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Research Article

Joint Association of Low Nadir Serum Sodium and Potassium with Worse Outcomes after Ischemic Stroke

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Background. Potassium and sodium are inextricably linked to the maintenance of cell potential and electrolyte homeostasis. Few studies have examined their joint relationship with outcomes after stroke. The objective of this study is to ascertain whether combined low nadir serum sodium and potassium levels are correlated with an unfavorable outcome in ischemic stroke. *Methods*. Retrospective cohort study of 2,920 consecutive patients with first-ever ischemic stroke. Serum sodium and potassium levels were measured at 10 consecutive time points over 10 days poststroke. The Youden Index was performed to identify patients with low nadir sodium (<140 mmol/L) and potassium (<3.65 mmol/L) levels, defined as a NaK score of 2. Multivariable logistic regression and Cox proportional hazard analysis were used to evaluate the independent relationship of sodium and potassium levels with clinical outcomes at three months. *Results*. A total of 2,920 patients with ischemic stroke were analyzed (mean age 62.14 ± 14.13 years; 60.19% male), of whom 740 (25.3%) with both low nadir sodium and potassium levels had a quintuple 3-month case fatality compared to other patients (10.6% vs. 2.1%). Multivariable analyses identified NaK = 2 as an independent predictor of 3-month death (adjusted odds ratio (OR) 2.23; 95% confidence interval (CI) 1.17-4.53; $p = 0.019$) and an unfavorable shift in the distribution of scores on the modified Rankin scale (adjusted OR 1.51, 95% CI 1.12-2.04; $p = 0.007$). *Conclusions*. Low sodium and potassium levels are common after ischemic stroke and are independent predictors of subsequent death.

1. Introduction

Electrolyte disturbances, such as hyponatremia and hypokalemia, are common in acute illnesses including stroke and other forms of cardiovascular disease [1, 2]. Hyponatremia is associated with increased mortality after stroke, both ischemic and intracerebral hemorrhage (ICH) [1, 3], while hypokalemia has a similar predictive significance regardless of age, stroke severity, and history of hypertension [4]. Moreover, recent research suggests that serum potassium levels have a near-linear association with the incidence of stroke [5]. However, it is uncertain whether a low sodium-to-potassium excretion ratio predicts cardiovascular events in community-dwelling adults better than either sodium or potassium alone [6].

Compared with admission parameters, recent studies indicate that a nadir value (e.g., albumin and hemoglobin levels), which might better reflect the severity of the acute event, has a stronger correlation with clinical outcomes. For example, low nadir albumin levels, evaluated based on the lowest point during hospitalization rather than at admission, were associated with an increased risk of acute worsening of renal function [7–9]. The trend of the nadir levels of serum sodium and potassium during hospitalization tends to represent their average levels, which in turn reflect the comprehensive impact during hospitalization, including the

acute phase of ischemic stroke and other potential influencing factors, thereby endowing them with predictive value. Additionally, since sodium and potassium levels are partly affected by diet and medications, nadir levels were more suitable for evaluating electrolyte disturbance rather than a single measurement at admission [1, 10].

We selected low nadir sodium and potassium levels as the potential biomarkers [3, 11] to examine their joint effects on the relationship with outcomes after stroke [6]. We hypothesized that low nadir serum sodium and potassium levels, even in the normal range, might act synergistically to increase the risk of poor outcomes after ischemic stroke.

2. Methods

The data that support the findings of this study are available upon reasonable request from the corresponding author. The local ethics committee approved the study protocol.

2.1. Study Design and Participants. We analyzed the database from the Chengdu Stroke Registry between January 2009 and April 2016. This is an ongoing database that contains information on consecutive patients with stroke admitted to West China Hospital since January 2002 [12]. The registry is approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University; this committee approved the protocol for this study [13]. Written informed consent was obtained from all participants or their legal guardians. Patients with first-ever ischemic stroke were consecutively recruited: they had to be adults (≥18 years); diagnosed with first-ever ischemic stroke according to the World Health Organization criteria, with brain computed tomography (CT) or magnetic resonance imaging (MRI) scans; within 24 hours of the presumed symptom onset. Patients underwent clinical assessments by certified neurologists at baseline and three months poststroke.

2.2. Procedures. Information about baseline demographic characteristics was obtained predominantly through in-person interviews with patients and family members. In-hospital details, including clinical features and diagnosis, were obtained through a combination of medical records and interviews with patients or their families. Follow-up details were obtained primarily through telephone interviews. Medical history variables included the existence of any of the following: hypertension, diabetes mellitus, hyperlipidemia, stroke, and heart disease (including any history of atrial fibrillation/heart attack/myocardial infarction, angina, coronary heart disease, or valvular heart disease), either self-reported or diagnosed before ischemic stroke onset in-hospital. Comorbidities were defined if the patient had coronary heart disease, congestive heart failure, cancer, leukocythemia, chronic pulmonary disease, diabetes mellitus, hepatic insufficiency, or renal insufficiency. For this study, information about acute reperfusion and electrolyte-related therapies during hospitalization was collected, such as mannitol, saline solution, and potassium intake. Stroke severity on admission was assessed on the National Institutes of Health Stroke Scale (NIHSS, where scores range from 0 to 42, with higher scores indicating greater neurological deficit [14]). The key clinical outcomes were death and a composite of death/disability at three months, defined by scores of 3 to 6 on the modified Rankin scale (mRS) [15]. Follow-up was 89% (2605/2920).

Participants admitted for the first time with a diagnosis of ischemic stroke were included in the study. Exclusion criteria from the study were as follows: presence of brain tumor or other stroke mimic, hypertension treated with diuretics, absence of informed consent, onset of symptoms > 48 hours, presence of do-not-treat or do-not-resuscitate orders, and absence of sodium or potassium value.

We collected serum sodium and potassium levels over a period of 10 consecutive days, which conformed to the median hospitalization stay for stroke patients of 10 days (7-14 days). Nadir sodium and potassium levels were defined as the lowest value during hospitalization. According to the Health Industry Standard of China (WS/T 404.3-2012; reference interval for common clinical biochemistry tests/ part 3: serum potassium, sodium, and chloride), hyponatremia was defined as sodium levels < 137 mmol/L and hypokalemia as potassium levels < 3.5 mmol/L.

2.3. Statistical Analysis. Categorical variables are presented as counts (%), and the continuous or discrete variables are presented as mean (standard deviation (SD)) or median (interquartile range (IQR)). Student's t-test, the χ^2 test, ANOVA, Mann–Whitney U test, Fisher's exact test, and Kruskal-Wallis test were used for univariate analysis among scales with relevant variables as appropriate. Associations of clinical characteristics with death were analyzed using logistic regression or Cox proportional hazard models, whereas associations of clinical characteristics with mRS were analyzed using shift analysis of the full range of scores on the mRS. The hazard ratio (HR) was calculated using Cox proportional hazard modeling with adjustment for potential confounders. Data are reported as odds ratios (OR) and 95% confidence intervals (CI). Where appropriate, adjusted ORs are reported. Age, sex, NIHSS, albumin, serum creatinine, random blood glucose, systolic blood pressure, pneumonia, comorbidities, and reperfusion and electrolyte-related therapies during hospitalization (e.g., saline, potassium intake, and mannitol), identified as confounding variables in the total cohort, were adjusted in all multivariable models. Two-sided p values are reported, with $p < 0.05$ considered statistically significant in all tests unless another threshold was given. All statistical analyses were performed in R Core Team (2017) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/).

3. Results

A total of 3,101 patients with acute ischemic stroke were screened, but 181 patients were excluded for the following reasons: presence of brain tumor or other stroke mimic, hypertension treated with diuretics, absence of informed consent, onset of symptoms > 48 hours, presence of do-not-treat or do-not-resuscitate orders, and absence of sodium or

Table 1: Baseline characteristics of the study population, stratified by the nadir NaK scale.

Characteristics	Total $n = 2920$	NaK = 0 $n = 832$	NaK = 1 $n = 1348$	NaK = 2 $n = 740$	p value
Age, years	63.1 ± 14.1	61.7 ± 13.9	63.7 ± 13.7	63.9 ± 15.1	0.373
Sex (male)	1,754 (60.2%)	517 (62.2%)	838 (62.3%)	399 (54.1%)	<0.001
Medical history, *n* (%)					
Hypertension	1,443 (49.4%)	384 (46.2%)	682 (50.6%)	377 (50.9%)	0.083
Diabetes mellitus	523 (17.9%)	128 (15.4%)	257 (19.1%)	138 (18.6%)	0.078
HD history	202 (6.9%)	50 (6.0%)	97 (7.2%)	55 (7.4%)	0.465
Hyperlipidemia	1029 (41%)	296 (41%)	473 (41%)	260 (41%)	0.975
Smoking	936 (32.1%)	292 (35.1%)	435 (32.3%)	209 (28.2%)	0.014
Alcohol	646 (22.1%)	207 (24.9%)	297 (22.0%)	142 (19.2%)	0.025
Clinical status					
NIHSS	4 (2-10)	3 (1-6)	4 (2-10)	7 (3-12)	<0.001
GCS	15 (13-15)	15 (14-15)	15 (13-15)	*n* (12–15)	<0.001
SBP (mmHg)	143.5 ± 24.1	141.9 ± 23.2	143.9 ± 23.8	144.6 ± 25.3	0.019
DBP (mmHg)	84.1 ± 14.6	83.4 ± 14.0	84.4 ± 15.0	84.4 ± 15.6	0.161
Albumin (g/L)	40.4 ± 5.1	40.9 ± 4.7	40.4 ± 5.3	39.8 ± 5.2	<0.001
INR (second)	1.07 ± 0.15	1.05 ± 0.15	1.07 ± 0.16	1.08 ± 0.16	0.001
Blood glucose (mmol/L)	7.77 ± 3.60	6.68 ± 2.52	7.88 ± 3.77	8.50 ± 3.81	0.001
Urea nitrogen (mmol/L)	5.66 (4.50-7.09)	5.65 (4.57-7.02)	5.74 (4.53-7.21)	5.47 (4.30-6.90)	0.788
Creatinine (μmol/L)	78.0 (66.0-93.2)	79.5 (66.0-93.0)	78.0 (67.0, 94.0)	75.9 (64.0-92.0)	0.265
Triglyceride (mmol/L)	1.29 (0.94-1.86)	1.33 (0.97, 1.87)	1.27 (0.93-1.86)	1.31 (0.95-1.83)	0.404
Electrolyte					
s-sodium level baseline	139.9 ± 3.9	142.5 ± 2.0	139.6 ± 3.6	137.7 ± 4.2	<0.001
s-potassium level baseline	3.79 ± 0.43	4.01 ± 0.28	3.81 ± 0.45	3.50 ± 0.39	<0.001
s-sodium level	140.7 ± 4.8	142.6 ± 3.4	140.6 ± 4.6	139.7 ± 5.3	<0.001
s-potassium level	3.89 ± 0.48	4.03 ± 0.34	3.92 ± 0.49	3.77 ± 0.51	<0.001
Therapy in hospital					
Mannitol (mL)	2250 (1250-3750)	1750 (750-3000)	2250 (1250-3500)	2875 (1500-4875)	<0.001
Potassium intake total (g)	9.83 (4.68-15.86)	6.86 (2.81-14.04)	9.62 (4.68-15.44)	9.83 (5.62-17.63)	<0.001
Saline total (mL)	4850 (3000-8200)	4100 (2430-6275)	4900 (3000-8300)	6250 (3500-10200)	<0.001
Complication					
Respiratory infection	628 (21.5%)	98 (11.8%)	299 (22.2%)	231 (31.2%)	<0.001
Urinary tract infection	88 (3.0%)	8 (1.0%)	45 (3.3%)	35 (4.7%)	<0.001

Descriptive statistics were calculated using mean ± SD or median (IQR) for continuous variables and frequencies for categorical variables. Abbreviations: HD: heart disease; NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; SBP: systolic blood pressure; DBP: diastolic blood pressure; HCT: hematocrit; INR: international normalized ratio; SD: standard deviation; IQR: interquartile range; s-sodium: serum sodium; s-potassium: serum potassium.

potassium values (Supplementary Figure 1). Thus, 2,920 patients were included in the final analysis, with 1,754 (60.2%) male with a mean age of 63.1 ± 14.1 years. The baseline sodium and potassium levels were 139.9 ± 3.9 mmol/L and 3.79 ± 0.43 mmol/L, respectively, and the mean sodium and potassium levels during hospitalization were 140.7 ± 4.8 mmol/L and 3.89 ± 0.48 mmol/L, respectively (Table 1).

Neither hyponatremia (adjusted odds ratio (aOR) 1.46, 95% confidence interval (CI) 0.96-2.19; $p = 0.072$) nor hypokalemia (aOR 1.33, 95% CI 0.84-2.10; $p = 0.218$) in isolation exhibited an association with 3-month mortality. Furthermore, the combined presence of hyponatremia and hypokalemia did not demonstrate a synergistic effect in elevating the odds of this outcome (aOR 1.31, 95% CI 0.69-2.43; $p = 0.392$, Supplementary Table 1).

Figure 1 illustrates that utilizing the Youden Index with different cut-off values for serum sodium (140 mmol/L) and serum potassium (3.65 mmol/L) enhances the predictive performance for 3-month mortality. Subsequently, patients were categorized into three groups based on the nadir NaK scale (NaK) from 0 to 2, high nadir sodium (≥140 mmol/L) and potassium (≥3.65 mmol/L) were defined as 0, low nadir sodium (<140 mmol/L) or potassium levels (<3.65 mmol/L) were defined as 1, and both low nadir sodium and potassium levels were defined as 2 (Table 1). There were 1556 (53.3%) patients with low nadir sodium and 1272 (43.6%) with low

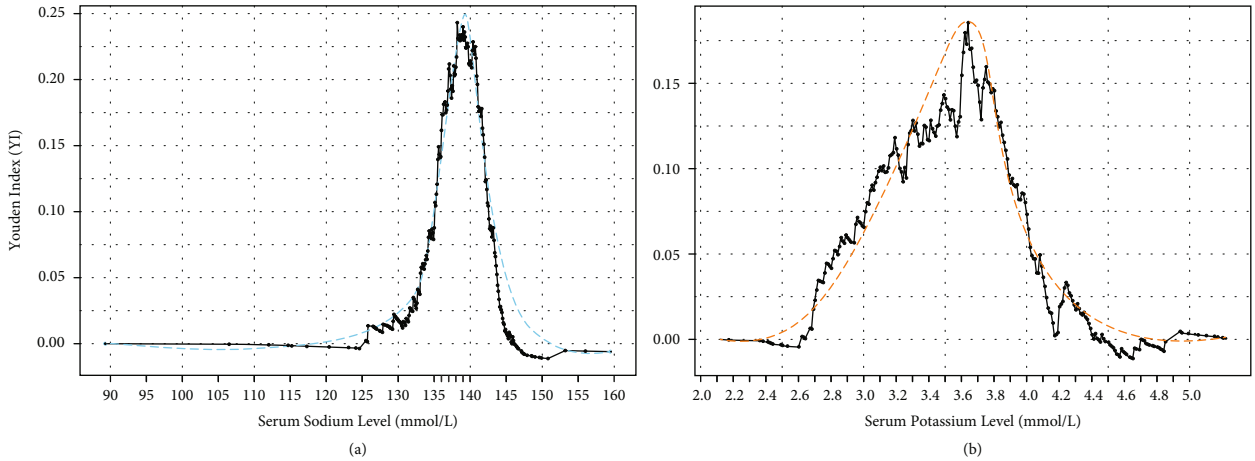

FIGURE 1: Youden Index plots to determine optimal cut-off points for serum (a) sodium and (b) potassium for prediction of 3-month mortality after ischemic stroke. The optimal cut point of s-sodium levels was 139.2 mmol/L with the highest YI value at 0.243, whereas the optimal cut point of the s-potassium level was 3.64 mmol/L with the highest YI value at 0.185. Based on these results, a low s-sodium level was defined as less than 140 mmol/L, whereas a low s-potassium level was defined as less than 3.65 mmol/L.

nadir potassium levels. In comparison with patients having a NaK score of 0, those with NaK = 2 were less likely to be male (54.1% vs. 62.2%), had higher NIHSS scores (7 vs. 3), higher systolic blood pressure (144.6 vs. 141.9 mmHg), lower hemoglobin (132.8 vs. 136.6 g/L), lower albumin (39.8 vs. 40.9 mmol/L), higher blood glucose (8.50 vs. 6.68 mmol/L), higher INR (1.08 vs. 1.05), a higher frequency of complication such as respiratory (31.2% vs. 11.8%) and urinary tract (4.7% vs. 1.0%) infections, and a higher frequency of 3-month mortality (10.6% vs. 2.1%, Table 1).

The 10-day course of mean sodium and potassium levels was plotted based on the nadir NaK scale. Sodium levels in patients with NaK = 0 were significantly higher than those with NaK = 1 or 2 ($p < 0.001$; Figure 2(a)). As depicted in Figure 2(b), patients with NaK = 1 and 2 exhibited significantly lower baseline potassium levels (3.81 and 3.50 mmol/L, respectively) compared to 4.01 mmol/L in patients with NaK = 0. By the end of the 10 days, potassium levels had risen to 4.10 and 4.04 mmol/L in patients with NaK = 1 and 2, respectively.

We conducted additional investigations into the association between the NaK scale and 3-month outcomes using multivariate models (Table 2). Compared with patients with NaK = 0, those with NaK = 2 exhibited an increased risk of 3-month mortality with an adjusted odds ratio (aOR) of 2.23 (95% CI 1.17-4.53; $p = 0.019$). Supplementary Figure 2 graphically represents the correlation between the nadir NaK scale and neurological recovery on the mRS: 45% of patients with NaK = 2 exhibited poor 3-month mRS scores of 3-6, compared to 33.3% of patients with NaK = 1 and 18.7% of patients with NaK = 0 ($p < 0.001$). The multivariable shift analysis showed a significant favorable shift in the distribution of scores on the mRS with low nadir sodium and potassium (NaK = 2) levels (aOR for the shift towards higher mRS scores 1.51, 95% CI 1.12-2.04; $p = 0.007$).

Subgroup analyses were conducted to explore associations, revealing no heterogeneity based on age, sex, level of consciousness, stroke severity, and the use of specific therapies (Supplementary Figure 3). Kaplan–Meier survival curves over 90 days are presented in Supplementary Figure 4. Overall, 10.6% ($n = 70$) of patients with a NaK score of 2 versus 2.1% ($n = 16$) of patients with a NaK score of 0 were dead, indicating an approximately 4-fold difference in mortality (log-rank $p < 0.001$). Further analysis using the Cox proportional hazards model demonstrated a significantly higher risk of death over time (NaK = 2 vs. NaK = 0: adjusted hazard ratio (HR) 3.01, 95% CI 1.41-6.46; $p = 0.005$; NaK = 1 vs. NaK = 0: adjusted HR 1.93, 95% CI 0.86-4.32; $p = 0.085$).

4. Discussion

In this study, the first to examine the joint association of nadir sodium and potassium with outcomes in ischemic stroke, we have demonstrated that low nadir sodium and potassium levels were correlated with elevated case fatality and disability.

Recent research has suggested that serum potassium was linearly associated with an increased incidence of stroke, even within the normal range [5]. We defined the cut points of <140 mmol/L and <3.65 mmol/L, selected using the Youden Index, to determine low sodium and potassium, respectively, and to define a nadir NaK scale. The combination of nadir serum sodium and potassium enhanced the strength of association in the predictive model, supporting the hypothesis that they are independent predictors of adverse clinical outcomes. Previous studies have typically examined these biochemical variables separately, but O'Donnell et al. proposed that the combination of moderate sodium with high potassium intakes is associated with reduced mortality and serious cardiovascular events in a population-based study [6]. Another research has reported that the urinary sodium-to-potassium secretion ratio is associated with cardiovascular events or mortality in international community-dwelling participants [16, 17].

Potential detrimental mechanisms associated with low sodium levels in stroke could involve an inappropriate secretion of antidiuretic hormone (ADH) triggered by the

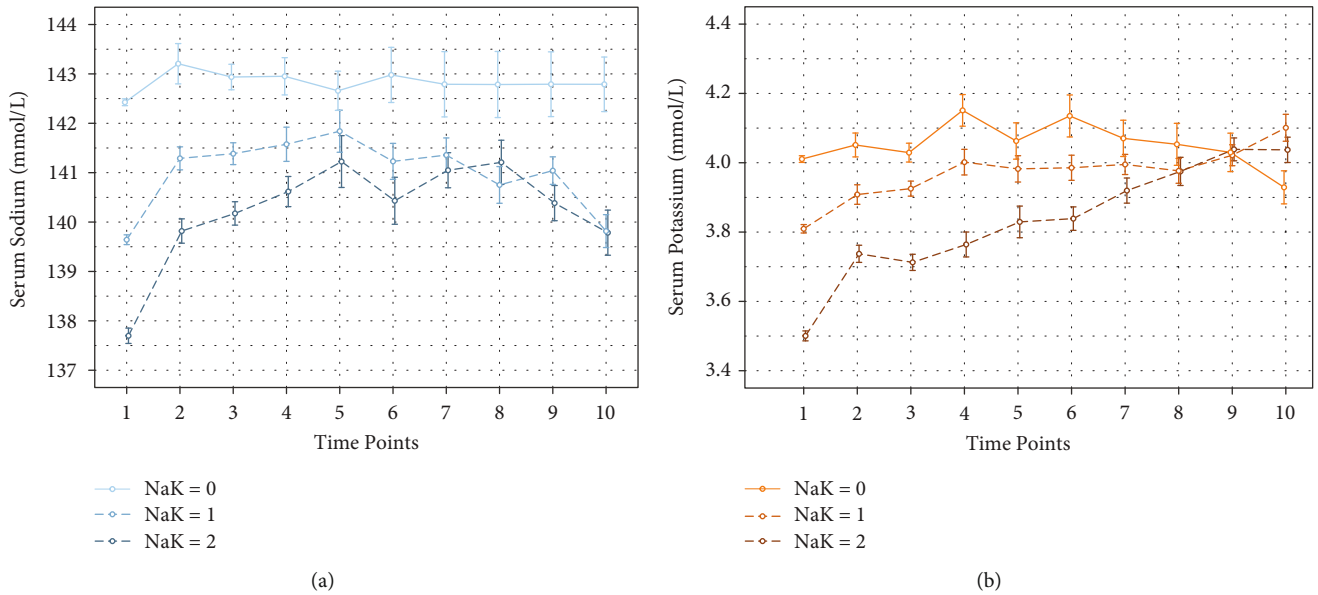

Figure 2: Graphic depiction of mean serum (a) sodium or (b) potassium levels for all patients according to the nadir NaK scale over 10 days.

Table 2: Multivariable analysis of the association between NaK scale and 3-month outcomes.

Variables	3-month death				3-month modified Rankin scale			
	NaK = 1		NaK = 2		NaK = 1		NaK = 2	
	Odds ratio	*p* value	Odds ratio	*p* value	Odds ratio	*p* value	Odds ratio	*p* value
Sex	1.07 (0.62-1.86)	0.811	0.86 (0.49-1.49)	0.589	0.80 (0.62-1.04)	0.101	0.69 (0.52-0.91)	0.009
Age	1.03 (1.01-1.06)	0.013	1.03 (1.01-1.06)	0.002	1.03 (1.02-1.04)	0.001	1.03 (1.02-1.04)	0.001
NIHSS	1.10 (1.06-1.14)	0.001	1.11 (1.07-1.14)	0.001	1.19 (1.16-1.22)	0.001	1.17 (1.14-1.20)	0.001
Creatinine	1.00 (1.00-1.01)	0.131	1.00 (1.00-1.00)	0.829	1.01 (1.00-1.01)	0.007	1.00 (1.00-1.01)	0.344
Albumin	0.95 (0.90-1.00)	0.068	0.98 (0.93-1.04)	0.543	0.99 (0.97-1.01)	0.256	0.99 (0.96-1.02)	0.424
Blood glucose	1.03 (0.96-1.10)	0.383	1.01 (0.93-1.09)	0.843	1.00 (0.98-1.03)	0.932	1.02 (1.00-1.05)	0.142
SBP	1.00 (0.98-1.01)	0.487	0.99 (0.98-1.00)	0.179	1.00 (1.00-1.01)	0.107	1.00 (1.00-1.01)	0.591
Comorbidities*	1.33 (0.44-3.50)	0.582	0.76 (0.23-2.11)	0.631	1.18 (0.78-1.77)	0.425	0.83 (0.52-1.31)	0.424
Pneumonia	2.64 (1.48-4.74)	0.001	1.70 (0.96-3.00)	0.068	1.64 (1.18-2.27)	0.003	1.72 (1.22-2.42)	0.002
Saline	1.02 (0.72-1.42)	0.893	1.15 (0.79-1.63)	0.452	1.17 (0.99-1.38)	0.060	1.11 (0.92-1.33)	0.262
Mannitol	0.85 (0.60-1.18)	0.346	0.75 (0.50-1.08)	0.142	0.82 (0.70-0.97)	0.017	0.94 (0.79-1.11)	0.484
Potassium intake	1.30 (0.85-1.97)	0.218	0.94 (0.60-1.45)	0.788	1.02 (0.83-1.24)	0.870	0.89 (0.72-1.10)	0.284
NaK scale	1.52 (0.80-3.08)	0.221	2.23 (1.17-4.53)	0.019	1.29 (0.99-1.67)	0.057	1.51 (1.12-2.04)	0.007

Notes: In models of both multivariable logistic regression and shift analysis, the patients with NaK = 0 were considered as the reference group. All models were adjusted for age, sex, NIHSS scale, albumin, serum creatinine, random blood glucose, systolic blood pressure, pneumonia, and electrolyte-related therapies during hospitalization, such as saline, potassium intake, and mannitol. *Comorbidities were defined as any history of diseases such as coronary heart disease, congestive heart failure, cancer, leukocythemia, chronic pulmonary disease, diabetes mellitus, hepatic insufficiency, or renal insufficiency. Abbreviations: aOR: adjusted odds ratio; NIHSS: National Institutes of Health Stroke Scale; SBP: systolic blood pressure; NaK: nadir low sodium and potassium scale.

overstimulation of the neurohumoral axis or by cerebral hypoperfusion in elderly patients with baroreceptor failure [18, 19]. Another possible mechanism leading to hyponatremia is cerebral salt wasting (CSW). Factors such as increased blood volume, sympathetic stimulus, or elevated angiotensin II promote the release of natriuretic peptide. This, in turn, results in a reduction in the activity of the renin-angiotensin-aldosterone system, affecting the distal tubules of the kidneys, leading to increased excretion of urinary sodium and ultimately causing hyponatremia [20]. Besides, secondary adrenal insufficiency due to pituitary ischemia or hemorrhage can lead to hyponatremia or hypokalemia. Cortisol is primarily secreted by the adrenal glands and plays a crucial role in facilitating free water excretion in the kidney. Insufficient cortisol levels result in the inability to effectively excrete a free water load, leading to the development of dilutional hyponatremia [21]. Conversely, potassium might act directly or indirectly through sodium allostasis upon vascular smooth-muscle cell contraction to induce hypertension [22].

In clinical practice, some stroke patients, especially elderly individuals, may experience alterations in serum

sodium and potassium levels due to the use of medications such as thiazides or furosemide. Thiazides and thiazide-like agents are common diuretics that can lead to low sodium or low potassium levels. They act solely in the distal tubules and do not interfere with the ability of ADH, which is crucial for the development of hyponatremia [23, 24]. Additionally, when used in combination with potassium-sparing diuretics such as amiloride, they may exacerbate hyponatremia [25]. Furthermore, furosemide has less of an impact on sodium and potassium compared to thiazide diuretics because it impairs both renal concentrating and diluting mechanisms [23, 24].

Hyponatremia and hypokalemia are prevalent electrolyte abnormalities encountered in clinical practice. The multitude of underlying etiologies necessitates a meticulous differential diagnosis, taking into account various comorbidities, concurrent medications, clinical examination findings, and various laboratory measurements. This comprehensive approach is crucial for guiding decisions regarding management [26–30].

Studies indicate a frequency of hyponatremia ranging from 10 to 30% across various serious conditions that require hospital admission [31, 32]. Questions have been raised as to whether restoration of sodium to normal levels improves outcomes after acute stroke [30]. On the one hand, reversing hyponatremia, irrespective of direct or indirect causes, could offer benefits, but on the other hand, there are potential harms related to arrhythmias.

The strengths of our study encompass a sizable sample size, the incorporation of repeated biochemical measures, and comprehensive details on various management strategies employed during hospitalization, such as the infusion of saline solutions, potassium intake, and mannitol usage. However, inherent limitations exist in observational studies like ours, characterized by a single-center cohort design and challenges related to residual confounding. These limitations constrain our ability to make definitive causal inferences.

5. Conclusion

Low nadir sodium and potassium levels are common in patients with ischemic stroke, and their combination is predictive of adverse 3-month outcomes.

Abbreviations

CIs: Confidence intervals
CT: Computed tomography
CSW: Cerebral salt wasting
GCS: Glasgow Coma Scale
HR: Hazard ratio
ICH: Intracerebral hemorrhage
IQR: Interquartile range
NaK: NaK scale, low nadir sodium and potassium scale
MRI: Magnetic resonance imaging
mRS: Modified Rankin scale score
NIHSS: National Institutes of Health Stroke Scale
OR: Odds ratio
SD: Standard deviation
SIADH: Syndrome of inappropriate antidiuretic hormone secretion
s-potassium: Serum potassium
s-sodium: Serum sodium
YI: Youden Index.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

Ethical Approval

All methods were performed in accordance with the Declaration of Helsinki and must have been approved by the Biomedical Research Ethics Committee and the Committee on Human Research of West China Hospital, Sichuan University (2013 [124]).

Consent

Informed consent was obtained from participants or their guardians.

Conflicts of Interest

The authors report no conflicts of interest concerning this study.

Authors' Contributions

ML, SZ, ZF, and TC designed and conducted the study. ZF, TC, PL, ZZ, and ZW collected the data and constructed the database. ZF, TC, PL, ZW, YW, QS, and CY analyzed the data. ML, SZ, ZF, TC, PL, and ZZ wrote the paper. All authors reviewed the manuscript. Zijuan Feng and Ting Chen contributed equally to this work.

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Supplementary Materials

Supplementary Table 1: multivariable logistic regression analysis of the association between hyponatremia and hypokalemia and 3-month death. Supplementary Figure 1: flow chart illustrating the process of inclusion and exclusion of our study participants. Supplementary Figure 2: dichotomized analysis

of the modified Rankin Scale (mRS) distribution at 3-month for all patients according to the classification of the nadir NaK scale. Supplementary Figure 3: effects of low nadir s-sodium and s-potassium levels on 3-month death in ischemic stroke patients by age, sex, state of consciousness, severity, and therapies. Supplementary Figure 4: Kaplan-Meier survival curve from day 0 to day 90 in patients according to the classification of the nadir NaK scale. *(Supplementary Materials)*

References

[1] J. B. Kuramatsu, T. Bobinger, B. Volbers et al., "Hyponatremia is an independent predictor of in-hospital mortality in spontaneous intracerebral hemorrhage," *Stroke*, vol. 45, no. 5, pp. 1285–1291, 2014.

[2] D. Rusinaru, O. Buiciuc, L. Leborgne, M. Slama, Z. Massy, and C. Tribouilloy, "Relation of serum sodium level to long-term outcome after a first hospitalization for heart failure with preserved ejection fraction," *American Journal of Cardiology*, vol. 103, no. 3, pp. 405–410, 2009.

[3] R. L. Soiza, K. Cumming, A. B. Clark et al., "Hyponatremia predicts mortality after stroke," *International Journal of Stroke*, vol. 10, Supplement A100, pp. 50–55, 2015.

[4] S. E. Gariballa, T. G. Robinson, and M. D. Fotherby, "Hypokalemia and potassium excretion in stroke patients," *Journal of The American Geriatrics Society*, vol. 45, no. 12, pp. 1454–1458, 1997.

[5] L. S. Johnson, N. Mattsson, A. Sajadieh, P. Wollmer, and M. Söderholm, "Serum potassium is positively associated with stroke and mortality in the large, population-based Malmö preventive project cohort," *Stroke*, vol. 48, no. 11, pp. 2973–2978, 2017.

[6] M. O'Donnell, A. Mente, S. Rangarajan et al., "PURE Investigators. Joint association of urinary sodium and potassium excretion with cardiovascular events and mortality: prospective cohort study," *BMJ*, vol. 364, p. 1772, 2019.

[7] E. J. Peterson, T. M. H. Ng, K. A. Patel, M. Lou, and U. Elkayam, "Association of admission vs. nadir serum albumin concentration with short-term treatment outcomes in patients with acute heart failure," *Journal of International Medical Research*, vol. 46, no. 9, pp. 3665–3674, 2018.

[8] K. M. Trentino, M. F. Leahy, F. M. Sanfilippo et al., "Associations of nadir haemoglobin level and red blood cell transfusion with mortality and length of stay in surgical specialties: a retrospective cohort study," *Anaesthesia*, vol. 74, no. 6, pp. 726–734, 2019.

[9] S. T. Zhang, Y. Shu, Y. L. Chen et al., "Low hemoglobin is associated with worse outcomes via larger hematoma volume in intracerebral hemorrhage due to systemic disease," *MedComm*, vol. 3, no. 1, p. e96, 2022.

[10] S. R. Martha, J. F. Fraser, and K. R. Pennypacker, "Acid-base and electrolyte changes drive early pathology in ischemic stroke," *Neuromolecular Medicine*, vol. 21, no. 4, pp. 540–545, 2019.

[11] B. Rodrigues, I. Staff, G. Fortunato, and L. D. McCullough, "Hyponatremia in the prognosis of acute ischemic stroke," *Journal of Stroke & Cerebrovascular Diseases*, vol. 23, no. 5, pp. 850–854, 2014.

[12] W. D. Tao, M. Liu, M. Fisher et al., "Posterior versus anterior circulation infarction," *Stroke*, vol. 43, no. 8, pp. 2060–2065, 2012.

[13] M. Liu, X. Q. Jiang, and C. You, "The importance of the etiological study and standard etiological diagnosis in intracerebral hemorrhage," *Chinese Journal of Neurology*, vol. 46, no. 6, pp. 361–364, 2013.

[14] T. Brott, J. R. Marler, C. P. Olinger et al., "Measurements of acute cerebral infarction: lesion size by computed tomography," *Stroke*, vol. 20, no. 7, pp. 871–875, 1989.

[15] R. de Haan, M. Limburg, P. Bossuyt, J. van der Meulen, and N. Aaronson, "The clinical meaning of Rankin 'handicap' grades after stroke," *Stroke*, vol. 26, no. 11, pp. 2027–2030, 1995.

[16] M. O'Donnell, A. Mente, S. Rangarajan et al., "Urinary sodium and potassium excretion, mortality, and cardiovascular events," *New England Journal of Medicine*, vol. 371, no. 7, pp. 612–623, 2014.

[17] M. J. O'Donnell, S. Yusuf, A. Mente et al., "Urinary sodium and potassium excretion and risk of cardiovascular events," *Jama-journal of The American Medical Association*, vol. 306, no. 20, pp. 2229–2238, 2011.

[18] R. W. Schrier, S. Sharma, and D. Shchekochikhin, "Hyponatraemia: more than just a marker of disease severity?," *Nature Reviews Nephrology*, vol. 9, no. 1, pp. 37–50, 2013.

[19] B. K. Wallace, S. Foroutan, and M. E. O'Donnell, "Ischemia-induced stimulation of Na-K-Cl cotransport in cerebral microvascular endothelial cells involves AMP kinase," *American Journal of Physiology-cell Physiology*, vol. 301, no. 2, pp. C316–C326, 2011.

[20] M. Cerdà-Esteve, E. Cuadrado-Godia, J. J. Chillaron et al., "Cerebral salt wasting syndrome: review," *European Journal of Internal Medicine*, vol. 19, no. 4, pp. 249–254, 2008.

[21] J. Martin-Grace, R. Dineen, M. Sherlock, and C. J. Thompson, "Adrenal insufficiency: physiology, clinical presentation and diagnostic challenges," *Clinica Chimica Acta*, vol. 505, pp. 78–91, 2020.

[22] H. J. Adrogué and N. E. Madias, "Sodium and potassium in the pathogenesis of hypertension," *New England Journal of Medicine*, vol. 356, no. 19, pp. 1966–1978, 2007.

[23] G. Liamis, H. Milionis, and M. Elisaf, "A review of drug-induced hyponatremia," *American Journal of Kidney Diseases*, vol. 52, no. 1, pp. 144–153, 2008.

[24] G. Liamis, H. Milionis, and M. Elisaf, "Blood pressure drug therapy and electrolyte disturbances," *International Journal of Clinical Practice*, vol. 62, no. 10, pp. 1572–1580, 2008.

[25] C. Johnston, L. Webb, J. Daley, and G. S. Spathis, "Hyponatraemia and moduretic-grand mal seizures: a review," *Journal of The Royal Society of Medicine*, vol. 82, no. 8, pp. 479–483, 1989.

[26] R. Wald, B. L. Jaber, L. L. Price, A. Upadhyay, and N. E. Madias, "Impact of hospital-associated hyponatremia on selected outcomes," *Archives of Internal Medicine*, vol. 170, no. 3, pp. 294–302, 2010.

[27] C. P. Kovesdy, E. H. Lott, J. L. Lu et al., "Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure," *Circulation*, vol. 125, no. 5, pp. 677–684, 2012.

[28] P. Gines and R. W. Schrier, "Renal failure in cirrhosis," *New England Journal of Medicine*, vol. 361, no. 13, pp. 1279–1290, 2009.

[29] E. J. Hoorn, J. Lindemans, and R. Zietse, "Acute and concomitant deterioration of hyponatremia and renal dysfunction

associated with heart and liver failure," *Clinical Nephrology*, vol. 65, no. 4, pp. 248–255, 2006.

[30] G. Liamis, F. Barkas, E. Megapanou et al., "Hyponatremia in acute stroke patients: pathophysiology, clinical significance, and management options," *European Neurology*, vol. 82, no. 1-3, pp. 32–40, 2020.

[31] E. J. Hoorn and R. Zietse, "Hyponatremia and mortality: moving beyond associations," *American Journal of Kidney Diseases*, vol. 62, no. 1, pp. 139–149, 2013.

[32] A. Upadhyay, B. L. Jaber, and N. E. Madias, "Incidence and prevalence of hyponatremia," *American Journal of Medicine*, vol. 119, no. 7, pp. S30–S35, 2006.