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석 사 학 위 논 문

# Effects of Hyponatremia on Early Neurological Deterioration and Functional Outcomes in Patients with Acute Ischemic Stroke

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# 김수민의 석사학위 논문을 인준함

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## Acknowledgement

본 논문을 완성하기까지 많은 분들의 도움이 있었기에 감사의 마음을 글로 전합니다. 먼저, 연구를 시작하는 단계에서부터 마지막까지 방향을 잡아주시고 아낌없는 지도와 조언을 해주신 지도교수 홍정호 교수님께 깊은 감사를 드립니다. 교수님의 지도 덕분에 이 논문을 완성할 수 있었습니다.

또한, 바쁘신 일정 중에도 본 연구의 완성을 위해 애써주신 심사위원장 손성일 교수님과 이주엽 교수님께도 감사드립니다. 두 분의 조언은 연구의 완성도를 높이는 데 큰 도움이 되었습니다.

마지막으로 연구를 진행하는 동안 항상 아낌없는 믿음과 응원을 보내준 사랑하는 가족들과 연구실에서 함께 지내며 연구에 많은 도움을 준 동료들에게도 감사의 마음을 전합니다. 가족과 동료들의 응원이 있었기에 어려운 과정들도 극복할 수 있었으며, 본 연구를 잘 마무리할 수 있었던 것 같습니다.

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2025년 2월

김 수 민

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# 1. Introduction

Sodium is a vital electrolyte in the body and its imbalance in patients with ischemic stroke can lead to various neurological complications (1). Hyponatremia can cause brain edema, seizures, and altered consciousness, potentially affecting neurological deterioration and short-term outcomes (2, 3). Many studies have examined the association between hyponatremia and increased functional disability and mortality in patients with ischemic stroke (2-5). Patients with hyponatremia at admission often show worse functional outcomes, and failure to normalize sodium levels may further worsen short-term prognosis (4-8). Although related studies exist, few have specifically explored the effects of hyponatremia on early neurological decline (END) in patients with acute ischemic stroke. This gap in knowledge leads to an incomplete understanding of how sodium imbalance influences recovery in this patient group.

This study investigated the effects of hyponatremia on END and functional outcomes in patients with acute ischemic stroke.

## 2. Materials and Methods

### 2.1. Study population:

This was a retrospective, single-center, observational study including 6,068 patients diagnosed with stroke who were admitted to the Department of Neurology at Keimyung University Dongsan Hospital between May 2014 and May 2024. We excluded 6 patients under the age of 18, 98 who arrived at the hospital more than 7 days after the onset of stroke symptoms, 77 patients with hemorrhagic stroke, and 5 patients whose electrolyte laboratory data were unavailable. Ultimately 5,882 patients were included in the study.

This study was approved by the institutional review board (IRB) of Dongsan Hospital (IRB number 2024-09-019). Patient records were reviewed and analyzed in accordance with the Declaration of Helsinki.

### 2.2. Clinical data collection:

In this study, data on demographics, diagnoses, clinical characteristics, past medical histories, and laboratory findings were collected retrospectively using the Clinical Data Warehouse and Dongsan stroke registry collected prospectively. Collected demographic information included age, sex, body mass index (BMI), premorbid modified Rankin Scale (mRS) score, initial National Institutes of Health Stroke Scale (NIHSS) score, and time from stroke onset to hospital arrival. Diagnosis data included ischemic stroke and transient ischemic attack (TIA).

Medical history information included hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, atrial fibrillation, smoking history, and previous stroke. Data on recanalization therapies included intravenous tissue plasminogen activator (IV tPA) and endovascular therapy (EVT). Laboratory findings included serum sodium, serum potassium, serum chloride, white blood cell (WBC) count, hemoglobin, platelet count, blood urea nitrogen (BUN), creatinine, glucose, and C-reactive protein (CRP). laboratory data were used from the first measurements taken upon admission to the hospital. In addition, serum sodium levels were measured using ion-selective electrode (ISE) technology. dyslipidemia was defined as a serum total cholesterol level greater than 240 mg/dL, an LDL cholesterol level exceeding 160 mg/dL after fasting for over 8 hours, a prior history of statin therapy, or a self-reported diagnosis confirmed by a physician (9). Clinical outcomes assessed were END, unfavorable functional outcome at discharge, discharge mortality, and unfavorable functional outcome at 3 months.

### **2.3. Definition of variables and clinical outcomes and collection:**

END was defined as any new neurologic symptoms or signs, or neurological worsening, indicated by an increase of  $\geq 1$  point in the motor subitem of the NIHSS score or an increase of  $\geq 2$  points in the total NIHSS score within the first 72 hours of hospitalization in the neurology department following symptom onset (10–13). An unfavorable functional outcome was defined as an mRS score of 3 to 6.

Stroke onset was identified as the moment when neurological deficits

were first detected. The time from onset to hospital arrival was calculated as the interval from when the patient or a witness first recognized the neurological deficits to the patient's arrival at the hospital emergency department (14).

Hyponatremia was characterized by a serum sodium level of less than 135 mmol/L, measured on admission (4, 8, 15).

## **2.4. Statistical analysis:**

Baseline characteristics of the study participants were expressed as frequencies (%) for categorical variables and as medians with interquartile ranges (IQR) for continuous variables. Categorical variables were compared using the chi-square test, and continuous variables were compared using the t-test. For variables with a non-normal distribution, Fisher's exact test and the Mann-Whitney U test were used.

Univariate analysis was performed to assess differences between patients with and without hyponatremia with a p-value < 0.05 considered statistically significant. To evaluate the independent association between hyponatremia and clinical outcomes, multivariable logistic regression analysis was conducted, and adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated. For multivariable analysis, variables whose P values were < 0.05 in the comparisons of baseline characteristics (Table 2-5) were chosen for adjustment. Variables with high collinearity (variance inflation factor  $\geq$  10) were excluded from the multivariable logistic regression model.

The association between serum sodium concentration at admission and the probability of END occurrence was evaluated through linear

regression analysis. Serum sodium concentration was treated as a continuous variable, and the predicted relationship based on the linear regression model, along with the corresponding 95% CI, was calculated. The results were visualized in a continuous linear graph, illustrating the linear relationship between serum sodium concentration and the probability of END occurrence.

All analyses were performed using R statistical software (version 4.4.1). P-values  $< 0.05$  were considered statistically significant.

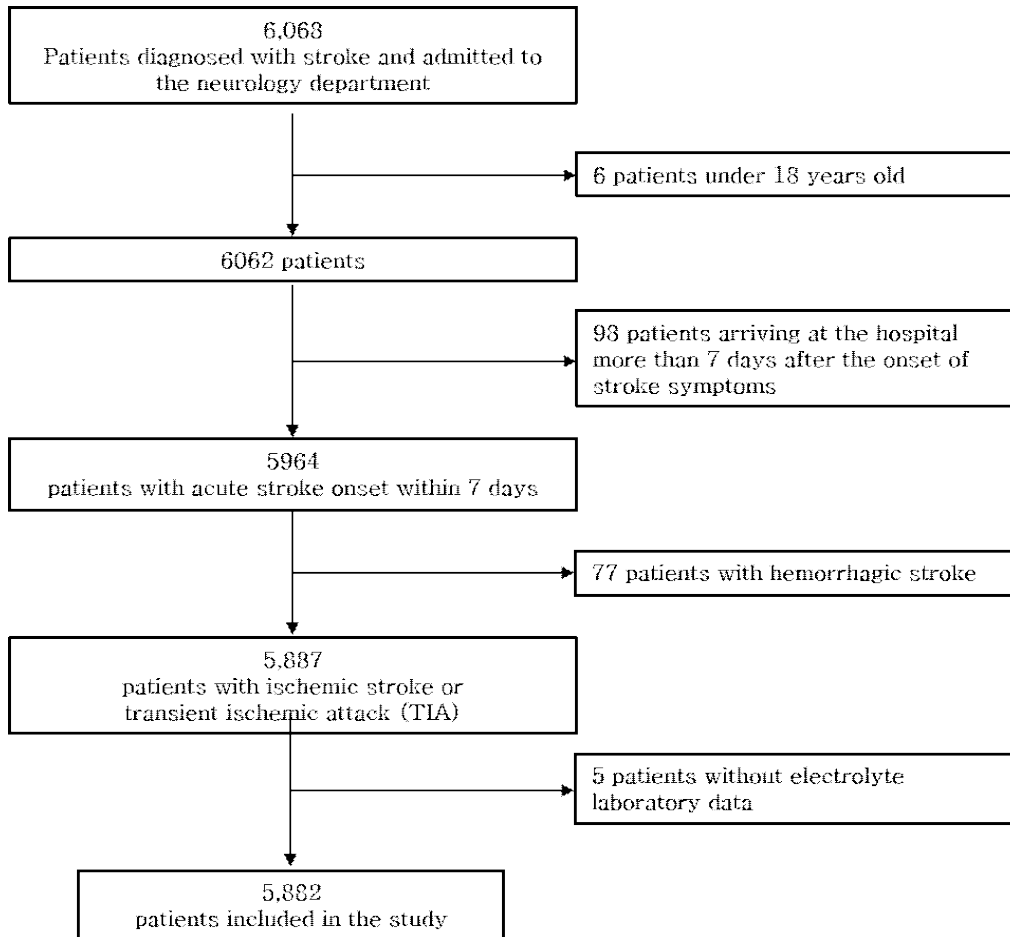


Figure 1. Patients inclusion flowchart.

### 3. Results

#### 3.1. Comparison of clinical characteristics and outcomes by hyponatremia:

Among the 5,882 patients included in this study, 668 (11.4%) had hyponatremia. Significant differences in demographic and clinical characteristics were observed between the hyponatremia and non-hyponatremia groups (Table 1). The median age of patients with hyponatremia was higher (73.0 years [64.0, 80.0] vs. 71.0 years [61.0, 79.0],  $p < 0.001$ ), and there was a higher proportion of men (59.6% vs. 55.0%,  $p < 0.05$ ). BMI was significantly lower in the hyponatremia group (22.9 [20.8, 25.1] vs. 23.5 [21.4, 25.6],  $p < 0.001$ ), and the proportion of patients with premorbid mRS scores  $\geq 2$  was higher (20.2% vs. 10.3%,  $p < 0.001$ ).

Hyponatremia was more frequently associated with ischemic stroke (93.4% vs. 90.2%,  $p < 0.01$ ) and less commonly with transient ischemic attack (TIA) (6.6% vs. 9.8%,  $p < 0.01$ ). Hypertension (66.9% vs. 61.8%,  $p < 0.01$ ) and diabetes mellitus (49.0% vs. 31.6%,  $p < 0.001$ ) were more prevalent in the hyponatremia group. There were no significant differences in the history of dyslipidemia, coronary heart disease, atrial fibrillation, smoking, or previous stroke.

Laboratory findings indicated that patients with hyponatremia had higher WBC counts ( $8.0 [6.2, 10.5] \times 10^3/\mu\text{L}$  vs.  $7.3 [5.9, 8.9] \times 10^3/\mu\text{L}$ ,  $p < 0.001$ ) and CRP levels ( $2.4 [0.7, 12.4] \text{ mg/L}$  vs.  $1.2 [0.4, 4.1] \text{ mg/L}$ ,  $p < 0.001$ ), while hemoglobin levels were lower ( $12.7 [10.9, 14.2] \text{ g/dL}$  vs.  $13.4 [12.1, 14.6] \text{ g/dL}$ ,  $p < 0.001$ ). Additionally, BUN ( $18.0 [13.0, 26.0]$

mg/dL vs. 16.0 [13.0, 21.0] mg/dL,  $p < 0.001$ ) and creatinine (0.9 [0.7, 1.2] mg/dL vs. 0.8 [0.7, 1.0] mg/dL,  $p < 0.05$ ) were significantly elevated in the hyponatremia group.

END occurred more frequently in patients with hyponatremia than in those without it (19.2% vs. 13.3%,  $p < 0.001$ ), and these patients had higher discharge NIHSS scores (3.0 [1.0, 10.0] vs. 2.0 [0.0, 5.0],  $p < 0.001$ ). Unfavorable functional outcomes (mRS 3 - 6) were more common in the hyponatremia group at discharge (54.8% vs. 34.2%,  $p < 0.001$ ) and at 3 months (46.2% vs. 27.9%,  $p < 0.001$ ). Additionally, discharge mortality was higher in the hyponatremia group (6.6%) than in the non-hyponatremia group (2.9%,  $p < 0.001$ ) (Table 1).

### 3.2. Predictors of END:

Age, initial NIHSS score, shorter onset-to-arrival time, type of ischemic stroke, hyponatremia, and WBC count were significant predictors of END (Table 2). Older age slightly increased the odds of END (OR 1.01, 95% CI [1.00, 1.02],  $p < 0.05$ ), while a higher NIHSS score on admission was strongly associated with an increased risk of END (OR 1.05, 95% CI [1.04, 1.06],  $p < 0.001$ ). Patients arriving at the hospital sooner after symptom onset showed a greater risk for END (OR 0.85, 95% CI [0.79, 0.91],  $p < 0.001$ ). Ischemic stroke, compared to TIA, was also significantly linked to an increased risk of END (OR 5.69, 95% CI [3.39, 10.5],  $p < 0.001$ ). Hyponatremia was a significant risk factor for END (OR 1.29, 95% CI [1.03, 1.62],  $p < 0.05$ ), and higher WBC levels were similarly associated with an increased likelihood of END (OR 1.03, 95% CI [1.00, 1.05],  $p < 0.05$ ).



Figure 2 shows the association between serum sodium levels at admission and the risk of END, as modeled using a linear regression approach. The results revealed a negative linear relationship, with lower serum sodium levels associated with an increased risk of END. Figure 2 includes a reference line representing the mean probability of END occurrence (14%) calculated from the study dataset. This reference line served as a visual benchmark, allowing for a comparison between the predicted probability of END based on serum sodium levels measured on admission and the average END risk in the dataset. A restricted cubic spline (RCS) model was applied to evaluate the relationship between serum sodium levels at admission and END occurrence more precisely. Nonlinear regression analysis revealed a significant nonlinear relationship, with the risk of END increasing when serum sodium levels fell below 130 mmol/L ( $p < 0.001$ ).

### 3.3. Predictors of discharge mortality:

High NIHSS scores on admission were a key predictor of discharge mortality (OR 1.12, 95% CI [1.09, 1.15],  $p < 0.001$ ). Laboratory findings linked to mortality at discharge included WBC count (OR 1.14, 95% CI [1.09, 1.19],  $p < 0.001$ ), platelet count (OR 0.99, 95% CI [0.99, 1.00],  $p < 0.001$ ), initial glucose (OR 1.00, 95% CI [1.00, 1.01],  $p < 0.01$ ), and CRP (OR 1.01, 95% CI [1.00, 1.01],  $p < 0.01$ ). However, hyponatremia was not significantly linked to discharge mortality (OR 1.37, 95% CI [0.86, 2.15],  $p = \text{NS}$ ). END was the strongest predictor of mortality (OR 30.1, 95% CI [19.9, 46.8],  $p < 0.001$ ), underscoring its substantial impact on discharge outcomes (Table 3).

### **3.4. Predictors of unfavorable functional outcomes at discharge and 3 Months:**

Multivariate logistic regression analysis identified several predictors of unfavorable functional outcomes at both discharge and 3 months (Tables 4&5). Age was a consistent predictor, with older patients demonstrating a higher likelihood of poor outcomes at discharge (OR 1.04, 95% CI [1.03, 1.05],  $p < 0.001$ ) and at 3 months (OR 1.04, 95% CI [1.03, 1.05],  $p < 0.001$ ). Premorbid disability ( $mRS \geq 2$ ) was strongly associated with unfavorable functional outcomes at discharge (OR 10.7, 95% CI [8.18, 14.2],  $p < 0.001$ ) and at 3 months (OR 6.02, 95% CI [4.77, 7.63],  $p < 0.001$ ), emphasizing its substantial impact on intermediate-term recovery.

A higher initial NIHSS score emerged as one of the strongest predictors at both time points, with an OR of 1.27 (95% CI [1.24, 1.29],  $p < 0.001$ ) for discharge outcomes and 1.22 (95% CI [1.19, 1.24],  $p < 0.001$ ) for 3-month outcomes. Delays in hospital arrival were also significant predictors, with longer delays associated with unfavorable outcomes at discharge (OR 1.06, 95% CI [1.01, 1.12],  $p < 0.05$ ) and at 3 months (OR 1.10, 95% CI [1.03, 1.16],  $p < 0.01$ ). Interestingly, this finding contrasts with its relationship with END, where shorter durations were linked to an increased risk.

Regarding laboratory findings, hyponatremia was an independent predictor at discharge (OR 1.61, 95% CI [1.27, 2.05],  $p < 0.001$ ) and at 3 months (OR 1.30, 95% CI [1.02, 1.65],  $p < 0.05$ ). Treatment modalities also influenced the outcomes: EVT reduced the risk of poor outcomes at discharge (OR 0.70, 95% CI [0.52, 0.94],  $p < 0.05$ ), while IV tPA demonstrated a protective effect at 3 months (OR 0.67, 95% CI [0.51, 0.87],  $p < 0.01$ ).

END was the most significant predictor of unfavorable outcomes at both discharge and 3 months, with an OR of 10.5 (95% CI [8.47, 13.1],  $p < 0.001$ ) at discharge and 7.15 (95% CI [5.85, 8.77],  $p < 0.001$ ) at 3 months, underscoring its critical role in influencing recovery trajectories.

### **3.5. Association of hyponatremia with clinical outcomes:**

Table 6 summarizes the association between hyponatremia and various clinical outcomes in patients with acute ischemic stroke. Hyponatremia was independently associated with several key outcomes, even after adjusting for confounding factors. Although hyponatremia consistently influenced functional outcomes at discharge, at 3 months, and END, its impact on mortality at discharge was insignificant.

Table 1A. Comparison of Clinical Characteristics and Outcomes in Patients With and Without Hyponatremia  
 (continued)

Variables	Total (N = 5882)	Without hyponatremia (N = 5214, 88.6%)	Hyponatremia (N = 668, 11.4%)	p value
Demographic information				
Age, years	71.0 [61.0, 79.0]	71.0 [61.0, 79.0]	73.0 [64.0, 80.0]	< 0.001***
Male, n (%)	3266 (55.5)	2868 (55.0)	398 (59.6)	< 0.05*
BMI, kg/m <sup>2</sup>	23.5 [21.3, 25.6]	23.5 [21.4, 25.6]	22.9 [20.8, 25.1]	< 0.001***
Premobid mRS $\geq$ 2, n (%)	673 (11.4)	538 (10.3)	135 (20.2)	< 0.001***
Initial NIHSS, score	3.0 [1.0, 6.0]	3.0 [1.0, 6.0]	4.0 [1.0, 9.0]	< 0.001***
Time from onset to arrival, hour	0.4 [1.0, 1.3]	0.3 [1.0, 1.3]	0.4 [0.1, 1.3]	NS
Diagnosis, n(%)				< 0.01**
Ischemic stroke	5328 (90.6)	4704 (90.2)	624 (93.4)	
TIA	554 (9.4)	510 (9.8)	44 (6.6)	
Risk factors & medical history, n (%)				
Hypertension	3668 (62.4)	3221 (61.8)	447 (66.9)	< 0.01**
Diabetes mellitus	1977 (33.6)	1650 (31.6)	327 (49.0)	< 0.001***
Dyslipidemia	1086 (18.5)	978 (18.8)	108 (16.2)	NS
Coronary heart disease	604 (10.3)	521 (10.0)	83 (12.4)	NS
Atrial fibrillation	1139 (19.4)	1027 (19.7)	112 (16.8)	NS
Smoking	2073 (35.2)	1829 (35.1)	244 (36.5)	NS
Stroke	1372 (23.3)	1203 (23.1)	169 (25.3)	NS

Table 1B. Comparison of Clinical Characteristics and Outcomes in Patients With and Without Hyponatremia

Variables	Total (N = 5882)	Without hyponatremia (N = 5214, 88.6%)	Hyponatremia (N = 668, 11.4%)	p value
Recanalization therapy, n (%)				
IV tPA	562 (9.6)	492 (9.4)	70 (10.5)	NS
EVT	548 (9.3)	473 (9.1)	75 (11.2)	NS
Laboratory findings				
WBC, 10 <sup>3</sup> /μL	7.3 [5.9, 9.1]	7.3 [5.9, 9.0]	8.0 [6.2, 10.5]	< 0.001***
Hemoglobin, g/dL	13.3 [12.0, 14.6]	13.4 [12.1, 14.6]	12.7 [10.9, 14.2]	< 0.001***
Platelet, 10 <sup>3</sup> /μL	227.0 [187.0, 275.0]	227.0 [188.0, 274.0]	233.0 [181.8, 285.5]	< 0.001***
BUN, mg/dL	16.0 [13.0, 21.0]	16.0 [13.0, 21.0]	18.0 [13.0, 26.0]	< 0.001***
Creatinine, mg/dL	0.8 [0.7, 1.0]	0.8 [0.7, 1.0]	0.9 [0.7, 1.2]	< 0.05*
Glucose, mg/dL	125.0 [106.0, 160.0]	123.0 [106.0, 156.0]	145.0 [117.0, 225.3]	< 0.001***
CRP, mg/L	1.2 [0.4, 4.7]	1.2 [0.4, 4.1]	2.4 [0.7, 12.4]	< 0.001***
Outcome				
END, n (%)	821 (14.0)	693 (13.3)	128 (19.2)	< 0.001***
Discharge mortality, n (%)	193 (3.3)	149 (2.9)	44 (6.6)	< 0.001***
Discharge NIHSS, score	2.0 [0.0, 5.0]	2.0 [0.0, 5.0]	3.0 [1.0, 10.0]	< 0.001***
Unfavorable outcome at discharge, n (%)	2149 (36.5)	1783 (34.2)	366 (54.8)	< 0.001***
Unfavorable outcome at 3 months, n (%)	1735 (29.9)	1434 (27.9)	301 (46.2)	< 0.001***

BMI: body mass index; BUN: blood urea nitrogen; CRP: c-reactive protein; END: early neurological deterioration; EVT: endovascular treatment; IV tPA: intra-venous tissue plasminogen activator; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NS: non-significant; TIA: transient ischemic attack; WBC: white blood cell. Continuous variables are expressed as the median (IQR). Categorical variables are expressed as counts (%); \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ ; \*\*\*:  $p < 0.001$ .

Table 2. Multivariable Logistic Regression Analysis for END

Variables	Multivariable analysis		
	OR	95% CI	p value
Age, years	1.01	[1.00, 1.02]	< 0.05*
BMI, kg/m <sup>2</sup>	1.00	[0.97, 1.02]	NS
Premobid mRS $\geq$ 2, n (%)	0.85	[0.67, 1.08]	NS
Initial NIHSS, score	1.05	[1.04, 1.06]	< 0.001**
Time from onset to arrival, hour	0.85	[0.79, 0.91]	< 0.001**
Ischemic stroke (TIA as reference)	5.69	[3.39, 10.5]	< 0.001**
Dyslipidemia	0.85	[0.69, 1.05]	NS
Atrial fibrillation	0.84	[0.69, 1.03]	NS
IV tPA	1.07	[0.84, 1.36]	NS
EVT	1.25	[0.98, 1.59]	NS
Hyponatremia	1.29	[1.03, 1.62]	< 0.05*
WBC, 10 <sup>3</sup> / $\mu$ L	1.03	[1.00, 1.05]	< 0.05*
Creatinine, mg/dL	0.95	[0.87, 1.02]	NS
Glucose, mg/dL	1.00	[1.00, 1.00]	NS
CRP, mg/L	1.00	[1.00, 1.01]	NS

BMI: body mass index; CI: confidence interval; CRP: c-reactive protein; EVT: endovascular treatment; IV tPA: intra-venous tissue plasminogen activator; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NS: non-significant; OR: odds ratio; TIA: transient ischemic attack; \*:  $p < 0.05$ ; \*\*:  $p < 0.001$ .

Table 3. Multivariable Logistic Regression Analysis for Mortality at Discharge

Variables	Multivariable analysis		
	OR	95% CI	p value
Age, years	1.01	[0.99, 1.02]	NS
Male, n (%)	1.06	[0.67, 1.66]	NS
BMI, kg/m <sup>2</sup>	0.98	[0.93, 1.03]	NS
Premobid mRS $\geq$ 2, n (%)	1.48	[0.92, 2.35]	NS
Initial NIHSS, score	1.12	[1.09, 1.15]	< 0.001**
Time from onset to arrival, hour	0.89	[0.71, 1.07]	NS
Ischemic stroke (TIA as reference)	0.56	[0.19, 2.38]	NS
Dyslipidemia	0.85	[0.48, 1.43]	NS
Coronary heart disease	1.60	[0.95, 2.61]	NS
Atrial fibrillation	1.22	[0.80, 1.85]	NS
Smoking	0.81	[0.48, 1.35]	NS
EVT	1.48	[0.96, 2.27]	NS
Hyponatremia	1.37	[0.86, 2.15]	NS
WBC, 10 <sup>3</sup> / $\mu$ L	1.14	[1.09, 1.19]	< 0.001**
Hemoglobin, g/dL	0.92	[0.83, 1.01]	NS
Platelet, 10 <sup>3</sup> / $\mu$ L	0.99	[0.99, 1.00]	< 0.001**
BUN, mg/dL	1.01	[0.99, 1.02]	NS
Glucose, mg/dL	1.00	[1.00, 1.01]	< 0.01*
CRP, mg/L	1.01	[1.00, 1.01]	< 0.01*
END	30.1	[19.9, 46.8]	< 0.001**

BMI: body mass index; CI: confidence interval; CRP: c-reactive protein; END: early neurological deterioration; EVT: endovascular treatment; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NS: non-significant; OR: odds ratio; TIA: transient ischemic attack; WBC: white blood cell; \*:  $p < 0.01$ ; \*\*:  $p < 0.001$ .

Table 4. Multivariable Logistic Regression Analysis for Unfavorable Functional Outcome at Discharge

Variables	Multivariable analysis		
	OR	95% CI	p value
Age, years	1.04	[1.03, 1.05]	< 0.001***
Male, n (%)	0.81	[0.67, 0.98]	< 0.05*
BMI, kg/m <sup>2</sup>	0.98	[0.96, 1.01]	NS
Premobid mRS $\geq$ 2, n (%)	10.7	[8.18, 14.2]	< 0.001***
Initial NIHSS, score	1.27	[1.24, 1.29]	< 0.001***
Time from onset to arrival, hour	1.06	[1.01, 1.12]	< 0.05*
Ischemic stroke (TIA as reference)	5.30	[3.43, 8.51]	< 0.001***
Hypertension	0.94	[0.80, 1.11]	NS
Diabetes mellitus	1.26	[1.06, 1.51]	< 0.01**
Dyslipidemia	1.11	[0.91, 1.35]	NS
Coronary heart disease	1.31	[1.03, 1.66]	< 0.05*
Atrial fibrillation	0.70	[0.57, 0.87]	< 0.001***
Smoking	0.91	[0.75, 1.10]	NS
Stroke	1.66	[1.40, 1.98]	< 0.001***
IV tPA	0.79	[0.61, 1.02]	NS
EVT	0.70	[0.52, 0.94]	< 0.05*
Hyponatremia	1.61	[1.27, 2.05]	< 0.001***
WBC, 10 <sup>3</sup> /μL	1.08	[1.05, 1.11]	< 0.001***
Hemoglobin, g/dL	0.98	[0.94, 1.02]	NS
Platelet, 10 <sup>3</sup> /μL	1.00	[1.00, 1.00]	NS
BUN, mg/dL	1.00	[0.99, 1.00]	NS
Glucose, mg/dL	1.00	[1.00, 1.00]	NS
CRP, mg/L	1.01	[1.00, 1.01]	< 0.01**
END	10.5	[8.47, 13.1]	< 0.001***

BMI: body mass index; CI: confidence interval; CRP: c-reactive protein; END: early neurological deterioration; EVT: endovascular treatment; IV tPA: intra-venous tissue plasminogen activator; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NS: non-significant; OR: odds ratio; TIA: transient ischemic attack; WBC: white blood cell; \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ ; \*\*\*:  $p < 0.001$ .



Table 5. Multivariable Logistic Regression Analysis for Unfavorable Functional Outcome at 3 months

Variables	Multivariable analysis		
	OR	95% CI	p value
Age, years	1.04	[1.03, 1.05]	< 0.001***
Male, n (%)	0.98	[0.81, 1.19]	NS
BMI, kg/m <sup>2</sup>	0.97	[0.94, 0.99]	< 0.01**
Premobid mRS $\geq$ 2, n (%)	6.02	[4.77, 7.63]	< 0.001***
Initial NIHSS, score	1.22	[1.19, 1.24]	< 0.001***
Time from onset to arrival, hour	1.10	[1.03, 1.16]	< 0.01**
Ischemic stroke (TIA as reference)	3.48	[2.25, 5.59]	< 0.001***
Hypertension	0.91	[0.77, 1.08]	NS
Diabetes mellitus	1.26	[1.05, 1.51]	< 0.05*
Dyslipidemia	0.97	[0.79, 1.20]	NS
Coronary heart disease	1.21	[0.95, 1.54]	NS
Atrial fibrillation	0.90	[0.73, 1.10]	NS
Smoking	0.83	[0.68, 1.01]	NS
Stroke	1.81	[1.52, 2.16]	< 0.001***
IV tPA	0.67	[0.51, 0.87]	< 0.01**
EVT	0.80	[0.60, 1.06]	NS
Hyponatremia	1.30	[1.02, 1.65]	< 0.05*
WBC, 10 <sup>3</sup> / $\mu$ L	1.08	[1.05, 1.11]	< 0.001***
Hemoglobin, g/dL	0.93	[0.89, 0.97]	< 0.001***
Platelet, 10 <sup>3</sup> / $\mu$ L	1.00	[1.00, 1.00]	< 0.05*
BUN, mg/dL	1.00	[0.99, 1.01]	NS
Creatinine, mg/dL	1.07	[0.99, 1.15]	NS
Glucose, mg/dL	1.00	[1.00, 1.00]	NS
CRP, mg/L	1.01	[1.01, 1.02]	< 0.001***
END	7.15	[5.85, 8.77]	< 0.001***

BMI: body mass index; CI: confidence interval; CRP: c-reactive protein; END: early neurological deterioration; EVT: endovascular treatment; IV tPA: intra-venous tissue plasminogen activator; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NS: non-significant; OR: odds ratio; TIA: transient ischemic attack; WBC: white blood cell; \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ ; \*\*\*:  $p < 0.001$ .

Table 6. Association between Hyponatremia and Clinical Outcomes

	Unadjusted model			Multivariable logistic model		
	OR	95% CI	p value	OR	95% CI	p value
END	1.55	[1.25, 1.90]	< 0.001	1.29	[1.03, 1.62]	< 0.05*
Mortality at discharge	2.40	[1.68, 3.36]	< 0.001	1.37	[0.86, 2.15]	NS
Unfavorable functional outcome at discharge	2.33	[1.98, 2.75]	< 0.001	1.61	[1.27, 2.05]	< 0.001**
Unfavorable functional outcome at 3 months	2.22	[1.88, 2.62]	< 0.001	1.30	[1.02, 1.65]	< 0.05*

CI: confidence interval; END: early neurological deterioration; mRS: modified Rankin Scale; NS: non-significant; OR: odds ratio; \*:  $p < 0.05$ ; \*\*:  $p < 0.001$ .

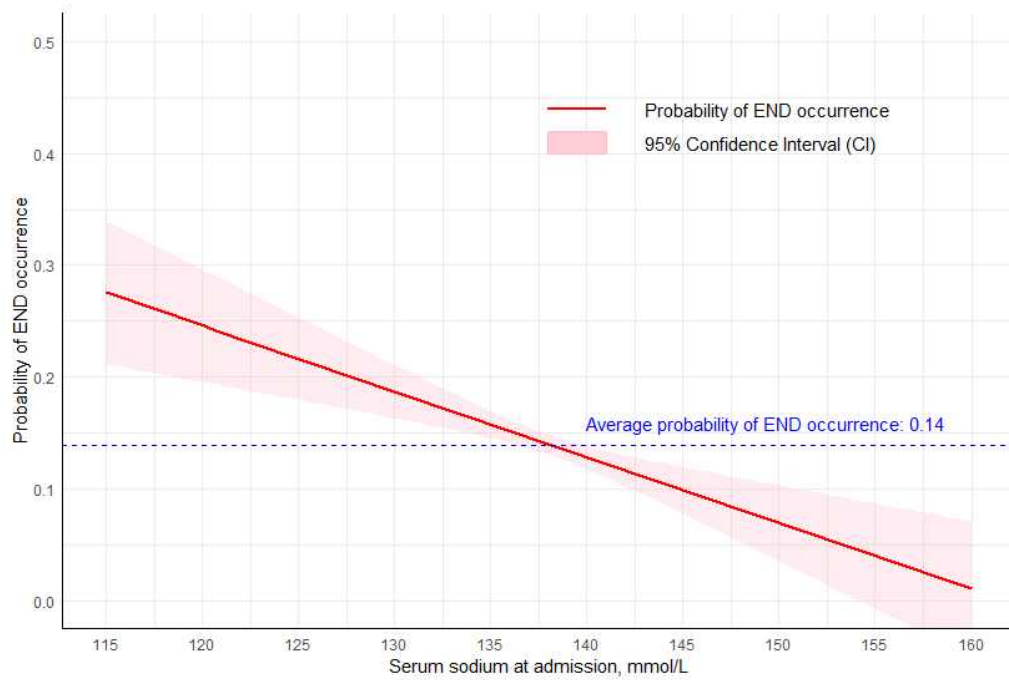


Figure 2. Relationship between serum sodium concentration at admission and probability of END occurrence. END: early neurological deterioration.

## 4. Discussion

This study, analyzed the effects of hyponatremia on END and functional outcomes in patients with acute ischemic stroke. The findings revealed a significant association between hyponatremia and an increased risk of END as well as unfavorable functional outcomes at discharge and at 3 months. However, no significant association was observed between hyponatremia and mortality at discharge.

Hyponatremia has been reported in 7–16% of patients with ischemic stroke, which corresponds to the 11.4% prevalence identified in this study (4, 7, 8). Previous studies have primarily focused on the relationship between hyponatremia (5, 7, 8) and intermediate-to long-term mortality or functional outcomes (4–6, 8), with limited investigation into its effects on END, which typically occurs during hospitalization. Based on the results of this study, hyponatremia appears to be a significant independent factor contributing to END. The mechanisms underlying END and poor functional outcomes at discharge and at 3 months in patients with hyponatremia remain unclear. Hyponatremia contributes to focal edema, systemic inflammation and oxidative stress, which are closely linked to END and poorer functional recovery (16, 17). This may exhibit a linear dose-response relationship, especially with respect to the probability of END occurrence.

However, these pathophysiological effects may not directly result in immediate mortality during hospitalization. In the present study, no statistically significant association was found between hyponatremia and discharge mortality after adjusting for confounding variables, consistent with the findings of other studies (4). Mortality during hospitalization is often driven by severe stroke complications such as massive infarction

or infection, which may overshadow the contribution of hyponatremia. In this study, factors such as high stroke severity, elevated WBC and CRP levels (infection markers), and increased serum glucose, were more predictive of mortality. Another explanation is that the direct effect of END on mortality was much stronger (OR of 30.1 in Table 3). This overshadowing effect of END may have diluted the independent contribution of hyponatremia to mortality. In this study, END also played a significant role in functional outcomes at discharge and 3 months. These findings suggest that END mediates the relationship between hyponatremia and functional outcomes at discharge and after discharge. Taken together, hyponatremia affects END and functional outcomes more significantly than discharge mortality, because its primary effects worsen neurological recovery rather than cause immediate life-threatening complications.

Early hospital arrival was associated with an increased risk of END, but simultaneously correlated with improved discharge and post-discharge functional outcomes. This finding aligns with the evidence showing that END is more frequent with early hospital arrival, whereas delayed arrival negatively affects functional outcomes. These opposing effects highlight the complexity of balancing early treatment to prevent END and minimize delays in therapy for better overall outcomes.

Despite the wealth of relevant data, this study has several limitations. First, as a retrospective analysis was conducted at a single center, the generalizability of the findings may be limited. Second, the data were collected over ten-year, during which updates in clinical guidelines, changes in treatment protocols, and advancements in diagnostic tools may have occurred. These changes have influenced the data uniformity and led to minor discrepancies in the sodium concentration

measurements. Additionally, variations in patient demographics or treatment strategies throughout the study period should be considered. Third, this study focused exclusively on serum sodium levels at admission, without adequately considering the influence of fluctuations in sodium levels throughout hospitalization. Further prospective research is necessary to better understand how changes in electrolyte levels affect patient outcomes. Fourth, this study did not provide a detailed evaluation of the underlying causes of hyponatremia. This limitation complicates the development of personalized treatment strategies to address the complex pathophysiology of hyponatremia. Additionally, although this study observed a potential protective effect of hypernatremia on END, hypernatremia was defined as a serum sodium level  $> 145$  mmol/L (5, 18), and the proportion of patients with hypernatremia was only 0.54%. The small sample size limits the statistical power to draw definitive conclusions.

In conclusion, this study confirmed that hyponatremia is a significant predictor of END and an unfavorable functional outcomes in patients with acute ischemic stroke. The link between hyponatremia and END highlights its potential to indirectly influence functional outcomes through its impact on END. This findings emphasize the importance of maintaining electrolyte balance in managing acute ischemic stroke. However, further research is needed to assess whether correcting hyponatremia can reduce the risk of END, improve recovery, and mitigate long-term disability.

## 5. Summary

This study examined the effect of hyponatremia on END and functional outcomes in a cohort of 5,882 patients diagnosed with acute ischemic stroke. Hyponatremia, defined as a serum sodium concentration below 135 mmol/L, was present in 668 patients (11.4%).

A multivariable logistic regression analysis was conducted to examine the independent relationship between hyponatremia and clinical outcomes. After adjusting for relevant variables, hyponatremia was identified as an independent risk factor for END (OR 1.29, 95% CI [1.03, 1.62],  $p < 0.05$ ), unfavorable functional outcomes at discharge (OR 1.61, 95% CI [1.27, 2.05],  $p < 0.001$ ) and at 3 months (OR 1.30, 95% CI [1.02, 1.65],  $p < 0.05$ ). However, no significant association was observed between hyponatremia and mortality at discharge (OR 1.37, 95% CI [0.86, 2.15],  $p = \text{NS}$ ).

Notably, END appears to mediate the relationship between hyponatremia and functional outcomes, suggesting that hyponatremia primarily influences recovery trajectories through its impact on END. Maintaining optimal electrolyte balance may improve functional recovery and reduce the burden of long-term disability in patients with acute ischemic stroke.

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# Effects of Hyponatremia on Early Neurological Deterioration and Functional Outcomes in Patients with Acute Ischemic Stroke

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## **(Abstract)**

Although hyponatremia is associated with functional disability and mortality in patients with ischemic stroke, its impact on early neurological deterioration (END) remains underexplored. This study evaluated the effects of hyponatremia on END and functional outcomes in patients with acute ischemic stroke. A retrospective analysis of 5,882 patients admitted to Keimyung University Dongsan Hospital (May 2014 - May 2024) identified hyponatremia (serum sodium  $< 135$  mmol/L) in 668 patients (11.4%). END was defined as a  $\geq 1$ -point increase in the NIHSS motor subscore or a  $\geq 2$ -point increase in total NIHSS within 72 hours. Patients with hyponatremia had significantly higher rates of END, unfavorable functional outcomes, and discharge mortality.

Multivariable logistic regression confirmed hyponatremia as an independent predictor of END (OR 1.29, 95% CI [1.03, 1.62]), poor functional outcomes at discharge (OR 1.61, 95% CI [1.27, 2.05]), and at 3 months (OR 1.30, 95% CI [1.02, 1.65]), but not discharge mortality (OR 1.37, 95% CI [0.86, 2.15]). Hyponatremia is an important predictor of END and poor functional outcomes in acute ischemic stroke, potentially influencing outcomes indirectly. Further studies are needed to explore whether correcting hyponatremia can reduce the risk of END and improve patient recovery.

# 급성기 허혈성 뇌졸중 환자에서 저나트륨혈증이 조기 신경학적 악화와 기능적 결과들에 미치는 영향

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## (초록)

저나트륨혈증이 허혈성 뇌졸중 환자의 기능적 장애 및 사망률과의 관련성에 대한 연구는 일부 존재하나, 저나트륨혈증이 조기 신경학적 악화(early neurological deterioration, END)에 미치는 영향에 대한 연구는 부족하다. 본 연구는 급성기 허혈성 뇌졸중 환자에서 저나트륨혈증이 END와 기능적 예후에 미치는 영향을 평가하였다. 2014년 5월부터 2024년 5월까지 계명대학교 동산병원 신경과에 입원한 급성기 허혈성 뇌졸중 환자를 대상으로 후향적 분석을 시행하였다. END는 입원 후 72시간 이내에 운동 능력이 1점 이상 악화되거나 NIHSS 점수가 2점 이상 증가한 경우로 정의하였으며, 기능적 예후를 평가하기 위해 퇴원 시 사망률, 퇴원 시 및 퇴원 후 3개월 시점의 수정된 랭킨 척도(mRS)를 사용하였다. 저나트륨혈증은 혈청 나트륨 농도가  $< 135$  mmol/L로 정의하였으며, 저나트륨혈증 유무에 따라 임상적 특성과 결과를 비교하였다. 저나트륨혈증 환자는 전체 5,882명 환자

중 668명(11.4%)을 차지하였고, END의 발생, 퇴원 시 나쁜 기능적 결과(mRS 점수 3-6), 퇴원 후 3개월 시점의 나쁜 기능적 결과(mRS 점수 3-6) 및 퇴원 시 사망률의 비율이 높았다. 다변량 로지스틱 회귀 분석 결과, 변수들을 보정한 후에도 저나트륨혈증은 END (OR 1.29, 95% CI [1.03, 1.62]), 퇴원 시 나쁜 기능적 결과 (OR 1.61, 95% CI [1.27, 2.05]) 및 3개월째 나쁜 기능적 결과 (OR 1.30, 95% CI [1.02, 1.65])의 독립적인 예측 인자로 확인되었다. 그러나 퇴원 시 사망률 (OR 1.37, 95% CI [0.86, 2.15])과의 연관성은 유의미하지 않았다. 저나트륨혈증은 급성기 허혈성 뇌졸중 환자에서 END와 나쁜 기능적 예후에 중요한 독립적인 인자로, 특히 END를 통해 기능적 결과에 간접적인 영향을 미칠 수 있음을 시사한다. 이 연구는 급성기 허혈성 뇌졸중 관리에서 전해질 균형 유지의 중요성을 강조하며, 향후 저나트륨혈증 교정이 END 위험 감소와 장기적인 기능적 회복에 미치는 영향을 규명하기 위한 연구가 필요하다.