Anaesth Intensive Care 2014; **42:** 584–591

Sodium concentration in urine greater than in the plasma: possible biomarker of normal renal function and better outcome in critically ill patients

A. T. MACIEL*, D. VITORIO†, L. D. SALLES‡, M. PARK§

Intensive Care Unit, Hospital São Camilo Pompéia, São Paulo, Brazil

SUMMARY

Correct interpretation of the urinary sodium concentration (NaU) and its relation to renal function in critically ill patients is lacking. Our aim was to evaluate the relationship between simultaneous NaU value and serum creatinine (sCr). The hypothesis is that a NaU value greater than 140 mmol/l (normal equivalent value in plasma) is only found in patients with normal sCr. We made a retrospective analysis of 1153 simultaneous samples of NaU and sCr, divided according to diuretic use in the previous 24 hours and grouped in five distinct NaU ranges (< 20, 20 to 39, 40 to 139, 140 to 169, ≥ 170 mmol/l). NaU values below 140 mmol/l were found simultaneously with both normal and increased sCr. NaU values above 140 mmol/l were almost always found in patients with normal sCr, even if diuretics were used. Median sCr values in the NaU ranges above 140 mmol/l were significantly lower than in the other NaU ranges. Estimated glomerular filtration rates were lower and intensive care unit and hospital mortalities were higher in patients with NaU values lower than 140 mmol/l compared to patients with a NaU higher than 140 mmol/l. We concluded that a high natriuretic capacity reflects significant residual renal function in the critically ill. NaU greater than normal plasma sodium is a possible biomarker of normal/improving renal function and also of better outcome. Sole NaU values below 140 mmol/l are difficult to interpret but it is possible that very low NaU values may signify some threat to normal kidney function and worse prognosis even in the presence of normal sCr. Our way to interpret NaU values in critically ill patients needs further careful evaluation.

Key Words: urine sodium, serum creatinine, biomarker, acute kidney injury, critically ill patients, outcome

Urinary sodium concentration (NaU) is classically used to distinguish functional and structural acute kidney injury (AKI)[1]. Its use, however, has been consistently criticised[2,3]. We have recently suggested that interpretation of NaU in AKI is misleading in its current form, i.e., low values (< 20 mmol/l) meaning prerenal AKI and 'high' values (> 40 mmol/l) meaning acute tubular necrosis[4]. Our previous results[5] suggested that the early phase of AKI development is characterised by decreases in NaU and even persistent AKI, classically interpreted as a predominantly structural AKI, is frequently characterised by persistent low NaU values. This is probably due to microcirculatory impairment in the kidneys leading to decreases in glomerular filtration pressure in the presence of preserved global capacity of the tubules to retain sodium until advanced AKI stages. Diuretic use may 'blind' our view of this phenomenon since it may increase NaU by blocking tubular sodium reabsorption. In addition, NaU value is usually assessed only after other signs of AKI have emerged (oliguria, increased serum creatinine [sCr]) and sequential measurements are usually not evaluated. We believe that a low NaU value in the presence of normal sCr is a sign of stress to the kidneys and may be associated with an increased risk of AKI due to the fact that injured kidneys are not able to excrete high concentrations of sodium.

The term 'high' is not well defined for NaU values, especially in critically ill patients. NaU values in normal volunteers were recently evaluated and mean value was around 100 mmol/l[6]. The aim of the present study was to compare simultaneous values of sCr and NaU in order to evaluate sCr distribution across different ranges of NaU. We hypothesised that low NaU value ranges would include both normal and increased sCr values. On the other hand, only patients

* MD, Assistant Intensivist, Intensimed Research Group, Intensive Care Unit, Hospital São Camilo Pompéia, and Intensive Care Unit, Department of Medical Emergencies, Hospital das Clínicas, São Paulo, Brazil
† MD, Assistant Intensivist, Intensimed Research Group
‡ RN, Research nurse, Intensimed Research Group
§ MD, PhD, Assistant Intensivist, Intensive Care Unit, Department of Medical Emergencies, Hospital das Clínicas, São Paulo, Brazil

Address for correspondence: Dr Alexandre Toledo Maciel. Email: alexandre.toledo@imedgroup.com.br

Accepted for publication on July 9, 2014

Table 1
General characteristics of the 275 patients included in the study

Gender (male/female)	126/149
Age (years), mean ± SD	65±19
SAPS 3 predicted risk of mortality – median% [P25,P75]	13% [3,34]
Serum sodium (mmol/l) – first measurement per patient (n=275) – mean ± SD	140±6
Associated diseases	
Heart failure	19 (7%)
COPD	7 (3%)
Cirrhosis	5 (2%)
ICU support	
Vasopressor	80 (29%)
Mechanical ventilation	74 (27%)
Diuretic	83 (30%)
Renal replacement therapy	27 (10%)
Mortality: n (%)	
ICU	44 (16%)
Hospital	63 (23%)
Main diagnosis at ICU admission – n (% of total)	
Medical admissions	186 (67%)
Septic syndromes	79 (28)
Cardiovascular syndromes	37 (13)
Neurologic syndromes	30 (11)
Respiratory failure – other causes	13 (5)
Gastrointestinal bleeding	6 (2)
Other diagnosis	21 (8)
Surgical admissions	91 (33%)
Neurosurgery	22 (8)
Genitourinary	19 (7)
Gastrointestinal	18 (7)
Orthopaedic	13 (5)
Vascular	6 (2)
Thoracic	5 (2)
Trauma	4 (1)
Head/neck	3 (1)
Plastic	1 (0)

P25 and P75 signify 25th and 75th percentile. SD=standard deviation, SAPS=Simplified Acute Physiology Score, COPD=chronic obstructive pulmonary disease, ICU=intensive care unit.

with normal sCr values would have high ranges of NaU values. We also compared Simplified Acute Physiology Score 3[7] predicted risk of mortality, need of renal replacement therapy (RRT) and intensive care unit (ICU) and hospital mortality between patients with a first measurement of NaU higher or lower than 140 mmol/l as well as the diagnostic performance of this first NaU measurement in predicting RRT and mortality.

METHODS

The study was approved by the Local Ethics Committee (protocol number 23180613.7.0000.0062). From February to August 2013, both sCr and NaU (spot urine sample) were measured simultaneously, once daily in all patients with an indwelling urinary catheter as part of the routine tests of our ICU. For the purpose of this analysis, we retrospectively eval-

uated all simultaneous measurements of sCr and NaU from consecutive patients during the mentioned period. Patients with chronic renal failure, bladder irrigation, kidney transplantation and samples which were collected after previous RRT in the same ICU stay were excluded. Diuretic use in the preceding 24 hours was also recorded. We have defined five ranges of NaU (mmol/l) based on the cut-off values[1] currently used: < 20 (very low), 20 to 39 (low), 40 to 139 (intermediate), 140 to 169 (high), ≥ 170 (very high). Normal sCr was considered < 106 μmol/l. Estimated glomerular filtration rates were calculated using both the Modified Diet in Renal Disease[8] and Cockcroft-Gault[9] equations.

Statistical Analysis

The normality of data distribution was analysed with the Shapiro-Wilk goodness-of-fit model. Continuous variables were expressed as mean ± standard deviation for parametric data or median (percentile 25th, percentile 75th) for non-parametric data. The analysis was done with Kruskal-Wallis test for three or more non-paired groups, Mann-Whitney U test for two different groups and Pearson's chi-square or Fisher's test as appropriate for categorical variables. When necessary, the Dunn's post hoc test was used. Multiple collinearity among variables in the multivariate analysis was considered absent if the variance inflation factors were less than 2.5. The area under the curve and 95% confidence interval were calculated based on the receiver operating characteristic analysis. Density plots were used to show the distributions and medians of sCr according to the categories of NaU. Sigma plot 12.0® (Systat Software Inc, San Jose, CA, USA) and SPSS 19.0® (IBM, Armonk, NY, USA) softwares were used to build the graphics and to do the statistical analysis.

RESULTS

During the six-month study period, 903 patients were admitted in our ICU. Of these, 292 patients had simultaneous sCr and NaU at some time during their ICU stay (a total of 1380 samples). One hundred and twenty-one samples of 15 patients were excluded due to a history of chronic renal failure. An additional 106 samples were excluded due to previous RRT in the same ICU stay. Two patients were excluded because all samples of these patients were collected at some time after RRT. A total of 1153 samples from 275 patients were included. The main general characteristics of these patients were described in Table 1.

Density plots of the serum creatinine across different ranges of urinary sodium

We have observed a wide range of NaU values: from 2 mmol/l to 335 mmol/l. Normal and increased sCr values were observed in very low and low and intermediate NaU value ranges (Figure 1). NaU equal or greater than 140 mmol/l (normal sodium concentration in plasma), although unusual (16% of the measurements), were basically found in the normal sCr range (Figure 1). This pattern is the same with or without diuretic use in the previous 24 hours (Figures 2 and 3). Median sCr values in the high/very high NaU ranges were significantly lower than in the other NaU ranges, in all patients group and in the non-diuretic group. In the diuretic group, the median sCr value in the very high NaU range was significantly lower than in the very low, low and intermediate NaU ranges (Figure 3). Median sCr values in the low/very low NaU ranges were at least 106 μmol/l in all three groups and significantly higher in the diuretic group in comparison to the non-diuretic group in the very low (151 versus 106 μmol/l, $P=0.02$) and intermediate (133 versus 88 μmol/l, $P < 0.001$) NaU ranges.

In order to exclude the bias caused by more than one sample per patient, we made an additional density plot using only the first sample collected per patient, i.e., 275 samples (Figure 4). The distribution of the sCr across the NaU ranges was similar to that with all samples (Figure 1). Median sCr in all NaU ranges as well as the percentage of sCr lower than 106 μmol/l were also very similar.

High versus low urinary sodium at first measurement, estimated glomerular filtration rates and outcomes

Using these same 275 samples, we compared the Simplified Acute Physiology Score 3[7] predicted risk of mortality, need of RRT during ICU stay and ICU and hospital mortalities between patients with the first measurement of NaU lower than 140 mmol/l and patients with NaU equal or higher than 140 mmol/l. The results are shown in Table 2. Estimated glomerular filtration rates were significantly higher and need of RRT was lower but not statistically significant in patients with NaU equal or higher than 140 mmol/l in comparison to patients with NaU lower than 140 mmol/l. Disease severity at ICU admission and both ICU and hospital mortalities were significantly lower in patients in whom the first sample of NaU was equal or higher than 140 mmol/l. Selecting only the 158 patients with sCr lower than 106 μmol/l, the median sCr was not statistically different between patients with NaU lower or higher than 140 mmol/l

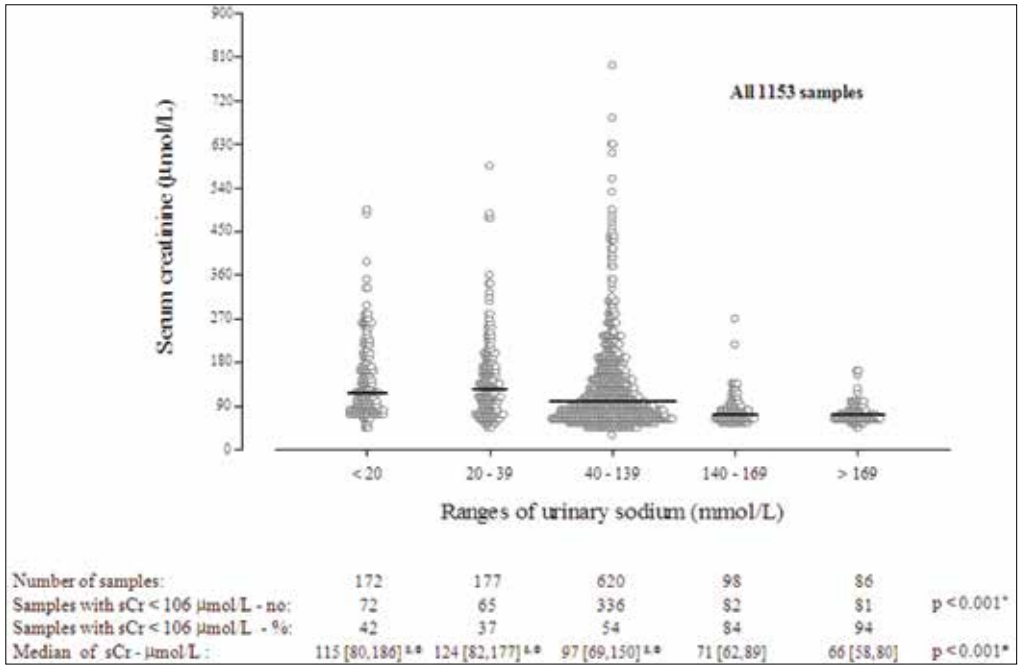

FIGURE 1: Density plot of all 1153 samples of sCr divided according to the simultaneously collected value of NaU. * Pearson's chi-square test, # Kruskal-Wallis test, & P <0.05 Dunn's post hoc analysis versus urinary sodium > 169 mmol/l, Φ P <0.05 Dunn's post hoc analysis versus urinary sodium 140 to 169 mmol/l. Black horizontal lines: median sCr. sCr=serum creatinine, NaU=urinary sodium concentration.

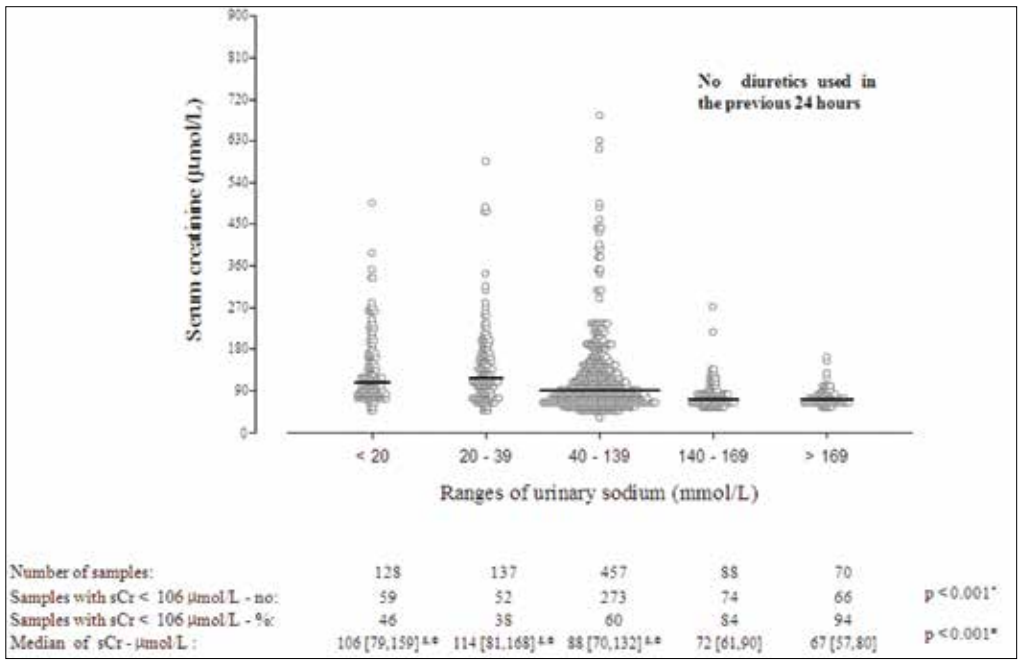

FIGURE 2: Density plot of 880 samples of sCr divided according to the simultaneously collected value of NaU. Only samples that were collected in the absence of diuretics in the previous 24 hours were included. * Pearson's chi-square test, # Kruskal-Wallis test, & P <0.05 Dunn's post hoc analysis versus urinary sodium > 169 mmol/l, Φ P <0.05 Dunn's post hoc analysis versus urinary sodium 140 to 169 mmol/l. Black horizontal lines: median sCr. sCr=serum creatinine, NaU=urinary sodium concentration.

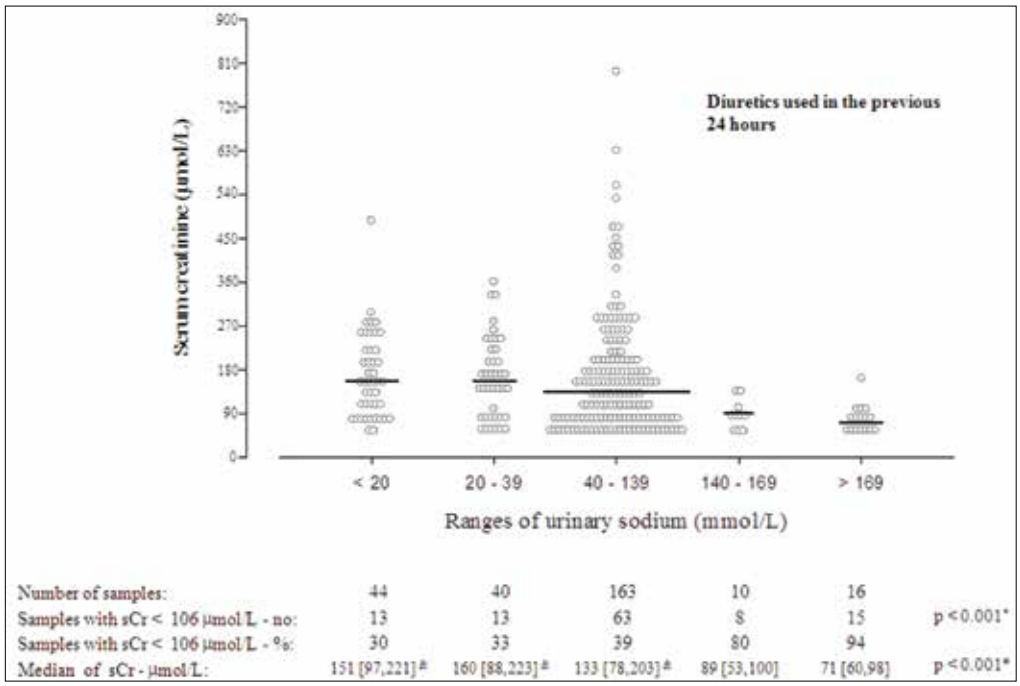

FIGURE 3: Density plot of 273 samples of sCr divided according to the simultaneously collected value of NaU. Only samples that were collected with the use of diuretics in the previous 24 hours were included. * Peasron's chi-square test, # Kruskal-Wallis test, & P <0.05 Dunn's post hoc analysis versus urinary sodium > 169 mmol/l. Black horizontal lines: median sCr. sCr=serum creatinine, NaU=urinary sodium concentration.

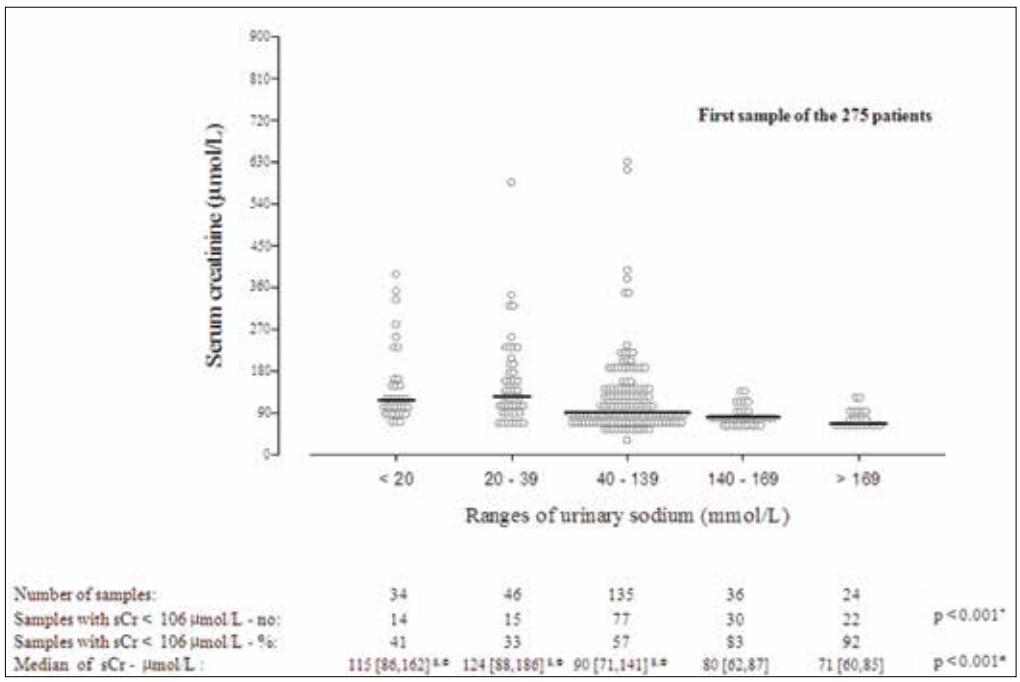

FIGURE 4: Density plot of 275 samples of sCr representing the first sample of each one of the 275 patients included in the study, divided according to the simultaneously collected value of NaU. * Pearson's chi-square test, # Kruskal-Wallis test, & P <0.05 Dunn's post hoc analysis versus urinary sodium > 169 mmol/l, Φ P <0.05 Dunn's post hoc analysis versus urinary sodium 140 to 169 mmol/l. Black horizontal lines: median sCr. sCr=serum creatinine, NaU=urinary sodium concentration.

(80 and 71 μmol/l, respectively, $P=0.08$). Median estimated glomerular filtration rates were also very similar between these two groups. However, patients with sCr lower than 106 μmol/l who died during their hospital stay had a significantly lower simultaneous NaU value than patients with normal sCr value who survived to hospital discharge (median NaU values 64 and 111 mmol/l, respectively, $P=0.02$).

Diagnostic performance of the first measurement of urinary sodium in predicting the need of RRT, ICU and hospital mortalities

The ability of the first NaU measured per patient in predicting RRT, ICU and hospital mortalities was statistically significant but only modest in terms of capability (Table 3). Sensitivity, specificity, positive and negative predictive values for RRT, ICU and hospital mortalities using the NaU cut-off value of 140 mmol/l are also shown in Table 3. NaU value higher than 140 mmol/l was more likely to be considered as a reassurance for better renal function and final renal outcome due to its high negative predictive value.

Urinary sodium value as an independent predictor of outcome

Since NaU seems to be related to outcome, we hypothesised that this effect might be independent of simultaneous sCr—many patients had normal sCr but low NaU at admission. To test this hypothesis, we made a multivariate analysis including Simplified Acute Physiology Score 3 predicted risk of mortality, age, sCr and NaU. No significant collinearity was found between these variables. Higher NaU values were associated with a lower risk of hospital mortality independently of Simplified Acute Physiology Score 3 predicted risk of mortality and concomitant sCr (Table 4).

DISCUSSION

This brief report revealed the distribution of sCr values across different NaU ranges in a heterogeneous population of critically ill patients. The main finding was that high/very high NaU values (considered here as greater than normal plasma sodium values, around 140 mmol/l) were not frequently found but appeared to be almost exclusively coming from patients with normal renal function. This may be an indirect sign that natriuretic capacity is related to kidney function and that only normal kidneys are able to excrete high concentrations of NaU. The association between a low NaU value and a higher simultaneous sCr level suggests that a low natriuretic capacity is related to impaired renal function. This is more obvious after diuretic administration: the inability to excrete high concentrations of sodium after diuretic use is a possible marker of even more impaired renal function – note that, in the diuretic group, the median sCr in the very low and intermediate NaU ranges were higher than in these same NaU ranges in the no-diuretic group. Higher median sCr values were expected in all NaU ranges in the diuretic group since diuretics are usually used more frequently in patients with some degree of renal impairment. It is noteworthy that diuretic use only increased NaU values to above 140 mmol/l in patients with low sCr levels (Figure 3).

Although NaU value had a relatively low accuracy in predicting RRT and mortality, a very high sensitivity and negative predictive value using the cut-off value 140 mmol/l implies that high NaU value is not only a possible marker of good renal function but it signs for a better prognosis and a very low risk of RRT or death.

We have previously suggested that decreases in NaU may precede increases in sCr[5] and NaU may

Table 2

Different glomerular filtration rate estimates and outcomes according to the first urinary sodium value measured per patient

	NaU < 140 mmol/l (n=215)	NaU ≥ 140 mmol/l (n=60)	*P* value
eGFR (MDRD) [P25,P75]	52 [35,81]	82 [69,95]	< 0.001
eGFR (C-G) [P25, P75]	53 [31,91]	88 [63,107]	< 0.001
SAPS 3 predicted risk of mortality (%)	16 [4,36]	4 [1,13]	< 0.001
RRT during ICU stay: n (%)	25 (12%)	2 (3%)	0.08
ICU mortality: n (%)	41 (19%)	3 (5%)	< 0.01
Hospital mortality: n (%)	60 (28%)	3 (5%)	< 0.001

P25 and P75 signify 25th and 75th percentile. NaU=urinary sodium concentration, eGFR (MDRD)=estimated glomerular filtration rate using the Modified Diet in Renal Disease equation, eGFR (C-G)=estimated glomerular filtration rate using the Cockcroft-Gault equation, SAPS=Simplified Acute Physiology Score, RRT=renal replacement therapy, ICU=intensive care unit.

Table 3
Diagnostic performance, sensitivity, specificity, positive and negative predictive values for RRT, ICU and hospital mortalities using a urinary sodium cut-off value of 140 mmol/l at its first measurement per patient

	AUC (CI 95%, *P* value)	Sensitivity	Specificity	PPV	NPV
Renal replacement therapy	0.689 (0.589–0.788, 0.001)	92.6%	23.4%	11.6%	96.7%
ICU mortality	0.691 (0.611–0.772, <0.001)	93.2%	24.7%	19.1%	95.0%
Hospital mortality	0.685 (0.615–0.756, <0.001)	95.2%	26.9%	27.9%	95.0%

RRT=renal replacement therapy, ICU=intensive care unit, AUC=area under the curve, CI=confidence interval, PPV=positive predictive value, NPV= negative predictive value.

Table 4
Multivariate analysis of distinct variables in order to evaluate the independent effect of each one in hospital mortality

	OR (95% CI)	*P* value
SAPS 3 predicted risk of mortality	44.408 (9.637–204.637)	< 0.001
Age	0.999 (0.980–1.018)	0.904
Serum creatinine	1.107 (0.818–1.498)	0.500
Urinary sodium	0.992 (0.985–0.998)	0.011

Variance Inflation Factor was lower than 2.5 for all variables. The *P* values are based on 5000 bootstrap samples. OR=odds ratio, SAPS=Simplified Acute Physiology Score.

remain at low levels after sCr normalisation[10]; these are the reasons why we must carefully evaluate patients with normal sCr but with low/very low NaU values. We have found that, in the presence of normal sCr, NaU assessment may be useful also in terms of predicting prognosis.

A significant limitation of these analyses was the simultaneous evaluation of a single pair of sCr and NaU. We believe that sequential evaluation of these variables is much more important and relevant. Based on the findings of this study, we hypothesise that a low NaU value probably represents an alert signal even when sCr remains in the normal range. On the other hand, increases in NaU to above the plasma sodium level may suggest renal recovery.

Of the five samples with sCr equal or above 106 μmol/l and NaU in the very high range, four samples came from the same patient who was admitted in the ICU after a total right nephrectomy. If this patient was excluded from the analysis, we would reach an almost 100% of patients with simultaneous normal sCr if they had a very high NaU level. This nephrectomised patient had a sCr of 89 μmol/l before surgery, which gradually increased after surgery until it reached 159 μmol/l in three days. Interestingly, there was no impairment in his diuresis during ICU stay and his blood urea nitrogen remained below 7.1 mmol/l. His last sCr measured in the ward before hospital discharge remained around 160 μmol/l, with an estimated creatinine clearance of 63 ml/minute, which could be his new baseline values with a single kidney (no subsequent sCr of this patient was available). It is possible that patients with mild chronic kidney failure may still have the capacity to have very high NaU values, but these patients were excluded from the present study.

One may argue that an increased NaU level, together with an increased sCr, may be classically considered a marker of structural AKI. We believe that, even in the presence of major tubular damage and inability to reabsorb sodium, simultaneous decreases in glomerular filtration rate would lead to significant decreases in sodium filtration. Since sodium filtration is the major source of sodium inside the tubules, increases in NaU will always be limited with the progression of kidney impairment. We have previously suggested that patients who reach Acute Kidney Injury Network Stage 3 may have higher NaU than patients with Acute Kidney Injury Network Stage 2 but not as high as in normal functioning kidneys[5]. Therefore, values above 140 mmol/l would suggest filtration recovery and not progression of the tubular damage.

The fact that we have chosen 106 μmol/l as the cut-off value for normal sCr, and that we have evaluated renal function based on sCr values without a baseline creatinine for each patient, are important additional limitations. It is possible that there were patients with sCr less than 106 μmol/l who met criteria for an Acute Kidney Injury Network creatinine-based diagnosis of AKI[11] and patients with more than 106 μmol/l who did not meet any criteria for AKI.

Independent of the cut-off used, the fact that the density of normal sCr values increased in the high/very high NaU ranges (Figures 1 to 4) suggests that NaU concentration may be related to renal function and that high NaU values (above 140 mmol/l, its equivalent in plasma) may be suggestive of normal/

improving renal function, even in the presence of diuretics. NaU measurement may also be useful as an additional prognostic marker independent of sCr.

CONCLUSIONS

Patients with AKI have a limited capacity to increase NaU, even with the addition of loop diuretics. Natriuretic capacity is probably an alternative approach to evaluate renal function. NaU values above 140 mmol/l may reflect preserved renal function. The higher the NaU, the greater the chance of normal sCr for values above plasma sodium level. Normal sCr with a low/very low NaU must signify potential threats to the kidneys and worse prognosis. Since the majority of the NaU values in many patients are neither low nor high but intermediate values, the best approach to interpret NaU, is to do sequential measurements. The old paradigm of 'pre-renal' and 'renal' azotaemia based on single measured cut-off NaU values of 20 and 40 mmol/l[1] must be re-evaluated. Further analyses are planned in order to investigate this issue in more detail, taking into account other variables such as urine output, sodium balance and AKI stages.

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