Electrolytes and clinical outcomes in patients with acute ischemic stroke or transient ischemic attack

Anxin Wang[1,2], Xue Tian[3,4], Hongqiu Gu[1,2], Yingting Zuo[3,4], Xia Meng[1,2], Pan Chen[1,2], Hao Li[1,2], Yongjun Wang[1,2]

[1]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [2]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [3]Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, Beijing, China; [4]Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, China

Contributions: (I) Conception and design: Y Wang, A Wang; (II) Administrative support: Y Wang; (III) Provision of study materials or patients: X Meng, P Chen, H Li, Y Wang; (IV) Collection and assembly of data: A Wang, H Gu; (V) Data analysis and interpretation: A Wang, X Tian, Y Zuo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yongjun Wang, MD. China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, No. 119 South 4th Ring West Road, Fengtai District, Beijing 100070, China. Email: yongjunwang@ncrcnd.org.cn.

Background: Abnormal electrolytes were closely related to the prognosis of various diseases, the prognostic role of electrolytes in stroke has not been investigated well. We aimed to investigate the association between electrolytes and clinical outcomes in patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA).

Methods: Data were recruited from the China National Stroke Registry III study. Patients were classified into three groups according to tertiles and the normal range of each electrolyte. Multivariable logistic and Cox proportional hazards regressions were adopted to explore the associations of electrolytes with poor functional outcomes [modified Rankin Scale (mRS) 3–6/2–6] and all-cause death at 3 months and 1 year.

Results: A total of 10,299 eligible patients were enrolled. After adjusted for confounding factors, the first tertile electrolytes were associated with increased risk of poor functional outcome (mRS score 3–6) at 1 year, the adjusted odds ratios (95% confidence intervals) were 1.33 (1.14–1.55) for potassium, 1.41 (1.20–1.60) for sodium, 1.27 (1.08–1.48) for chloride, compared with the second tertile. Similar results were found when poor functional outcome was defined as mRS score 2–6 and all-cause death. However, almost no significant association was present of calcium with these outcomes. All results were consistent when each electrolyte was classified into three groups according to the normal range and the outcomes timepoint was set at 3 months.

Conclusions: Lower levels of potassium, sodium, chloride but not calcium were associated with higher risk of poor functional outcomes and death in patients with AIS or TIA.

Keywords: Electrolytes; acute ischemic stroke (AIS); transient ischemic attack (TIA); clinical outcomes

Introduction

Ischemic stroke and transient ischemic attack (TIA) are common cerebrovascular diseases and associated with high disability and mortality rates (1). The world health organization has reported that approximately 15 million people suffer a stroke annually, of which 5 million are fatal and 5 million result in permanent disability (2). Identifying and controlling stroke-related risk factors would be extremely important in the treatment and secondary prevention of stroke.

Electrolyte disorders as a complication of dehydration,

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diabetes, renal failure, or myocardial infraction are frequently observed in clinical practice (3-5). Hypokalemia, hyponatremia, hypochloremia, and hypocalcemia were common electrolyte abnormalities encountered in clinical practice. Previous studies have demonstrated that these electrolyte disorders were also closely related to the prognosis of heart failure (6), acute coronary syndrome (7), chronic kidney disease (8), hypertension (9) intracerebral hemorrhage (8), and acute pancreatitis (10). Although some studies have investigated the prognosis role of hypokalemia, hyponatremia, and hypochloremia in stroke, the sample size was small and the results were conflicting (11-17). Furthermore, limited data from large multicenter prospective studies were available to evaluate the role of electrolytes in the prognosis of stroke, and the associations of each electrolyte category with short- and long-term outcomes in patients with stroke have not been investigate well.

Therefore, in the present study, we aimed to investigate the associations of electrolytes (potassium, sodium, chloride, and calcium) with poor functional outcomes and all-cause death among patients with acute ischemic stroke (AIS) or TIA at the time point of 3 months and 1 year, using data from the multicenter cohort of the Third China National Stroke Registry (CNSR-III). We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-741).

Methods

Study population

Data were derived from the CNSR-III, which is a nationwide prospective registry for patients presented to hospitals with acute ischemic cerebrovascular events. The registry recruited patients consecutively from 201 hospitals of 22 provinces and four municipalities between August 2015 and March 2018 in China. Finally, 15,166 patients with AIS or TIA within 7 days from the onset of symptoms were enrolled. The design of the CNSR-III has been described in detail previously (18). The CNSR-III was approved by ethics committees of Beijing Tiantan Hospital and all participating centers. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants or their legal proxies have provided written informed consent. The study was approved by the ethics committee of Beijing Tiantan Hospital (No.: KY2015-001-01) and all study centers gave ethical approval

of the study protocol.

Baseline data collection

Baseline data were collected through a direct interview or medical records, including age, sex, body mass index (BMI, kg/m^2), medical history of hypertension, diabetes mellitus, dyslipidemia, stroke or TIA, atrial fibrillation or flutter, peripheral vascular disease, heart failure; stroke types (IS or TIA), the etiology classification of ischemic stroke performed according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria (19), smoking status, medication use (including using of cholesterol-lowering, antihypertensive, antidiabetic, antiplatelet, and anticoagulant agents); National Institutes of Health Stroke Scale (NIHSS); time from onset of symptoms to admission, and laboratory test of plasm lipids, fasting blood glucose (FBG), estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hs-CRP).

Electrolyte testing and definition of electrolyte abnormalities

Fasting serum and plasma specimens were extracted and transported through cold chain to the core laboratory in Beijing Tiantan Hospital. All specimens were stored at –80 ℃ until detected centrally and blindly. Concentrations of serum electrolytes were analyzed by automated hematology analyzer. All measurements were performed by laboratory personnel who were blinded to patients' clinical situations.

Follow-up and outcome evaluation

Participants were followed-up via face-to-face or telephone interview at for clinical outcomes at 3 months and 1 year by trained research personnel. Poor functional outcome was defined as modified Rankin Scale (mRS) score ranged 3–6/2–6. All-cause death was defined as death from any cause and was confirmed on a death certification from the participating hospital or the local citizen registry.

Statistical analysis

Continuous variables were presented as medians and interquartile range because of skewed distribution. Categorical variables were presented as frequencies and percentages. The nonparametric Wilcoxon or Kruskal-Wallis test were used to compare group differences for

continuous variables, and chi-square tests were used for categorical variables.

In the main analyses, participants were divided into three groups by electrolyte tertiles for each electrolyte category, and the second tertile was defined as the reference group. The associations of electrolytes with poor functional outcomes and all-cause death were investigated with logistic regression and Cox proportional hazard models, respectively. Unadjusted and adjusted models were constructed, the adjusted model was adjusted for all variables at baseline. The robust sandwich estimator for the covariance matrix was used in the models accounting for the clustering effect at the hospital level. In addition, to capture the dose-response relationship, the association between electrolytes and the outcomes on a continuous scale was examined using restricted cubic splines, with 3 knots at the 10th, 50th, 90th percentiles of each electrolytes distribution (20). Reference points for serum potassium, sodium, chloride, and calcium were the median (3.93, 141, 104, and 2.25 mmol/L, respectively) of the reference group (the second tertile), and odds ratio (OR)/hazard ratio (HR) was adjusted for all confounding variables. Furthermore, ordinal logistic regression was applied to estimate the common odds ratio for a shift in the direction of a worse outcome on the mRS score at both 3 months and 1 year according to each electrolyte category.

In the secondary analysis, we aimed to determine the association of hypoelectrolytemia and hyperelectrolytemia with these outcomes. The participants were classified into 3 groups according to normal range of electrolytes, and those with normal range were taken as the reference. The reference range of serum potassium, sodium, chloride, and calcium were 3.5–4.7 mmol/L (21), 135–145 mmol/L (21), 98–109 mmol/L (16,22), and 2.25–2.58 mmol/L (21), respectively. Values less than the lower range were considered as hypoelectrolytemia, and values greater than the upper range as hyperelectrolytemia.

Statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were 2-sided and the significance level was set at 0.05.

Results

Baseline characteristics

We excluded 4,533 patients without available data on electrolytes, and 334 patients with missing available mRS at the time point of 3 months or 1 year, therefore, a total of 10,299 patients were eligible for the current analysis. The included patients had less men, were more likely to have a history of dyslipidemia, higher total cholesterol, high-density lipoprotein cholesterol, FBG and hs-CRP level, and a lower proportion of IS, large-artery atherosclerosis, cholesterol-lipid agents, lower eGFR, sodium and chloride levels (Table S1 in the online-only data supplement).

Baseline characteristics of the patients stratified by survival status are presented in *Table 1*. The median age of the included patients was 63 years, and 6,980 (67.77%) were men. The median (interquartile range) of potassium, sodium, chloride, and calcium were 3.93 (3.68–4.19), 141.00 (139.00–142.70), 104.00 (101.70–1.06.10), and 2.25 (2.17–2.34) mmol/L, respectively. The survivors were younger, had more men, higher BMI, more current smokers, antiplatelet agents takers, a higher proportion of NIHSS ≤15, higher TG, eGFR, sodium, chloride, and calcium levels; and were less likely to have a history of stroke, arterial fibrillation/flutter, heart failure, a lower proportion of IS, large-artery atherosclerosis, anticoagulant agents, lower baseline NIHSS score, FBG and hs-CRP levels than non-survivors. Moreover, compared with patients without poor functional outcomes (mRS score <3 or 2), those with poor functional outcomes had the similar pattern of baseline characteristic (Table S2 in the online-only data supplement).

Association of electrolytes with poor functional outcomes

Poor functional outcome (mRS score 3–6) occurred in 1,477 (14.34%) patients and mRS score 2–6 occurred in 2,787 (27.06%) patients at 3 months, while at 1-year follow-up, 1,396 (13.55%) patients had mRS score 3–6, 2,503 (24.30) patients had mRS score 2–6.

The association between electrolytes and poor functional outcomes are presented as *Table 2* and *Figure 1*. At the time point of 1 year, after adjusted for potential covariates, electrolytes in the first tertile group were associated with increased risk of poor functional outcome (mRS score 3–6), the adjusted ORs with 95% CIs were 1.33 (1.14–1.55) for potassium, 1.41 (1.20–1.60) for sodium, and 1.27 (1.08–1.48) for chloride, compared with the second tertile of electrolytes. Multivariable-adjusted spline regression models showed L-shaped associations of potassium, sodium, and chloride with the risk of poor functional outcome (mRS score 3–6) (*Figure 2A,B,C*). Furthermore, there were significant shifts in the distribution of the mRS scores

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Table 1 Baseline characteristics of patients according to survival status at 1 year

Characteristics	Overall (n=10,299)	Survivors (n=9,974)	Non-survivors (n=325)	P value
Age, y	63 [54–70]	62 [54–70]	71 [64–79]	<0.0001
Men, n (%)	6,980 (67.77)	6,785 (68.03)	195 (60.00)	0.0023
BMI, kg/m^2	24.49 (22.58–26.57)	24.49 (22.6–26.57)	23.67 (21.22–25.95)	<0.0001
Medical history, n (%)				
Hypertension	6,438 (62.51)	6,226 (62.42)	212 (65.23)	0.3034
Diabetes mellitus	2,365 (22.96)	2,282 (22.88)	83 (25.54)	0.2620
Dyslipidemia	869 (8.44)	850 (8.52)	19 (5.85)	0.0876
Stroke or TIA	2,244 (21.79)	2,132 (21.38)	112 (34.46)	<0.0001
Atrial fibrillation/flutter	714 (6.93)	638 (6.40)	76 (23.38)	<0.0001
Peripheral vascular disease	74 (0.72)	71 (0.71)	3 (0.92)	0.6573
Heart failure	69 (4.62)	58 (4.18)	11 (10.58)	0.0027
Stroke type/subtype, n (%)				
Ischemic stroke	9,575 (92.97)	9,257 (92.81)	318 (97.85)	0.0005
TIA	724 (7.03)	717 (7.19)	7 (2.15)	
TOAST, n (%)				
Large-artery atherosclerosis	2,600 (25.25)	2,499 (25.06)	101 (31.08)	<0.0001
Cardioembolism	633 (6.15)	591 (5.93)	42 (12.92)	
Small-vessel occlusion	2,086 (20.25)	2,063 (20.68)	23 (7.08)	
Other determined etiology	134 (1.30)	125 (1.25)	9 (2.77)	
Undetermined etiology	4,846 (47.05)	4,696 (47.08)	150 (46.15)	
Current smoker, n (%)	3,200 (31.07)	3,138 (31.46)	62 (19.08)	<0.0001
Medication in hospital, n (%)				
Cholesterol-lowering agents	9,813 (95.97)	9,509 (96.02)	304 (94.41)	0.1479
Antihypertensive agents	4,784 (46.79)	4,629 (46.74)	155 (48.14)	0.6219
Hypoglycemic agents	2,555 (24.99)	2,477 (25.01)	78 (24.22)	0.7476
Antiplatelet agents	9,935 (97.16)	9,642 (97.36)	293 (90.99)	<0.0001
Anticoagulant agents	1,061 (10.38)	1,007 (10.17)	54 (16.77)	0.0001
NIHSS score on admission	3 [1–6]	3 [1–6]	6 [3–12]	<0.0001
≤15, n (%)	10,063 (97.71)	9,782 (98.07)	281 (86.46)	<0.0001
>15, n (%)	236 (2.29)	192 (1.93)	44 (13.54)	
Time from onset of symptoms to admission, h	14.00 (2.00–45.00)	14.00 (3.00–46.00)	12.00 (3.00–33.00)	0.0733
Lipid level				
TC, mmol/L	4.02 (3.35–4.78)	4.01 (3.35–4.78)	4.08 (3.36–4.83)	0.7888
LDL, mmol/L	2.34 (1.74–3.01)	2.34 (1.73–3.00)	2.51 (1.87–3.17)	0.0732

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Overall (n=10,299)	Survivors (n=9,974)	Non-survivors (n=325)	P value
HDL, mmol/L	0.94 (0.78–1.13)	0.94 (0.78–1.13)	0.99 (0.78–1.18)	0.1647
TG, mmol/L	1.37 (1.03–1.87)	1.37 (1.03–1.88)	1.20 (0.90–1.64)	0.0001
FBG, mmol/L	5.56 (4.90–6.91)	5.55 (4.90–6.90)	6.01 (5.06–7.78)	0.0023
eGFR, mL/min/1.73 m^2	92.93 (80.85–101.84)	93.17 (81.38–102.10)	83.09 (65.99–92.99)	<0.0001
Hs-CRP, mg/L	1.84 (0.82–4.83)	1.79 (0.81–4.63)	5.92 (1.57–23.73)	<0.0001
Potassium, mmol/L	3.93 (3.68–4.19)	3.93 (3.69–4.19)	3.90 (3.60–4.26)	0.5750
Sodium, mmol/L	141.00 (139.00–142.70)	141.00 (139.00–142.70)	140.00 (137.50–142.40)	0.0005
Chloride, mmol/L	104.00 (101.70–1.06.10)	104.00 (101.70–106.10)	103.20 (100.31–106.00)	0.0026
Calcium, mmol/L	2.25 (2.17–2.34)	2.25 (2.17–2.34)	2.23 (2.14–2.33)	0.0047

Continuous variables are expressed as median with interquartile range. Categorical variables are expressed as frequency with percentage. BMI, body mass index; TIA, transient ischemic Attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, The National Institutes of Health Stroke Scale; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein.

Table 2 Adjusted odds ratio (95% confidence interval) for poor functional outcome (mRS score 3–6) according to tertiles of serum electrolyte indicators

Electrolyte indicator	Tertiles	mRS score 3–6 at 3 months			mRS score 3–6 at 1 year		
		Events, n (%)	Unadjusted	Adjusted[†]	Events, n (%)	Unadjusted	Adjusted[†]
Potassium, mmol/L	T1 (<3.78)	592 (17.28)	1.38 (1.20–1.59)	1.20 (1.12–1.51)	556 (16.23)	1.39 (1.21–1.61)	1.33 (1.14–1.55)
	T2 (3.78–4.09)	432 (12.85)	Reference	Reference	406 (12.08)	Reference	Reference
	T3 (>4.09)	453 (12.90)	1.06 (0.91–1.23)	1.07 (0.91–1.25)	434 (12.36)	1.09 (0.94–1.27)	1.09 (0.92–1.28)
Sodium, mmol/L	T1 (<139.70)	598 (17.45)	1.41 (1.22–1.63)	1.22 (1.13–1.55)	561 (16.37)	1.49 (1.28–1.73)	1.41 (1.20–1.60)
	T2 (139.70–141.90)	398 (12.90)	Reference	Reference	361 (11.70)	Reference	Reference
	T3 (>141.90)	481 (12.70)	1.00 (0.86–1.16)	1.01 (0.86–1.19)	474 (12.51)	1.13 (0.97–1.32)	1.13 (0.96–1.33)
Chloride, mmol/L	T1 (<102.50)	578 (16.91)	1.40 (1.21–1.61)	1.30 (1.11–1.52)	534 (15.62)	1.35 (1.17–1.56)	1.27 (1.08–1.48)
	T2 (102.50–105.47)	445 (13.02)	Reference	Reference	424 (12.40)	Reference	Reference
	T3 (>105.47)	454 (13.11)	0.91 (0.78–1.05)	0.92 (0.78–1.08)	438 (12.56)	0.94 (0.81–1.09)	0.94 (0.80–1.11)
Calcium, mmol/L	T1 (<2.20)	526 (15.47)	1.04 (0.90–1.20)	0.99 (0.85–1.16)	527 (15.50)	1.11 (0.96–1.28)	1.05 (0.90–1.22)
	T2 (2.20–2.30)	497 (14.19)	Reference	Reference	476 (13.59)	Reference	Reference
	T3 (>2.30)	454 (13.36)	0.95 (0.82–1.10)	1.00 (0.85–1.16)	393 (11.57)	0.81 (0.70–0.94)	0.85 (0.72–1.00)

[†], adjusted for age, gender, body mass index, history of hypertension, diabetes mellitus, dyslipidemia, stroke or TIA, atrial fibrillation/flutter, peripheral vascular disease, heart failure, stroke type, TOAST, current smoke, cholesterol-lowering agents, antihypertensive agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, NIHSS, time from onset of symptoms to admission, total cholesterol, high-density cholesterol lipoprotein, fasting blood glucose, estimated glomerular filtration rate, and high sensitivity C-reactive protein. mRS, modified Rankin Scale.
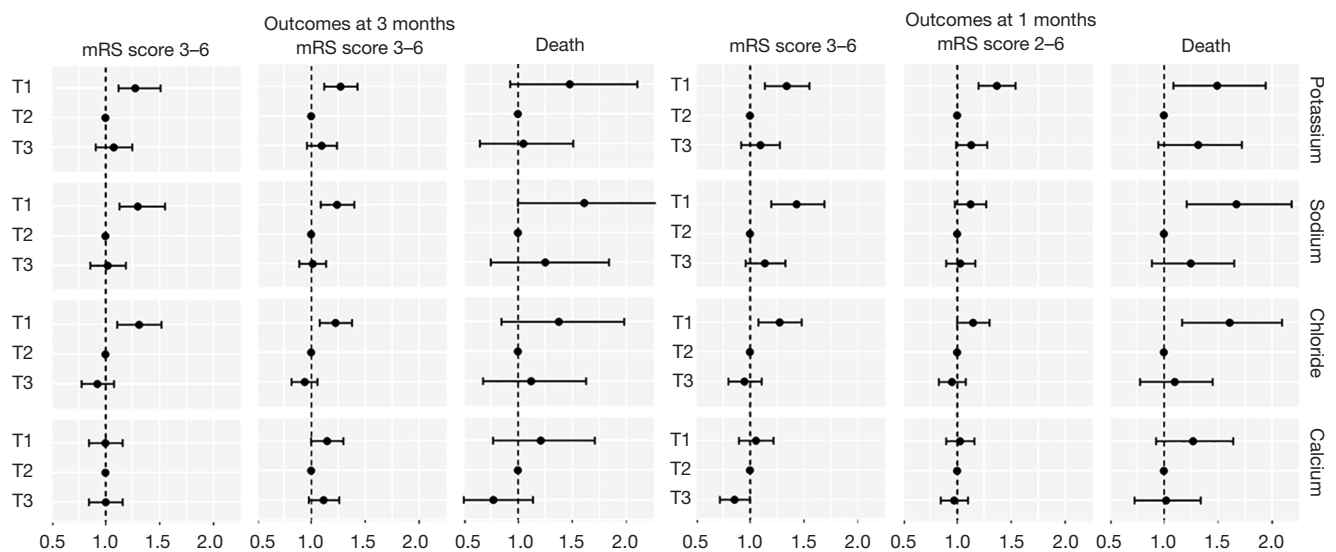
Figure 1 The odds ratio/hazard ratio and 95% confidence interval of poor functional outcomes (mRS score 3–6/2–6) and all-cause death at 3 months and 1 year by quartiles of potassium, sodium, chloride, and calcium in the adjusted model. Adjusted for age, gender, body mass index, history of hypertension, diabetes mellitus, dyslipidemia, stroke or TIA, atrial fibrillation/flutter, peripheral vascular disease, heart failure, stroke type, TOAST, current smoke, cholesterol-lowering agents, antihypertensive agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, NIHSS, total cholesterol, high-density cholesterol lipoprotein, fasting blood glucose, estimated glomerular filtration rate, and high sensitivity C-reactive protein. mRS, modified Rankin Scale.

according to the levels of potassium, sodium, chloride (Figure S1 in the online-only data supplement). However, calcium was not related to poor functional outcome (mRS score 3–6) in above analyses (*Figure 2D*). These relationships were consistent at 3 months (*Table 2*, *Figure 1*, and Figure S1 in the online-only data supplement).

Similar results were observed for the association of hypokalemia (adjusted OR, 1.37; 95% CI, 1.15–1.63), hyponatremia (adjusted OR, 1.66; 95% CI, 1.22–2.25), hypochloremia (adjusted OR, 1.59; 95% CI, 1.24–2.04) and hypocalcemia (adjusted OR, 1.09; 95% CI, 0.95–1.25) with poor functional outcome (mRS score 3–6) in the secondary analysis (Tables S3-S6 in the online-only data supplement). Additional, hyperkalemia was related to 46% higher risk of mRS score 3–6 at 1 year (Table S3 in the online-only data supplement).

Same pattern of results was observed when poor functional outcome was defined as mRS score 2–6 except that calcium in the first tertile (adjusted OR, 1.14; 95% CI, 1.00–1.30) was slightly related to a higher risk of poor functional outcome (mRS score 2–6) at 3 months (*Table 2*, *Figure 2E,F,G,H*, Tables S3-S7, and Figure S1 in the online-only data supplement).

Associations of electrolytes and all-cause death

A total of 158 (1.53%) and 325 (3.16) patients ended up with death at 3 months and 1 year follow-up. In the adjusted model, the relationship of the first tertile of potassium, sodium and chloride were also associated with elevated risk of all-cause death at 1 year follow-up, the adjusted HRs with 95% CIs were 1.45 (1.09–1.94), 1.62 (1.21–2.18) and 1.56 (1.17–2.09), respectively. No significant association was presented for calcium (*Table 3*, *Figure 1*).

Secondary analysis for the relationship of hypoelectrolytemia and all-cause death at 1 year yielded the similar results. Hyponatremia (adjusted HR, 1.58; 95% CI, 1.16–2.15), hyponatremia (adjusted HR, 2.02; 95% CI, 1.30–3.15), and hypochloremia (adjusted HR, 1.86; 95% CI, 1.26–2.77) were associated with increased risk of all-cause (Tables S3-S6 in the online-only data supplement). We also found that hyperkalemia (adjusted HR, 1.87; 95% CI, 1.14–3.07) increased the risk of all-cause death. Nevertheless, there was no significant association of hypocalcemia with all-cause mortality (*Table 3* and Table S6 in the online-only data supplement). Subgroup analysis stratified by stroke subtypes showed the association between electrolytes and all-cause mortality was consistent across patients with IS
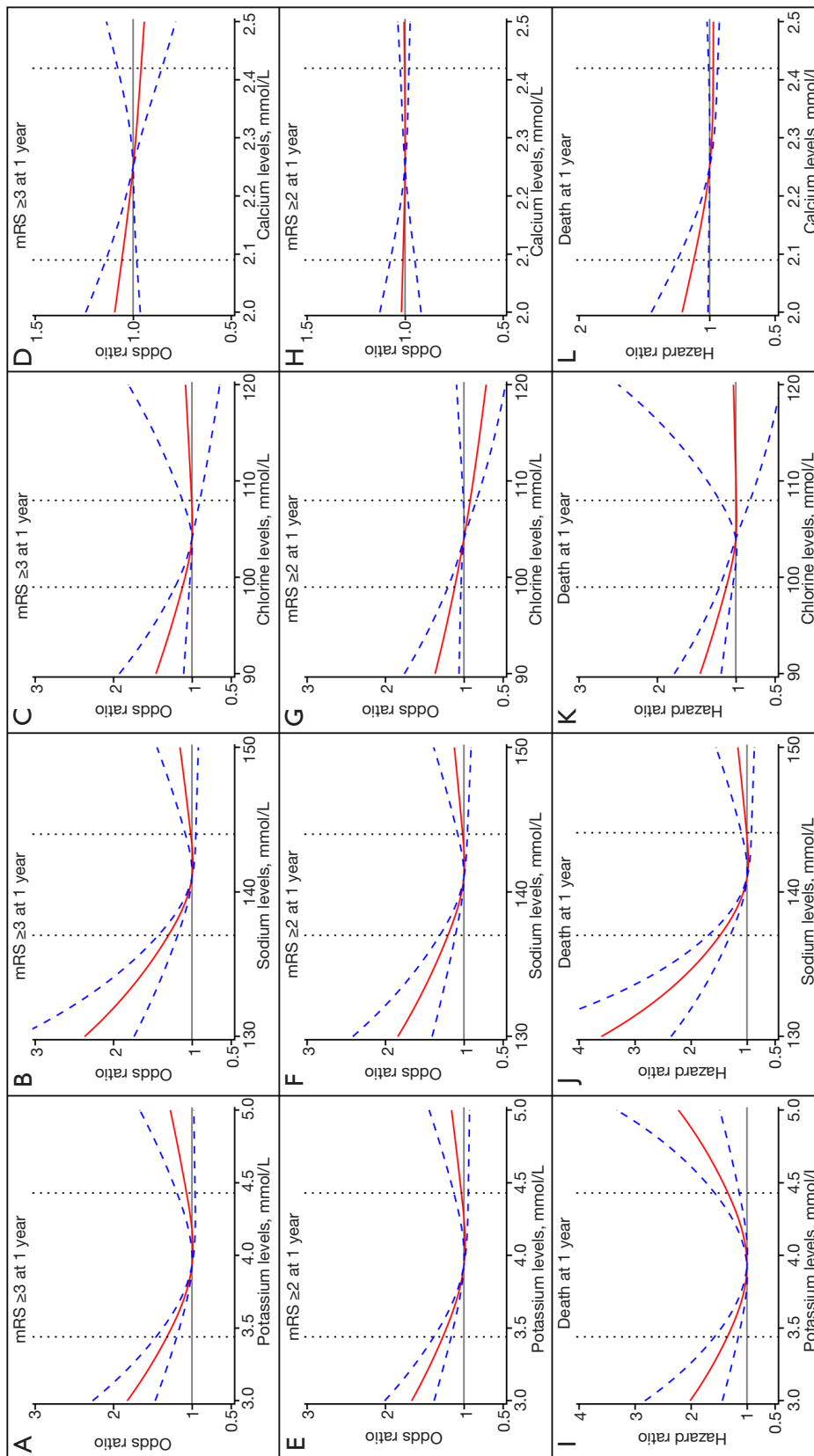
Figure 2 Association of electrolytes levels with risk of all-cause death and poor functional outcome at 1 year. (A,B,C,D) mRS score 3–6; (E,F,G,H) mRS score 2–6; (I,J,K,L) All-cause death. Red line represented adjusted hazard ratio, the blue dashed lines with 95% confidence limits. Adjusted for age, gender, body mass index, history of hypertension, diabetes mellitus, dyslipidemia, stroke or TIA, atrial fibrillation/flutter, peripheral vascular disease, heart failure, stroke type, TOAST, current smoke, cholesterol-lowering agents, antihypertensive agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, NIHSS, total cholesterol, high-density cholesterol lipoprotein, fasting blood glucose, estimated glomerular filtration rate, and high sensitivity C-reactive protein. mRS, modified Rankin Scale.

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Table 3 Adjusted hazard ratio (95% confidence interval) for all-cause mortality according to tertiles of serum electrolyte indicators

Electrolyte indicator	Tertiles	Death at 3 months			Death at 1 year		
		Events, n (%)	Unadjusted	Adjusted[†]	Events, n (%)	Unadjusted	Adjusted[†]
Potassium, mmol/L	T1 (<3.78)	62 (1.81)	1.44 (0.97–2.13)	1.40 (0.93–2.10)	123 (3.59)	1.47 (1.10–1.94)	1.45 (1.09–1.94)
	T2 (3.78–4.09)	44 (1.31)	Reference	Reference	83 (2.47)	Reference	Reference
	T3 (>4.09)	52 (1.48)	1.13 (0.75–1.71)	0.99 (0.65–1.51)	119 (3.39)	1.38 (1.04–1.85)	1.28 (0.95–1.72)
Sodium, mmol/L	T1 (<139.70)	74 (2.16)	1.77 (1.18–2.64)	1.52 (1.00–2.31)	142 (4.14)	1.78 (1.33–2.37)	1.62 (1.21–2.18)
	T2 (139.70–141.90)	38 (1.23)	Reference	Reference	75 (2.43)	Reference	Reference
	T3 (>141.90)	46 (1.21)	1.14 (0.74–1.78)	1.17 (0.75–1.84)	108 (2.85)	1.24 (0.92–1.68)	1.21 (0.89–1.65)
Chloride, mmol/L	T1 (<102.50)	64 (1.87)	1.54 (1.03–2.31)	1.30 (0.85–1.98)	140 (4.10)	1.71 (1.29–2.27)	1.56 (1.17–2.09)
	T2 (102.50–105.47)	42 (1.23)	Reference	Reference	83 (2.43)	Reference	Reference
	T3 (>105.47)	52 (1.50)	1.30 (0.85–1.98)	1.05 (0.68–1.63)	102 (2.95)	1.10 (0.82–1.49)	1.07 (0.78–1.45)
Calcium, mmol/L	T1 (<2.20)	69 (2.03)	1.24 (0.85–1.82)	1.15 (0.77–1.71)	135 (3.97)	1.29 (0.99–1.70)	1.24 (0.93–1.64)
	T2 (2.20–2.30)1	53 (1.51)	Reference	Reference	98 (2.80)	Reference	Reference
	T3 (>2.30)	36 (1.06)	0.65 (0.41–1.01)	0.72 (0.46–1.14)	92 (2.71)	0.90 (0.66–1.20)	0.99 (0.73–1.34)

†, adjusted for age, gender, body mass index, history of hypertension, diabetes mellitus, dyslipidemia, stroke or TIA, atrial fibrillation/flutter, peripheral vascular disease, heart failure, stroke type, TOAST, current smoke, cholesterol-lowering agents, antihypertensive agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, NIHSS, time from onset of symptoms to admission, total cholesterol, high-density cholesterol lipoprotein, fasting blood glucose, estimated glomerular filtration rate, and high sensitivity C-reactive protein.

and TIA (P for interaction >0.05 for all).

Consistently, multivariable-adjusted spline regression showed a U-shaped association for potassium, L-shaped associations for sodium and chloride, and no significant association for calcium with all-cause death (*Figure 2I,J,K,L*).

Moreover, all these relationships were consistent at 3 months, except the effect of hypokalemia on all-cause death disappeared (*Table 3* and Tables S3-S6 in the online-only data supplement).

Discussion

The major finding of the current study was that lower levels of potassium, sodium and chloride were significantly associated with elevated risk of poor functional outcomes and death in patients with AIS or TIA. However, almost no significant association was present of calcium with these outcomes.

Hypokalemia is a common electrolyte disorder and complication of hospitalized patients, and a lower level of serum potassium has been proved to be correlated with increased ischemic stroke risk (23). Nevertheless, evidence surrounding the relationship between serum potassium and the prognosis of stroke was limited and conflicting. A retrospective study of 361 patients with AIS showed that hypokalemia at the initial admission was associated with a worse poor prognosis with respect to the mRS score 3–6 following first-ever AIS (11). An observational study with 421 stroke patients revealed that a lower plasma potassium at admission was associated with the 3-month mortality rate of AIS (12). While another observational study of 475 patients demonstrated no association was found between serum potassium levels and short- and long-term outcomes of AIS (13). The discrepancy might be due to the differences in the population characteristics, and the small sample of these studies. Our analyses consisted of 10,299 patients with AIS or TIA had more power and suggested that hypokalemia was a predictor of all-cause death and poor functional outcomes for stroke. Possible mechanism may be that hypokalemia could reduce conductance hyperpolarization in potassium channel of cells, promote formation of free radicals and endothelial dysfunction (24), and the influence of potassium on stroke outcomes could be related directly to the physiological effect of lower extracellular potassium concentration on membrane depolarization leading to events such as a vasoconstriction and deterioration of neurological function

(12,24,25). Hyperkalemia is a frequent clinical abnormality in patients with chronic kidney disease (26). Epidemiological and clinical data have identified hyperkalemia was a potential risk factor for poor outcomes of acute myocardial infarction and chronic kidney disease (27,28). Results from our study showed that hyperkalemia was associated with all-cause death and poor functional outcome regarding to mRS score 3–6 at 1 year, while the associations disappeared for other outcomes and when timepoint was set at 3 months, which indicated the prognostic role of hyperkalemia may be extent to patients with AIS or TIA in some degree, and it still needed further investigations.

Although hyponatremia has gained wide recognition as a predictor of long-term mortality after stroke, the effect of hyponatremia on short-term mortality was inconsistent (14-17). Rodrigues *et al.* and a meta-analysis study reported that hyponatremia was related to increased mortality in-hospital and at 3 months in IS patients (14,15). Whereas two other studies showed that hyponatremia was not associated with either in-hospital, 30- or 90-day mortality after IS (16,17). The variation among those studies may be explained by many factors, such as inclusion criteria, ethnicity, and sample size. Findings of our study confirmed that hyponatremia was a predictor of all-cause death at 3 months and 1 year. Moreover, we also found hyponatremia was associated with poor functional outcomes of AIS or TIA, which has not been investigated well in previous studies. Mechanisms of the enhanced mortality and poor functional outcomes in hyponatremic patients would be hyponatremia may promote cerebral edema, increase intracranial pressure and then affect cerebral perfusion, which led to vascular injury after stroke (15,23,29).

The association of lower chloride levels and mortality has been shown in chronic kidney disease, hypertensive and postoperative patients (9,30,31). Nevertheless, literatures on prognostic role of hypochloremia in stroke were scarce, to our best knowledge, only one study with 3,314 patients showed hypochloremia at admission was independently associated with in-hospital mortality in AIS patients (16). The significant associations of hypochloremia and all-cause death and poor functional outcomes in our study suggested that hypochloremia could be used as one of the predictors of adverse outcomes of stroke in clinical practice. Possible mechanisms underlying the relationship of hypochloremia and poor prognosis of stroke may be that lower chloride might upregulate inflammatory cytokines and reflect a high anion gap and high rennin level, which may lead to poor outcomes and mortality after stroke indirectly (32,33).

Hypocalcemia is common in critically ill patients, and it has been considered as an indicator of poor prognosis for acute pancreatitis (10). Up to date, the association of calcium with clinical outcomes in patients with AIS or TIA has not been investigated yet. In our study, almost no significant relationships were present for calcium and these outcomes, except the slight association with mRS score 2–6 at 3 months. Possible mechanism for the insignificant associations may be that calcium works in combination with other ions such as potassium, sodium, and magnesium to provide an ionic balance to the vascular membrane and vasodilatation (34).

The strengths of our study include that the study is a large multicenter registry with more than 10,000 patients, supporting sufficient statistical power. Nevertheless, there were still some limitations on our study. Firstly, changes in electrolyte balance have been claimed to play a role in the pathophysiology of ischemic event (35). Clinical data found that a modified serum electrolyte pattern characterized by hypokalemia, hyponatremia, and hypochloremia was more common than hyperkalemia, hypernatremia, and hyperchloremia in stroke patients (36,37). However, our analysis only focused on baseline electrolytes and without accounting for the dynamic changes in electrolytes, which could provide more valuable information to understand the mechanism of the associations. Secondly, equipment heterogeneity at each research centers may lead to biased results, while this may have little impact, since the equipment in each research center is under strict quality control in daily use.

Conclusions

The study showed that lower levels of potassium, sodium, chloride but not calcium were independent predictors of all-cause death and poor functional outcomes in patients with AIS and TIA. The findings of our study may promote their potential use in clinical practice as markers for outcomes in stroke.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Beijing Tiantan Hospital (No.: KY2015-001-01) and all study centers gave ethical approval of the study protocol. Written consents were obtained from all participants or their legal representatives.

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