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

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Abstract

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

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

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

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

Patients: 98 patients with TAH<125 mmol/l were included, divided according to treatment response in volume-depleted TAH requiring volume substitution or SIAD-like TAH requiring fluid restriction.

Intervention: We computed sensitivity analyses with ROC curves.

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

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

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

Introduction

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

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

Thiazide and thiazide-like diuretics exert their mechanism of action not only on sodium, but also on chloride and potassium. We therefore aimed to evaluate the possible role of the imbalance between these 3 ions in the differential diagnosis of TAH. To do so, we calculated the simplified strong ion difference (*serum sodium* + *potassium* – *chloride*), a part of the Stewart model for acid-base disturbances[10,11]. In brief, the Stewart model represents an alternative to bicarbonate-centered approaches and is especially used in anesthesiology and intensive care. According to Stewart, acid-base balance is the result of the strong ions difference (SID, calculated as the sum of measured cations minus the sum of measured anions), weak acids, and partial pressure of carbon dioxide (pCO2), and aims to maintain electroneutrality in extracellular fluid[12]. In stable patients with no critical illness (absence of severe hypoalbuminemia, of acute renal failure and/or respiratory failure), the simplified aSID could be sufficient to evaluate acid-base balance. A value >40 mmol/L identifies patients with fluid depletion and contraction alkalosis due to relative hypochloremia, whereas a value

<40 mmol/L identifies patients with acidosis due to relative excess of water and therefore in need of fluid restriction[12].

Chloride and potassium balance in urine represents a sodium-independent marker of kidney response to diuretic induced volume depletion[13]. Processes going on at the level of intercalated cells are not completely understood, but there is increasing evidence of a sodium independent chloride reabsorption in response to changes in volume and metabolic status[14,15]. A low urine chloride is a known sign of hypovolemia[16]. It triggers renin release and intercalated cells activation, thus aggravating potassium depletion caused by thiazide[17]. Therefore, we further aimed to investigate the diagnostic potential of the balance between chloride and potassium in urine in the differential diagnosis of TAH. The goal of our analysis was to find an additional tool for the initial assessment of profound hyponatremia in the context of hospitalization and unreliable canonical urine indices.

Material and methods

Study design and participants

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

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

Study procedure and outcomes

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

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

Simplified apparent strong ion difference (aSID) at baseline was calculated with the formula *serum sodium + potassium - chloride*[11]. Urine chloride and potassium score (ChU) at baseline was calculated with the formula *urine chloride - urine potassium* in mmol/L. FUA was calculated according to standard in % of excretion[9].

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

Statistical analysis

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

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

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

All analyses were performed using R statistical software[19].

Results

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

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

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

Descriptive Analysis

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

Sensitivity analysis

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

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

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

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

Taken together for differential diagnosis of TAH, these parameters showed an area under the curve of 90%. *ROC Curves* are displayed in *Figure 1*. We obtained similar results after excluding the 6 patients treated initially with 3% hypertonic saline infusion (data not shown); the 26 patients using antidepressants, antiepileptics or neuroleptics (Supplementary material, Table II and Figure I[20]); and patients taking diuretics other than thiazides (Supplementary material, Table III and Figure II[20]).

Comparison with bicarbonate levels

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

Two-step diagnostic approach

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

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 83.3% in identifying patients with volume-depleted TAH (AUC 88.3%, 95% CI 66.8-100%).

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 identifying patients with volume-depleted TAH (AUC 84.0%, 95% CI 69.3-98.6%).

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

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

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

Discussion

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

One could argue that withdrawal of thiazide or thiazide-like diuretic is effective in hyponatremia treatment, and therefore additional treatments are not required. However, sodium levels in general only slightly increase after withdrawing of thiazides and therefore drug withdrawal alone may be insufficient[21]. Especially in the context of profound hyponatremia it is important to not put the patients at risk of a further decrease in sodium levels, and thus to immediately start with the appropriate treatment[22]. As both volume-depleted and SIAD-like TAH appear euvolemic and have similar urine indices, the choice of an appropriate treatment represents a clinical challenge.

In our study, a simplified aSID excluded the need of fluid substitution for values <39 mmol/L with a high sensitivity, and showed a high specificity for the need of fluid substitution for values >42 mmol/L. Because a higher aSID is indicative of an alkalosis in the model of Stewart, we postulate that patients with aSID >42 mmol/L have a thiazide or thiazide-like diuretic-induced contraction alkalosis[17]. Interestingly, bicarbonate did not display the same efficacy in identifying these alkalotic patients. This might be explained by the fact that a high bicarbonate level does not identify univocally metabolic alkalosis[23] and is therefore not useful in identifying patients with contraction alkalosis. Importantly,

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

In a second step, we found that the assessment of chloride and potassium balance in urine (ChU) could represent a valid tool for the differential diagnosis of TAH, especially in patients for whom the aSID is not conclusive (39 ≥ aSID ≤42 mmol/L). A low urine chloride is a known sign of hypovolemia and its assessment is usually used in hyponatremic hypovolemic patients with metabolic alkalosis due to vomiting, in whom the natriuresis caused by the bicarbonaturia prevents from using urine sodium to identify hypovolemia[16]. In our study, a markedly reduced chloride excretion as compared to potassium identified patients in need of fluid substitution with a 100% positive predictive value, whereas a higher chloride excretion as compared to potassium identified patients in need of fluid restriction. Interestingly, assessment of urine chloride alone did not show the same efficacy in identifying patients with volume-depletion (data not shown). This might be due to the fact that in the context of TAH with volume depletion and metabolic alkalosis, renin is released and intercalated cells are activated, causing kaliuresis and chloride reabsorption[17].

Furthermore, we confirm the cut-offs of FUA proposed by Fenske and colleagues as a complementary analysis with ChU[9]. A FUA <12% showed a ppv of 85.7% in identifying patients in need for fluid substitution, with a lower AUC as compared to ChU, whereas ChU and FUA together showed a AUC of 0.9.

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

Our study has several limitations. Firstly, it was a retrospective, exploratory analysis based on chart reviews so that a prospective validation based on power analysis is needed. Further studies should especially validate our cut-off for ChU in the two-step approach, as the number of patients was modest. Yet, we collected data prospectively for assessment of hyponatremia diagnosis and treatment, and assessment of the treatment response was prospectively defined. Secondly, most of the patients had volume depleted-TAH, in contrast to literature data showing a higher rate of SIAD-like TAH[21]. However, this might be due to the fact that our treatment response was based on the initial treatment response, and that SIAD-like TAH might have developed later on.

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

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Data availability statement:

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

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Legends

Table1

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

Table 2

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

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

Figure 1

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

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

Figure 2

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

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

Figure 3

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

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

Table 2

TAH 98 patients	Value	Sensitivity	Specificity	Cut-off	PPV	NPV
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 mmol/L	28	14.5	85.0	>28	72.7	31.5
	26	25.4	60.0	>26	63.6	22.6
	22	74.5	50.0	<22	41.7	80.4

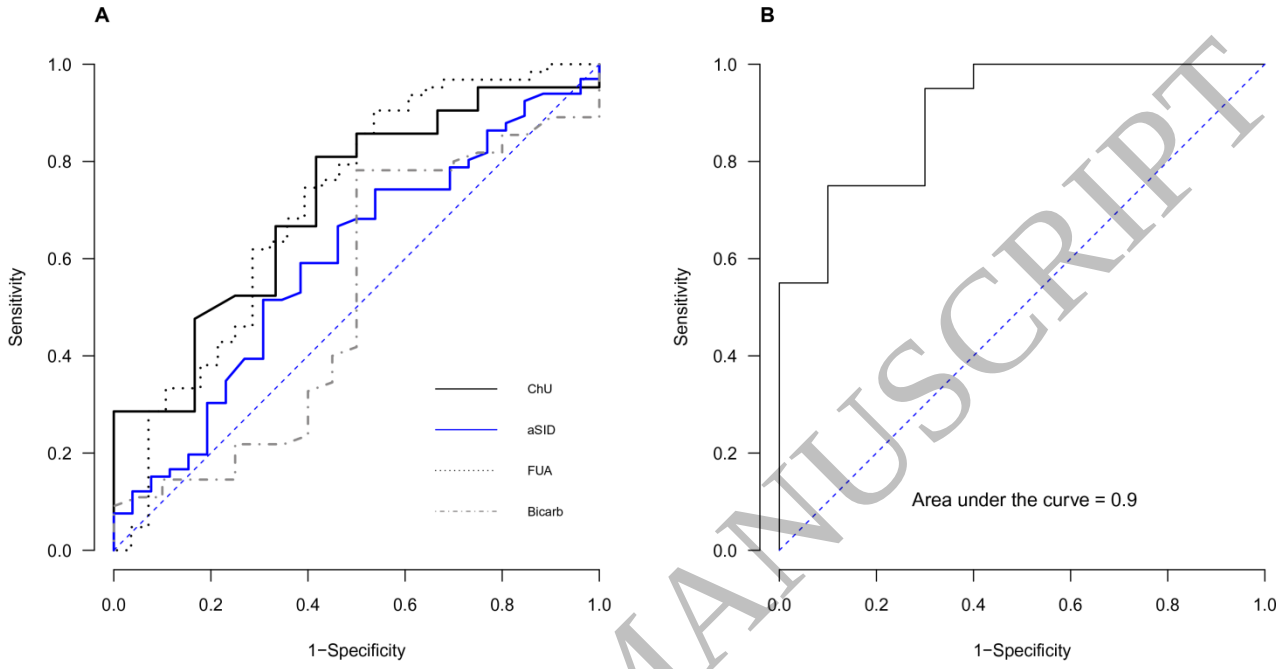

Figure 1
297x210 mm (16 x DPI)

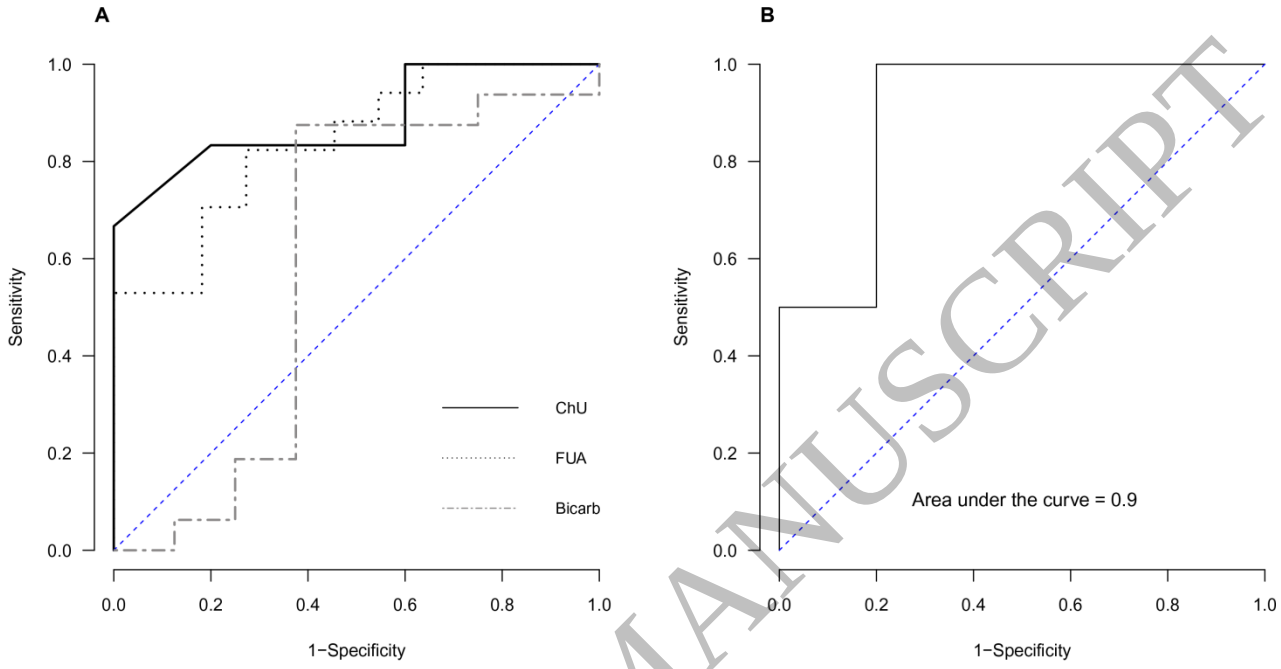

Figure 2
297x210 mm (16 x DPI)

Two-step approach for differential diagnosis of TAH

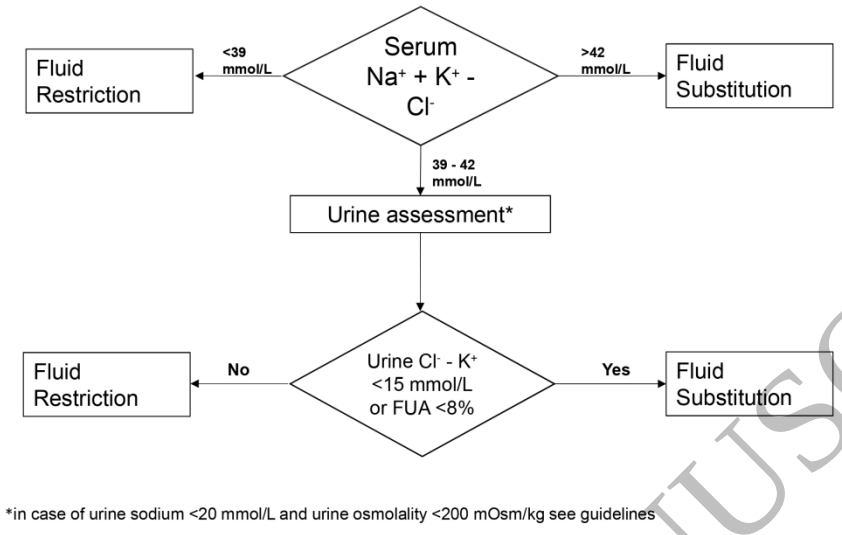

Figure 3
297x169 mm (16 x DPI)