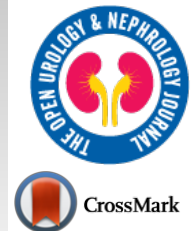




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## RESEARCH ARTICLE

### Urine Neutrophil Gelatinase-Associated Lipocalin Measured at Admission to Predict Recovery from Acute Kidney Injury of Vietnamese ICU Patients

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#### Abstract:

#### Aims:

To evaluate the predictive value of urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) measured at the time of admission during the recovery from Acute Kidney Injury (AKI) after 90 days.

#### Materials and Methods:

This study includes 101 adult patients admitted to the Intensive Care Unit (ICU) who were diagnosed as AKI (96 patients had been collected 24-hour urine and 5 patients with anuria). Acute kidney injury was diagnosed using the Acute Kidney Injury Network (AKIN) criteria. Urine NGAL was measured at admission using the BioVendor Human Lipocalin-2/NGAL ELISA.

#### Results:

The ratio of complete recovery patients after 90 days reached 71.9%. The mean of urine NGAL concentration in the recovery group was 242.04 ng/ml, lower significantly than that of non-recovery patients (371.1 ng/ml),  $p=0.007$ . At the cut-off value for 740.03 ng/ml, urine NGAL measured at admission predicted complete recovery with the area under the curve of ROC for urine NGAL = 0.888,  $p<0.001$ . Based on the multivariate regression analysis, serum urea, serum creatinine and urine NGAL were independent factors that effected the proportion of recovery in AKI patients (OR=0.856,  $p=0.023$ ; OR=1.014,  $p=0.012$  and OR=0.993,  $p<0.001$ , respectively).

#### Conclusion:

Serum urea, serum creatinine and urine NGAL were independent factors that effected the proportion of recovery in AKI patients. Urine NGAL in AKI patients measured at the time of the admission time to ICU can be used as a prognostic biomarker of recovery.

**Keywords::** AKI, SA-AKI, Urine NGAL, Recovery, ICU, Neutrophil.

#### Article History

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## 1. INTRODUCTION

The incidence of Acute Kidney Injury (AKI) in all hospitalized patients is nearly 7% [1]. In ICU patients, the overall mortality of AKI patients requiring renal replacement

therapy is about 60.3% [2]. AKI leads to an alarming increase in morbidity and mortality as well as is a major risk factor for the development of complications [3]. There are many causes of AKI in patients who are treated at ICU, in which sepsis is a common cause and accounts for a high proportion [4 - 10]. Although acute kidney damage is caused by various factors, however, histopathological images show that acute renal tubular lesions are common ones [9, 11 - 14]. Lipocalin-related

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neutrophil gelatinase (NGAL) is normally secreted from renal tubular cells in low concentrations. Cell apoptosis occurs after epithelial cell damage, leading to an increase of NGAL expression from renal tubular epithelial cells into the urine [15]. Several studies have shown that NGAL is elevated after ischemic or nephrotoxic injury [4, 8, 16, 17] and therefore, it can be detected in the plasma and urine of AKI patients [15, 17]. The quick recovery of renal function in patients with acute kidney injury is a requirement in treatment. The slower the kidney function recovery, the higher the risk of turning into chronic kidney disease. Therefore, the prognostic factors for renal function recovery in patients with acute kidney injury have been mentioned by many studies [18 - 22]. Urine NGAL is known as a prognostic factor for outcomes and mortality in AKI patients [23 - 25], but the role of urine NGAL at admission to predict renal recovery from AKI is not actually mentioned by many studies.

## 2. MATERIALS AND METHODS

### 2.1. Study Design and Setting

We conducted a prospective study on 101 AKI patients who were admitted to the Intensive Care Unit (ICU), in which 96 patients have urine output and 5 anuria patients. Patients less than 16 years old, with chronic kidney disease, organ transplantation, malignancy, pregnancy and patients who have stayed in ICU for < 48 h were excluded from our study.

Some medical conditions such as diabetes mellitus, hypertension, liver disease, surgical treatment and presence of sepsis were noted. The Sequential Organ Failure Assessment (SOFA) score was used to define Single Organ Failure (SOF) and Multiple Organ Failure (MOF) [26]. SOFA score > 3 in a particular organ was defined as SOF and two or more organs failure were confirmed as MOF (Table 1) [27].

**Table 1. Definitions of Single Organ Failure.**

| Organ                  | Definition   |
|------------------------|--|
| Liver Failure          | SOFA $\geq 3$ (serum bilirubin $\geq 6$ mg/dL) or Maddrey's DF $> 32$  |
| Renal Failure          | Defined as AKI, according to the Acute Kidney Injury Network criteria  |
| Nervous system failure | SOFA $\geq 3$ (Glasgow Coma Scale $\leq 9$ )   |
| Respiratory failure    | SOFA $\geq 3$ (PaO <sub>2</sub> /FiO <sub>2</sub> $< 200$ and mechanically ventilated)                               |
| Circulatory failure    | SOFA $\geq 3$ (use of norepinephrine, epinephrine, or dopamine [dopamine $> 5$ $\mu\text{g}/\text{kg}/\text{min}$ ]) |
| Coagulation failure    | SOFA $\geq 3$ (platelet count $< 50,000/\mu\text{L}$ )   |

SOFA: Sequential Organ Failure Assessment

### 2.2. Definitions

Acute kidney injury was defined following Acute Kidney Injury Network (AKIN) criteria [7]: Absolute increase in serum creatinine  $\geq 0.3$  mg/dL ( $\geq 26.4$   $\mu\text{mol}/\text{L}$ ) and/or oliguria (urine output  $< 0.5$  mL/kg per hour) for  $> 6$  hours. Patients were classified as sepsis-associated acute kidney injury (SA-AKI) or non-SA-AKI. The severity of AKI was divided into 3 stages that depend on Serum Creatinine concentration (SCr).

Complete recovery from AKI was defined based on the criteria of Acute Disease Quality Initiative (ADQI) after 90 days [28, 29].

### 2.3. Laboratory Measurements

Some biochemical indices such as blood urea, SCr and serum electrolytes were measured at admission. SCr was measured daily thereafter. The steady level of creatinine at 4 weeks before admission or the lowest SCr during hospitalization was estimated to define baseline SCr.

### 2.4. Collecting 24h Urine and Determine the Level of Urine NGAL

At the time of admission, patient's blood was taken for testing and was given a catheter to collect urine for 24 hours. After 24 hours, the volume of urine was measured, taking 5 ml of urine to determine NGAL level and then calculate the 24-hour urine NGAL concentration. Urine NGAL was measured by ELISA method using BioVendor Human Lipocalin-2/NGAL kit.

### 2.5. Study Outcomes

During the study, we followed up the proportion of AKI suffering during hospitalization as well as the proportion of recovery and hospital mortality in AKI patients.

### 2.6. Statistical Analyses

Continuous variables are described as mean and standard deviations. Compare two or more average values using t-test or ANOVA's test. Categorical data are described in terms of the frequency with percentage and are analyzed by the Chi-square test. ROC curve model is used to evaluate the prognostic value of urine NGAL in the recovery of AKI patients. Multivariate regression analysis was performed to identify the predictors of AKI recovery after 90 days. Kaplan–Meier analysis was done in the study. Statistical analysis was done using Statistical Package for Social Science (SPSS) version 20.0 (Chicago, IL, USA). A *p*-value  $< 0.05$  was considered significant.

## 3. RESULTS

The baseline demographic and laboratory characteristics in AKI patients were shown in Table 2. The mean age of AKI patients was  $64.94 \pm 17.3$  years old, 60.4% were male, 26% was diabetes, 57.3% was sepsis, and 27.1% was MOF. After 90 days, the ratio of complete recovery from AKI was 71.9%. There were no differences of age, sex, anemia, diabetes, hypertension serum creatinine, ratio of sepsis and MOF between recovery and non-recovery patients with *p*  $> 0.05$ . However, the level of serum urea and ratio of oliguria of non-recovery patients were significantly higher than those of recovery ones, *p*  $< 0.05$  (Table 3). The mean concentration of urine NGAL (ng/ml) was significantly higher in non-recovery patients as compared to the complete recovery patients (371.1 compared with 242.04, *p*  $< 0.01$ ) (Table 3). Logistic regression analysis that helps to identify the independent risk factors of recovery was shown in Table 4. Serum urea, serum creatinine and urine NGAL at the admission were independent risk factors (*p* = 0.023; 0.012 and  $< 0.001$  respectively).

**Table 2. Baseline demographic and laboratory characteristics of patients (n=96).**

| Clinical Characteristics and Laboratory Parameters | Mean ± SD/ Median        | N,%       |
|--|--------------------------|-----------|
| Ages   | 64.94 ± 17.3             | N/A       |
| Number of male (n,%)                               | N/A                      | 58 (60.4) |
| Diabetes (n,%)                                     | N/A                      | 25 (26)   |
| Hypertension (n,%)                                 | N/A                      | 20 (20.8) |
| Anemia (n,%)                                       | N/A                      | 53 (55.2) |
| Blood urea (mmol/l)                                | 10.35 (8.02 – 17.2)      | N/A       |
| Serum creatinine (µmol/l)                          | 175 (151 – 243.5)        | 96 (100)  |
| - Stage I  | 160.5 (148 – 180.75)     | 68 (70.8) |
| - Stage II   | 274 (247 – 318)          | 21 (21.9) |
| - Stage III  | 466 (435 – 547)          | 7 (7.3)   |
| Cause of AKI                                       | N/A                      | 55 (57.3) |
| - Sepsis   |                          | 41 (42.7) |
| - Non-Sepsis                                       |                          |           |
| MOF (n,%)  | N/A                      | 26 (27.1) |
| Oliguria (n,%)                                     | N/A                      | 31 (32.3) |
| Urine NGAL (ng/ml)                                 | 292.97 (135.65 – 691.25) | N/A       |
| Duration of ICU stay (days)                        | 9 (5 – 14)               | N/A       |
| Recovery from AKI (n,%)                            | N/A                      | 69 (71.9) |
| Non-recovery from AKI (n,%)                        | N/A                      | 27 (29.1) |
| - Mortality  |                          | 16 (16.7) |
| - CKD  |                          | 11 (11.4) |

AKI: Acute Kidney Injury, MOF: Multiple Organ Failure, NGAL: Neutrophil gelatinase-associated Lipocalin, ICU: Intensive Care Unit, CKD: Chronic Kidney Disease.

**Table 3. Comparison of laboratory parameters in recovery and Non-recovery patients.**

| Clinical Characteristics and Laboratory Parameters | Recovery (n=69)          | Non-Recovery (n=27)     | p      |
|--|--------------------------|-------------------------|--------|
| Ages   | 64.72 ± 17.44            | 65.48 ± 17.26           | 0.848  |
| Number of male (n,%)                               | 40 (58)                  | 18 (66.7)               | 0.433  |
| Diabetes (n,%)                                     | 20 (29)                  | 5 (18.5)                | 0.293  |
| Hypertension (n,%)                                 | 14 (20.3)                | 6 (22.2)                | 0.834  |
| Anemia (n,%)                                       | 39 (56.5)                | 14 (51.9)               | 0.679  |
| Blood ure (mmol/l)                                 | 9.5 (7.85 – 14.35)       | 17 (9 – 25.8)           | 0.004* |
| Serum creatinine (µmol/l)                          | 167 (150 – 233)          | 183 (162 – 334)         | 0.061  |
| Cause of AKI                                       |                          |                         |        |
| - Sepsis   | 36 (52.2)                | 19 (70.4)               | 0.105  |
| - Non-Sepsis                                       | 33 (47.8)                | 8 (29.6)                |        |
| MOF (n,%)  | 16 (23.2)                | 10 (37.0)               | 0.170  |
| Oliguria (n,%)                                     | 18 (26.1)                | 13 (48.1)               | 0.038* |
| Urine NGAL (ng/ml)                                 | 242.04 (124.57 – 569.88) | 371.1 (222.29 – 917.05) | 0.007* |

AKI: Acute Kidney Injury, MOF: Multiple Organ Failure, NGAL: Neutrophil gelatinase-associated Lipocalin, \* Statistical significance.

**Table 4. Result of multivariate logistic regression analysis showing predictors of recovery from AKI.**

| Variable                               | Odds Ratio | 95% CI         | p       |
|--|------------|----------------|---------|
| Age <60                                | 0.586      | 0.124 – 2.756  | 0.498   |
| Male                                   | 0.707      | 0.173 – 2.89   | 0.629   |
| Non-Anemia                             | 1.984      | 0.346 – 11.369 | 0.442   |
| Non – Sepsis                           | 3.409      | 0.563 – 20.644 | 0.182   |
| Non – Oliguria                         | 1.822      | 0.379 – 8.763  | 0.454   |
| Non - MOF                              | 1.739      | 0.335 – 9.019  | 0.51    |
| Serum urea (mmol/l)                    | 0.856      | 0.749 – 0.978  | 0.023*  |
| Serum Creatinine at admission (µmol/l) | 1.014      | 1.003 – 1.024  | 0.012*  |
| Urine NGAL (ng/ml)                     | 0.993      | 0.989 – 0.996  | <0.001* |

AKI: Acute Kidney Injury, MOF: Multiple Organ Failure, NGAL: Neutrophil gelatinase-associated Lipocalin, \* Statistical significance.

Fig. (1) showed the ROC curve for urine NGAL to predict recovery from AKI patients. Area Under the Curve (AUC) was 0.888 ( $p = 0.001$ ) and cut-off value was 740.03 ng/ml. This test had a sensitivity of 97.1% and the specificity of 70.4%.

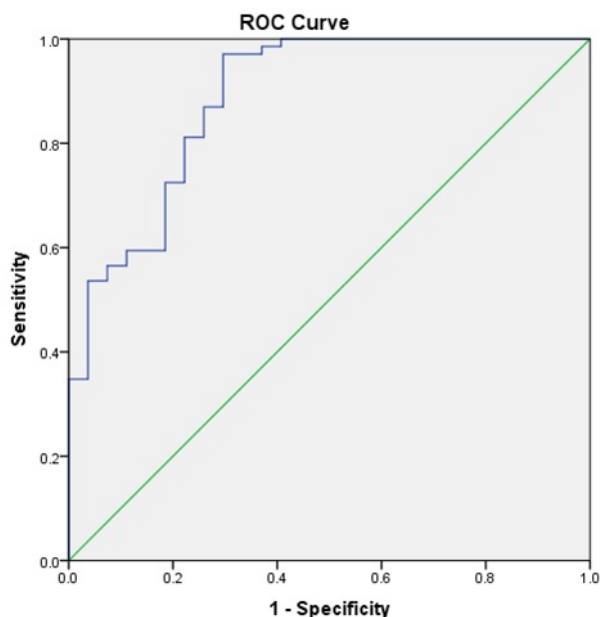


Fig. (1). Receiver Operating Characteristics (ROC) curves for prediction of recovery from AKI.

Based on the concentration of urinary NGAL, we divided all patients into 2 equal subgroups (patients with urine NGAL  $< 292.97$  ng/ml and  $\geq 292.97$  ng/ml). Serum urea and creatinine concentration in a group of higher uNGAL concentration were significantly higher than that in group of lower uNGAL ( $p = 0.019$  and  $< 0.001$ , respectively). The group of lower uNGAL concentration had a lower proportion of oliguria and a higher proportion of recovery than that in group of higher uNGAL concentration ( $p = 0.016$  and  $< 0.001$ , respectively).

#### 4. DISCUSSION

Previously, the severity of AKI was graded by RIFLE criteria based on the change of serum creatinine and urine output [30]. However, the Acute Kidney Injury Network (AKIN) modified these criteria with a small change in serum creatinine concentration to diagnose AKI stage I ( $\geq 26.5$   $\mu\text{mol/L}$  from baseline within 48 h) [7]. With this adjustment, the sensitivity of AKI diagnostic has been improved. Nowadays, AKI is mostly diagnosed by increasing serum creatinine which can be affected by various factors. Serum creatinine only rises when more than half of renal function has been lost [30].

Various studies had shown that serum and urine NGAL were reliable biomarkers for the prediction of AKI [15, 31], especially in patients after cardiac or non-cardiac surgery [8, 32, 33], kidney transplantation [34], trauma [35] and IgA nephropathy [36]. There are many different diagnostic criteria for early diagnosis of AKI, including tests to assess kidney function such as serum creatinine. However, creatinine does not help eliminate acute kidney failure from other kidney failure conditions. Another solution is the serum and urine NGAL. The advantage of NGAL is to reflect the status of

damaged kidney function in real-time and it can be used to examine the progressive kidney disease [37].

There are a lot of studies which indicated an early diagnostic and predictive value of urine NGAL in patients with AKI. However, in our study, we looked at the value of urine NGAL at the time of admission to predict recovery when NGAL had not been affected by the treatment. We used urine test to measure NGAL concentration instead of blood because urinary diagnostics is noninvasive method and do not be affected by serum protein status.

In recent decades, although there have been many studies using urine NGAL to predict outcome and mortality in patients with acute renal injury, however, few studies have used urinary NGAL to predict the complete recovery of renal function after 90 days. Yet, acute kidney failure is sometimes defined as an acute increase in creatinine. However, the introduction of Acute Kidney Injury (AKI) has contributed to alerting clinicians with appropriate management behavior, avoiding severe complications of acute renal failure. There have been many studies showing that recurrent kidney damage will lead to chronic kidney failure and must depend on hemodialysis. We followed AKI patients after 90 days of admission, reassessing kidney function by re-quantifying creatinine levels every month. The diagnostic criteria for complete recovery are the patient's serum creatinine concentration returning to the baseline creatinine level without any treatment methods. We had 69 patients (in total 96 patients) with a complete recovery from AKI. When comparing factors related to renal function recovery, we found that only 3 factors i.e urea concentration, oliguria and urine NGAL concentration are related factors, in which urine NGAL is the most closely related factor. Thus, it is possible to use NGAL as the best predictor of recovery of AKI patients. Using the ROC curve, we found that the point of cutting urine NGAL concentration is 740.03 ng/ml, which had valuable prognosis recovery in our study (Fig. 1).

Septic AKI is one of the most common problems in ICU patients. We had 55 patients (57.3%) diagnosed as SA-AKI in which sepsis patients had all sources of infection such as lung infection, urinary infection, abdomen infection, etc. Our result was similar to the study of Bagshaw SM *et al.* [38], with 51.8% (43/83 patients). In patients with sepsis, there are various factors that contribute important roles in the formation of AKI including both hemodynamic and nonhemodynamic factors [39]. In contrast, non-sepsis AKI patients included all causes of AKI such as hypovolemia, impaired cardiac function, renal ischemia, nephrotoxic drugs, glomerular damage, intrarenal and extrarenal obstruction. In Table 4, we created a multivariate logistic regression to identify various factors that affected the recovery in patients with AKI. We realized that serum urea, serum creatinine and urine NGAL were independent factors that effected the proportion of recovery in AKI patients (OR=0.856,  $p=0.023$ ; OR=1.014,  $p=0.012$  and OR=0.993,  $p<0.001$  respectively). For further assessment of the role of urine NGAL, increasing the characteristics of acute renal failure, we divided patients into two equal groups: one group of lower urine NGAL levels and one group of higher urine NGAL levels. Our results showed that group of higher urine NGAL levels had a higher concentration of serum urea and creatinine, higher proportion of oliguria and lower proportion of recovery than that in group of lower uNGAL levels (Table 5).

**Table 5. Baseline characteristics of the AKI patients according to urine NGAL concentrations.**

| Clinical Characteristics and Laboratory Parameters | Lower Group (uNGAL < 292.97 ng/ml), n= 48 | Higher Group (uNGAL ≥ 292.97 ng/ml), n= 48 | <i>p</i> |
|--|---|--|----------|
| Ages   | 67.04 ± 15.5426                           | 62.83 ± 18.83                              | 0.236    |
| Number of male (n,%)                               | 28 (58.3)                                 | 30 (62.5)                                  | 0.676    |
| Diabetes (n,%)                                     | 15 (31.3)                                 | 10 (20.8)                                  | 0.245    |
| Hypertension (n,%)                                 | 12 (25)                                   | 8 (16.7)                                   | 0.315    |
| Anemia (n,%)                                       | 30 (62.5)                                 | 23 (47.9)                                  | 0.151    |
| Blood ure (mmol/l)                                 | 9.2 (7.2 – 14.4)                          | 12.75 (9 – 20.95)                          | 0.019*   |
| Serum creatinine (μmol/l)                          | 152.5 (144.75 – 177.75)                   | 203.5 (169.25 – 261.75)                    | <0.001*  |
| Cause of AKI                                       |   |  |          |
| - Sepsis   | 25 (52.1)                                 | 30 (62.75)                                 | 0.302    |
| - Non-Sepsis                                       | 23 (47.9)                                 | 18 (37.5)                                  |          |
| MOF (n,%)  | 9 (18.8)                                  | 17 (35.4)                                  | 0.066    |
| Oliguria (n,%)                                     | 10 (20.8)                                 | 21 (43.8)                                  | 0.016*   |
| Recovery (n,%)                                     | 43 (89.6)                                 | 26 (54.2)                                  | < 0.001* |

AKI: Acute Kidney Injury, MOF: Multiple Organ Failure, NGAL: Neutrophil gelatinase-associated Lipocalin, \* Statistical significance. Urine NGAL: AUC =0.888, *p* = 0.001 (Cut-off value = 740.03 ng/ml), Se=97.1%, Spe=70.4%

## CONCLUSION

In conclusion, serum urea, serum creatinine and urine NGAL were independent factors that effected the proportion of recovery in AKI patients. Urine NGAL in AKI patients measured at the time of admission to ICU can be used as a prognostic biomarker of recovery.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethical Committee of Vietnam Military Medical University (No. 2890/QĐ/HVQY).

## HUMAN AND ANIMAL RIGHTS

Animals did not participate in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008.

## CONSENT FOR PUBLICATION

Informed consent was obtained from all the participants.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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