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Early Prediction of Acute Kidney Injury (AKI) in Egyptian Infants and Children with Circulatory Shock

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ABSTRACT

Background: *The early prediction of acute kidney injury (AKI) by the currently used clinical and or laboratory data remains inadequate. Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) is a biomarker of acute kidney injury (AKI) even on top of chronic kidney disease.*

Objectives*: was to determine uNGAL levels as early diagnostic and prognostic biomarker for AKI in critically ill children with shock.*

Subjects and Methods: *The present study was carried out on 70 pediatric patients with circulatory shock who were admitted to the Pediatric Intensive Care Unit (PICU) of Tanta University Hospital. They were subdivided into 2 groups, Group (1): 25 shock with no AKI as controls. Group (2):45 shock with AKI meeting criteria of AKIN. Urine samples were collected daily for 4 days from the patients and urinary NGAL levels were measured by ELISA test on the admission day and on day 1 after admission***.**

Results: *There was a significant increase in urinary NGAL levels in shocked patients with AKI (groups 2) when compared with shocked patients without AKI (P < 0.001). ROC curve of uNGAL reported that it was a good diagnostic marker for AKI development; at day 1, the cutoff value 48.54 ng/mL had a sensitivity and specificity of 79.49 and 73.14, respectively, and the area under the curve (AUC) of 0.82 (95% confidence interval [CI], 0.75–0.87) for predicting AKI. At day 2, the cutoff value 190.92 ng/mL had a sensitivity and specificity of 90.0 and 64.66, respectively, and the AUC of 0.76 (95% CI, 0.70–0.88) for predicting AKI.*

Conclusion: *Urinary NGAL can predict AKI well in critically ill shocked pediatric patients and can predicted their indication for dialysis.*

Keywords: *Acute kidney injury prediction, Neutrophil gelatinase-associated lipocalin, shock.*

INTRODUCTION

Shock is a circulatory failure that results in inadequate tissue perfusion. About 35 % of all critically ill adult and pediatric patients present with shock. Acute kidney injury (AKI) is a common complication in shocked patients, affecting about one quarter of all ICU admissions and is associated with high mortality [1,2]

AKI is commonly diagnosed by rising serum creatinine; but this leads to late diagnosis and is insensitive as the increase may not be detected early in subtle acute kidney injuries. Serum creatinine requires hours to days to accumulate. It increases in serum only after loss of half of renal function. Lack of an early predictive biomarker for AKI in shocked children leads to a delay in diagnosis thus delay in prevention and treatment of AKI.[3] Recently, many publications have studied different biomarkers for the early prediction of AKI, which facilitate earlier diagnosis thus adequate treatment, less complications and more favourable prognosis .[4,5]

As a promising biomarker, neutrophil gelatinase associated lipocalin (NGAL) is physiologically expressed at very low levels in several human tissues, including the kidneys, lungs, stomach, and colon.[6] uNGAL is a highly sensitive biomarker for diagnosing AKI as its levels increase by 10 fold within 3 hours after ischemic Injury and sustaine for few days after the initial kidney insult. [7,8] Little publications have studied the level of uNGAL as an early indicator of AKI in pediatric shock.

The aim of the present work was to study the levels of uNGAL as an early indicator of diagnosing AKI and a prognostic factor (dialysis need) in children with shock.

MATERIALS AND METHODS

Design of the study and Setting

The present prospective cohort study was carried out after approval from research ethical committee centers of Tanta University Hospital and obtaining an informed oral or written consents from parents of included children.

Inclusion Criteria

70 infants and children with shock who were admitted in Pediatric Intensive care unit (NICU) of Tanta University Hospital from December 2016 to December 2017 were enrolled in the study within 6 h from the diagnosis of circulatory shock with normal kidney functions and followed up consecutively for 4 days during their stay in PICU.

The Subjects were Subdivided Into 2 Groups

Group (1): 25 patients with shock without AKI as control group.

Group (2): Included 45 patients with shock and AKI .

Shock was diagnosed on the basis of the Empiric Criteria of Circulatory Shock, which required at least four criteria out of altered mental status (AMS), heart rate >100 beat/min, respiratory rate > 22/min, or PaCO2 < 32 mmHg, arterial hypotension (systolic blood pressure < 90 mmHg or mean arterial blood pressure ≤ 70 mmHg) for >20 min duration, urine output < 0.5 mL/kg/h, or arterial base deficit < −5 mEq/L.

AKI was diagnosed when 0.3 mg/dl or 50 % increase in serum creatinine of reference range occurred within 48 hours according to the Acute Kidney Injury Network (AKIN) criteria for seum creatinine.[9]

Exclusion Criteria

Patients of circulatory shock with pre-existing renal insufficiency (baseline serum creatinine > 2 mg/dl), recent use of nephrotoxic drugs, urinary tract infection (presence of > 50 pus cells/HPF), known cases of polycystic kidney, lupus nephritis, IgA nephropathy, known cases of cancer or post-renal transplant subjects were excluded.

All Patients and Controls Were Subjected to the Following

- **History Taking:** About age, sex and admission diagnosis, duration of hospital stay and drugs.
- **Clinical Examination:** Included body weight, oedema and vital signs every 2 hours (heart rate, temperature, mean arterial blood pressure) which were assessed for the evaluation of sepsis .
- **Laboratory investigations**: which included on admission, baseline serum creatinine, and blood urea Nitrogen (BUN) levels, Complete blood counting (CBC), arterial blood gases, uric acid, liver function tests, serum electrolytes, serum protein, albumin, and eGFR were done at days 2, 3, and 4.
- Urine output was closely monitored every hour, and daily assessment of serum creatinine and its change in relation to its baseline levels on admission (if normal) was carried out. [10]
- 24 hour urinary collection for volume and protein estimation.
- Serum creatinine as baseline renal function test was assessed in spot blood samples obtained on admission and then reassessed daily at constant intervals (every 24 h) for 4 days. Simultaneously, urine samples were collected on the day of admission from all involved patients by clean catch mid stream voids or from inserted indwelling Foley catheters. Urine samples were collected daily for 4 days from shocked patients.
- Urinary NGAL level was assessed by Human ELISA kit (Epitope Diagnostics, Inc., San Diego, USA) on admission day and on day 5. In group 2, it was measured from samples at day 1 (within the first 6 h of the patient admission (Day 1) and after 24 hours from admission (day 2) as per the manufacturer's protocol. [11]
- 4-Pelvi-abdominal ultra sonography: To rule out any prior kidney disease.

Sampling for Laboratory Investigations

About 6 ml venous blood sample was withdrawn from patients and controls, 2 ml blood sample was used for CBC estimation through using EDTA vacationer tubes and the remainder of blood were put into plain tubes for centrifugation and separation of serum which used for estimation of urea, and creatinine levels. Morning urine sample from patients were collected by one of two techniques, either clean catch mid stream method or urinary Catheterization method using 8 French polyethylene feeding tube to collected into sterile container and centrifuged for about 20 minutes. After being centrifuged at 5000b p m for 15 minutes, the urine and blood supernatant samples were frozen within 2 h of collection at −80°Ctill the time of NGAL assay. Another 24-

hour urine collection was used for estimation of urine protein /24 hr collection. Samples were thawed and mixed thoroughly just before the assay to avoid erroneous results of repeated freeze/ thaw cycles. Other 24-hour urine collection samples were kept into sterile containers at refrigerator at degree from 2 to 8 degrees Celsius and then the samples were re-warmed to room temperature just before urinary assessment and urine protein / 24 hr collection.

Severity of illness in the first 24 hours of admission was assessed by Pediatric Risk of Mortality score (PRISM III), [12] length of hosoital stay was recorded and the follow up was with the Sequential Organ Failure Assessment (SOFA) score for outcome [13]

Statistical Analysis

The continuous data were summarized using descriptive statistics (mean ± standard deviation). Statistical differences between the mean values were compared using Student's *t* test. A difference between the two values was considered to be significant if the $P < 0.05$. The association between two or more categorical variables was tested by Chi square statistics using appropriate correction. Before carrying out any test on continuous data, the normalcy of data was tested. The two sample *t* test was used to see the difference between the mean of two different groups if data were normally distributed. If data were not normally distributed, the Mann–Whitney test was used to test the level of significance between two values. One way analysis of variance (ANOVA) was used to test the difference among two groups in case of normally distributed data. Receiver operating characteristics curve was used to test the efficiency of uNGAL in predicting AKI. All calculations were done using STATA IC13 (Texas) and MedCalc Version 17.5.5 software (Belgium). [14]

RESULTS

The demographic, clinical and laboratory data of the involved patients were summarized in Table 1. Mean age in case group was 4.6 ± 1.5 years in comparison to control 4.1 ± 1.5 years. 44(97.8%) versus 22(88%) of patients with altered mental status (AMS),

Out of the 45 cases diagnosed as shock with AKI, hypovolemia was the main cause of shock (22 patients, 48.9%). Cardiogenic shock constituted 5 (11.1%), septic shock constituted 12 (26.7%), and distributive shock constituted 6 (13.3%), while in control group, circulatory shock due to hypovolemia was 10 (40%), cardiogenic cause was 7 (28%), septic cause was 6 (24%), and distributive cause was 2 (8%) ($P > 0.05$) [Table1].

Table1. *Demographic , clinical and laboratory data in studied subjects.*

	Group 1:Shock (Control) (No = 25)	**Group 2 :Shock+ AKI (No = 45)**	**P value**
Age distribution at time of study (years)			
Range	0.6 –8.5 years	0.4-9 years	0.17
Mean± SD	4.06 ± 1.5	4.57±1.5	
Causes of shock: No(%)			
Hypovolemic	10(40)	22(48.9)	>0.05
Cardiogenic	7(28)	5(11)	>0.05
Septic	6(24)	12(26.7)	>0.05
Distributive	2(8)	6(13.3)	>0.05
Diastolic blood pressure after fluid therapy**(mmHg)Mean± SD**	75.8± 4.5	58.6 ± 9.5	<0.01
Systolic blood pressure after fluid therapy **(mmHg) Mean± SD**	111.2± 7.3	89.4 ± 11.1	<0.01
Mean blood pressure after fluid therapy **(mmHg) Mean± SD**	40.6 ±16.8	36.8±22.6	<0.01
Length of PICU stay (Mean± SD)	13.6±2.3	12.2±2.5	<0.05*
Mortality :No (%)	6 (24)	36 (80)	< 0.001
Urinary output (ml/kg/hr) Mean± SD	0.9 ± 0.5	0.8 ± 0.5	0.82
Altered mental status: No	22	44	<0.01
%	88	97.7	
PRISM score: Range	1-22	2-24	
(Mean± SD)	9.5±1.79	9±1.27	0.25
Hemoglobin (Mean± SD)	9.1±2.9	7.7±1.2	<0.01*
Base deficit(mEq/L): Range	−18.8-5.6	−28.8-8.6	<0.005*
Mean± SD	-4.6 ± 7	-10.6±9	

** Significant difference, ** highly Significant difference.*

Urine output was slightly lower in cases in comparison to control (P = 0.82). Mean arterial blood pressure was lower in cases with comparison to control (P < 0.01). The base deficit showed significantly lower values in the cases group − 10.6 ± 9 compared to the controls − 4.6 ± 7 (P < 0.01). Both the PICU stay days and number of deaths were significantly higher in the cases group rather than the controls [Table 2].

Table2. *Urinary NGAL levels in the studied cases and controls.*

Urinary NGAL		Group 1 Shock , no AKI (No = 25)	Group 2 Shock+ AKI (No = 45)
Urinary NGAL the day 1	**Range in ng/ml**	4.2-24	34-134
	Mean± SD in ng/ml	14.5 ± 9.4	48.3± 34.3
Urinary NGAL the day 2	**Range in ng/ml**	3-56	25-148
	Mean± SD in ng/ml	20.5 ± 25.4	190±30.4
P value		P >0.05	P < 0.05

AKI= acute kidney injury; NGAL,

Urinary NGAL = neutrophil gelatinase-associated lipocalin

P= comparison between NGAL in Group 1 on the day1 and 2.

Compared to the controls, serum creatinine of the cases showed significantly higher values at all days, except at day 1 which showed comparable values to the controls [Figure 1].

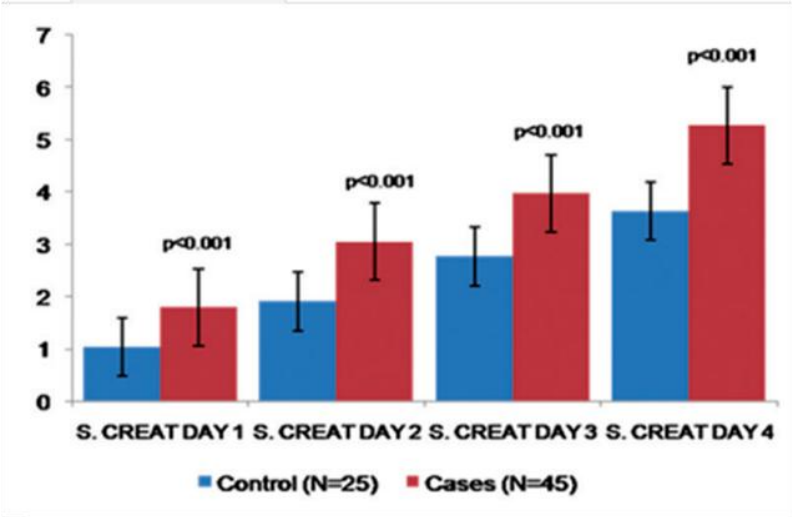

Figure1. *Comparison between serum creatinine in both groups at days 1,2,3and 4.*

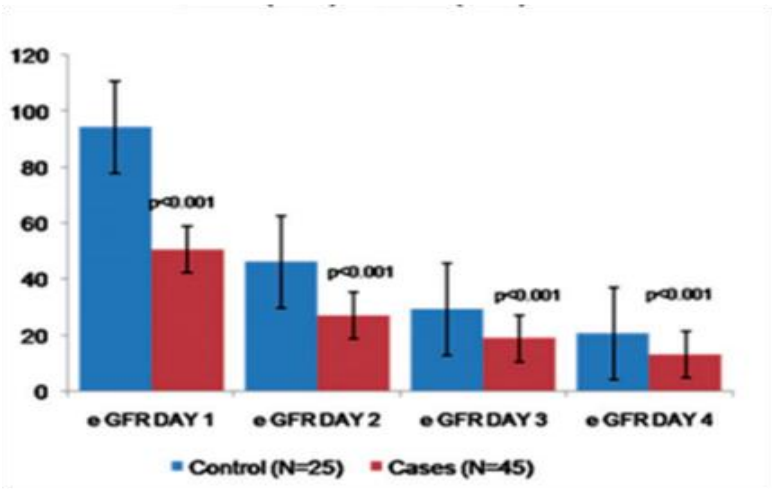

Figure2. *Comparison between GFR in both groups at days 1,2,3 and 4.*

As regard uNGAL, it showed significantly higher values at day 1 and day 2 in the cases' group when compared to the controls [Figure 3].

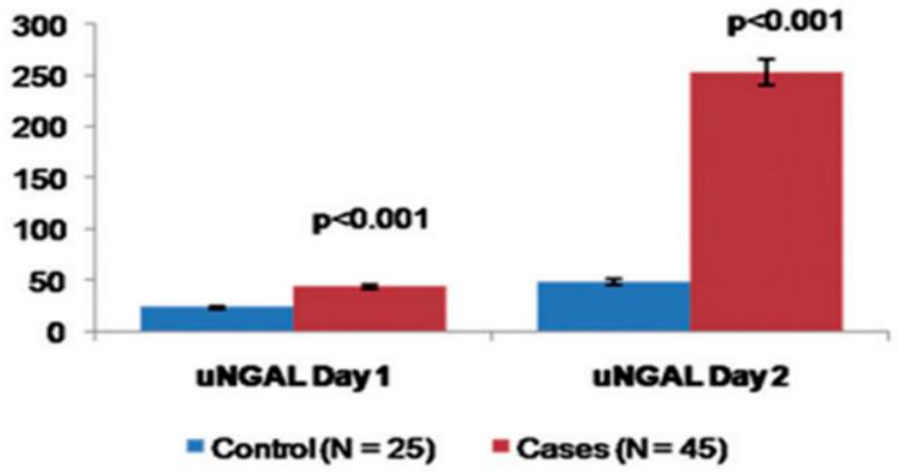

Figure3. *Comparison between Urinary neutrophil gelatinase-associated lipocalin in both groups at days 1and 2.*

As development of AKI further leads to changes in urinary output. Effect of urinary output on uNGAL using one-way ANOVA test showed increase level of uNGAL at day 1 was 48.3 ± 34.4 (ng/ml). and on day 2 was 190 ± 30.4 (ng/ml). High value of uNGAL at day 1 and day 2 without increase in serum creatinine reflects further development of AKI on 3rd and 4th day [Table 1].

Table3. *Validity of urine neutrophil gelatinase-associated lipocalin in the prediction of diagnosis and prognosis of acute kidney injury.*

	Sensitivity	Specificity	95 % Confidence Interval(CI)	AUC	Cut off value (ng/mL)
As diagnostic for AKI at day 1	79.5	73.1	(0.75-0.87)	0.82	48.5
As diagnostic for AKI at day 2	90	64.7	(0.7-0.9)	0.76	190.9
As prognostic (dialysis indication) at day 1	79.5	74.1	(0.75-0.87)	0.8	45.5
As prognostic (dialysis indication) at day 2	90	64.7	(0.75-0.88)	0.81	201

ROC= Receiver Operating Characteristic curve analysis, PPV= Positive predictive value

NPV= Negative predictive value

There was statistically no significant difference in PICU stay in days between the cases and the controls; the survivors of the cases stayed for 12.18 ± 2.52 days compared to 13.60 ± 2.27 days for the controls (P < 0.001), and those who died from cases stayed for 5 ± 2.5 (2–15) days compared to 7.8 ± 5.4 (2–13) days for the controls (P < 0.001). uNGAL values were toward gradual increasing trends at day 1 and day 2 in both cases and control groups.

There was statistically significant increase in mortality rate in cases group when compared to the controls.

Thirty-six patients (80%) in group 2 have died compared to 6 (24%) of controls (P < 0.001). Nine patients (20%) in group 2 have survived compared to 19 (76%) of controls (P < 0.001) [Table1]. Our results denoted that acute kidney injury in our studied shocked pediatric patients can be predicted by estimation of urinary neutrophil gelatinase-associated lipocalin.

The best cutoff value in this study was 48.5 ng/mL and 190.9 ng/mL at days 1and 2, respectively, to determine AKI. At day1, uNGAL at cutoff value of 48.5 ng/mL had a sensitivity and specificity of 79.5 and 73.1, respectively, and the area under the curve (AUC) of 0.8 (95% confidence interval [CI], 0.75–0.87) for predicting AKI. At day 2, uNGAL at cutoff value of 190.9 ng/mL had a sensitivity and specificity of 90 and 64.7, respectively, and the AUC of 0.76 (95% CI,

0.70–0.88) for predicting AKI [Table 3 and Figures 4 & 5].

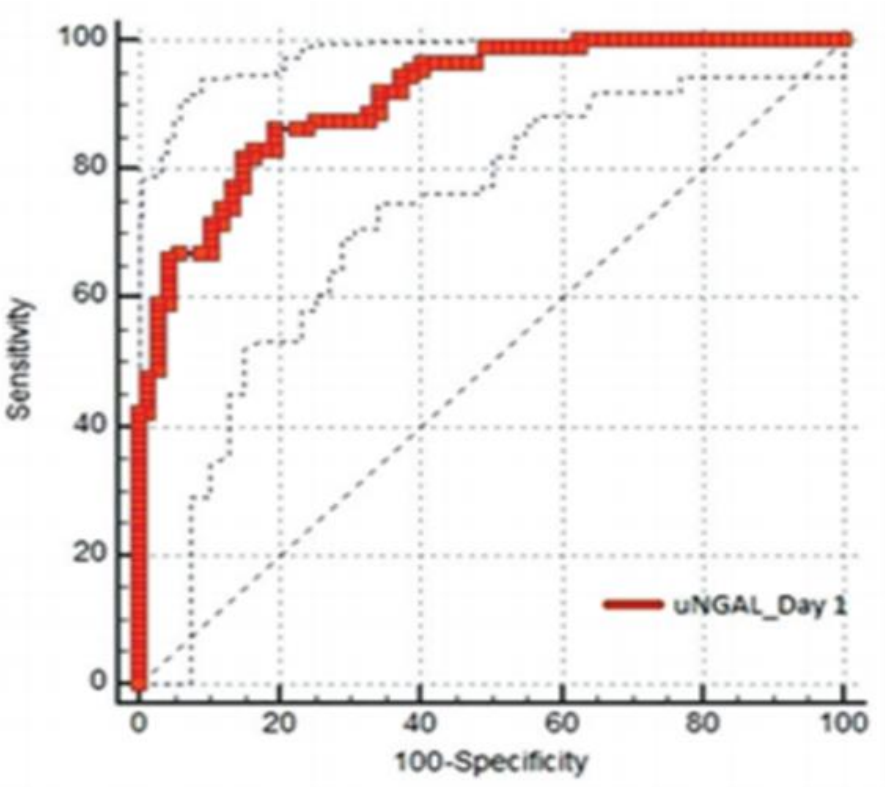

Figure4. *ROC curve for u NGAL as early diagnostic marker for AKI in shocked pediatric patients at day 1.*

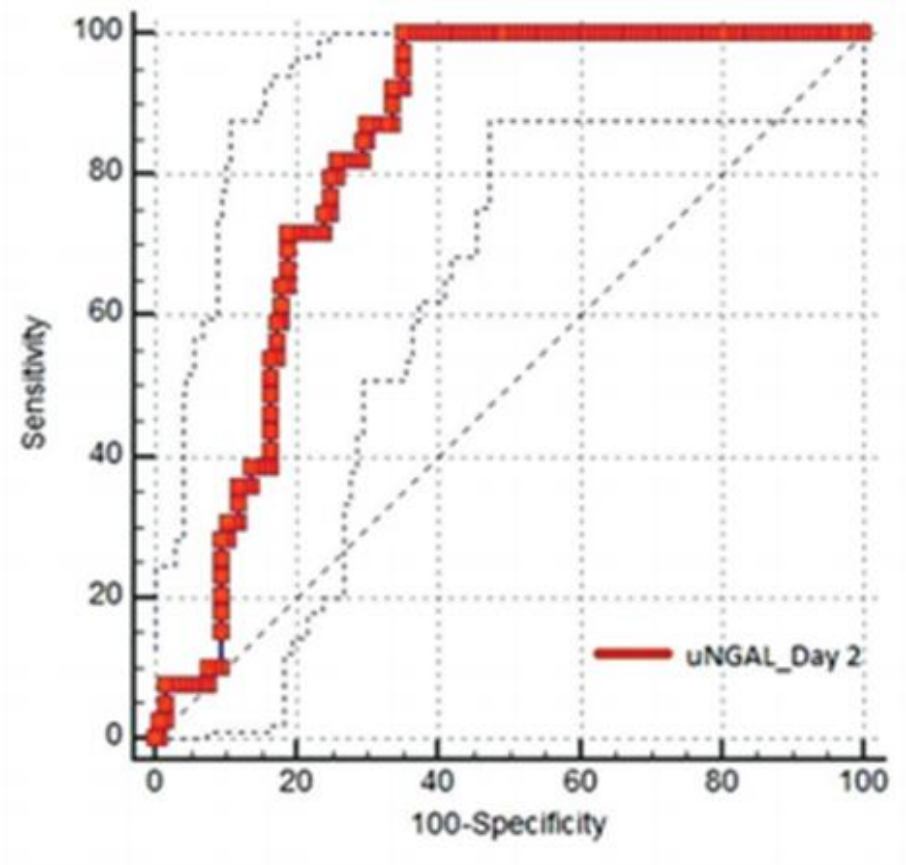

Figure5. *ROC curve for u NGAL as early diagnostic marker for AKI in shocked pediatric patients at day 1.*

Renal replacement therapy (Hemodilysis or peritoneal dialysis) as treatmentof AKI in shocked children can be predicted by evaluating urinary neutrophil gelatinase - associated lipocalin level. At day 1, the cutoff value 45.5 ng/ mL had a sensitivity and specificity of 79.49 and 74.1, respectively, and the AUC of 0.82 (95% CI, 0.75–0.87) for predicting the need of hemodialysis. At day 2, the cutoff value 201 ng/mL had a sensitivity and specificity of 90 and 64.7, respectively, and the AUC of 0.82 (95% CI, 0.75–0.88) for predicting the need of hemodialysis [Table 3 and Figure 6].

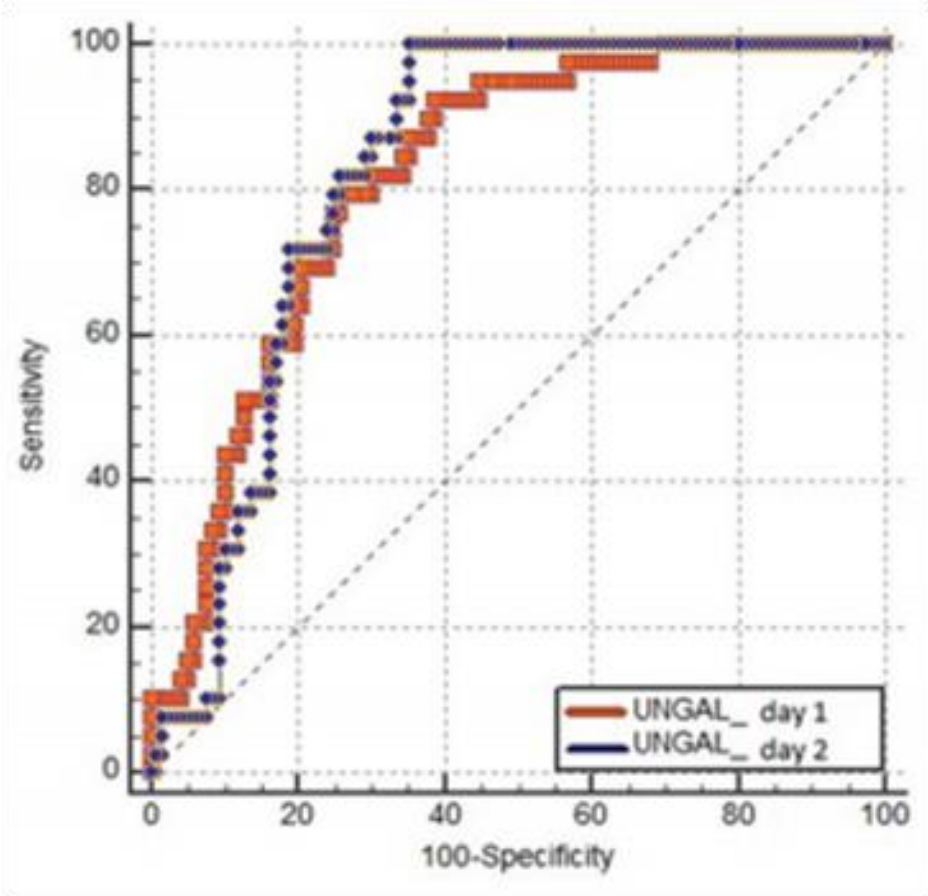

Figure6. *ROC curve for u NGAL as early predictor for need of AKI cases for dialysis in shocked pediatric patients at days 1 &2.*

DISCUSSION

Updates in technology and modern applications of biochemistry lead to discovery of newer novel biomarkers for AKI which enhanced the early prediction of AKI secondary to ischemic injury to renal tubule cells. These biological markers can help in early prediction of AKI and thus improves short term and long term sequlae of AKI. [3,4]

A criteria should be fulfilled for the ideal urinary biomarker for diagnosing AKI which include sensitivity, specificity, easy measurability, cheapness, simple interpretation, capacity of reflecting time-dependent changes according to severity of renal injury. [15]

The neutrophil gelatinase-associated lipocalin (NGAL) is mostly the most promising biological predictor for AKI in critically ill settings, while in our study, the patients with circulatory shock were in early stages of acute renal failure.

Cruz et al. have studied about three hundred adult patients admitted to ICU, nealy half of them have developed AKI during ICU admission. Plasma NGAL was a good biomarker for AKI occurance within next two days of admission (AUC 0.76, 95% CI 0.7–0.9).[16] Constantin et al. have prospectively studied about ninty adult patients who were admitted to ICU, plasma NGAL has also predicted AKI with a good sensitivity and specificity (82% and 97% respectively) with AUC 0.9 (CI=0.7–0.97).[17]

An Egyptian research work was done by Fouda et al. on forty five critically ill adult patients diagnosed as shock has reported that uNGAL at day 1 and day 2 after admission showed sensitivity and specificity of (62% and 69%) and (75% and 80%), respectively, for the prediction of AKI.[18]

In this pediatric study, at day 1, the cutoff value of 48.5 ng/mL had a sensitivity and specificity of 79.5 and 73.1, respectively, and the AUC of 0.82 (95% CI, 0.75–0.87) for predicting AKI so our study results are compatible to previous studies which were conducted on adults.

In a prospective study conducted by Mishra et al. in patients undergoing cardiopulmonary bypass(CPB) surgery, they found that uNGAL concentrations >50 ng/mL reliably predicted AKI in patients at only 2 h following CPB with 100% sensitivity and 98% specificity.[19]

Less optimistic results were reported among adult patients undergoing cardiac surgery; uNGAL levels were consistently higher at 1, 3, 18, and 24 h postoperatively in patients who ultimately developed AKI with best cutoff of 213 ng/mL at 18 h postoperatively (with a sensitivity of 73% and a specificity of 78%).[20]

To predict the need for hemodialysis in shocked AKI patients at day 1, uNGAL at cut off 45.5 ng/mL had a sensitivity and specifi city of 79.5 and 74.1, respectively. On day 2, uNGAL at cutoff value of 201ng/mL had a sensitivity and specificity of 90 and 64.7, respectively, for predicting the need of hemodialysis. Our study result showed that on day1 at low cutoff value, uNGAL had good diagnostic accuracy, while on day 2, sensitivity was improved but specificity decreased for prediction of renal replacement therapy (RRT).

Our results agreed with a previously done study by Fan et al. who showed that the peak uNGAL were significantly higher in patients receiving hemodialysis compared with those not receiving hemodialysis (median, 456 ng/mL vs. 341 ng/mL; $P < 0.0001$). At a cutoff level of 494 ng/mL, the sensitivity and specificity of the peak uNGAL in predicting hemodialysis were 89% and 71%, respectively.[21]

Our results were in accordance with Albeladi et al who reported that uNGAL on day 1 at cutoff level of 500 ng/mL had sensitivity 75%, specificity 80% for hemo or peritoneal dialysis and 1000 ng/mL for day 2 levels (with sensitivity 87.5 %; specificity 88%).[22]

Our study has concluded that the sensitivity and specificity of uNGAL are relatively higher on the 1st day itself in the pediatric patients of circulatory shock. So different measures can be adopted from early time to prevent the progression of AKI to further complications. Nephrotoxic medications should be avoided at an early stages of shock and or AKI , fluid therapy can be managed accordingly. The use of uNGAL in pediatric patients with shock at an early stages will help in foreseeing and preventing the possibility of AKI, but it will also reduce AKI‐related complications, PICU stay, and mortality.

LIMITATIONS OF THE STUDY

One of limitations of this study included a relatively small number of patients and thus our findings may be prone to mistakes. Validation is required in further studies on a larger scale with varied population.

CONCLUSIONS

A significant increase in uNGAL was observed in PICU patients following circulatory shock. uNGAL represents a good early predictor biomarker of AKI following circulatory shock and could predict the development of AKI 1–3 days earlier than serum creatinine. uNGAL at 1st day following shock could predict further development of AKI. uNGAL may also be helpful in prediction for the need of RRT.

RECOMMENDATIONS

There was a high validity of uNGAL to predict the occurrence of AKI in shock pediatric patients, its use in critically ill patients should be encouraged as it has early diagnostic and prognostic values of AKI in shocked children. This is especially useful in developing arab countries like Egypt where there is an urgent need to early detect and prevent complications of AKI thus to reduce economic burden and mortality from AKI.

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