The data revealed that Group I comprised of 32 patients, whereas Group II comprised of 43 patients.

Table 1: Age distribution of study patients in two groups

Age (Years)	Group I		Group II		P-value
	No.	%age	No.	%age	
18-29	2	6.3	20	46.5	<0.001*
30-59	25	78.1	18	41.9	
≥ 60	5	15.6	5	11.6	
Total	32	100	43	100	
Mean±SD	49.7±10.52		35.8±9.43		

Group 1 (GOS≤3); Group II (GOS>3): *Statistically Significant Difference (P-value<0.05)

The mean age of patients in Group I was 49.7±10.52 years, while in Group II, it was 35.8±9.43 years. The P-value for the age difference between the two groups was<0.001, indicating a statistically significant difference. The age distribution was further analyzed by grouping patients into three age groups. In the 18-29 age group, 2 patients (6.3%) belonged to Group I, while 20 patients (46.5%) belonged to Group II. In the 30-59 age group, 25 patients (78.1%) were in Group I, and 18 patients (41.9%) were in Group II. In the age group of 60 and above, 5 patients (15.6%) were in Group I, and 5 patients (11.6%) were in Group II. We found that Group I included 25 males (78.1%) and 7 females (21.9%), while Group II included 31 males (72.1%) and 12 females (27.9%). A statistical analysis was performed using a P-value of 0.553, indicating a non significant difference in gender distribution between the two groups.

Table 2: Association of pupil reaction and GOS score

Parameter		Group I		Group II		P-value
		No.	%age	No.	%age	
Pupil	Isocoria	25	78.1	39	90.7	0.233
	Anisocoria	7	21.9	4	9.3	
Pupil reaction	Non-reactive	11	34.4	6	14.0	0.036*
	Reactive	21	65.6	37	86.0	

Group 1 (GOS≤3); Group II (GOS>3): *Statistically Significant Difference (P-value<0.05)

The table shows the comparison of pupil responses in two groups of patients with traumatic brain injury (Group I and Group II). The first row indicates the percentage of patients with equal-sized pupils (isocoria) in Group I (78.1%) and Group II (90.7%) with a P-value of 0.233. The second row shows the percentage of patients with unequal-sized pupils (anisocoria) in Group I (21.9%) and Group II (9.3%). The third row displays the percentage of patients with non-reactive pupils in Group I (34.4%) and Group II (14.0%) witha P-value of 0.036. The last row shows the percentage of patients with reactive pupils in Group I (65.6%) and Group II (86%).

Table 3: Lactate levels on different days of ICU admission					
Time Interval	Group I		Group II		P-value
	Mean	SD	Mean	SD	
Day 0	2.28	0.46	2.26	0.53	0.865
Day 3	2.92	0.54	1.73	0.39	<0.001*
Day 7	2.07	0.27	2.04	0.31	0.663

Group 1 (GOS≤3); Group II (GOS>3): *Statistically Significant Difference (P-value<0.05)

In this study, lactate levels (mmol/l) were measured and compared between two groups, Group I and Group II. On Day 0, the lactate levels for Group I and Group II were 2.28±0.46 and 2.26±0.53, respectively, with a non-significant P-value of 0.865. However, on Day 3, the lactate levels for Group I and Group II were 2.92±0.54 and 1.73±0.39, respectively, with a highly significant P-value of <0.001. On Day 7, the lactate levels for Group I and Group II were 2.07 ±0.27 and 2.04±0.31, respectively, with a non-significant P-value of 0.663. The lactate levels on day 3 were found significantly higher in patients having GOS≤3 and also there was a significant correlation (r=0.415) between lactate on Day 0 and lactate on Day 3.

Table 4: Calcium levels on different days of ICU admission						
Ca (mmol/l)	Time Interval	Group I		Group II		P-value
		Mean	SD	Mean	SD	
Ionized	Day 0	1.09	0.23	1.12	0.29	0.631
	Day 3	0.93	0.14	1.27	0.25	<0.001*
	Day 7	1.19	0.19	1.24	0.21	0.291
Non-ionized	Day 0	2.05	0.31	2.09	0.35	0.609
	Day 3	1.98	0.25	2.14	0.28	0.013*
	Day 7	2.23	0.31	2.29	0.34	0.435

Group 1 (GOS≤3); Group II (GOS>3): *Statistically Significant Difference (P-value<0.05)

The ionized Ca levels (mmol/l) for Group I and Group II were compared at Day 0, Day 3, and Day 7. The results showed that there was no significant difference in ionized Ca levels between the two groups at Day 0 (1.09 ± 0.23 for Group I vs 1.12±0.29 for Group II, P-value=0.631) and Day 7 (1.19± 0.19 for Group I vs 1.24±0.21 for Group II, P-value=0.291). However, at Day 3, the ionized Ca levels were significantly lower in Group I (0.93±0.14) compared to Group II (1.27±0.25), with a P-value of <0.001. In addition, the non-ionized Ca levels (mmol/l) were also compared between the two groups at Day 0, Day 3, and Day 7. The results showed that there was no significant difference in non- ionized Ca levels between the two groups at Day 0 (2.05± 0.31 for Group I vs 2.09±0.35 for Group II, P-value=0.609) and Day 7 (2.23±0.31 for Group I vs 2.29±0.34 for Group II, p=0.435). However, at Day 3, the non-ionized Ca levels were significantly lower in Group I (1.98±0.25) compared to Group II (2.14±0.28), with a P-value of 0.013.

Discussion

The study examined the possible prognostic factors of mortality and morbidity in severe traumatic brain injury, focusing on lactate and hypocalcemia. The results showed a significant difference in age between the two groups of patients with Group I (patients with high lactate and hypocalcemia) having a mean age of 49.7±10.52 years, and Group II (patients with normal lactate and hypocalcemia) was having a mean age of 35.8±9.43 years. Age is an important factor to consider in traumatic brain injury, as older age has been associated with worse outcomes. The finding of a higher mean age in Group I is consistent with previous studies that have reported older age as a risk factor for poor outcomes in traumatic brain injury (8, 9).The study also analyzed age distribution in three age groups (18-29, 30-59, and 60 and above) and found a significant difference in age distribution between the two groups. Group II had a higher percentage of younger patients in the 18-29 age group (46.5%) compared to Group I (6.3%), while Group I had a higher percentage of older patients in the 30-59 age group (78.1%) compared to Group II (41.9%).This finding is consistent with previous studies that have reported a U-shaped relationship between age and traumatic brain injury outcomes, with worse outcomes in both younger and older patients (10). Younger patients may have more severe injuries due to higher energy trauma, while older patients may have pre-existing comorbidities that increase the risk of complications. Overall, the results of this study suggest that age is an important factor to consider in the prognosis of severe traumatic brain injury, and that lactate and hypocalcemia may be useful prognostic markers. However, further research is needed to confirm these findings and determine the optimal treatment strategies for patients with these risk factors. The results of the study suggest that thepresence of non-reactive pupils may be a potential prognostic factor for mortality and morbidity in severe traumatic brain injury (TBI) patients. Group I, with a higher percentage of non-reactive pupils, had a significantly higher mortality and morbidity rate compared to Group II. The higher percentage of anisocoria in Group I may indicate a more severe injury and further support the association with worse outcomes. These findings are consistent with previous studies that have demonstrated the prognostic value of pupil reactivity in TBI patients. A study by Steyerberg et al. (2008) showed that the presence of non-reactive pupils was associated with a significantly higher mortality rate in severe TBI patients (11). Similarly, a study by Joseph M et al. (2011) found that the absence of pupil reactivity was a significant predictor of poor neurological outcomes in TBI patients (12). In addition, the results suggest that lactate and hypocalcemia may also be potential prognostic factors for mortality and morbidity in severe TBI patients. These factors were not directly measured in the study, but their association with non-reactive pupils and worse outcomes has been previously reported. A study by Wang et al. (2022) found that elevated lactate levels were associated with increased mortality and worse neurological outcomes in TBI patients(2). Similarly, a study by Manuel et al (2015) found that hypocalcemia was associated with increased mortality in TBI patients (13).

Lactate is not merely considered a waste product, as its accumulation in the brain and the resulting lactic acidosis are deemed potential key factors for secondary insults and a significant cause of cell death and brain ischemia after traumatic brain injury (TBI) (14). Cureton et al. conducted a study on lactate in traumatic injury, in which 555 TBI patients were evaluated, and concluded that higher levels of lactate were linked to more severe head trauma, with a significance level of $p<0.0001$ (15). In this study, we measured blood lactate levels on three days, i.e., on admission day, day 3, and day 7, and analyzed patient outcomes using the Glasgow Outcome Scale (GOS). On comparing the two groups, there was no statistical significance on Day 0 with a P-value

of 0.865. On Day 3, the lactate values in group I with a GOS score ≤3 were significantly higher than those in group II, with a mean of 2.92±0.54 in Group I and a mean of 1.73±0.39 in Group II, with a P-value <0.001. On day 7, there was no statistical significance between the two groups, with a P-value of 0.663. In this study, we found a weak correlation between lactate levels on Day 0 and Day 3, with a correlation coefficient of r=0.415 (weak correlation). Our findings are consistent with those of Kuhna et al., who reported that elevated lactate levels were common on Day 3 in patients with GOS ≤3, with a statistically significant p value of 0.002 on day 3 and a correlation coefficient of 0.333 between lactate on day 3 and day 0 (16). Vinas-rios JM et al. hypothesized that a change from aerobic to anaerobic mitochondrial pathways occurs following trauma, leading to neuro inflammatory responses and lactate accumulation (17). Yan EB et al. considered the disruption of the aerobic mitochondrial pathway to be an essential aspect, resulting from decreased mean arterial pressure values and inadequate tissue oxygenation, leading to lactate accumulation (18). Zauner AMJ et al. hypothesized that measures such as maintaining sufficient brain perfusion and avoiding acidosis could protect against inflammation and disrupted aerobic mitochondrial metabolism, thus enhancing patient outcomes (19). However, Laode RA et al. showed contrary results in their study, where lactate levels were considered predictors of TBI on admission day, day 1, and day 7, and a statistical significance was found between lactate levels and GOS score on day 0 and day 1, with p values of 0.033 and 0.011, respectively, but not on day 7, with a p value of 0.938 (20). The difference in results could be attributed to the fact that their study exclusively focused on TBI patients who underwent surgery, with early surgical intervention measures aimed at reducing blood lactate levels, a small sample size of 60 patients, whereas our study includes both surgically managed and conservatively managed patients.

Calcium has been extensively scrutinized in the context of traumatic brain injury, and is known to play a pivotal role in this condition. It has been associated with delayed cell death and damage following such injuries. In present study, we monitored the levels of both ionized and non-ionized calcium for three days, namely on day zero, day three, and day seven of ICU admission. Our findings reveal a significant difference in ionized calcium levels on the third day of admission between groups GOS ≤3 and GOS >3, with a mean of 0.93 ± 0.14 in Group I and a mean of 1.27 ± 0.25 in Group II. This disparity is statistically significant (P-value<0.001) and is in line with similar observations made in prior studies, such as the one conducted by Manuel et al, which also noted a significant correlation between calcium levels and mortality on the third day of ICU admission (p<0.008) . BalbinoM etal's study on the relationship between hypocalcemia and poor outcomes after TBI postulates that the sudden influx of intracellular calcium leads to the initiation of apoptosis, causing the inhibition of enzymatic processes in mitochondria and activation of lipases (21). Sanchez-Rodriguez et al's study on 122 patients with moderate and severe TBI also supports the association between serum ionized calcium levels (<1.10 mmol/l) on the third day after head trauma and mortality (p<0.0009) (22). The authors of this study also found a significant association between protein S100 b and IL-6 levels on day three of TBI, with p values of 0.002 and 0.007, respectively (22). They hypothesize that the hypocalcemia observed on day three may be due to the increase in inflammatory proteins and molecules. Kuhna et al's study also reported a correlation between hypocalcemia and poor outcomes in TBI on the third day of admission to the ICU (p=0.002) (16). Our study's results suggest that hyperlactemia and hypocalcemia may serve as significant and readily available markers to assess the severity of brain damage three days after trauma. These findings indicate the presence of several pathological mechanisms, including neuro-

inflammation, altered vessel autoregulation, and hypoxia.

Conclusion

The present study demonstrated that prognostic markers such as age, pupil reactivity, and laboratory markers like calcium and lactate have a significant impact on the outcome of traumatic brain injury (TBI). The outcome in patients of advanced age, predominantly male gender, was unfavorable. Patients with non-reactive pupils had a higher chance of mortality. Furthermore, lactate and calcium levels were found to be correlated with the outcome of TBI patients. Hypocalcemia of serum ionized calcium, defined as <1.10 mmol/l, was observed in patients with a Glasgow Outcome Scale (GOS) score ≤3 on day 3 of admission to the intensive care unit (ICU). Moreover, higher serum lactate levels, defined as >2.0 mmol/l, were found in TBI patients with GOS score of ≤3 on day 3 of ICU admission.These results indicate that calcium and lactate levels are reliable markers for the severity of brain damage following TBI due to various pathologic mechanisms such as direct mechanical trauma, neuro-inflammation, altered vessel auto-regulation, hypoxia, and metabolic changes. These markers can be utilized to triage, prognosticate, and evaluate the severity of TBI patients, especially in resource-limited settings where these markers are readily available. Timely intervention mayenhance the prognosis.

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