Prevalence of hypohydration and its association with stroke severity and independence outcomes in acute ischemic stroke patients

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A B S T R A C T

Hypohydration has been suggested increasing the risk of vascular diseases, and it is associated with poor prognosis and worse functional outcome in stroke. Most studies have used blood parameters to determine patients' hydration status. The aim of this study was to measure urine osmolality (uOsm) and its influence on stroke severity and independence. A prospective descriptive study was conducted in stroke patients admitted to a stroke unit. All patients underwent neurological evaluation at admission and discharge using the National Institute of Health Stroke Scale (NIHSS). Independence at discharge was evaluated with the Barthel Index (BI) and the modified Rankin Scale (mRS). uOsm was measured at admission. Patients were grouped in "poor fluid intake" (PF) and "euhydration" (EU), the latter if uOsm $\leq$ 500 mOsm/kg. Among 119 included patients, the prevalence of PF was 52%, with no difference observed between groups in demographics or blood samples analyses. PF had higher chances of NIHSS > 8 at admission (OR: 4.7 95% CI: 1.3–17.0; p = 0.02), lower BI at discharge (β: −15.3 95% CI: −26.7 to −3.8; p = 0.01), and worse mRS at discharge (OR: 4.01 95% CI: 1.2–14.0; p = 0.02). These findings are consistent with previous results, suggesting that uOsm may be a factor significantly associated with stroke severity and independence outcome after acute ischemic stroke.

1. Introduction

Hypohydration has been recently confirmed being a predisposing factor for several diseases, and having a relevant effect on cerebrovascular health [1]. Stroke is one of the leading causes of death and disability worldwide, and factors such as disease severity and associated disabilities are predictive of a greater lack of independence. An emerging body of literature suggested hypohydration may predict poor outcomes after stroke, finding high plasma osmolality and blood urea nitrogen on creatinine ratio (BUN/Cr) being associated with clinical and functional outcomes in large samples of patients with ischemic [2,3], and ischemic and haemorrhagic stroke [4]. It was suggested that in patients with ischemic stroke, BUN/Cr $\geq$ 15 was associated with higher infection rates, worse discharge Barthel Index (BI), and worse modified Rankin Scale (mRS). Moreover, hypohydration was associated with higher admission costs. The results were confirmed in ischemic patients treated with the tissue plasminogen activator (tPA), therefore suggesting close monitoring of hydration status despite the use of thrombolytic therapy [5].

Defining hypohydration is often "elusive" [6], and a common consensus for diagnosis is missing [7], as outlined in a recent systematic review on dehydration and acute stroke [8]. Despite serum biomarkers being more commonly reported in clinical studies, urine biomarkers such as 24-h urine osmolality (uOsm) and urine specific gravity (USG) may better reflect a mild and gradual dehydration condition, or chronic low fluid intake [9]. To our knowledge there is a scarcity of studies investigating the effects of chronic low fluid intake prior to the stroke event, on stroke severity and independence. Therefore, this study aimed to investigate the prevalence of hypohydration at stroke onset, considering uOsm as the gold standard for urine biomarkers. Additionally, since a "grey area between dehydration and euhydration" may be present [10], a single urinary sampling uOsm cut-off value of 500 mOsm/kg has been chosen to define hydration status [11].

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2. Materials and methods

2.1. Participants and protocol

A prospective observational study was conducted on patients consecutively admitted to a university hospital stroke unit from August 2017 to June 2018, with a diagnosis of acute ischemic stroke confirmed by neuroimaging evaluation. Informed consent was obtained following institutional regulations. All patients were admitted to the stroke unit if stroke onset occurred <24 h and were treated according to clinical evaluation. Exclusion criteria were selected based on a general protocol that included other longitudinal evaluations: wake-up stroke, poor prognosis in the 3 days following the hospital admission, urinary incontinence, diagnosis of chronic renal disease or serum creatinine at admission >1.5 mg/dL, serum glucose >10.0 mmol/L. A detailed collection of anamnestic and demographic data was performed upon admission, considering pre-admission therapies and comorbidities, such as hypertension (HTN), diabetes (DM), dyslipidaemia, atrial fibrillation (AF), cancer, and hormonal diseases. Stroke severity evaluation was performed by a trained neurologist using the National Institute of Health Stroke Scale (NIHSS) at admission and at discharge from the stroke unit, while independence at discharge was evaluated by a trained nurse with the BI and mRS. These tools have been strongly validated as measures for functional assessment in acute stroke trials, and complete methodology is described elsewhere [12]. The NIHSS is composed by a 15-item neurological impairment scale. The BI is a popular tool using a 10-item scale in which patients are judged upon degree of assistance required for basic activities of daily living (ADL). The mRS consists of a 7-point hierarchical, ordinal scale to measure functional independence [12]. Anamnestic mRS was collected during the first days of hospitalization, asking patients or their caregivers to determine the level of independence prior to the stroke event. Post-stroke complications were grouped in aphasia, dysphagia, haemorrhagic events, neurological worsening, and cardiovascular events. All participants included in the study were tested for dysphagia on the day of admission. A trained nurse administered the 3-ounce water swallow test following standard protocols and in case of suspected dysphagia the test was repeated by a licensed speech pathologist [13]. Fluid intake and therapy were not manipulated in this study, and patients spontaneously consumed food and fluids or were treated with artificial nutrition according to the diagnosis of dysphagia post stroke. A description of common fluid and energy intake in acute stroke patients during hospitalization can be found in a recent paper [14]. Patients were treated with the tPA and were discharged according to medical examination. The present study was approved by the Institutional Review Board and regional Ethics Board (CEUR) and was conducted following the guidelines of the declaration of Helsinki.

2.2. Blood and urine samples collection

Blood and urine samples were collected by a licensed nurse at patient admission to the stroke unit as part of standard clinical practice and following standard protocols and were immediately sent to the hospital laboratory for biochemical analyses. Times at admission (and sample collection) were grouped in 6-h time zones (8:00–14:00, 14:00–20:00, 20:00–2:00, 2:00–8:00) [15]. Blood sample analyses included serum sodium (Na^+), potassium (K^+), glucose (Glu), urea (U) and creatinine (Cr) following standard procedures (AU680, Beckman Coulter, USA). Blood urea nitrogen (BUN) was obtained by dividing urea value by 2.14. Blood serum osmolality (sOsm) was calculated by the equation: 2[Na +] + 2[K +] + [Glucose] + [BUN] (all values in mmol/L) [3]. Urine osmolality (uOsm) was obtained following appropriate protocols and techniques with the depression of the freezing point method (Osmo Station OM-6060, Arkray, Japan).

2.3. Reference values for hydration status, stroke severity and outcome

Hydration status was estimated based on uOsm values measured at admission, with urine concentration >500 mOsm/kg indicating an "poor fluid intake" status, as suggested in the most recent literature on 24-h urine samples [11]. This value was chosen in agreement with previous findings in stroke patients using a USG cut-off value of 1.010 [16], similar to the 1.013 value associated with uOsm 500 mOsm/kg [17]. Therefore, patients were classified as "poor fluid intake" (PF) and "euhydration" (EU) according to this cut-off value. While the BI is commonly reported as a continuous variable, the NIHSS is usually reported as a continuous or dichotomous variable or using a cut-off value of 8 as indicative of "severe stroke" [2]. To predict poor independence or functional outcome, a mRS >2 was considered [5].

2.4. Statistical analysis

All analyses were conducted using IBM SPSS Statistics (v.22.0, Chicago, IL, USA). At our knowledge no study was found in the literature showing urine biomarkers association with clinical and functional outcomes in acute stroke patients; therefore, sample size estimation (GPower) [18] was based on previous results defining hydration status on serum biomarkers, showing poor outcome was present in 43% of the hypohydrated sample compared with 18% of the euhydrated sample [19]. Considering an alpha error of 0.05 and power of 0.8, a sample size of 118 participants was estimated. Normal distribution of data was tested with the Kolmogorov-Smirnov test. Continuous variables with a normal distribution are presented as mean and standard deviations (SDs), those with a skewed distribution as median and inter-quartile ranges (IQRs), and categorical variables as counts and percentages (%). Subgroups were defined based on hydration status. Differences between groups were tested with Student's *t* test for normally distributed continuous variables, Mann-Whitney *U* test for skewed variables, and Pearson's chi square for categorical variables. To determine the association between the prevalence of PF and both clinical and functional outcomes, and to correct for confounding factors, at first stage a univariate analysis was conducted between demographic factors (age, sex, and BMI), clinical variables (including prevalence of HTN, DM, and AF), and PF, with NIHSS at admission, NIHSS at discharge, BI, and mRS. Those factors were selected based on previous publications on this topic [8,20]. Variables which were significantly associated ($p < 0.05$) with outcomes in the univariate analysis, were included in a multivariate analysis using a backward stepwise regression (linear or binary logistic according to the outcome). For the purpose of this study, if PF was found not significant at the univariate analysis, the multivariate regression was not performed. Results are presented as odds ratio (OR) for logistic regression, and β for linear regression, with 95% confidence intervals for B (CI 95%). A value of $p < 0.05$ was considered significant.

3. Results

3.1. Patients' characteristics

A sample of 119 participants (69 ± 16 y) with a diagnosis of ischemic stroke admitted to the stroke unit was included in the analysis. Among this sample, 52% were characterized by uOsm at admission >500 mOsm/kg and they were therefore classified as

PF. No significant difference was observed between groups for demographics, presence of HTN, DM, dyslipidaemia, cancer, or hormonal diseases. A smaller proportion of patients with AF was found in PF (6% vs 23%, $\chi 2 = 5.94$, $p = 0.02$). Blood sample analyses showed no significant difference between groups, with mean BUN/Cr value of 20.1 ± 5.3 in EU and 21.0 ± 6.0 in EU ($t = -3.86$, $p = 0.70$), and calculated serum osmolality of 297 ± 5 mOsm/L in EU and 299 ± 4 in PF ($t = -1.52$, $p = 0.13$) (Table 1).

3.2. Stroke characteristics and outcome

EU and PF were characterized by a similar distribution of stroke according to Bamford's classification and 60% were treated with tPA therapy with no difference between groups ($\chi 2 = 4.45$, $p = 0.22$). No difference was found between groups for admission times of the day ($\chi 2 = 4.22$, $p = 0.24$). Length of stay in the stroke unit was similar between groups (8 ± 2 days, $t = -1.06$, $p = 0.29$) and no significant difference between groups was found in terms of post-stroke complications or mortality (2%, $\chi 2 = 0.01$, $p = 0.95$). No significantly different NIHSS was found between EU and PF at admission (4, IQR: 3 vs 5, IQR: 6, respectively; $p = 0.44$), and EU and PF at discharge (1, IQR: 2 vs 1, IQR: 7, respectively; $p = 0.16$). A lower BI at discharge was found in PF compared to EU (92, IQR: 76 vs 100, IQR: 5, respectively, $p = 0.01$) (Fig. 1). No significant difference was found for anamnestic mRS between groups, whereas larger prevalence of poor mRS outcome at discharge was found in PF and compared to EU (36% vs 14%, respectively; $\chi 2 = 5.87$, $p = 0.02$) (Table 2).

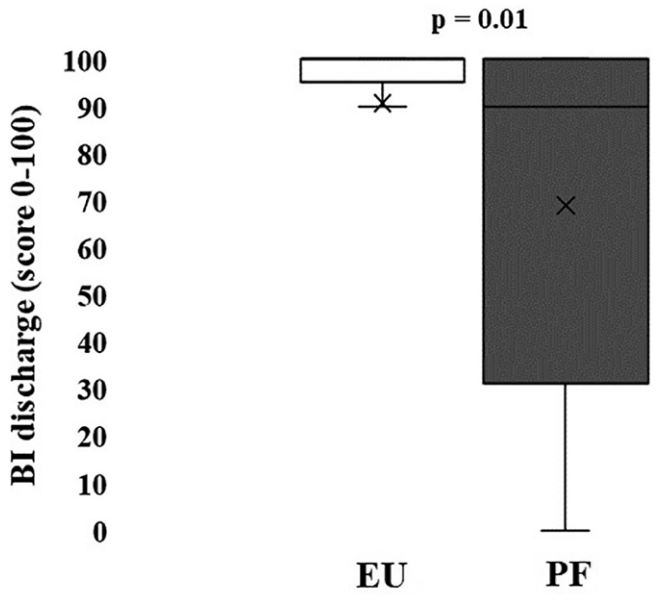

Fig. 1. Difference in BI at discharge between "euhydration" and "poor fluid intake" groups. Boxplots representing Barthel Index (BI) score at discharge in acute stroke patients grouped in the "euhydration" group (uOsm ≤ 500 mOsm/kg, EU) (white), or "poor fluid intake" group (uOsm > 500 mOsm/kg, PF) (grey). Higher values indicating good functional outcome. Significance value for between-groups non-parametric comparison.

3.3. Association of hydration status with clinical and functional outcome

The univariate model suggested significant associations between male sex (OR: 3.9 95% CI: 1.3–11.9; $p = 0.02$) and PF (OR: 3.3 95% CI: 1.1–9.9; $p = 0.03$) with the NIHSS score expressed as a dichotomous variable. When those factors were included in the multivariate regression, both male sex (OR: 3.9 95% CI: 1.2–12.3; $p = 0.02$) and PF (OR: 4.7 95% CI: 1.3–17.0; $p = 0.02$) remained significantly associated with a more sever stroke (NIHSS >8). When the univariate analysis was conducted with stroke severity at discharge, no association with PF was found. Factors associated in the univariate analysis with the BI at discharge were BMI (β: −2.1 95% CI: −4.0 to −0.1; $p = 0.04$), NIHSS at baseline (β: −3.3 95% CI: −4.4 to −2.2; $p < 0.01$), and PF (β: −21.6 95% CI: −34.6 to −8.6; $p = 0.01$). Among these, only NIHSS at baseline (β: −4.6 95% CI: −6.8 to −2.5; $p < 0.01$) and PF (β: −15.3 95% CI: −26.7to −3.8; $p = 0.01$) remained significant in the multivariate analysis. Factors associated in the univariate analysis with a worse mRS score at discharge (>2) were BMI (OR: 1.2 95% CI: 1.0–1.4; $p = 0.02$), HTN (OR: 3.5 95% CI: 1.1–11.4; $p = 0.04$), NIHSS at baseline (OR: 1.2 95% CI: 1.1–1.4; $p < 0.01$), tPA (OR: 3.9 95% CI: 1.5–10.1; $p < 0.01$) and PF (OR: 3.5 95% CI: 1.2–9.8; $p = 0.02$); NIHSS at baseline (OR: 1.3 95% CI:

Table 1
Demographic and clinical characteristics of acute stroke patients. Data are presented as mean ± sd or proportion as appropriate.

Personal Characteristics at Admission	EU n = 57	PF n = 62	Total n = 119	Sig.
Age (y)	72 ± 13	66 ± 18	69 ± 16	0.63
Sex (M/F, %)	53/47	50/50	53/47	0.46
Mass (kg)	75 ± 15	73 ± 18	74 ± 16	0.58
BMI ($kg \cdot m^{-2}$)	25.0 ± 4.5	25.4 ± 5.4	25.3 ± 4.9	0.72
Comorbidities (%)				
Hypertension	72	58	66	0.14
Diabetes	25	18	22	0.37
Dislipidemia	28	22	26	0.52
Cancer	11	4	7	0.20
Atrial Fibrillation	23	6	14	**0.02**
Hormonal	11	5	7	0.40
Blood sample analyses				
sNa (mmol/L)	138 ± 3	139 ± 2	139 ± 2	0.50
sK (mmol/L)	3.9 ± 0.4	3.9 ± 0.3	3.9 ± 0.3	0.54
sGlu (mmol/L)	6.8 ± 1.7	6.9 ± 2.1	6.9 ± 1.8	0.80
sCr (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.84
sU (mmol/L)	35.7 ± 10.1	36.7 ± 10.2	36.6 ± 12.6	0.96
BUN/Cr	20.1 ± 5.3	21.0 ± 6.0	20.9 ± 5.9	0.70
c-sOsm (mOsm/L)	297 ± 5	299 ± 4	298 ± 5	0.13

Notes: Participants' age (y), sex (M/F, %), body mass (Mass, kg), body mass index (BMI, $kg \cdot m^{-2}$), comorbidities frequency (%) and blood sample analyses: serum sodium (sNa, mmol/L), potassium (sK, mmol/L), glucose (sGlu (mmol/L), creatine (sCr,), urea (sU, mmol/L), BUN/cr, and calculated osmolality (c-sOsm (mosm/L). Results are organized in participants with urine osmolality ≤500 mOsm/kg (eurhydration, EU) and >500 mOsm/kg (poor fluid intake, PF). Significance value for intergroup comparison. Bold values for $p < 0.05$.

Table 2
Stroke characteristics, complications, and clinical and functional outcome. Data are presented as proportion, median (IQR), or mean ± sd as appropriate.

Stroke Characteristics and Outcome	EU n = 57	PF n = 62	Total n = 119	Sig.
Bamford Stroke class (%)				0.22
LACI	21	25	22	
PACI	66	50.0	60	
POCI	9	10	10	
TACI	4	16	10	
Time at admission (%)				
8:00–14:00	23	28	25	0.24
14:00–20:00	45	42	44	
20:00–2:00	20	19	19	
2:00–8:00	12	11	12	
tPA (%)	64	59	60	0.64
NIHSS admission	4 (3)	5 (6)	5 (4)	0.44
NIHSS discharge	1 (2)	1 (7)	1 (3)	0.16
BI discharge	100 (5)	92 (76)	100 (30)	**0.01**
mRS > 2 anamnestic (%)	2	2	2	1.00
mRS > 2 discharge (%)	14	36	25	**0.02**
Complications (%)				
Hemorragic events	2	4	3	0.59
Infections	8	2	5	0.15
Neurologic	0	4	4	0.16
Dysphagia	20	26	25	0.40
Length of stay (days)	8 ± 2	8 ± 3	8 ± 2	0.29
Mortality (%)	2	2	2	0.95

Notes: Bamford Stroke Classification: *LACI* lacunar infarct, *PACI* partial anterior circulation infarct, *POCI* posterior circulation infarct, *TACI* total anterior circulation infarct (%), time at admission grouped in different times of the day (from 8:00 to 14:00, from 14:00 to 20:00, from 20:00 to 2:00, from 2:00 to 8:00), tissue plasminogen activator (tPA) administration (%), National Institute of Healthy Stroke Scale (NIHSS) at admission and discharge, Barthel Index (BI) at discharge, poor independence (mRS > 2) (%) anamnestic and at discharge, complications frequency (%). Results are summarized for participants with urine osmolality ≤500 mOsm/kg (eurhydration, EU) and >500 mOsm/kg (poor fluid intake, PF). Significance value for intergroup comparison. Bold values for $p < 0.05$.

1.2–1.4; p = 0.02), tPA (OR: 4.0 95% CI: 1.6–10.3; p < 0.01) and PF (OR: 4.01 95% CI: 1.2–14.0; p = 0.02) remained statistically significant in the multivariate analysis.

4. Discussion

Results from this study suggest a prevalence of a "poor fluid intake" status, based on uOsm at admission, in 52% of acute ischemic stroke patients. This proportion seems to be comparable with previous results detecting the prevalence of "hypohydration" based on blood parameters (namely, BUN/Cr > 15) for between 48% and 53% of stroke patients [4,21]. Nevertheless, detection of hypohydration strongly depends both on the biomarker and its cut-off value, as shown in a study conducted on a large sample of ischemic stroke patients using a urea-to-creatinine ratio (U:C) > 80 that found a prevalence of hypohydration in 36% of the sample on the day of admission [19]. Therefore, a common consensus is currently lacking to define hypohydration in clinical studies, in particular in acute stroke patients [8].

Despite the common use of blood parameters such as serum osmolality or BUN/Cr to determine hydration status, which showed higher values in stroke patients compared with healthy controls [22], blood biomarkers may be more indicated to define acute changes in hydration status, whereas biomarkers of urine concentration are highly useful for daily hydration monitoring, and they may be of clinical relevance for the evaluation of health-associated risks [15,23,24]. In our sample, we observed different a prevalence of poor fluid intake between urine and blood samples; these findings are in-line with the above mentioned differences in assessing hydration status. Urine specific gravity (USG) > 1.010 was suggested to be associated with a 2.78 times increased risk of stroke in evolution (SIE) [25]. Recent evidence suggests a 24-h urine concentration above 500 mOsm/kg may reflect a reduced fluid intake status, and represents more gradual dehydration [11]; nevertheless, a 24-h collection may be impractical in some clinical settings and single urine sampling may be more feasible. Due to circadian variation, urinary biomarkers are subject to within-day fluctuations with first-morning sample tending to overestimate 24-h values, while mid- to late-afternoon spot urine sample equivalent to corresponding 24-h values in free-living healthy young adults [15]. In this sample, most patients (44%) were admitted in the afternoon (14:00–20:00), and 25% were admitted in the morning (8:00–14:00). However, since wake-up stroke patients (i.e., where a patient awakens with stroke symptoms that were not present prior to falling asleep) were excluded, it may be speculated that only a small fraction of collected samples were first-morning voids. Since of the significant association between PF and EU with NIHSS, BI and mRS, this study encourages the implementation of the 500 mOsm/kg cut-off when single urinary samples are collected.

In current sample similar demographics, blood electrolytes concentration, stroke characteristics, and administered therapy were found in participants showing uOsm values suggesting PF or EU hydration status. Findings from this study found a clinical evaluation of stroke severity (NIHSS > 8) more common in PF patients compared to EU, with a 4-times higher risk of a severe stroke. Despite potential reduced severity at admission, no significant effect was observed on the NIHSS at discharge from the stroke unit. Two measures of independence at discharge were used to observe the effects of hydration status on recovery. The BI, a 0–100 score whose higher scores predict a higher degree of independence, was found being associated with hydration status, suggesting PF was significantly associated with lower scores. Nevertheless, different patients were classified within the higher values of the scale, potentially affecting results. The mRS is a scale of functional independence and is commonly reported as dichotomous with values >2 indicating poor prognosis and worse outcome. In our sample, a 4-times higher risk of worse mRS was found in PF patients compared to the EU. Thrombolytic therapy is crucial for ischemic stroke management and recovery. Since results from this study included tPa administration in the multivariate model and similar proportions of patients in the two groups received tPA, this study confirms previous findings indicating that hypohydration remains a

significant prognostic factor also in participants treated with tPA [5].

The mechanisms involved in the protective effect of hydration on ischemic stroke are still a debated issue, but some hypotheses have been proposed suggesting dehydration may reduce brain perfusion, increase fatigue, and impair neuroplasticity [8]. An animal model of chronic dehydration found altered metabolic activity in some regions of the brain, with many brain regions having a reduced metabolism [26]. In humans, studies described the role of hydration using blood viscosity, showing that individuals with higher blood viscosity were characterized by a higher burden of atherosclerotic disease [27,28]. Moreover, preliminary results suggest better hydration status may be associated with the development of collateral flow after occlusion, a predictor of favourable outcome [29]. While on the one hand clinical outcome and stroke severity may be explained by the above-mentioned factors, on the other worse functional outcome observed in hypohydrated individuals may be described by the influence of hydration status on cognitive function, fatigue, and position hypotension, factors that may contribute to a better engagement in physical therapy and rehabilitation [30]. Since hypohydration is classically reported not only at admission but also during hospitalization as recently observed [14], some trials showed that fluid therapy based on BUN/Cr or USG may prevent SIE and foster better outcomes in ischemic stroke patients [16,31].

4.1. Study considerations, novelty, and practical application

To the best of our knowledge, this is the first study measuring uOsm in acutely admitted ischemic stroke patients as a measure of hypohydration and its effect on stroke severity and outcome. This biomarker was selected based on the emerging scientific production proposing a 24-h uOsm cut-off value of 500 mOsm/kg to describe a "poor fluid intake" status and its association with poor health and increased risk of several diseases [11]. Since the results presented in this study were based on a single urine sampling, a limitation of this study may depend on the different times of the day the sample was collected. Nevertheless, statistical analysis showed a similar time at admission distribution between groups, and PF was independently associated with outcomes. The sample included in this study had strict inclusion/exclusion criteria, therefore results should be generalized only to moderately severe strokes being treated in a stroke unit. Discharge occurred 8 ± 2 days after stroke; therefore, present results refer to short-term independence outcomes and future data may be collected to evaluate long-term effects. Additionally, present results indicate an association between hydration status and outcomes, and more studies are needed before a causation effect may be confirmed.

5. Conclusions

Results from this study confirm previous findings observing a significant association of hypohydration with poor prognosis and worse functional outcome after acute ischemic stroke. Prevalence of "poor fluid intake", defined by uOsm > 500 mOsm/kg, may characterize about half of the acutely admitted stroke patients and in absence of kidney diseases, but it may not be identified by serum osmolality. A single urine sampling "poor fluid intake" status was found to potentially being associated with a more severe stroke at admission and worse independence outcome at discharge. These preliminary findings promote the inclusion of hydration status evaluation after cerebrovascular diseases and encourage further studies to determine the potential pathophysiological mechanisms involved. A 24-h urine osmolality cut-off value of 500 mOsm/kg may be translated in clinical practice during single spot sampling. In the absence of a common consensus on the best biomarker and its cut-off value, the measurement of both serum and urine parameters should be considered.

Declaration of Competing Interest

The authors declare no conflict of interest for this study, and this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. ACQUA@BRAIN was part of the standard care of the ASUITs stroke unit and was supported by regional fundings for quality improvement.

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