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ORIGINAL ARTICLE

Fractional Excretion of Urea: A Simple Tool for the Differential Diagnosis of Acute Kidney Injury in ICU Patients

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ABSTRACT

Keyword: Acute kidney injury, FEUrea, FENa.

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Background: Fractional excretion of filtered sodium (FENa) is a tool utilized to determine the origin of acute renal damage. **Objectives:** to determine, within certain limitations, how useful fractional excretion of urea (FEUrea) is as a clinical tool for distinguishing between acute tubular necrosis (ATN) and prerenal azotemia (PRA) in intensive care unit (ICU) patients with AKI. **Methodology**: This cross-sectional trial was done amongst May 2023 and January 2024 and one hundred and six participants were involved in the analysis. All participants' demographic and laboratory data are used to determine the cause of AKI as well as the clinical evaluation. Using these data, FEUrea and FENa were calculated. **Results**: The mean age in the PRA group was 48.91 ± 11.41 while in the ATN group 49.55 ± 10.38. We detected that FEUrea and FENa were significantly increased in the ATN group than PRA group (P value 0.044 and <0.001 respectively). FEUrea and FENa can significantly predict ATN (P value 0.041 and P value under 0.001 respectively) at different cut-off values. **Conclusion**: Our findings highlight the clinical value of FEUrea and FENa as indicators in the early discrimination of ATN from PRA in ICU patients with Acute kidney injury, facilitating timely and targeted interventions based on the underlying etiology.

INTRODUCTION

Multiple signs are required to diagnose Acute Kidney Injury (AKI). All the following are deemed to be dangerous: serum creatinine levels that are 1.5 times higher than baseline within the preceding 7 days; a urine volume that is < 0.5 mL/kg/h for at least 6 hours; or a rise of 0.3 mg/dL or more (≥26.5 micromoles/L) within 48 hours **[1].**

Urinary tract obstruction is one of the main reasons of AKI, and the other causes are generally distributed into two categories: intrinsic causes in which there is renal tissue damage, and prerenal causes, with low perfusion of the kidneys leading to immediate reversible renal dysfunction **[2].**

The Fractional excretion of filtered sodium (FENa) has been functioned to ascertain the reason of AKI. It could distinguish between ATN in addition to prerenal azotemia PRA **[3].** However, low fractional excretion of sodium (<1 percent) may be found in some conditions that are associated with intrinsic AKI such as myoglobinuria, sepsis, non-oliguric acute tubular necrosis (ATN), and contrast nephropathy **[4].** Another restriction in the use of FENa is that diuretics are used frequently to treat prerenal conditions to enhance urine output. In addition, a prerenal condition, characterized by elevated urine Na and, consequently, FENa, can occur in euvolemic patients who take diuretic medications in excess. PRA is linked to elevated urine sodium and FENa in other contexts as well **[5].**

Therefore, under circumstances of reduced renal perfusion and elevated vasopressin and RAAS, the fractional excretion of urea FEUrea ought to diminish. On the flip side, reabsorption should be impaired and its fractional excretion increased in the event of renal tubular injury. Diuretics that act more distally do not influence urea absorption since it is mostly controlled in the proximal tubules **[6]**. Therefore, it could be utilized to differentiate between ATN and PRA at an early stage. Independent patient cohorts further confirmed FEUrea's diagnostic utility, and the results demonstrated good diagnostic accuracy (sensitivity in addition to specificity above ninety percent) **[7].**

The aim of this investigation is to compare the efficacy of FEUrea in patients with PRA and renal AKI as a clinical tool for distinguishing among ATN and PRA in in intensive care unit ICU patients with AKI.

SUBJECTS AND METHODS

The Aswan University Hospital in Egypt was the site of this cross-sectional trail. Institutional Review Board (IRB) approval was received for this research from Aswan University's Faculty of Medicine. All subjects provided written informed consent. The identification details of all subjects were maintained in confidentiality and safeguarded from public access.

Between May 2023 and January 2024, patients admitted to the ICU with acute kidney injury (AKI) and aged above 18 years were recruited for the study, while those with a history of kidney transplantation, obstructive uropathy, or undergoing renal replacement therapy were excluded. A total of 106 participants met the inclusion criteria, with the sample size calculated using OpenEpi software at 80% power, considering a FEUrea of 23% in pre-renal azotemia (PRA) and 44% in acute tubular necrosis (ATN) **[8].** Participants were divided into two groups based on FENa and FEUrea thresholds: PRA (FENa <1% or FEUrea <35%) and ATN (FENa >2% or FEUrea >50%). Intermediate cases were classified using clinical judgment, including urine microscopy, response to fluid therapy, and overall clinical context.

All persons were exposed to Demographic statistics such as gender, age, and smoking history. Laboratory measurements as urine urea also creatinine, serum Na^+, as well as urine Na+ serum urea and creatinine. Also, they evaluated clinically, and the cause of AKI was determined. For the purpose of calculating FEurea, we utilized the following formula, which involved the utilization of admission values of serum urea and serum creatinine, as well as spot measurements of urine

creatinine and urine urea. [(urine urea ÷ serum urea) ÷ (urine creatinine ÷ plasma creatinine)] x 100%. Utilizing serum admission values Na+, spot quantification of urinary creatinine, serum creatinine, in addition to spot measurement of urine Na+, we used the following formula to calculate fractional excretion of Na. [(urine sodium × serum creatinine) ÷ (serum sodium × urine creatinine)] x 100%.

- **Statistical Analysis:**

Data was analyzed statistically utilizing SPSS version 26 (IBM Inc., Armonk, NY, USA). In order to determine if the statistical distribution was normal, the Shapiro-Wilk test and histograms were used. Mean±SD were utilized to show quantitative parametric data, and unpaired Student's t-tests were used to assess it. The median and interquartile range (IQR) were utilized to express quantitative non-parametric data, which were then evaluated using the Mann-Whitney test. The frequency and percentage (%) of qualitative data were reported and evaluated with either the Chi-square test or Fisher's exact test, depending on the situation.

The total diagnostic performance was evaluated using ROC curve analysis, where the area under the curve (AUC) indicates test efficacy (an AUC greater than 50% signifies acceptable performance, while an AUC approaching 100% represents optimal performance). A significant result was defined as a two-tailed P value below 0.05.

RESULTS

This study includes one hundred and six participants, 47 males in addition to 59 females, they were separated into two groups: PRA group and ATN group. The mean age in the PRA group was 48.91 ± 11.41 while in the ATN group was 49.55 ± 10.38. Their BMI was 28.92 ± 6.93 and 29.9 ± 5.54 respectively. There was an insignificant variance among the examined groups **(Table 1).**

Table (1): Demographic data of the studied groups.

		PRA group (n=53)	ATN group (n=53)	P value
Age (years)	**Mean ± SD**	48.91 ± 11.41	49.55 ± 10.38	0.763
	Range	31 - 69	29 - 67	
Gender	**Male**	27 (50.94%)	20 (37.74%)	0.171
	Female	26 (49.06%)	33 (62.26%)	
BMI (kg/m^2)	**Mean ± SD**	28.92 ± 6.93	29.9 ± 5.54	0.420
	Range	16.84 - 41.79	18.9 - 43.29	

BMI: body mass index

As regards the presence of comorbidities, in the PRA group, 20 patients had DM while 11 had HTN. In the ATN group, 15 patients had DM while 13 had HTN. There was an insignificant alteration among the examined groups **(Table 2).**

Table (2): Comorbidities of the studied groups.

	PRA group (n=53)	**ATN group (n=53)**	**P value**
DM	20 (37.74%)	15 (28.3%)	0.302
HTN	11 (20.75%)	13 (24.53%)	0.643

DM: diabetes mellitus, HTN: hypertension

Multiple causes were suggested to induce AKI, but we found that infections were the prominent cause in PRA group, while GIT bleeding is the cause in ATN group. There was insignificant variance amongst both groups **(Table 3).**

Table (3): Causes of AKI of the studied groups.

	PRA group (n=53)	**ATN group (n=53)**	**P value**
Diuretic use	11 (20.75%)	12 (22.64%)	0.868
Infections	15 (28.3%)	12 (22.64%)	
GIT bleeding	13 (24.53%)	16 (30.19%)	
Other	14 (26.42%)	13 (24.53%)	

AKI: acute kidney injury, GIT: gastrointestinal tract

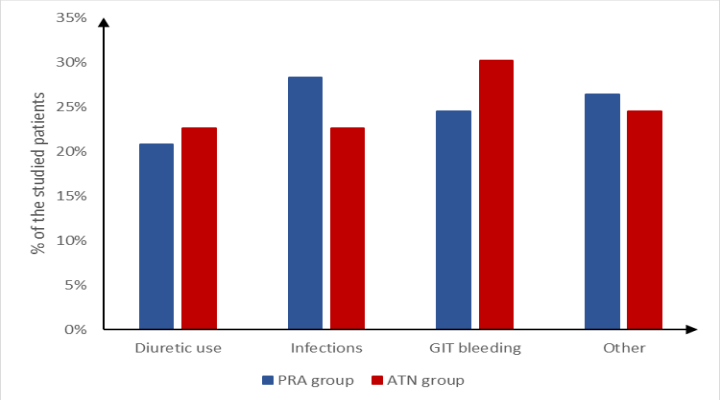

Figure (3): Causes of AKI of the studied groups.

Table (4): Vital signs of the studied groups.

		PRA group (n=53)	ATN group (n=53)	P value
SBP (mmHg)	**Mean ± SD**	104.96 ± 9.44	105.58 ± 9.42	0.735
	Range	94 - 124	94 - 123	
DBP (mmHg)	**Mean ± SD**	60.91 ± 7.8	62.13 ± 8.92	0.453
	Range	50 - 82	51 - 81	
Pulse (beats/min)	**Mean ± SD**	89.55 ± 9.03	87.19 ± 7.37	0.144
	Range	76 - 105	75 - 103	
RR (breaths/min)	**Mean ± SD**	19.58 ± 4.11	20.55 ± 4.71	0.265
	Range	13 - 27	13 - 27	

SBP: systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate

FEUrea and FENa were significantly increased in ATN group than PRA group (P value 0.044 and <0.001 respectively) **(Table 5).**

Table (5): FEUrea and FENa of the studied groups.

		PRA group (n=53)	ATN group (n=53)	P value
FEUrea (%)	**Median**	22.78	39.22	**0.044***
	IQR	11.28 - 47.04	16.72 - 61.73	
FENa (%)	**Median**	0.25	0.93	**<0.001 ***
	IQR	0.08 - 0.54	0.44 - 2.12	

FE: fractional excretion, *: significant as P value ≤ 0.05

FEUrea can significantly predict ATN (AUC= 0.614, P value 0.041) at cut off >26.81%, 69.81% sensitivity, 58.49% specificity, 62.7% PPV and 66% NPV. FENa can significantly predict ATN (AUC= 0.783, P value <0.001) at cut off >0.43%, 75.47% sensitivity, 71.70% specificity, 72.7% PPV and 74.5% NPV **(Table 6).**

Table (6): Diagnostic value of FEUrea and FENa in differentiation of ATN cases from PRA cases in AKI patients.

	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	P value
FEUrea (%)	>26.81	0.614	69.81	58.49	62.7	66	**0.041***
FENa (%)	>0.43	0.783	75.47	71.70	72.7	74.5	**<0.001***

FE: fractional excretion, AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value, *: significant as P value ≤ 0.05

Serum creatinine and urine Na were significantly increased in the group of ATN than PRA group. Urine creatinine and urine urea were significantly decreased in ATN group than PRA group. Hb, TLC, platelets, serum urea, and serum Na were insignificantly changed among each of the groups **(Table 7).**

Table (7): Laboratory investigations of the studied groups.

		PRA group (n=53)	ATN group (n=53)	P value
Hb (g/dl)	**Mean ± SD**	13.23 ± 1.74	13.12 ± 1.92	0.743
	Range	9.6 - 16	9.6 - 16	
TLC ($x10^9$/L)	**Mean ± SD**	9.91 ± 4.35	9.61 ± 4.45	0.726
	Range	4.5 - 19.3	4.6 - 18.8	
Platelets ($x10^9$/L)	**Mean ± SD**	286.4 ± 79.2	298.74 ± 94.29	0.467
	Range	157 - 435	150 - 449	
Serum creatinine (mg/dl)	**Mean ± SD**	2.33 ± 0.87	2.99 ± 0.91	**<0.001***
	Range	0.8 - 3.8	1.5 - 4.5	
Serum urea (mg/dl)	**Mean ± SD**	44.34 ± 9.92	45.45 ± 13.62	0.632
	Range	15 - 55	17 - 64	
Serum Na	**Mean ± SD**	134.08 ± 6.44	135.38 ± 6.05	0.286

(mmol/L)	**Range**	125 - 145	125 - 145	
Urine creatinine (mg/dl)	**Mean ± SD**	170.79 ± 76.28	108.02 ± 49.67	**<0.001 ***
	Range	47 - 298	23 - 198	
Urine urea (mg/dl)	**Median**	778	484	**0.006***
	IQR	421 - 1064	294 - 800	
Urine Na (mmol/L)	**Median**	27	44	**0.001***
	IQR	11 - 36	24 - 68	

Hb: hemoglobin, TLC: total leucocyte count, *: significant as P value ≤ 0.05

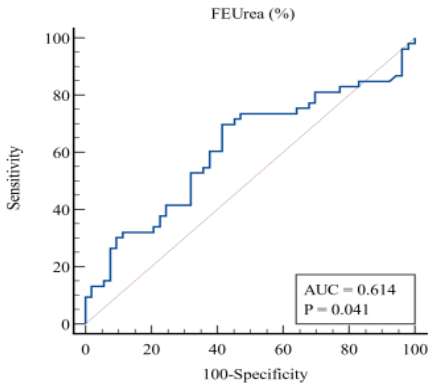

Figure (4): ROC curve of FEUrea in differentiation of ATN.

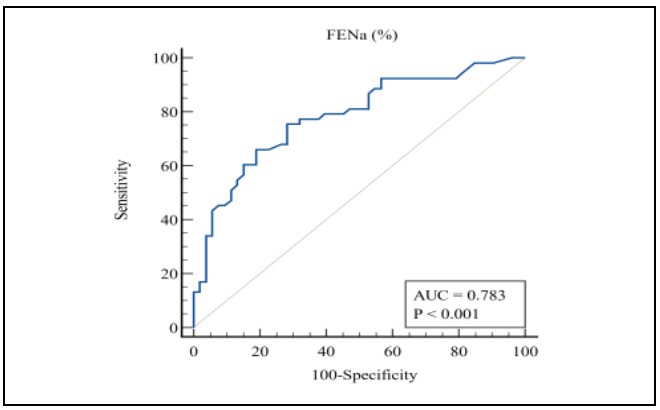

Figure (5): ROC curve of FENa in differentiation of ATN.

DISCUSSION

Acute kidney injury (AKI) is a common condition encountered in hospitalized patients and is associated with significant morbidity and mortality. The fractional excretion of sodium (FENa) has traditionally been used to differentiate prerenal azotemia (PRA) from acute tubular necrosis (ATN). However, its diagnostic utility may be limited by factors such as diuretic use and sepsis, which can confound the results **[8].**

The glomerulus filters and the proximal and distal tubules reabsorb urea. Urea reabsorption is enhanced by vasopressin and the renin-angiotensin-aldosterone system (RAAS). In PRA, reduced renal perfusion and increased RAAS activity decrease the fractional excretion of urea (FEUrea). Conversely, in conditions involving renal tubular damage, such as ATN, urea reabsorption decreases, leading to increased FEUrea levels. Importantly, urea reabsorption is primarily regulated by the proximal tubules, rendering FEUrea less influenced by the effects of diuretics **[9].**

In present study, demographic variables such as age, gender, and BMI, as well as comorbidities like diabetes mellitus and hypertension, did not show significant differences between groups. These findings align with those of **Patidar et al.,** who reported no statistical differences in these characteristics among their study groups. Additionally, serum creatinine and urine sodium levels were significantly higher in the ATN group compared to the PRA group. Both FEUrea and FENa were also markedly elevated in the ATN group **[8].**

Present findings correspond with the results of **Aksoy et al**., who reported significantly lower FEUrea and FENa values in the Risk stage compared to the Injury and Failure stages of AKI [**9]. Dewitte et al.** demonstrated that FEUrea was lower in transient AKI (33% [25–39]) than in persistent AKI (47% [36–61]) (P = 0.001) **[10].**

Our study showed that FEUrea significantly predicts ATN (AUC = 0.614, P = 0.041) at a cutoff >26.81%, with a sensitivity of 69.81% and specificity of 58.49%. Patidar et al. reported a higher FEUrea cutoff for ATN (>33%), while cutoffs for PRA ranged between 21% and 33%. **Aksoy et al.** confirmed FEUrea's effectiveness in distinguishing PRA from renal damage but noted reduced sensitivity (50%) and specificity (77.1%) in their cohort due to viral etiologies [9]. Additionally, infectious diarrhea may have led to increased intestinal urea loss, elevating FEUrea levels in PRA cases against expectations **[11].**

Fahimi et al. demonstrated that FEUrea is a more effective marker than FENa for differentiating PRA from intrinsic renal failure. A FEUrea value below 35% was more accurate than a FENa value under 1% in identifying prerenal conditions, despite both markers being elevated in intrinsic renal failure. They found that a FEUrea threshold below 35% effectively identified prerenal failure in adults **[12].** Carvounis et al. similarly reported high sensitivity (90%) and specificity (96%) for a FEUrea threshold <35% in distinguishing PRA **[13]. Dewitte et al**. established 40% as the optimal FEUrea threshold for predicting transient AKI [10]. Other studies have corroborated the utility of both FEUrea and FENa in distinguishing prerenal from intrinsic renal damage, with FEUrea demonstrating greater accuracy in patients on diuretics **[14-15].**

In present study, FENa was also a significant predictor of ATN (AUC = 0.783, P < 0.001) at a cutoff >0.43%, with 75.47% sensitivity, 71.70% specificity, 72.7% positive predictive value, and 74.5% negative predictive value. Aksoy et al. supported using FENa to distinguish PRA from

renal damage **[9]. Pepin et al**. found FENa to be more effective in differentiating transient from persistent AKI in non-diuretic-treated patients **[16].** A meta-analysis reported pooled sensitivity (90%) and specificity (82%) for FENa in distinguishing prerenal from intrinsic AKI **[17].**

CONCLUSION

Our study demonstrated significant differences in serum creatinine, urine sodium, urine creatinine, urine urea, FEUrea, and FENa between the ATN and PRA groups. Both FEUrea and FENa were significantly elevated in the ATN group, highlighting their utility as diagnostic markers. ROC analysis confirmed that both indices predict ATN with reasonable sensitivity, specificity, and predictive values. These findings support the clinical application of FEUrea and FENa in the early differentiation of ATN from PRA in ICU patients with AKI, facilitating timely and targeted interventions. Further studies with larger cohorts are recommended to validate these results and optimize clinical outcomes.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

The ethical aspects of this investigation were approved by the Institutional Review Board (IRB) at the Faculty of Medicine, Aswan University. Pre-enrollment written informed consent was obtained from every subject. The identification information of all subjects was protected from public access and maintained in confidentiality.

Conflict of interests:

No conflicts of interest are disclosed by the authors.

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