Dysnatremia and 6-Month Functional Outcomes in Critically Ill Patients With Aneurysmal Subarachnoid Hemorrhage: A Prospective Cohort Study

OBJECTIVES: To investigate the association between plasma sodium concentrations and 6-month neurologic outcome in critically ill patients with aneurysmal subarachnoid hemorrhage.

DESIGN: Prospective cohort study.

SETTING: Eleven ICUs in Australia and New Zealand.

PARTICIPANTS: Three-hundred fifty-six aneurysmal subarachnoid hemorrhage patients admitted to ICU between March 2016 and June 2018. The exposure variable was daily measured plasma sodium.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Six-month neurologic outcome as measured by the modified Rankin Scale. A poor outcome was defined as a modified Rankin Scale greater than or equal to 4. The mean age was 57 years (±12.6 yr), 68% were female, and 32% (n = 113) had a poor outcome. In multivariable analysis, including age, illness severity, and process of care measures as covariates, higher mean sodium concentrations (odds ratio, 1.17; 95% CI, 1.05–1.29), and greater overall variability—as measured by the sd (odds ratio, 1.53; 95% CI, 1.17–1.99)—were associated with a greater likelihood of a poor outcome. Multivariable generalized additive modeling demonstrated, specifically, that a high initial sodium concentration, followed by a gradual decline from day 3 onwards, was also associated with a poor outcome. Finally, greater variability in sodium concentrations was associated with a longer ICU and hospital length of stay: mean ICU length of stay ratio (1.13; 95% CI, 1.07–1.20) and mean hospital length of stay ratio (1.08; 95% CI, 1.01–1.15).

CONCLUSIONS: In critically ill aneurysmal subarachnoid hemorrhage patients, higher mean sodium concentrations and greater variability were associated with worse neurologic outcomes at 6 months, despite adjustment for known confounders. Interventional studies would be required to demonstrate a causal relationship.

KEYWORDS: aneurysmal subarachnoid hemorrhage; critical care; hypernatremia; hyponatremia

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) in Australia is estimated at 10 per 100,000 person-years (1). Those affected are relatively young, with a mean age of 55 years, and survivors are likely to have a substantial burden of functional impairment (2, 3).

The commonest electrolyte disturbance in aSAH is dysnatremia, which can manifest as either an elevated or reduced plasma sodium concentration, although hyponatremia is more common (4–6). Hyponatremia may arise from a syndrome of cerebral salt wasting or inappropriate antidiuresis (7, 8). Distinguishing between these two entities is often difficult, and, in practice, management usually consists of avoidance of volume depletion and treatment...
with hypertonic solutions (9). Hypernatremia may occur as a result of diabetes insipidus secondary to cerebral injury (10) or secondary to treatment with hypertonic solutions. Intracerebral fluid shifts due to these abnormalities have the potential to lead to poor outcomes (11, 12); however, studies examining the relationship between dysnatremia and outcome have reported conflicting results (4). Therefore, there is uncertainty in how best to manage changes in plasma sodium concentrations in patients with aSAH (13).

We studied a large cohort of critically ill aSAH patients and performed a detailed assessment examining the variability, duration, and trends in plasma sodium concentration and their association with 6-month neurologic outcomes. We hypothesized that both hypernatremia and hyponatremia, as well as the pattern of sodium change, would be associated with differential neurologic outcomes.

**METHODS**

The Prospective Observational Multicentre Study of Aneurysmal Subarachnoid Haemorrhage in Australia and New Zealand-SAH study was a prospective multicenter observational study of aSAH patients admitted to ICUs in Australia and New Zealand (3). All patients admitted to a participating center, during their initial hospital admission post aSAH, were screened for eligibility. Inclusion/exclusion criteria are provided in Table S1 (http://links.lww.com/CCX/A653). Ethics approval to undertake the study was obtained at each participating site (Queensland, South Australia, and New South Wales [HREC/16/QRBW/204]; Victoria [HREC/15/ Alfred/8]; Western Australia [HREC/16/SCGG/74]; and New Zealand [16/NTB/172]).

Demographics, illness severity (as measured by the Acute Physiology and Chronic Health Evaluation [APACHE] III score), comorbidities, ICU and neurosurgical management, and clinical outcomes were collected prospectively. The severity of the SAH was classified using the World Federation of Neurological Surgeons (WFNS) clinical grading system (14) and Fisher scale (based on the clot burden identified on CT head) (15), as determined by the principal investigator at each site. A high WFNS severity was defined as a WFNS grade of 3 or more. Delayed cerebral ischemia (DCI) was defined as any neurologic deterioration (e.g., hemiparesis, aphasia, altered consciousness) presumed related to ischemia that persisted for more than 1 hour and could not be explained by other physiologic abnormalities noted on standard radiographic, electrophysiologic, or laboratory findings (16).

Daily data collection included fluid balance, the nature and volume of any hypertonic fluids administered, and the use of fludrocortisone and sodium tablets as management strategies for hyponatremia.

Neurologic outcome at 6 months postevent was determined by telephone assessment (by trained staff from either local sites or centrally) using the modified Rankin Scale (mRS) (17).

**Measurement of Plasma Sodium**

All plasma sodium concentration measurements performed as part of routine clinical care were recorded up to a maximum of 10 per day for each day of the patient’s ICU stay. Plasma sodium concentrations obtained from both arterial blood gas analysis and venous blood sample analysis were included. All aspects of the ICU management of the patient, including frequency of blood sampling, were performed at the treating clinician’s discretion. Samples were analyzed at each site using local pathology protocols.

**Sodium Metrics**

Plasma sodium exposure was measured via multiple sodium concentration measurements over the duration of the stay in ICU equating to multiple measures over multiple days. Mean sodium concentration over the stay in ICU was used to quantify sodium exposure and variability in sodium concentrations was evaluated based on the measured sd.

**Outcomes**

The primary outcome was neurologic outcome at 6 months posthospital discharge, as measured by the mRS. The secondary outcomes were ICU and hospital length of stay (LOS) and incidence of DCI.

**Statistical Analysis**

All analyses were performed according to a prespecified statistical analysis plan, with continuous data reported as the mean (sd) or median (interquartile range [IQR]), as appropriate, and categorical data as counts.
We dichotomized the mRS such that patients with an mRS greater than or equal to 4 were considered to have a poor outcome and patient with mRS less than 4 had a favorable outcome. A death in hospital or within 6 months post discharge was assigned an mRS of 6.

We used multivariable logistic regression to model binary outcomes (poor/favorable outcome as measured by mRS and incidence of DCI) and multivariable negative binomial regression to model count outcomes (hospital and ICU LOS). For the latter models, we report results as mean LOS ratio (MLR). All fitted models were hierarchical with hospital site as a random effect. Regression models examined the association with mean sodium concentration while in ICU and the variability of this concentration and outcome adjusted by predefined covariates including sex, age, WFNS severity, APACHE III score, hours from admission to neurovascular intervention, method of aneurysm obliteration and sodium treatment methods including sodium tablets, fludrocortisone, and sodium fluids (3).

In constructing the regression model of the association of sodium measures with a DCI, only sodium concentrations up until the DCI event were used. We modeled the longitudinal change in sodium concentration over time using generalized additive models (GAMs) that allow for the functional forms of the models to be nonlinear (18, 19). A GAM takes the strength of generalized linear regression and incorporates additional flexibility informed by the changes in sodium per person over time. Sodium was considered a continuous normally distributed variable over time. GAM models over time allow every sodium reading to contribute to the model at the time (hr) of the reading. We divided the data into two groups based on mRS outcome and constructed two independent GAM models using penalized regression splines and a thin plate smoother with each patient modeled as a random effect and with a fixed-effect covariates set including sex, age, hospital, WFNS severity, APACHE III score, time to intervention, method of securement, and sodium treatment methods.

To account for missing mRS scores, we performed sensitivity analyses in which all missing scores were imputed as mRS greater than or equal to 4 and again as mRS less than 4. Further sensitivity analyses were conducted to assess the impact of deaths within 48 hours on the primary model and the use of other forms of sodium measurements including maximum and minimum sodium values over the time in ICU, and the proportion of time above or below a prespecified range (upper and lower bounds of 150 and 135 mmol/L, respectively). Further details of methods relating to the sensitivity analyses are presented in the Supplementary Material (http://links.lww.com/CCX/A653).

We performed the analyses using R Version 3.6.3 (Vienna, Austria. https://www.R-project.org/) with regressions performed using functions from the lme4 (20) package and GAM analysis performed using mgcv (18).

**RESULTS**

In 11 neurosurgical referral centers in Australia and New Zealand, between March 2016 and June 2018 (inclusive), we enrolled 359 acute aSAH patients requiring ICU admission. Two patients withdrew consent, and in one patient, sodium measurements were missing, leaving 356 individuals from whom data were available. In 33 patients, there was no recorded mRS and death could not be confirmed (Fig. S1, http://links.lww.com/CCX/A653).

The baseline characteristics overall and by neurologic outcome at 6 months are presented in Table 1. The mean age of the patients was 57 years (± 12.6 yr) and 68% were female. The proportion of patients presenting with a severe (defined as a WFNS ≥ 3) aSAH was 42%, and 40% of the cohort suffered at least one episode of DCI. The median time of onset of DCI was in the third day after admission to hospital (IQR, 1–6). The proportion of patients with a poor neurologic outcome (defined as mRS ≥ 4 at 6 mo post discharge) was 32%. Over 60% of the patients presenting with a WFNS grade V aSAH were noted to have a poor outcome at 6 months, compared with just under 10% in those patients with a grade I WFNS bleed.

The total number of sodium measurements per person over their time in ICU was 34.0 (sd, 52.6); these were similar regardless of the neurologic outcome (mean 32.9, sd 29.7 vs mean 33.7, sd 22.8 for the mRS ≥ 4 and mRS < 4 groups, respectively, 95% CI of change: −5.5 to 7.1).

**Relationship Between Plasma Sodium Concentrations and Outcomes**

Multivariable logistic regression analysis was performed based on the two outcome groups (Table 2).
An increase in mean sodium concentration throughout the time spent in ICU (odds ratio [OR], 1.17; 95% CI, 1.05–1.29) and greater variability (expressed as sds) in sodium concentrations (OR, 1.53; 95% CI, 1.17–1.99) were associated with poor outcome. Poor outcomes were also associated with an increase in age (OR, 1.06; 95% CI, 1.03–1.09), an increase in APACHE III score (1.02; 95% CI, 1.00–1.04), and a prolonged interval between admission and neurovascular intervention in hours (OR, 1.01; 95% CI, 1.00–1.02).

Relationship Between Plasma Sodium Concentrations and Secondary Outcomes

Associations between the mean sodium concentration and sd, and the incidence of DCI were identified by multivariable logistic regression (Table S2, http://links.lww.com/CCX/A653). Mean sodium concentrations and variability of these concentrations were not associated with the incidence of DCI (mean sodium: OR, 0.95; 95% CI, 0.86–1.04 and sd of sodium: OR, 1.06; 95% CI, 0.82–1.37).

LOS in ICU and LOS in hospital were modeled as multivariable negative binomials adjusted for the same covariate as the primary outcome (Table S3, http://links.lww.com/CCX/A653). Increased variability in sodium concentration was associated with longer stays in both ICU and hospital with MLR (1.13; 95% CI, 1.07–1.20 and 1.08; 95% CI, 1.01–1.15, respectively.) There was no statistically significant association between mean sodium concentration and either ICU or hospital LOS. Admission with a high WFNS value, a longer time from admission to neurovascular intervention and the need for surgical clipping all had a positive association with an extended LOS in both ICU and the hospital in general.
Use of Sodium Treatments While in ICU

Just under 60% of patients received some form of sodium treatment while in ICU, with a greater proportion of patients with a favorable outcome receiving treatment compared with a poor outcome (47.6% and 28.3%, respectively) (Table 3). Nearly 25% of people were treated with sodium tablets (containing 600 mg sodium per tablet), and if treated, a mean of 7.2 tablets (sd 3.1) were received each day. The mean fludrocortisone dose for

| Characteristic                                         | OR (95% CIs)     | p    |
|--------------------------------------------------------|------------------|------|
| Mean sodium                                            | 1.17 (1.05–1.29) | 0.003|
| sd of sodium                                           | 1.53 (1.17–1.99) | 0.002|
| Male                                                   | 1.41 (0.72–2.79) | 0.321|
| Age                                                    | 1.06 (1.03–1.09) | > 0.001|
| High World Federation of Neurosurgeons Score severity  | 1.79 (0.88–3.68) | 0.120|
| Acute Physiology and Chronic Health Evaluation III score | 1.02 (1.00–1.04) | 0.007|
| Hours from admission to neurovascular intervention     | 1.01 (1.00–1.02) | 0.036|
| Surgical clipping                                      | 1.78 (0.86–3.66) | 0.120|
| Treated with sodium tablets (600 mg sodium per tablet) | 0.47 (0.16–1.40) | 0.174|
| Treated with fludrocortisone                           | 1.93 (0.55–6.76) | 0.305|
| Treated with hypertonic sodium fluids                  | 0.93 (0.39–2.24) | 0.873|

OR = odds ratio.
High severity was defined as a World Federation of Neurosurgeons Score ≥ 3.

| Characteristic                                         | mRS < 4 (n = 210) | mRS ≥ 4 (n = 113) | Total (n = 323) |
|--------------------------------------------------------|-------------------|------------------|----------------|
| Any sodium treatment                                    |                   |                  |                |
| Percent untreated (%)                                   | 47.6              | 28.3             | 40.9           |
| Sodium tablets (600 mg sodium per tablet)               |                   |                  |                |
| Percent treated (%)                                     | 30.5              | 10.6             | 23.5           |
| Mean number of tablets per day (sd)                     | 7.2 (3.3)         | 7.2 (2.2)        | 7.2 (3.1)      |
| Fludrocortisone                                         |                   |                  |                |
| Percent treated (%)                                     | 10.5              | 6.2              | 9.0            |
| Mean fludrocortisone doses per day in μg (sd)           | 238.3 (136.8)     | 241.0 (145.6)    | 229.6 (131.6)  |
| Hypertonic saline                                       |                   |                  |                |
| Percent treated with either 3% or 20% saline (%)        | 34.8              | 26.5             | 31.9           |
| Percent treated with 3% saline (%)                      | 22.4              | 11.5             | 18.6           |
| Mean volume of 3% saline administered per day in mL (sd)| 496.0 (351.1)     | 505.6 (414.1)    | 511.4 (371.1)  |
| Percent treated with 20% saline (%)                     | 8.1               | 9.7              | 8.7            |
| Mean volume of 20% saline administered per day in mL (sd)| 61.3 (47.1)       | 60.6 (43.5)      | 46.3 (48.0)    |
| Other forms of sodium treatment                         |                   |                  |                |
| Percent treated (%)                                     | 7.1               | 8.0              | 7.4            |

mRS = modified Rankin Scale.

TABLE 2.
Multivariable Model

TABLE 3.
Sodium Treatment While in ICU
the 9% of patients was nearly 230 μg/d (sd 131.6 μg/d). Between 25% and 35% of patients were treated with some form of hypertonic saline, with 3% of saline being more commonly administered than 20% saline.

**Sodium Changes Over Time Using Generalized Additive Models**

The change in plasma sodium for the two outcome groups was measured from admission to ICU discharge. The shapes of the functional forms of sodium concentration over time are shown in Figure 1. Patients with a favorable 6-month mRS outcome (Fig. 1A) displayed a comparatively stable sodium concentration over time, between 137 and 143 mmol/L. Patients with a poor 6-month mRS outcome (Fig. 1B) had a marked downward trajectory in sodium from day 3 (144 mmol/L) to day 16 in ICU (136 mmol/L) and a greater amount of variability within the functional form. A plot of residual against predicted values for the change in sodium concentration over time for the two outcome groups is presented in Figure S2 (http://links.lww.com/CCX/A653).

**Sensitivity Analyses**

Sensitivity analyses were performed to assess the impact of missing outcomes (Table S4, http://links.lww.com/CCX/A653), as well as the sodium concentration summarization method (Table S5, http://links.lww.com/CCX/A653). Further sensitivity analysis was performed by censoring the 29 patients who died within 48 hours of arriving in ICU (Table S6, http://links.lww.com/CCX/A653). Results indicate no significant differences in the models.

**DISCUSSION**

A higher mean value and greater variability in plasma sodium concentrations while in ICU were associated with a greater likelihood of a poor neurologic outcome at 6 months in critically ill aSAH patients. Furthermore, a high initial sodium concentration, followed by a gradual decline from day 3 onwards, was the specific pattern observed in those with a poor outcome. Finally, mean and variability of sodium concentrations while in ICU were not significantly associated with the risk of DCI, but increased sodium variability was associated with a longer ICU and hospital LOS.

The relationship between plasma sodium concentrations and neurologic outcomes in aSAH remains a matter of debate. Previous studies have reported that high sodium concentrations (5, 21) and greater variability (22) are associated with worse neurologic outcomes and mortality in aSAH, and our findings replicate this. Hypernatremia may reflect severe brain injury resulting in diabetes insipidus or may be a marker of treatment with hyperosmolar therapy for cerebral edema, both of which are plausibly associated with worse 6-month outcomes (23). Equally, increased variability may reflect the consequence of attempts to correct hypernatremia with hypotonic fluids or attempts to correct hyponatremia with hypertonic solutions.

The predictive value of hyponatremia in aSAH is less clear. Several studies have reported that hyponatremia is associated with a greater risk of developing...
cerebrovascular spasm or cerebral infarction (24–26). However, other studies have found no relationship between hyponatremia and functional outcome or mortality (5, 27). There are several potential explanations for this discrepancy. This includes: 1) differences in how hyponatremia is defined (which can be categorized as either present or absent or by varying threshold values and varying numbers of samples), 2) reporting of analyses and models that do not account for duration or severity (e.g., temporal changes over the course of an admission), and 3) use of variable outcome measures, with only a few studies reporting on long-term neurologic status.

Our nonlinear analyses showed marked differences in the patterns of sodium concentration over the course of the ICU stay between patients with favorable and poor outcomes. Those who did poorly manifested an initial peak of sodium concentrations followed by a steady decline. This may represent an initial period of cerebral damage resulting in a later syndrome of inappropriate antidiuretic hormone secretion. In contrast, patients with a favorable outcome exhibited a much more stable sodium trajectory. To our knowledge, this is the first description of this phenomenon in aSAH patients.

Our findings imply that hypernatremia and greater sodium variability, as well as the trajectory of these values over time in critically ill aSAH patients, are associated with poor neurologic outcomes at 6 months. Given that rapid changes in sodium concentrations are known to be associated with osmotic shock-induced neuronal damage, (28) our findings provide the additional epidemiological rationale for future interventional studies aimed at minimizing variability, and maintaining a steady trajectory in plasma sodium concentrations, in this patient group.

Our study has several strengths. We have collected data prospectively from multiple centers across Australia and New Zealand and obtained a large number of data points for analysis. We have used several analytical techniques considering variability, duration and severity and temporal fluctuations in sodium concentrations, with a robust patient-centered primary outcome of 6-month neurologic status.

Limiting our conclusions, as with any observational work, is the fact we cannot infer any causative relationship. Our primary outcome measure may not detect small, but clinically important, outcome differences. Our analysis is hypothesis-generating, and therefore, we did not formally correct for multiple comparisons. Reported secondary outcomes should therefore be interpreted cautiously. Additionally, our strategy used sodium measurements taken for clinical purposes that may have led to a sampling bias, although the number of measurements collected was similar in the two outcome groups. The use of different sampling methods may also have influenced our results. Point of care testing using direct ion-selective electrodes may be more accurate than indirect techniques commonly used in hospital laboratories, especially in hypoproteinemia, commonly seen in critically ill patients (29). Discrepancies between these techniques may have potentially contributed to the variation in sodium measurements we observed.

CONCLUSIONS

In critically ill patients with aSAH, a pattern of initial high sodium concentrations followed by gradual decline was associated with a worse neurologic outcome at 6 months. A higher mean sodium concentration, and greater variability in ICU, were also associated with worse outcomes. These findings provide the epidemiological rationale for future interventional studies aimed at minimizing plasma sodium variability in this patient group.

1   The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia.
2   Royal Brisbane and Women’s Hospital, Brisbane, QLD, Australia.
3   The Wesley Hospital, Brisbane, QLD, Australia.
4   The University of Queensland, Brisbane, QLD, Australia.
5   Royal North Shore Hospital, Sydney, NSW, Australia.
6   Northern Clinical School, Sydney Medical School, University of Sydney, Sydney, NSW, Australia.
7   Royal Melbourne Hospital, Melbourne, VIC, Australia.
8   Sir Charles Gairdner Hospital, Perth, WA, Australia.
9   Austin Health, Melbourne, VIC, Australia.
10  Hunter New England Health, Wallsend, NSW, Australia.
11  The Alfred Hospital, Melbourne, VIC, Australia.
12  Royal Adelaide Hospital, Adelaide, SA, Australia.
13  Wellington Hospital, Wellington, New Zealand.
14  Christchurch Hospital, Christchurch, New Zealand.
15  Auckland City Hospital, Auckland, New Zealand.
16  Gold Coast University Hospital, Gold Coast, QLD, Australia.
17  Discipline of Acute Care Medicine, Department of Surgical Specialties, The University of Adelaide, Adelaide, SA, Australia.
18  Department of Neurocritical Care Medicine, The National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom.
REFERENCES

1. Lai L, Morgan MK: Incidence of subarachnoid haemorrhage: An Australian national hospital morbidity database analysis. J Clin Neurosci 2012; 19:733–739
2. Rinkel GJ, Algra A: Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. Lancet Neurol 2011; 10:349–356
3. The PROMOTE Investigators: Six-month mortality and functional outcomes in aneurysmal sub-arachnoid haemorrhage patients admitted to intensive care units in Australia and New Zealand: A prospective cohort study. J Clin Neurosci 2020; 80:92–99
4. Mapa B, Taylor BE, Appelboom G, et al: Impact of hyponatremia on morbidity, mortality, and complications after aneurysmal subarachnoid hemorrhage: A systematic review. World Neurosurg 2016; 85:305–314
5. Qureshi AI, Suri MF, Sung GY, et al: Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2002; 50:749–755; discussion 755–746
6. Sherlock M, O’Sullivan E, Agha A, et al: The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. Clin Endocrinol (Oxf) 2006; 64:250–254
7. Berendes E, Walter M, Cullen P, et al: Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. Lancet 1997; 349:245–249
8. Brimioulle S, Orellana-Jimenez C, Aminian A, et al: Hyponatremia in neurological patients: Cerebral salt wasting versus inappropriate antidiuretic hormone secretion. Intensive Care Med 2004; 30:125–131
9. Diringer MN, Bleck TP, Claude Hemphill J 3rd, et al; Neurocritical Care Society: Critical care management of patients following aneurysmal subarachnoid hemorrhage: Recommendations from the Neurocritical Care Society’s Multidisciplinary Consensus Conference. Neurocrit Care 2011; 15:211–240
10. Beseoglu K, Etminan N, Steiger HJ, et al: The relation of early hyponatremia with clinical outcome in patients suffering from aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg 2014; 123:164–168
11. Diringer MN, Zazulia AR: Hyponatremia in neurologic patients: Consequences and approaches to treatment. Neurologist 2006; 12:117–126
12. Arieff Al, Guisado R: Effects on the central nervous system of hypernatremic and hyponatremic states. Kidney Int 1976; 10:104–116
13. Tominey S, Bawjea K, Woodfield J, et al: Investigation and management of serum sodium after subarachnoid haemorrhage (SaSH): A survey of practice in the United Kingdom and Republic of Ireland. Br J Neurosurg 2021 Jan 20, [online ahead of print]
14. Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg 1988; 68:985–986
15. Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 1980; 6:1–9
16. Vergouwen MD, Vermeulen M, van Gijn J, et al: Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: Proposal of a multidisciplinary research group. Stroke 2010; 41:2391–2395
17. Wilson JT, Hareendran A, Grant M, et al: Improving the assessment of outcomes in stroke: Use of a structured interview to assign grades on the modified Rankin Scale. Stroke 2002; 33:2243–2246
18. Wood S: Generalized Additive Models: An Introduction With R. Boca Raton, FL, Chapman and Hall/CRC, 2017
19. Pedersen EJ, Miller DL, Simpson GL, et al: Hierarchical generalized additive models in ecology: An introduction with mgcv. PeerJ 2019; 7:e6876
20. Bates D, Mächler M, Bolker B, et al: Fitting linear mixed-effects models using lme4. J Stat Softw 2015; 67:1–48
21. Spatenco B, Bradac O, Skrabalek P: Outcome and frequency of sodium disturbances in neurocritically ill patients. Acta Neurol Belg 2013; 113:139–145
22. Bales J, Cho S, Tran TK, et al: The effect of hyponatremia and sodium variability on outcomes in adults with aneurysmal subarachnoid hemorrhage. World Neurosurg 2016; 96:340–349
23. Adrogue HJ, Madias NE: Hyponatremia. N Engl J Med 2000; 342:1493–1499
24. Chandy D, Sy R, Aronow WS, et al: Hyponatremia and cerebrovascular spasm in aneurysmal subarachnoid hemorrhage. Neurol India 2006; 54:273–275
25. Wijdicks EF, Vermeulen M, Hijdra A, et al: Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: Is fluid restriction harmful? Ann Neurol 1985; 17:137–140
26. Hasan D, Wijdicks EF, Vermeulen M: Hyponatremia is associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. Ann Neurol 1990; 27:106–108
27. Zheng B, Qiu Y, Jin H, et al: A predictive value of hyponatremia for poor outcome and cerebral infarction in high-grade aneurysmal subarachnoid hemorrhage patients. J Neurosurg Psychiatry 2011; 82:213–217
28. Kleinschmidt-DeMasters BK, Norenberg MD: Rapid correction of hyponatremia causes demyelination: Relation to central pontine myelolysis. Science 1981; 211:1068–1070
29. Dimeski G, Morgan TJ, Presnell JJ, et al: Disagreement between ion selective electrode direct and indirect sodium measurements: Estimation of the problem in a tertiary referral hospital. J Crit Care 2012; 27:326.e9–e16