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SUPPLEMENTARY METHODS

Supplementary Methods S1. Clinical Volume Status Assessment Protocol

Clinical volume status was assessed using a structured, standardized protocol, independently performed by two trained observers. The goal was to exclude patients with hypervolemic hyponatremia.

The protocol consisted of the following four components:

1. History

- Fluid intake and output (oral intake, vomiting, diarrhea, gastrointestinal drainage, polyuria)
- Recent weight changes
- Use of diuretics and laxative agents
- Symptoms of volume depletion, such as dizziness, lightheadedness, thirst, or reduced urine output
- Symptoms of volume overload, including dyspnea, orthopnea, or rapid weight gain

2. Vital Signs

- Supine and standing blood pressure and heart rate, when feasible and safe, to evaluate for orthostatic hypotension (defined as a drop in systolic BP ≥ 20 mmHg or diastolic BP ≥ 10 mmHg)
- Pulse volume and peripheral perfusion

3. Physical Examination

- Skin turgor (evaluated at the clavicle or sternum)
- Mucous membrane moisture (oral and conjunctival)
- Capillary refill time

- Jugular venous pressure (JVP): Measured with the patient positioned at 30–45°

4. Signs of Volume Overload

- Pulmonary examination for crackles
- Peripheral edema (pitting edema in lower extremities)
- Ascites or abdominal distension

Each observer independently recorded findings and made a preliminary classification.

Final volume status classification required consensus between the two assessors.

Supplementary Methods S2. Inclusion and exclusion criteria

Inclusion Criteria:

- Adults aged ≥ 18 years who were hospitalized
- Significant hyponatremia (serum sodium ≤ 130 mmol/L)
- Hypoosmolality (serum osmolality < 275 mOsm/kg)
- Patients were required to receive at least 2000 mL of 0.9% saline unless they experienced worsening hyponatremia symptoms or a further decline in serum sodium levels.

Exclusion Criteria:

- Clinically evident hypervolemia
- Patients currently receiving a saline infusion or who have received one within the past 48 h.
- Hypothyroidism (thyroid-stimulating hormone > 10 mIU/mL)
- Known or suspected primary or secondary adrenal insufficiency, including:
 - Morning serum cortisol ≤ 3 $\mu\text{g/dL}$
 - Cortisol 3–13.5 $\mu\text{g/dL}$ with inadequate response on ACTH stimulation test
- Bladder dysfunction/incontinence
- Unable/unwilling to comply with study procedures
- Urine osmolality ≤ 100 mOsm/kg
- Current use of diuretics or use of diuretics within the past 48 h
- Serum bicarbonate > 30 mmol/L
- Overcorrection of serum sodium (serum sodium increase of more than 10 mmol/L in the first 10 h or more than 18 mmol/L in 48 h after saline infusion)

- Significant renal insufficiency, defined as estimated GFR <60 mL/min/1.73 m² (calculated using the CKD-EPI formula) or a diagnosis of acute kidney injury
- Decompensated liver cirrhosis (ascites or history of hepatic encephalopathy and varices)
- Symptomatic heart failure
- Nephrotic syndrome
- Hemodynamic instability (SBP <90 mmHg and MAP <65 mmHg)
- Severe hyperglycemia, defined as random plasma glucose >300 mg/dL at the time of diagnosis
- Receiving renal replacement therapy
- Women who are pregnant or breastfeeding
- Post-kidney transplant status
- Gross hematuria
- Hydronephrosis

Supplementary Methods S3. Procedures at Baseline

After obtaining a detailed medical history, we performed the standardized clinical and biochemical evaluation of serum and urine. The biochemical assessment before saline infusion included venous sampling of serum glucose, urea, creatinine, uric acid, sodium, potassium, chloride, bicarbonate, osmolality, cortisol, and thyroid-stimulating hormone, as well as urinary sampling of sodium, potassium, osmolality, uric acid, and creatinine. Additionally, clinicians were not blinded to the urine chemistry results during the evaluation.

Supplementary Method S4. Classification of symptoms of hyponatremia

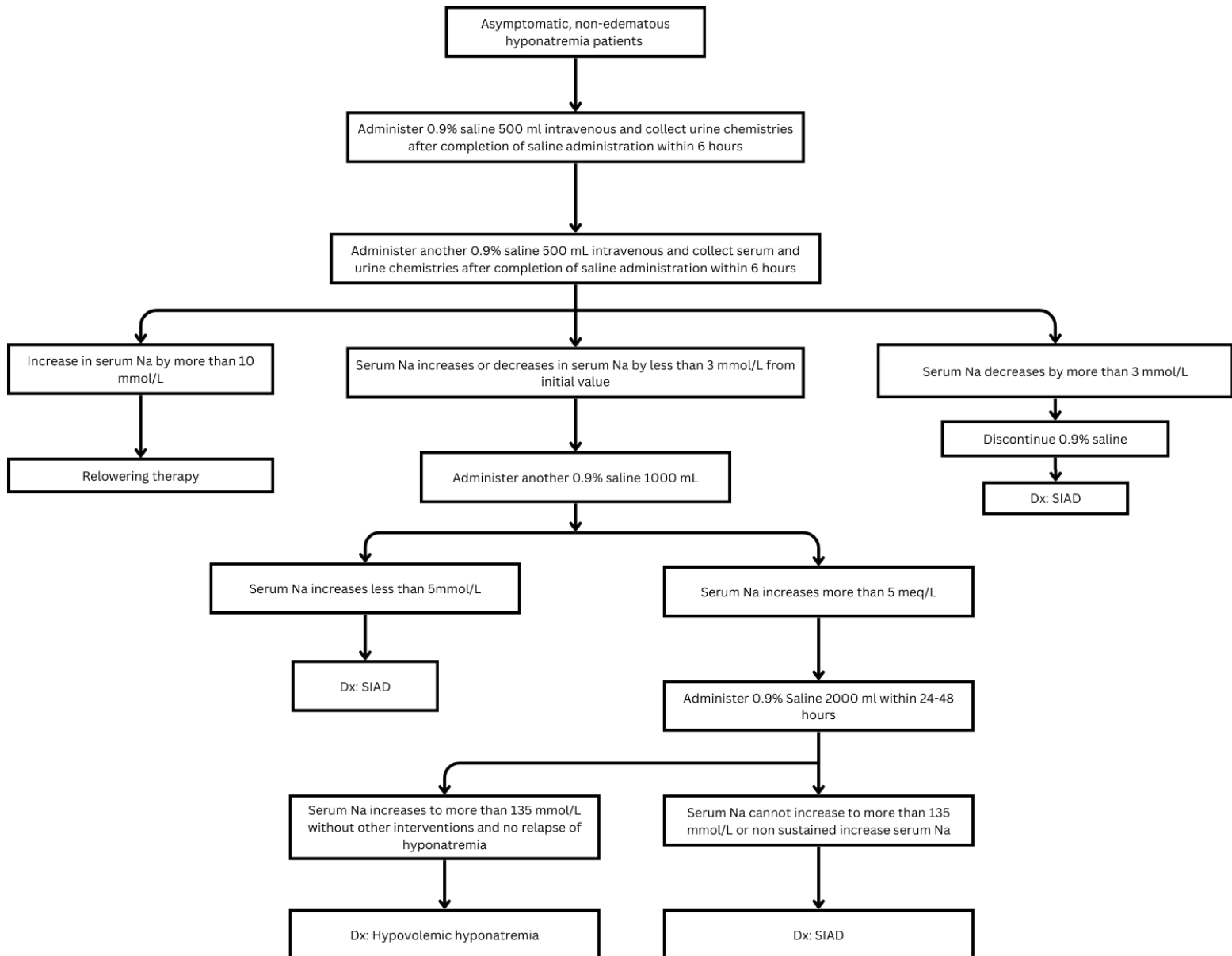
Severity	Symptom
Moderately severe	Nausea without vomiting Confusion Headache
Severe	Vomiting Cardiorespiratory distress Abnormal and deep somnolence Seizures Coma (Glasgow Coma Scale ≤ 8)

Supplementary Method S5. Sample size calculation

The sample size was calculated to compare the diagnostic performance of two tests using their AUCs. Assuming an AUC of 0.8⁴ before and 0.95 after infusion, with a difference of 0.15, a two-sided α of 0.05, a power of 80%, and a correlation between the two AUCs of 0.50, the required sample size was determined to be 100 participants⁵.

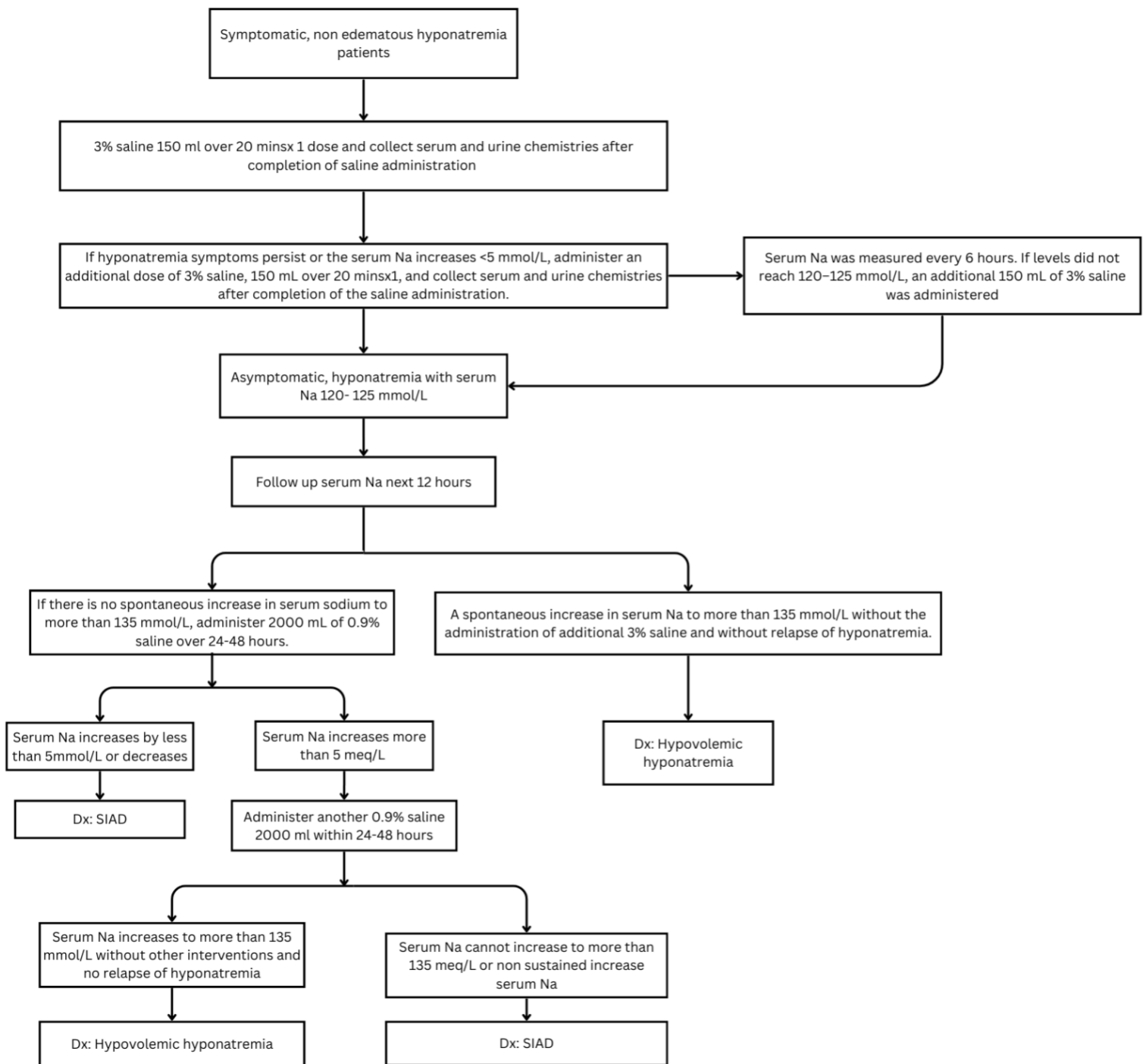
SUPPLEMENTARY FIGURES

Supplementary Figure S1: Saline infusion test for patients receiving 0.9% saline



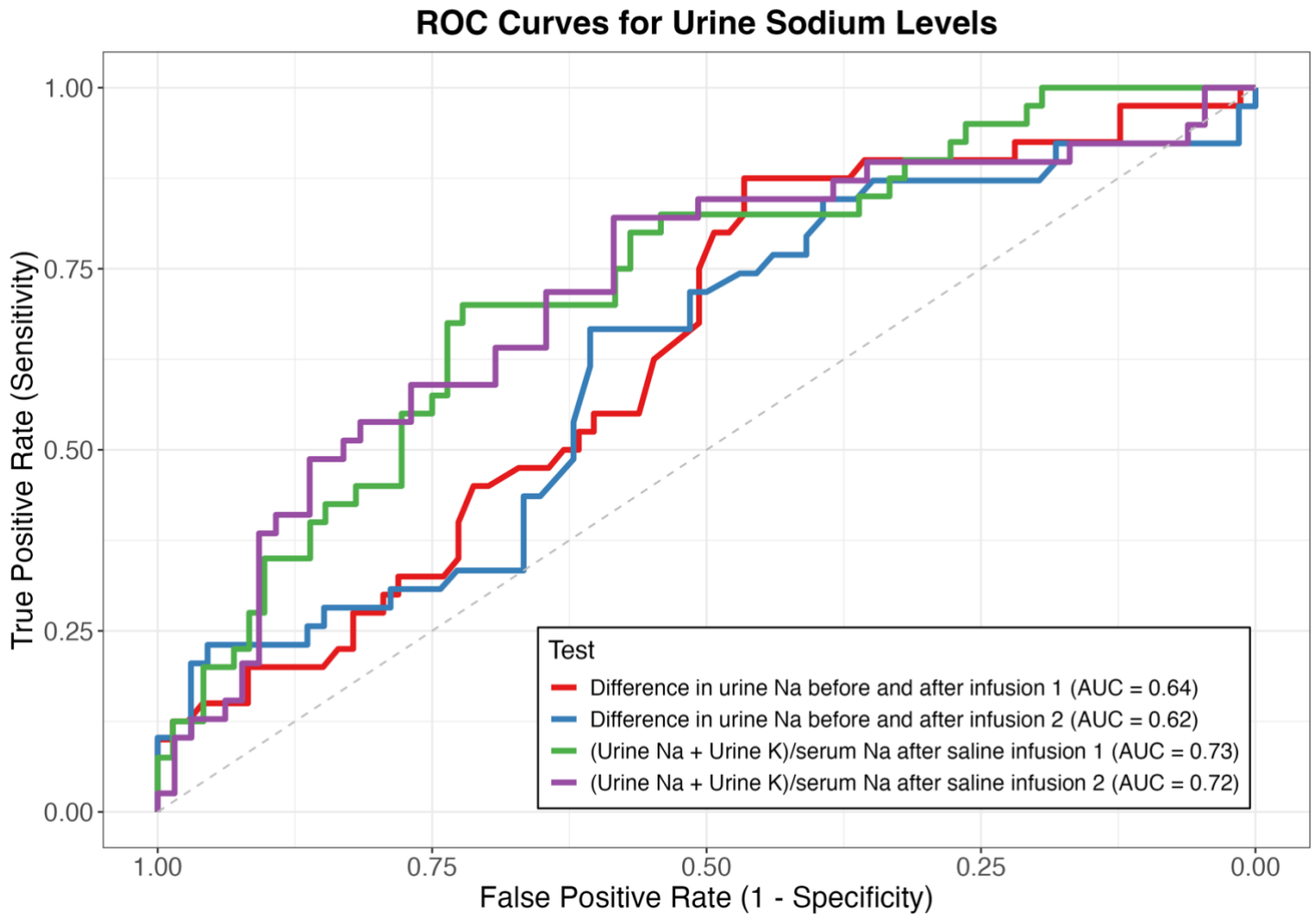
Dx, diagnosis; Na, sodium; SIAD, syndrome of inappropriate diuresis

Supplementary Figure S2: Saline infusion test for patients receiving 3% saline



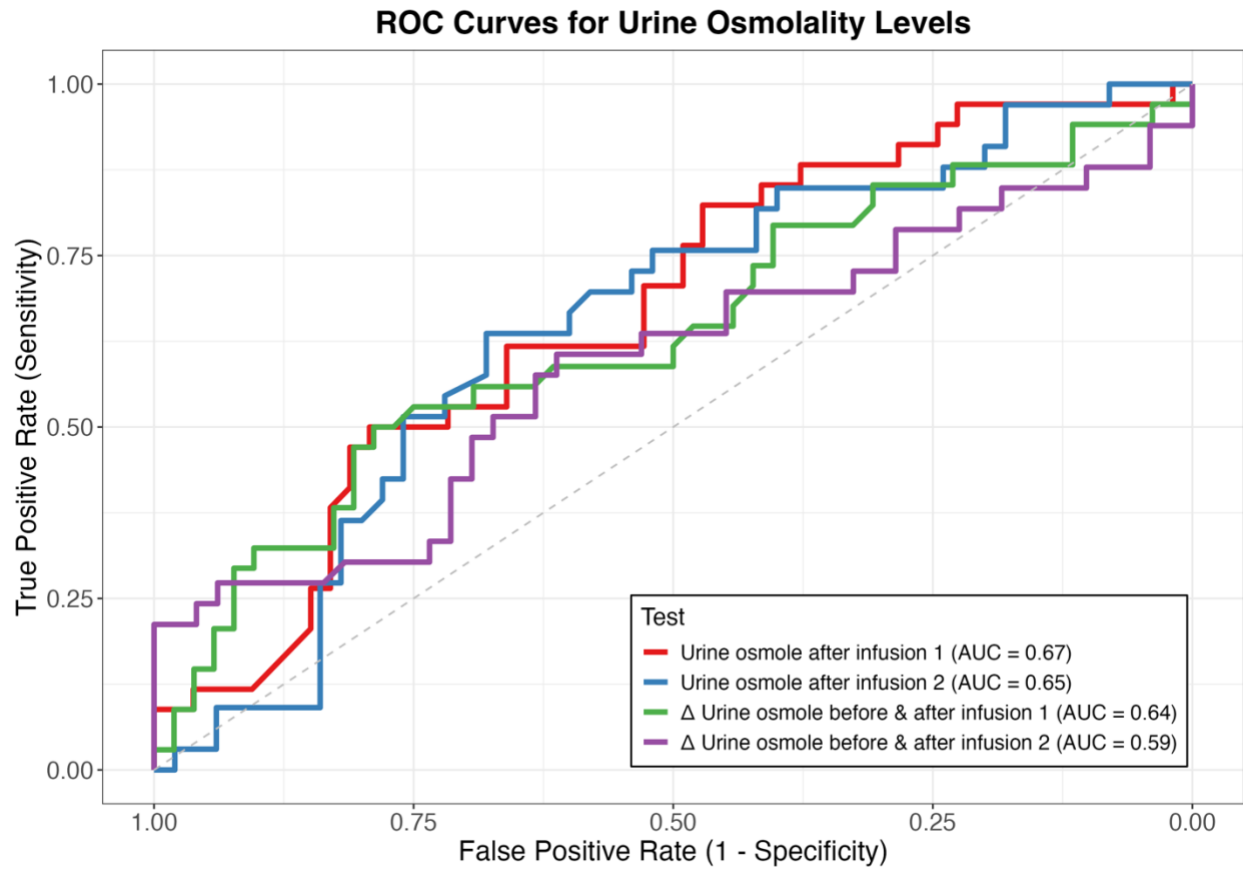
Min, minute; Na, sodium; Dx, diagnosis; SIAD, syndrome of inappropriate diuresis

Supplementary Figure S3: Receiver operating characteristic curves for diagnosing hypovolemic hyponatremia using changes in urine sodium levels and the ratio of (urine sodium + urine potassium) to serum Na after saline infusion at Time 1 and Time 2



AUC, area under the receiver operating characteristic curve; Na, sodium; K, potassium

Supplementary Figure S4: Areas under the receiver operating characteristics curves for the diagnosis of hypovolemic hyponatremia by Urine osmole after saline infusion and difference in urine osmole before and after saline infusion at Time 1 and Time 2



AUC, area under the receiver operating characteristic curve; Na, sodium; K, potassium

SUPPLEMENTARY TABLES

Supplementary Table S1: Causes of SIAD

Causes of SIAD – no. (%)	73 (100)
Malignancy	19 (26.0)
Lung cancer	9 (12.3)
Head, Eye, Ear, Nose, Throat cancer	3 (4.1)
Hematologic malignancy	3 (4.1)
Hepatobiliary-pancreas malignancy	1 (1.4)
Gynecological malignancy	1 (1.4)
Gastrointestinal tract malignancy	1 (1.4)
Primary brain tumor	1 (1.4)
Pulmonary disease	12 (16.4)
Neoplasm	6 (8.2)
Non-tuberculous infection	2 (2.7)
Tuberculous infection	4 (5.4)
Neuropsychiatric disorders	14 (19.1)
Neoplasm	10 (13.7)
Infection	2 (2.7)
Vascular	2 (2.7)
HIV infection	3 (4.1)
Drug-associated	10 (19.2)
Narcotic	1 (1.3)

Antipsychotic/antidepressant	6 (8.2)
Chemotherapy	3 (4.1)
Idiopathic	15 (20.5)

HIV, human immunodeficiency virus; no, number; SIAD, syndrome of inappropriate antidiuresis

Supplementary Table S2: Diagnostic accuracy of urinary biomarkers before and after saline infusion (excluding 3% Saline) in predicting hypovolemic hyponatremia

Test	Full cohort		Diagnosis accuracy		Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
	(exclude 3% saline)		% (95% CI)	no./total no.	% (95% CI)	no./total no.	% (95% CI)	no./total no.	% (95% CI)	no./total no.	% (95% CI)	no./total no.
	AUC	Cutoff										
Urine Na ₀ with predefined cutoff, mmol/L	0.59 (0.49–0.70)	30.0	72.6 (63.4–80.5)	68/96	40 (24.9–56.7)	12/35	90.4 (81.2–96.1)	56/61	69.6 (47.1–86.8)	12/17	73.3 (63.0–82.1)	56/79
Urine Na ₀ , mmol/L	0.59 (0.46–0.72)	21.5	67.7 (57.4–76.9)	65/96	42.9 (26.3–60.6)	15/35	82.0 (70.0–90.6)	50/61	57.7 (36.9–76.6)	15/26	71.4 (59.4–81.6)	50/70
Urine Na ₁ , mmol/L	0.74 (0.64–0.85)	24.5	74.0 (64.0–82.4)	71/96	62.9 (44.9–78.5)	22/35	80.3 (68.2–89.4)	49/61	64.7 (46.5–80.3)	22/34	79.0 (66.8–88.3)	49/62
Urine Na ₂ , mmol/L	0.72 (0.60–0.83)	44.6	68.1 (57.7–77.3)	64/94	71.4 (53.7–85.4)	25/35	66.1 (52.6–77.9)	39/59	55.6 (40.0–70.4)	25/45	79.6 (65.7–89.8)	39/49
Urine Na ₀ plus Urine Na ₁ , mmol/L	0.63 (0.54–0.72)	As above	70.8 (60.7–79.7)	68/96	34.3 (19.1–52.2)	12/35	91.8 (81.9–97.3)	56/61	70.6 (44.0–89.7)	12/17	70.9 (59.6–80.6)	56/79
Urine Na ₀ plus Urine Na ₂ , mmol/L	0.64 (0.56–0.73)	As above	71.3 (61.0–80.1)	67/94	37.1 (21.5–55.1)	13/35	91.5 (81.3–97.2)	54/59	72.2 (46.5–90.3)	13/18	71.1 (59.5–80.9)	54/76
Difference in Urine Na ₀ and Urine Na ₁ , mmol/L	0.64 (0.53–0.76)	-6.25	67.7 (57.4–76.9)	65/96	17.1 (6.6–33.6)	6/35	96.7 (88.7–99.6)	59/61	75.0 (34.9–96.8)	6/8	67.0 (56.2–76.7)	59/88
Difference in Urine Na ₀ and Urine Na ₂ , mmol/L	0.61 (0.49–0.73)	-2.35	68.1 (57.7–77.3)	64/94	17.1 (6.6–33.6)	6/35	98.3 (90.9–100)	58/59	85.7 (42.1–99.6)	6/7	66.7 (55.7–76.4)	58/87
(Urine Na ₁ + Urine K ₁) / serum Na	0.61 (0.50–0.72)	0.45	60.2 (50.1–69.7)	62/103	63.4 (46.9–77.9)	26/41	58.1 (44.8–70.5)	36/62	50.0 (35.8–64.2)	25/52	70.6 (56.2–82.5)	36/51
(Urine Na ₂ + Urine K ₂) / serum	0.58	0.48	60.6	60/99	60.0	24/40	61.0	36/59	51.1	24/47	69.2	36/52

Na	(0.460.70)		(50.3–70.5)		(43.3–75.1)		(47.4–73.5)		(36.1–65.9)		(54.9–81.3)	
Urine osmole ₁ , mOsm/kg	0.67	350	60.9	53/87	82.4	28/34	47.2	25/53	50.0	28/56	80.6	25/31
	(0.55–0.78)		(49.9–71.2)		(65.5–93.2)		(33.3–61.4)		(36.3–63.7)		(62.5–92.5)	
Urine osmole ₂ , mOsm/kg	0.65	267	66.3	55/83	63.6	21/33	68.0	34/50	56.8	21/37	73.9	34/46
	(0.53–0.77)		(55.1–76.3)		(45.1–79.6)		(53.3–80.5)		(39.5–72.9)		(58.9–85.7)	
Difference in urine osmole ₀ and urine osmole ₁ , mOsm/kg	0.64	125	67.4	58/86	50.0	17/34	78.8	41/52	60.7	17/28	70.7	41/58
	(0.51–0.76)		(56.5–77.2)		(32.4–67.6)		(65.3–88.9)		(40.6–78.5)		(57.3–81.9)	
Difference in urine osmole ₀ and urine osmole ₂ , mOsm/kg	0.59	57	41.5	34/82	84.8	28/33	12.2	6/49	39.4	28/71	54.5	6/11
	(0.460.72)		(30.7–52.9)		(68.1–94.9)		(4.6–24.8)		(28.0–51.7)		(23.4–83.3)	

Abbreviations: AUC, area under the receiver operator characteristic curve; Na, sodium; Urine Na₀, urine sodium measured before saline infusion; Urine Osmole₀, urine osmolality measured before saline infusion; Urine Na₁, urine sodium measured at Time 1; Urine K₁, urine potassium measured at Time 1; Urine Osmole₁, urine osmolality measured at Time 1; Urine Na₂, urine sodium measured at Time 2; Urine K₂, urine potassium measured at Time 2; Urine Osmole₂, urine osmolality measured at Time 2.

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