НИРКИ KIDNEYS

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Correlation of urinary neutrophil gelatinase-associated lipocalin levels as an early diagnostic marker for acute kidney injury in patients with sepsis

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Abstract. ***Background.*** *The exact association between urinary neutrophil gelatinase-associated lipocalin (uNGAL) and acute kidney injury (AKI) is unknown in a critical care setting, in which the population is heterogeneous and the aetiology of AKI is unclear. Aim of this study is to clarify if uNGAL level is an early diagnostic marker for AKI in patients with sepsis.* ***Materials and methods.*** *The current study was conducted on 86 sepsis patients. The prevalence of AKI was identified among them. The role of uNGAL in predicting AKI development, mortality rate and length of the intensive care unit (ICU) stay were analyzed. Sensitivity and specificity were calculated, and the area under the receiver operating characteristic curve was considered as the optimal uNGAL cut-off level for detecting all classifications of AKI.* ***Results.*** *Most patients belonged to the age group of 51–60 years and their mean age was 54.6 years. Most patients (65.11 %) were males. 26.75 % had both type 2 diabetes mellitus and hypertension. AKI was detected in 89 % of subjects in the current study, as per KDIGO definition. 15.12 % of patients had stage 1 CKD, 15.12 % had stage 2 CKD, and stage 3 CKD was diagnosed in 4.65 % of cases. Mortality rate was 11 %, and 89 % of patients were discharged. The mean ICU length of stay among patients with AKI is 8.9 days. There is significant association between the mean ICU length of stay and AKI presence (p = 0.03). 17.4 % (n = 15) of patients required renal replacement therapy. There is a very significant difference in mean baseline uNGAL in patients with and without AKI: 149.9 and 73.2 ng/ml, respectively (p = 0.0006). This indicated that baseline uNGAL levels predict AKI. The mean uNGAL in people with AKI was 356 ng/ml and in those without AKI, it was 95 ng/ml. There is a very significant difference in mean uNGAL 48 hours after in patients with and without AKI (p < 0.0001). At a cut-off value of 120, there were 69 true positive cases, 9 true negative cases, 0 false positive cases, and 8 false negative cases. Based on these, the sensitivity of uNGAL at baseline in detecting AKI is 89.61 %, specificity is 100 %, and accuracy is 90.70 %. At a cut-off point of 120, there were 77 true positive cases, 8 true negative cases, 1 false positive case, and 0 false negative cases. Based on these, the sensitivity of uNGAL 48 hours after was 100 %, specificity 88.89 %, and accuracy was 98.84 %. There is a significant association between uNGAL levels and the ICU length of stay (p = 0.00).* ***Conclusions.*** *Sensitivity analysis was done in cut-off value of 120 for urinary NGAL in predicting AKI. From these results we conclude that urinary NGAL at the time of ICU admission is a reliable marker of renal function in sepsis patients. There is a significant correlation between AKI presence and urinary NGAL, and the ICU length of stay. We recommend not to use uNGAL alone in predicting AKI. It should be combined with glomerular filtration rate to reliably detect AKI development. Study findings indicate that sepsis patients with elevated uNGAL require proper management with close monitoring of blood pressure, urine output and appropriate doses of diuretics to avoid the development of AKI.*

Keywords: *acute kidney injury; urinary neutrophil gelatinase-associated lipocalin; specificity; renal replacement therapy*

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Introduction

Severe acute kidney injury (AKI) raises the mortality and morbidity of hospitalized patients. Recent studies suggest that a small decrease in renal function, as indicated by serum creatinine, is a predictor of mortality and duration of hospital stay. Laboratory literature showed that early intervention is required and essential in preventing various pathophysiologic events that cause AKI. But serum creatinine, the vital AKI biomarker that is used in various clinical settings, is often a late marker of reduced glomerular filtration rate. This limits the ability to identify AKI at an early stage and initiate appropriate clinical action. So, currently, the research was focused on detecting earlier markers of AKI [1, 2]. Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein that was isolated as a significant biomarker of AKI through genomic microarray technology [3]. It is expressed in low quantities usually, but it raises significantly in the presence of epithelial injury and inflammation [4]. The study done by Mishra et al. [5] found a great rise in urinary neutrophil gelatinase-associated lipocalin (uNGAL) two days before the rise of serum creatinine in patients with AKI after cardiopulmonary bypass. These findings were also confirmed in a study done on AKI adults after cardiac surgery, which identified that uNGAL was significantly increased 1–3 hours after surgery. Some other studies found a strong relationship between uNGAL and AKI in transplantation of kidney, diarrhoea-associated haemolytic-uremic syndrome, and lupus nephritis [6, 7].

AKI is a very common entity in admitted patients. In the United States, around 1 % of hospital-admitted patients have AKI. AKI affects patient management to a significant extent in terms of treatment options. Most of the medications or procedures that use contrast media may have to be delayed due to the presence of AKI. As most of the drugs are excreted through the kidney, doses should be modified due to decreased renal function. It may be even necessary to frequently monitor drug levels. Around 95 % of nephrologist consultations are due to AKI. Hence, AKI is an important contributor to extended hospital stays and morbidity [8].

It is unknown exactly the link between uNGAL and AKI in a critical care setting, in which the population is heterogeneous, and the aetiology of AKI is unclear. Also, the prevalence of sepsis in the intensive care unit (ICU) may reduce the usage of uNGAL as a biomarker of renal injury. Hence, in the current research, we studied uNGAL concentrations in critically ill patients with sepsis to determine, if there is an association between uNGAL and AKI.

The current study was carried out at Apollo Health City, Jubilees Hills, Hyderabad, Telangana. It is a tertiary care centre attached to a general hospital with 550 beds. All facilities were available in the Department of General Medicine to assess the parameters mentioned in this study. The investigator of this study was well qualified to conduct the study. Medical and surgical ICUs were available at our tertiary care centre to deal with any emergencies arising during the study tenure.

The purpose of this study is to know if uNGAL levels as an early diagnostic marker for acute kidney injury in patients with sepsis and to predict acute kidney injury in critically ill patients earlier and to evaluate the outcomes in the form of length of the hospital stay, requirement of renal transplantation and mortality rate in patients with AKI.

Materials and methods

The current study was conducted in the Department of General Medicine, Apollo Health City, Jubilee Hills, Hyderabad, India.

Study period: 18 months, January 2021 to July 2022.

Data collection: 17 months, August 2021 to November 2022.

Type of study: prospective, observational study. The study is prospective as the assessments were done two times, at baseline and again 48 hours after ICU admission. The study is observational, as intervention is in the form of therapy was not given to all study patients, as a part of the study. The study participant's clinical environment was not changed, so the study is an observational study.

Source of data: after getting approval from the Institutional Ethics Committee, patients admitted into ICU of our tertiary care institution was taken as study sample.

Sampling procedure: convenience sampling. It is a kind of non-probability sampling procedure, in which the sample is taken from a group of people who are easy to reach. It is also known as grab or availability sampling.

Sample size calculation. As per the study of Alobaidi [9], the prevalence of AKI in sepsis is 4.2 %.

$$N = Z^2PQ / E^2,$$

where N is sample size; P is prevalence; $Q = 1 - P$; E is error (5 %); Z is confidence levels (98 %). N = 88.

The minimum sample size is 88. We included 88 patients but the data was incomplete for 2 subjects, so we did the data analysis for 86 patients.

All 86 patients provided informed consent to participate in the study.

Inclusion criteria: patients aged above 18 years admitted into AIMSR with sepsis, males and females.

Exclusion criteria: patients who underwent kidney transplantation; pregnant and lactating women; patients who had cardiorespiratory arrest 72 hours before biomarker assessment; patients in stage 4 and stage 5 of chronic kidney disease; patients with confirmed or suspected acute glomerulonephritis, acute interstitial nephritis, post renal CKD, renal vasculitis; patients who stayed in ICU for AKI for less than 24 hours. Exclusion criteria were assessed mainly through oral history, medical records and lab tests to rule out the above-mentioned conditions.

Methodology

After getting informed consent from all patients, uNGAL assessment was done for all patients included in the study, done within 72 hours of ICU admission. Baseline uNGAL is the estimated value of uNGAL at the time of admission. Peak value of uNGAL is the maximum value during hospital stay.

All subjects were daily monitored for serum creatinine, urine output, length of stay, need for renal replacement therapy was assessed.

A clean midstream urine sample (10 mL) was collected in a sterile test tube and centrifuged at 5,000 rpm for 15 minutes.

The supernatant was transferred to an Eppendorf tube and stored at –80 °C until assayed for urine NGAL. Test was performed on the same equipment by the same operator in the Hospital of Apollo Institute of Medical Sciences and Research.

Urine is analyzed for NGAL at the time of admission (classified uNGAL-1) and at 48 hours after admission (uNGAL-2) using the BioVendor Human Lipocalin-2/NGAL ELISA, which is a sandwich enzyme immunoassay for the quantitative measurement of human NGAL as per producer protocol.

Primary outcome was levels of uNGAL and its correlation with AKI, secondary outcome — to know hospital mortality, length of stay.

Parameters assessed:

— age;
— gender;
— incidence of AKI;
— presence of co-morbidities, if yes — what are they;
— CKD if present, stage of CKD;
— uNGAL at baseline;
— uNGAL 48 hours after admission;
— serum creatinine at baseline and daily assessment;
— urine output at baseline and at 48 hours;
— cut-off uNGAL with sensitivity, specificity, positive (PPV) and negative predictive value (NPV).

AKI is defined and classified as per KDIGO criteria. Worsening AKI is defined as an increase in the RIFLE category (from Risk to Injury, Risk to Failure, or Injury to Failure) within 48 hours after enrollment.

Baseline serum creatinine is defined as the lowest creatinine value in the last 6 months before AKI or for those without this measurement, the lowest value achieved during hospitalization in the absence of dialysis.

Day 0 is defined as the calendar day of admission and thus its length varies depending on the time of presentation.

We did complete clinical workup for all the cases which includes detailed history from relatives, physical examination, vitals, and systemic examination.

Statistical analysis

The following assumption on the data was made:

1. Dependent variables are normally distributed.

2. Skewed variables were converted into log values to attain normal distribution.

The data collected was processed in MS Excel 2019 and analysis was carried out using Microsoft Excel and statistical software called Epi Info free version 7.2.5.0. P-value < 0.05 was considered statistically significant. Frequencies and percentages were also used. Mean and SD were used. Categorical findings were assessed with chi-square test. Quantitative measures were assessed using an unpaired t-test.

Sensitivity and specificity were calculated, and the area under a receiver operating characteristic curve was considered as the optimal uNGAL cut-off level for detecting all classifications of AKI.

Ethical statement. Permission from the Institutional ethical committee attached to AIMSR, Jubilee Hills, Hyderabad, Telangana was taken before conducting the study. Every patient was explained the whole process and advantages of availing their data for the study. Patients were also told that their information will be kept confidential. After she/he accepts, an informed consent form was given in the local language or understandable language and the person was asked to sign it or put a thumb impression. They were assured that their doubts, if any to be clarified at any time.

Results

The current study was conducted on 86 patients admitted with sepsis in ICU at our tertiary care centre. AKI presence was predicted using uNGAL levels.

Demographics. Most patients (27.9 %) were in the age group of 51 and 60 years, followed by 23.26 % of patients were in 61 to 70 years, 17.4 % were in 41 to 50 years, 10.47 % were in 31 to 40 years, 9.3 % were in 71 to 80 years, 5.81 % were in 21 to 30 years, 2.33 % of patients were in 18 to 20 years age group. The mean age of study population was 54.6 years. Most of the patients (65.11 %) were males in the current study.

Co-morbidities. Totally 32.55 % of patients had no co-morbidities in this study. 8.14 % had type 2 diabetes mellitus and hypothyroidism. 26.75 % had both type 2 diabetes mellitus and hypertension. 11.63 % had hypertension alone. 20.93 % had type 2 diabetes mellitus alone.

AKI was observed in 89.53 % (n = 77) of subjects as per KDIGO definition. 88.37 % of patients were discharged in stable condition, and the mortality rate was 11.63 %. Among 77 patients with AKI, 10 patients were expired.

The mean ICU length of stay in patients with AKI is 8.9 days. This was more compared to ICU length of stay among patients with no AKI. There is significant association between ICU length of stay and AKI presence (Table 1).

Relation between age and AKI presence. There is significant association between the mean age of patients with AKI and without AKI, as per t-test (P = 0.02). The mean age in patients with AKI is 55.9 years and the mean age in patients without AKI is 43.8 years (Table 2).

Table 1. Association between hospital stay and AKI presence (t-test, p = 0.03)

AKI	Observation	Total	Mean	Variance	Std Dev.
No	9.0000	52.0000	5.7778	6.9444	2.6352
Yes	77.0000	691.0000	8.9740	18.2362	4.2704

AKI	Minimum	25 %	Median	75 %	Maximum	Mode
No	3.0000	4.0000	5.0000	7.0000	10.0000	4.0000
Yes	1.0000	6.0000	8.0000	12.0000	18.0000	7.0000

Renal replacement therapy. Totally 17.4 % (n = 15) of patients required renal replacement therapy. Whereas among 77 patients with AKI, 15 patients needed renal replacement therapy. According to KDIGO, 15.12 % (n = 13) of patients had stage 1 CKD, 15.12 % (n = 13) of patients had stage 2 CKD, 4.65 % (n = 4) had stage 3 CKD, and 65.12 % (n = 56) of subjects had no CKD.

Association between uNGAL-1 and AKI presence. There is significant difference in mean uNGAL-1 in patients with AKI and in patients without AKI, as per t-test (p = 0.0006). The mean uNGAL in patients with AKI is 149.9 ng/ml. The mean uNGAL in patients without AKI is 73.2 ng/ml. This indicated that baseline uNGAL levels predict AKI (Table 3).

UNGAL at 48 hours and AKI presence. There is a very significant difference in mean uNGAL at 48 hours in patients with AKI and in patients without AKI, as per t-test (p = 0.00). The mean uNGAL in patients with AKI is 356 ng/ml. The mean uNGAL in patients without AKI is 95 ng/ml (Table 4).

Serum creatinine at baseline, after 24 and 48 hours. Mean serum creatinine was normal during the time of admission. But the mean serum creatinine was elevated by 24 and 48 hours of admission. The mean serum creatinine at 24 hours is 2.30 ± 0.88 mg/dl. The mean serum creatinine at baseline is 0.85 ± 0.24 mg/dl. The mean serum creatinine at 48 hours is 2.46 ± 1.26 mg/dl.

Role of serum creatinine at baseline in detecting AKI. There is no significant difference in baseline mean serum creatinine in patients with and without AKI, as per t-test (p = 0.21). The mean serum creatinine in patients with AKI at baseline is 0.87 mg/dl. The mean serum creatinine in patients without AKI is 0.75 mg/dl. This indicates that baseline serum creatinine didn't detect AKI.

Sensitivity, specificity, and accuracy of uNGAL at baseline in detecting AKI. At a cut-off value of 120, there were 69 true positive cases, 9 true negative cases, 0 false positive cases, and 8 false negative cases. Based on these, the sensitivity of uNGAL at baseline in detecting AKI is 89.61 %, specificity is 100 %, and accuracy is 90.70 % (Table 6).

Sensitivity, specificity, and accuracy of uNGAL at 48 hours in detecting AKI. At a cut-off value of 120, there were 77 true

Table 2. Association between age and AKI presence (t-test, p = 0.04)

AKI	Observation	Total	Mean		Variance	Std Dev.
No	9.0000	395.0000	43.8889		319.1111	17.8637
Yes	77.0000	4309.0000	55.9610		202.4064	14.2270
AKI	**Minimum**	**25 %**	**Median**	**75 %**	**Maximum**	**Mode**
No	18.0000	34.0000	47.0000	52.0000	72.0000	18.0000
Yes	24.0000	47.0000	59.0000	65.0000	91.0000	60.0000

Table 3. Mean uNGAL levels at baseline in AKI and non-AKI patients (t-test, p = 0.0006)

AKI	Observation	Total	Mean		Variance	Std Dev.
No	9.0000	659.0000	73.2222		1236.1944	35.1596
Yes	77.0000	11544.0000	149.9221		3952.2570	62.8670
AKI	**Minimum**	**25 %**	**Median**	**75 %**	**Maximum**	**Mode**
No	15.0000	61.0000	80.0000	98.0000	118.0000	15.0000
Yes	28.0000	122.0000	128.0000	172.0000	390.0000	128.0000

Table 4. Mean uNGAL levels at 48 hours in AKI and non-AKI patients (t-test, p < 0.0001)

AKI	Observation	Total	Mean		Variance	Std Dev.
No	9.0000	863.0000	95.8889		867.8611	29.4595
Yes	77.0000	27470.0000	356.7532		2370.5830	48.6886
AKI	**Minimum**	**25 %**	**Median**	**75 %**	**Maximum**	**Mode**
No	26.0000	95.0000	100.0000	116.0000	124.0000	116.0000
Yes	269.0000	313.0000	352.0000	395.0000	461.0000	312.0000

Table 5. Role of serum creatinine at baseline in predicting AKI (t-test, p = 0.1873)

AKI	Observation	Total	Mean		Variance	Std Dev.
No	9.0000	6.8200	0.7578		0.1065	0.3264
Yes	77.0000	64.4400	0.8708		0.0527	0.2295
AKI	**Minimum**	**25 %**	**Median**	**75 %**	**Maximum**	**Mode**
No	0.4600	0.5200	0.6700	0.7500	1.4000	0.4600
Yes	0.3500	0.6800	0.8300	1.0800	1.3200	0.9000

positive cases, 8 true negative cases, 1 false positive case, and 0 false negative cases. Based on these, the sensitivity was 100 %, specificity is 88.89 %, and accuracy is 98.84 % (Table 7).

Relation between uNGAL at baseline and mortality rate. Baseline uNGAL levels predicted mortality rate. Baseline uNGAL levels were significantly higher in patients who expired, compared to patients who were discharged in stable condition, as per t-test (p = 0.03).

Relation between uNGAL at baseline and ICU length of stay. UNGAL levels at baseline predicted ICU stay, patients with more uNGAL levels at baseline had prolonged hospital stay, as per ANOVA (p = 0.00).

Urine output was reduced in 49 (56.98 %) patients during day 1. Urine output was reduced in 49 patients during day 2.

Mean TLC count. The mean TLC count was 12,013 cells/cc.

Table 6. Sensitivity, specificity, accuracy of uNGAL at baseline in detecting AKI, %

Statistics	Value	95% CI
Sensitivity	89.61	80.55 to 95.41
Specificity	100.00	66.37 to 100.00
Disease prevalence	89.53	81.06 to 95.10
PPV	100.00	
NPV	52.94	36.86 to 68.43
Accuracy	90.70	82.49 to 95.90

Table 7. Sensitivity, specificity, accuracy of uNGAL at 48 hours in detecting AKI

Statistics	Value	95% CI
Sensitivity	100.00	95.32 to 100.00
Specificity	88.89	51.75 to 99.72
Disease prevalence	89.53	81.06 to 95.10
PPV	98.72	92.39 to 99.80
NPV	100.00	
Accuracy	98.84	93.69 to 99.97

Discussion

We included 86 patients in the current study based on sample size calculation and eligibility criteria. The clinical, demographic and renal profile was assessed for all patients. Association between categorical findings were done using a chi-square test. Percentages and frequencies were also used for every parameter. Association between numerical findings were done using t-test. ANOVA test is used wherever necessary. Sensitivity analysis was done for cut-off value of 120 for uNGAL in predicting AKI.

Acute kidney injury was seen in 89 % of subjects in the current study, as per KDIGO definition. There is significant association between the mean age of patients with AKI and without AKI, as per t-test. The mean age in patients with AKI is 55.9 years and the mean age in patients without AKI is 43.2 years in the current study.

In a study done by Rocha et al. [10], among 75 patients, 47 patients had AKI, 28 patients without AKI. The prevalence of AKI was 60 %.

The mean age in patients with AKI was 71.3 years. The mean age in patients without AKI was 71.7 years. There is no significant association between the mean age of patients with AKI and without AKI, as per t-test (P = 0.82), in contrast to our study. AKI presence was defined as per KDIGO criteria based on raise in serum creatinine or a decrease of urine output, similar to the current study.

Co-morbidities. 32.55 % of patients had no co-morbidities in the current study. 8.14 % had type 2 diabetes mellitus and hypothyroidism. 26.75 % had both type 2 diabetes mellitus and hypertension. 11.63 % had hypertension alone. 20.93 % had type 2 diabetes mellitus alone.

15.12 % of patients had stage 1 CKD. 15.12 % of patients had stage 2 CKD. 4.65 % had stage 3 CKD. 65.12 % of subjects had no CKD in our study.

In the study of Rocha, 60 among 75 sepsis patients had hypertension. The most common co-morbidity was hypertension followed by type 2 diabetes mellitus. Diabetes was seen in 33.3 % patients. Chronic kidney disease was seen in 49.3 % of patients. COPD was seen in 22.7 % of patients.

Prevalence of AKI. Acute kidney injury was seen in 89.5 % of subjects in the current study, as per KDIGO definition.

Table 8. Relation between uNGAL at baseline and mortality rates (t-test, p = 0.0366)

AKI	Observation	Total	Mean	Variance	Std Dev.
No	76.0000	9453.0000	124.3816	4410.5058	66.4116
Yes	10.0000	1734.0000	173.4000	7173.3778	84.6958

AKI	Minimum	25 %	Median	75 %	Maximum	Mode
No	12.0000	102.0000	115.0000	119.0000	390.0000	118.0000
Yes	61.0000	112.0000	149.5000	251.0000	320.0000	118.0000

Table 9. TLC levels

Obs.	Total	Mean	Std Dev.		
86.0000	1033185.0000	12013.7791	4890		
Minimum	**25 %**	**Median**	**75 %**	**Maximum**	**Mode**
1110.0000	8500.0000	12000.0000	15600.0000	26410.0000	10000.0000

In a study by Radhey Shyam et al. [11] among 150 patients with septicaemia, 25.33 % had AKI. They come under group 1 and 74.67 % had no AKI. They come under group 2. Among 25.33 % of patients with AKI, 28.95 % had stage 1 AKI, 34.25 % had stage 2 AKI and 36.8 % had stage 3 AKI.

Mortality and morbidity in patients with sepsis and AKI. The mortality rate is 11.63 %. 89 % of patients got discharged in stable condition in the current study.

There is no significant association between mortality and AKI presence in our study, as per the chi-square analysis.

Among 77 patients with AKI, 10 patients expired. The mean ICU length of stay in patients with AKI is 8.9 days. This was more compared to ICU length of stay among patients with no AKI. There is significant association between ICU length of stay and AKI presence.

In the study of Radhey Shyam et al., 60.0 % of patients were discharged from the hospital. 40 % were expired. The mortality rate is more in group 1 compared to group 2 patients who don't have AKI. There is a significant difference in mortality rates in patients with AKI and without AKI, in contrast to our study.

The mean ICU length of stay was more in group II (21.29 ± 1.89 days) compared to group I (13.67 days). There is no statistically significant difference between two groups in contrast to the current study.

In the study of Rocha, the in-ICU mortality was 53.3 %. The reason for this could be due to inclusion of only elderly patients. The mortality rate is more compared to other studies [12, 13].

We believe there were differences because these studies also included elderly patients in general wards of the hospital and not only in ICUs.

The mortality rate of AKI sepsis patients was 63.8 % which was significantly higher than patients without AKI.

In a prospective [14] study done on elderly AKI patients, who were aged more than 60 years, performed in Brazil, mortality rate of the elderly AKI patients was 54 %.

Kohli et al. [15] reported in 2007, in a prospective study that there is high mortality rate of 61 % in the elderly patients with AKI aged above 60 years in a tertiary care center of India.

Due to old age, elderly septic AKI patients are more prone to develop multi organ dysfunction syndrome, which will raise the mortality rate. So, it is vital to pay more attention to treatment of sepsis and co-morbidities of elderly AKI patients. Also, the diagnosis in elderly patients can be delayed or difficult, due to loss of muscle mass, and low baseline creatinine level, hiding an increase of its values, justifying the search for biomarkers like NGAL.

Urinary NGAL levels. There is significant difference in mean uNGAL-1 in patients with AKI and in patients without AKI, as per t-test ($p = 0.0006$). The mean uNGAL in patients without AKI is 73.2. The mean uNGAL in patients withs AKI is 149.9. This indicated that baseline uNGAL levels predict AKI.

There is a very significant difference in mean uNGAL at 48 hours in patients with AKI and in patients without AKI, as per t-test ($p = 0.00$). The mean uNGAL in patients with AKI is 356. The mean uNGAL in patients without AKI is 95. This indicated that uNGAL levels at 48 hours also predict AKI in our study.

In sepsis, kidney is one of the most commonly affected organs. Around 47.0 % AKI cases are associated with sepsis, as per Singbartl et al. [16].

It is difficult to use NGAL to detect AKI associated with sepsis, as NGAL levels raises in sepsis irrespective of AKI presence.

Rocha et al. showed that there is no significant difference in the mean urinary NGAL levels at baseline and after 48 hours between survivors and non-survivor AKI patients with sepsis, which is in contrast to the current study ($p = 0.08$ and $p = 0.13$).

Kim et al. study demonstrated that NGAL to be one useful predictor of AKI in patients with sepsis, but there is no significant difference in uNGAL concentration in patients with and without AKI [17].

Accuracy of NGAL in detecting AKI. At a cut-off value of 120, there were 69 true positive cases, 9 true negative cases, 0 false positive cases, and 8 false negative cases. Based on these, the sensitivity of uNGAL at baseline in detecting AKI is 89.61 %, specificity is 100 %, accuracy is 90.70 % at day 1.

At a cut-off value of 120, there were 77 true positive cases, 8 true negative cases, 1 false positive case, and 0 false negative cases. Based on these, the sensitivity was 100 %, specificity is 88.89 %, accuracy is 98.84 % at day 2.

Park H.S. et al. [18] reported a higher urinary NGAL in AKI with sepsis patients compared to sepsis without AKI and they also found good predictive power of NGAL in identifying AKI with sepsis. The AUC for predicting AKI was more for urinary NGAL of 0.820 compared to serum procalcitonin concentration of 0.76.

In the study of Rocha et al., it was found that mean uNGAL as an excellent predictor of AKI. The sensitivity and specificity were more than 89 % at baseline, similar to the current study. The accuracy of NGAL on days 1 and 2 as predictors of mortality was intermediate, with sensitivity between 65 and 77 % and specificity less than 60 %, which was less compared to our study. The study finally found that uNGAL was an excellent predictor of AKI in septic patients and anticipate the diagnosis of AKI in 2 days. At a cut-off value of uNGAL of 12.21, the sensitivity to predict AKI is 71.5 %, specificity is 54 %. At a cut-off value of uNGAL of 13.29, the sensitivity to predict AKI is 65 %, specificity is 51 %. Specificity was less compared to sensitivity.

In the study of Munna Lal Patel et al. [19], urinary NGAL levels were measured at 12, 24 and 48 hours of ICU admission of sepsis patients. The mean uNGAL levels at 12 hours were 80.00 ± 7.00 ng/mL and 128.13 ± 22.46 ng/mL at 24 hours. They were significantly higher compared to non-AKI sepsis patients, similar to the current study.

At baseline or 12 hours, at uNGAL cut-off value of 34.32 ng/mL, it had a sensitivity and specificity of 86.36 % and 80.60 % in predicting AKI. At the cut-off value of 199.99 ng/mL, the sensitivity and specificity were 90.0 and 64.66 % in predicting AKI. Specificity was less compared to sensitivity.

Previous studies reported that the incidence of AKI among elderly patients ranged from 22 to 40 %, with most of the patients in stage 1 disease [20, 21].

Stage of AKI. In our current study, 15 % of patients belonged to stage 1 of CKD. Whereas in a study of Rocha et al., 62.7 % of patients had AKI and most of them had AKI stage 3, which is in disagreement with the previous studies.

Strengths of this study

This study assessed the renal profile of patients with sepsis. Urinary NGAL levels at time of admission alerted to take early steps to prevent significant morbidity and mortality and need for renal replacement therapy.

The study helped to identify various risk factors of AKI. It helps to improve clinical outcomes and prevent various complications.

The information of study findings helps clinicians to manage sepsis patients effectively.

Co-morbidities were identified all subjects due to various lab tests done.

Economic benefit to patients

A part of travel expenses was reimbursed to all subjects for travelling to our institution regularly.

ICU treatment medications were provided free of cost to all patients.

All the lab investigations were done free of cost to all subjects.

Recommendations for future studies

1. Studies comparing the efficacy and safety of various treatment regimens can be done.

2. Multicenter studies including various tertiary care hospitals and certain specialized clinics could be done as more patient populations from different backgrounds could be involved.

3. Meta-analysis of existing research could be done.

4. Studies can be done on the comparison of AKI pattern in patients from rural and urban areas and among patients with various socioeconomic status can be done

5. Studies on assessing cardiac profile in AKI patients with sepsis can be done.

6. Studies on comparing cases and controls like case-control study on patients with and without AKI can be done.

Limitations of the current study

In this study, the sample size was 86, indicating that the study sample was small, and the primary limitation was the interpretation of results. Results for small studies were less reliable compared to larger studies. Larger studies with more subjects produce narrow confidence intervals (95 to 99 %) and more accurate results.

Conclusions

From these results, we conclude that urinary NGAL at the time of ICU admission is a reliable marker of renal function in sepsis patients. There is significant correlation between AKI presence and urinary NGAL, and ICU length of stay. We recommend not to use uNGAL alone in predicting AKI. It should be combined with glomerular filtration rate to reliably detect AKI development. These study findings indicate that sepsis patients with elevated uNGAL require proper management with close monitoring of blood pressure and urine output and appropriate doses of diuretics to avoid the development of AKI. Future studies should be done in various clinical settings on larger numbers of patients and healthy individuals to confirm the effectiveness of urinary NGAL in determining renal function and disease progression.

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Кореляція рівнів ліпокаліну, асоційованого з желатиназою нейтрофілів, у сечі як ранній діагностичний маркер гострого ураження нирок у пацієнтів із сепсисом

Резюме. Актуальність. Невідомий точний зв'язок між ліпокаліном, асоційованим із желатиназою нейтрофілів, у сечі (uNGAL) та гострим пошкодженням нирок (ГПН) у реанімаційних умовах, коли популяція є гетерогенною, а етіологія ГПН неясна. **Мета:** з'ясувати, чи є рівні uNGAL раннім діагностичним маркером ГПН у пацієнтів із сепсисом. **Матеріали та методи.** Поточне дослідження проведено за участю 86 хворих на сепсис, серед яких було визначено поширеність ГПН. Проаналізовано роль uNGAL у прогнозуванні розвитку ГПН, рівня смертності та тривалості перебування у відділенні інтенсивної терапії. Були розраховані чутливість і специфічність, а площа під кривою робочої характеристики приймача вважалася пороговим рівнем uNGAL, оптимальним щодо виявлення всіх типів ГПН. **Результати.** Більшість пацієнтів належали до вікової групи 51–60 років, середній вік становив 54,6 року. Більшість хворих (65,11 %) були чоловіками, 26,75 % мали цукровий діабет 2-го типу та гіпертензію. ГПН спостерігалося в 89 % суб'єктів поточного дослідження згідно з визначенням KDIGO. ХХН 1-ї стадії діагностовано в 15,12 % пацієнтів, 2-ї — у 15,12 %, 3-ї стадії — у 4,65 %. Рівень смертності становив 11 %, 89 % пацієнтів були виписані. Середня тривалість перебування хворих із ГПН у реанімації становить 8,9 дня. Існує значний зв'язок між середньою тривалістю перебування у відділенні інтенсивної терапії і наявністю ГПН ($p = 0,03$). Замісної ниркової терапії потребували 17,4 % ($n = 15$) пацієнтів. Існує вірогідна різниця в середньому базовому рівні uNGAL в осіб із ГПН та без нього: 149,9 і 73,2 нг/мл відповідно ($p = 0,0006$). Це вказує на те, що базові рівні uNGAL дозволяють спрогнозувати ГПН. Середнє значення uNGAL у хворих із ГПН становить 356 нг/мл, в осіб без ГПН — 95 нг/мл. Через 48 годин спостерігається дуже значна різниця в середньому рівні uNGAL у пацієнтів із ГПН та без нього ($p < 0,0001$). При граничному значенні 120 було 69 істинно позитивних, 9 істинно негативних, 0 хибнопозитивних і 8 хибнонегативних випадків. Виходячи з цього, чутливість uNGAL на початковому рівні у виявленні ГПН становить 89,61 %, специфічність — 100 %, а точність — 90,70 %. При граничному значенні 120 було 77 істинно позитивних випадків, 8 істинно негативних випадків, 1 хибнопозитивний випадок і 0 хибнонегативних випадків. З огляду на це чутливість uNGAL через 48 годин становила 100 %, специфічність — 88,89 %, а точність — 98,84 %. Існує вірогідний зв'язок між рівнем uNGAL і тривалістю перебування у відділенні інтенсивної терапії ($p = 0,00$). **Висновки.** Аналіз чутливості проводився при пороговому значенні 120 для uNGAL щодо прогнозування ГПН. Таким чином, ми робимо висновок, що uNGAL на момент надходження у відділення інтенсивної терапії є надійним маркером функції нирок у пацієнтів із сепсисом. Існує суттєва кореляція між наявністю ГПН, рівнем uNGAL та тривалістю перебування у відділенні інтенсивної терапії. Ми рекомендуємо не використовувати тільки uNGAL для прогнозування ГПН — його слід поєднувати зі швидкістю клубочкової фільтрації, щоб надійно діагностувати ГПН. Результати дослідження вказують на те, що пацієнти із сепсисом і підвищеним рівнем uNGAL потребують належного лікування з ретельним контролем артеріального тиску та виділення сечі, уживання відповідних доз діуретиків, щоб уникнути розвитку ГПН.

Ключові слова: гостре ураження нирок; ліпокалін, асоційований із желатиназою нейтрофілів, у сечі; специфічність; замісна ниркова терапія