Incidence of Hypophosphatemia in Patients with Severe Traumatic Brain Injury and Its Impact on Mortality: A retrospective study

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Abstract

Background: Hypophosphatemia is a common electrolyte disturbance in critically ill patients, particularly those with severe traumatic brain injury (TBI). Phosphate plays essential roles in bone structure, cellular energy metabolism, membrane integrity, and acid-base balance. Despite its clinical relevance, data on the incidence, risk factors, and consequences of hypophosphatemia in TBI patients remain limited.

Methods: We conducted a retrospective observational study of patients with severe TBI admitted to a surgical intensive care unit (ICU). Serum phosphate levels were measured at ICU admission and at 72 hours. We evaluated the incidence of hypophosphatemia, its potential causes and its clinical consequences.

Results: Among 94 patients with severe TBI, hypophosphatemia occurred in 55.6% at ICU admission and persisted in 49% at 72 hours. Risk factors included insulin therapy, respiratory alkalosis, catecholamine administration, higher mannitol use, and greater illness severity. Hypophosphatemia was associated with longer mechanical ventilation, higher incidence of arrhythmias, and increased nosocomial infections. Importantly, hypophosphatemia remained an independent predictor of 28 day mortality after adjustment for confounding variables.

Conclusions: Hypophosphatemia is frequent and clinically significant in patients with severe TBI, contributing to multiple systemic complications and worse outcomes. Routine monitoring of serum phosphate and targeted supplementation, particularly in severe cases, may be warranted. Further prospective studies are needed to determine whether correcting moderate hypophosphatemia improves prognosis in this population.

Keywords:

Hypophosphatemia; Traumatic brain injury; Neurocritical care;

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Introduction

Phosphorus, the principal intracellular anion, is essential for all living organisms and plays a critical role in maintaining both the structural and functional integrity of cells. It is a major constituent of the phospholipid bilayer of cell membranes and participates in numerous biological processes, including adenosine triphosphate (ATP) production, glycolysis, pH buffering, 2,3-diphosphoglycerate (2,3-DPG) synthesis, mitochondrial function, enzymatic regulation, signal transduction, and nucleotide metabolism [1–3].

Phosphorus also serves as a substrate for ATP generation, which is crucial for normal neurological function and muscle contraction. Therefore, maintaining normal serum phosphate levels is of paramount importance. Despite its physiological significance, serum phosphate remains a neglected parameter in clinical practice.

Due to limited awareness regarding hypophosphatemia, practices surrounding its diagnosis and management vary widely. Some units do not routinely monitor phosphate level, while others administer supplementation prophylactically, such as before initiating parenteral nutrition or mechanical ventilation.

Hypophosphatemia can have significant clinical consequences, particularly in the intensive care setting. It impairs cellular energy metabolism and is associated with reduced cardiac and diaphragmatic contractility[4-6]. In sepsis, hypophosphatemia occurs in up to 60% of cases and may contribute to leukocyte dysfunction [7,8].

Normal plasma phosphate levels range from 0.80 to 1.60 mmol/L. Hypophosphatemia is reported in 2–3% of hospitalized patients; however, this likely underestimates its true prevalence due to the lack of routine phosphate monitoring. In patients with traumatic brain injury (TBI), the prevalence can be as high as 50% [9].

Severe hypophosphatemia defined as serum phosphate < 0.3 mmol/L.Several factors contribute to hypophosphatemia in neurocritical care, including malnutrition, gastric aspiration, liver failure, sepsis, chronic alcoholism, respiratory alkalosis, volume expansion, glucose infusions, hemodialysis, administration of mannitol, antacids, catecholamines, and sodium bicarbonate.

Unlike other electrolyte disturbances, such as dysnatremia or dyskalemia, phosphate disturbances are often overlooked in TBI management. Hypophosphatemia frequently goes undiagnosed, as it is asymptomatic or manifests with non-specific symptoms, including fatigue or irritability. It has been associated with prolonged ICU and hospital stays. However, whether hypophosphatemia directly affects mortality in neurosurgical ICU patients remains controversial.

Although several studies have linked hypophosphatemia in the ICU to increased mortality, it remains unclear whether it is a causative factor or simply a marker of illness severity. Data evaluating the impact of phosphate levels at ICU admission on outcomes in patients with

severe traumatic brain injury (TBI) are limited. We hypothesized that hypophosphatemia negatively influences 28-day mortality in neurocritical care patients. To investigate this, we performed a retrospective, single-center cohort study comparing 28-day mortality between patients with hypophosphatemia and those with normal phosphate levels. The primary outcome was 28-day mortality.

Patients and Methods

1. Study Population

This was an observational retrospective study conducted from January 1, 2015, to December 31, 2018, in the Surgical Intensive Care Unit (ICU) of Military Teaching Hospital, Mohammed V Rabat, Morocco.

Inclusion criteriawere:

1. Isolated TBI (Glasgow Coma Scale < 12)
2. Age ≥16 years
3. Availability of serum phosphate measurement at ICU admission and at 72 hours
4. the 28-day follow-up

Exclusion criteriawere:

1. Age <16 years
2. Pregnancy
3. Loss to follow-up
4. Absence of phosphate measurement at ICU admission
5. Hyperphosphatemiaat admission

During the study period, 1,569 patients were admitted, of whom 143 had TBI. After applying exclusion criteria, 49 patients were excluded, yielding a final cohort of 94 patients.

2. Clinical and Biological Data Collection

Patient data were extracted from medical records. Collected variables included:Demographics and baseline characteristics: age, sex, initial GCS, mechanism of injury, medical history, nutritional status, APACHE II score.

Biological parameters: serum phosphate at admission and 72 h, serum potassium, sodium, calcium, creatinine, arterial pH, pCO_2, bicarbonate, and urine output prior to admission.

Therapeutic interventions: fluid resuscitation, corticosteroids, catecholamines, insulin therapy, mannitol administration, therapeutic hypothermia, mechanical ventilation, and tracheostomy.

Outcomes: occurrence of seizures, arrhythmia, nosocomial infection, duration of mechanical ventilation, ICU length of stay, hospital length of stay, and 28-day mortality.

3. Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 .Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), and categorical variables as counts and percentages.

Comparisons between groups were performed using the Student's t-test or Mann–Whitney U test for continuous variables and Chi-square test for categorical variables.

Univariate analysis assessed associations between clinical/biological variables and 28-day mortality. Variables with $p < 0.05$ were included in a multivariate logistic regression model to identify independent predictors, with calculation of odds ratios (OR) and 95% confidence intervals (CI). A *p-value* < 0.05 was considered statistically significant.

Results

1. Patient Characteristics

Among 1,569 ICU admissions, 94 patients met inclusion criteria. Of these, 59 (62.7%) had hypophosphatemia and 35 (37.3%) had normal phosphate levels. Patient characteristics are summarized in Table 1.

Variables	Total (n=94)	Control (n=35)	Hypophosphatemia (n=59)	*p-value*
Clinicalcharacteristics				
Age (years) mean ± SD	44.15 ± 18.38	44.87 ± 8.12	44.35 ± 8.7	0.32
Male sex, n (%)	68 (72.3%)	24 (68%)	44 (74.5%)	0.21
GCS score (mean ± SD)	7.9 ± 1.5	8.24 ± 1.3	7.83 ± 1.16	0.08
Mechanism of traumatic brain injury (%)				
Road traffic accident	78 (82%)	28 (80%)	50 (84%)	0.08
Work-related accident	3 (3.1%)	2 (5%)	1 (1.6%)	0.02
Domestic accident	6 (6.3%)	2 (5%)	4 (6.7%)	0.12
Other	7 (7.4%)	3 (8.5%)	4 (6.7%)	0.07
Medicalhistory				
Diabetesmellitus, n (%)	22 (23%)	5 (14.2%)	17 (28%)	0.002
Hypertension (HTN), n (%)	9 (9.5%)	4 (11%)	5 (8%)	0.18
Kidneydisease, n (%)	3 (3%)	1 (2.8%)	2 (3%)	0.23
Alcoholism, n (%)	27 (28.7%)	5 (14.2%)	22 (37.2%)	0.001
Nutrition (%)				
Enteral nutrition	80 (85%)	30 (85%)	50 (84.7%)	0.32
Parenteral nutrition	3 (3%)	1 (2.8%)	2 (3%)	0.44
Mixed nutrition	11 (11.7%)	4 (11.4%)	7 (11.8%)	0.27
APACHE II score (mean ± SD)	21.2 ± 5.8	13.7 ± 4.9	26.3 ± 4.7	0.01
Diuresis (ml) mean ± SD	1150 ± 130	713 ± 95	1430 ± 185	0.01
Biologicalparameters				
Phosphate at admission (mmol/L) median [IQR]	0.68 [0.47, 1.08]	1.12 [0.90, 1.25]	0.48 [0.34, 0.59]	0.01
Phosphate at 72h (mmol/L) median [IQR]	0.72 [0.53, 1.15]	1.20 [0.98, 1.30]	0.54 [0.43, 0.68]	0.01
Potassium (mmol/L) median [IQR]	3.6 [3.3, 4.2]	3.9 [3.6, 4.4]	3.4 [3.2, 3.8]	0.01
Creatinine (μmol/L) median [IQR]	81 [65, 108]	78 [52, 95]	83 [68, 112]	0.25
Calcium (mmol/L) median [IQR]	1.91 [1.72, 2.04]	1.98 [1.76, 2.02]	1.92 [1.77, 2.08]	0.62
pH (median [IQR])	7.42 [7.38, 7.45]	7.38 [7.34, 7.42]	7.47 [7.42, 7.50]	0.01
pCO2 (mmHg) median [IQR]	34 [32, 38]	38 [35, 40]	32 [30, 35]	0.01
HCO3- (mmol/L) median [IQR]	21 [18, 25]	20 [17, 24]	22 [18, 26]	0.32
Therapeutic interventions				
Fluid resuscitation (ml) mean ± SD	1280 ± 180	850 ± 150	1500 ± 200	0.01
Corticosteroids, n (%)	28 (30%)	7 (20%)	21 (35%)	0.01
Mannitol (ml) mean ± SD	210 ± 40	162 ± 35	240 ± 44	0.01
Insulintherapy, n (%)	68 (72%)	22 (63%)	46 (77%)	0.01
Hypothermia, n (%)	7 (7.5%)	3 (8.5%)	4 (6.7%)	0.25
Catecholamines, n (%)	38 (40%)	12 (34%)	26 (44%)	0.01
Mechanical ventilation, n (%)	88 (93.6%)	33 (94%)	55 (93%)	0.65
Tracheostomy, n (%)	50 (53%)	18 (51%)	32 (54%)	0.18

Table1: Clinical Characteristics, Biological Parameters and therapeutic interventions of the Study Population

The mean age was 44.2 ± 8.4 years, and 72.3% were male, with no significant differences between groups. The mean APACHE II score was 21.2 ± 5.8. Overall 28-day mortality was 37%. Road traffic accidents accounted for 82% of injuries. The mean initial GCS was 7.9 ± 1.5.Diabetes mellitus and chronic alcohol use were significantly more frequent in the hypophosphatemia group, while hypertension and chronic kidney disease prevalence were similar between groups.

Pre-ICU admission urine output was higher in hypophosphatemic patients (mean 1,430 ± 185 mL). Nutritional support was primarily enteral (85%), with exclusive parenteral nutrition in 3% and combined enteral–parenteral in 11.7%.

2. Incidence of Hypophosphatemia

Median serum phosphate at admission was 0.68 mmol/L (IQR 0.47–1.08). Hypophosphatemia occurred in 54/106 patients (55.6%), including eight with severe hypophosphatemia (<0.3 mmol/L).At 72 hours, 12 normophosphatemic patients developed phosphate <0.6 mmol/L, while 19 hypophosphatemic patients normalized (>0.8 mmol/L). Overall, hypophosphatemia incidence declined from 55.6% to 49%, with median phosphate rising to 0.72 mmol/L.

3. Biological Parameters

Serum potassium and arterial pCO_2 were lower in hypophosphatemic patients. Median arterial pH was 7.47 vs. 7.38 in controls. Serum bicarbonate, creatinine, and calcium did not differ significantly.

4. Therapeutic Interventions

Hypophosphatemic patients received larger pre-ICU admission fluid volumes (1,500 ± 200 mL vs. 850 ± 150 mL, $p = 0.01$) and more mannitol (240 ± 44 mL). Short-term corticosteroids were used in 35% vs. 20% ($p = 0.01$).

Catecholamine support was required in 40%, and insulin therapy in 72%. Therapeutic hypothermia was applied in 9.5%. Eighty-eight patients were intubated, and 50 underwent tracheostomy for prolonged ventilation.

5. Outcomes

28-day mortality was higher in hypophosphatemic patients (40% vs. 31%, $p = 0.01$). Median ICU stay was longer (17 vs. 10 days, $p = 0.01$), as was total hospital stay. Duration of mechanical ventilation was also increased (median 14 days). Seizure incidence was 24%, with no difference between groups. (Table2)

	Total (n = 94)	Control (n = 35)	Hypophosphatemia (n = 59)	*p* value
Seizures, *n* (%)	23 (24%)	9 (25%)	14 (23.7%)	0.28
Arythmia,*n* (%)	36 (38%)	12 (34%)	24 (40%)	0.03
Nosocomial infections, *n* (%)	58 (61%)	19 (54%)	39 (66%)	0.04
Duration of mechanical ventilation, days (median [IQR])	10 (4–14)	7 (3–10)	14 (5–17)	0.01
ICU length of stay, days (median [IQR])	14 (6–19)	10 (5–13)	17 (8–21)	0.01
Hospital length of stay, days (median [IQR])	37 (27–43)	31 (24–38)	42 (32–47)	0.01
28-day mortality, *n* (%)	35 (37%)	11 (31%)	24 (40%)	0.01

Table 2: Clinical outcomes according to serum phosphate status

6. Predictive factors of 28-day mortality.

Univariate analysis demonstrated that APACHE II score, hypocapnia, cardiac arrhythmias, and hypophosphatemia were significantly associated with 28-day mortality. Age, sex, hypokalemia, and nosocomial infection did not reach statistical significance.

Multivariate logistic regression revealed that hypophosphatemia remained an independent predictor of 28-day mortality (OR 1.75, 95% CI 1.15–2.10, p = 0.01), along with APACHE II score. The other variables lost their independent predictive value. (Table 3)

Associatedfactors	Univariateanalysis			Multivariateanalysis		
	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age	1.52 (0.58, 2.3)		0.45	–	–	–
Male sex	0.80 (0.6, 3.5)		0.63	–	–	–
APACHE II	1.5 (1.35, 1.6)		**0.01**	1.45 (1.28, 1.51)		**0.01**
Hypocapnia	1.21 (1.15, 1.35)		**0.02**	1.3 (0.86, 2.3)		0.56
Hypokalemia	0.84 (0.35, 2.05)		0.72	–	–	–
Hypophosphatemia	**1.85 (1.25, 2.4)**		**0.01**	**1.75 (1.15, 2.1)**		**0.01**
Cardiacarrhythmia	1.12 (1.05, 1.35)		**0.04**	1.06 (0.75, 1.25)		0.47
Nosocomial infection	1.6 (0.8, 3.5)		0.85	–	–	–

Table 3: Predictive factors of 28-day mortality.

Discussion

Phosphorus is essential for life, present in all organisms, and abundant in the diet (e.g., meat, fish, dairy, nuts, soy). It is a key component of numerous biomolecules, fulfilling both structural and functional roles.Approximately 85% of total body phosphorus (~600 g in

adults) is stored in bone, serving as the primary phosphate reservoir. Phosphorus is mobilized to the bloodstream or incorporated into bone tissue according to metabolic and hormonal demands.

Phosphorus is a major constituent of biological membranes, primarily as phospholipids forming bilayers with embedded proteins. Cellular membranes contain ~40% lipids, predominantly phospholipids. It participates in intracellular signaling, enzyme regulation, and metabolic pathways such as glycolysis and cholesterol synthesis, which rely on phosphorylated intermediates. Serum phosphate depletion reduces 2,3-BPG levels, impairing tissue oxygen delivery [10].Phosphate acts as an effective urinary buffer (pKa 6.8) and contributes to urinary pH regulation, though its buffering capacity in blood is relatively modest [11].

It is important to note that hypophosphatemia does not necessarily indicate phosphorus depletion. Hypophosphatemia may occur in the presence of low, normal, or even elevated total body phosphorus levels. In the latter two cases, a shift of phosphate from the extracellular to the intracellular compartment is observed. Conversely, phosphorus depletion may exist despite normal, low, or high serum phosphate levels. Phosphorus depletion corresponds to a reduction in total body phosphorus content.

The normal plasma phosphate concentration ranges from **0.80 to 1.60 mmol/L**. Hypophosphatemia can be arbitrarily divided into **moderate** (plasma phosphate 0.32–0.60 mmol/L) and **severe** forms (plasma phosphate <0.32 mmol/L).

The reported incidence of hypophosphatemia varies from **0.2% to 2.2%** among all hospitalized patients, but may reach **21.5% or higher** in certain patient series. During hospitalization, its incidence tends to increase; thus, a single measurement likely underestimates the true occurrence of hypophosphatemia.

We conducted an observational study of a specific cohort of patients with **traumatic brain injury (TBI)** admitted to a **surgical intensive care unit**, in order to investigate the incidence of hypophosphatemia and its relationship with mortality. We reported an incidence of **55.6%** in our population.

Previous studies have demonstrated that the incidence of hypophosphatemia varies widely depending on hospital settings and clinical conditions (Table 4). Hypophosphatemia is particularly frequent in cases of **sepsis (80%) [7]**, **brain death (72%) [12]**, and may reach **100%** in patients with severe burns, as reported in a 1997 study [13].

To our knowledge, only one previous study, conducted in 2000, focused specifically on patients with traumatic brain injury. That study included 18 patients and reported an incidence of **61%** [19], which is relatively close to the incidence observed in our cohort (**55.6%**). (Table 4)

Author	Year	Study population / Clinical setting	Number of patients	Definition of hypophosphatemia	Prevalence	Incidence
Goldstein *et al* [16]	1985	ThoracicsurgeryCardiacsurgery	34 40	< 0.80 mmol/L	–	56% 50%
Zazzo*et al* [15]	1995	Surgical ICU	208	< 0.80 mmol/L < 0.50 mmol/L < 0.20 mmol/L	–	28.8% 17.9% 2.4%
Buell*et al* [20]	1998	Hepaticsurgery	35	< 0.80 mmol/L	–	67%
Cohen *et al* [14]	2004	Cardiacsurgery	566	< 0.48 mmol/L	–	34.3%
Salem *et al* [17]	2005	Hepaticsurgery	20	< 0.70 mmol/L	–	100%
Daily *et al* [18]	1990	Trauma patients	12	< 0.80 mmol/L < 0.50 mmol/L	–	75% 56%
Kruse*et al* [21]	1992	Mixed ICU	418	< 0.80 mmol/L	–	28%
Mariké*t al* [22]	1996	Refeeding after >48 h of fasting	62	< 0.65 mmol/L < 0.32 mmol/L	–	34% 6%
Berger *et al* [13]	1997	Burn patients	16	< 0.80 mmol/L < 0.30 mmol/L	–	100% 50%
Barak *et al* [7]	1998	Sepsis Infection without sepsis Sepsis with negative blood cultures Sepsis with positive blood cultures	99 32 37 30	< 0.80 mmol/L	80% 81% 65% 80%	–
Poldermanet *al* [19]	2000	Head trauma	18	< 0.60 mmol/L	61%	–
Milionis*et al* [23]	2002	Intensive cardiac care unit	86	< 0.77 mmol/L	13%	–
Domínguez-Roldán*et al* [12]	2005	Brain-dead patients	50	< 0.80 mmol/L	72%	–
Presentstudy (*Andaloussiet al*, 2019)	2019	Head trauma	106	< 0.80 mmol/L < 0.30 mmol/L	**55.6%7.5 %**	–

Table 4: Prevalence and incidence of hypophosphatemia.

Our findings clearly demonstrate that patients with severe traumatic brain injury are at high risk of developing hypophosphatemia. This observation supports routine measurement of serum phosphate levels upon ICU admission in this population.

Since 2012, our unit has implemented systematic phosphate assessment at admission and again at 72 hours of hospitalization. Our results showed that the incidence of hypophosphatemia at 72 hours decreased slightly to 49%, indicating that this disturbance remains frequent even after initial stabilization. This practice remains clinically relevant, as it helps identify patients who require closer monitoring to prevent the development of severe hypophosphatemia, a condition that may necessitate phosphate supplementation before initiating other intensive interventions such as nutritional support or prolonged mechanical ventilation.

The 72-hour measurement also helps identify patients in whom phosphate levels normalize spontaneously—mainly those with redistribution hypophosphatemia—and who therefore do not require exogenous supplementation beyond that provided by nutritional intake.

Hypophosphatemia arises via three principal mechanisms: decreased intestinal absorption, intracellular redistribution, and increased urinary losses. Dietary deficiency is rare due to ubiquitous phosphorus intake. Prolonged malnutrition or impaired intestinal absorption (e.g., chronic antacid use) may cause depletion [24]. Vitamin D deficiency reduces intestinal absorption and increases renal phosphate excretion, making hypophosphatemia an early marker of deficiency [25]. Most cases of acute hypophosphatemia result from shifts into cells, often triggered by intravenous glucose and insulin administration. Refeeding syndrome in malnourished patients and insulin therapy for diabetic ketoacidosis also cause intracellular phosphate uptake [26].

In our cohort, diabetic patients and those receiving insulin were more common in the hypophosphatemic group (28% vs. 14.2%, p=0.02; 77% vs. 63%, p=0.01, respectively). Respiratory alkalosis due to hyperventilation, common in agitated or intubated TBI patients, promotes phosphate influx into cells. Hypocapnia ($PaCO_2$ 32 vs. 38 mmHg, p=0.01) and elevated pH (7.47 vs. 7.38, p=0.01) were associated with hypophosphatemia. Renal phosphate wasting is a frequent contributor, particularly in TBI patients with polyuria from mannitol therapy or central diabetes insipidus. In our cohort, hypophosphatemic patients received higher mannitol volumes (240 vs. 162 mL, p=0.01) and exhibited higher urine output (1430 vs. 713 mL, p=0.01). Increased crystalloid administration and corticosteroid use may have contributed but were unlikely primary drivers.

Although previous studies have linked hypophosphatemia to poor outcomes in critically ill patients [27,28], few studies have examined the relationship between admission phosphate levels and outcomes in general ICU populations, and none, to our knowledge, have focused on patients with traumatic brain injury.

In our observational study of traumatic brain injury patients, hypophosphatemia was associated with higher mortality. After adjusting for the confounding factors, hypophosphatemia remained more frequent among non-survivors. Hypophosphatemic patients were also more severely ill, but after adjusting for other risk factors, hypophosphatemia remained an independent predictor of mortality.

Some studies support an association between hypophosphatemia and increased mortality. Zazzo et al. [15] prospectively studied 208 surgical ICU patients, defining hypophosphatemia as <0.8 mmol/L, with a prevalence of 28.8% and higher mortality among hypophosphatemic patients (30% vs. 15.2%; $p < 0.05$). Sankaran et al. [29] studied 302 ICU patients with bacterial pneumonia, defining hypophosphatemia as <0.77 mmol/L, and found it in 44.7% of patients, who had higher mortality (31.9% vs. 13.2%; $p < 0.001$).

However, these studies were small, used different definitions of hypophosphatemia, and did not evaluate the independent relationship between phosphate levels and outcomes after adjusting for disease severity. Only Suzuki et al. [28] andDemirjian et al. [30] assessed the independent association between hypophosphatemia and mortality, finding no significant association after adjustment.

In 2019, Wang et al. demonstrated in a heterogeneous cohort of 946 ICU patients that admission hypophosphatemia was an independent predictor of 28-day mortality [31]. Our study confirms these findings and is the first to examine the independent association between hypophosphatemia and mortality in patients with traumatic brain injury.

Our study has several limitations: its retrospective, single-center design limits generalizability. Only two phosphate measurements were available, restricting assessment of dynamic changes. Urinary phosphate excretion and kinetic analysis were not performed.

Conclusion

Hypophosphatemia in critically ill patients, particularly those with TBI, is common and may contribute to cardiac, respiratory, neuromuscular, hematologic and immunologic complications. It can be asymptomatic but also life-threatening, and is independently associated with increased 28-mortality in this population.

Serum phosphate should be routinely monitored in severe TBI patients, and supplementation considered for symptomatic patients or when levels fall below 0.32 mmol/L. Whether correcting moderate hypophosphatemia improves outcomes in TBI remains uncertain and warrants prospective trials. Multicenter studies are needed to clarify optimal phosphate management strategies in this population.

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