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RESEARCH ARTICLE

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Ionized hypocalcemia as a prognostic factor of early mortality in traumatic brain injury

Jihad Mamdouh Mahanna Ahmed, Gamal Mohammad Ahmad Elewa, Mohamed Sidky Mahmoud Zaki, Sherif George Anis Said and Ahmed Abd El Ghani Khalifa Ragab

Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Traumatic brain injury (TBI) is a common neurological condition. It can affect mental, physical, and cognitive functions and is a common cause of mortality. Electrolytes imbalance is common in those patients. Effective therapy of electrolytes abnormalities improves neurological outcome and reduces mortality. Therefore, we **studied** the predictive significance of ionized hypocalcemia for early mortality in TBI patients.

Patients and method: This observational study in the intensive care units of the Ain Shams University hospitals was done on sixty adult patients with TBI of both sexes, divided into two groups: group A (ionized hypocalcemic patients), and group B (normocalcemic patients). On admission, medical history, physical examination including neurological evaluation, and appropriate investigations were performed. Ionized calcium was measured at the start of the 28-day study and then every five days after that.

Results: There was no statistically significant difference between the two groups for demographic data, brain injury type, or the number of intubated patients ($p > 0.05$). There was a statistically significant difference for diffuse axonal damage, subdural hemorrhage, cerebral edema, GCS, and mean blood pressure ($p < 0.001$). Serum ionized calcium in group A was significantly lower than in group B on the day of admission and day five ($p < 0.001$). On the day of admission, there was a significant difference in serum sodium ($p < 0.05$). In both groups, there was a significant difference in the ICU stay as regards survivors ($p < 0.001$). There was a statistically significant difference in 28-day mortality between the two groups ($p = 0.001$).

Conclusion: In TBI patients, ionized hypocalcemia on admission and on day five, hypernatremia and disturbed conscious level are strongly linked to greater fatality rates.

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Traumatic brain injury; ionized hypocalcemia; mortality

1. Introduction

A prevalent neurological condition is traumatic brain injury (TBI). A mechanical external force causes this damage, which is a leading cause of death as well as a permanent or reversible impairment of mental, physical, and psychosocial functions [1]. TBI comes in a variety of forms that may coexist and significantly overlap. Primary versus secondary injuries [2] and foc used versus diffuse injuries [3] are two ways to categorize them. The Glasgow Coma Scale (GCS) [4] also categorizes TBI as mild, moderate, and severe.

The process of TBI is extremely diverse, and it has significant effects on patients' physical, emotional, and behavioral aspects [5]. TBI may result in different degrees of macroscopic and cellular alterations, which can be seen through a clinical exam and imaging tests. Patients may exhibit a variety of clinical symptoms, including unconsciousness, nausea, vomiting, headache, and seizures. Indicators of underlying TBI include bruising, scalp lacerations, and periorbital or mastoid ecchymosis suggesting fractures of the skull base [6].

Age, particularly advancing age, subdural hematoma, subarachnoid hemorrhage, coagulopathy, GCS, and hypoxia are among factors that affect prognosis [7].

Due to the release of several mediators that increase vasogenic and cytotoxic cerebral edema, including glutamate, lactate, potassium, calcium (Ca^{+2}), nitric oxide, arachidonic acid and its metabolites, free oxygen radicals, kinins, and histamine. TBI patients have a high risk of electrolyte disturbances [8,9].

Serum calcium (Ca^{+2}) is one of the most important electrolyte abnormalities associated with variable clinical manifestations in patients with TBI mainly development of tetany which may lead to seizures or coma [10].

2. Aim of the study

The purpose of the study was to investigate the predictive significance of ionized hypocalcemia in TBI patients.

-Primary outcome: 28-day mortality rate in individuals with TBI and lower ionized calcium levels.

-Secondary outcomes: neurological deficit and organ dysfunction.

CONTACT Jihad Mamdouh Mahanna Ahmed gehadmahanna@gmail.com Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, 38 Abbassia, Next to the Al-Nour Mosque, Cairo 1181, Egypt

3. Patients and method

The Pan African Clinical Trial registration number is **PACTR202204664745348** and the trial was carried out after receiving ethical approval (approval number is **FMASU MD 87/2022**) from the Research Ethical Committee of Faculty of Medicine, Ain Shams University. All participants or their closest relatives provided informed written consent before the study's initiation. Ain Shams University hospitals' ICU were the setting for this prospective observational study.
The study period was one year.

Sample Population:
The study included Adults (≥18 years old) of both sexes who had been admitted to the hospitals with TBI.
Exclusion criteria of the patients were refusal to sign the consent to participate in the study, physical state in ASA III and IV, TBI lasting more than a day, multisystem trauma, including exposed fractures, thoracic injuries, and abdominal organs like the liver or spleen that have been lacerated, conditions like hyperparathyroidism, acute pancreatitis, and hydrochlorothiazide therapy that impact calcium metabolism, pregnancy and other electrolyte disturbance as hyperphosphatemia and hypomagnesemia.

Sampling method:
Consecutive sampling according to inclusion and exclusion criteria.

Sample size:
A sample size of at least 60 patients (30 patients in each group), divided into control and study groups, was sufficient to meet the goals of the study by using the G power program to calculate sample size, setting power at 80%, alpha error at 5%, and assuming a medium effect size difference (0.5) in mortality rates between TBI patients with ionized hypocalcemia and those with normal ionized calcium levels [11,12].

Study Procedure:
On sixty TBI patients, this prospective observational study was done. Exact medical histories were obtained, physical examination, neurological assessments (conscious level using GCS, any neurological deficits), and appropriate investigations including serum ionized calcium were all performed on patients upon admission to the ICU in the facilities run by Ain Shams University.
Admitted patients with TBI were treated in accordance with the ICU protocol and Advanced Trauma Life Support (ATLS) standards. Blood samples were collected anaerobically, without pressure or stasis, for the purpose of sampling for ionized calcium.
Clinical data, including hemodynamics (heart rate, mean arterial pressures, and respiration rate), neurological assessment, and demographic data were all present at the time of hospital admission.
Patients who met the inclusion criteria were split into two groups based on their serum ionized calcium levels: the control group included those with normal levels (1.16 to 1.31 mmol/l), and the study group included those with low levels (less than 1.10 mmol/l, at which was corrected gradually).
Upon admission, hypocalcemia-related hypotension was treated, and we next investigated any further causes of hypotension.

Data collection tools:
Demographic information, associated medical conditions, hemodynamics, neurological assessment (GCS), CT brain findings, length of ICU stay, 28-day mortality rate, laboratory variables including serum sodium level, ionized calcium level on admission, 5th day, 10th day, 15th day, 20th day, 25th day, and 28th day were evaluated and recorded. Because our study persisted for a longer duration (28 days), we reduced calcium records.

Statistical analysis:
To find any significant differences between the two groups, all data were logged, tabulated, evaluated, and statistically compared. We used IBM SPSS 20 for Windows, a statistical software program for social sciences. Data was supplied, and the type of data was properly analyzed.
– Mean and Standard deviation (+ SD) for numerical data with a parametric normal distribution.
– Median and range are not typically distributed.
– The frequency and percentage of non-parametric numerical data.
The statistical significance of the normally distributed parametric variables was evaluated using an independent sample t-test. The link between two qualitative variables was investigated using the Chi square test ($\mathbf{X^2}$). However, Fisher's Exact Test was performed when the predicted count was less than 5 in more than 20% of the cells.
We utilized Fisher's Exact Test or the Mann Whitney u test, as appropriate, to analyze non-normally distributed data.
P-value significance level:
– $p >$ or = 0.05: Non significant (NS).
– $p < 0.05$: Significant (S).

4. Results

Sixty patients with TBI who met the inclusion criteria for this prospective trial were all enrolled (Figure 1).

With no statistically significant difference between the groups under study (p-value >0.05), groups were equivalent in terms of demographic information and comorbidities. Compared to normocalcemic patients, those with hypocalcemia had considerably lower mean arterial blood pressure (MAP) upon admission.With relation to heart rate, respiration rate, and pH, there were no other notable differences. No statistically significant difference existed between the studied groups as regards intubated patients (Table 1).

5. Traumatic brain injury type and effect

Groups were comparable in trauma type and effect, neurological data and intervention. Number of patients was statistically significantly higher in hypocalcemic than normocalcemic patients regarding diffuse axonal injury, brain edema and lower GCS, but lower in subdural hemorrhage (SDH) in hypocalcemic than normocalcemic patients (Table 2).

6. Laboratory variables

Serum Na^+ was significantly higher in hypocalcemic patients on admission. Ionized Ca^{+2} was significantly lower on admission and on day 5, but after that, there was no significant difference (Table 3, Figures 2).

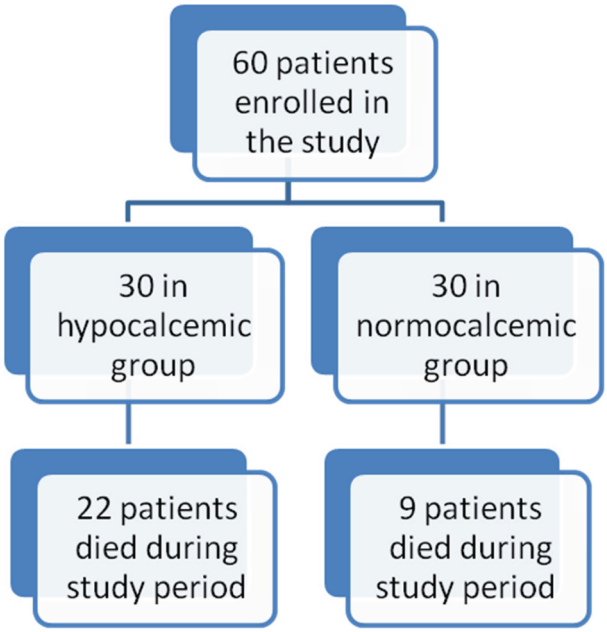

Figure 1. Flow chart of the study.

The length of ICU stays did not differ statistically significantly between the groups. The length of time that survivors in both groups spent in the ICU, however, varied significantly. More survivors with hypocalcemia than those with normocalcemia experienced it. Regarding 28-day mortality rate, significantly more patients died in hypocalcemic than normocalcemic patients (Figure 3), (Table 4).

7. Correlations

Pearson correlations (r) were done between serum Na^{+}, GCS, and ionized Ca^{+2} on admission. Ca^{+2} and Na^{+} had a weak negative correlation, GCS and Na^{+} had a moderate negative correlation (Figure 4), and Ca^{+2} and GCS had a strong positive correlation (Figure 5), (Table 5).

Table 1. Comparison between groups according to demographic data, comorbidities, hemodynamics, respiration rate, pH and intubated patients.

Demographic data		Hypocalcemia	Normocalcemia	p-value
Age (years) (mean ± SD)		43.73 ± 15.95	47.20 ± 19.28	0.451[a]
BMI (Kg/m^2) (mean ± SD)		80.17 ± 10.38	76.67 ± 7.81	0.145[a]
Sex (Numbers and %)	**female**	6 (20.0%)	2 (6.7%)	0.129[b]
	male	24 (80.0%)	28 (93.3%)	
Comorbidities (Numbers and %)	**Hypertension**	13 (43.3%)	7 (23.3%)	0.1
	DM	8 (26.7%)	7 (23.3%)	0.766
	ISHD	5 (16.7%)	9 (30.0%)	0.222
MAP (mmHg) (mean ± SD)		59.17 ± 8.96	68.70 ± 9.60	**<0.001***
Heart rate (beat/m) (mean ± SD)		75.73 ± 7.56	76.30 ± 5.52	0.741
Respiration rate (breath/m) (mean ± SD)		13.07 ± 3.87	14.10 ± 2.40	0.219
pH (mean ± SD)		7.345 ± 0.03	7.352 ± 0.03	0.42
Intubated patients (Numbers and %)		14(46.7%)	12(40%)	0.6

Data expressed as mean ± SD, numbers and %, beats/min, breath/min, a = student t test, b = chi square, BMI = body mass index, DM = diabetes mellitus, IHD = ischemic heart disease.
MAP = mean arterial pressure, pH = potential of hydrogen.
*P statistically significant (< 0.05).

Table 2. Trauma type and effect among study groups.

		Hypocalcemia	Normocalcemia	p-value [X2]
Type of trauma (Numbers and %)	Fall from height	5 (16.7%)	7 (23.3%)	0.129
	RTA	25 (83.3%)	23 (76.7%)	
Type of brain injury (Numbers and %)	SDH	12 (40.0%)	21 (70.0%)	**0.02***
	SAH	15 (50.0%)	20 (66.7%)	0.19
	IVH	5 (16.7%)	6 (20.0%)	0.739
	Diffuse axonal injury	8 (26.7%)	0 (0.0%)	**0.002***
	Brain edema	22 (73.3%)	5 (16.7%)	<0.001*
	Brain contusion	12 (40.0%)	12 (40.0%)	1
	Fractures	16 (53.3%)	14 (46.7%)	0.6
Neurological symptoms	GCS	Median (Range)	Median (Range)	**<0.001***
		5 [3–11]	13 [4–15]	
	Fits (Numbers and %)	5 (16.7%)	7 (23.3%)	0.519
Neurological intervention (Numbers and %)		10 (33.3%)	8 (26.7%)	0.573

Data expressed as numbers, %, median and range.
RTA = road traffic accidents, SDH = subdural hemorrhage, SAH = subarachnoid hemorrhage, IVH = intraventricular hemorrhage, GCS = Glasgow Coma Scale.
*P statistically significant (< 0.05).

Table 3. Laboratory variables among study groups.

	Hypocalcemia	Normocalcemia	p-value [t]
Ionized Ca^{+2} (mmol/l) on admission (mean ± SD)	0.71 ± 0.14	1.27 ± 0.29	**<0.001***
Ca^{+2} (mmol/l) on day 5	0.79 ± 0.17	1.05 ± 0.11	**<0.001***
(mean ± SD)	*n* = 27	*n* = 30	
Ca^{+2} (mmol/l) on day 10	1.07 ± 0.11	1.12 ± 0.14	0.193
(mean ± SD)	*n* = 19	*n* = 30	
Ca^{+2} (mmol/l) on day 15	1.06 ± 0.07	1.06 ± 0.20	0.974
(mean ± SD)	*n* = 13	*n* = 22	
Ca^{+2} (mmol/l) on day 20	1.17 ± 0.10	1.10 ± 0.17	0.255
(mean ± SD)	*n* = 10	*n* = 16	
Ca^{+2} (mmol/l) on day 25	1.14 ± 0.06	1.12 ± 0.09	0.627
(mean ± SD)	*n* = 8	*n* = 13	
Ca^{+2} (mmol/l) on day 28	0.98 ± 0.27	1.16 ± 0.14	0.084
(mean ± SD)	*n* = 8	*n* = 10	
Serum Na^{+} (ml/l) on admission (mean ± SD)	145.33 ± 9.34	139.53 ± 6.50	**0.007***

Data expressed as mean ± SD, mmol/l, ml/l, *T* = student t test.
Ca^{+2} = calcium, Na^{+} = sodium.
*P statistically significant (< 0.05).

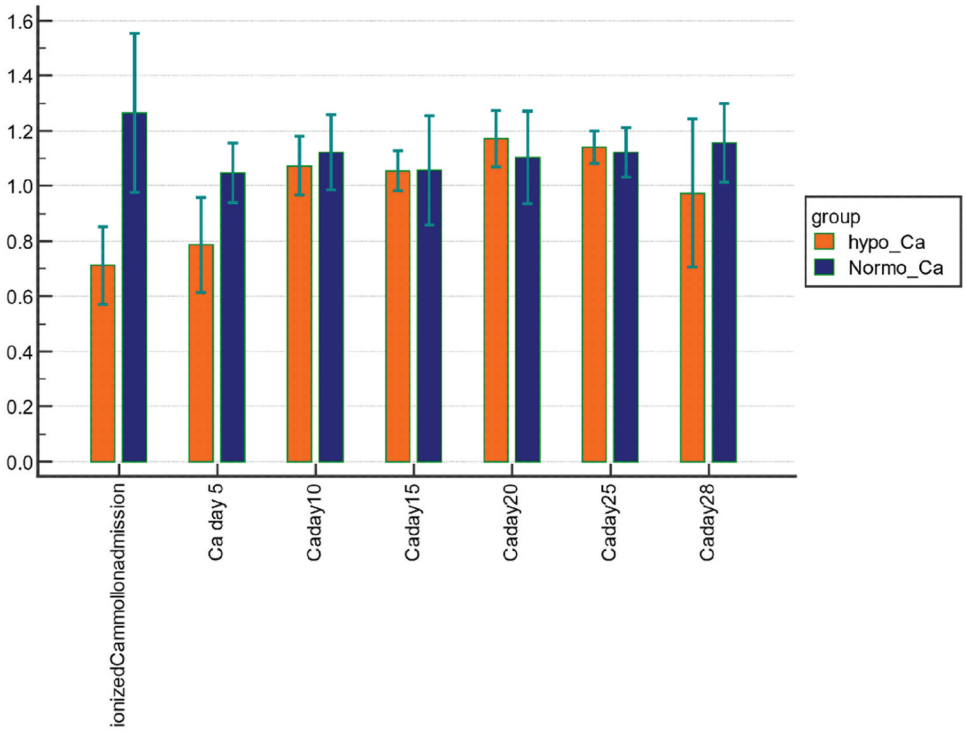

Figure 2. Graph between groups as regard ionized Ca^{+2}.

8. ROC analysis

Roc analysis was done for ionized Ca^{+2} and showed AUC 0.788 and cut off value ≤ 1.16 mmmol with sensitivity 100% and specificity 55.1% (Table 6, Figure 6).

9. Discussion

This prospective observational study was done to assess the prognostic value of on-admission ionized calcium for TBI patients. Ionized hypocalcemia may be linked to higher mortality after TBI [13]. But it's still unclear how it works in TBI. The pathophysiology of induced neuronal cell death is facilitated by it [14]. Possible causes include increased Ca + 2 consumption by inflammatory proteins that injured neuronal cells discharge into the extracellular environment. Ca + 2 levels in the intracellular space are consequently reduced [15]. Additionally, associated metabolic acidosis and inadequate post-traumatic cerebral perfusion result in neuronal cell hypoxia and mitochondrial dysregulation, which lead to neuronal cell death [16].

The Lethal diamond of TBI, which also includes acidosis and coagulopathy, should include ionized hypocalcemia [17].

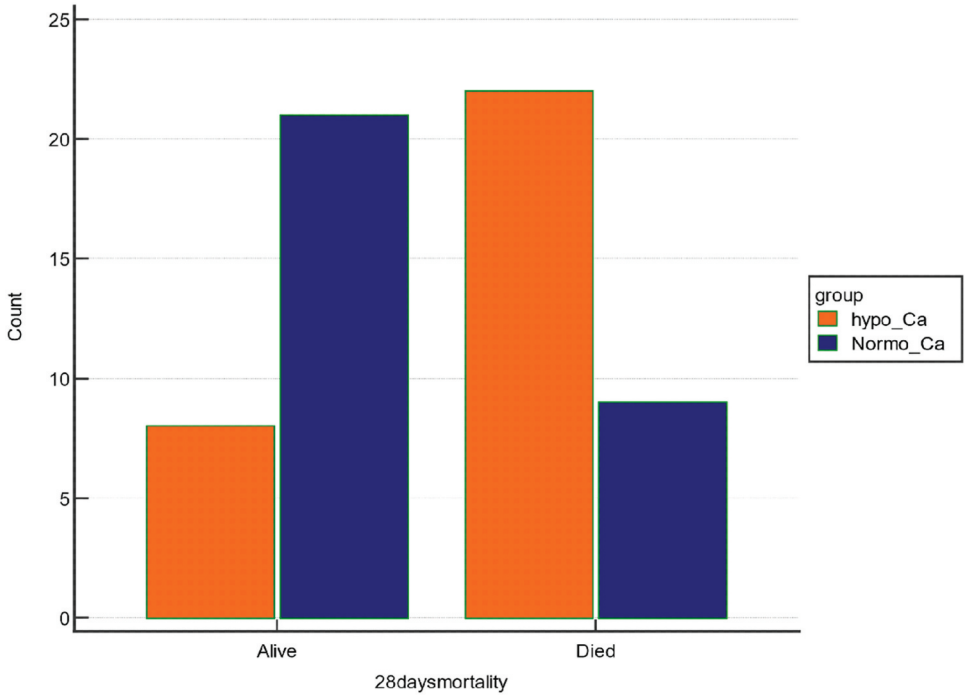

Figure 3. Graph between study groups as regard 28-day mortality rate.

Table 4. Comparison between groups according to duration of ICU stay, survivors in study groups regarding the duration and 28-day mortality rate.

		Hypocalcemia	Normocalcemia	
		Median (Range)	Median (Range)	p- value
Duration of ICU stay (days)		14 [6–28]	8.5 [3–28]	0.082
Survivors numbers of patients		8	21	
Duration of ICU stay for survivors (days)		Median (Range)	Median (Range)	
		20 [15–28]	6 [3–15]	<0.001*
28- day mortality rate (number and %)	Alive	8 (26.7%)	21 (70.0%)	
	Died	22 (73.3%)	9 (30.0%)	0.001*

Data expressed as median, range, numbers and %, p value X2 Chi square
P statistically significant (<0.05).

Our findings are consistent with those of **Cherry et al**. [18], who showed that entrance ionized hypocalcemia (defined as ≤1.0 mmol/L) was associated with an increased mortality in 396 American trauma patients, and that 23% of the research group was hypocalcemic on admission. Mortality rates were 26.4% and 16.7% in the hypocalcemic and normocalcemic groups (p 0.05; odds ratio, 1.92).

Magnotti et al. [19] and **Vasudeva et al**. [20] found that ionized hypocalcemia was linked to higher mortality rates of 56.2% and 50%, respectively. In 2020, **Vasudeva et al**. [20] conducted a retrospective research on 226 trauma victims in Australia. The hypocalcemic cohort study had a greater mortality rate after hospital discharge (25.6% vs. 15.0%, $p = 0.047$).

An inverse proportional connection was shown between higher mortality and ionized Ca^{+2} levels in a prospective research by **Vivien et al**. [21] on 212 patients, 64% of whom were hypocalcemic. Hypocalcemia didn't usually return to normal in hypocalcemic trauma ICU patients, confirming its predictive relevance.

Age, the absence of pupillary reactivity, ionized hypocalcemia (<1.10 mmol/L), and presence of interleukin 6 (IL 6) on day three were included in the logistic regression model developed by **Vinas-Rios et al**. [11]. Poor Glasgow Outcome Scores were noted in 34.08% of the patients (R2 = 34.3%, $p = 0.001$). Age was demonstrated to be a known risk factor for poor outcomes in TBI patients, being significant ($p = 0.001$) between analyzed groups.The majority of patients with TBIs were older than 65 and commonly had severe disabilities or passed away (GCS <3). Older people had worse outcomes, which led to a selection bias because of their declining health, insufficient elimination of free radicals, and accumulation of pro-inflammatory proteins that cause cellular death. Thought to be a potential selection bias, serum ionized calcium was a finding unrelated to age [11].

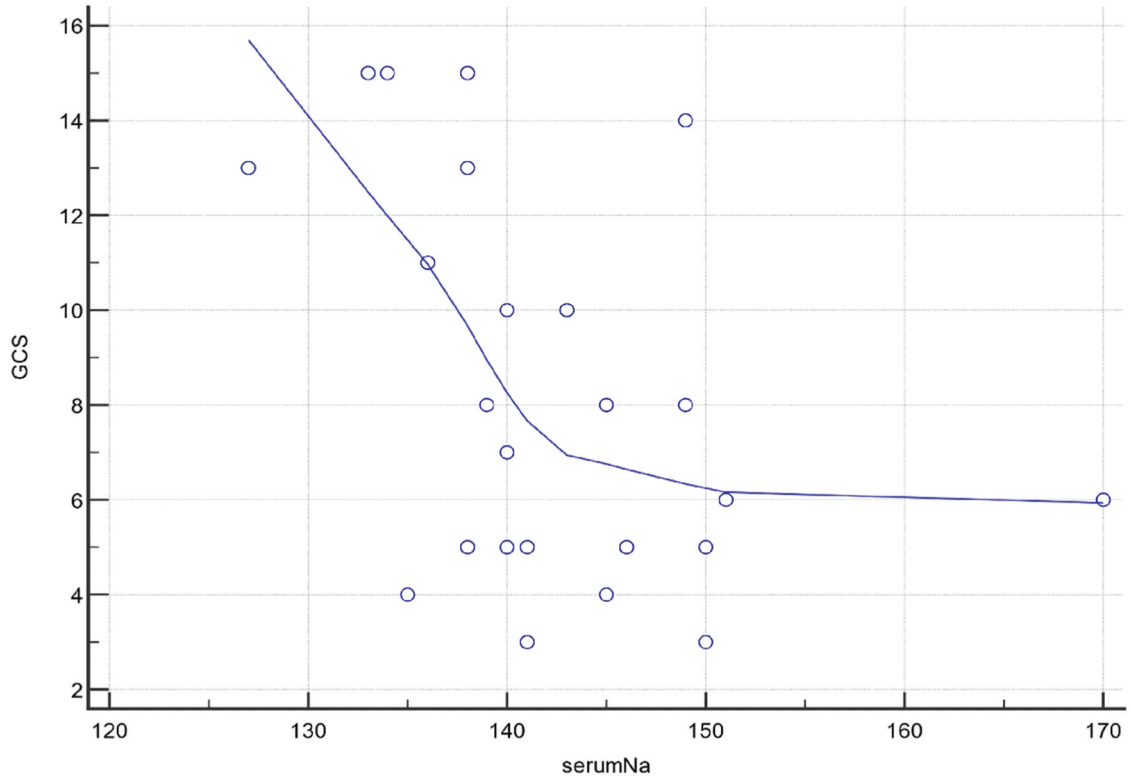

Figure 4. Scattered diagram for correlation between GCS and Na^{+}.

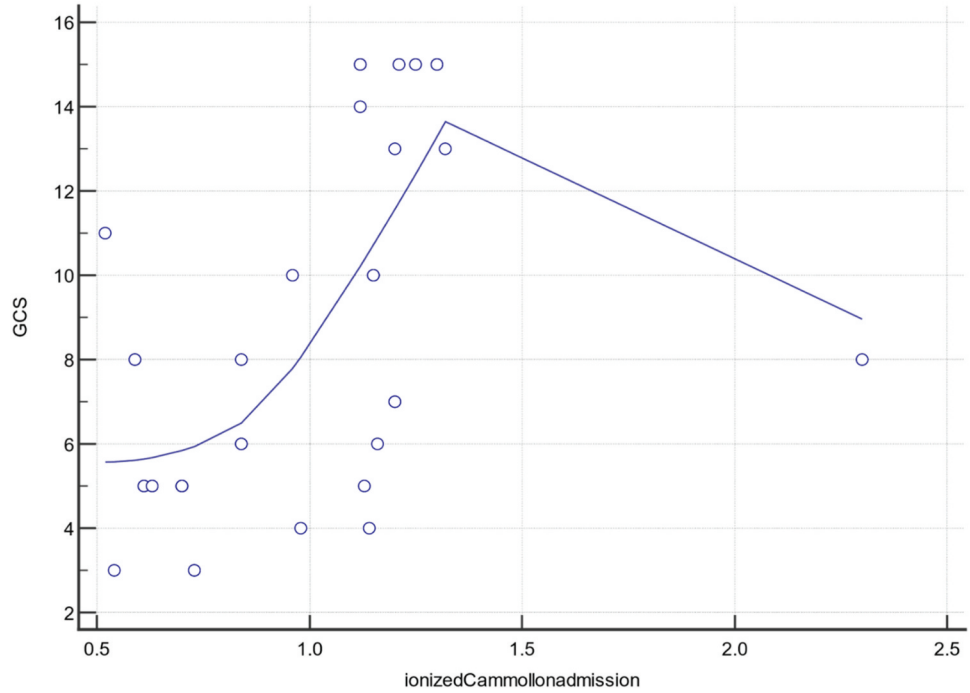

Figure 5. Scattered diagram for correlation between GCS and Ca^{+2}.

Vinas-Rios et al. [13] conducted a different study on 99 patients who had moderate or severe TBI found a significant difference in GCS (0.041) and mean arterial pressure (0.018) at admission. It also showed that there were no notable differences in the demographic characteristics, basal pH levels, duration of ICU stay, or days of intubation. On the third day, the sensitivity (83.76%) and specificity (66.66%) for ionized serum Ca^{+2} were found to be highest at 1.11 mmol/L, with an OR value of 6.45 (CI 95%: 2.02–20.55).

The ICU routinely measured mean pressure throughout our study; as a result, it wasn't recorded

Table 5. Pearson correlation between on admission, GCS and ionized Ca^{+2}.

		Ionized Ca^{+2} on admission	GCS
Serum on admission	r	−0.120	−0.409
	P	0.3604	0.0012
	n	60	60

Table 6. ROC analysis.

Area under the ROC curve (AUC)	0.788
Significance level P	<0.0001
Cut off value	≤1.16
Sensitivity	100.00
Specificity	55.17

but will be used in subsequent studies. We treated hypocalcemia-related hypotension.

Ionized hypocalcemia on day five of admission and poor outcomes following severe trauma were linked in our study. Numerous processes, including neuroinflammation, neuronal hypoxia, reduced cerebrovascular autoregulation, and degree of brain edema, were implicated in TBI and served as solid prognostic indicators [23]. Because of the disrupted energy metabolism brought on by hypoxia and hypoperfusion following TBI, the sodium/potassium pump on the neuronal cell membrane is unable to maintain the normal ion gradient, which changes the influx of Ca^{+2}, ultimately resulting in neuronal cell death [24]. This rise in intracellular Ca^{+2} inhibits mitochondrial enzymes and activates lipases, which is a crucial step in the apoptotic process. Ionized hypocalcemia may result from pro-inflammatory molecules such as Interleukin 6 (IL-6) chelating Ca^{+2}. Lactate is one of the main indicators of acidosis, which is caused by increased metabolic molecules caused by aerobic mitochondrial pathway disturbance [25].

The intrinsic and extrinsic pathways of coagulation, platelet activity, cardiac contractility, and vascular smooth muscle contraction all depend on ionized Ca^{+2}. Since the cardiac sarcoplasmic reticulum cannot store sufficient quantities, extracellular Ca^{+2} is necessary for myocardial contractility. Significant hypocalcemia can cause heart failure and arrhythmias. Post-TBI, platelet activation, platelet aggregation, and clot strength were reduced in hypocalcemic patients [26]. Additionally, when ionized Ca^{+2} levels fall below 0.8–0.9 mmol/L, cardiac contractility declines, which is linked to higher mortality [27].

Additionally, the researchers **Lippi et al**. [28] and **WANKASI et al**. [29] found a substantial rise in total and ionized Ca^{+2} after applying a tourniquet ($p < 0.05$) compared to data acquired without one. This was brought on by prolonged tourniquet application, which caused anaerobic glycolysis, increasing plasma lactate levels, lowering blood pH, and artificially raising the concentration of ionized Ca^{+2}. A reduction in pH and accompanying rise in H^{+} causes Ca^{+2} to be

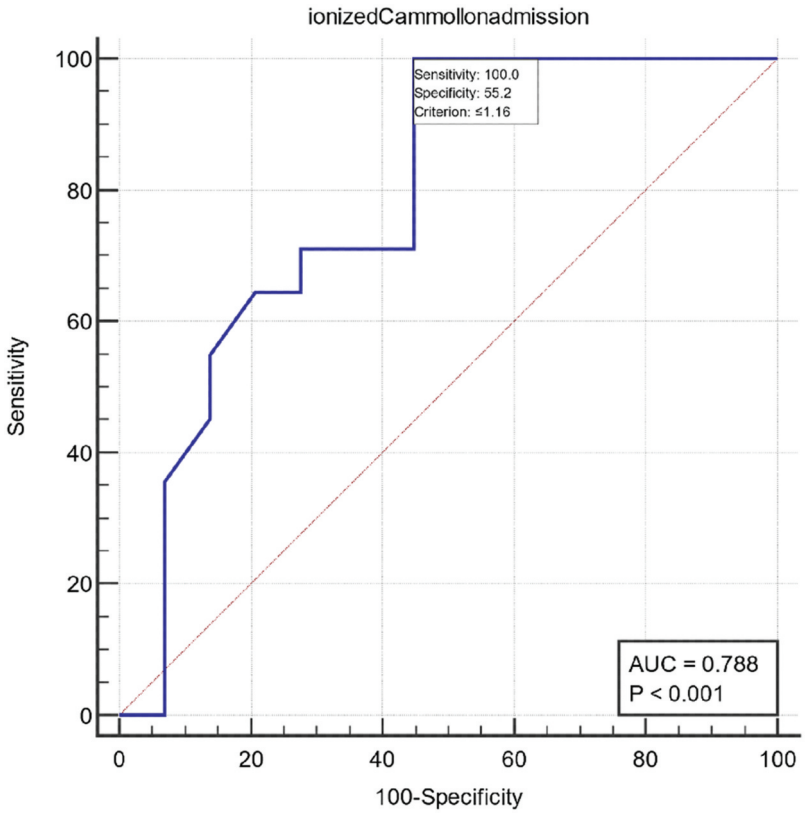

Figure 6. ROC analysis curve.

displaced from its binding sites, increasing the concentration of ionized Ca^{+2}. This is how pH affects the serum Ca^{+2} concentration. This observation emphasized the conclusions reached by other authors [29] who also noted a rise in total and ionized Ca^{+2} after a prolonged tourniquet application. Therefore, prolonged tourniquet was avoided in our investigation to reduce erroneous outcomes.

Our results are consistent with the research conducted by **Maggiore et al**. [30]. In severe TBI patients, they discovered that hypernatremia upon admission was linked to a threefold increase in the adjusted hazard ratio of ICU death [31]. Also, **Li et al**. [32] found that in TBI patients admitted to the ICU, severe hypernatremia was a separate risk factor with a very high odds ratio for mortality.

The association between hypernatremia and increased mortality in our study was merely observational; it was not our primary goal and not a definite finding. It needs additional research.

Shehata et al.'s [33] found that severe TBI patients who had hypernatremia on admission had a greater mortality rate and required longer ICU stay. The researchers concluded that GCS was irrelevant to the association between hypernatremia and mortality in TBI patients. The results of this earlier study showed a significant relationship between postoperative death in TBI patients, low GCS, and hypernatremia.

In 2018, **Pin-on et al**. [34] did a further study that showed isolated postoperative hypocalcemia was not a factor in predicting death in TBI patients ($p = 0.79$). Overall, it was determined that bad outcomes were caused by a vicious cycle produced by hypoperfusion, acidosis, and hypocalcemia. According to the study, postoperative hypocalcemia was caused by blood transfusions and the citrate chelation of serum ionized Ca + 2. Packed red blood cells and freshly frozen plasma frequently contain the preservative and anticoagulant citrate. It is quickly removed from circulation after being digested by liver enzymes. Metabolic processes are delayed by acidosis and hypoperfusion [35].

10. Conclusion

Significantly increased fatality rates in TBI patients are associated with low serum ionized calcium on admission and on day 5, as well as hypernatremia on admission and disrupted conscious state.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Contribution from authors

Gamal Eldin Mohammad Ahmad Elewa, Mohamed Sidky Mahmoud Zaki, Sherif George Anis Said, Ahmed Abd El Ghani Khalifa Ragab contributed substantially in the designing of the research; creating the ideas; editing and reviewing the paper. **Jihad Mamdouh Mahanna Ahmed** : contributed mainly in performing the procedures of the experiment; analyzing and interpreting the data; as well as writing the paper.

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References

[1] Georges A, Das JM. Traumatic brain injury. In: StatPearls.Treasure island. (FL): StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK459300/

[2] Graham DI, Gennarelli TA. Pathology of brain damage after head injury. In: Cooper P Golfinos J, editors. Textbook of traumatic brain injury. Vol. 3. New York: McGraw-Hill; 2000. pp. 133–153.

[3] Hill CS, Coleman MP, Menon DK. Traumatic axonal injury: mechanisms and translational opportunities. Trends Neurosci. 2016;39(5):311–324. doi: 10.1016/j.tins.2016.03.002

[4] Teasdale G, Jennett B. Assessment and prognosis of coma after head injury. Acta Neurochir (Wien). 1976;34(1–4):45–55. PMID 961490. S2CID 32325456. doi: 10.1007/BF01405862

[5] Haarbauer–Krupa J, Pugh MJ, Prager EM, et al. Epidemiology of chronic effects of traumatic brain injury. J Neurotrauma. 2021;38(23):3235–3247. doi: 10.1089/neu.2021.0062

[6] Mirza FA, JF F. Traumatic brain injury. In: Ferri FF, editor. Ferri's Clinical Advisor. Elsevier; 2022. p. 1515–19.

[7] Kim YJ. A systematic review of factors contributing to outcomes in patients with traumatic brain injury. J Clin Nurs. 2011;20(11–12):1518–1532. doi: 10.1111/j.1365-2702.2010.03618.x

[8] Unterberg AW, Stover J, Kress B, et al. Edema and braintrauma. Neuroscience. 2004;129(4):1019–1027. doi: 10.1016/j.neuroscience.2004.06.046

[9] Lath R. Hyponatremia in neurological diseases in ICU. Indian Journal of Critical Care Medicine. 2007;9(1):47–51. doi: 10.4103/0972-5229.16270

[10] Peacock M. Calcium metabolism in health and disease. M Clin J Am Soc Nephrol. 2010;5(Supplement_1):S23–S30. doi: 10.2215/CJN.05910809

[11] Vinas-Rios JM, Sanchez-Aguilar M, Kretschmer T, et al. Hypocalcaemia as a prognostic factor of early mortality in moderate and severe traumatic brain injury and its role with protein S-100b. J Neurol Disord. 2017;5(3):342. doi: 10.4172/2329-6895.1000346

[12] Wray JP, Bridwell RE, Schauer DO, et al. The diamond of death: hypocalcemia in trauma and resuscitation. Am J Emerg Med. 2021;41:104–109. doi: 10.1016/j.ajem.2020.12.065

[13] Vinas-Rios JM, Sanchez-Aguilar M, Sanchez-Rodriguez JJ, et al. Hypocalcaemia as a prognostic factor of early mortality in moderate and severe traumatic brain injury. Neurol Res. 2014;36(2):102–106. doi: 10.1179/1743132813Y.0000000272

[14] Merlo L, Cimino F, Angileri FF, et al. Alteration in synaptic junction proteins following traumatic brain injury. J Neurotrauma. 2014;31(16):1375–1385. doi: 10.1089/neu.2014.3385

[15] Raj R, Siironen J, Kivisaari R, et al. Factors correlating with delayed trauma center admission following traumatic brain injury. Scand J Trauma Resusc Emerg Med. 2013;21(1):21–67. doi: 10.1186/1757-7241-21-67

[16] Yokobori S, Hosein K, Burks S, et al. Biomarkers for the clinical differential diagnosis in traumatic brain injury-a systematic review. CNS Neurosci Ther. 2013;19(8):556–565. doi: 10.1111/cns.12127

[17] Ditzel RM Jr, Anderson JL, Eisenhart WJ, et al. A review of transfusion-and trauma-induced hypocalcemia: is it time to change the lethal triad to the lethal diamond? J Trauma Acute Care Surg. 2020;88(3):434–439. doi: 10.1097/TA.0000000000002570

[18] Cherry RA, Bradburn E, Carney DE, et al. Do early ionized calcium levels really matter in trauma patients. The Journal of Trauma: Injury, Infection, And Critical Care. 2006;61(4):774–779. doi: 10.1097/01.ta.0000239516.49799.63

[19] Magnotti LJ, Bradburn EH, Webb DL, et al. Admission ionized calcium levels predict the need for multiple transfusions: a prospective study of 591 critically ill trauma patients. J Trauma. 2011;70(2):391–395. doi: 10.1097/TA.0b013e31820b5d98

[20] Vasudeva M, Mathew JK, Fitzgerald MC. Hypocalcaemia and traumatic coagulopathy: an observational analysis. Vox Sang. 2020;115(2):189–195. doi: 10.1111/vox.12875

[21] Vivien B, Langeron O, Morell E, et al. Early hypocalcemia in severe trauma. Crit Care Med. 2005;33(9):1946–1952. doi: 10.1097/01.CCM.0000171840.01892.36

[22] Kamal VK, Agrawal D, Pandey RM. Prognostic models for prediction of outcomes after traumatic brain injury based on patients admission characteristics. Brain Inj. 2016;30:393–406. doi: 10.3109/02699052.2015.1113568

[23] Dias CR, Leite HP, Nogueira PC, et al. Ionized hypocalcemia is an early event and is associated with organ dysfunction in children admitted to the intensive care unit. Journal of Critical Care. 2013;28(5):810–815. doi: 10.1016/j.jcrc.2013.03.019

[24] Lima FD, Souza MA, Furian AF, et al. Na+,K±ATPase activity impairment after experimental traumatic brain injury: relationship to spatial learning deficits and oxidative stress. Behav Brain Res. 2008;193(2):306–310. doi: 10.1016/j.bbr.2008.05.013

[25] Manuel VR, Martin SA, Juan SR, et al. Hypocalcemia as a prognostic factor in mortality and morbidity in moderate and severe traumatic brain injury. Asian J Neurosurg. 2015;10(3):190–194. doi: 10.4103/1793-5482.161171

[26] Matthay ZA, Fields AT, Nunez-Garcia B, et al. Dynamic effects of calcium on in vivo and ex vivo platelet behavior after trauma. J Trauma Acute Care Surg. 2020;89(5):871–879. doi: 10.1097/TA.0000000000002820

[27] Hall C, Nagengast AK, Knapp C, et al. Massive transfusions and severe hypocalcemia: an opportunity for monitoring and supplementation guidelines. Transfusion. 2021;61(Suppl 1):S188–94. doi: 10.1111/trf.16496

[28] Lippi G, Salvagno GL, Montagnana M, et al. Influence of short-term venous stasis on clinical chemistry testing. Clin Chem Lab Med. 2005;43(8):869–873. doi: 10.1515/CCLM.2005.146

[29] Wankasi MM, Agoro, et al. The effect of tourniquet application on serum calcium and inorganic phosphorus determination. J Health, Med Nurs. 2019;65 www.iiste.org ISSN 2422-8419. doi: 10.7176/JHMN

[30] Maggiore U, Picetti E, Antonucci E, et al. The relation between the incidence of hypernatremia and mortality in patients with severe traumatic brain injury. Crit Care. 2009;13(4):R110. doi: 10.1186/cc7953

[31] Kirsten Y, Renkema R, Rene J, et al. Calcium and phosphate homeostasis. Clin Chem Lab Med. 2008;5:57–59.

[32] Li M, Hu YH, Chen G. Hypernatremia severity and the risk of death after traumatic brain injury. Injury. 2013;44(9):1213–1218. doi: 10.1016/j.injury.2012.05.021

[33] Shehata M, Ragab D, Khaled M, et al. Impact of hypernatremia on patients with severe traumatic brain injury. Crit Care. 2010;14(Suppl 1):355. doi: 10.1186/cc8587

[34] Pin-On P, Saringkarinkul A, Punjasawadwong Y, et al. Serum electrolyte imbalance and prognostic factors of postoperative death in adult traumatic brain injury patients. 2018 Nov;97(45):e13081. doi: 10.1097/MD.0000000000013081

[35] Fidelindo L, Chen Leon L. Daniel B.Managing hypocalcemia in massive blood transfusion. Nursing. 2017;47(5):26–32. doi: 10.1097/01.NURSE.0000515501.72414.e3