Urine Electrolyte to Predict Treatment Failure of Fluid Restriction in Syndrome of Inappropriate Antidiuresis

A Prospective Multicenter Study

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Key Points

- The Furst equation helps identify patients at risk of fluid restriction failure in syndrome of inappropriate antidiuresis, although its predictive performance is limited.
- Additional urinary biomarkers beyond the Furst equation may not improve the prediction of fluid restriction response.

Abstract

Background The syndrome of inappropriate antidiuresis (SIAD) is a common cause of hyponatremia in hospitalized patients, with fluid restriction (FR) as the first-line treatment. However, up to 50% of patients fail to respond to FR, highlighting the need for reliable predictors of treatment failure. Therefore, this study aimed to evaluate the predictive performance of urinary biomarkers, including the Furst equation (the ratio of the sum of urinary sodium and potassium concentrations to plasma sodium), urine osmolality, and urine output, in identifying nonresponders to FR.

Methods This prospective multicenter cohort study was conducted at two medical centers in Thailand from September 2022 to June 2024 and included 79 hospitalized patients with SIAD. Response to FR was defined as an increase in serum sodium level of ≥3 mEq/L by day 4, with no decrease in serum sodium levels at any point during the FR period. Predictive performance was assessed using sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) for each biomarker. Multivariable logistic regression analysis incorporating all urinary biomarkers was also performed.

Results Overall, 59% of patients failed to respond to FR by day 4, and adherence to FR was modest (72%). The Furst equation demonstrated the best predictive performance, with an optimal cutoff of 0.86 (sensitivity: 55.3%; specificity: 70.2%, AUC: 0.65). Combining the Furst equation with urine osmolality and urine output improved specificity to 91.0%, although sensitivity decreased to 32.3%. A multivariable logistic regression model achieved similar discrimination (AUC: 0.67) compared with the Furst equation alone.

Conclusions Although the Furst equation can identify nonresponders to FR, its predictive performance is limited. Our findings suggest that other urinary biomarkers beyond the Furst equation may not improve overall predictive accuracy for predicting nonresponse to FR. These findings highlight the need for more effective predictive tools. Further studies are warranted to validate these results and optimize treatment strategies for SIAD.

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Introduction

The syndrome of inappropriate antidiuresis (SIAD) is a common cause of hyponatremia, affecting approximately 40% of hospitalized patients with hyponatremia.[1–3] SIAD results from inappropriate secretion of arginine vasopressin in response to nonosmotic stimuli such as malignancy, medications, and central nervous system or pulmonary disorders. Hyponatremia in hospitalized patients has been associated with prolonged hospital stays,[1,4–6] increased hospital costs,[1,6] readmissions,[5] and higher mortality rates.[1,4,6–8]

Clinical guidelines recommend fluid restriction (FR) as the first-line treatment for SIAD.[9,10] Although FR can modestly increase serum sodium levels, approximately 50% of patients fail to respond.[11] Nonetheless, FR remains the most cost-effective and least toxic therapy compared with alternative treatments such as tolvaptan, urea, sodium-glucose cotransporter 2 inhibitors (SGLT2i), or the combination of sodium chloride tablets and diuretics. Early and effective correction of hyponatremia in hospitalized patients is crucial because delayed correction is associated with higher mortality rates,[12,13] whereas rapid resolution is linked to shorter hospital stays[12,13] and reduced health care costs.[1] Therefore, accurately identifying patients likely to respond to FR, and those who are not, is clinically important. Clinical guidelines indicate that patients with high urine osmolality (>500 mOsm/kg) and a combined urine sodium and potassium concentration exceeding the serum sodium level, defined by the Furst equation ($U_{Na}+U_K/S_{Na}>1$), are unlikely to respond to FR.[10] However, these recommendations are primarily based on pathophysiologic principles, where high urine osmolality or elevated ratio of urine sodium plus potassium to serum sodium indicates negative electrolyte-free water clearance. They may not fully consider real-world factors, such as patient adherence to FR, solute intake, and underlying causes of SIAD, all of which can influence treatment response.

Conflicting results have been reported regarding the ability of the Furst equation to predict FR.[11,14] One study, limited by a small sample size of only 22 patients, did not find a significant association between the Furst equation and FR response.[11] Another study demonstrated marginal significance; however, it was a secondary analysis that evaluated FR response over a short observation period of only 1 day, which may have been insufficient to determine treatment efficacy accurately.[14]

Given the high prevalence of SIAD in hospitalized patients and the lack of robust, high-quality data to guide response to FR in real-world clinical settings, we conducted a prospective cohort study to address these gaps. This study aimed to evaluate the predictive performance of the Furst equation in identifying nonresponders to FR. We hypothesized that a Furst equation value >1 would accurately identify patients unlikely to respond to FR.

Methods

This prospective multicenter cohort study was conducted at Hatyai Hospital, a regional referral center, and Phanatnikhom Hospital, a tertiary care hospital in Thailand, between September 2022 and June 2024. Patients were consecutively recruited from general internal medicine and subspecialty wards, representing a hospitalized population admitted primarily for medical conditions such as pulmonary disease, malignancy, and neuropsychiatric disorders. A total of 91 patients aged 18 years or older with hypotonic hyponatremia (serum sodium level <130 mEq/L and serum osmolality <275 mOsm/kg) due to SIAD were recruited. The diagnosis of SIAD was based on Bartter and Schwartz criteria.[15] The diagnostic criteria were as follows: (*1*) serum osmolality <275 mOsm/kg; (*2*) urine osmolality >100 mOsm/kg; (*3*) clinical euvolemia confirmed by history and physical examination, as evaluated by two independent physicians; (*4*) urine sodium level >30 mEq/L; and (*5*) an eGFR ≥45 ml/min per 1.73 m^2 and absence of diagnosed AKI, hypothyroidism, glucocorticoid deficiency, and diuretic therapy.

Patients were enrolled prospectively during hospitalization once they fulfilled all eligibility criteria, including the ability to be observed prospectively for a minimum of 4 days after enrollment. Before enrollment, patients were informed that they would need to remain hospitalized for at least 4 days after initiating FR to allow consistent monitoring of serum sodium levels and adherence to the study protocol, which was essential for accurately assessing the primary outcome.

Patients were eligible for enrollment at any time during hospitalization, provided they satisfied all inclusion and exclusion criteria (Supplemental Method 1). However, patients who had already received specific treatments for SIAD before enrollment—including FR, sodium chloride tablets, diuretics, SGLT2i, urea, or tolvaptan—were excluded from participation. This study was conducted in accordance with the Declaration of Helsinki. The study protocol (Thai Clinical Trials Registry, TCTR20221206001) was approved by the Institutional Review Board of Hatyai Hospital (approval number HYH EC 045-65-01) and the Chonburi Provincial Health Office (approval number CBO Rec 66–080). All patient data were analyzed anonymously, and written informed consent was obtained from all patients or their legal guardians, as applicable.

Baseline Procedures

After obtaining a detailed medical history, a standardized clinical and biochemical evaluation of serum and urine samples was performed. The biochemical assessment before FR included venous sampling for determining serum glucose, urea, creatinine, uric acid, sodium, potassium, chloride, bicarbonate, osmolality, morning cortisol, and thyroid-stimulating hormone levels, as well as urinary sampling for determining sodium, potassium, osmolality, uric acid, and creatinine levels. In addition, clinicians were not blinded to the urine chemistry results during the evaluation.

FR Protocol

Patients were instructed to restrict their daily oral fluid intake to <800 ml. Although a FR of <1 L per day is often recommended,[16] we chose the 800 ml limit for several reasons. First, this limit allows for administering any necessary intravenous fluids during hospitalization. Second, it

is more achievable for patients compared with a more stringent restriction of <500 ml per day; in a previous randomized controlled trial, only 43% of patients assigned to restrict their fluid intake to <500 ml per day adhered to the protocol.[17] FR was prescribed for a total duration of 7 days. Adherence to FR was assessed daily during hospitalization. Compliance was ensured through daily monitoring and recording of fluid intake (oral and intravenous), as well as patient education and regular reinforcement by the clinical care team. BP, volume status, fluid intake, and output were monitored daily. Blood samples were collected at baseline and on days 2, 4 (after 3 days of treatment), and 7 to measure plasma urea, electrolytes, and creatinine. In addition, blood samples were collected if patients developed symptoms of hyponatremia (Supplemental Method 2). All patients were advised to maintain a normal dietary sodium intake. If intravenous fluids were required for antibiotic administration, the pharmacist was consulted to minimize the volume of diluent, and other intravenous fluids were prohibited during FR if possible. Adherence to the FR protocol was defined as maintaining a total fluid intake (oral plus intravenous) of <1000 ml/d for >75% of the hospital stay. Patients who developed AKI, as defined by the Kidney Disease Improving Global Outcomes guidelines,[18] were classified as nonresponders to FR. Patients with hypotension, defined as a BP of <90/60 mm Hg on bedside measurement, or those who were lost to follow-up, were also classified as nonresponders to FR. Other treatments for hyponatremia, such as sodium chloride tablets, diuretics, SGLT2i, urea, or tolvaptan, were not permitted during the study.

Response to FR Criteria

Response to FR at day 4 was defined as an increase in serum sodium level of at least 3 mEq/L. Response to FR at day 7 was defined as meeting the day 4 response criteria and demonstrating either an increase of >5 mEq/L from baseline or achieving a serum sodium level of >130 mEq/L. In addition, there must be no decrease in serum sodium levels at any point during the FR period. We selected the criterion of increase in serum sodium level of >3 mEq/L by day 4 as the measure of FR response to facilitate comparison with the previous study.[11,19] Day 7 was selected because it represents a reasonable target for increasing serum sodium levels to normal or near-normal levels. Adjunctive therapy was permitted only after patients were identified as nonresponders. Patients who received adjunctive treatment before the day 4 evaluation were classified as nonresponders at day 4, regardless of any subsequent improvements in serum sodium levels. Similarly, patients who received adjunctive therapy between days 4 and 7 were considered nonresponders for the day 7 evaluation. Thus, the classification of response strictly reflected outcomes attributable to FR alone, without influence from adjunctive treatments.

Predictor of Nonresponders

Predictors, including urine osmolality and the Furst equation ($U_{Na}+U_K/S_{Na}$), of nonresponders were identified at baseline. In addition, 24-hour urine output measured on day 1 after initiating FR was used as a predictor.

Statistical Analysis

Patients were categorized as responders or nonresponders to FR on the basis of their response to the FR criteria on day 4. Categorical variables are presented as number and percentage, and differences between the two groups were assessed using the chi-square test or Fisher exact test, as appropriate. Continuous variables are presented as mean, SD, median, and interquartile range, depending on distribution normality. Differences between groups were evaluated using the Student *t* test for normally distributed variables or the Wilcoxon rank-sum test for non-normally distributed variables. Missing baseline data were singly imputed using predictive mean matching. Although multiple imputations were generated using the mice package in R,[20] only the first imputed dataset was used for analysis. This approach was chosen to simplify the analytical process while preserving representativeness and ensuring practical interpretability of the results.

The primary outcome was the accuracy of the Furst equation in predicting nonresponders to FR at day 4. Predictive performance was evaluated using the area under the receiver operating characteristic curve (AUC). A nested bootstrapping approach was used using the R package cutpointr[21] to determine the optimal cutpoint by identifying the threshold that maximizes the Youden index. The inner bootstrap estimated cutpoints, while the outer bootstrap assessed the stability and generalizability of performance metrics, including AUC, sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy. These metrics were calculated for both predefined cutpoints based on international guidelines[10] and *post hoc*–derived optimal cutpoints, along with their 95% exact binomial confidence intervals.

We also conducted multivariable logistic regression analysis using continuous values of the Furst equation, urine osmolality, day 1 urine output, age, sex, and serum creatinine. More details of the statistical analysis and sample size calculation are provided in the Statistical Analysis Plan. All analyses were conducted using the statistical software package R (R Core Team, 2024)[22] with a significance level (α) of 5%.

Results

Baseline Characteristics

A total of 91 patients were deemed suitable for inclusion, and 79 of these patients received FR from September 2022 to December 2024 (Figure 1). Among these, 32 (41%) patients responded to FR by day 4, while 47 (59%) did not. Only one patient was lost to follow-up during the study. This patient had met the response criteria at day 4 but was discharged prior to the day 7 evaluation and did not return for scheduled follow-up. Owing to the absence of subsequent laboratory or clinical data, this patient was conservatively classified as a nonresponder in the day 7 analysis, in accordance with the study's prespecified analytic plan.

Eighteen (22.8%) patients were admitted primarily for hyponatremia, whereas the remaining 61 (77.2%) were hospitalized for other conditions and later diagnosed with SIAD. The most common SIAD etiologies were malignancy (30.4%), pulmonary disease (24.1%), and idiopathic causes

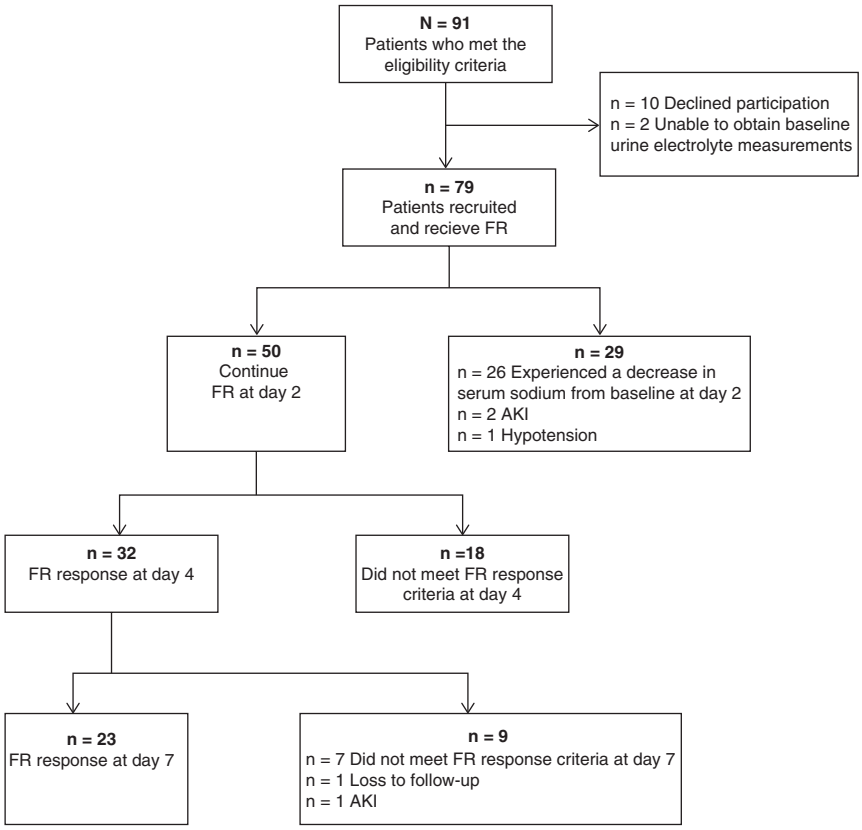

Figure 1. Study flow diagram. A visual representation of the study flow. FR, fluid restriction.

(22.8%), followed by neuropsychiatric disorders (8.9%), medication-induced SIAD (7.6%), and HIV-associated SIAD (6.3%). Baseline characteristics, including demographic and clinical variables, were comparable between responders and nonresponders (Table 1).

No significant differences were observed between responder and nonresponder groups with respect to median serum sodium levels (126 [123–128] versus 126 [124–128] mEq/L, $P = 0.88$) and mean urine osmolality (424±159 versus 439±149 mOsm/kg, $P = 0.68$). However, the Furst equation was significantly higher among nonresponders (1.0 [0.7–1.2]) than among responders (0.8 [0.6–0.8], $P = 0.01$).

FR Adherence

Fluid intake and urine output during the first 4 days were not significantly different between the two groups (Figure 2). The overall adherence rate was 72% in the study participants. Adherence to FR was greater in responders than in nonresponders (84% versus 64%, $P = 0.084$), although this difference was not statistically significant.

Change in Serum Sodium Levels

Overall, 26 (33%) patients showed a decrease in serum sodium level from baseline by day 2. An additional 18 (23%) patients failed to meet the FR response criteria by day 4 (Figure 1). By day 4, the median change in serum sodium from baseline was 7.0 mEq/L (4.0–9.0) among responders and 0.3 mEq/L (−0.5–2) among nonresponders. Of the patients who responded by day 4, 23 (29%) achieved an increase in serum sodium levels of >5 mEq/L, and 24 (30%) reached serum sodium levels >130 mEq/L.

An additional nine (11%) patients failed to meet the FR response criteria by day 7. The median change in serum sodium level from baseline was 7.3 mEq/L (6.1–10.7) in responders and 2.1 mEq/L (0.1–3.0) in nonresponders. Among patients who responded by day 7, 19 (24%) achieved an increase in serum sodium level of >5 mEq/L, and 20 (25%) exceeded the level of 130 mEq/L.

Predictive Performance of Urinary Biomarkers in Predicting Nonresponse to FR at Day 4

Table 2 presents the predictive performance of individual predictors, rule-based combinations, and multivariable modeling approaches in identifying nonresponse to FR. Among individual biomarkers, the Furst equation demonstrated the best performance with an AUC of 0.65 (0.53–0.77), while urine osmolality and urine output showed lower discriminative ability with AUCs of 0.51 (0.38–0.65) and 0.55 (0.36–0.70), respectively.

For individual biomarkers, the Furst equation showed the best balance of sensitivity and specificity at an optimal cutoff of 0.86, achieving 60.9% accuracy (48.4 to 72.5), 55.3% sensitivity (37.4 to 75.0), and 70.2% specificity (41.6 to 90.0). By contrast, urine osmolality and

Table 1. Baseline characteristics of syndrome of inappropriate antidiuresis patients with and without response to fluid restriction

Characteristic	Responders (n=32)	Nonresponders (n=47)
Age, yr	67±14	67±14
Female sex, n (%)	16 (50)	15 (32)
BMI, kg/m^2	19.3 (17.5–21.3)	19.8 (17.5–21.5)
BUN, mg/dl	13 (9–15)	10 (9–13)
Serum creatinine, mg/dl	0.69±0.2	0.70±0.2
eGFR, ml/min per 1.73 m^2	94±18	96±19
Serum sodium, mEq/L	126 (123–128)	126 (124–128)
Serum osmole, mOsm/kg	256 (245–267)	258 (246–262)
Serum uric acid, mg/dl	2.8 (2.2–3.9)	2.9 (2.2–4.2)
FE uric acid, (%)	14.8 (8.3–21.5)	15.0 (9.9–21.0)
Urine sodium, mEq/L	59.6 (42.7–87.4)	87.8 (62.5–112)
Urine potassium, mEq/L	27.9 (12.9–45.3)	28.4 (18.4–36.8)
Urine osmole, mOsm/kg	424±159	439±149
Furst equation	0.8 (0.6–0.8)	1.0 (0.7–1.2)
Urine output day 1, ml	1300 (1188–1725)	1450 (1050–1775)
Etiology of SIAD		
Pulmonary disease	6 (18.8)	13 (27.7)
Malignancy	11 (34.3)	13 (27.7)
Neuropsychiatric disorder	2 (6.3)	5 (10.6)
Medication	3 (9.4)	3 (6.4)
HIV disease	1 (3.1)	4 (8.5)
Idiopathic	9 (28.1)	9 (19.1)

Data are presented as mean±SD, median (interquartile range), or number (percent). BMI, body mass index; FE, fractional excretion; SIAD, syndrome of inappropriate antidiuresis.

urine output alone demonstrated poor specificity, with values below 50%, despite sensitivities of 56.1% and 57.9%, respectively.

Combined Furst equation and urine osmolality achieved a specificity of 84.8% (71.4 to 100) and PPV value of 81.5% (66.5 to 100.0), although the sensitivity remained modest at 46.5% (29.4 to 63.2). The addition of urine output further improved the specificity to 91.0% (80.0 to 100) and PPV to 83.6% (60.0 to 100); however, the sensitivity dropped to 32.3% (17.6 to 47.1). Notably, similar specificity (84.4%) could be achieved by simply raising the Furst equation threshold to 1.053, with comparable sensitivity (44.7%)

The multivariable logistic regression model achieved an AUC of 0.67 (0.52–0.80). Among all predictors included, the Furst equation was the only variable that reached statistical significance (P = 0.029). At the optimal threshold, the model demonstrated a sensitivity of 54.0% (33.0 to 73.3) and a specificity of 73.8% (41.7 to 93.8). Receiver operating characteristic (ROC) curves for all predictors are presented in Figure 3. The full model equations and corresponding regression coefficients for day 4 are provided in the Supplemental Appendix.

Predictive Performance of Urinary Biomarkers in Predicting Nonresponse to FR at Day 7

At day 7, the Furst equation demonstrated the highest discriminative performance among individual biomarkers, with an AUC of 0.66 (0.54–0.81). The multivariable logistic regression model achieved improved performance with an AUC of 0.72 (0.57–0.86). Detailed day 7 performance metrics are presented in Supplemental Table 1. ROC curves are presented in Supplemental Figure 1. Complete model equations with regression coefficients are available in the Supplemental Appendix.

Patients with SIAD Who Had a Predictor of Nonresponse to FR

Overall, 35 (44%) had a Furst equation value of >0.86, 46 (58%) had a urine osmolality of >398 mOsm/kg, and 46 (58%) had a urine output of <1353 ml. Among these, 26 (33%) patients had a Furst equation value of >0.86 and a urine osmolality of >398 mOsm/kg, whereas 15 (19%) patients met the criteria for all three predictors. In addition, 68 (86%) patients exhibited at least one predictor for nonresponse to FR.

Adverse Events

The adverse events reported in the study participants are summarized in Supplemental Table 2. Hypokalemia was the most frequent adverse event in seven patients (three responders and four nonresponders). Three patients had AKI and four reported fatigue, which was more common in nonresponders. One nonresponder experienced hypotension, which was attributed to antihypertensive medication. Among the patients who developed AKI, two experienced sepsis during hospitalization, and one had diarrhea.

Discussion

This prospective multicenter study evaluated the utility of urinary biomarkers for predicting FR failure in hospitalized patients with SIAD. The Furst equation consistently

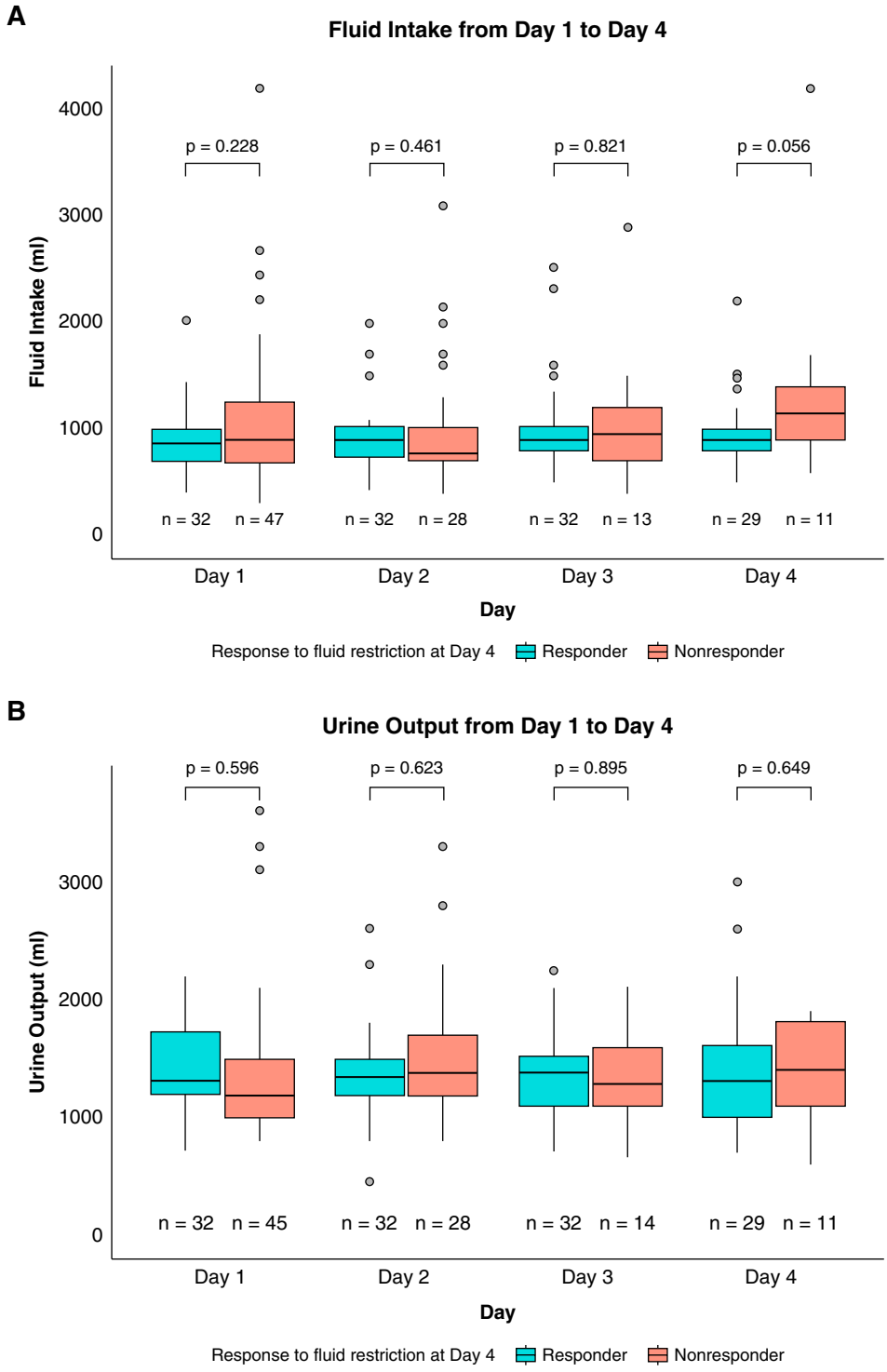

Figure 2. Fluid intake and urine output during the first 4 days of FR. Box plots showing (A) daily fluid intake (ml) and (B) daily urine output (ml) over the first 4 days of FR. Boxes represent the IQR, with the thick horizontal line indicating the median. Whiskers extend to the most extreme data points within 1.5 times the IQR from the box edges. Outliers, if present, are shown as individual points. IQR, interquartile range.

outperformed urine osmolality and urine output as an individual predictor across time points, demonstrating modest but superior discriminative ability. When we incorporated all available predictors into a multivariable logistic regression model, the resulting AUC remained comparable with that of the Furst equation alone.

Our prospective study evaluated the predictive performance of the Furst equation in identifying nonresponse to

Table 2. Predictive performance of urinary biomarkers in predicting nonresponse to fluid restriction by day 4

Test	Full Cohort		Sensitivity	Specificity	PPV	NPV
	AUC	Cutoff	% (95% CI)			
Furst equation with predefined cutoff	NA[a]	1	49.3 (33.3 to 66.7)	77.9 (62.5 to 100.0)	77.8 (59.9 to 100.0)	48.9 (33.3 to 66.7)
Furst equation	0.65 (0.53–0.77)	0.86	55.3 (37.4 to 75.0)	70.2 (41.6 to 90.0)	74.9 (57.1 to 91.7)	50.0 (35.2 to 66.8)
Urine osmole with predefined cutoff, mOsm/kg	NA[a]	500	32.3 (18.7 to 44.4)	65.1 (49.8 to 84.7)	59.6 (37.5 to 83.5)	37.4 (24.9 to 50.0)
Urine osmole, mOsm/kg	0.51 (0.38–0.65)	396	56.1 (27.6 to 87.5)	43.1 (15.4 to 69.2)	60.4 (42.9 to 75.0)	39.0 (22.2 to 53.9)
Urine output, with predefined cutoff, ml	NA[a]	1500	77.3 (62.5 to 92.9)	31.2 (13.3 to 50.2)	61.7 (47.4 to 76.2)	49.5 (25.0 to 75.1)
Urine output, ml	0.55 (0.36–0.70)	1353	57.9 (22.1 to 88.9)	44.8 (16.6 to 77.0)	54.5 (37.4 to 72.8)	31.2 (0.0 to 50.0)
Furst equation and urine osmole	NA[a]	As above[b]	46.5 (29.4 to 63.2)	84.8 (71.4 to 100.0)	81.5 (66.5 to 100.0)	50.9 (35.7 to 64.7)
Furst equation and urine osmole and urine output	NA[a]	As above[c]	32.3 (17.6 to 47.1)	91.0 (80.0 to 100.0)	83.6 (60.0 to 100.0)	48.5 (33.3 to 61.9)
Model[d]	0.67 (0.52–0.80)	0.64	54.0 (33.0 to 73.3)	73.8 (41.7 to 93.8)	76.2 (57.1 to 92.9)	52.3 (35.7 to 69.3)

AUC, area under the receiver operating characteristic curve; CI, confidence interval; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value;.
[a]AUC was not calculated for rule-based combinations or predefined cutoffs. These represent fixed decision rules at specific operating points and do not generate a full receiver operating characteristic curve.
[b]Furst equation >0.86 and urine osmolality >396 mOsm/kg.
[c]Furst equation >0.86, urine osmolality >396 mOsm/kg, and urine output <1353 ml.
[d]Multivariable logistic regression model including Furst equation, urine osmolality, urine output, age, sex, and serum creatinine as continuous predictors.

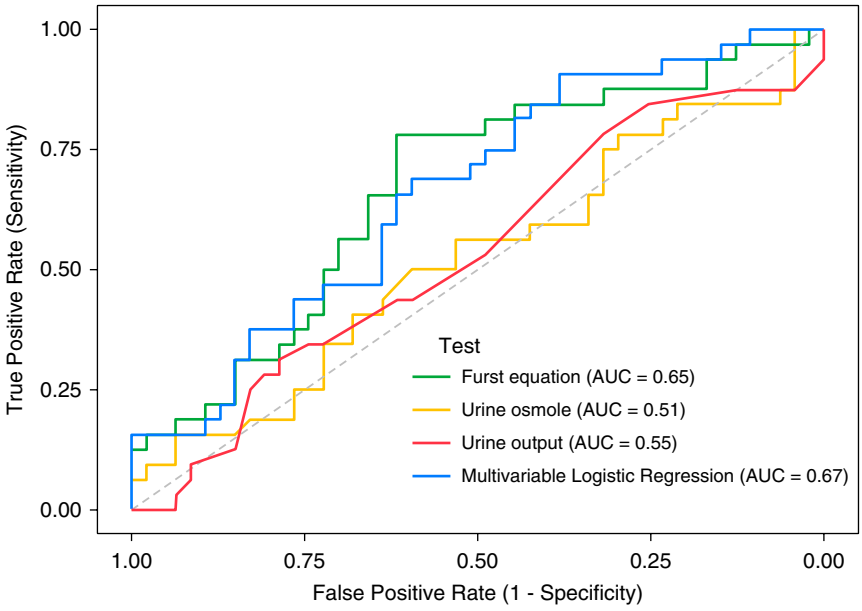

Figure 3. ROC curves and AUC analysis for the Furst equation, urine osmolality, urine output, and the multivariable logistic regression model for day 4 nonresponse prediction. The figure shows the ROC curves for each individual predictor and the multivariable logistic regression model, illustrating their ability to predict nonresponse to FR. The AUC for the Furst equation, urine osmolality, and urine output was 0.65, 0.51, and 0.55, respectively. The multivariable logistic regression model, combining the Furst equation, urine osmolality, urine output, age, sex, and serum creatinine, achieved an AUC of 0.67. An AUC >0.5 indicates predictive utility, with values closer to 1 representing stronger performance. AUC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic.

FR and found its performance to be modest, with limited sensitivity and specificity. Several reasons may explain why the Furst equation fails to predict FR response accurately. First, achieving the recommended level of FR is challenging for hospitalized patients, who often require intravenous fluids for medication administration, making strict adherence to FR difficult. Second, the Furst equation depends on a single measurement of urine and serum electrolytes, which may not capture the dynamic changes in urine electrolytes during FR. Third, transient causes of SIAD, such as medication effects or acute illnesses, may compromise the predictive performance of the Furst equation. Finally, the equation is a simplified model that focuses solely on the ratio of urine sodium and potassium to serum sodium, without accounting for other factors influencing water balance, such as urine output or dietary solute intake.

The predictive performance of urine osmolality is lower than that of the Furst equation, despite high urine osmolality also indicating low free water clearance. This discrepancy arises because major urinary solutes, including sodium and potassium salts, contribute to effective osmotic forces in extracellular and intracellular fluids, along with urea, an ineffective osmole.[23] As urea excretion does not alter plasma sodium levels, electrolyte-free water clearance —estimated by the Furst equation—offers a more accurate predictive tool.[23]

Our study demonstrates that the response to FR is suboptimal, with only 41% of patients responding. This finding aligns with the results of previous studies, which reported a response rate of 56%–59%.[11,14] In addition, our results align with those of the prior literature highlighting the limited predictive value of the Furst equation in identifying patients who will respond to FR. In a prospective randomized trial by Garrahy *et al.*, only 1 of 4 (25%) patients with a Furst equation >1 experienced a serum sodium increase of more than 3 mmol/L, compared with 11 of 18 (61%) patients with a Furst equation <1; however, this difference was not statistically significant.[11] Similarly, in a prospective observational study, Winzeler *et al.* reported that the Furst equation was only marginally associated with nonresponse to FR (odds ratio, 2.7; 95% confidence interval, 1.0 to 7.6; $P = 0.05$).[14] These findings align with those of our study, in which the Furst equation demonstrated modest predictive performance. Collectively, this evidence underscores the need to explore alternative or adjunctive biomarkers to better identify patients unlikely to benefit from FR alone.

Given that FR is only moderately effective, identifying patients likely to fail FR is critically essential. While individual urinary biomarkers demonstrated limited discriminative ability, rule-based combinations yielded improved specificity, but at the cost of markedly reduced sensitivity. Notably, similar specificity gains could be achieved by simply increasing the threshold of the Furst equation, indicating that these trade-offs likely result from threshold optimization rather than from superior discriminatory performance of combined biomarkers.

Findings from the multivariable logistic regression model indicate that adding additional urinary biomarkers to the Furst equation did not meaningfully improve overall predictive accuracy. Importantly, the Furst equation

was the only predictor to retain statistical significance within the model, suggesting that it captures most of the predictive information provided by the other assessed variables. These results support the utility of the Furst equation as a standalone tool for predicting FR response in patients with SIAD.

The best cutoff values for each predictor are lower in our study than those previously suggested. This adjustment enhances sensitivity while only marginally reducing specificity. However, future larger, prospective studies are warranted to confirm the utility of these cutoff values.

Our study has several limitations. First, there is no standardized definition of response to FR. We chose a 3 mEq/L increase in serum sodium level after FR as our criterion, based on data from a previous study that showed approximately 50% of patients randomized to FR achieved this increase by day 4.[11] Second, our sample size is relatively small and was calculated based on the AUC of the Furst equation, which may limit the statistical power to detect the significance of other predictors. Third, our study was conducted among hospitalized patients, where we could not control intravenous fluid intake, which may have reduced adherence rates, as only 72% of the entire cohort adhered to the FR protocol. However, these results reflect real-world conditions, where achieving prescribed FR in hospitalized patients is often challenging, leading to suboptimal responses to FR. Fourth, adherence to the FR protocol was higher in the responder group. Although this difference was not statistically significant, it may have affected the predictive performance of the Furst equation and other indices. Fifth, transient causes of SIAD could not be excluded, which may have also influenced the predictive accuracy of the Furst equation and other indices. Sixth, the clinicians were not blinded to urine chemistry results, which could introduce bias. However, adherence to FR response criteria can help reduce this bias. Seventh, our analysis used single imputation for missing baseline data. While simplifying the analytical process, this approach systematically understates variability, potentially leading to understated SEM and inflated statistical significance. Eighth, although the lack of external validation is a key limitation, we performed internal validation using a nested bootstrap approach to assess the stability and generalizability of the predictive performance. Ninth, we acknowledge that the Youden index, while useful for exploratory cutpoint selection, does not account for SIAD prevalence or the unequal clinical consequences of false-positive and false-negative predictions. These factors are essential in real-world decision making and may influence the appropriateness of any given threshold. Therefore, the cutpoints identified in this study should be viewed as preliminary. Future research should incorporate decision-analytic frameworks that consider disease prevalence and the clinical effect of misclassification to define more meaningful and applicable thresholds. Finally, the reliability of FR after patient discharge could not be confirmed. Although patients were instructed to restrict fluid intake to <1 L per day, adherence to this recommendation in a nonhospital setting may be difficult. Despite these limitations, our study's strengths include its prospective multicenter design and demonstration that optimizing the Furst equation threshold alone achieves similar performance to biomarker combinations.

Our study provides several clinical implications: First, multivariable analysis confirmed the Furst equation as the primary independent predictor, with additional urinary biomarkers providing no significant incremental value. This suggests clinicians focus on the Furst equation alone for predicting FR failure, streamlining assessment, and reducing laboratory burden. Second, early identification of nonresponders and rapid correction of hyponatremia may help reduce hospital length of stay,[12,13] lower health care costs,[1] and potentially decrease mortality.[12,13]

In conclusion, this study evaluated the utility of urinary biomarkers for predicting FR failure in patients with SIAD. The Furst equation demonstrated modest predictive performance, while the inclusion of additional biomarkers did not offer significant incremental value. Despite limitations, such as a relatively small sample size and variability in adherence to FR, our findings suggest that clinicians may reasonably prioritize the Furst equation to guide initial risk stratification, potentially streamlining clinical decision making. Larger studies are needed for external validation and to explore additional predictive markers. In addition, there is an urgent need for randomized trials to assess whether biomarker-guided strategies can improve patient-centered outcomes and mitigate the effect of misclassification in this population.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/B196.

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Declarative Statements

This study includes clinical experimentation and received Institutional Review Board or Ethics Committee approval. All patients provided written informed consent. This study includes clinical experimentation and complies with the Declaration of Helsinki.

Data Availability Statements

Original data generated for the study will be made available on reasonable request to the corresponding author. Observational Data. The deidentified individual participant data collected during the study and a data dictionary defining each field in the dataset will be made available to researchers who propose to use the data for individual patient data meta-analysis. Requests for data access can be directed to the corresponding author at kittiphan.chien@cpird.in.th.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/B197.

Supplemental Method 1. Inclusion and exclusion criteria.

Supplemental Method 2. Classification of symptoms of hyponatremia.

Supplemental Table 1. Predictive performance of urinary biomarkers in predicting nonresponse to FR by day 7.

Supplemental Table 2. Adverse events.

Supplemental Figure 1. ROC curves and AUC analysis for the Furst equation, urine osmolality, urine output, and the multivariable logistic regression model for day 7 nonresponse prediction.

Supplemental Appendix. Logistic regression model equations for day 4 and day 7 nonresponse prediction.

Statistical Analysis Plan

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