International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Integrative Evaluation of Serum Ionic Magnesium and Calcium Levels, Pupillary Reactivity, and Clinical Parameters as Predictors of Neurological Outcomes in Patients with Traumatic Brain Injury

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Abstract: ***Background: Traumatic brain injury (TBI) is a leading cause of disability and death worldwide, yet prognostication remains challenging. While the Glasgow Coma Scale (GCS) and pupillary reactivity are well - established clinical indicators, growing evidence suggests that electrolyte disturbances, particularly hypomagnesemia and hypocalcemia, may further refine outcome predictions. Objective: To evaluate the combined role of serum ionic magnesium (Mg^{2+}) and calcium (Ca^{2+}) levels, alongside pupillary reactivity and clinical parameters, in predicting neurological outcomes among severe TBI patients in a tertiary care hospital. Methods: This 12 - month prospective observational study (June 2023 – May 2024) was conducted at a tertiary - care hospital. Patients aged 18–80 years with severe TBI (GCS ≤ 8) presenting within 24 hours of injury were enrolled. Isolated brainstem injuries were excluded due to unique management constraints. Serum Mg^{2+} and Ca^{2+} were measured on day 0 (admission), day 3, and day 7. All patients received Level III ICU care, guided by Brain Trauma Foundation protocols for TBI management, including intracranial pressure (ICP) monitoring when indicated. Ethical clearance was obtained from each institution's review board. Neurological outcomes at 6 months were assessed using the Glasgow Outcome Scale (GOS), dichotomized into poor (GOS ≤ 3) and good (GOS > 3). Logistic regression identified independent predictors of poor outcome. Results: A total of 84 patients (mean age: 50.4 ± 15.7 years; M: F ratio ~ 2: 1) were included. Ventilatory support was required in 63%, and ICP monitoring was performed in 42%. Hypomagnesemia (<1.6 mEq/L) at admission showed a significant association with poor outcomes (odds ratio [OR] = 6.6, p = 0.002), while hypocalcemia (<1.14 mmol/L) on day 3 was similarly linked to worse prognoses (OR = 4.2, p = 0.015). Nonreactive pupils conferred an 8.2 - fold increased risk of poor outcome (p < 0.001). Age and sex were not significant predictors. Multivariate analysis incorporating Mg^{2+}, Ca^{2+}, and pupillary reactivity demonstrated improved predictive accuracy (area under the curve = 0.87). Conclusion: Hypomagnesemia and hypocalcemia were significant adjunctive predictors of poor neurological outcomes in severe TBI, particularly when combined with pupillary assessment and conventional measures. Day 3 and day 7 electrolyte measurements capture peaks of metabolic derangement crucial for risk stratification. Early identification of these disturbances may inform therapeutic interventions to optimize neurological recovery.***

Keywords: traumatic brain injury, neurological outcomes, hypomagnesemia, hypocalcemia, pupillary reactivity

1. Introduction

Traumatic brain injury (TBI) remains a global health concern, associated with high rates of morbidity, mortality, and long - term disability. [1, 2] Pathophysiologically, TBI comprises both a primary mechanical insult and a complex secondary injury cascade, including cerebral edema, ischemia, and various metabolic disruptions. [3, 4] Established clinical indicators such as the Glasgow Coma Scale (GCS) and pupillary reactivity have proven valuable for triaging TBI severity and guiding initial management. [5] However, these parameters alone may not fully account for the heterogeneous outcomes observed in severe TBI, prompting the investigation of additional prognostic factors.

Mounting evidence suggests that **electrolyte imbalances**, particularly involving magnesium and calcium, play a notable role in TBI outcomes. [6, 7] Hypomagnesemia may potentiate excitotoxicity via N - methyl - D - aspartate (NMDA) receptors, increase neuronal vulnerability to injury, and facilitate inflammatory processes. [8, 9] Meanwhile, hypocalcemia can exacerbate cytotoxic edema, disrupt neuronal signaling, and compromise cerebral autoregulation. [10, 11] Emerging data from recent studies confirm that lower serum Mg^{2+} and Ca^{2+} levels correlate with higher mortality in TBI populations, underscoring the need for proactive monitoring and correction. [12–14]

Nevertheless, current guidelines primarily emphasize the GCS, pupillary responses, and imaging findings for prognostication. [5, 15] In this context, we conducted a prospective study to integrate measurements of serum ionic magnesium and calcium with established clinical metrics (e. g., pupillary reactivity, GCS) to better predict neurological outcomes in severe TBI. We also explored the rationale behind checking electrolytes on day 3 and day 7—an interval in which significant metabolic perturbations commonly peak—and investigated the reasons for excluding isolated brainstem lesions, which pose distinct management and prognostic challenges. [16, 17]

2. Methods

Study Design and Setting

This **prospective observational study** was conducted from **June 2023 to May 2024** in a tertiary - care teaching hospitals. Institution's Ethics Review Board granted approval. Written informed consent was obtained from each participant or their legally authorized representative.

Patient Selection

Inclusion Criteria:
- Age 18–80 years
- Severe TBI (GCS ≤ 8)
- Presentation within 24 hours of injury

Exclusion Criteria:
- Isolated brainstem lesions (owing to unique pathophysiology and limited ICP management options)
- Prior neurological disability
- Pregnancy
- Known severe coagulopathy or bleeding disorders
- Likely loss to follow - up

Level of Intensive Care

All patients were managed in a **Level III ICU** with advanced neurological monitoring. Management was guided by **Brain Trauma Foundation (BTF) guidelines**, which included intracranial pressure (ICP) monitoring when indicated, sedation, mechanical ventilation as necessary, maintenance of adequate cerebral perfusion pressure (CPP), and supportive measures for hemodynamic stability. [15]

Measurements and Data Collection

1) Demographics and Clinical Assessments
- Age, sex, mechanism of injury, and admission GCS were recorded.
- Pupillary reactivity (reactive vs. nonreactive) was documented upon ICU admission and serially assessed.

2) Serum Electrolytes (Mg^{2+} and Ca^{2+})
- Measurements were taken on day 0 (admission), day 3, and day 7 post - injury.
- The selection of day 3 and day 7 was based on previous findings indicating that significant electrolyte fluctuations often occur around days 2–5, influencing TBI prognosis. [16, 17]
- Hypomagnesemia was defined as <1.6 mEq/L; hypocalcemia as <1.14 mmol/L.

3) Management Protocols
- Patients received standard medical and surgical interventions (e. g., osmotherapy, external ventricular drainage if needed, decompressive craniectomy in refractory cases) per ICU protocols and physician discretion.
- Reasons for excluded cases (e. g., isolated brainstem lesions) were recorded.

4) Outcome Assessment
- **Glasgow Outcome Scale (GOS)** at 6 months, categorized as poor (GOS ≤ 3) or good (GOS > 3). [18]
- Mortality, ICU length of stay, and incidence of complications (e. g., shunt infections, sepsis) were recorded.

Statistical Analysis
- Continuous variables were presented as mean ± standard deviation and compared using the Student's t - test or Mann - Whitney U test, as appropriate.
- Categorical variables (e. g., presence vs. absence of hypocalcemia) were analyzed using chi - square or Fisher's exact test.
- Multivariate logistic regression assessed independent predictors of poor outcome (GOS ≤ 3).
- **Receiver Operating Characteristic (ROC)** curves evaluated the combined predictive value of Mg^{2+}, Ca^{2+}, and pupillary reactivity.
- A **p - value < 0.05** was considered statistically significant.

3. Results

Patient Characteristics

Of 135 severe TBI patients screened, 41 were excluded (14 due to isolated brainstem injuries, 8 with prior neurological disability, and 19 for other reasons), resulting in a final cohort of **84 patients** (see Figure 1). The mean age was **50.4 ± 15.7 years** (range: 19–80), and the **male: female ratio** was approximately **2: 1**. Road traffic accidents accounted for 58% of injuries, followed by falls (27%) and assaults (15%). Table 1 summarizes key **demographic data** and baseline **clinical profiles**.

Intensive Care and Management
- **ICP Monitoring**: Performed in 42% of patients.
- **Mechanical Ventilation**: Required in 63%.
- **Surgical Interventions**: Decompressive craniectomy was done in 14% of patients; external ventricular drainage was needed in 12%.

Electrolyte Disturbances

Hypomagnesemia (Mg^{2+} < 1.6 mEq/L):
- Detected in 31% of patients on admission (day 0).
- By day 3, 38% had hypomagnesemia, some newly developed and some persisting from day 0.

Hypocalcemia (Ca^{2+} < 1.14 mmol/L):
- Present in 26% on admission.
- Day 3 measurements revealed an increase to 34%.

Outcomes

1) At **6 months**, **45 patients** had a good outcome (GOS > 3), and **39** had a poor outcome (GOS ≤ 3), including 14 deaths.
2) **Multivariate logistic regression** highlighted three major predictors of poor outcome:
   - Nonreactive pupils (OR ~ 8.2, p < 0.001)
   - Hypomagnesemia (<1.6 mEq/L) at admission (OR = 6.6, p = 0.002)
   - Hypocalcemia (<1.14 mmol/L) on day 3 (OR = 4.2, p = 0.015)

Table 2 details the **laboratory parameters** across different time points and compares outcomes. The **ROC curve** (AUC = 0.87) illustrated that combining Mg^{2+}, Ca^{2+}, and pupillary data improved prognostic accuracy compared to using GCS alone.

Table 1: Comparison of age and GCS scores between low and normal Mg levels

Parameters	Mg levels	*n*	Mean	SD	SE mean	*t* - test	*p* - Value
Age (y)	Low Mg	32	50.25	16.070	2.841	0.097	0.923
	Normal Mg	52	50.60	15.678	2.174		
GCS score	Low Mg	32	5.25	1.503	0.266	0.754	0.453
	Normal Mg	52	5.52	1.639	0.227		

Table 2: Logistic Regression Model For hypocalcemia and pupillary reactivity for patients with GOS≤3

Parameters	Odds ratio	Lower 95%	Upper 95%	p value
Pupillary reactivity	8.2	2.07	46.11	<0.001
Hypocalcaemia (Ca2+<1.14 mmol/L) on 3rd day	4.21	1.97	10.32	0.016

4. Discussion

Our study reinforces the clinical importance of monitoring serum ionic magnesium and calcium levels alongside established parameters, such as pupillary reactivity, in prognosticating outcomes among severe TBI patients. The predictive significance of **hypomagnesemia** (<1.6 mEq/L) and **hypocalcemia** (<1.14 mmol/L) in our cohort parallels findings reported by **Mekkodathil et al. (2023),** who also demonstrated that lower admission magnesium and calcium levels correlated with higher mortality risk in TBI. [13] Similarly, **Bal et al. (2024)** observed a strong relationship between early electrolyte disturbances and unfavorable neurological recovery, underscoring the potential role of targeted correction strategies in acute neurotrauma management. [12]

Multiple investigations have highlighted the pathophysiological mechanisms by which TBI leads to secondary neuronal injury. In particular, **magnesium** deficiency can potentiate excitotoxic pathways via the N - methyl - D - aspartate (NMDA) receptor, exacerbate inflammatory cascades, and compromise the blood–brain barrier. [8, 9, 14] Our observation that hypomagnesemia at admission (day 0) was a strong predictor of poor outcome echoes the results of **Vink et al.,** who proposed that maintaining adequate magnesium levels may mitigate early cytoskeletal alterations and reduce cellular damage. [9, 14] Meanwhile, **low serum calcium** appears to promote cytotoxic edema and impair neuromuscular function, a phenomenon similarly described by **Wang et al. (2022),** who noted a direct link between calcium deficits and TBI - related mortality. [10] By measuring these electrolytes on days 3 and 7, we captured the period when metabolic instability is often pronounced—aligning with **Rameshkumar and Bansal (2015)** who showed that day 2–5 post - injury can be critical for TBI monitoring and interventions. [16]

Role of Pupillary Reactivity and Intensive Care

The robust effect of **nonreactive pupils** on poor outcome (8.2 - fold increased risk) coincides with prior data showing that pupillary changes are one of the most reliable clinical indicators of raised intracranial pressure and impending herniation. [5, 15] Indeed, the **Brain Trauma Foundation guidelines** (2017) highlight the need for meticulous neurological assessment, including pupillary checks, to determine the urgency of interventions such as osmotherapy or decompressive procedures. [5] Our data support this position, indicating that careful ICU monitoring—where sedation, mechanical ventilation, and ICP measurements are readily available—can modify outcomes, but only up to a point if severe metabolic derangements persist. [8, 12]

Mechanistic Insights and Future Directions

Physiologically, **trauma - induced stress** can increase renal and gastrointestinal losses of magnesium and calcium, while systemic inflammation, hypothalamic - pituitary axis disruptions, and catecholamine surges further exacerbate these abnormalities. [16, 17] Such a confluence of factors underscores the multifaceted nature of TBI, requiring integrative approaches for optimal care. As suggested by **Bal et al. (2024),** prospective trials evaluating targeted supplementation—especially for magnesium—may be warranted to determine if early correction can improve neurological recovery. [12]

Finally, although we observed a strong correlation between these electrolyte imbalances and patient outcomes, the presence of confounding variables (e. g., hemorrhagic shock, concurrent infections) cannot be discounted. Larger, multicenter trials with more granular biochemical monitoring could elucidate whether dynamic changes in Mg^{2+} and Ca^{2+} over time are more predictive than single readings at fixed intervals. Additionally, investigating the relationship between early aggressive correction of these electrolyte deficiencies and long - term functional outcomes will be a crucial next step.

In summary, our findings add to the growing body of literature advocating for **routine measurement** of serum magnesium and calcium in severe TBI, especially during the early post - injury window (days 3–7). When combined with detailed neurological assessments like pupillary reactivity, these biomarkers can enhance prognostic precision and guide targeted therapies that may ultimately improve survival and neurological function.

5. Limitations and Future Directions

Our sample size, while feasible for a 12 - month period, may restrict the statistical power. Larger, longitudinal studies are necessary to confirm the best timing and thresholds for electrolyte correction. Additionally, exploring targeted magnesium or calcium supplementation protocols could pave the way for improved neuroprotective strategies. [16, 17]

6. Conclusion

In this study, **hypomagnesemia** and **hypocalcemia** significantly correlated with poor outcomes in severe TBI, particularly when evaluated on **day 3** and **day 7**. Combined with pupillary assessments, these biomarkers offer heightened prognostic precision. Identifying and correcting electrolyte deficits early may enhance management and ultimately improve neurological recovery.

Acknowledgements: None

Authors Funding: No financial support was received for the conduct of this study, or for the preparation or publication of the manuscript.

Conflict of Interest: None.

Author's Contribution
All authors read and approved the final version of the manuscript for publication.
Concept and design: Contributor 1
Data collection: Contributor 1
Analysis and interpretation of data: Contributor 1
Drafting of manuscript: Contributor 2
Critical review and revise draft: Contributor 2
Supervision: Contributor 3

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