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Urine Neutrophil Gelatinase-Associated Lipocalin for Assessment of Acute Kidney Injury Following Liver Transplantation

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Abbreviations:
AKI: acute kidney injury;
LT: liver transplantation;
UNGAL: urinary neutrophil gelatinase-associated lipocalin;
Neutrophil Gelatinase-Associated Lipocalin1 (NGAL 1);
AKIN: Acute Kidney Injury Network;
RIFLE: end-stage kidney disease;
O.D.: optical density;
IQR: interquartile range.

ABSTRACT

Background: acute kidney injury (AKI) is a prevalent complication that occurs following liver transplantation (LT). Aim: to evaluate the value of urinary neutrophil gelatinase-associated lipocalin (UNGAL) in detecting AKI following LT.
Material and Methods: the present study adopted a randomized, prospective, double-blinded design. The trial was carried out on 38 patients who underwent evaluation for AKI following LT at Menoufia University's National Liver Institute. The study took place between January 2023 and June 2024.
Results: NGAL 2 exhibited a marked elevation in the AKI group compared to the non-AKI group ($p < 0.001$). No substantial difference was observed among the groups under study in relation to Neutrophil Gelatinase-Associated Lipocalin1 (NGAL 1).
Conclusion: the results obtained indicate that AKI was manifested in 63.16% of the patients (24 out of 38) following LT.
Key words: Neutrophil Gelatinase-Associated Lipocalin, Acute kidney injury, liver transplantation, liver transplantation

INTRODUCTION

Acute Kidney Injury is diagnosed based on progressive serum creatinine levels' changes over a period of 48 hours. AKI is categorized using either the Acute Kidney Injury Network (AKIN) criteria (1), end-stage kidney disease (RIFLE) criteria, failure, risk, injury, or loss of kidney function (2). AKI incidence in hospital inpatients is linked to higher rates of mortalities, morbidity, and utilization of hospital resources (3). AKI incidence following LT, as reported in the literature, exhibits significant variability, ranging from 14% to 97% (4-8). Furthermore, it is linked to elevated mortalities, graft loss, morbidity, prolonged hospitalization and ICU stay following LT, and the progression of chronic kidney

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disease (9). It is crucial to identify AKI reliable biomarkers in this population since the physiological abnormalities linked to end-stage liver failure and cirrhosis, as well as the physiological alterations resulting from the transplant procedure, render the measurement of creatinine in this patient group unreliable (10). AKI early identification of following LT can enable early nephrotoxins avoidance and renal physicians' early intervention. Therefore, developing reliable and early biomarkers for AKI is of paramount significance (11). LT is the surgical procedure of replacing a damaged liver with a healthy liver obtained from a different individual. Although donor organ availability is a significant constraint, it is a viable therapy option for acute liver failure as well as end-stage liver disease. Orthotopic transplantation is the standard procedure, which involves the removal of the native liver and the replacement of it with the donor organ in the identical anatomical position of the original liver (12). The surgical operation is challenging as it requires precise extraction of the donor organ and careful placement into the recipient. Hepatic transplantation is subject to strict regulations and is only carried out at approved transplant medical facilities by highly skilled transplant physicians and their accompanying medical teams. The duration of the procedure is contingent upon the outcome, and it ranges from 4 to 18 h (12). LT is often highly successful, and the majority of individuals are ultimately able to resume their regular activities thereafter. Typically, individuals may take a year to achieve complete recovery (13). The 25 kDa protein NGAL is quickly released by injured nephrons and has been shown to reliably detect AKI in patients who have had significant heart surgery and have decreased graft function post-renal transplant (14).

The aim of this study was to evaluate the value of UNGAL in detecting AKI following LT.

MATERIAL AND METHODS

Study Setting and Design

The present study adopted a randomized, prospective, double-blinded design. The study was conducted from January 2023 to June 2024 at Menoufia University's National Liver Institute on 38 patients assessed for AKI following LT.

Method of Data Collection

Collection of blood samples as well as serial urine involved 38 patients subjected to LT and then samples were analyzed. The recipients were monitored intraoperatively via arterial and central venous catheters, and trans-esophageal echocardiography was available as needed.

The transplantation of the liver graft was performed utilizing conventional piggy-back and caval replacement methods. No patients randomized in this experiment had veno-venous bypass intervention. A 500-1000 cc solution of warm 4.5% human albumin was used to rinse the grafts.

AKI is characterized by a rise in serum creatinine levels of 0.3 mg/dl or more within 48 hours, an elevation in serum creatinine levels to 1.5 times the baseline of the previous seven days, or a urine output of less than 0.5 mL/kg/h for 6 hours. An elevated risk of AKI was established based on the existence of one or more AKI risk factors, including sepsis, advanced age, intake of nephrotoxic drugs, and prior chronic morbidities.

Study Population

Inclusion criteria were age ≥18 years, LT from a living donor, and adult patients undergoing first elective living donor LT.

Exclusion criteria included the rates of glomerular filtration (utilizing the Modification of Diet in Renal Disease formula) < 60 mL/min/1.73 m^2, AKI during transplantation, urgent transplantation, re-transplantation, age < 18, and grafts transported on the organ ox machine perfusion system.

Study Tool

We classified the patients into two distinct groups: Group 1 comprised 24 subjects who were diagnosed with AKI following LT. These patients were evaluated using urinary NGAL. Group 2: 14 patients did not develop AKI following LT. They were collected and assessed by UNGAL.

Each patient underwent the following:

A. Clinical examination and detailed history;

B. Laboratory tests:

Sampling: seven mL of venous blood sample were withdrawn using sterile venipuncture and then divided into four tubes; 2 ml was withdrawn in K2 EDTA for complete blood count analyzed using Sysmex XS- 1800i hematology analyzer (Sysmex, Kobe, Japan). Three ml plain tube with clot activator for serum preparation for liver and kidney function tests (serum bilirubin,

transaminases levels, creatinine and urea levels) using Cobas 6000 analyser (c 501 module-Diagnostics, Germany) and FDPS by latex agglutination kit. Other tube containing 3.2% sodium citrate to prepare platelet poor plasma for coagulation profile testing using Sysmex CS-1600 automated hemostasis analyser (Sysmex, Kobe- Japan). These tests withdrawn on the admission day for LT and during the first postoperative week. Urine samples were collected for UNGAL measurement during the first postoperative week. NGAL was assayed using ELISA kits (Biolegeng, UK).

C. Materials supplied (table 1).

Table 1

Name	96 determinations
Microelisa stripplate	12*8strips
Standard	0.3ml*6tubes
Sample Diluent	6.0ml
HRP-Conjugate reagent	10.0ml
20X Wash solution	25ml
Chromogen Solution A	6.0ml
Chromogen Solution B	6.0ml
Stop Solution	6.0ml
Closure plate membrane	2
User manual	1
Sealed bags	1

D. Reagent preparation:

The solution was diluted with distilled or deionized water at a 1:20 ratio.

E. Assay procedure.

- Prior to commencing the assay procedure, all reagents were prepared. It is advisable each sample and standard be applied to the Microelisa Stripplate in duplicate.
- A volume of 50 microliters of the standard was introduced into the standard well, while 10 microliters of the sample were introduced into the testing sample well before adding 40 microliters of the sample diluent. There were no additions introduced to the blank well.
- Subsequently, 100 microliters of HRP-conjugate reagent were introduced into each well, sealed with an adhesive strip, and left to incubate at 37°C for 1 h.
- Each well underwent aspiration and washing, and this process was repeated four times, resulting in a total of five thorough washes. The washing procedure included filling each well with a washing solution (400 µl) utilizing manifold dispenser, a squirt bottle, or auto washer.
- Complete liquid removal at every stage is crucial for optimum performance. After the final washing, any residual wash solution was eliminated by either aspiration or decantation. Subsequently, the plate is inverted and blotted using clean paper towels.
- Chromogen solutions B and A (50 µl for each solution) were introduced to each well. The solution is gently mixed before incubation at 37°C for 15 min and protected from light.
- Afterward, 50 µl stop solution was added to each well. The color of the wells shall be transitioned from blue to yellow. Gently tap the plate to ensure that the wells are thoroughly mixed if the color change is not uniform or the color in the wells is green. The optical density (O.D.) was determined to be red at 450 nm (within 15 min) utilizing a microtiter plate reader.
- Calculation of the results: Result calculation was done automatically.

Ethical Considerations

Prior to the commencement of the study, each participant completed a written consent that was authorized by Menoufia Faculty of Medicine's local Ethical Research Committee. Additionally, the Institutional Review Board was obtained (No.11/2022 INT.4).

Sample Size

Minimum sample size calculated is 30 participants according to community department using the following formula (24):

$$n_{Case} = n_{Non\text{-}case} \geq \frac{Z^2_{1-\alpha/2} V(AUC)}{d^2}$$

$$V(AUC) = \left(0.0099 \times e^{-a^2/2}\right) \times (6a^2 + 16)$$

$$a = Z_{AUC} \times 1.414$$

Alpha (α): Type 1 error
AUC: Estimated Area Under the ROC curve
d: Estimation error

Our study was conducted on 38 patients.

Data Analysis

The IBM SPSS software program version 20.0 was

employed to analyze the data that was entered into the computer (Armonk-NY-IBM-Corp). The qualitative data were presented using numerical values and percentages. The Shapiro-Wilk test was utilized to verify distribution normality. The quantitative data were statistically analyzed using measures such as mean, interquartile range (IQR), SD, range (minimum and maximum), and median. The level of significance was set at 5% level.

RESULTS

It was demonstrated that there were no substantial differences between the examined groups in terms of sex and age (p>0.05). There was no marked difference between the examined groups in terms of HCC, HBV, HCV and hepatorenal (p > 0.05). There was no discernible difference between the groups examined regarding creatinine. Nevertheless, the creatinine level in the AKI group exhibited a substantial increase in comparison to the non-AKI group (*table 2*).

Compared to the non-AKI group, the urea level exhibited a substantial increase in the AKI group (p < 0.001). In comparison to the non-AKI group, the AKI group exhibited a substantial increase in platelet count (p < 0.001). Nevertheless, there were no marked differences between the groups examined regarding other parameters (WBCS-HB- Bilirubin-PT). In comparison to the non-AKI group, the AKI group exhibited a substantial rise in ALT (p < 0.001). Nonetheless, no substantial difference was observed between the groups that were examined in terms of other parameters (AST- INR).

In comparison to the non-AKI group, the AKI group exhibited a substantial elevation in NGAL 2 (p < 0.001). Nevertheless, there was no discernible distinction between the groups that were examined in relation to NGAL 1 (*tables 3, 4, 5,* and *6*).

DISCUSSION

AKI is a prevalent complication among patients who undergo LT. Recent research has demonstrated that even mild or transient post-LT AKI is linked to a prolonged hospitalization or intensive care stay, diminished organ survival, and elevated mortality (15).

Table 2 - Comparison between the two studied groups according to Creatinine level before and after transplant

Creatinine (mg/dl)	Total (n = 38)	Non-AKI (n = 14)	AKI (n = 24)	U	p
Before					
Min. – Max.	0.40 – 1.20	0.40 – 1.10	0.40 – 1.20	164.500	0.917
Mean ± SD.	0.75 ± 0.22	0.74 ± 0.21	0.75 ± 0.23		
Median (IQR)	0.70 (0.60 – 0.90)	0.70 (0.60 – 0.90)	0.75 (0.60 – 0.95)		
After					
Min. – Max.	0.80 – 5.00	0.80 – 1.30	1.50 – 5.00	0.000*	<0.001*
Mean ± SD.	1.68 ± 0.79	1.00 ± 0.14	2.08 ± 0.73		
Median (IQR)	1.65 (1.10 – 1.90)	0.95 (0.90 – 1.10)	1.90 (1.70 – 2.20)		

IQR: Inter quartile range; SD: Standard deviation; U: Mann Whitney test; p: p value for comparing between the two studied groups.
*: Statistically significant at p ≤ 0.05

Table 3 - Comparison between the two studied groups according to urinary NGAL1 and NGAL2

	Total (n = 38)	Non-AKI (n = 14)	AKI (n = 24)	t	p
NGAL 1				1.511	0.140
Min. – Max.	62.60 – 85.22	63.06 – 85.22	62.60 – 82.17		
Mean ± SD.	72.82 ± 6.18	74.77 ± 6.93	71.68 ± 5.54		
Median (IQR)	71.86 (68.0 – 77.52)	75.44 (69.66 – 80.17)	71.09 (67.19 – 76.85)		
NGAL 2				2.465*	0.019*
Min. – Max.	53.25 – 84.12	53.25 – 84.12	60.98 – 81.39		
Mean ± SD.	70.76 ± 6.75	67.44 ± 7.63	72.69 ± 5.47		
Median (IQR)	71.33 (66.85 – 75.04)	68.25 (66.40 – 69.54)	73.54 (70.91 – 76.01)		

NAGAL 1: Before centrifugation of the sample; NAGAL2: After centrifugation of the sample; IQR: Inter quartile range; SD: Standard deviation; t: Student t-test; p: p-value for comparing between the two studied groups
*: Statistically significant at p ≤ 0.05

Table 4 - Diagnostic performance for NGAL 2 to discriminate AKI (n= 24) from non-AKI (n = 14)

	AUC	p	95% C. I	Cut off	Sensitivity	Specificity	PPV	NPV
NGAL 2	0.768	0.006*	0.596 – 0.940	>69.54	83.33	78.57	87.0	73.3

*: statistically significant at $p \leq 0.05$; p-value: probability value; CI: Confidence Intervals; AUC: Area Under a Curve; NPV: Negative predictive value; PPV: Positive predictive value.

Table 5 - Diagnostic performance for NGAL 2 to discriminate AKI (n= 24) from Non-AKI (n = 14)

	AUC	p	95% C. I	Cut off	Sensitivity	Specificity	PPV	NPV
NGAL 2	0.768	0.006*	0.596 – 0.940	> 69.54	83.33	78.57	87.0	73.3
eGFR	1.000	< 0.001*	1.0 – 1.0	≤ 56	100.0	100.0	100.0	100.0
Creatinine after transplantation	1.000	< 0.001*	1.0 – 1.0	> 1.3	100.0	100.0	100.0	100.0

Table 6 - Univariate and multivariate Logistic regression analysis for the parameters affecting AKI (n = 24) from Non-AKI (n = 14)

	Univariate		#Multivariate	
	p	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
Sex (Female)	0.286	3.421(0.357 – 32.783)	-	-
Age	0.295	1.046(0.962 – 1.137)	-	-
HBV	0.265	0.333(0.048 – 2.297)	-	-
HCV	0.810	0.833(0.189 – 3.670)	-	-
HCC	0.617	0.633(0.106 – 3.801)	-	-
Hepatorenal	0.999	–	-	-
Creatinine Before	0.877	1.271(0.061 – 26.441)	-	-
Creatinine After	0.991	–	-	-
Urea	0.006*	1.116(1.032 – 1.207)	0.106	1.438(0.926 – 2.232)
eGFR	0.992	–	-	-
Hb	0.589	0.860(0.498 – 1.485)	-	-
WBC	0.072	1.095(0.992 – 1.210)	-	-
PLT (103)	0.003*	1.036(1.012 – 1.060)	0.094	1.029(0.995 – 1.064)
AST	0.587	1.001(0.996 – 1.007)	-	-
ALT	0.011*	1.023(1.005 – 1.041)	0.150	1.095(0.968 – 1.240)
INR	0.710	0.820(0.287 – 2.340)	-	-
NGAL 1	0.141	0.917(0.818 – 1.029)	-	-
NGAL 2	0.033*	1.144(1.011 – 1.296)	0.146	1.565(0.856 – 2.860)

OR: Odd's ratio; C.I: Confidence interval; LL: Lower limit; UL: Upper Limit; #: All variables with p<0.05 were included in the multivariate; *: Statistically significant at $p \leq 0.05$; Hosmer and Lemeshow Test = χ^2(p)= 0.889(0.996).

The literature on AKI occurrence following LT shows a wide range of incidence rates, ranging from 14% to 97% (15). Our unit's review of liver transplant outcomes revealed a post-transplant incidence of AKI of 50%, with 24% of patients necessitating Renal Replacement Therapy (RRT) (16).

Numerous biomarkers indicating early kidney injury have been identified. While these new biomarkers for AKI have previously been evaluated in general intensive-care populations, they have also been used in LT recipients (16). The small, secreted polypeptide known as NGAL is increased in response to tubular damage and can be immediately detected in both plasma and urine. Plasma NGAL is a more accurate predictor of AKI than serum creatinine within 24 hours following LT (17).

Further investigations with a limited number of patients have shown that plasma NGAL may identify post-LT AKI as early as 1–2 h following reperfusion (17, 18).

Prior research examining the function of UNGALs following LT has been limited by the difficulty of obtaining urine samples from individuals with anuria during the transplantation procedure (18).

The present investigation included the collection of recently obtained urine samples from all participants. Our objective was to evaluate the significance of NGAL in the prediction of AKI following LT. A randomized, prospective, double-blinded study was carried out on 38 patients evaluated for AKI following LT.

Following transplantation, patients were divided into two cohorts. The first group consisted of 24 patients who were diagnosed with AKI following LT, whereas the second group included 14 individuals who did not have AKI following LT. The current investigation revealed no statistically significant differences among the examined groups in terms of sex, age, HCC, HCV, HBV, hepatorenal, and creatinine levels prior to transplantation.

Consequently, no secondary variables may influence the scope of our findings. Utilizing Cr in AKI diagnosis was shown to be very beneficial, considering its enhanced accuracy as the severity of postoperative AKI escalated (18).

The current investigation demonstrated a significant elevation in creatinine levels and urea in the AKI group as compared to the non-AKI group. Nevertheless, eGFR was substantially reduced. The obtained result is consistent with the findings of Mogawer et al., who demonstrated a statistically significant rise in average serum Cr levels on days 1, 3, and 7 following surgery as compared to three months following surgery (19).

Furthermore, our findings indicate a substantial rise in platelet levels in the AKI group compared to the non-AKI group ($p< 0.001$). Nevertheless, no substantial differences were detected among the examined groups regarding other indicators (WBCS-HB- Bilirubin - PT). This finding is consistent with other studies since increasing evidence indicates that platelets contribute to AKI progression (20).

This research demonstrated that urine NGAL levels, measured on LT completion, may precisely identify individuals who develop AKI. For cut-off values >69.54, NGAL2 demonstrated a substantial AUC that could distinguish between AKI and non-AKI.

The univariate analysis of this research revealed significant outcomes for blood urea level, platelet count, ALT, and NGAL2. However, no other parameters demonstrated relevance in the multivariate analysis. Furthermore, our findings indicate that NGAL2 in the AKI as well as non-AKI groups had a notable positive association with creatinine levels and a negative association with eGFR. Nevertheless, in the non-AKI group, NGAL2 had an inverse relationship with platelets. An ROC curve was constructed for the assessment of the diagnostic accuracy of NGAL2 in detecting AKI following LT. After LT, NGAL2, eGFR, and creatinine demonstrated substantial AUC in diagnosing AKI at cut-off values of >699.5, <56, and >1.3, respectively.

Previous research has shown the capacity of early markers for kidney injury, like NGAL, to identify AKI at early stages (21).

Nieman et al.reported that PNGAL levels exceeding 139 ng/ml following portal reperfusion were a reliable indicator of AKI progression (AUC = 0.79) (21,22).

UNGAL values obtained during portal reperfusion and 6 hours postoperatively were strong indicators of AKI within seven days (AUC values = 0.67 and 0.76), respectively. Previous investigations have revealed that individuals who experienced AKI had notably elevated levels of uNGAL (23).

AKI was observed in 487 patients (19.2%) in the meta-analysis by Haase et al., encompassing 19 trials and 2538 patients. NGAL was demonstrated to be a robust predictor of AKI, with an odds ratio (OR) of 18.6 and an AUC of 0.81. Analyzing many populations, the most effective threshold value identified in those studies ranged from 100 to 270 ng/ml. The authors suggested 150 ng/ml as a value for AKI diagnosis (23).

Conversely, Marcelino et al. found no substantial variation in absolute NGAL values (23).

CONCLUSION

The results of this research demonstrate that UNGAL levels measured on LT completion can accurately identify patients who develop AKI with a sensitivity and specificity of 83.33 and 78.57, respectively, as well as serum creatinine and eGFR with 100% specificity and sensitivity.

Following LT, AKI was observed in 63.16% of patients (24 out of 38) in our investigation. This was attributed to the following:

- Massive blood transfusion and acute blood loss.
- Acute portal vein thrombosis and hepatic artery thrombosis.
- Nephrotoxic and immunosuppressive drugs.

Recommendations:

- Further investigations with a substantial sample size should be performed to validate our findings.
- Accurate prediction of AKI following LT is of paramount significance for patient outcomes in specialist transplant centers. In addition to urine NGAL, serum NGAL is a significant biomarker utilized for this purpose. The significance of serum NGAL in evaluating AKI expands beyond liver transplants to include other organ transplantations as well.

- It is advisable to refrain from using nephrotoxic drugs. Early administration of antibiotics is crucial in patients with any bacterial infection. Diuretics must be used cautiously and terminated even in the case of a slight elevation in serum creatinine levels. Additionally, we suggest ensuring optimal hemostatic stability in patients pre-, intra-, and post-operatively.

Conflict of Interests

No there is no conflict of interest.

Funds: no funds.

Ethical Approval

Prior to the commencement of the study, each participant completed a written consent that was authorized by Menoufia Faculty of Medicine's local Ethical Research Committee. Additionally, the Institutional Review Board was obtained [No.11/ 2022INT.4].

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