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A valuable and intuitive diagnostic tool for acute kidney injury in Liver cirrhosis is the fractional excretion of urea and sodium

Enas Ahmed Reda ALKareemy[1], Marwa M. Thabet[2], Ali Hamdy[1], Nermeen Mahmoud Mobarez[1ũ], Essam M. Abdel Aziz[1]

[1]Department of Internal Medicine, Assiut University Hospital, Faculty of Medicine, Assiut University, Egypt
[2]Department of Clinical Pathology, Assiut University Hospital, Faculty of Medicine, Assiut University, Egypt

1- alkareemy@aun.edu.eg
2- d_marwa25@yahoo.com
3- AliHamdy@aun.edu.eg
4- nermeen.mobarez0349@med.aun.edu.eg
5- essam.nephro@gmail.com

Corresponding author:Nermeen Mahmoud Mobarez
Department of Internal Medicine, Assiut University Hospital, Faculty of Medicine, Assiut University, Egypt.
Email: nermeen.mobarez0349@med.aun.edu.eg

Abstract

Background: Prerenal and renal acute kidney injury (AKI) phenotypes could develop among patients with decompensated cirrhosis. Their prognosis and outcomes for therapy vary significantly. Each AKI type has a unique treatment approach; thus, it's critical to diagnose and initiate therapy for each immediately. **Aim of the study**: We aimed to determine if fractional excretion of Urea and Sodium (FEUrea and FENa) may be valuable for distinguishing AKI phenotypes. **Methods**: An observational study was conducted between May 2022–and May 2022. Enrolled in the trial were 50 cirrhotic patients without AKI and 100 cirrhotic patients with AKI. Every patient had a comprehensive clinical evaluation and history taking. Both groups' fractional excretion of urea and sodium was measured (Trial registration number Trial Register NCT0367563). **Results:** Both studied groups had insignificant differences in terms of

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demographic data. FEUrea (%) was significantly higher in the AKI patients than in the non-AKI patients, owing to elevated urea levels in the AKI. However, plasma FENa (%) concentration in the non-AKI controls significantly increased compared to that in the AKI patients. Also, FEurea (%) and FENa (%) concentrations were significantly higher in the renal-AKI patients than in those with the pre-renal-AK. FEurea at a cut-off point > 36.6% had 90.9% sensitivity and 86.5% specificity, with the area under the curve (AUC) being 0.911 for the prediction of AKI. In comparison, FENa at a cut-off point > 0.88% had 90.6% sensitivity and 77.5% specificity, with an AUC of 0.986 for the prediction of AKI. **Conclusion** Both FEurea and FENa can be utilized to predict AKI early. More verified research is needed.

Keywords: Kidney injury, Fraction excretion, Urea, Sodium, Cirrhosis

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1. Introduction

One frequent and sometimes fatal consequence of liver disease among people is renal failure. A purely "functional" type of renal failure known as hepatorenal syndrome (HRS) is characterized by hyperactivity of endogenous vasoactive systems and pronounced abnormalities in the arterial circulation. It frequently affects individuals with cirrhosis. [1]. Acute kidney injury (AKI), the term given to describe the early loss of renal function in cirrhosis patients, has been divided into prognostic categories based on varying degrees of severity. 25% to 50% of cirrhosis patients who are hospitalized for an acute episode of hepatic decompensation may have renal impairment as a consequence of either an abrupt deterioration, an underlying chronic kidney disease, or both [2]. AKI is linked with increased patient mortality rate with cirrhosis; thus, it is crucial to diagnose and determine the mechanism behind AKI and begin treatment immediately for maximum possibility of reversal [3].

The primary reasons for AKI in this setting are (1) prerenal azotemia (PRA), which is caused by decreases in intravascular volume (for example, aggressive diuretic treatment or diarrhea); (2) hepatorenal syndrome type 1 (HRS), acute kidney injury (AKI) that does not respond to albumin infusion and withdrawal of diuretics in the absence of identifiable causes; and (3) acute tubular necrosis (ATN), which is caused by intrinsic damage [4]. People who have cirrhosis are most likely to experience acute kidney injury (AKI) when they are exposed to practically any sort of bacterial infection. In most cases, acute kidney injury (AKI) brought on by a bacterial infection is sufficient to satisfy the diagnostic criteria for hepatorenal syndrome (HRS) [4].

In cirrhotic individuals, serum creatinine (sCr) overestimates renal function for a variety of reasons: Patients with cirrhosis produce less creatinine due to muscle atrophy, urinary tubules secrete more creatinine, increased volume of distribution may dilute sCr, and as a last resort, elevated bilirubin levels may cause problems with assays used to measure creatinine levels. [5–7].

As a result, in cases where there is reduced renal perfusion and an elevated renin-angiotensin-aldosterone system (RAAS), as seen in HRS type 1 or cirrhosis with prerenal azotemia (PRA), the fractional excretion of urea should decrease. Renal tubular damage,

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on the other hand, ought to decrease reabsorption and raise its fractional excretion. Diuretics acting further distally have little effect on urea absorption since it is primarily controlled in the proximal tubules [8,9]. Therefore, it is hypothesized that fractional urea excretion (FEUrea) may be of clinical help in early differentiation of ATN and PRA and type 1 HRS in cirrhosis patients and AKI with ascites [10].

Prerenal azotemia is indicated explicitly by fractional excretion of urea (FEUrea) ([urine urea nitrogen/blood urea nitrogen)/(urine creatinine/plasma creatinine)] X 100) less than 35%, while ATN is indicated explicitly by > 50% [11]. The objective of this study aimed to assess FEUrea's diagnostic performance in AKI differential diagnosis in cirrhosis and ascites patients. More specifically, FEUrea's capacity to distinguish between HRS and Prerenal azotemia and ATN.

2. Patients and methods

2.1. Study design and setting.

An observational study with a prospective design was carried out in the Internal Medicine Department between May 2021 and May 2022.

2.2. Selection criteria

The enrolled patients with liver cirrhosis (LC) are based on clinical, laboratory, radiological, and endoscopic data. Patients that exhibit one or more of the following traits were excluded: prior liver/kidney transplant, hepatocellular carcinoma, acute or chronic renal replacement therapy, and/or advanced chronic kidney disease (stage IV/V).

2.3. Participants

Overall, 100 cirrhotic patients with AKI and another 50 cirrhotic patients without AKI were covered by the study. Patients with AKI were subdivided into either the pre-renal group (n=89) or the renal group (n=11). Criteria for the diagnosis of acute renal damage and to distinguish between pre-renal and renal azotemia. KDIGO describes AKI as any or all of the following: 1) an increase in serum creatinine by 0.3 mg/dL or more within 48 hours, 2) an increase in serum creatinine to 1.5 times baseline or more during the last seven days, or 3) urine output below 0.5 mL/kg/h for 6 hours [12].

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There are five criteria for distinguishing renal from prerenal azotemia. *First*: History (exogenous toxins such as drugs or endogenous toxins such as myoglobin, or even prolonged renal hypoperfusion that turned unresponsive to appropriate corrective measures or a high dose of loop diuretics, all favor ATN; volume depletion, decreased cardiac output, or vasodilation associated with sepsis, liver failure, and anaphylaxis favor pre-renal azotemia that is related to pre-renal azotemia). Second: Physical examination (heart rate, blood pressure, orthostatic abnormalities, cardiac sounds, pulmonary abnormalities, pedal edema, or ascites). Third: The urine analysis's results were conducted by a renal service member (Patients with ATN may have muddy brown granular casts and urine sediment in pre-renal patients). Fourth: Urinary sodium (UNa): Prerenal is favored by UNa <15 mEq/L; ATN is compatible with UNa greater than 20. Fifth: Fractional excretion of sodium (FENa) below 1% suggests the existence of prerenal azotemia, whereas levels above 1% indicate the presence of acute tubular necrosis (ATN). The formula to compute FENa is FENa = (Sodium Excretion x 100)/ (total filtered load).

In all patients, the following laboratory data were done: 24 hrs urinary creatinine, urine analysis with microscopy, urine urea, complete blood counts, and basic metabolic profile (blood urea, serum creatinine, electrolytes), hepatic panel (liver enzymes, bilirubin, albumin, total protein, alkaline phosphatase) and prothrombin time. Estimated the role of Fractional Excretion of Urea. The formula for calculating FE_{Urea} as a percentage is:

$$(S_{Cr} \times U_{Urea}) / (S_{Urea} \times U_{Crz}) \times 100.$$

(S_{Cr}: serum creatinine; U_{Urea}: urine urea; S_{Urea} serum urea; U_{Cr}: urine creatinine).

3. Ethical approval and consent of participation

The Ethics Review Board of the Faculty of Medicine at Assiut University gave their consent to the study protocol before its implementation. Informed written consent was collected from all participants in compliance with the Helsinki Declaration **(Clinicaltrails.gov NCT03675633).**

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4. Statistical analysis

Using SPSS software, version 25, which was developed by SPSS Inc., which is situated in Chicago, Illinois, United States of America, the data analysis was carried out. The Chi-square test was utilized to compare the categorical variables that were present in both groups. On the other hand, the Student T-test was utilized to compare the continuous variables. To do statistical analysis, we used the Shapiro-Wilkes test to determine whether the data were normally distributed. It was determined through the utilization of the receiver operating curve (ROC) analysis that the appropriate cut-off values for the continuous FEurea (%) and FENa (%) variables were obtained. If a p-value is less than 0.05, then it is regarded to be statistically significant. Using SPSS software, version 25, which was developed by SPSS Inc., which is situated in Chicago, Illinois, United States of America, the data analysis was carried out.

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5. Results

5.1. Demographic data in the two studied groups

Demographic data in study groups indicated that there was no significant difference between the AKI and non-AKI groups relating to age and gender hypertension, diabetes, and chronic heart failure (**Table 1**) (P>0.05).

5.2. Laboratory data in AKI and non-AKI groups

The AKI group had significantly higher levels of serum creatinine and blood urea, as well as significantly decreased levels of urine creatinine and urine and serum sodium, in comparison to the non-AKI group. FEurea (%) was significantly higher in AKI patients

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compared to non-AKI due to increased urea levels in the AKI. However, plasma FENa (%) concentration in the non-AKI controls was significantly increased in comparison to the AKI patients (**Table 2, Figures 1,2**).

5.3. Laboratory data of acute kidney injury patients (pre-renal and renal groups)

The urine creatinine level elevated significantly ($p<0.001$) within the prerenal AKI group as compared to renal AKI patients. It was noticed that there was a significant rise in urinary Na, FEurea (%), and FENa (%) in renal AKI patients ($p<0.001$). Although statistically showing no significance, blood urea and serum Na (mmol/L) were higher, while the urine urea was Lower in patients with renal AKI than in those with prerenal AKI (**Table 3**).

5.4. Accuracy of fraction excretion of urea and sodium in predicting acute kidney injury

It was found that FEurea at a cut-off point > 36.6% had 90.9% sensitivity and 86.5% specificity, with the area under the curve (AUC) at 0.911 for the prediction of AKI. In comparison, FENa at a cut-off point > 0.88% had 90.6% sensitivity and 77.5% specificity with an AUC of 0.986 for the prediction of AKI **(Table 4, Figure 3).**

6. Discussion

This observational clinical study started with 150 patients, who were assigned into two groups: 100 AKI patients and 50 non-AKI patients. They were then evaluated in terms of their patient characteristics, clinical data, comorbidity, and laboratory findings. AKI patients were classified into a pre-renal group (89 patients) and a renal group (11 patients), and the correlation between groups and patient characteristics, clinical data, and laboratory findings was then reevaluated.

Based on the findings of this study, the mean age of presentation was 51.93 ±9.39 years in the AKI group and 50.90 ±8.98 years in the non-AKI group. All these previous studies have shown that the range of age is between 50 to 61 years. [13,14]. These results corroborate with a prospective observational cohort study done on 55 AKI cases and 50

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age-matched control non-AKI with mean age (55.0 ± 10.0 & 50.0 ± 10.2) years, respectively. [15]. Patients above the age of 50 are at higher risk of developing AKI due to a decrease in renal reserve and a decrease in GFR. [16].

In our study gender, 70 patients (70.0%) in the AKI group and 32 patients (64.0%) in the non-AKI group were male individuals. These findings are similar to those described in another study, which showed that 71.4% of the participants (75/105) were males, significantly more than females [17]. Noting this phenomenon, it's thought that despite advances in understanding the pathogenesis of AKI. Furthermore, men have a higher prevalence of all these well-established risk factors for AKI compared to women [18].

The level of acute kidney injury (AKI) is assessed based on the presence of relative azotemia, which is characterized by an elevation in serum creatinine (SC) levels, or oliguria, which is defined as a reduction in urine output (UO). However, patients who exhibit both oliguria and azotemia and those in whom these deficiencies persist are more prone to experiencing more severe disease and thus poorer outcomes; it explains increased serum creatinine and decreased urinary creatinine in AKI in cirrhotic patients [19]. Patients who fulfill both the serum creatinine and urine output criteria for acute kidney injury (AKI) have significantly worse outcomes compared to patients who only show AKI based on one criterion despite minimal variations in their baseline characteristics [19–21].

Our results show serum Na (mmol/L) and Urinary Na in the AKI group was 128.53 ± SD 8.4 vs. 25.14 ± SD 2.41, and was significantly decreased than non-AKI, which was 136.66 ± SD 13.27 vs. 121.60 ± SD 40.44 ($P = 0.006$) and ($P < 0.001$) respectively. Recently, Previous study revealed that in comparison to the group that served as the reference (136.0–144.9 mmol/L), the AKI patients who had hyponatremia when they were admitted to the hospital (< 136.0 mmol/L) or hypernatremia (≥145.0 mmol/L) had higher 90-day death rates [16].

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It is worth noting that the sodium concentration in urine is typically low in prerenal acute kidney injury (AKI) cases, measuring less than 20 mmol/l. This is because the kidney makes a conscious effort to conserve sodium in such situations. On the other hand, in cases of intrarenal AKI, the urine sodium concentration tends to be high, exceeding 40 mmol/l. This is partly due to the detrimental impact of tubular injury on the process of sodium reabsorption. [22]. The FeNa interpretation relies on the assumption that in prerenal states, the tubules that are functioning correctly will reabsorb sodium, whereas the tubules that are damaged will not [23–25].

During our investigation, FEurea (%) was significantly higher in patients with AKI (mean 31.84 ±5.48) than in those with non-AKI (6.79 ± 3.94) due to increased urea level in AKI. The mean plasma FENa (%) concentration in the non-AKI controls was 0.84 ±0.62. The plasma FENa (%) levels were significantly decreased in the AKI patients 0.7 ±0.83. It was reported that the range of FeUrea was 32 % (28 to 40) in patients without AKI and 41% (29 to 54) in patients with persistent AKI [26].

Based on the cause of acute kidney injury, we separated the patients into two groups: the prerenal group and the renal group. the results of laboratory data; There was a significant difference regarding FEurea (%) (27.16 ±16.17 versus 69.70 ±48.50, p <0.001) and FENa (%) (27.16 ±16.17 versus 2.37 ±1.24, p <0.001) in pre-renal and renal groups. A similar pattern of results was obtained in a prior investigation, which discovered that there were significant variations in the median FeUrea levels among different AKI morphologies in the derivation cohort of patients admitted with cirrhosis and ascites between February 2010 and September 2013 (pr-renal 30.1 vs. renal 43.6; $P < 0.001$) and the validation cohort (pre-renal 23.1 vs. renal 44.7; $P < 0.001$) [10]. Additionally, Fractional excretion of urea (FEUrea) was introduced to discriminate between prerenal and intrinsic AKI, and it was demonstrated to be more accurate in patients with AKI receiving diuretics [27].

In the current study, it was found that FEurea at a cut-off point > 36.6% had 90.9% sensitivity and 86.5% specificity, with the area under the curve (AUC) was 0.911 for prediction of AKI. In comparison, FENa at a cut-off point > 0.88% had 90.6% sensitivity

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and 77.5% specificity, with an AUC of 0.986 for the prediction of AKI. Previous studies noticed the highest sensitivity was in favor of FEurea (%) (86.5 %), then the FENa (%) (77. 5%). An AUROC of 0.96 (95% confidence interval [CI], 0.91, 1.00) was obtained for FEUrea. The ideal cut-off was found to be 33.41% by use of the Youden index. Above 33.41% projected ATN [10].

Another study in decompensated cirrhosis reported that FENa cut-off 0.567 showed an AUC of 86.6% (95% CI: 81.3 – 92.0) with a sensitivity of 89.47% (95% CI: 78.48 – 96.04) with a specificity of 71.33% (95% CI: 63.18 – 78.58) for differentiating ATN – AKI versus non-ATN AKI (p-value 0.001). The findings of this study revealed that there was a significant difference ($P = 0.0001$; $P < 0.05$) in FE urea % among PRA and ATN groups (26.28±2.89, and 47.37±10.53, respectively) [28].

It turned out that low FE_{UN} (≤35%) is a more sensitive and specific measure than FE_{Na} for distinguishing acute renal failure caused by prerenal azotemia from that induced by ATN, particularly in cases when diuretics had been used [9]. The main limitations of the present study are its single-center conduction, lack of long-term patient follow-up, and relatively small sample size.

7. Conclusion

In individuals with liver cirrhosis, FEurea and FENa are potential indicators for the early diagnosis of acute kidney injury. Future research is necessary to validate these results.

8. Statements and Declarations

- **Acknowledgments:** Not applicable
- **Data availability:** The data used in this research are available from the senior author upon any reasonable request.
- **Compliance with Ethical Standards**
- **Conflict of interest:** The authors have no relevant financial or non-financial interests to disclose.
- **Funding:** No funds, grants, or other support was received.

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- **Ethical approval**: The study protocol received approval from the Ethics Review Board of the Faculty of Medicine, Assiut University. Informed written consent was collected from all participants by the declaration of Helsinki.*Clinicaltrails.gov* NCT03675633.
- **Author contributions:** All authors contributed to the study's conception and design. Conceptualization: [Enas Ahmed Reda ALKareemy, Essam M. Abdel Aziz], Methodology: [Marwa M. Thabet, Ali Hamdy, Nermeen Mahmoud Mobarez], Formal analysis and investigation: [Marwa M. Thabet, Ali Hamdy, Nermeen Mahmoud Mobarez], Writing - original draft preparation: [Marwa M. Thabet, Ali Hamdy, Nermeen Mahmoud Mobarez], Writing - review and editing: [Enas Ahmed Reda ALKareemy, Essam M. Abdel Aziz], Supervision: [Enas Ahmed Reda ALKareemy, Essam M. Abdel Aziz]. All authors read and approved the final manuscript.

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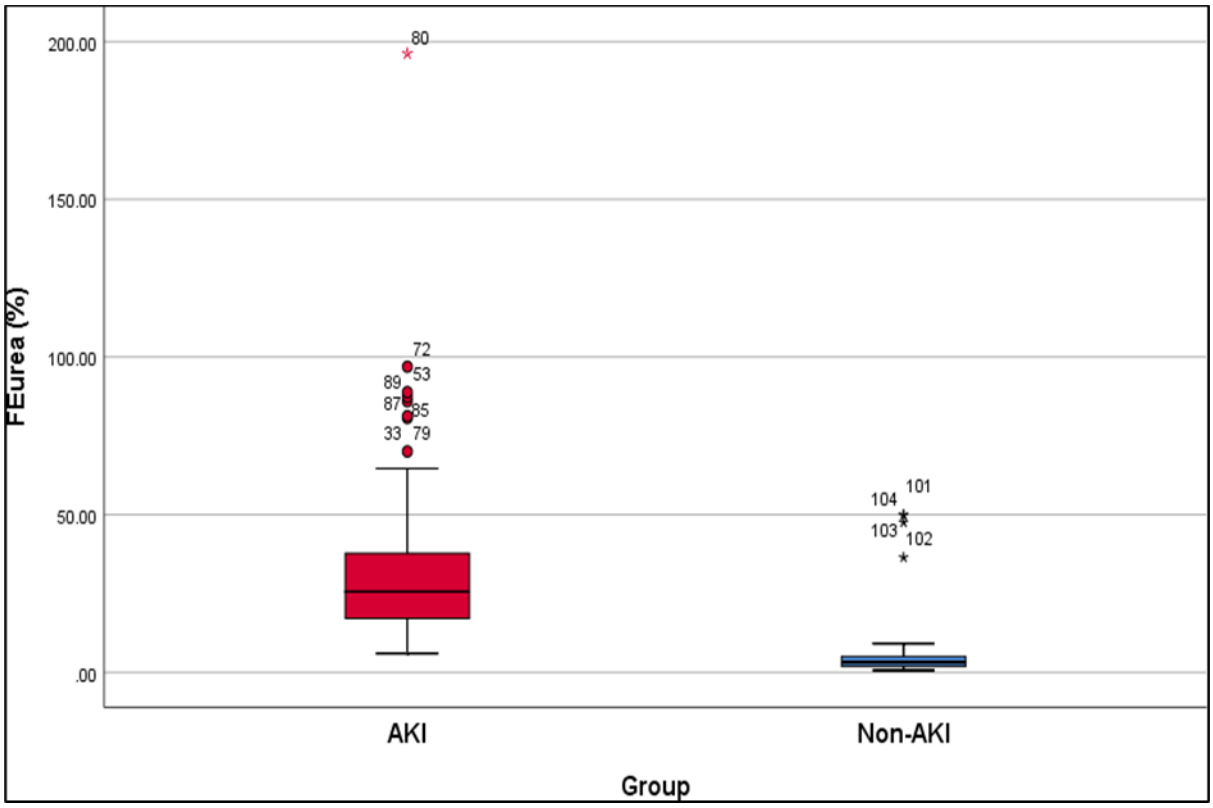

Figure 1: FEurea (%) in the study groups. FEurea: fractional excretion of urea; AKI: acute kidney injury.

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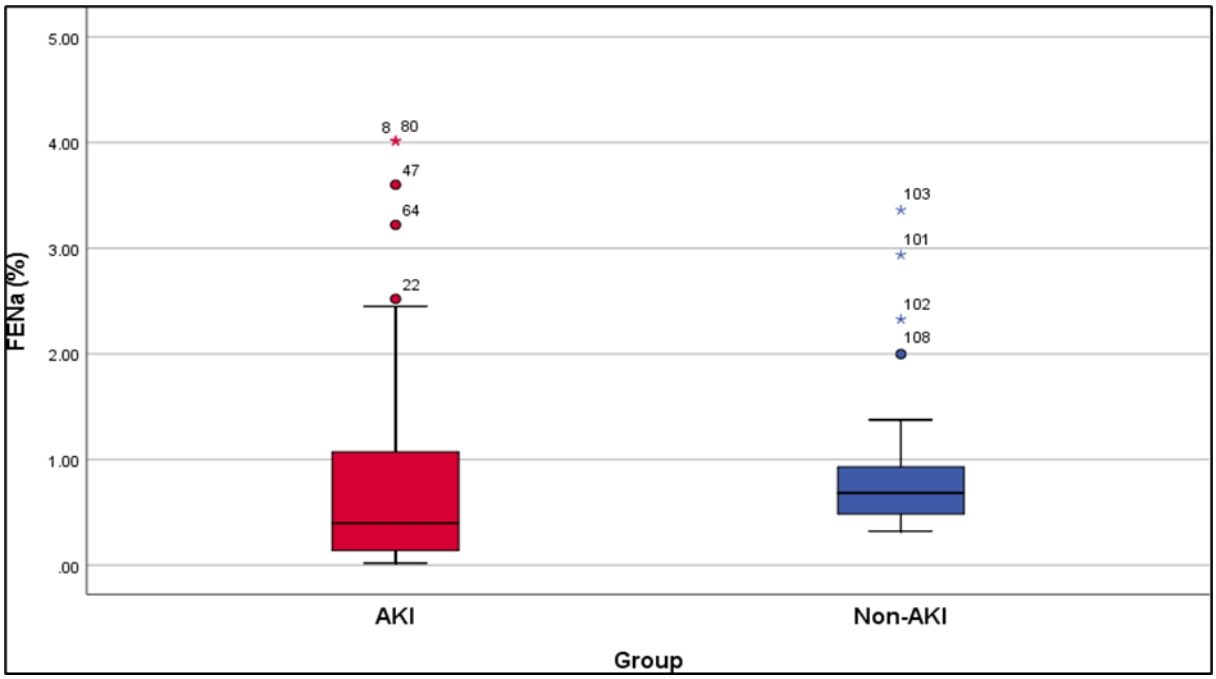

Figure 2: FENa (%) in the study groups. FENa: fractional excretion of urea; AKI: acute kidney injury.

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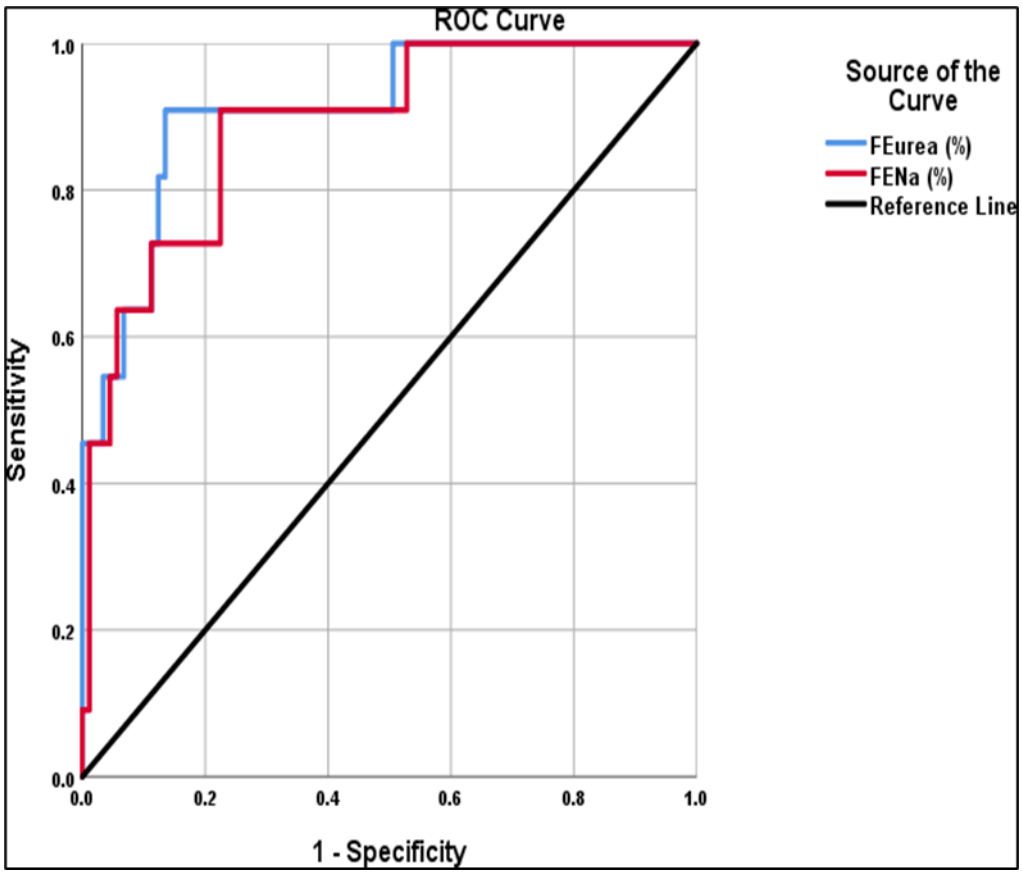

Figure 3: Accuracy of FEurea and FENa in prediction of acute kidney injury. FEurea: fractional excretion of urea; FENa: fractional excretion of sodium.

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Table 1: Demographic data in the two studied groups.

Items		**Group**				p-value
		AKI group (N=100)		**Non-AKI group (N=50)**		
Age (Mean ±SD)		51.93 ±9.39		50.90 ±8.98		0.469
		n	%	n	%	
Gender	male	70	70.0%	32	64.0%	0.458
	female	30	30.0%	18	36.0%	
Hypertension		10	10.0%	6	12.0%	0.708
Diabetes		7	7.0%	4	8.0%	0.825
Chronic heart failure		6	6.0%	4	8.0%	0.643

Data expressed as frequency (percentage), mean ±SD. *P* value was significant if < 0.05.

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Table 2: Laboratory data in the two studied groups.

Items	Group		p-value
	AKI group (N=100)	Non-AKI group (N=50)	
Blood urea (mg/dl)	50.85 ±39.17	28.32 ±5.72	<0.001
Serum creatinine (mg/dl)	2.27 ±0.83	0.96 ±0.34	<0.001
Urinary urea	196.06 ±95.48	114.54 ±65.10	<0.001
Urinary creatinine	78.70 ±32.92	116.83 ±42.17	<0.001
Serum Na (mmol/L)	128.53 ±8.40	136.66 ±13.27	0.006
Urinary Na	25.14 ±2.41	121.60 ±40.44	<0.001
FEurea (%)	31.84 ±5.48	6.79 ± 3.94	<0.001
FENa (%)	0.7 ±0.83	0.84 ±0.62	0.005

Data expressed as mean ± SD. P value was significant if < 0.05. FEurea: fractional excretion of urea; FENa: fractional excretion of sodium

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Table 3: Laboratory data of acute kidney injury patients (pre-renal and renal groups).

Items	**Acute kidney injury group (N=100)**		p-value
	Pre-renal group (N=89)	**Renal group (N=11)**	
Blood urea (mg/dl)	28.04 ±29.78	53.54 ±82.18	0.716
Serum creatinine (mg/dl)	2.29 ±0.85	2.13 ±0.70	0.679
Urinary urea	200.32 ±99.33	161.59 ±44.31	0.080
Urinary creatinine	83.39 ±30.75	40.78 ±25.21	<0.001
Serum sodium (mmol/L)	128.06 ±8.38	132.36 ±7.89	0.128
Urinary sodium	20.41 ±20.69	63.36 ±36.50	<0.001
FEurea (%)	27.16 ±16.17	69.70 ±48.50	<0.001
FENa (%)	0.49 ±0.46	2.37 ±1.24	<0.001

Data expressed as mean ± SD. P value was significant if < 0.05. FEurea: fractional excretion of urea; FENa: fractional excretion of sodium,

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Table 4: Accuracy of fraction excretion of urea and sodium in prediction of acute kidney injury

	AUC	P value	95% CI		Cut off point	Sensitivity	Specificity
			lower	upper			
FEurea (%)	0.911	<0.001	0.822	0.988	36.6	90.9%	86.5%
FENa (%)	0.986	<0.001	0.790	0.986	0.88	90.6 %	77.5 %

AUC: area under curve; CI: confidence interval; FEurea: fractional excretion of urea; FENa: fractional excretion of sodium.

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Date:	7/21/2024
Your Name:	Nermeen Mahmoud Mobarez
Manuscript Title:	A valuable and intuitive tool for acute kidney injury in liver cirrhosis is the fractional excretion of urea and sodium
Manuscript Number (if known):	Submission ID: JGIM-D-24-01767

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