1874-303X/19 *Send Orders for Reprints to reprints@benthamscience.net*

60

The Open Urology & Nephrology Journal

Content list available at: https://openurologyandnephrologyjournal.com

RESEARCH ARTICLE

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

Le V. Thang[1], Nguyen T. Kien[1,*], Pham N. H. Tuan[5], Nguyen T. T. Dung[1], Truong Q. Kien[1], Do M. Ha[1], Pham Q. Toan[1], Nguyen T. T. Ha[1], Diem T. Van[1], Nguyen Van Duc[1], Vu X. Nghia[2], Nguyen H. Dung[3], Nguyen T. T. Huong[4], Hoang T. Vinh[1] and Le T. Ha[6]

[1]*Military Hospital 103, Ha Noi, Viet Nam*
[2]*Vietnam Military Medical University, Ha Noi, Viet Nam*
[3]*Bach Mai Hospital, Ha Noi, Viet Nam*
[4]*Ha Noi Kidney Hospital, Ha Noi, Viet Nam*
[5]*Trung Vuong Hospital, Ho Chi Minh, Viet Nam*
[6]*108 Military Central Hospital, Ha Noi, Viet Nam*

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	Received: May 28, 2019	Revised: September 19, 2019	Accepted: September 20, 2019

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

* Address correspondence to this author at the Department of Hematology and Blood Transfusion, Military Hospital 103, Vietnam Military Medical University, 261 Phung Hung, Ha Dong, Ha Noi, Vietnam; Tel: +84835773357;
E-mail: bs.ntkien@gmail.com

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 ≥3 (serum bilirubin ≥ 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 ≥3 (Glasgow Coma Scale ≤9)
Respiratory failure	SOFA ≥3 (PaO2/FiO2 <200 and mechanically ventilated)
Circulatory failure	SOFA ≥3 (use of norepinephrine, epinephrine, or dopamine [dopamine >5 μg/kg/min])
Coagulation failure	SOFA ≥3 (platelet count <50,000/μL)

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 ≥0.3 mg/dL (≥26.4 μmol/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 ± 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) - Stage I - Stage II - Stage III	175 (151 – 243.5) 160.5 (148 – 180.75) 274 (247 – 318) 466 (435 – 547)	96 (100) 68 (70.8) 21 (21.9) 7 (7.3)
Cause of AKI - Sepsis - Non-Sepsis	N/A	55 (57.3) 41 (42.7)
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,%): - Mortality - CKD	N/A	27 (29.1) 16 (16.7) 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 - Non-Sepsis	36 (52.2) 33 (47.8)	19 (70.4) 8 (29.6)	0.105
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%.

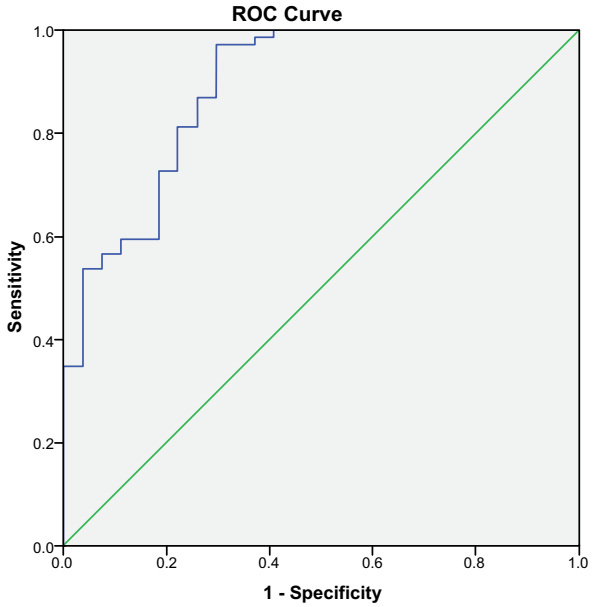

Fig. (1). Receiver Operating Characteristics (ROC) curves for prediction of recovery from AKI.

Based on the concentration of urinary NGAL, we divided all patients into 2 equal subgroups (patients with urine NGAL < 292.97 ng/ml and ≥ 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 (≥26.5 μmol/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	*p*
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 - Non-Sepsis	25 (52.1) 23 (47.9)	30 (62.75) 18 (37.5)	0.302
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.

ACKNOWLEDGEMENTS

In this study, we had been strongly supported by clinical application funding of our local hospital and university to complete our research.

REFERENCES

[1] Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002; 39(5): 930-6. [PubMed]. [http://dx.doi.org/10.1053/ajkd.2002.32766] [PMID: 11979336]

[2] Uchino S, Kellum JA, Bellomo R, *et al.* Beginning and ending supportive therapy for the kidney (BEST Kidney) investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294(7): 813-8. [PubMed]. [http://dx.doi.org/10.1001/jama.294.7.813] [PMID: 16106006]

[3] Chertow GM, Soroko SH, Paganini EP, *et al.* Mortality after acute renal failure: Models for prognostic stratification and risk adjustment. Kidney Int 2006; 70(6): 1120-6. [PubMed]. [http://dx.doi.org/10.1038/sj.ki.5001579] [PMID: 16850028]

[4] Khatami MR, Sabbagh MR, Nikravan N, *et al.* The role of neutrophil-gelatinase-associated lipocalin in early diagnosis of contrast nephropathy. Indian J Nephrol 2015; 25(5): 292-6. [http://dx.doi.org/10.4103/0971-4065.147370] [PMID: 26628795]

[5] Lameire NH, Vanholder RC, Van Biesen WA. How to use biomarkers efficiently in acute kidney injury. Kidney Int 2011; 79(10): 1047-50. [http://dx.doi.org/10.1038/ki.2011.21] [PMID: 21527944]

[6] Lewington AJ, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: A global perspective of a silent killer. Kidney Int 2013; 84(3): 457-67. [http://dx.doi.org/10.1038/ki.2013.153] [PMID: 23636171]

[7] Mehta RL, Kellum JA, Shah SV, *et al.* Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11(2): R31. [http://dx.doi.org/10.1186/cc5713] [PMID: 17331245]

[8] Mishra J, Dent C, Tarabishi R, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005; 365(9466): 1231-8. [http://dx.doi.org/10.1016/S0140-6736(05)74811-X] [PMID: 15811456]

[9] Aslan A, van den Heuvel MC, Stegeman CA, *et al.* Kidney histopathology in lethal human sepsis. Crit Care 2018; 22(1): 359. [http://dx.doi.org/10.1186/s13054-018-2287-3] [PMID: 30591070]

[10] Thang LV, Tuan PNH, Kien NT, *et al.* Serum neutrophil gelatinase-associated lipocalin measured at admission to predict mortality in sepsis-associated acute kidney injury of Vietnamese critically ill patients. Open Urol Nephrol J 2018; 11: 100-8. [http://dx.doi.org/10.2174/1874303X01811010100]

[11] Martin-Sanchez D, Ruiz-Andres O, Poveda J, *et al.* Ferroptosis, but not necroptosis, is important in nephrotoxic folic acid-induced AKI. J Am Soc Nephrol 2017; 28(1): 218-29. [http://dx.doi.org/10.1681/ASN.2015121376] [PMID: 27352622]

[12] Glassford NJ, Skene A, Guardiola MB, *et al.* Interobserver agreement for post mortem renal histopathology and diagnosis of acute tubular necrosis in critically ill patients. Crit Care Resusc 2017; 19(4): 337-43. [PMID: 29202260]

[13] Langenberg C, Bagshaw SM, May CN, Bellomo R. The

histopathology of septic acute kidney injury: A systematic review. Crit Care 2008; 12(2): R38.
[http://dx.doi.org/10.1186/cc6823] [PMID: 18325092]

[14] Kiss N, Hamar P. Histopathological evaluation of contrast-induced acute kidney injury rodent models. BioMed Res Int 2016; 20163763250 [Review].
[http://dx.doi.org/10.1155/2016/3763250] [PMID: 27975052]

[15] Devarajan P. NGAL for the detection of acute kidney injury in the emergency room. Biomarkers Med 2014; 8(2): 217-9.
[http://dx.doi.org/10.2217/bmm.13.149] [PMID: 24521016]

[16] Ahn JY, Lee MJ, Seo JS, Choi D, Park JB. Plasma neutrophil gelatinase-associated lipocalin as a predictive biomarker for the detection of acute kidney injury in adult poisoning. Clin Toxicol (Phila) 2016; 54(2): 127-33.
[http://dx.doi.org/10.3109/15563650.2015.1118487] [PMID: 26683351]

[17] Mishra J, Ma Q, Prada A, *et al.* Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003; 14(10): 2534-43.
[http://dx.doi.org/10.1097/01.ASN.0000088027.54400.C6] [PMID: 145 14731]

[18] Srisawat N, Murugan R, Kellum JA. Repair or progression after AKI: A role for biomarkers? Nephron Clin Pract 2014; 127(1-4): 185-9.
[http://dx.doi.org/10.1159/000363254] [PMID: 25343847]

[19] Nie S, Feng Z, Xia L, *et al.* Risk factors of prognosis after acute kidney injury in hospitalized patients. Front Med 2017; 11(3): 393-402.
[http://dx.doi.org/10.1007/s11684-017-0532-9] [PMID: 28493198]

[20] Bouchard J, Acharya A, Cerda J, *et al.* A prospective international multicenter study of AKI in the intensive care unit. Clin J Am Soc Nephrol 2015; 10(8): 1324-31.
[http://dx.doi.org/10.2215/CJN.04360514] [PMID: 26195505]

[21] Jung HY, Lee JH, Park YJ, *et al.* Duration of anuria predicts recovery of renal function after acute kidney injury requiring continuous renal replacement therapy. Korean J Intern Med (Korean Assoc Intern Med) 2016; 31(5): 930-7.
[http://dx.doi.org/10.3904/kjim.2014.290] [PMID: 26867084]

[22] Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after Acute Kidney Injury (AKI): What is the role of baseline kidney function and recovery? A systematic review. BMJ Open 2015; 5(1)e006497
[http://dx.doi.org/10.1136/bmjopen-2014-006497] [PMID: 25564144]

[23] Bennett M, Dent CL, Ma Q, *et al.* Urine NGAL predicts severity of acute kidney injury after cardiac surgery: A prospective study. Clin J Am Soc Nephrol 2008; 3(3): 665-73.
[http://dx.doi.org/10.2215/CJN.04010907] [PMID: 18337554]

[24] Schley G, Köberle C, Manuilova E, *et al.* Comparison of plasma and urine biomarker performance in acute kidney injury. PLoS One 2015; 10(12)e0145042
[http://dx.doi.org/10.1371/journal.pone.0145042] [PMID: 26669323]

[25] Nga HS, Medeiros P, Menezes P, Bridi R, Balbi A, Ponce D. Sepsis and AKI in clinical emergency room patients: The role of urinary NGAL. BioMed Res Int 2015; 2015413751
[http://dx.doi.org/10.1155/2015/413751] [PMID: 26266256]

[26] Vincent JL, Moreno R, Takala J, *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22(7): 707-10.
[http://dx.doi.org/10.1007/BF01709751] [PMID: 8844239]

[27] Vincent JL, de Mendonça A, Cantraine F, *et al.* Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998; 26(11): 1793-800.
[http://dx.doi.org/10.1097/00003246-199811000-00016] [PMID: 9824069]

[28] Chawla LS, Bellomo R, Bihorac A, *et al.* Acute Disease Quality Initiative Workgroup 16.. Acute kidney disease and renal recovery: Consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol 2017; 13(4): 241-57.
[http://dx.doi.org/10.1038/nrneph.2017.2] [PMID: 28239173]

[29] Forni LG, Darmon M, Ostermann M, *et al.* Renal recovery after acute kidney injury. Intensive Care Med 2017; 43(6): 855-66.
[http://dx.doi.org/10.1007/s00134-017-4809-x] [PMID: 28466146]

[30] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8(4): R204-12.
[http://dx.doi.org/10.1186/cc2872] [PMID: 15312219]

[31] Nickolas TL, O'Rourke MJ, Yang J, *et al.* Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med 2008; 148(11): 810-9.
[http://dx.doi.org/10.7326/0003-4819-148-11-200806030-00003] [PMID: 18519927]

[32] Dent CL, Ma Q, Dastrala S, *et al.* Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: A prospective uncontrolled cohort study. Crit Care 2007; 11(6): R127.
[http://dx.doi.org/10.1186/cc6192] [PMID: 18070344]

[33] Shavit L, Dolgoker I, Ivgi H, Assous M, Slotki I. Neutrophil gelatinase-associated lipocalin as a predictor of complications and mortality in patients undergoing non-cardiac major surgery. Kidney Blood Press Res 2011; 34(2): 116-24.
[http://dx.doi.org/10.1159/000323897] [PMID: 21311195]

[34] Mishra J, Ma Q, Kelly C, *et al.* Kidney NGAL is a novel early marker of acute injury following transplantation. Pediatr Nephrol 2006; 21(6): 856-63.
[http://dx.doi.org/10.1007/s00467-006-0055-0] [PMID: 16528543]

[35] Makris K, Markou N, Evodia E, *et al.* Urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early marker of acute kidney injury in critically ill multiple trauma patients. Clin Chem Lab Med 2009; 47(1): 79-82.
[http://dx.doi.org/10.1515/CCLM.2009.004] [PMID: 19055468]

[36] Ding H, He Y, Li K, *et al.* Urinary neutrophil gelatinase-associated lipocalin (NGAL) is an early biomarker for renal tubulointerstitial injury in IgA nephropathy. Clin Immunol 2007; 123(2): 227-34.
[http://dx.doi.org/10.1016/j.clim.2007.01.010] [PMID: 17360238]

[37] Mori K, Nakao K. Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. Kidney Int 2007; 71(10): 967-70.
[http://dx.doi.org/10.1038/sj.ki.5002165] [PMID: 17342180]

[38] Bagshaw SM, Bennett M, Devarajan P, Bellomo R. Urine biochemistry in septic and non-septic acute kidney injury: A prospective observational study. J Crit Care 2013; 28(4): 371-8.
[http://dx.doi.org/10.1016/j.jcrc.2012.10.007] [PMID: 23159144]

[39] Wan L, Bagshaw SM, Langenberg C, Saotome T, May C, Bellomo R. Pathophysiology of septic acute kidney injury: What do we really know? Crit Care Med 2008; 36(4)(Suppl.): S198-203.
[http://dx.doi.org/10.1097/CCM.0b013e318168ccd5] [PMID: 1838 2194]