PREDICTORS OF NON-RESPONSE TO FLUID RESTRICTION IN HYPONATREMIC PATIENTS DUE TO THE SYNDROME OF INAPPROPRIATE ANTIDIURESIS

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BACKGROUND & AIM

Background of the study:

- The syndrome of inappropriate antidiuresis (SIAD) is the most common cause of euvolemic hyponatremia.
- Preferred first-line treatment for most cases of SIAD is fluid restriction (FR).
- However, FR not always leads to successful correction of hyponatremia

Aim of the study:

To evaluate different laboratory parameters as predictors of non-response to FR in patients with hyponatremia due to SIAD.

PATIENTS AND METHODS

Setting:

Prospective observational cohort study of patients with profound hyponatremia (serum (s-) sodium <125 mmol/l) presenting to the emergency department of two Swiss referral centres.

Criteria of SIAD-diagnosis:

- S-osmolality <280 mmol/l, urine (u-) osmolality >200 mmol/l, clinical euvolemia, normal adrenal, renal and thyroid function.
- Further supporting criteria if available: fractional excretion (FE) of urea >35 %, FE of uric acid >12 %, u-sodium > 40 mmol/l.

Definition of FR: Total daily intake (enteral and parenteral) of ≤ 1000 ml

Definition of treatment response:

- Increase of s-sodium concentration >3 mmol/l within 24 hours -> response to FR
- Increase of s-sodium concentration ≤3 mmol/l within 24 hours -> non-response to FR.

Laboratory parameters: Daily measurement of s-sodium, initial determination of various s- and u-parameters, s-copeptin and s-mid-regional pro-atrial natriuretic peptide (s-MR-proANP)

RESULTS

Table 1. **Baseline characteristics of SIAD patients with and without response to FR (n=82)**

Characteristic	Responders (n=48)	Non-responders (n=34)	P value
Age (years), median (IQR)	73 (64-79)	64 (55-76)	0.09
Female, number (n) (%)	31 (32.3)	22 (45.4)	1.00
Diuretics, n (%)			
Total	20 (42)	11 (32)	0.49
Loop diuretics	6 (13)	0	1.00
Thiazide diuretics	13 (27)	10 (29)	1.00
Potassium-sparing diuretics	3 (6)	3 (9)	0.69
Laboratory parameters, median (IQR)			
S-sodium (mmol/l),	120 (115-123)	120 (119-122)	0.65
S-osmolality (mmol/kg)	250 (241-257)	252 (245-259)	0.59
FE-urea (%)	43 (35-58)	41 (32-49)	0.12
FE-uric acid (%)	13 (9-21)	15 (11-20)	0.36
U-sodium (mmol/l)	61 (37-82)	88 (56-138)	**0.0032**
U-osmolality (mmol/kg)	385 (301-438)	432 (331-597)	**0.0336**
S-urea (mmol/l)	3.8 (3.0-4.7)	4.0 (2.8-4.9)	0.6681
S-MR-proANP (pmol/l)	123 (103-282)	97 (60-127)	**0.003**
S-copeptin (pmol/l)	12 (5-28)	13 (5-31)	0.7792
Etiology of SIAD, n (%)			
Malignant disease	7 (15)	10 (29)	0.17
Lung	5 (10)	1 (3)	0.39
Central nervous system	7 (15)	9 (26)	0.26
Drugs	25 (52)	9 (26)	**0.024**
Others	4 (8)	5 (15)	0.48

The following parameters revealed significant association with failure to FR: U-osmolality, u-sodium, the electrolyte ratio [$U_{Na}+U_K/S_{Na}$ >1], s-urea and s-MR-proANP, whereas s-copeptin did not.

The best predictive marker was u-sodium, remaining significant also in multivariate analysis and after adjustment for diuretic use (*table 2+3*).

The diagnostic accuracy was best when u-sodium was combined with s-urea (*figure 1*).

Table 2. **Uni- and multivariate logistic regression analysis of predictors of non-response to FR**

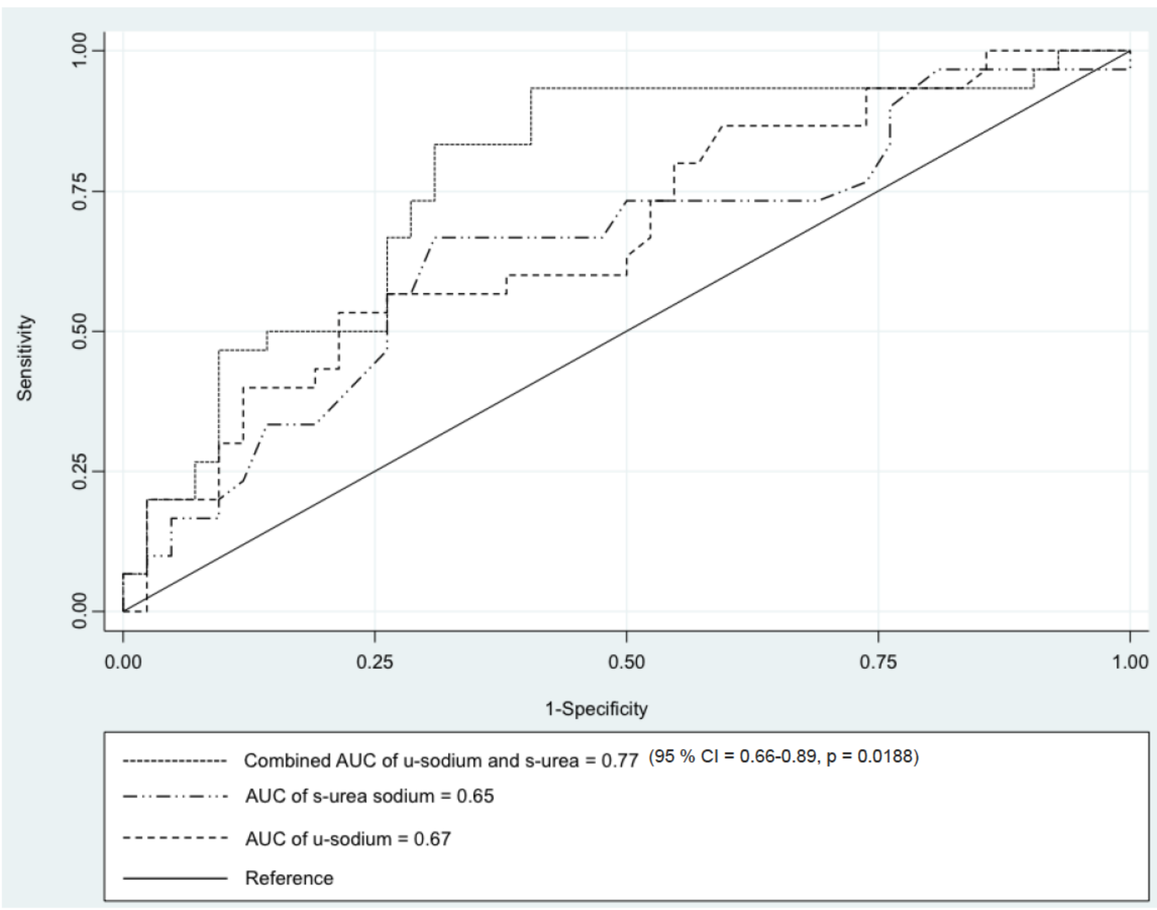
	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	ODDS (95 % CI)	P value	ODDS (95 % CI)	P value
U-sodium (mmol/l)	15.0 (2.4-95.8)	0.004	11.1 (1.7-74.8)*	0.013*
U-osmolality (mmol/kg)	34.8 (1.2-1038.8)	0.041	15.8 (0.3-790.4) *	0.167*
S-urea (mmol/l)	36.6 (1.3-1026.1)	0.034	20.1 (0.6-647.9)°	0.091°
S-MR-proANP (pmol/l)	0.03 (0.003-0.3)	0.004	0.006 (0.00003-1.2)°	0.059°

*° adjustment for age, sex, amount of total daily fluid intake during FR, drugs as etiology of SIAD, baseline levels of serum sodium concentration; *see ° and diuretics*

Table 3. **Optimal cut-offs of predictive parameters for non-response and response to FR**

	Predicted non-response to FR			Predicted response to FR		
	Cut-off value	Sensitivity (%)	Specificity (%)	Cut-off value	Sensitivity (%)	Specificity (%)
U-sodium (mmol/l)	≥ 130	33.3	91.3	≤ 50	87.9	41.3
U-osmolality (mmol/kg)	≥ 500	33.3	87.0	≤ 300	90.9	21.7
S-urea (mmol/l)	≥ 5	32.3	84.1	≤ 2.5	96.8	11.4
S-MR-proANP (pmol/l)	≤ 80	63.3	18.2	≥ 250	3.3	72.7

Figure 1. **Area under the curve of u-sodium and s-urea and its combination**



CONCLUSIONS

Easily measurable laboratory parameters, especially u-sodium, predict therapeutic response to FR and may facilitate early treatment choice in cases of hyponatremia due to SIAD.

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