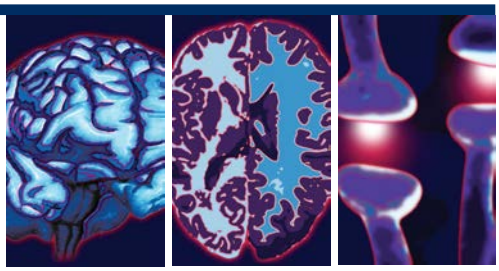

Increased Risk of Ischemic Stroke in Patients with Chronic Kidney Disease after Recurrent Dysnatremias: A Nationwide Population-Based Cohort Study

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Abstract

Dysnatremias are the common problems in chronic kidney disease (CKD) patients and associated with neurologic symptoms. Thus, the purpose of this study was to determine the association between dysnatremias (either hypernatremia or hyponatremia) and risk of stroke in CKD population. A retrospective cohort study was constructed using the claims data of the entire insured residents covered by Taiwan's universal health insurance from 2000 to 2011. Severe hyponatremia and hypernatremia are defined as the need of 3% sodium chloride treatment and the need of admission respectively. A total of 365 hyponatremia and 137 hypernatremia patients and 1983 matched comparisons were recruited. The incidence of stroke was defined using the International Classification of Diseases, 9th Revision, Clinical Modification. Cox proportional hazard regression and Kaplan–Meier curves were used for the analyses. In the analysis, CKD with dysnatremias were with more diabetes, heart failure, mental illness, liver cirrhosis, cancer history and diuretics treatment. Compared with comparisons, patients with dysnatremias, hyponatremia or hypernatremia patients had a 2.57 (95% CI: 1.91-3.46), 2.35 (95% CI: 1.67-3.29) and 3.35 (95% CI: 2.04-5.50) fold risks of stroke after adjusting for potential factors. There was similarly increased risk for ischemic stroke, but not for hemorrhagic stroke. In addition, patients with recurrent dysnatremias, the risk of stroke much increased [9.19 (95% CI: 5.79-14.6) for hyponatremia and 11.4 (95% CI: 5.66-23.1) for hypernatremia]. In conclusion, we suggest more intensive surveillance to prevent recurrent dysnatremias and ischemic stroke should be emphasized.

Keywords

Dysnatremias, Hyponatremia, Hypernatremia, Stroke, Ischemic stroke

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Introduction

Chronic kidney disease (CKD) patients are prone to dysnatremias, either hypo- or hypernatremia resulting from failure in urine dilution and from urine concentration. Symptoms in the central nervous system (CNS), including acute and chronic symptoms, are the main manifestations of dysnatremias [1]. Occurrence of dysnatremias carries high morbidity and mortality risk in CKD population [2,3].

A study has shown that CKD is associated with high risk of ischemic stroke [4]. The incidence of ischemic stroke in this population increases resulting from traditional and non-traditional factors [5]. Studies have also suggested that dysnatremias cause stroke [6-8], although these studies were conducted in individuals with relatively intact renal function. Whether dysnatremias contribute to occurrence of stroke in CKD population remains unknown. Only one single-center study has revealed that the relationship between hyponatremia and stroke is not significant in peritoneal dialysis patients [9].

The present study focused on severe dysnatremias in CKD population and is based on a retrospective cohort study based from a nationwide database. This study aimed to determine the following: (1) the incidence rates and risk factors of severe dysnatremias in CKD patients; (2) the association of severe dysnatremias and stroke, including ischemic and hemorrhagic stroke; and (3) the effect of frequent dysnatremias on risk of stroke.

Materials and Methods

■ Data source

Taiwan Bureau of National Health Insurance (TBNHI) has set up a single-payer insurance program for 13 public health insurance systems in 1995, and this program covers 99% of the population (http://www.nhi.gov.tw). This program included all medical records for each insured from January 1996 to December 2011. As per research recommendations, the TBNHI authorized the National Health Research Institutes to establish several National Health Insurance Research Databases (NHIRDs). Data used in this retrospective cohort study was obtained from Longitudinal Health Insurance Database (LHID), one of the NHIRDs. LHID includes one million insured from the beneficiaries who joined this program before 2000. NHIRD provided data to the ICD-9-CM for disease identification. In accordance with the Personal Information Protection Act, the information used to identify the beneficiaries or medical institutions is scrambled before being released to each researcher and the researcher must sign a written agreement declaring that they will not attempt to obtain the personal information of each insured. This study was also approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115). All study methods were performed in accordance with the approved guidelines.

■ Study participants

We collected data from patients newly diagnosed with CKD (ICD-9-CM 580–589) from 1998 to 2011. The patients whose CKD was followed by occurrence of severe dysnatremias were defined as dysnatremias group. The dysnatremia group was divided into two subgroups: 1. the hyponatremia group, which includes CKD patients with hyponatremia (ICD-9-CM 276.1) and received 3% sodium chloride treatment; and 2. the hypernatremia group, which includes CKD patients with hypernatremia (ICD-9-CM 276.0) and required hospital admission. In the dysnatremia group, the date of diagnosis of dysnatremias was defined as the index date. Patients who have had stroke (ICD-9-CM 430–438) before the index date were excluded. Comparison group includes CKD patients who did not develop dysnatremias before the end of 2011 and who were frequency matched with age, gender, year of CKD diagnosis, and year of index date at a rate of approximately 4:1.

■ End-point, comorbidity, and diuretics used

Our interesting end-point included stroke at admission. All study participants were followed from the index date until stroke occurred. Those who did not experience stroke were followed-up until the date of their withdrawal from the program or until the end of 2011. Stroke was classified into ischemic stroke (ICD-9-CM 433–438) and hemorrhagic stroke (ICD-9-CM 430–432). The comorbidities considered in this study include diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272), mental illness (ICD-9-CM 290–319), PAOD (ICD-9-CM 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8, and 447.9), ischemic heart disease (ICD-9-CM 410–414), liver cirrhosis (ICD-9-CM 571), brain cancer (ICD-9-CM 191, 192, and 225), other

types of cancer (ICD-9-CM 140–190, 193–224, and 226–239), atrial fibrillation (ICD-9-CM 427.31), and heart failure (ICD-9-CM 428, 398.91, and 402.x1). Diuretics were classified into loop diuretics, thiazide, and others. All comorbidity and diuretics used were defined before the index date.

■ Statistical analysis

Chi-square test was used to test the differences between the dysnatremias and comparison groups in terms of categorized age, gender, prevalence of comorbidity, and different types of diuretics used. The difference between the dysnatremias and comparison group in terms of mean age (continuous) was measured using t-test. The categorical and continuous variables in the two types of dysnatremias and in the comparison group were compared using chi-square test and ANOVA. The incidence for stroke (per 1000 person-years) was determined from the sum of event divided by the sum of person-years in the two different types of dysnatremias and in the comparison groups. Cox proportional hazard regression was used to compare the risk for overall stroke, ischemic stroke, and hemorrhagic stroke in the two types of dysnatremias group and in the comparison group. We used a test of scaled Schoenfeld residuals to examine the proportional hazard assumption, and the result was not violated ($p = 0.495$). Adjusted model was controlling age, gender, diuretics used and comorbidity which with a significantly different in crude model. The association between stroke and frequency of hyponatremia and hypernatremia was evaluated by Cox proportional hazard regression. Kaplan–Meier analysis was used to measure the cumulative incidence of stroke in the two dysnatremia subgroups and in the comparison group, and log-rank test used to assess the difference among the three cohorts. All statistical analyses were performed using SAS (version 9.4, SAS Insitius, Cary, NC). The significance level was set at a p value of <0.05 under a two-tailed test.

Result

We included 502 dysnatremia patients and 1983 comparisons from CKD patients **(Table 1)**. The dysnatremias group included 365 hyponatremia patients (72.7%) and 137 hypernatremia patients (27.3%). No significant difference was observed among the dysnatremias patients, as well as in age- and gender-matched comparisons. More men (53.0% vs. 47.0%) and elderlies (73.1% vs. 26.9%) exhibited dysnatremia. In addition, no significant difference in terms of age was observed between hyponatremic and hypernatremic patients (mean age: 73.3 years old vs. 72.0 years old). More women were included in the hypernatremia group (52.3% vs. 47.7%), whereas more men were found in the hyponatremia group (67.2% vs. 32.9%). In contrast to the comparison group, the dysnatremic patients displayed a higher incidence of diabetes (36.1% vs. 28.0%), heart failure (23.3% vs. 17.2%), mental illness (55.4% vs. 46.0%), liver cirrhosis (36.7% vs. 32.0%), cancer history (46.0% vs. 40.9%) and diuretics treatment (53.2% vs. 36.1%). Moreover, the hyponatremia group displayed a higher incidence of diabetes, liver cirrhosis, and cancer history but showed lower incidence of ischemic heart disease and mental illness than the hypernatremia or comparison group.

After 14 years of follow-up, the dysnatremic patients exhibited higher cumulative incidence for stroke than the comparison group **(Figure 1)**. During the study period, the incidence of stroke in the dysnatremia group was 2.68-fold higher than that in the comparison group (60.56 vs. 22.58 per 1000 person-years) **(Table 2)**. In contrast to the comparison group, the hyponatremic and hypernatremic patients displayed a 2.47- and 3.39-fold increased crude risk of stroke, respectively.

After controlling age, gender, diabetes, heart failure, ischemic heart disease, cancer and diuretics use, the dysnatremic, hyponatremic, and hypernatremic patients exhibited risks of stroke higher by 2.57- (95% CI: 1.91–3.46), 2.35-(95% CI: 1.67–3.29), and 3.35- (95% CI: 2.04–5.50) fold than the comparison group **(Figure 2)**. Dysnatremias also showed an increased risk for ischemic stroke (p values < 0.05 for both hyponatremia and hypernatremia), although no significant increased risk for hemorrhagic stroke was observed.

Table 3 shows the association between ischemic stroke and the frequency of hyponatremia and hypernatremia. The risk of ischemic stroke increased in recurrent patients regardless of the type of dysnatremia they exhibit. In contrast to the comparison group, recurrent patients with dysnatremia showed higher risks of ischemic stroke than the incident patients (increased from 1.14 to 9.41 for hyponatremia and 2.50 to 10.6 for hypernatremia patients; $p < 0.0001$ for both cases).

Table 1. Demographics profiles of patients with chronic kidney disease with hyponatremia, hypernatremia and matched patients without dysnatremias.

	Dysnatremias									
	Hyponatremia N = 365		Hypernatremia N = 137		All N = 502		Comparison group N = 1983			
	n	%	n	%	n	%	n	%	p-value[1]	p-value[2]
Age, year									0.88	0.88
<65	39	28.5	96	26.3	135	26.9	540	27.2		
65+	98	71.5	269	73.7	367	73.1	1443	72.8		
Mean (SD)	73.3	(16.3)	72.0	(13.0)	72.3	(14.0)	71.8	(13.8)	0.48[†]	0.47[#]
Gender									0.90	0.0005
Women	45	32.9	191	52.3	236	47.0	926	46.7		
Men	92	67.2	174	47.7	266	53.0	1057	53.3		
Comorbidity										
Diabetes	51	37.2	130	35.6	181	36.1	556	28.0	0.0004	0.002
Hypertension	90	65.7	274	75.1	364	72.5	1398	70.5	0.38	0.08
Hyperlipidemia	44	32.1	148	40.6	192	38.3	831	41.9	0.14	0.08
Ischemic heart disease	47	34.3	182	49.9	229	45.6	849	42.8	0.26	0.004
Heart failure	30	21.9	87	23.8	117	23.3	341	17.2	0.002	0.006
Mental illness	58	42.3	220	60.3	278	55.4	912	46.0	0.0002	<0.0001
PAOD	10	7.30	36	9.86	46	9.16	138	6.96	0.09	0.15
Liver cirrhosis	146	40.0	38	27.7	184	36.7	635	32.0	0.049	0.005
Cancer									0.04	0.02
Brain	8	2.19	4	2.92	12	2.39	26	1.31		
Non-brain	171	46.9	48	35.0	219	43.6	785	39.6		
Atrial fibrillation	17	4.66	4	2.92	21	4.18	61	3.08	0.21	0.29
Diuretics	65	47.5	202	55.3	267	53.2	715	36.1	<0.0001	<0.0001
Lasix	62	45.3	187	51.2	249	49.6	651	32.8	<0.0001	<0.0001
Thiazide	6	4.38	25	6.85	31	6.18	133	6.71	0.67	0.56
Others	7	5.11	46	12.6	53	10.6	87	4.39	<0.0001	<0.0001

Chi-square, [†]t-test and ANOVA.
1 p-value applies to patients with dysnatremia compared with patients without dysnatremia.
2 p-value applies to patients with different types of dysnatremia compared with patients without dysnatremia.

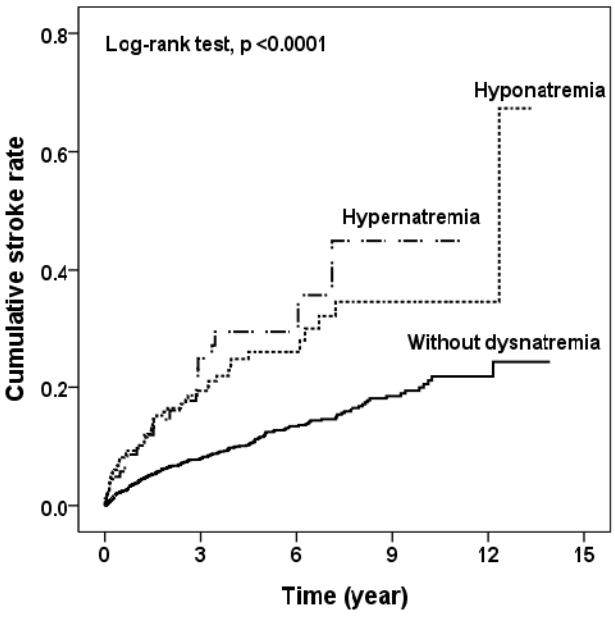

Figure 1: Cumulative stroke risk in hyponatremia and hypernatremia subgroups and in the comparison group.

Table 2: Incidence rate ratio of stroke compared with patients with chronic kidney disease with and without hyponatremia and hypernatremia.

Outcome	Event	Person-years	Rate	IRR (95%CI)
Stroke				
Without dysnatremias	170	7529	22.58	1.00 (reference)
Dysnatremias				
Overall	62	1024	60.56	2.68 (2.01–3.59)***
Hypernatremia	18	235	76.49	3.39 (2.08–5.51)***
Hyponatremia	44	789	55.80	2.47 (1.77–3.44)***
Ischemic stroke				
Without dysnatremias	144	7529	19.13	1.00 (reference)
Dysnatremias				
Overall	54	1024	52.74	2.76 (2.02–3.77)***
Hypernatremia	16	235	67.99	3.55 (2.12–5.96)***
Hyponatremia	38	789	48.19	2.52 (1.76–3.60)***
Hemorrhagic stroke				
Without dysnatremias	26	7529	3.45	1.00 (reference)
Dysnatremias				
Overall	8	1024	7.81	2.26 (1.02–5.00)*
Hypernatremia	2	235	8.50	2.46 (0.58–10.4)
Hyponatremia	6	789	7.61	2.20 (0.91–5.35)

Rate, per 1000 person-years
** p < 0.01, *** p < 0.001

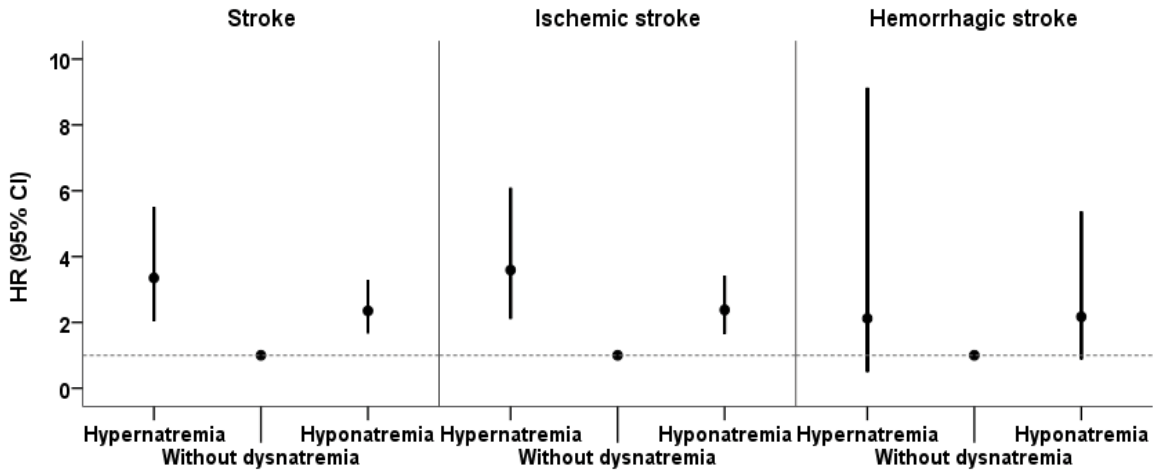

Figure 2: Adjusted hazard ratio for stroke and ischemic and hemorrhagic strokes among chronic kidney disease patients with hyponatremia, hypernatremia and without dysnatremias after controlling age, gender, diabetes, heart failure, ischemic heart disease, cancer, and diuretics use.

Table 3: Incidence rate ratio and hazard ratio of ischemic stroke stratified by frequency of hyponatremia and hypernatremia.

	N	Event	Person-years	Rate	IRR (95%CI)	Adjusted HR (95% CI)
Without dysnatremias	1983	144	7529	19.13	1.00 (reference)	1.00 (reference)
Hyponatremia						
≤1	153	15	673	22.29	1.17 (0.68–1.98)	1.14 (0.67–1.95)
> 1	212	23	115	199.28	10.4 (6.71–16.2)***	9.41 (5.73–15.4)***
P for trend					<0.0001	<0.0001
Hypernatremia						
≤1	52	9	206	43.79	2.29 (1.17–4.49)*	2.50 (1.26–4.97)**
> 1	85	7	30	234.71	12.3 (5.75–26.2)***	10.6 (4.78–23.5)***
P for trend					<0.0001	<0.0001

Adjusted for age, gender, diabetes, heart failure, ischemic heart disease, cancer, and diuretics use
*** p < 0.001

Discussion

To the best of our knowledge, this is the first study to show that dysnatremias (both hypo- and hypernatremia) are associated with stroke, especially ischemic stroke, in CKD population. Patients with dysnatremias showed higher incidence of diabetes, heart failure, mental illness, liver cirrhosis, cancer history, and diuretics treatment. Furthermore, recurrent dysnatremias increase the risk of stroke.

Dysnatremias can be classified into mild, moderate, and severe types based on symptoms. The prevalence rate of overall hypo- and hypernatremia in CKD patients was 3.83% and 0.55%, respectively, as revealed by our analysis of the dataset. In addition, the prevalence rate of severe hypo- and hypernatremia (data not shown) was 0.79% and 0.40%, respectively. These prevalence rates were much lower than those presented in a large-scale study conducted in America [3,10], possibly implying that clinical physicians in Taiwan seemed to omit the symptom of mild dysnatremias in CKD patients despite the high mortality rate [3,10]. Therefore, we focused on severe dysnatremias in the present study because of its greater severity and complexity, and it deserves more attention.

Dysnatremias patients displayed high prevalence rates of diabetes, chronic heart failure, mental illness, liver cirrhosis, malignancies, and diuretics use. Hyponatremia is possibly caused by reduced arterial effective volume in heart failure and liver cirrhosis, by inappropriate secretion of ADH in malignancy, and by renal sodium loss in diuretics use [1]. Diabetes is also an independent risk factor of hyponatremia as revealed in a study [11]. Moreover, hypernatremia is possibly caused by impaired access to water in mental illness [12]. In addition, loop diuretic is a risk factor for hypernatremia resulting from impaired concentration gradient in kidney medulla and from high water loss [11].

Three factors may explain the increased risk of ischemic stroke in hyponatremia. The first possible factor is hypoxia. In patients with hyponatremic encephalopathy, hypoxia usually develops through two mechanisms: neurogenic pulmonary edema and hypercapnia respiratory failure [13]. Hypoxia cannot only cause deterioration of cerebral edema [14] but also contributes to ischemic stroke. Studies have shown that hypoxia can increase resting blood pressure and cerebral vascular resistance [15]. In addition, hypoxia induces expression of proinflammatory transcription factors, leading to endothelial dysfunction and then to atherosclerosis [16]. Second, activation of the renin–angiotensin system (RAS) can increase the incidence of ischemic stroke. Hyponatremia is not only a marker representing the degree of RAS activation but also a contributory factor to RAS activation [17]. RAS activation can exert numerous adverse effects on vascular endothelium, resulting in atherosclerosis [18]. RAS activation can also lead to plaque rupture in atherosclerotic lesions, along with with cardiac and brain damage [19,20]. Third, a study has shown that hyponatremia impairs NO-dependent vasodilatation in cerebral artery [21]. Dysregulation of perfusion in cerebral vessels is possibly related to occurrence of ischemic stroke.

Ischemic stroke is often encountered in hypernatremic patients. In a previous case series, radiologic examination of the CNS of hypernatremic patients revealed that approximately 20% of patients had cerebral infarction [22]. High risk of ischemic stroke in hypernatremia may be attributed to two factors. First, numerous case reports have shown that hypernatremia is related to formation of thrombosis, including those that form in intra-cranial vessels [23]. In addition, serum hypertonicity can deform and render erythrocytes rigid, [24] which may result in increased blood viscosity [25] and thrombosis formation when combined with dehydration (often accompanied by hypernatremia). Second, a majority of hypernatremic patients are dehydrated. Studies have shown that dehydration is risk factor for ischemic stroke [26,27] because it can reduce cerebral blood flow and then precipitate in ischemic stroke and even result in sympathetic system activation, triggering the coagulation cascade [28]. However, the difference between hyponatremic and hypernatremic patients for the risk of stroke may be needed to further clarify in the future.

CKD is an established risk factor for stroke, and a meta-analysis has shown that CKD patients have 43% higher risk of stroke (both ischemic and hemorrhagic) [29]. Prevalence of stroke in this population is much higher than in general population. Traditional and non-traditional factors, as well as uremic-related factors, all contributed to endothelial dysfunction and development of atherosclerosis [5]. Atrial fibrillation is also common in CKD and associated with stroke occurrence [30]. Our study found that dysnatremia is an independent

risk factor for ischemic stroke after adjusting the co-morbidities. In the future, dysnatremia should be considered another non-traditional risk factor in CKD population.

Only a few studies have investigated recurrent dysnatremias. One study has shown that a quarter of patients with hyponatremia experience recurrent events and exhibit increased mortality risk within 1 year [31]. This phenomenon has possibly resulted from malnutrition and inappropriate follow-up and medical care. Our study found that more than half of severe dysnatremic patients have had recurrent events. In addition, these patients showed a much increased risk of stroke occurrence. This finding might imply that the cumulative damage caused by recurrent dysnatremias to the CNS should attract more attention from clinical physicians.

Dysnatremias are associated with high mortality risk [2,32] regardless of the underlying disease and type of patients (ambulatory or hospitalized). This finding is also applicable to healthy individuals [33]. However, the underlying mechanism for mortality has not yet been fully elucidated. In addition, the mechanisms of chronic symptoms of dysnatremias, such as chronic encephalopathy and dementia, also remain poorly understood. Our study might provide one possible explanation: chronic symptoms and high mortality risk of dysnatremias are partly caused by increased incidence of ischemic stroke.

The limitations of this study are the following. First, no detailed information on serum sodium is available; thus, we cannot determine whether a dose-dependent effect between dysnatremias and stroke exists. However, we know that severity of dysnatremias rely on symptoms rather than on absolute values of serum sodium. Thus, we defined our study in terms of severe dysnatremias because patients exhibiting these conditions are symptomatic and they require admission or 3% sodium chloride treatment. Second, we cannot consider all possible confounders of ischemic stroke, such as smoking habits, body mass index, and some non-traditional risk factors of CKD. Third, silent brain infarcts are common in CKD, [5] and these conditions may further affect stroke risk. Our study we excluded patients with symptomatic infarcts at recruitment, although silent infarcts cannot be distinguished. Fourth, our sample size is insufficiently large. Thus, the incidence of hemorrhagic stroke increased but not statistically significant.

In summary, increased risk of stroke, especially ischemic stroke, was observed in CKD patients with severe dysnatremias. Clinical physicians should be able to recognize the high-risk groups of patients that may develop dysnatremias and should prevent the occurrence of ischemic stroke. Finally, we suggest that intensive surveillance to prevent recurrent dysnatremias must be implemented.

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Author Contributions

M.C.C., T.M.Y., M.J.W., C.H.C., P.H.H., C.H.M., K.H.S., and C.J.C. designed the study. C.Y.L. and C.J.C. collected data and performed the statistical analyses. M.C.C., C.H.M., and C.J.C. drafted the manuscript. All authors have read and approved the final manuscript.

Additional Information

The authors disclose no competing financial interest.

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