Diagnostic usefulness of the random urine Na/K ratio in predicting therapeutic response for diuretics in cirrhotic patients with ascites

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Background
Ascites is a major complication of liver cirrhosis that carries a poor prognosis. Diuretics are used in treatment of ascites in addition to salt restriction. Monitoring of diuretic response can be achieved by measurement of 24-h urinary sodium.

Aim of the study
The aim of the study was to evaluate the accuracy of using spot urinary sodium/potassium ratio as an alternative to 24-h urinary sodium in assessment of dietary sodium compliance in patients with liver cirrhosis receiving diuretics.

Patients and methods
Sixty patients presenting with liver cirrhosis and ascites were admitted at Cairo University Hospital. All the patients were subjected to full history taking, clinical examination, laboratory investigations including liver function tests, renal function tests, 24-h urine sample (for measuring of sodium) and spot urine sample (for sodium and potassium). The studied patients were divided into two groups: diuretic resistant group (those with 24-h urinary sodium <78 mEq) and diuretic sensitive group (with 24-h urinary sodium >78 mEq). The patients in diuretic resistant group were 18 patients (30%) and those in diuretic sensitive group were 42 patients (70%).

Results
Spot urine Na/K ratio was significantly lower in patients in the diuretic resistant group (2.4 ± 2.2) than in the sensitive group (4.7 ± 2.3) ($P < 0.05$). The cutoff point of Na/K ratio that showed highest accuracy was 3.0.

Conclusion
This study revealed highly significant correlation between 24-h urinary sodium and spot urine sodium/potassium ratio with sensitivity 75% and specificity 91.67% at cutoff point of 3.

Keywords:
ascites, diuretics, liver cirrhosis, urine Na/K ratio

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Introduction

Hepatitis C virus is one of the endemic diseases in Egypt. Prevalence of hepatitis C virus in Egypt is about 15%. Complications occur in 10–20% of infected people including liver cirrhosis [1].

Ascites is the most common complication of liver cirrhosis. Approximately 50% of the patients with 'compensated' cirrhosis develop ascites during 10 years of observation [2].

One of pathogenesis of ascites is secondary to renal retention of sodium and water because of underlying activation of neurohormonal mechanisms [3]. Therefore, patients who accumulate ascites have urinary excretion of sodium that is significantly lower than their dietary salt intake. This means that, to achieve successful ascites mobilization, patients should have a negative sodium balance. This can be achieved through education regarding dietary sodium restriction, in addition to oral diuretic therapy [4].

Di *et al.* one is useful only in a small number of patients; hence, diuretics are very important for urinary sodium loss of more than 78 mmol/day. Most patients with cirrhosis and fluid overload are treated with a combination of dietary sodium restriction and diuretics. This approach is effective in ~90% of the patients and 10% are considered diuretic-resistant and second-line therapy is indicated for ascites mobilization [5].

Monitoring of cirrhotic patients with ascites usually requires 24-h urine collection to evaluate urinary sodium secretion. However, the main problem here is that it may be difficult for the patient to accurately collect 24-h urine. Spot urine Na^+/K^+ ratio has been proposed as an accurate alternative measurement to

detect diuretic-sensitive patients (excretion>78 mmol of sodium per day), when the ratio more than a given cut value (one in some studies) is equivalent to 24-h sodium more than 78 mmol Na/day [6].

Aim of the study

(1) To evaluate the accuracy of spot urinary Na/K ratio as an alternative to 24-h urinary sodium in monitoring response to treatment in patients with cirrhosis and ascites treated with diuretics.
(2) To identify the best cutoff point for Na/K ratio.

Patients and methods

(1) The study was conducted on 60 patients with liver cirrhosis, known to have ascites by ultrasound and clinical examination, and on diuretics (frusemide and spironolactone) and sodium free diet. Admitted at Internal Medicine Department in Cairo University Hospital over 6 months from 9–2012 till 3–2013. Informed consent was taken from every patient.

Exclusion criteria

(1) Evidence of intrinsic renal disease.
(2) Evidence of portosystemic encephalopathy.
(3) Hyponatraemia (<120 mEq/l).
(4) Ascites to cause other than liver cirrhosis.
(5) Serum electrolyte imbalance.

Patients were subjected to the following:

(1) Full medical history taking and thorough clinical examination with special stress on:
    (a) Symptoms and signs of chronic liver disease and ascites.
    (b) History of diuretics use, type, dosage, and duration.
(2) Laboratory investigations including:
    (a) Complete blood picture.
    (b) Liver profile: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, total serum protein and albumin, and prothrombin time.
    (c) Renal function tests and electrolytes: serum creatinine, blood urea nitrogen (BUN), serum sodium, and serum potassium.
    (d) Twenty-four hours urine sample for calculation of total urinary sodium and proteins.
    (e) Spot urine sample for measurement of sodium and potassium and complete urine analysis.
(3) Abdominal ultrasound.

Results

The study was conducted on 60 patients with liver cirrhosis and ascites with history of diuretic therapy.

Table 1 shows the demographic and descriptive data of all the studied cases. There were 51 male patients (85%), and nine female patients (15%). Their mean age was 52.9 ± 6. All patients were on loop diuretics plus K sparing diuretics (spironolactone). According to Child–Pugh classification; 29 patients (48.3%) were Child class B, 30 patients (50%) were Child class C, and one patient (1.7%) was Child class A (Tables 2–10 and Fig. 1).

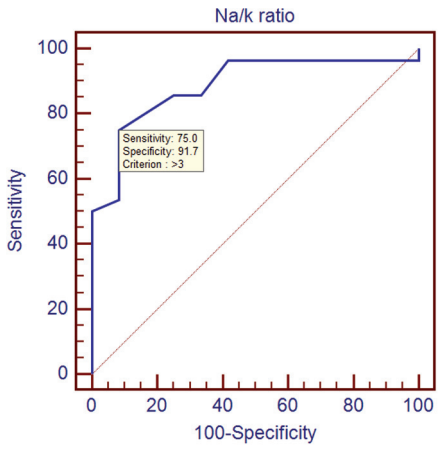
Patients were divided into two main groups:

(1) Diuretic resistant group (those with 24-h urinary sodium less than 78 mEq/day), which

Table 1 The demographic and descriptive data of all the studied cases

Variables	Mean ± SD	Range
Age	52.9 ± 6.1	45–65
Sex [*n* (%)]		
Males	51 (85)	
Females	9 (15)	
Sensitivity [*n* (%)]		
Diuretics sensitive	42 (70)	
Diuretics resistance	18 (30)	
Child–Pugh class [*n* (%)]		
Child A	1 (1.7)	
Child B	29 (48.3)	
Child C	30 (50)	

Figure 1



Receiver operating characteristic (ROC) curve for the best cutoff points of Na/K ratio to differentiate between diuretic resistant (DR) and diuretic sensitive (DS) ascites. Area under the curve (AUC) = 0.887; 95% confidence interval (CI) = 0.747–0.965; significance, $P < 0.0001$ (HS). The best cutoff points were: 2.7 is the cutoff value that has 85.71% sensitivity and 75% specificity; 3.0 is the cutoff value that has 75% sensitivity and 91.67% specificity; 3.2 is the cutoff value that has 71.43% sensitivity and 91.67% specificity; 3.25 is the cutoff value that has 64.29% sensitivity and 91.67% specificity.

Table 2 Descriptive statistics of all cases for liver functions (*N* = 60)

Variables	Minimum	Maximum	Mean	SD
AST (U/l)	17	267	67.8	45.04
ALT (U/l)	8	101	47.02	24.6
Albumin (g/dl)	1.6	5.1	2.7	0.6
Total bilirubin (mg/dl)	0.7	11.5	3.2	2.6
Direct bilirubin (mg/dl)	0.1	10.2	1.9	2.1
Total protein (g/dl)	4	8.6	6.4	1.02
ALP (U/l)	53	240	129.1	52.5
PT (s)	12.7	37.6	19.8	5.2
PC %	20	90	52.7	17.5
INR	1.07	4.2	1.7	0.5

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time; PC: prothrombin concentration.

Table 3 Descriptive statistics of all cases for kidney function (*N* = 60)

Variables	Minimum	Maximum	Mean	SD
Creatinine (mg/dl)	0.3	1.3	0.9	0.2
BUN (mg/dl)	6	43	17.5	9.01
Na (mmol/l)	135	144	138.7	2.7
K (mmol/l)	2.4	5.7	3.8	0.6

BUN, blood urea nitrogen.

Table 4 Descriptive statistics of all cases for the 24-h urinary Na and Na/K ratio (*N* = 60)

Variables	Minimum	Maximum	Mean	SD
24-h urinary Na (mmol)	54	420	192.8	109.08
Na/K ratio	1.4	10	4.08	2.2

Table 5 Shows age distribution and Child classification in both groups

Variables	DS (*N* = 42) (mean ± SD)	DR (*N* = 18) (mean ± SD)	*P*
Age	51.7 ± 5.8	55.9 ± 9.6	0.058
Child–Pugh class [*n* (%)]			
Child A	1 (2)	0	
Child B	23 (55)	6 (33.3)	<0.05
Child C	18 (43)	12 (66.6)	<0.05

DR, diuretics resistance; DS, diuretics sensitive.

consists of 18 patients (30%). Their mean age was 55.9 ± 9.6 years, according to Child–Pugh classification there were six patients (33%) of Child class B, 12 patients (67%) of Child class C.

(2) Diuretic sensitive group (those with 24-h urinary sodium more than 78 mEq/day), which consists of 42 patients (70%). Their mean age was 51.7 ± 5.8 years, according to Child–Pugh classification there was one patient (2%) of Child class A, 23 patients (55%) of Child class B, 18 patients (43%) of Child class C.

Discussion

Ascites is a major complication of liver cirrhosis, occurring in 50% of cirrhotic patients over 10 years of follow-up. The development of ascites is associated with 50% mortality over 2 years, and signifies the need to consider liver transplantation [7].

One of the pathogenesis of ascites in patients with liver cirrhosis was portal hypertension, which provokes systemic vasodilation being most evident in the splanchnic vasculature. This leads to further increase in filtration and ascites formation. On the other side, it leads to systemic vascular underfilling that stimulates sympathetic nervous system and renin–angiotensin–aldosterone system to produce renal vasoconstriction and increases sodium reabsorption to fill the systemic vasculature. Sodium retention leads to more ascites formation as it leaks into peritoneal cavity [8].

The usual treatment for ascites in patients with cirrhosis is dietary sodium restriction and diuretics [9].

Development of refractory ascites is associated with worse prognosis and shortened survival [10].

Tests to confirm diet compliance have been studied. The most accepted one now is collection of 24-h urinary sodium. Patients with 24-h urinary sodium

Table 6 Comparison between both groups as regard the liver functions and there was no significance statistically (*P* > 0.05)

Variables	Group 1 (DS) (*n* = 42) (mean ± SD)	Group 2 (DR) (*n* = 18) (mean ± SD)	*P*	Significance
AST (U/l)	72.2 ± 52.07	57.5 ± 45.7	0.2	NS
ALT (U/l)	48.9 ± 23.5	42.5 ± 23.4	0.4	NS
Albumin (g/dl)	2.7 ± 0.6	2.5 ± 0.7	0.4	NS
Total bilirubin (mg/dl)	3.3 ± 2.8	3.2 ± 2.6	0.9	NS
Direct bilirubin (mg/dl)	1.9 ± 2.3	1.8 ± ± 2.1	0.7	NS
Total protein (g/dl)	6.4 ± 1.07	6.5 ± 1.3	0.5	NS
ALP (U/l)	130 ± 51.3	127.08 ± 53.5	0.8	NS
PT (s)	19.7 ± 5.6	20.1 ± 4.9	0.8	NS
PC %	52.5 ± 17.8	52.5 ± 17.8	0.9	NS
INR	1.7 ± 0.6	1.7 ± 0.4	0.7	NS

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DR, diuretics resistance; DS, diuretics sensitive; INR, international normalized ratio; PT, prothrombin time; PC: prothrombin concentration.

Table 7 Comparison between both groups as regard the kidney functions and there was no significance statistically (*P* > 0.05)

Variables	Group 1 (DS) (*n* = 42) (mean ± SD)	Group 2 (DR) (*n* = 18) (mean ± SD)	*P*	Significance
Creatinine (mg/dl)	0.9 ± 0.2	1.06 ± 0.2	0.07	NS
BUN (mg/dl)	18.07 ± 9.7	16.3 ± 9.1	0.5	NS
Na (mmol/l)	138.2 ± 2.7	139.7 ± 22.2	0.1	NS
K (mmol/l)	3.8 ± 0.4	3.9 ± 0.8	0.6	NS

BUN, blood urea nitrogen; DR, diuretics resistance; DS, diuretics sensitive.

Table 8 Comparison between both groups as regard the hematological parameters and there was no significance statistically (*P* > 0.05)

Variables	Group 1 (DS) (*n* = 42) (mean ± SD)	Group 2 (DR) (*n* = 18) (mean ± SD)	*P*	Significance
WBCs ($10 \times 3/cm^2$)	6.4 ± 4.3	4.5 ± 3.8	0.06	NS
Hemoglobin (g/dl)	10.05 ± 1.8	10.5 ± 2.5	0.5	NS
Platelets ($10 \times 3/cm^2$)	97.7 ± 54	98.5 ± 57.7	0.9	NS

DR, diuretics resistance; DS, diuretics sensitive; WBC, white blood cell.

Table 9 Comparison between both groups as regard the 24-h urinary Na and Na/K ratio and it was statistically significant (*P* < 0.01)

Variables	Group 1 (DS) (*n* = 42) (mean ± SD)	Group 2 (DR) (*n* = 18) (mean ± SD)	*P*	Significance
24-h urinary Na (mmol)	246.9 ± 83.8	66.5 ± 8.3	<0.01	HS
Na/K ratio	4.7 ± 2.3	2.4 ± 2.2	<0.01	HS

DR, diuretics resistance; DS, diuretics sensitive.

Table 10 Compares between the four different cutoff points of Na/K ratio to differentiate between diuretic resistance and diuretic response

Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
>2.7	85.71	75.00	88.9	69.2
>3	75.00	91.67	95.5	61.1
>3.2	71.43	91.67	95.2	57.9
>3.25	64.29	91.67	94.7	52.4

It revealed that the best cutoff point was 3.0; NPV, negative predictive value; PPV, positive predictive value; Sensitivity = 75%; specificity = 91.67%; positive predictive value = 95.5%; negative predictive value = 61.1%.

excretion exceeding 78 mEq should be losing weight and if they are not responding then dietary sodium restriction should be the next step not increasing the diuretic dose or labeling as refractory ascites [11]. The explanation for this is that to lose weight, patients should have negative sodium balance. Patients compliant to dietary sodium restriction is to receive 2 g sodium per day that is equivalent to 88 mEq. Nonurinary sodium losses are 10 mEq/day. So to lose sodium, urinary loss should exceed 78 mEq/day (88–10 mEq/day) [12].

Measuring sodium in spot urine specimen should be easier and more convenient for the patient when compared with 24-h urine collection. The lack of accuracy is the problem as excretion of sodium is not uniform all over the day. Random urinary sodium concentrations are of value when they are 0 mmol/l or greater than 100 mmol/l but are not helpful when they are intermediate, which is the case in most samples so this test cannot be used as a reliable alternative [13].

This study evaluated the accuracy of using spot urinary sodium/potassium ratio as an alternative to 24-h urinary sodium in assessment of diuretic response in cirrhotic patients and ascites.

This study was carried on 60 patients having liver cirrhosis receiving diuretics for ascites; there were 51 males (85%) and nine females (15%), their age ranged from 45–65 years. Patients were divided into two groups according to 24-h urinary sodium excretion, those with sodium less than 78 mEq/24 h were labeled as diuretic resistant and those with more than 78 mEq as diuretic sensitive group.

In the present study, patients in diuretic resistant group were 18 patients (30%) and those in diuretic sensitive group were 42 patients (70%). In the study carried by Stiehm *et al.* [14], 7% of samples were from diuretic resistant patients and 93% of samples were from diuretic sensitive patients. While in the study by Karatapanis *et al.* [15], 9.8% of the samples were from diuretic resistant patients and the remaining 90.2% from diuretic sensitive patients. In the study done by El-Bokl *et al.* [16], 60% of samples were diuretic resistant, whereas 40% of samples were diuretic sensitive. In the study carried by Park *et al.* [17] patients in diuretic resistant group were 18 patients (45%) and those in diuretic sensitive group were 22 patients (55%).

In the present study, there was no significant statistical difference as regard to age between the two groups. El-Bokl *et al.* [16] and Cho *et al.* [18] reported similar finding.

Patients with more advanced liver disease have more deterioration in liver function and marked degree of circulatory dysfunction and neurohumoral activation, including antidiuretic hormone, which results in enhanced sodium renal tubular reabsorption, and therefore, more diuretic resistance [5,8].

This was noted in the present study, as patients in the diuretic resistant group had more advanced liver disease in the form of lower serum albumin, higher

serum bilirubin, and international normalized ratio when compared with those in the diuretic sensitive group, but no parameters were statistically significant ($P < 0.05$). Similar results were found in the study carried out by El-Bokl *et al*. [16], but only the difference as regard to serum albumin was statistically significant ($P < 0.05$). Also results reported by Cho *et al*. [18] and Spahr *et al*. [19] were close to ours but none of those parameters were significantly different between both groups. This maybe due to small number of the studied sample in the present study.

Serum albumin, bilirubin, and international normalized ratio are included in the Child–Pugh classification, which reflects the liver function status. In the current study, patients in the diuretic resistant group with Child class C were 66%, whereas only 43% of patients in diuretic sensitive group were Child class C with statistically significant difference between both groups. Similar results were reported by Stiehm *et al*. [14], El-Bokl *et al*. [16], and Spahr *et al*. [19]. However, in the study by Cho *et al*. [18] the difference between both groups as regard to Child–Pugh class was not statistically significant.

In the present study, there were no difference between both the groups regarding the alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, same results reported by El-Bokl *et al*. [16] and Spahr *et al*. [19].

In the current study, there was no difference between both groups as regards serum Na or K.

In the study done by El-Bokl *et al*. [16] and also Spahr *et al*. [19] serum sodium in the resistant group was significantly lower than in the sensitive group. In our study, it may be a relatively small number (18 patients, 30%) of the resistant group, which is the cause of lack of difference between both groups as regards serum Na. Also in our study exclusion criteria included no electrolyte imbalance or hyponatremia (serum Na <120).

In this study, there was no significant difference between both groups as regards serum creatinine or BUN, in contrast to Stiehm *et al*. [14] and El-Bokl *et al*. [16] who reported a significantly higher BUN in the resistant group, than in the sensitive group. May be due to that the exclusion criteria in our study included no evidence of intrinsic renal disease.

There was highly significant statistical difference between 24-h urinary sodium in both the groups, being lower in the diuretic resistant group than in the diuretic sensitive group. Also in the study done by El-Bokl *et al*. [16] and Cho *et al*. [18]; 24-h urinary sodium in the resistant group was lower than in the sensitive group.

The present study revealed that spot urine Na/K ratio was significantly lower in patients in the diuretic resistant group (2.4 ± 2.2) than in the sensitive group (4.7 ± 2.3) ($P < 0.05$). Similar finding was noted by Stiehm and colleagues [14–16], where patients in the resistant group had significantly lower Na/K ratio than in the sensitive group.

In the present study, we tested the correlation between spot urine Na/K and 24-h urinary sodium using the receiver operating characteristic curve. We found a significant correlation with sensitivity 75% and specificity 91.6%. Similar results were reported by Stiehm *et al*. [14], with sensitivity 63.8%, specificity 91% and accuracy 89.1%. In the study by Karatapanis *et al*. [15], there was also highly significant correlation with accuracy 86%. In the study carried out by El-Bokl *et al*. [16], there was also a highly significant correlation with sensitivity 87.5%, specificity 87.5%, and accuracy 87%. In the study carried by Park *et al*. [17], there was also a highly significant correlation with sensitivity 77.8% and specificity 90.9%. A single difference is that in our study, the cutoff point of Na/K ratio that showed highest accuracy was 3.0, whereas in the studies done by Metaxaki *et al*. [6], Stiehm *et al*. [14], and Karatapanis *et al*. [15] was one. In the study done by El-Bokl *et al*. [16], the highest accuracy 87% was at a cutoff point 2.5. While in the study done by Park *et al*. [17] was 1.25.

Conclusion

This study revealed highly significant correlation between 24-h urinary sodium and spot urine sodium/potassium ratio with sensitivity 75% and specificity 91.67% at cutoff point of 3.

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Conflicts of interest

There are no conflicts of interest.

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