

1 **Chloride and Potassium Assessment are a helpful tool for Differential Diagnosis of Thiazide**
2 **Associated Hyponatremia**

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2

3 **Abstract**

4 *Context:* Differential diagnosis of thiazide associated hyponatremia (TAH) is challenging. Patients can
5 either have volume depletion or a syndrome of inappropriate antidiuresis (SIAD)-like presentation.

6 *Objective:* To evaluate the impact of the simplified apparent strong ion difference in serum (aSID),
7 *sodium+potassium-chloride*) as well as the urine chloride and potassium score (ChU, chloride-
8 potassium in urine) in the differential diagnosis of TAH, in addition to assessment of fractional uric acid
9 excretion (FUA).

10 *Design:* Post-hoc analysis of prospectively collected data from June 2011 to August 2013.

11 *Setting:* Hospitalized patients enrolled at University Hospital Basel and University Medical Clinic
12 Aarau, Switzerland.

13 *Patients:* 98 patients with $\text{TAH} < 125 \text{ mmol/l}$ were included, divided according to treatment response in
14 volume-depleted TAH requiring volume substitution or SIAD-like TAH requiring fluid restriction.

15 *Intervention:* We computed sensitivity analyses with ROC curves.

16 *Main Outcome Measure:* positive predictive value (ppv) and negative predictive value (npv) of aSID,
17 ChU, and FUA in differential diagnosis of TAH.

18 *Results:* An $\text{aSID} > 42 \text{ mmol/l}$ had a ppv of 79.1% in identifying patients with volume-depleted TAH,
19 whereas a value $< 39 \text{ mmol/l}$ excluded it with a npv of 76.5%. In patients for whom aSID was
20 inconclusive, a $\text{ChU} < 15 \text{ mmol/l}$ had a ppv of 100% and a npv of 83.3% whereas $\text{FUA} < 12\%$ had a ppv
21 of 85.7% and a npv of 64.3% in identifying patients with volume-depleted TAH.

22 *Conclusion:* In patients with TAH, assessment of aSID, potassium and chloride in urine can help
23 identifying patients with volume-depleted TAH requiring fluid substitution from patients with SIAD-like
24 TAH requiring fluid restriction.

1 Introduction

2 Patients undergoing thiazide or thiazide-like treatment are at risk for hyponatremia^{1,2}, with a reported
3 incidence of hyponatremia up to 30% in hospitalized patients³. Patients with thiazide or thiazide-like
4 associated hyponatremia (TAH) can either present with a diuretic-induced volume depletion and
5 consequent hypovolemic hyponatremia, or with a picture of euvolemic hyponatremia mimicking a
6 syndrome of inappropriate antidiuresis (SIAD), in which case it is referred to as SIAD-like TAH^{4,5}.

7 The *European Clinical Practice Guidelines (ECPG)*⁶ for diagnosis and management of hypotonic
8 hyponatremia propose a diagnostic algorithm based on urine indices (especially the measurement of
9 urine osmolality and sodium) instead of the classical volume status assessment, of which the low
10 sensitivity and specificity are well recognized⁷. However, the use of urine indices is of little utility in
11 patients with TAH, because thiazide and thiazide-like diuretics promote natriuresis and alter urine
12 dilution⁸. Fenske et al. proposed the use of fractional uric acid excretion (FUA) in the differential
13 diagnosis of TAH⁹, however, their recommendation was based on data of only 7 patients.

14 Thiazide and thiazide-like diuretics exert their mechanism of action not only on sodium, but also on
15 chloride and potassium. We therefore aimed to evaluate the possible role of the imbalance between
16 these 3 ions in the differential diagnosis of TAH. To do so, we calculated the simplified strong ion
17 difference (*serum sodium + potassium – chloride*), a part of the Stewart model for acid-base
18 disturbances^{10,11}. In brief, the Stewart model represents an alternative to bicarbonate-centered
19 approaches and is especially used in anesthesiology and intensive care. According to Stewart, acid-
20 base balance is the result of the strong ions difference (SID, calculated as the sum of measured
21 cations minus the sum of measured anions), weak acids, and partial pressure of carbon dioxide
22 (pCO₂), and aims to maintain electroneutrality in extracellular fluid¹². In stable patients with no critical
23 illness (absence of severe hypoalbuminemia, of acute renal failure and/or respiratory failure), the
24 simplified aSID could be sufficient to evaluate acid-base balance. A value >40 mmol/L identifies
25 patients with fluid depletion and contraction alkalosis due to relative hypochloremia, whereas a value

1 <40 mmol/L identifies patients with acidosis due to relative excess of water and therefore in need of
2 fluid restriction¹².

3 Chloride and potassium balance in urine represents a sodium-independent marker of kidney response
4 to diuretic induced volume depletion¹³. Processes going on at the level of intercalated cells are not
5 completely understood, but there is increasing evidence of a sodium independent chloride
6 reabsorption in response to changes in volume and metabolic status^{14,15}. A low urine chloride is a
7 known sign of hypovolemia¹⁶. It triggers renin release and intercalated cells activation, thus
8 aggravating potassium depletion caused by thiazide¹⁷. Therefore, we further aimed to investigate the
9 diagnostic potential of the balance between chloride and potassium in urine in the differential
10 diagnosis of TAH. The goal of our analysis was to find an additional tool for the initial assessment of
11 profound hyponatremia in the context of hospitalization and unreliable canonical urine indices.

12

13 **Material and methods**

14 *Study design and participants*

15 This was a post-hoc analysis of a prospective observational study. Full details of the study rationale,
16 design and statistical analyses can be found elsewhere¹⁸. Briefly, from June 2011 to August 2013, 303
17 patients with profound hyponatremia presenting to the medical emergency department of the
18 University Hospital Basel and the University Medical Clinic Aarau in Switzerland were included. The
19 primary endpoint of the original study was to evaluate plasma copeptin as a diagnostic marker in the
20 differential diagnosis of profound hyponatremia. Inclusion criteria were full legal age, initial serum
21 sodium level <125 mmol/L, and a serum osmolality <280 mmol/kg. Patients with hyponatremia due to
22 hyperglycemia were excluded from the analysis. The study protocol was approved by the Ethic
23 Committee of north-west Switzerland (EKNZ), and all patients provided informed consent form, or in
24 case of impaired mental state their relatives. For the present analysis, we included all patients with a
25 thiazide or a thiazide-like diuretic therapy at admission. We excluded patients with a urine sodium <20

1 mmol/l or a urine osmolality <200 mOsm/kg, as these cut-offs allow a straight-forward differential
2 diagnosis of hyponatremia (i.e., hypovolemia, tea and toast syndrome, beer potomania or primary
3 polydipsia)^{4,6}.

4 *Study procedure and outcomes*

5 Baseline characteristics (e.g., age, sex, body mass index (BMI), comorbidities, medication and vital
6 signs) were collected at study inclusion. Blood and urine analyses were routinely performed on
7 admission at the central laboratories of the respective hospitals. According to protocol of the original
8 study, urine indices were needed before any treatment start. In the majority of the patients (81.6%,
9 n=80) urine indices were therefore obtained within the first 6 hours and in 90.8% of the patients (n=
10 89) within the first 12 hours. For patients in need of 3% saline, urine indices were postponed at the
11 day after 3% saline. Hyponatremia treatment and frequency of serum sodium measurements during
12 the hospitalization were at discretion of treating physician. Information about hyponatremia treatment
13 was collected daily.

14 All patients taking a thiazide or a thiazide-like diuretic were defined as having TAH, regardless from
15 comorbidities and comedications. Patients responding to fluid substitution were defined as volume-
16 depleted TAH, whereas patients responding to fluid restriction were defined as SIAD-like TAH. Good
17 treatment response was defined as a sodium increase of at least 4 mmol/L in the first 24 hours after
18 treatment start or >130 mmol/L at discharge based on retrospective chart review. In case patients
19 received 3% hypertonic saline, treatment response was defined as an increase of at least 4 mmol/L in
20 the first 24 hours starting from the day after hypertonic saline infusion.

21 Simplified apparent strong ion difference (aSID) at baseline was calculated with the formula *serum*
22 *sodium + potassium - chloride*¹¹. Urine chloride and potassium score (ChU) at baseline was calculated
23 with the formula *urine chloride - urine potassium* in mmol/L. FUA was calculated according to standard
24 in % of excretion⁹.

1 We conducted the analysis both for all the three parameters together and in a two-step approach, with
2 1) the blood score aSID, because immediately available and 2) the urine scores ChU and FUA for
3 unclear cases.

4 *Statistical analysis*

5 We performed a descriptive and a sensitivity analysis of TAH patients.

6 Results of the descriptive analysis are shown as mean +/- standard deviation (SD) in case of normally
7 distributed continuous variables, median with interquartile range (IQR) in case of not normally
8 distributed continuous variables, and in number (n) and percentage (%) in case of dichotomous
9 variables. Two group comparison of continuous baseline variables were performed using the *Mann-
10 Whitney test* and of categorical baseline variables using the *Chi-Square test with Yates correction*. A
11 two-sided p-value of <0.05 was considered to be statistically significant.

12 The sensitivity analysis was carried out computing receiver operating characteristic (ROC) curves as
13 well as positive and negative predictive value to compare the performance of aSID, ChU and FUA at
14 different cut-offs in discriminating whether a patient was in need of fluid substitution or not. Finally, we
15 built a ROC curve with these 3 parameters together. As the interpretation of aSID is based on the
16 assumption that volume depletion in TAH patients is associated with a contraction alkalosis, we
17 carried out the same sensitivity analyses using the classic acid-base marker serum bicarbonate at
18 different cut-off for comparison.

19 All analyses were performed using R statistical software¹⁹.

21 **Results**

22 Out of the initial 303 hospitalized patients with profound hypotonic hyponatremia, we excluded 129
23 patients because they had no thiazide or thiazide like diuretic therapy (n= 127), or because data were
24 missing (n= 2). We further excluded 48 patients who received no treatment or switched treatment
25 during hospitalization, and 28 with urine sodium <20 mmol/l or urine osmolality <200 mmol/kg. The
26 final set consisted of 98 patients, 69 (70.4%) with volume-depleted TAH, and 29 (29.6%) with SIAD-

1 like TAH. Thiazide or thiazide-like diuretic was discontinued in all patients. Among the 69 patients with
2 volume-depleted TAH, 57 (82.6%) received 0.9% sodium chloride, and 12 (17.4%) received another
3 type of isotonic fluid substitution (ringer lactate solution, crystalloid solution). Among the 29 patients
4 with SIAD-like TAH, none was treated with second-line treatments (i.e., oral urea, vaptans, sodium
5 chloride tablets). Six patients received hypertonic saline infusion (4 with volume-depleted TAH, 2 with
6 SIAD-like TAH). Details about serum sodium course are displayed in *Table 1* of *Supplementary*
7 *material*²⁰.

8 Sixty-two out of 98 patients (63.3%) met the treatment success criterion of an increase of ≥ 4 mmol/L in
9 the first 24 hours after treatment start, and 36 patients (36.7%) of the threshold of 130 mmol/L at
10 discharge. Among the latter group, 19 (52.8%) were undergoing a fluid restriction.

11 *Descriptive Analysis*

12 Table 1 shows the baseline characteristics of our cohort of TAH patients. Patients with SIAD-like TAH
13 were on average younger than patients with volume-depleted TAH and had slightly more often an
14 antidepressant, an antiepileptic or a neuroleptic therapy. No relevant differences could be found in
15 sex, body mass index, baseline labor parameters, therapy with diuretics other than thiazide or
16 presence of comorbidities between the 2 groups. Patients with volume-depleted TAH showed a
17 median (IQR) aSID of 42.2 (39.2-44.2) mmol/L and a median (IQR) ChU of 15.0 (3.0-35.0) mmol/L,
18 whereas patients with SIAD-like TAH had a median (IQR) aSID of 40.4 (38.7-42.9) mmol/L and a
19 median (IQR) ChU of 39.6 (15.3-52.1) mmol/L.

20 *Sensitivity analysis*

21 Detailed results of sensitivity analyses at different cut-offs are displayed in *Table 2*.

22 A simplified aSID >42 mmol/L showed a positive predictive value (ppv) of 79.1% in identifying patients
23 with volume-depleted TAH, whereas a value <39 mmol/L excluded the need of fluid substitution with a
24 negative predictive value (npv) of 76.5%. The area under the curve (AUC) was 59.4% with 95%
25 confidence interval (CI) 46.4-72.5%.

1 A urine score ChU <10 mmol/l showed a ppv of 77.8% in identifying patients with volume-depleted
2 TAH, <5 mmol/L a ppv of 100%, whereas a value >40 mmol/L excluded the need of fluid substitution
3 with a npv of 72.0% (AUC 71.2%, 95% CI 52.6%-89.8%).

4 A FUA <8% showed a ppv of 80.6% in identifying patients with volume-depleted TAH, whereas a
5 value >12% excluded the need of fluid substitution with a npv of 80.0% (AUC 71.0%, 95% CI 58.5%-
6 83.5%).

7 Taken together for differential diagnosis of TAH, these parameters showed an area under the curve of
8 90%. *ROC Curves* are displayed in *Figure 1*. We obtained similar results after excluding the 6 patients
9 treated initially with 3% hypertonic saline infusion (data not shown); the 26 patients using
10 antidepressants, antiepileptics or neuroleptics (Supplementary material, Table II and Figure I²⁰); and
11 patients taking diuretics other than thiazides (Supplementary material, Table III and Figure II²⁰).

12 *Comparison with bicarbonate levels*

13 A serum bicarbonate >28 mmol/L suggested the need of fluid substitution with a ppv of 72.7%,
14 whereas a value <22 mmol/L excluded fluid substitution with a npv of 80.4%. (AUC 51.6%, 95%CI
15 35.5%-67.7%).

16 *Two-step diagnostic approach*

17 For the 29.6% of TAH patients showing an aSID value between the cut-off values ≥ 39 and ≤ 42 mmol/L
18 (29 patients; 18 in need of fluid substitution, 11 in need of fluid restriction), we performed a sensitivity
19 analysis of ChU and FUA at different cut-offs and selected the most accurate ones.

20 For urine score ChU (n=11) we found that a cut-off of 15 mmol/L had a ppv of 100% and a npv of
21 83.3% in identifying patients with volume-depleted TAH (AUC 88.3%, 95% CI 66.8-100%).

22 For FUA (n=28) we found that a cut-off of 12% had a ppv of 85.7% and a npv of 64.3% npv in
23 identifying patients with volume-depleted TAH (AUC 84.0%, 95% CI 69.3-98.6%).

24 Taken together for differential diagnosis of TAH in patients with aSID ≥ 39 and ≤ 42 mmol/L, these
25 parameters showed an area under the curve of 90%. *ROC Curves* are displayed in *Figure 2*.

1 *Comparison with bicarbonate levels in patients with aSID ≥ 39 and ≤ 42 mmol/L*

2 A serum bicarbonate >26 mmol/L showed 75.0% specificity, 6.2% sensitivity, and a ppv of 33.3% in
3 identifying patients with volume-depleted TAH, whereas a value <22 mmol/L excluded fluid
4 substitution with 81.2% sensitivity, 62.5% specificity, and a npv of 62.5% (AUC 59.4%, 95% CI 28.2-
5 90.5%).

6

7 **Discussion**

8 This secondary analysis of 98 hospitalized patients with profound hypotonic hyponatremia showed
9 that chloride and potassium in addition to calculation of fractional uric acid excretion represents a
10 useful tool in the differential diagnosis of TAH.

11 One could argue that withdrawal of thiazide or thiazide-like diuretic is effective in hyponatremia
12 treatment, and therefore additional treatments are not required. However, sodium levels in general
13 only slightly increase after withdrawing of thiazides and therefore drug withdrawal alone may be
14 insufficient²¹. Especially in the context of profound hyponatremia it is important to not put the patients
15 at risk of a further decrease in sodium levels, and thus to immediately start with the appropriate
16 treatment²². As both volume-depleted and SIAD-like TAH appear euvolemic and have similar urine
17 indices, the choice of an appropriate treatment represents a clinical challenge.

18 In our study, a simplified aSID excluded the need of fluid substitution for values <39 mmol/L with a
19 high sensitivity, and showed a high specificity for the need of fluid substitution for values >42 mmol/L.
20 Because a higher aSID is indicative of an alkalosis in the model of Stewart, we postulate that patients
21 with aSID >42 mmol/L have a thiazide or thiazide-like diuretic-induced contraction alkalosis¹⁷.
22 Interestingly, bicarbonate did not display the same efficacy in identifying these alkalotic patients. This
23 might be explained by the fact that a high bicarbonate level does not identify univocally metabolic
24 alkalosis²³ and is therefore not useful in identifying patients with contraction alkalosis. Importantly,

1 results remained similar after excluding patients using antidepressants, antiepileptics or neuroleptics,
2 and patients using other type of diuretics, all drugs that represent potential confounders.

3 In a second step, we found that the assessment of chloride and potassium balance in urine (ChU)
4 could represent a valid tool for the differential diagnosis of TAH, especially in patients for whom the
5 aSID is not conclusive ($39 \geq \text{aSID} \leq 42$ mmol/L). A low urine chloride is a known sign of hypovolemia
6 and its assessment is usually used in hyponatremic hypovolemic patients with metabolic alkalosis due
7 to vomiting, in whom the natriuresis caused by the bicarbonaturia prevents from using urine sodium to
8 identify hypovolemia¹⁶. In our study, a markedly reduced chloride excretion as compared to potassium
9 identified patients in need of fluid substitution with a 100% positive predictive value, whereas a higher
10 chloride excretion as compared to potassium identified patients in need of fluid restriction.
11 Interestingly, assessment of urine chloride alone did not show the same efficacy in identifying patients
12 with volume-depletion (data not shown). This might be due to the fact that in the context of TAH with
13 volume depletion and metabolic alkalosis, renin is released and intercalated cells are activated,
14 causing kaliuresis and chloride reabsorption¹⁷.

15 Furthermore, we confirm the cut-offs of FUA proposed by Fenske and colleagues as a complementary
16 analysis with ChU⁹. A FUA $<12\%$ showed a ppv of 85.7% in identifying patients in need for fluid
17 substitution, with a lower AUC as compared to ChU, whereas ChU and FUA together showed a AUC
18 of 0.9.

19 According to these findings, we propose a two-step approach for differential diagnosis of TAH with 1)
20 the calculation of blood aSID and 2) the calculation of urine scores ChU and FUA for patients in whom
21 step 1 is inconclusive, as displayed in *Figure 3*. Despite the lower diagnostic accuracy of the blood
22 score, we chose it as a first step because blood values are faster available than urine samples, and
23 the cut-offs of 39 resp. 42 mmol/l showed a good reliability in the sensitivity analysis. Evaluation of
24 simplified aSID allows a prompter reaction to profound hyponatremia in the group of patients showing
25 an aSID <39 or >42 mmol/L.

1 Our study has several limitations. Firstly, it was a retrospective, exploratory analysis based on chart
2 reviews so that a prospective validation based on power analysis is needed. Further studies should
3 especially validate our cut-off for ChU in the two-step approach, as the number of patients was
4 modest. Yet, we collected data prospectively for assessment of hyponatremia diagnosis and
5 treatment, and assessment of the treatment response was prospectively defined. Secondly, most of
6 the patients had volume depleted-TAH, in contrast to literature data showing a higher rate of SIAD-like
7 TAH²¹. However, this might be due to the fact that our treatment response was based on the initial
8 treatment response, and that SIAD-like TAH might have developed later on.

9 Despite these limitations, our study suggests new tools and a pragmatic two-step approach in the
10 differential diagnosis of profound TAH, proposing sodium independent urine indices. Further studies
11 are needed to validate the two-step approach and the present results.

12

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16

17 **Data availability statement:**

18 Some or all datasets generated during and/or analyzed during the current study are not publicly
19 available but are available from the corresponding author on reasonable request.

20

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11

12 **Legends**

13 **Table1**

14 Baseline characteristics and descriptive analysis. Comparisons were carried out using *Mann-*
15 *Whitney test* for continuous variables and *Chi-Square test with Yates correction* for categorical
16 variables. TAH= thiazide associated hyponatremia; SIAD= syndrome of inappropriate antidiuresis;
17 SD= standard deviation; BMI= body mass index; IQR= interquartile range; Comorbidities= presence of
18 chronic heart failure, lung disease or renal failure.

19 **Table 2**

20 Sensitivity analyses at different cut-offs for fluid substitution in differential diagnosis of thiazide
21 associated hyponatremia TAH. TAH= Thiazide associated hyponatremia; PPV= positive predictive
22 value; NPV= negative predictive value; aSID= apparent strong ion difference, Serum Sodium+Serum

1 Potassium-Serum Chloride; Na^+ = Sodium; K^+ = Potassium; Cl^- = Chloride; ChU= Urine Chloride-Urine
 2 Potassium; FUA= fractional uric acid excretion.

3 **Figure 1**

4 **A** ROC Curves for fluid substitution in patients with thiazide associated hyponatremia. ChU= Urine
 5 Chloride-Urine Potassium; aSID= simplified apparent strong ion difference, Serum Sodium+Serum
 6 Potassium-Serum Chloride; FUA= fractional uric acid excretion; Bicarb= Bicarbonate

7 **B** ROC curve for a multivariable model including simplified apparent strong ion difference (aSID),
 8 difference between chloride and potassium in urine (ChU), and fractional uric acid excretion (FUA) for
 9 fluid substitution in thiazide associated hyponatremia.

10 **Figure 2**

11 **A** ROC Curves for fluid substitution in patients with thiazide associated hyponatremia and simplified
 12 apparent strong ion difference ≤ 42 mmol/l and ≥ 39 mmol/l (n=29). ChU= Urine Chloride-Urine
 13 Potassium; FUA= fractional uric acid excretion; Bicarb= Bicarbonate

14 **B** ROC curve for a multivariable model including difference between chloride and potassium in urine
 15 (ChU), and fractional uric acid excretion (FUA) for fluid substitution in patients with thiazide associated
 16 hyponatremia and an inconclusive apparent strong ion difference (aSID) of 39-42 mmol/L.

17 **Figure 3**

18 Two-step approach with first blood assessment and second urine assessment for differential diagnosis
 19 of thiazide associated hyponatremia. Na^+ = Sodium; K^+ = Potassium; Cl^- = Chloride; FUA= fractional uric
 20 acid excretion.

21 **Table 1**

| | Whole sample TAH | Volume- depleted TAH | SIAD-like TAH | p SIAD-like TAH vs volume-depleted |
|--|------------------------|----------------------------|---------------|--|
|--|------------------------|----------------------------|---------------|--|

| | n= 98 | n= 69 | n= 29 | TAH |
|--|--------------|--------------|--------------|------------|
| Age in years | 74.5 | 75.8 | 71.4 | 0.051 |
| Mean +/- SD | (11.0) | (10.5) | (11.6) | |
| Sex male | 22 | 15 | 7 | 0.996 |
| yes n (%) | (22.4) | (21.7) | (24.1) | |
| BMI kg/m2 | 23.8 | 23.8 | 24.3 | 0.236 |
| Median (IQR) | (22.5-28.2) | (21.8-27.4) | (23.3-30.3) | |
| Loop diuretics | 17 | 11 | 6 | 0.784 |
| yes n (%) | (17.3) | (15.9) | (20.7) | |
| Potassium-sparing diuretics yes n (%) | 10 | 6 | 4 | 0.693 |
| | (10.2) | (8.7) | (13.8) | |
| Antidepressant, antiepileptic or neuroleptics yes n (%) | 26 | 14 | 12 | 0.056 |
| | (26.5) | (20.3) | (41.4) | |
| Baseline Serum Sodium mmol/L Median (IQR) | 120 | 120 | 120 | 0.443 |
| | (116-122) | (115-121) | (116-123) | |
| Baseline Serum Potassium mmol/L Median (IQR) | 3.5 | 3.5 | 3.8 | 0.032 |
| | (3.1-4.0) | (3.0-3.9) | (3.2-4.3) | |
| Baseline Serum Chloride mmol/L Median (IQR) | 81.0 | 80.5 | 83.0 | 0.135 |
| | (75.0-86.0) | (74.0-84.0) | (78.5-86.5) | |
| Baseline Serum Creatinine umol/L Median (IQR) | 67.5 | 67.0 | 68.0 | 0.744 |
| | (53.0-80.7) | (51.0-93.0) | (54.0-76.0) | |
| Baseline Serum Albumin g/L Median (IQR) | 37.0 | 37.0 | 36.7 | 0.759 |
| | (34.0-39.0) | (34.0-39.0) | (33.5-40.1) | |
| Baseline Serum Bicarbonate mmol/L Median (IQR) | 23.4 | 23.4 | 22.9 | 0.839 |
| | (21.4-26.5) | (21.9-25.9) | (21.0-27.2) | |
| Baseline Urine Osmolality mOsm/kg Median (IQR) | 352 | 336 | 393 | 0.286 |
| | (271-485) | (271-474) | (298-500) | |
| Baseline Urine Sodium mmol/L Median (IQR) | 54.4 | 53.0 | 62.0 | 0.159 |
| | (43.0-81.7) | (40.0-76.0) | (45.0-92.0) | |
| Comorbidities yes n (%) | 43 | 28 | 15 | 0.346 |
| | (43.9) | (40.6) | (51.7) | |
| Central nervous system comorbidities yes n (%) | 33 | 21 | 12 | 0.417 |
| | (33.7) | (30.4) | (41.4) | |

1 Table 2

| TAH | Value | Sensitivity | Specificity | Cut-off | PPV | NPV |
|--|-----------|-------------|-------------|---------------|-------------|-------------|
| 98 patients | | | | | | |
| Simplified aSID | 38 | 89.7 | 17.9 | <38 | 38.5 | 75.3 |
| Serum | 39 | 79.5 | 35.7 | <39 | 38.5 | 76.5 |
| Na⁺ + K⁺ - Cl⁻ | 40 | 46.1 | 71.2 | >40 | 76.7 | 36.4 |
| mmol/L | 42 | 51.5 | 65.4 | >42 | 79.1 | 36.0 |
| | 44 | 30.3 | 80.8 | >44 | 78.3 | 30.0 |
| ChU | 0 | 14.2 | 100 | <0 | 100 | 40.0 |
| Urine | 5 | 28.6 | 100 | <5 | 100 | 44.4 |
| Cl⁻ - K⁺ | 10 | 33.3 | 83.3 | <10 | 77.8 | 41.7 |
| mmol/L | 25 | 66.7 | 66.7 | <25 | 77.8 | 53.3 |
| | 40 | 85.7 | 41.7 | >40 | 62.5 | 72.0 |
| FUA | 15 | 90.5 | 46.4 | >15 | 68.4 | 79.2 |
| % | 12 | 76.1 | 57.1 | >12 | 51.6 | 80.0 |
| | 8 | 39.7 | 78.6 | <8 | 80.6 | 36.1 |
| Serum Bicarbonate | 28 | 14.5 | 85.0 | >28 | 72.7 | 31.5 |
| mmol/L | 26 | 25.4 | 60.0 | >26 | 63.6 | 22.6 |
| | 22 | 74.5 | 50.0 | <22 | 41.7 | 80.4 |

2

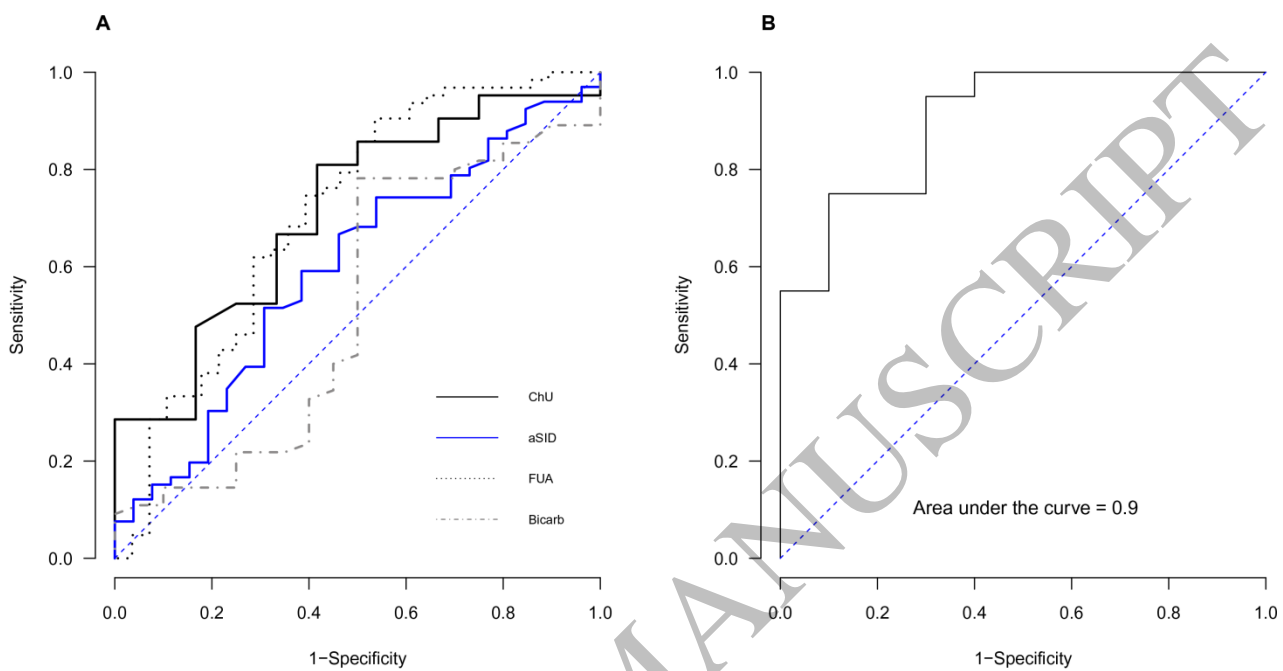


Figure 1
297x210 mm (16 x DPI)

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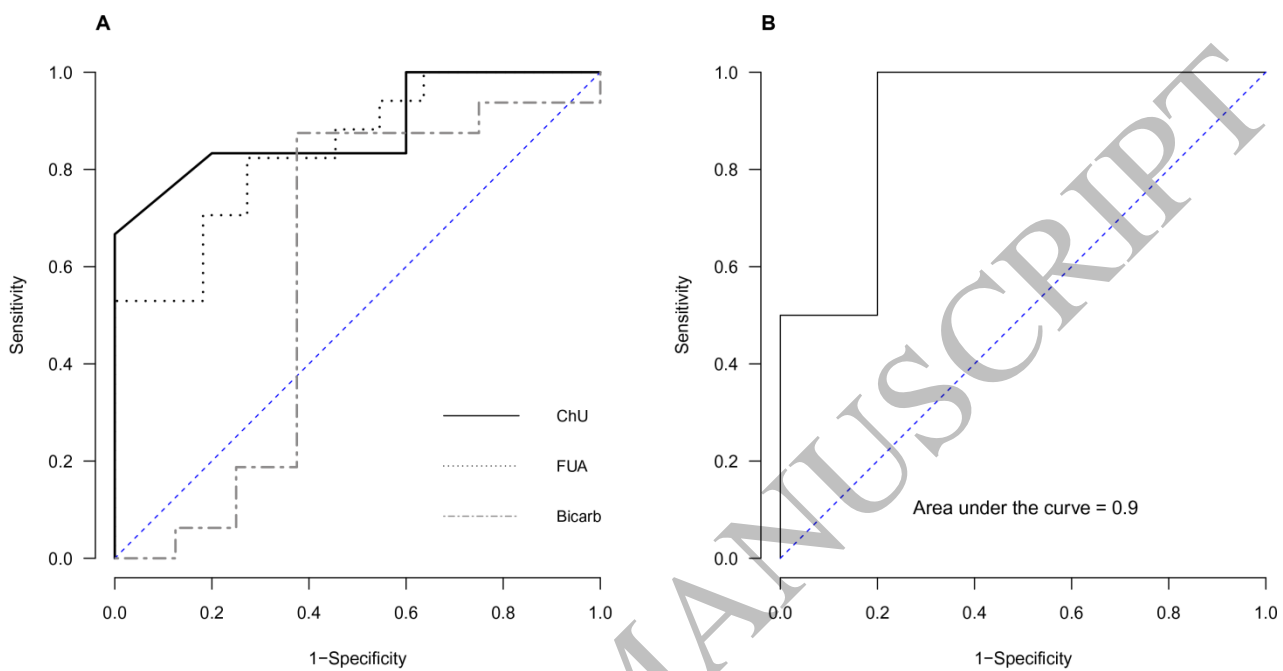
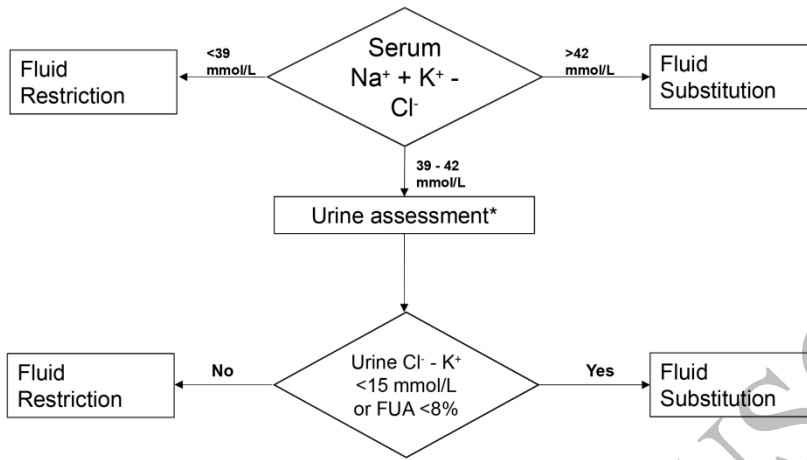


Figure 2
297x210 mm (16 x DPI)

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2
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Two-step approach for differential diagnosis of TAH



*in case of urine sodium <20 mmol/L and urine osmolality <200 mOsm/kg see guidelines

Figure 3
297x169 mm (16 x DPI)

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2
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