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Electrolyte Levels in Poor Prognosis and Early Neurological Deterioration in Patients With Acute Ischemic Stroke

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ABSTRACT

Discrepancies in serum electrolyte levels have been observed between stroke patients and healthy individuals. Previous studies have indicated an association between electrolytes and all-cause mortality as well as cardiovascular events in stroke patients. However, there still lacks comprehensive analysis on the connection between electrolytes and negative outcomes in hypertensive individuals with early neurological deterioration (END). Totally 1341 patients treated with thrombolysis for acute ischemic stroke at the First Affiliated Hospital of Wenzhou Medical University were included. Outcomes included END, 3-month, 6-month, and 1-year poor prognosis. Logistic regression assessed the correlation and restricted cubic spline analysis examined dose-response relationships. Subgroup analysis validated the relationship between electrolytes and prognosis in hypertensive patients. A total of 242 patients exhibited a 3-month poor prognosis. Significant differences were observed in Cl^-, Ca^{2+}, and Mg^{2+} levels between mRS binary classification. Logistic regression identified Cl^- as the strongest predictor for 3-month, 6-month, and 1-year mRS score and Ca^{2+} for END. Restricted cubic spline analysis revealed relationships between higher concentrations of Na^+ and poorer prognosis. In the hypertension subgroup, a higher concentration of Na^+ indicated worse 6-month and 1-year outcomes and a lower concentration of Ca^{2+} was linked to a higher risk of END. The concentration of Na^+ is related to adverse clinical outcomes, while that of Cl^- and Ca^{2+} are associated with END. Among hypertensive patients, elevated levels of Na^+ and $Ca2^+$ concentration are respectively associated with 6-month poor prognosis and END. Monitoring the electrolytes may promote the early identification of individuals at high risk of poor functional outcomes.

1 | Introduction

Stroke is the second leading cause of death globally as well as the third leading cause of disability and mortality worldwide [1]. Currently, a common and well-recognized clinical treatment for acute ischemic stroke (AIS) patients is intravenous injection of alteplase (recombinant tissue plasminogen activator). Previous meta-analysis suggests that intravenous thrombolysis within 4.5h

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of stroke could achieve better therapeutic effects than delayed management [2]. However, a considerable proportion of patients would still suffer from early neurological deterioration (END) and poor prognosis after this treatment, which is directly associated with an unsatisfied recovery. Therefore, it is crucial to find biomarkers to predict the END and prognosis of stroke patients.

Electrolytes are an important chemical composition in the human body. In particular, serum potassium (K^+), serum sodium (Na^+), serum chloride (Cl^-), serum magnesium (Mg^{2+}), and serum calcium (Ca^{2+}) are important electrolytes in the body that play a significant role in the physiological and affect human health. From the water, vegetables, nuts, and other foods, people obtain electrolytes, which can regulate body functions, including adjusting blood pressure [3].

Electrolytes have been researched to be associated with various diseases such as cardiovascular disease, hypertension, diabetes, and metabolic syndrome. Previous studies have reported that abnormal levels of electrolytes such as K^+, Ca^{2+}, Na^+, and Mg^{2+} can affect the mortality and morbidity of stroke patients. In patients with acute heart failure, hyperkalemia at discharge has been identified as an independent predictor of 1-year all-cause mortality; Additionally, a high Ca^{2+} level at baseline has been associated with 1-year all-cause mortality after ischemic stroke [4, 5]. Hyponatremia is independently associated with higher mortality in <75-year-old acute stroke patients, and genetically higher Mg^{2+} concentration is associated with a lower risk of cardiogenic stroke [6, 7]. Meanwhile, it is important to emphasize the significant influence of hypertension on strokes [8]. However, there remains a paucity of comprehensive investigations into the relationship between electrolyte levels and prognosis or END, especially among stroke patients, including those with hypertension.

Therefore, our purpose is to explore the relationship between electrolyte levels (K^+, Na^+, Cl^-, Mg^{2+} and Ca^{2+}) and 3- and 6-month poor prognosis as well as END of AIS thrombolytic patients.

Exploring the relationship between serum electrolytes and outcome endpoints can not only assist clinicians in devising early prognostic assessments for stroke patients but also contribute to planning rehabilitation strategies following stroke onset.

2 | Materials and Methods

2.1 | Study Participants

In this retrospective design, we included 1341 thrombolytic AIS patients admitted to the First Affiliated Hospital of Wenzhou Medical University from January 1, 2018, to December 31, 2022. Patients were excluded without baseline data or outcome data, and were further excluded if: (1) were diagnosed with malignant tumor; (2) had electrolyte metabolism disorder or lipid metabolism disorder; (3) verified with autoimmune disease; (4) had epilepsy at admission; (5) diagnosed with liver dysfunction, cirrhosis or acute hepatitis; and (6) had renal failure [estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2] or acute renal insufficiency. Finally, 686 patients were included in this study (Figure S1).

2.2 | Data Acquisition

Baseline data, including age, gender, smoking, alcohol status, medical history, prestroke modification Rankin Scale (mRS) score, and National Institutes of Health Stroke Scale (NIHSS) scored at admission and 24h after admission through face-to-face interviews or medical records were obtained by trained study coordinators.

2.3 | Collection and Determination of Serum Samples

Blood samples were measured by laboratory personnel in the First Affiliated Hospital of Wenzhou Medical University, who were unaware of the patient's clinical conditions. Baseline blood samples were collected in a fasting state within 24h of admission. K^+, Na^+, Cl^-, Ca^{2+}, and Mg^{2+} were measured by colorimetry. Other items of blood biochemistry measurements include total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), plasma albumin eGFR, and fasting plasma glucose (FPG).

2.4 | Outcome Assessment

Clinical outcomes were obtained by trained research coordinators who were blinded to the baseline characteristics of the participants and conducted face-to-face or telephone interviews at 3 months, 6 months, and 1 year. In our study, adverse outcomes include END and poor functional outcome at 3 months, 6 months, or 1 year. mRS score ranges from 0 (no symptoms) to 6 (death). Poor functional outcome was defined as a mRS score of 3–6, and END was defined as an increase of NIHSS $\geq$ 4 within 24h after admission.

2.5 | Statistical Analysis

We divided the patients into five groups according to the quintiles of each electrolyte level. Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. Variables with normal distribution were expressed as mean with standard deviation (SD); for non-normality, variables were expressed as medians with interquartile ranges and using the Kruskal–Wallis test to compare the differences. Continuous variables that followed a normal distribution were tested by *T*-test, and categorical variables were tested by chi-square test or Fisher exact test. Logistic regression models were applied to assess the relationship between serum electrolytes and clinical outcomes among general patients or hypertension subgroup, then expressed with odds ratios (OR) and 95% confidence intervals (CI). By comparing baseline groups, elements with statistical differences are included in the adjusted variables. Multiple models were constructed as follows: Model 1: unadjusted; Model 2: adjusted for age, sex; Model 3: adjusted for age, sex, baseline NIHSS, atrial fibrillation, hypertension, albumin, eGFR, total cholesterol, triglyceride, LDL-C, and FPG.

The application of antihypertensive drugs is integrated into the sensitivity analysis in the study to measure the model's stability.

To capture the dose-response relationship, we fitted restricted cubic splines with three knots at the 10th, 50th, and 90th percentiles for each electrolyte, after adjusting for potential confounders. We further performed a subgroup analysis for hypertensive patients.

All p values were 2-tailed and under 0.05 was considered statistically significant. All analyses were conducted in IBM SPSS Statistics for Windows, version 26.0. Restricted cubic splines were produced using R 4.3.2.

2.6 | Ethical Review

The study was approved by the Institutional Ethics Committee review board of the First Affiliated Hospital of Wenzhou Medical University and was performed in accordance with the Declaration of Helsinki.

3 | Results

3.1 | Baseline Characteristics

Baseline characteristics of included 686 patients were mentioned in Table 1. The average age of patients was 68 (59–76) years, and 65.5% were male. For serum electrolytes, we observed a significant difference in Cl^- levels between the mRS 0–2 and 3–6 groups (106.0 vs. 105.0, $p < 0.001$). Similarly, the median concentration of Ca^{2+} exhibited an obvious difference in mRS 0–2 group and mRS 3–6 group (2.23 vs. 2.19, $p = 0.004$). Furthermore, differences in the median concentration of Mg^{2+} also existed between the two groups (0.9 vs. 0.8, $p < 0.001$). Besides, mRS 0–2 group tended to be older age, higher baseline NIHSS, lower albumin, lower total cholesterol, lower LDL-C, lower triglyceride, higher fasting blood glucose, lower eGFR, female and had atrial fibrillation and hypertension medical history. These data indicated that Cl^- level, Ca^{2+} level, and Mg^{2+} level were associated with poor prognosis at 3 months between groups of stroke patients (Table 1).

In the baseline table, we observed that atrial fibrillation and hypertension had statistical differences and might be important factors affecting the poor prognosis of patients at 3 months. Since differences were found in mRS subgroups among hypertensive patients, we are interested in the group of patients with hypertension specifically. Results for further analysis, which is shown in Table S1, showed that the K^+ level and Na^+ level were significantly different between the hypertensive and normal patient groups. Relationships between hypertension and mRS score are presented in Figure 1.

3.2 | Serum Electrolytes and Clinical Outcomes

To explore whether electrolytes can independently predict prognosis and END, we performed logistic regression analysis on the five electrolytes. We found that Na^+ was significant for predicting 3-month poor prognosis (OR = 0.934; CI: 0.875–0.997; $p = 0.039$), 6-month poor prognosis (OR = 0.932; CI: 0.873–0.996; $p = 0.039$), and END (OR = 0.896; CI: 0.811–0.990; $p = 0.031$) in the unadjusted model (Model 1) as well as the model adjusted for age and sex (Model 2), but this significance disappeared after adjusting for all covariates (Model 3). However, Cl^- was consistently predictive of poor prognosis at 3 months, 6 months, and 1 year before and after adjustment, while its predictive ability for END disappeared after adjusting for all covariates (Model 3). After adjusting for all covariates (Model 3), Ca^{2+} was the only predictor of END and Mg^{2+} lost its predictive value for all clinical outcomes. These statistics confirm that Cl^- is an independent predictor of poor prognosis at 3 months (OR = 0.928; CI: 0.865–0.996; $p = 0.038$), 6 months (OR = 0.909; CI: 0.845–0.978; $p = 0.010$), and 1 year (OR = 0.924; CI: 0.857–0.995; $p = 0.037$), while Ca^{2+} is the independent predictor of END (OR = 0.007; CI: 0.000–0.351; $p = 0.013$) (Table 2). This relationship still exists in the sensitivity analysis of adjusted antihypertensive drugs (Table S2).

Furthermore, we divided each of the electrolytes into quintiles and explored their relationship with clinical outcomes, which was shown in Table 3. After quintile analysis of Na^+, we found that in hypertensive patients, concentration of 140.0–142.0 mmol/L was statistically different from the last quintile in terms of prognosis at 3 months; concentration of 138.0–142.0 mmol/L was statistically different from the last quintile in terms of prognosis at 6 months and 1 year; there was no significant difference in END, which means patients with baseline Na^+ levels of 138.0–142.0 mmol/L had a relatively better prognosis than the last quintile compared with higher and lower levels of Na^+.

3.3 | Dose-response Relationship of Serum Electrolytes

We further explored whether there was a dose-response relationship can be captured between the electrolyte levels and the outcomes in the overall population. Nonlinear tests revealed a significant association between Na^+ concentration and poor outcome at 3 months (p for non-linearity = 0.023), 6 months (p for non-linearity = 0.021) as well as at 1 year (p for non-linearity = 0.032). Similarly, there was a significant nonlinear relationship observed between Cl^- concentration and END (p for nonlinearity = 0.014). Conversely, Ca^{2+} concentration exhibited a linear relationship with END (p for linearity < 0.001). Our findings from restricted cubic spline analysis indicated that Na^+ concentration above the upper threshold of 142.6 mmol/L posed a risk factor for poor outcome at 3 months, while concentrations exceeding the upper threshold of 142.7 mmol/L were associated with an increased risk of poor outcome at 6 months. Besides, low levels of K^+ (less than 3.83 mmol/L) and high levels of Na^+ (more than 138.9 mmol/L) are associated with a heightened risk of adverse functional outcomes in the first year. Additionally, patients with Cl^- concentrations above 106.2 mmol/L and Ca^{2+} concentrations below 2.2 mmol/L demonstrated a relatively higher susceptibility to END. This indicates that in the general population, individuals with higher Na^+ concentrations exhibited a relatively poorer prognosis and were at a relatively higher risk of experiencing END compared to those with lower Na^+ concentrations; those with higher Cl^- concentrations also presented a relatively higher risk of early (Figures 2, S2, and S3).

TABLE 1 | Baseline characteristics according to 3-month mRS score.

Variables	Total ($n = 686$)	3-month mRS score		p value
		mRS 0–2 ($n = 444$)	mRS 3–6 ($n = 242$)	
Age (years)	68.0 (59.0–76.0)	65.0 (56.0–73.0)	73.0 (65.0–80.0)	<0.001
Sex (male %)	449 (65.5)	306 (68.9)	143 (59.1)	0.010
Smoking (n %)	242 (37.5)	167 (39.7)	75 (33.3)	0.113
Drinking (n %)	204 (31.7)	141 (33.5)	63 (28.3)	0.174
Baseline NIHSS	6 (4–12)	5 (3–8)	11 (7–16)	<0.001
Medical history				
Atrial fibrillation (n %)	152 (22.2)	78 (17.6)	74 (30.6)	<0.001
Hypertension (n %)	480 (70.0)	294 (66.2)	186 (76.9)	0.004
Diabetes (n %)	174 (25.4)	107 (24.1)	67 (27.7)	0.302
Laboratory data				
Albumin (mmol/L)	37.6 (35.2–39.9)	37.8 (35.4–40.0)	36.9 (34.6–39.4)	0.005
TC (mmol/L)	4.9 (4.1–5.6)	5.0 (4.2–5.7)	4.6 (3.8–5.5)	0.005
TG (mmol/L)	1.3 (0.9–1.8)	1.4 (1.0–1.9)	1.1 (0.9–1.6)	<0.001
HDL-C (mmol/L)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	0.874
LDL-C (mmol/L)	2.8 (2.2–3.3)	2.9 (2.3–3.3)	2.6 (2.0–3.2)	0.003
eGFR (mL/min/1.73 m^2)	92.1 (78.5–103.9)	95.4 (83.8–105.6)	86.2 (71.3–97.9)	<0.001
FPG (mmol/L)	5.5 (4.8–7.2)	5.3 (4.7–6.7)	6.3 (5.1–8.1)	<0.001
Serum electrolyte				
K^+ (mmol/L)	3.8 (3.6–4.0)	3.8 (3.6–4.0)	3.8 (3.5–4.0)	0.223
Na^+ (mmol/L)	140.0 (139.0–142.0)	140.0 (139.0–142.0)	140.0 (138.0–142.0)	0.119
Cl^- (mmol/L)	106.0 (104.0–108.0)	106.0 (104.0–108.0)	105.0 (103.0–107.0)	<0.001
Ca^{2+} (mmol/L)	2.2 (2.2–2.3)	2.2 (2.2–2.3)	2.2 (2.1–2.3)	0.004
P (mmol/L)	1.1 (0.9–1.2)	1.1 (0.9–1.2)	1.1 (0.9–1.2)	0.864
Mg^{2+} (mmol/L)	0.8 (0.8–0.9)	0.9 (0.8–0.9)	0.8 (0.8–0.9)	<0.001
END (n %)	77 (11.2)	16 (3.6)	61 (25.2)	<0.001

Abbreviations: eGFR, estimated glomerular filtration rate; END, early neurological deterioration; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; TC, total cholesterol; TG, triglyceride.

Outcomes of the hypertension subgroup were exhibited in Figures 3 and S3. Nonlinear tests indicated a relationship between Na^+ concentration and 6-month (p for nonlinearity = 0.025) or 1-year (p for nonlinearity = 0.031) poor prognosis as well as Ca^{2+} concentration had a nonlinear relationship with END (p for nonlinearity < 0.001). Hypertensive patients with Na^+ above the upper threshold of 141.0 mmol/L had a relatively worse 6-month prognosis and had a worse 1-year prognosis when Na^+ over 142.0 mmol/L, while Ca^{2+} below 2.2 mmol/L had a relatively higher risk of END. Besides K^+ below 3.73 mmol/L also indicates a higher probability of 1-year poor prognosis. These statistics indicated that higher Na^+ concentration had a relatively worse 6-month and 1-year prognosis, lower K^+ concentration had a relatively worse 1-year prognosis, and lower Ca^{2+} had a relatively higher risk of END.

4 | Discussion

Our study elucidated the association between serum electrolytes, especially baseline serum electrolytes levels, and END as well as poor prognosis, which was also evident in patients with hypertension. These findings underscore the potential importance of serum electrolyte levels as prognostic indicators in stroke patients.

Electrolytes play a crucial role in maintaining normal physiological functions within the human body, and their significance cannot be overstated in the prognosis of patients with AIS. Previous research has indicated a relationship between Ca^{2+} levels and first stroke [9]. In China, stroke is one of the leading causes of death and is a primary contributor to disability-adjusted

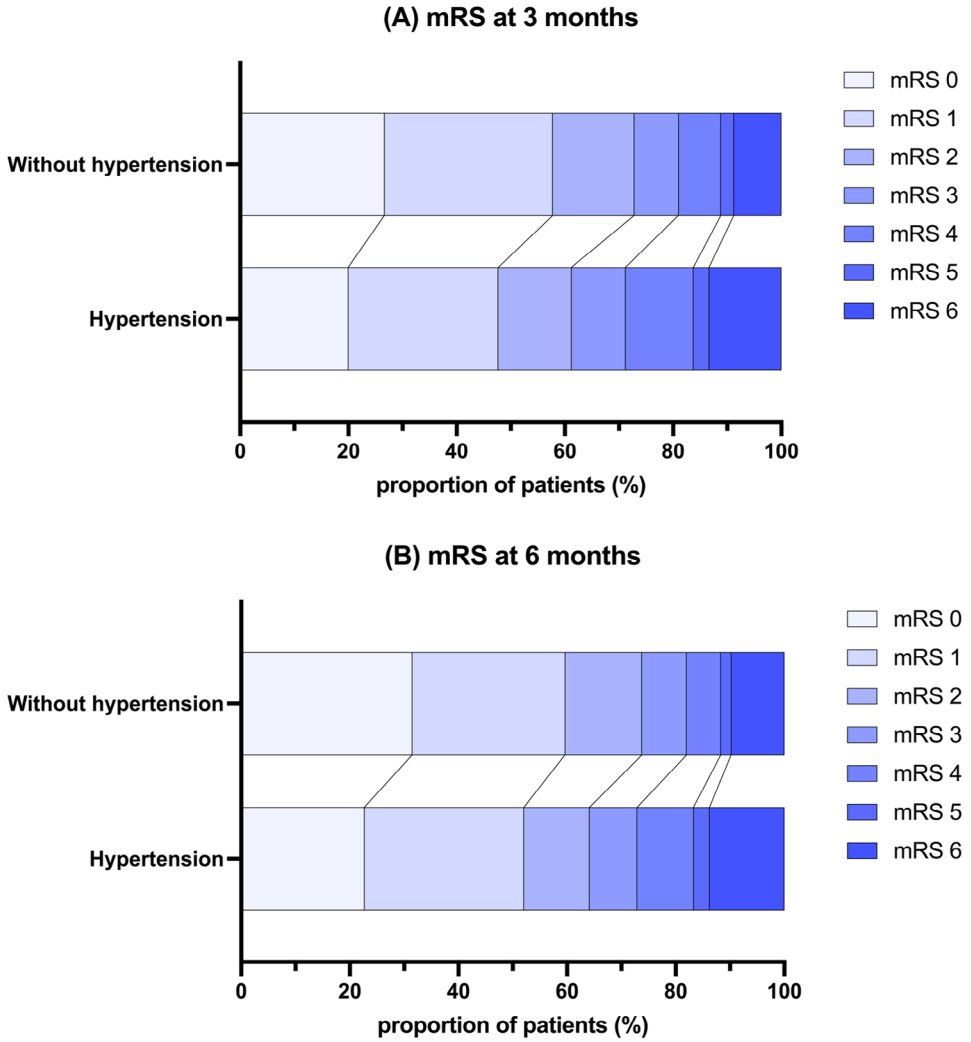

FIGURE 1 | Distribution of modified Rankin scale score between with and without hypertension groups at 3 and 6 months. (A) 3-month mRS distribution condition grouped by hypertension. (B) 6-month mRS distribution condition grouped by hypertension.

life years (DALYs) [10]. Hypertension, with which patients exhibit a higher incidence of stroke, serves as both a risk and contributory factor for stroke in individuals with arteriosclerosis [11, 12]. Prior studies have identified serum electrolytes, for example, Na^+ as potential influencing factors for hypertension [13]. Hence, our specific focus was on the prognosis and END in AIS patients with hypertension. We discovered that patients with relatively higher levels of Na^+ had poorer 6-month and 1-year prognoses, while those with lower Ca^{2+} concentrations faced increased risks of END, suggesting that screening for serum electrolytes in stroke patients could better draw up plans for patient care in prognosis. Assessments conducted 3 months after thrombolysis can promptly identify potential issues that may arise during the early recovery phase, such as the recovery of neurological function and the occurrence of complications. This is crucial for timely adjustments to the treatment plan and rehabilitation program. A 6-month assessment can observe the trend of the patient's condition and understand the mid-term recovery status. This period is a critical time for the recovery of neurological function. By comparing the results with those from the 3-month assessment, it is possible to judge the speed and extent of recovery and evaluate the effectiveness of the rehabilitation treatment. After a year of recovery and treatment, the patient's condition is relatively stable, and the mRS score at this time can accurately reflect the patient's long-term quality of life and functional status. This is important for assessing the long-term effects of thrombolysis treatment, the patient's quality of life, and their ability to reintegrate into society.

Mg^{2+}, an essential element within the human body, plays crucial roles in DNA synthesis, gene transcription and translation, and is vital in regulating muscle contraction, blood pressure, insulin metabolism, cardiac excitability, vascular tone, neurotransmission, and neuromuscular conduction [14, 15]. Mg^{2+} plays an important role in regulating cellular energy status, changing mitochondrial morphology and affecting cell vulnerability against biological stress [16]. On the other hand, Ca^{2+}, one of the most abundant minerals in the human body, is crucial for maintaining bone health, facilitating signal transduction, and regulating hormone secretion. Through Ca^{2+}-binding sites, Ca^{2+} can influence calmodulin and further regulate Cell survival signaling pathways including phosphatidylinositol 3-kinase and Akt, thus affecting neuronal survival [17]. Due to these mechanisms, the levels of Mg^{2+} and Ca^{2+} may have adverse

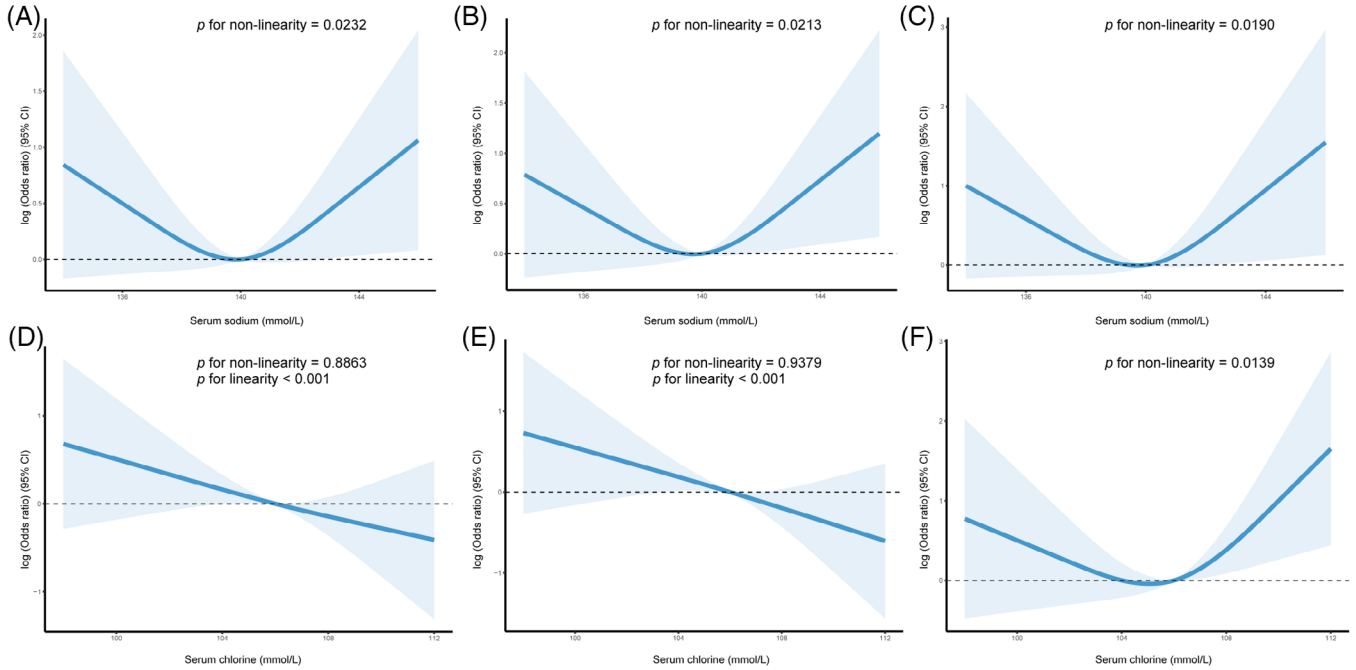

FIGURE 2 | The association between serum electrolytes and clinical outcomes. Adjusted for age, sex, baseline NIHSS, diabetes, triglyceride, eGFR, low-density lipoprotein, and fasting plasma glucose. (A) 3-month mRS with serum sodium. (B) 6-month mRS with serum sodium. (C) END with serum sodium. (D) 3-month mRS with serum Cl^-. (E) 6-month mRS with serum chlorine. (F) END with serum chlorine.

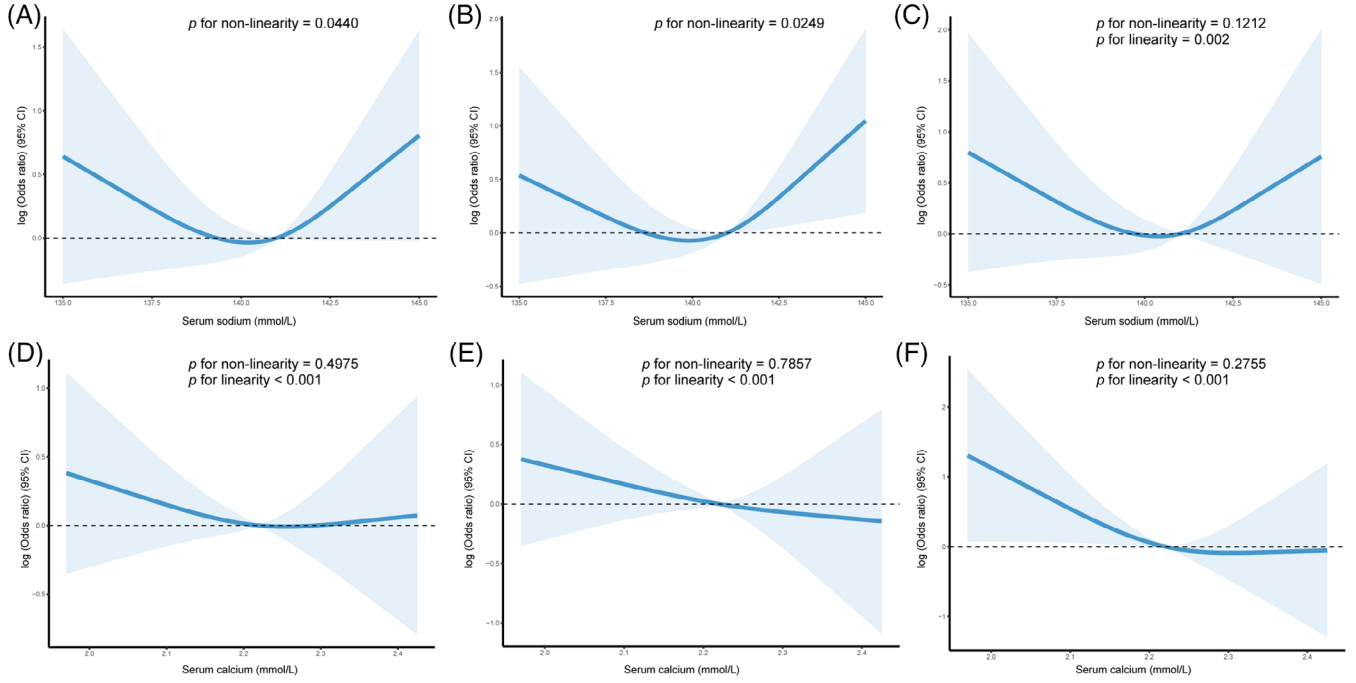

FIGURE 3 | The Association between serum electrolytes and clinical outcomes in hypertension patients.
Adjusted for age, sex, baseline NIHSS, diabetes, triglyceride, eGFR, low-density lipoprotein, and fasting plasma glucose. (A) 3-month mRS with serum sodium. (B) 6-month mRS with serum sodium. (C) END with serum sodium. (D) 3-month mRS with serum calcium. (E) 6-month mRS with serum calcium. (F) END with serum calcium.

TABLE 2 | The association between serum electrolytes and clinical outcomes.

Element	Model 1		Model 2		Model 3	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
3-month mRS						
K^+	0.723 (0.457–1.144)	0.166	0.643 (0.339–1.037)	0.070	0.694 (0.389–1.237)	0.215
Na^+	0.934 (0.875–0.997)	0.039	0.927 (0.867–0.992)	0.029	1.009 (0.928–1.098)	0.828
Cl^-	0.878 (0.832–0.928)	<0.001	0.878 (0.830–0.930)	<0.001	0.928 (0.865–0.996)	0.038
Ca^{2+}	0.087 (0.018–0.434)	0.003	0.151 (0.034–0.666)	0.013	0.268 (0.042–1.692)	0.161
Mg^{2+}	0.005 (0.000–0.074)	<0.001	0.013 (0.001–0.229)	0.003	0.324 (0.012–9.122)	0.508
6-month mRS						
K^+	0.724 (0.454–1.154)	0.174	0.633 (0.389–1.030)	0.066	0.614 (0.339–1.111)	0.107
Na^+	0.932 (0.873–0.996)	0.039	0.926 (0.864–0.993)	0.030	1.017 (0.933–1.109)	0.699
Cl^-	0.869 (0.822–0.919)	<0.001	0.868 (0.819–0.920)	<0.001	0.909 (0.845–0.978)	0.010
Ca^{2+}	0.112 (0.023–0.550)	0.007	0.186 (0.043–0.804)	0.024	0.640 (0.112–3.644)	0.615
Mg^{2+}	0.002 (0.000–0.030)	<0.001	0.005 (0.000–0.100)	0.001	0.223 (0.007–7.124)	0.396
1-year mRS						
K^+	0.715 (0.445–1.149)	0.166	0.608 (0.369–1.002)	0.051	0.597 (0.323–1.104)	0.100
Na^+	0.951 (0.889–1.017)	0.140	0.946 (0.881–1.015)	0.123	1.034 (0.945–1.132)	0.463
Cl^-	0.890 (0.842–0.890)	<0.001	0.890 (0.839–0.944)	<0.001	0.924 (0.857–0.995)	0.037
Ca^{2+}	0.094 (0.018–0.476)	0.004	0.157 (0.036–0.697)	0.015	0.796 (0.138–4.584)	0.798
Mg^{2+}	0.003 (0.000–0.057)	<0.001	0.010 (0.001–0.216)	0.003	0.814 (0.023–28.911)	0.910
END						
K^+	0.792 (0.386–1.623)	0.524	0.788 (0.383–1.581)	0.488	1.025 (0.432–2.431)	0.956
Na^+	0.896 (0.811–0.990)	0.031	0.896 (0.811–0.989)	0.029	0.976 (0.865–1.100)	0.688
Cl^-	0.948 (0.874–1.028)	0.199	0.952 (0.878–1.032)	0.231	1.019 (0.922–1.125)	0.716
Ca^{2+}	0.013 (0.001–0.158)	0.001	0.015 (0.001–0.188)	0.001	0.007 (0.000–0.351)	0.013
Mg^{2+}	0.001 (0.000–0.060)	0.001	0.001 (0.000–0.071)	0.001	0.020 (0.000–2.250)	0.104

Note: Model 1: unadjusted; Model 2: adjusted for age, sex; Model 3: adjusted for age, sex, baseline NIHSS, atrial fibrillation, hypertension, albumin, eGFR, total cholesterol, triglyceride, low-density lipoprotein cholesterol, and fasting plasma glucose.

Abbreviations: CI, confidence interval; END, early neurological deterioration; mRS, modified Rankin Scale; OR, odd ratio.

effects on the prognosis of patients. Hypernatremia increases extracellular fluid osmolarity, reducing intracellular volume and directly causing neural damage, thereby affecting the prognosis of stroke patients. Animal experiments have demonstrated that increases in extracellular Na^+ concentration within physiological ranges can elevate vascular von Willebrand factor (vWF) levels, thus increasing coagulability and the risk of thrombosis [18]. K^+ play a crucial role in regulating the ionic and osmotic gradients of cell membranes, and the primary mechanism by which they affect blood pressure is thought to be through sodium-potassium ATPase-mediated hyperpolarization of vascular smooth muscle [19]. Our findings revealed that stroke patients, especially those with hypertension, who had relatively lower Ca^{2+} levels, faced higher risks of END; stroke patients with higher Na^+ concentrations, including those with hypertension, tended to have poorer long-term prognoses. Our results are consistent with these mechanisms.

The strengths of our research are as follows. First, we comprehensively investigated the correlation between serum electrolytes and prognosis as well as END in AIS patients. This means that measuring electrolytes can become an effective means of predicting a patient's neurological function. Although Ca^{2+} and Na^+ lost statistical significance in Model 3, they cannot be ignored. The relationship between K^+ and prognosis is equally important, although it only has obvious statistical significance with 1-year mRS. Besides, we also explore the dose-response relationship between serum electrolyte concentration and outcomes in the general population, emphasizing its cutoff value of serum electrolytes, which can provide guidance for clinical practice. Lastly, we analyzed hypertension as a subgroup, filling the blank of previous electrolyte research in the field of hypertensive patients' prognosis.

Our study has several limitations. First, the current research may be affected by residual confounding factors. Although we had adjusted for many confounders, some potential confounders, such as physical activity or dietary habits, could not be adjusted for because of data deficiency. Besides, the included population was all Chinese, which may limit the applicability

TABLE 3 | Associations of serum electrolytes with clinical outcomes in hypertension patients.

Element	3-month mRS		6-month mRS		1-year mRS		END	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
K^+								
Q1 (≤3.52 mmol/L)	0.901 (0.437–1.857)	0.777	1.122 (0.531–2.373)	0.762	1.493 (0.687–3.246)	0.312	0.919 (0.330–2.556)	0.871
Q2 (3.52–3.73 mmol/L)	0.878 (0.416–1.850)	0.731	0.923 (0.421–2.026)	0.842	1.073 (0.473–2.433)	0.866	1.064 (0.376–3.010)	0.907
Q3 (3.73–3.91 mmol/L)	0.673 (0.311–1.456)	0.314	0.943 (0.426–2.084)	0.884	1.062 (0.465–2.429)	0.886	0.469 (0.136–1.617)	0.230
Q4 (3.91–4.08 mmol/L)	0.798 (0.368–1.729)	0.567	0.895 (0.402–1.990)	0.785	0.827 (0.358–1.911)	0.657	0.591 (0.180–1.942)	0.386
Q5 (>4.08 mmol/L)	Ref.		Ref.		Ref.		Ref.	
Na^+								
Q1 (≤138.0 mmol/L)	0.670 (0.311–1.440)	0.305	0.571 (0.261–1.253)	0.162	0.528 (0.233–1.199)	0.127	0.997 (0.358–2.777)	0.995
Q2 (138.0–140.0 mmol/L)	0.566 (0.283–1.132)	0.107	0.478 (0.235–0.975)	0.042	0.428 (0.205–0.894)	0.024	0.463 (0.160–1.339)	0.155
Q3 (140.0–141.0 mmol/L)	0.419 (0.194–0.904)	0.027	0.406 (0.185–0.893)	0.025	0.463 (0.209–1.028)	0.059	0.690 (0.233–2.048)	0.504
Q4 (141.0–142.0 mmol/L)	0.032 (0.141–0.780)	0.011	0.266 (0.109–0.651)	0.004	0.260 (0.103–0.657)	0.004	0.496 (0.137–1.790)	0.284
Q5 (>142.0 mmol/L)	Ref.		Ref.		Ref.		Ref.	
Cl^-								
Q1 (≤103.0 mmol/L)	2.028 (0.940–4.372)	0.071	2.070 (0.940–4.558)	0.071	1.887 (0.831–4.281)	0.129	0.566 (0.193–1.661)	0.300
Q2 (103.0–105.0 mmol/L)	1.299 (0.661–2.750)	0.489	1.409 (0.656–3.027)	0.380	1.340 (0.613–2.933)	0.463	0.760 (0.282–2.049)	0.587
Q3 (105.0–107.0 mmol/L)	1.348 (0.661–2.750)	0.411	1.255 (0.597–2.638)	0.549	0.934 (0.430–2.031)	0.864	0.531 (0.194–1.449)	0.216
Q4 (107.0–108.0 mmol/L)	1.175 (0.456–3.029)	0.739	1.419 (0.538–3.745)	0.479	2.279 (0.866–6.001)	0.095	0.581 (0.143–2.369)	0.449
Q5 (>108.0 mmol/L)	Ref.		Ref.		Ref.		Ref.	
Ca^{2+}								
Q1 (≤2.12 mmol/L)	1.063 (0.445–2.537)	0.891	1.158 (0.473–2.835)	0.749	0.958 (0.370–2.477)	0.929	2.054 (0.606–6.964)	0.248
Q2 (2.12–2.19 mmol/L)	1.227 (0.530–2.840)	0.633	1.208 (0.505–2.835)	0.671	1.715 (0.680–4.326)	0.253	2.186 (0.638–7.489)	0.213
Q3 (2.19–2.24 mmol/L)	1.013 (0.422–2.431)	0.977	1.142 (0.463–2.816)	0.773	1.355 (0.521–3.523)	0.533	0.809 (0.196–3.349)	0.770
Q4 (2.24–2.30 mmol/L)	0.889 (0.365–2.165)	0.796	0.794 (0.310–2.033)	0.631	0.933 (0.347–2.504)	0.890	0.918 (0.224–3.763)	0.905
Q5 (>2.30 mmol/L)	Ref.		Ref.		Ref.		Ref.	
Mg^{2+}								
Q1 (≤0.77 mmol/L)	0.981 (0.381–2.525)	0.969	1.416 (0.582–3.918)	0.503	1.193 (0.403–3.535)	0.750	2.700 (0.623–11.707)	0.184
Q2 (0.77–0.81 mmol/L)	1.105 (0.396–3.081)	0.848	1.768 (0.582–5.370)	0.315	2.573 (0.788–8.397)	0.117	3.025 (0.619–14.790)	0.172
Q3 (0.81–0.86 mmol/L)	0.948 (0.360–2.500)	0.915	1.338 (0.467–3.830)	0.588	1.398 (0.454–4.308)	0.560	1.474 (0.310–7.016)	0.626
Q4 (0.86–0.90 mmol/L)	0.837 (0.322–2.175)	0.715	1.385 (0.490–3.919)	0.539	1.858 (0.625–5.526)	0.265	2.035 (0.457–9.061)	0.351
Q5 (>0.90 mmol/L)	Ref.		Ref.		Ref.		Ref.	

Note: Adjusted for age, sex, baseline NIHSS, diabetes, triglyceride, eGFR, low-density lipoprotein cholesterol, and fasting plasma glucose.

Abbreviations: CI, confidence interval; END, early neurological deterioration; mRS, modified Rankin Scale; OR, odd ratio.

of the conclusion to other populations. Moreover, due to the retrospective nature of our study, causality cannot be established. We only measured serum electrolyte concentrations at baseline and did not continuously monitor them during hospitalization or follow-up, which hinders further understanding of the relationship between dynamic serum electrolyte concentrations and outcomes. Future investigations should aim to explore this area in more detail. Our findings contribute to a deeper understanding of the role of electrolyte disorders in the pathogenesis of AIS. By elucidating the relationship between serum electrolyte levels and stroke outcomes, we provide valuable insights that can inform novel approaches for the prevention and treatment of AIS. In clinical practice, by monitoring the electrolyte levels of patients with AIS, evaluating their condition, developing personalized treatment plans, and adjusting the dosage and type of drugs, we can improve their neurological function and enhance their rehabilitation outcomes.

5 | Conclusion

Overall, our study demonstrates that in the general population, Cl^- is an independent predictor of 3-month and 6-month poor prognosis and Ca^{2+} is an independent predictor of END. Besides, patients with relatively higher Na+ concentrations have relatively poorer outcomes and higher risks of END; relatively higher Cl^- concentrations are associated with a higher risk of END and lower Ca^{2+} levels are associated with a higher risk of END. In the hypertensive population, higher Na^+ concentrations are associated with poorer 6-month outcomes and lower Ca^{2+} levels pose a higher risk of END.

Author Contributions

Conceptualization and design: Yiyun Weng and Guangyong Chen. Methodology: Shengli Pan, Bohuai Yu, and Yilin Chen. Validation: Shengli Pan, Bohuai Yu, and Yilin Chen. Formal analysis: Shengli Pan, Bohuai Yu, Yilin Chen, Yufan Gao, and Wei Xie. Investigation: Yiyun Weng, Guangyong Chen, and Shengli Pan. Resources: Yiyun Weng and Guangyong Chen. Data curation: Shengli Pan, Bohuai Yu, Yilin Chen, Yufan Gao, Wei Xie, Yining Jin, Guoliang Zhou, Jialing Lou, Rui Zhang, and Chao Chen. Writing–original draft preparation: Shengli Pan, Bohuai Yu, and Yilin Chen. Writing–review and editing: Shengli Pan, Bohuai Yu, Yilin Chen, Yufan Gao, Wei Xie, Yining Jin, Guoliang Zhou, Jialing Lou, Rui Zhang, and Chao Chen. Visualization: Shengli Pan, Bohuai Yu, and Yilin Chen. Supervision: Yiyun Weng and Guangyong Chen. Project administration: Yiyun Weng and Guangyong Chen.

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Ethics Statement

Ethical approval was obtained from the hospital's institutional review board.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.