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Research article

Risk of pre-existing hyponatremia and mortality in patients with traumatic brain injury across age groups

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1. Introduction

Traumatic brain injury (TBI) is a serious public health concern and a leading cause of death and disability worldwide. In the US, approximately 2.8 million individuals sustain a TBI annually, resulting in more than 280,000 hospitalization and more than 50,000 TBI-related deaths, which is one-third of all injury-related deaths in the US [1]. The direct and indirect medical costs of TBI, including loss of productivity, were estimated to be total $76 billion in the US in 2010 [2]. Moreover, recent literature shows that more than 1.1% of the US population lives with TBI, and more than 40% of those with moderate-to-severe injuries have long-term disabilities [3] (see Figure 1).

Hyponatremia, defined as serum sodium less than 135 mmol/L, is one of the most common electrolyte imbalance in patients with TBI [4]. The incidence of hyponatremia in patients with TBI is reported to be 9.6–51% [5, 6, 7], and it is well established that hyponatremia is an independent predictor of poor neurological outcomes in these patients [8]. Additionally, hyponatremia induces loss of activity and personality changes, and severe hyponatremia causes confusion, seizure attacks, and even death [9].

The incidence of hyponatremia is higher in older individuals than younger individuals due to physiologic degeneration, multiple comorbidities, and polypharmacy [10]. Further, hyponatremia in older patients is occasionally chronic and mild, and typically considered to be asymptomatic, thus it is often ignored in general conditions or even after an incidence of disease or injury such as TBI [11]. Based on some studies, the impact of hyponatremia on mortality is greater in younger patients in many situations and diseases [12, 13].

Most studies on the incidence, mechanism, prognosis, and treatment of hyponatremia in patients with TBI are studies on the occurrence of hyponatremia due to cerebral salt-wasting (CSW), syndrome of inappropriate antidiuretic hormone secretion, and hypopituitarism [14, 15, 16]. Although previous studies have investigated radiological and clinical findings for their association with the prognosis of TBI, to our best knowledge, no study has evaluated the prognosis of initial hyponatremia.

We hypothesized that hyponatremia increases mortality in patients with TBI, and the prognostic value of hyponatremia would vary with age. In this study, we investigated the association between initial serum hyponatremia and mortality in TBI patients, and we also examined the differences in the impact of hyponatremia across the age group.

2. Methods

2.1. Study design and setting

This retrospective study included TBI patients, who were transported to Level-1 trauma center (Chonnma National University Hospital, CNUH) by emergecny medical service (EMS) between January 2018 and December 2019.

CNUH trauma center was strated in 2010 and has a team of expert physicians in various departments including general surgery, thoracic surgery, neurosurgery, orthopedic surgery, radiology, and emergency medicine. If EMS paramedics suspect that a patient has a major injury including TBI, paramedics report to the hospital at the scene or during transport. Immediately after emergency department (ED) arrival,

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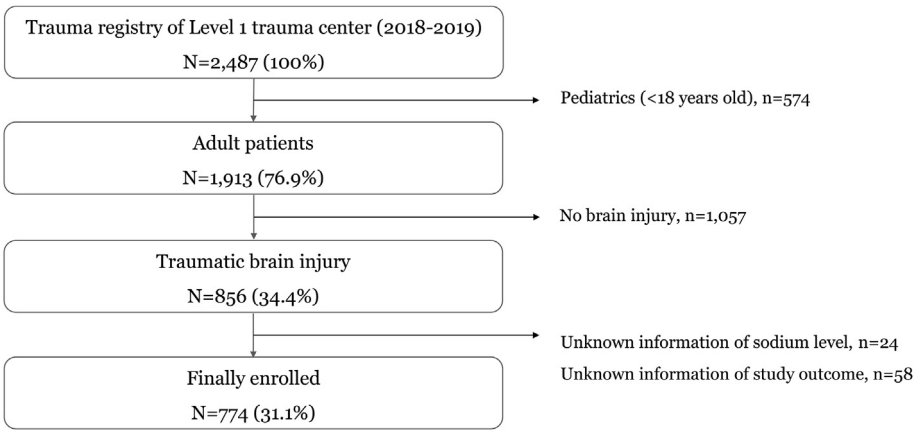

Figure 1. Study populations.

physical examiniation, computed tomography, and a blood test including serum electrolyte is performed, and if hyponatremia is observed, immediate treatment with a sodium-containing fluid is administrated.

The present study was approved by the Institutional Review Board of CNUH. Given the retrospective nature of the study and the use of anonymized patient data, requirements for informed consent were waived.

2.2. Study population

Our study population was adult patients with TBI who were visited to the level-1 hospital by EMS. We excluded patients who has unknown information of serum sodium level and study outcomes.

2.3. Main outcome and variables

The main outcome variable was mortality at hospital discharge, and the secondary outcome was 6-month mortality. The main exposure was the serum sodium level. Serum sodium levels were measured within 30 min of ED arrival; those with sodium level <135 mmol/L were defined as having hyponatremia, while those with sodium level between 135 mmol/L and 145 mmol/L were defined as having normonatremia. In addition, prehospital and hospital information were extracted from patients' electronic records, which included age, sex, comorbidities including hypertension, diabetes mellitus, and disorder of coagulation, mechanism and place of injury, injury severity based on the Abbreviated Injury Scale (AIS) and New Injury Severity Score (NISS), mental status, type of brain hemorrhage, electrolyte concentration, and osmolarity.

2.4. Statistical analysis

Characteristics of patient, prehospital and hospital variables, and clinical outcomes according to serum sodium levels were compared using the Wilcoxon rank-sum test for continuous variables and the Chi-square test for categorical variables. We conducted multivariable logistic regression analysis to calculated the effect sizes of hyponatremia on mortality compared to normonatremia in TBI patients. We calculated odds ratio (OR) with 95% confidence intervals (CIs). Finally, we performed interaction analysis between serum sodium levels and age on study outcomes. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Demographic findings

During the study period, details of 774 TBI patients who were transported to the ED by EMS were recorded in our registry; all were enrolled in the study as there was no unknown information on main exposure and study outcome variables.

The overall mean serum sodium level was 139 mmol/L. The characteristics of the study population according to the hyponatremia are shown in Table 1. Hyponatremia was observed in 102/774 (13.2%) patients. The proportion of mortality at hospital discharge was 7.8% (8/102) in the hyponatremia group and 10.1% (68/672) in the normonatremia group (p-value = 0.61). Mortality at 6 months was 23.5% (24/102) in the hyponatremia group and 19.9% (134/672) in the normonatremia group (p-value = 0.55).

The characteristics of the study population according to age group are shown in Table 2. Hyponatremia was observed in 9.1% (30/328) of the 18–64year-old group and 16.1% (72/446) in the ≥65-year-old group (p-value < 0.05). There was no statistically significant difference in mortality at hospital discharge between the two age groups (9.8% vs. 9.9%; p-value = 0.97).

3.2. Main results

In the multivariable logistic regression analysis, patients with hyponatremia had no significant difference in terms of mortality at hospital discharge (fully adjusted OR [95% CIs]: 0.69 [0.22–2.19]), and mortality at 6 months (1.16 [0.53–2.51]). In addition, effect of hyponatremia in old age group had no significant difference in terms of mortality at hospital discharge (1.74 [0.75–4.00], whereas mortality at 6-month was significantly higher in old age group compared to young age group (3.25 [1.68–6.29) (Table 3).

3.3. Interaction analysis

In the interaction analysis, there was an interaction effect between hyponatremia and age on mortality at 6 months. Using 65 years of age as a cut off, there were no statistical differences on mortality at hospital discharge and mortality at 6-month between the normonatremia and hyponatremia. Using 75 years of age as a cut-off (p for interaction <0.05), the adjusted ORs (95% CIs) were 0.24 (0.03–1.94) for the 18–74-year-old group and 1.53 (1.04–2.95) for the ≥75-year-old group (Table 4).

4. Discussion

Our study, which investigated the association between initial serum hyponatremia and mortality, suggested that hyponatremia did not increase mortality in the patients with TBI; however, in an interaction analysis of hyponatremia and age group on mortality, hyponatremia was significantly associated with mortality at 6-month after TBI in patients aged ≥75 years.

Most of the studies related to hyponatremia in patients with TBI are about hyponatremia that occurs as a result of TBI. These studies focus on whether the hyponatremia is consistent with the severity of TBI and

Table 1. Characteristics of the study population according to the serum sodium level.

Variables	All	Serum Sodium		P-value
		Hyponatremia <135 mmol/L	Normonatremia 135–145 mmol/L	
	N (%)	N (%)	N (%)	
All	774 (100.0)	102 (100.0)	672 (100.0)	
Age (years)				<0.05
18–64	328 (42.4)	30 (29.4)	298 (44.3)	
65-	446 (57.6)	72 (70.6)	374 (55.7)	
Sex				0.34
Female	244 (31.5)	38 (37.3)	206 (30.7)	
Underlying disease				
Hypertension	344 (44.4)	58 (56.9)	286 (42.6)	0.06
Diabetes	224 (28.9)	34 (33.3)	190 (28.3)	0.46
Disorder of coagulation	26 (3.4)	4 (3.9)	22 (3.3)	0.81
Mechanism of injury				0.25
Traffic	280 (36.2)	28 (27.5)	252 (37.5)	
Fall	344 (44.4)	56 (54.9)	288 (42.9)	
Other	150 (19.4)	18 (17.6)	132 (19.6)	
Place of injury				<0.05
Home	236 (30.5)	42 (41.2)	194 (28.9)	
Street	290 (37.5)	34 (33.3)	256 (38.1)	
Other	248 (32.0)	26 (25.5)	222 (33.0)	
Severity (AIS≥3)				
High AIS score of TBI	500 (64.6)	76 (74.5)	424 (63.1)	0.11
High AIS score of other region	164 (21.2)	8 (7.8)	156 (23.2)	<0.05
Severity of trauma (NISS)				<0.05
1–8	78 (10.1)	12 (11.8)	66 (9.8)	
9–15	154 (19.9)	8 (7.8)	146 (21.7)	
16–24	224 (28.9)	26 (25.5)	198 (29.5)	
25–75	318 (41.1)	56 (54.9)	262 (39.0)	
Vasopressor				0.08
Yes	56 (7.2)	10 (9.8)	46 (6.8)	
Glasgow Coma Scale				0.1
15	422 (54.5)	44 (43.1)	378 (56.2)	
13–14	104 (13.4)	18 (17.6)	86 (12.8)	
9–12	97 (12.5)	17 (16.7)	80 (11.9)	
3–8	151 (19.5)	23 (22.5)	128 (19.0)	
Types of hemorrhage				0.09
SDH	370 (47.8)	66 (64.7)	304 (45.2)	
SAH	144 (18.6)	16 (15.7)	128 (19.0)	
ICH	92 (11.9)	4 (3.9)	88 (13.1)	
EDH	74 (9.6)	8 (7.8)	66 (9.8)	
IVH & other	94 (12.1)	8 (7.8)	86 (12.8)	
Potassium (mmol/L)				<0.05
0–3.5	166 (21.4)	24 (23.5)	142 (21.1)	
3.5–5.0	578 (74.7)	66 (64.7)	512 (76.2)	
5.0-	30 (3.9)	12 (11.8)	18 (2.7)	
Chloride (mmol/L)				<0.05
0–96	40 (5.2)	28 (27.5)	12 (1.8)	
96–106	392 (50.6)	70 (68.6)	322 (47.9)	
106-	342 (44.2)	4 (3.9)	338 (50.3)	
Osmolarity (mmol/kg)				<0.05
0–275	60 (7.8)	40 (39.2)	20 (3.0)	
275–295	464 (59.9)	28 (27.5)	436 (64.9)	
295-	250 (32.3)	34 (33.3)	216 (32.1)	
Advanced airway				0.38
Yes	106 (13.7)	18 (17.6)	88 (13.1)	
Transfusion				0.35
Yes	78 (10.1)	14 (13.7)	64 (9.5)	

(*continued on next page*)

Table 1 (*continued*)

Variables	All	Serum Sodium		P-value
		Hyponatremia	Normonatremia	
		<135 mmol/L	135–145 mmol/L	
	N (%)	N (%)	N (%)	
Outcomes				
Mortality at hospital discharge	76 (9.8)	8 (7.8)	68 (10.1)	0.61
Mortality at 6-month	158 (20.4)	24 (23.5)	134 (19.9)	0.55

AIS, abbreviated injury scale; TBI, traumatic brain injury; NISS, new injury severity scale; SDH, subdural hemorrhage, SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; EDH, epidural hemorrhage; IVH, intraventricular hemorrhage.

Table 2. Characteristics of the study population according to age group.

Variables	All	Age		P-value
		18–64	65-	
	N (%)	N (%)	N (%)	
All	774 (100.0)	328 (100.0)	446 (100.0)	
Serum sodium (mmol/L)				<0.05
Hyponatremia (<135)	102 (13.2)	30 (9.1)	72 (16.1)	
Normonatremia (135–145)	672 (86.8)	298 (90.9)	374 (83.9)	
Sex				<0.05
Female	244 (31.5)	66 (20.1)	178 (39.9)	
Underlying disease				
Hypertension	344 (44.4)	62 (18.9)	282 (63.2)	<0.05
Diabetes	224 (28.9)	46 (14.0)	178 (39.9)	<0.05
Disorder of coagulation	26 (3.4)	10 (3.0)	16 (3.6)	0.77
Mechanism of injury				<0.05
Traffic	280 (36.2)	140 (42.7)	140 (31.4)	
Fall	344 (44.4)	120 (36.6)	224 (50.2)	
Other	150 (19.4)	68 (20.7)	82 (18.4)	
Place of injury				<0.05
Home	236 (30.5)	64 (19.5)	172 (38.6)	
Street	290 (37.5)	148 (45.1)	142 (31.8)	
Other	248 (32.0)	116 (35.4)	132 (29.6)	
Severity (AIS>=3)				
High AIS score of TBI	500 (64.6)	212 (64.6)	288 (64.6)	0.99
High AIS score of other region	164 (21.2)	82 (25.0)	82 (18.4)	0.12
Severity of trauma (NISS)				0.46
1–8	78 (10.1)	34 (10.4)	44 (9.9)	
9–15	154 (19.9)	58 (17.7)	96 (21.5)	
16–24	224 (28.9)	108 (32.9)	116 (26.0)	
25–75	318 (41.1)	128 (39.0)	190 (42.6)	
Vasopressor				0.96
Yes	56 (7.2)	24 (7.3)	32 (7.2)	
Glasgow Coma Scale				0.08
15	422 (54.5)	44 (43.1)	378 (56.3)	
13–14	104 (13.4)	17 (16.7)	87 (12.9)	
9–12	97 (12.5)	20 (19.6)	77 (11.5)	
3–8	151 (19.5)	21 (20.6)	130 (19.3)	
Types of hemorrhage				<0.05
SDH	370 (47.8)	122 (37.2)	248 (55.6)	
SAH	144 (18.6)	66 (20.1)	78 (17.5)	
ICH	92 (11.9)	46 (14.0)	46 (10.3)	
EDH	74 (9.6)	46 (14.0)	28 (6.3)	
IVH & other	94 (12.1)	48 (14.6)	46 (10.3)	
Potassium (mmol/L)				0.77
0–3.5	166 (21.4)	76 (23.2)	90 (20.2)	
3.5–5.0	578 (74.7)	240 (73.2)	338 (75.8)	

(*continued on next page*)

Table 2 (*continued*)

Variables	All	Age		P-value
		18–64	65-	
	N (%)	N (%)	N (%)	
5.0-	30 (3.9)	12 (3.7)	18 (4.0)	
Chloride (mmol/L)				0.02
0–96	40 (5.2)	20 (6.1)	20 (4.5)	
96–106	392 (50.6)	138 (42.1)	254 (57.0)	
106-	342 (44.2)	170 (51.8)	172 (38.6)	
Osmolarity (mmol/kg)				0.16
0–275	60 (7.8)	18 (5.5)	42 (9.4)	
275–295	464 (59.9)	190 (57.9)	274 (61.4)	
295-	250 (32.3)	120 (36.6)	130 (29.1)	
Advanced airway				0.66
Yes	106 (13.7)	42 (12.8)	64 (14.3)	
Transfusion				0.39
Yes	78 (10.1)	28 (8.5)	50 (11.2)	
Outcomes				
Mortality at hospital discharge	76 (9.8)	32 (9.8)	44 (9.9)	0.97
Mortality at 6-month	158 (20.4)	50 (15.2)	108 (24.2)	<0.05

AIS, abbreviated injury scale; TBI, traumatic brain injury; NISS, new injury severity scale; SDH, subdural hemorrhage, SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; EDH, epidural hemorrhage; IVH, intraventricular hemorrhage.

predicts the prognosis [5, 12, 16]. Although the cause of hyponatremia in TBI patients is unclear, syndrome of inappropriate antidiuretic hormone secretion, CSW, and hypopituitarism have been reported as potential causes of hyponatremia, which are related to high mortality and morbidity in patients with TBI [16, 17].

The incidence of hyponatremia after brain injury has been reported to be between 1.78 to 7.74 days. Since blood sampling in our study was performed immediately after arrival at the ED, the patients' serum sodium levels would have reflected the pre-existing sodium levels rather than the change in the sodium levels after the brain injury [5, 16].

Hyponatremia has a complex pathophysiology, is frequent, presents potentially serious clinical symptoms, and involves high-risk treatments [18]. Patients with acute hyponatremia develop neurological symptoms due to cerebral edema induced by the transfer of water to the brain. These may include seizures, mental illness, coma, and/or death [19].

In our study, hyponatremia was not associated with mortality at hospital discharge and 6 months in patients with TBI. However, it was a significant risk factor in increasing the 6-month mortality in older patients aged ≥75 years.

In the geriatric population, hyponatremia is a fairly common electrolyte imbalance, reported in approximately 7% of the general population aged ≥65 years [20] and 8–20% among long-term care or nursing home residents [21, 22]. Even in severe hyponatremia cases (sodium level <125 mmol/L sodium level), many patients with long-term hyponatremia appear to be asymptomatic, probably due to the restoration of brain cell volume brought about by the exit of intracellular electrolytes and organic osmolytes. However, loss of these solutes, which are important for the cell volume adaptation process, leaves the brain with reduced amounts of various substances such as glutamine, a major neurotransmitter essential for normal nerve function [23]. Glutamate is the principal excitatory neurotransmitter in the brain involved in motor, cognitive, and emotional functions. Although there is a debate about supplementation of glutamate in patients with TBI [24], the important role of glutamine is that of a precursor of the neurotransmitter amino acids [23]. Moreover, administration of glutamine after TBI was shown to reduce concentration of pro-inflammatory cytokines and apoptotic cells in gastrointestinal tissue, thus reducing TBI-related injury to the gastrointestinal mucosa in rats [25].

Table 3. Multivariable logistic regression analysis on study outcomes by the hyponatremia.

Study outcomes		Total	Outcome		Model 1	Model 2	Model 3
		N	N	%	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Mortality at hospital discharge							
Serum sodium (mmol/L)	135–145	672	68	10.1	1.00	1.00	1.00
	<135	102	8	7.8	0.77 (0.26–2.29)	0.86 (0.28–2.62)	0.69 (0.22–2.19)
Age	18–64	328	32	9.8	1.00	1.00	1.00
	65-	446	44	9.9	1.18 (0.59–2.37)	1.74 (0.77–3.92)	1.74 (0.75–4.00)
Mortality at 6-month							
Serum sodium (mmol/L)	135–145	672	134	19.9	1.00	1.00	1.00
	<135	102	24	23.5	1.17 (0.57–2.38)	1.34 (0.64–2.80)	1.16 (0.53–2.51)
Age	18–64	328	50	15.2	1.00	1.00	1.00
	65-	446	108	24.2	1.98 (1.15–3.40)	3.19 (1.69–6.02)	3.25 (1.68–6.29)

aOR, adjusted odds ratio; CI, confidence interval.
Model 1: adjusted age and gender.
Model 2: Model 1 + adjusted hypertension, diabetes mellitus, mechanism of injury, and place of injury.
Model 3: Model 2 + adjusted severity and type of hemorrhage.

Table 4. Interaction analysis between the hyponatremia and age group.

	Serum sodium				p-for interaction
	Normonatremia	Hyponatremia			
Mortality at hospital discharge		aOR	95% CI		
Age					0.61
18–64	ref.	0.62	0.07	5.62	
65-	ref.	0.72	0.19	2.81	
					0.11
18–74	ref.	0.42	0.25	2.54	
75-	ref.	0.83	0.20	3.48	
Mortality at 6 months					
Age					0.06
18–64	ref.	0.39	0.05	3.30	
65-	ref.	1.50	0.83	3.38	
					<0.05
18–74	ref.	0.24	0.03	1.94	
75-	ref.	1.53	1.04	2.95	

aOR, adjusted odds ratio; CI, confidence interval; ref, reference;

Age is also an independent risk factor for TBI, and in our results, patients aged ≥65 years had higher odds of 6-month mortality while patients aged ≥75 years had significantly higher odds of mortality at hospital discharge and after 6 months compared with younger patients. Furthermore, in previous studies, as glutamine concentration decreased as a result of aging, the deficit of the glutamatergic systems in the brain increased in the motor cortex of older patients [26]. Possible explanation is that glutamate deficiency caused by hyponatremia deteriorated the outcome of TBI by synergistic effect with a chronic decrease in glutamate due to aging.

In our study, pre-existing hyponatremia acted as a risk factor in older patients with TBI aged ≥75 years. Although further studies are needed to determine the optimal management strategy for pre-existing and TBI-related hyponatremia, management of usual hyponatremia in older patients and active correction of hyponatremia in patients with TBI should be considered.

4.1. Limitation

This study had several limitations. First, it was a single-center retrospective study involving a small population. Second, we could not perform analysis according to the severity of hyponatremia. Third, no information was obtained before the brain injury to measure the initial serum sodium level. Fourth, adjustment of sodium level after hospitalization may have affected clinical outcomes; however, it was not measured. Fifth, due to the retrospective nature of the study, while we analyzed the association between hyponatremia and mortality, our study results do not imply causality between hyponatremia and mortality. Sixth, although 'injury severity', a variable that can have the greatest influence on TBI outcome, was adjusted in the final model of multivariable logistic regression analysis, it cannot be said that the effect of 'injury severity' was completely excluded. Finally, the study design was not a randomized controlled trial, therefore there may be potential biases that were not controlled.

5. Conclusions

Pre-existing hyponatremia is a potential risk factor in older patients with TBI aged ≥75 years. Further studies are needed to determine the optimal management strategy for patients with TBI with hyponatremia, and management and active correction of usual hyponatremia in older patients should be considered.

Declarations

Author contribution statement

Eujene Jung: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Hyun Ho Ryu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Seok Jin Ryu: Contributed reagents, materials, analysis tools or data.

So Yeon Kong: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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