EXTRA nephron

Nephron Extra 2017;7:62–77
DOI: 10.1159/000477469
Received: March 23, 2017
Accepted: May 9, 2017
Published online: July 12, 2017

Original Paper

Urinary Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Acute Kidney Injury, Severe Kidney Injury, and the Need for Renal Replacement Therapy in the Intensive Care Unit

Fatma I. Albeladi[a] Haifa M. Algethamy[b]

[a]Department of Nephrology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [b]Department of Critical Care Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Keywords

Acute kidney injury · Renal failure · Critical care · Intensive care · Shock · Neutrophil gelatinase-associated lipocalin · Risk factors · Predictors · Sensitivity and specificity

Abstract

Background: Recent attempts were made to identify early indicators of acute kidney injury (AKI) in order to accelerate treatment and hopefully improve outcomes. This study aims to assess the value of urinary neutrophil gelatinase-associated lipocalin (uNGAL) as a predictor of AKI, severe AKI, and the need for renal replacement therapy (RRT). ***Methods:*** We conducted a prospective study and included adults admitted to our intensive care unit (ICU) at King Abdulaziz University Hospital (KAUH), between May 2012 and June 2013, who had at least 1 major risk factor for AKI. They were followed up throughout their hospital stay to identify which potential characteristics predicted any of the above 3 outcomes. We collected information on patients' age and gender, the Acute Physiology And Chronic Health Evaluation, version II (APACHE II) score, the Sepsis-Related Organ Failure Assessment (SOFA) score, serum creatinine and cystatin C levels, and uNGAL. We compared ICU patients who presented with any of the 3 outcomes with others who did not. ***Results:*** We included 75 patients, and among those 21 developed AKI, 18 severe AKI, and 17 required RRT. Bivariate analysis revealed intergroup differences for almost all clinical variables (e.g., patients with AKI vs. patients without AKI); while multivariate analysis identified mean arterial pressure as the only predictor for AKI ($p < 0.001$) and the SOFA score ($p = 0.04$) as the only predictor for severe AKI. For RRT, day 1 maximum uNGAL was the stronger predictor ($p < 0.001$) when compared to admission diag-

Fatma I. Albeladi
Faculty of Medicine, King Abdulaziz University Jeddah
Department of Medicine – Nephrology Division
Jeddah (Saudi Arabia)
E-Mail fatma.2.2014@gmail.com

nosis (p = 0.014). Day 1 and day 2 maximum uNGAL levels were good and excellent predictors for future RRT, but only fair to good predictors for AKI and severe AKI. ***Conclusions:*** Maximum urine levels of uNGAL measured over the first and second 24 h of an ICU admission were highly accurate predictors of the future need for RRT, however less accurate at detecting early and severe AKI.

Background

Whether their condition is the result of severe illness, injury, or recent surgery, patients who are critically ill are highly susceptible to acute kidney injury (AKI) [1–6], with a rate ranging from 5% to almost 90% [7, 8]. In one of the largest studies, Uchino et al. [5] analyzed the data of 29,269 patients admitted to critical care units in 54 hospitals across 23 countries, from September 2000 and December 2001, and identified clinically documented acute renal failure in 1,738 patients (5.7%). Among the latter, less than one-third had previously documented renal dysfunction [5]. In another sizeable study in Japan, Isshiki et al. [9] ascertained that some major adverse kidney events occurred in 102 patients (20.6%) of the total 495 patients studied. Furthermore, amongst 103 patients admitted to a coronary care unit, Yang et al. [6] reported diagnosed acute renal failure in 49 patients (47.6%), whereas Camou et al. [10] were able to detect AKI in 43 out of 50 patients (86%) admitted with sepsis to another critical care unit. Outcomes in critically ill patients who develop acute renal dysfunction are generally not good, with a mortality rate of up to 60% prior to discharge [5]. Moreover, chronic renal failure and the need for renal replacement therapy (RRT) are usually common outcomes among those who survive [4, 7–10].

For several decades, there have been attempts to identify biomarkers that can predict early AKI to promptly initiate aggressive kidney-sparing and life-saving treatment [11]. Many biomarkers were suggested, including tubular enzymes like alpha- and pi-glutathione S-transferase, N-acetyl-glycosaminidase, alkaline phosphatase, gamma-glutamyl trans-peptidase, Ala-(Leu-Gly)-aminopeptidase, and fructose-1,6-biphosphatase, low-molecular weight urinary proteins like alpha1- and beta2-microglobulin, retinol-binding protein, adenosine deaminase-binding protein, and cystatin C, urinary interleukins/adhesion molecules, and markers of glomerular filtration like pro-atrial natriuretic peptide (1–98) and cystatin C, among others [11].

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein expressed by neutrophils and various epithelial cells. It is a member of the lipocalin family of proteins, which transport small hydrophobic molecules like steroids, retinoids, and lipids [12, 13]. It was initially proposed by Mishra et al. [14] in 2003, as an indicator for early renal injury secondary to renal hypoperfusion. Since then, it has been studied in a variety of clinical contexts [7], both in children and adults, including renal injury due to cancer [15, 16], cancer chemotherapy [17–19], kidney surgery [20], kidney transplantation [21, 22], cardiac surgery [23–27], and systemic illness, especially sepsis [8, 28–30]. However, to date, uncertainty remains regarding the actual role of NGAL in the clinical setting, namely whether plasma or urinary NGAL (uNGAL) or a combination of the two is preferable, the best timing for NGAL acquisition, and the differences between the various commercially available NGAL assays [6, 24, 28, 30–33].

The general objective of this study was to identify how useful uNGAL is in a population of critically ill patients admitted to the intensive care unit (ICU) at a large tertiary care center in Saudi Arabia. More specifically, we sought to (1) follow the course of uNGAL levels over hospitalization, (2) determine how well elevated uNGAL levels, both at baseline and over the

course of hospitalization, can predict AKI, severe kidney injury including renal failure, the ultimate need for RRT and mortality as the combined outcome of severe kidney injury, or patient mortality in the ICU, and (3) identify the threshold of uNGAL (in ng/mL which optimizes diagnostic accuracy) in terms of combined sensitivity and specificity.

Methods

For this prospective cohort study, ethical approval was obtained from the Research Ethics Committee at King Abdulaziz University Hospital, as well as all needed administrative approvals. Prior to data collection, the study objectives and design were explained to all participants and then written consent was obtained from each patient.

We recruited a cohort of patients who were consecutively admitted to the ICU at King Abdulaziz University Hospital (KAUH) in Jeddah, the second largest city in Saudi Arabia. KAUH is a major referral center for all of western Saudi Arabia, with a metropolitan area population of 3.5 million people. To include a patient, he/she must be ≥18 years old and must either have a systolic blood pressure <90 mm Hg or a mean arterial pressure (MAP) <65 mm Hg, thereby requiring the administration of at least 1 vasopressor, inotrope, or both. Patients were excluded if their serum creatinine at presentation was >200 μmol/L, if they had a previously documented end-stage renal disease (ESRD), if they had documented obstructive uropathy, if they were on dialysis, or if they were pregnant. Recruitment took place over a 13-month period, from May 2012 until June 2013.

In addition to the current standard laboratory investigations, urine was collected and sent to measure uNGAL and serum cystatin C levels on the day of admission and immediately upon arrival to the ICU (time; t = 0, as well as at t = 6, 12, 24, and 36 h). After that, these levels were measured daily until day 4. Serum creatinine was measured by the hospital's clinical laboratory at baseline and then monitored as per standard ICU routine (i.e., at least once daily) throughout the ICU admission. Other variables that were measured included patients' urine output as well as their baseline Acute Physiology and Chronic Health Evaluation, version II (APACHE II) and Sepsis-Related Organ Failure Assessment or Sequential Organ Failure Assessment (SOFA) scores. The APACHE II is an instrument designed and validated to rate the severity of illness upon admission to the ICU. It is scored from 0 to 71, and the higher the scores the more severe is the disease. The SOFA is a scoring system specifically designed to monitor the patients' level of organ failure across 6 different domains: respiratory, cardiovascular, hepatic, coagulation, renal, and neurological. As per standard ICU protocol, we also assessed each patient's hemodynamic status, including MAP, any vasopressors and inotropic agents used and their dose, fluid balance (i.e., the need for mechanical ventilator support), and the need for RRT, including intermittent hemodialysis. Patients' mortality rate was also reported.

Treatment was administered to protect the kidneys from further injury when the observed level of uNGAL started to increase. The latter included: attempts to optimize the patient's MAP between 60 and 65 mm Hg to maintain adequate perfusion pressure, using vasopressors to avoid vasoconstriction and the worsening of renal perfusion, avoiding nephrotoxic and contrast agents as much as possible, and lastly if no response was apparent with optimized medical care, initiating early continuous RRT within 6 h of AKI recognition. Both the Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) criteria and cystatin C levels were used to define and stratify the severity of AKI. The following allocations were used based on prior research results: cystatin C <100 μg/L: normal, 100–499 μg/L: mild injury, 500–999 μg/L: moderate injury, and ≥1,000 μg/L: severe injury.

Data Analysis

The primary goal of bivariate analysis was to compare patients with AKI and those without, those with severe kidney injury or failure and those without, those requiring RRT and those who do not, and finally those with a "poor outcome," defined as severe kidney injury or failure, death, or both, and those with a good outcome. We compared the following variables: (1) patient demographics such as age and gender, (2) baseline clinical characteristics such as diagnosis on admission (e.g., septic shock, cardiogenic shock, traumatic shock, severe postoperative hypotension, or other), (3) baseline MAP; 24-h APACHE II score and 24-h SOFA score, (4) baseline serum creatinine and cystatin C, and (5) uNGAL levels; maximum on day 0 (first 24 h) and day 1 (next 24 h). For these comparisons between each two subgroups, the Student *t* test was used for continuous variables and Pearson χ^2 analysis was used for nominal and ordinal variables. Because of the multiple comparisons, in bivariate analyses a Bonferroni-adjusted *p* value ($p = 0.001$) was used as the threshold of statistical significance.

The primary goal of multivariate analysis was to identify predictors of AKI, severe kidney injury, the need for RRT, and a poor outcome (severe kidney injury/failure, death, or both), adjusted for all other variables. Because we only included 75 subjects, and assessed 10 independent variables for potential inclusion in the models, a stepwise (hierarchical) binary logistic regression was performed. The first model entered (through forward selection) patient age, gender, and diagnosis, and the second model added baseline APACHE II and SOFA scores to the step 1 model. The third model added baseline serum creatinine, cystatin C, and uNGAL levels, while the fourth model included baseline, mean, and minimum MAP. The fifth model included baseline, day 0, and day 1 maximum and mean uNGAL levels, and finally the sixth and last model included only those variables identified as potentially significant predictors ($p \leq 0.10$) across the other 5 models. It should be noted that when variables such as baseline, mean, and minimum MAP or the 5 uNGAL measurements were added, that model was recreated using only suitable variables. When 2 similar variables were found roughly equal, each was carried separately to the final model. For each step, any variable with $p < 0.20$ was retained for the next step. For the final model, a $p < 0.10$ value was selected as the threshold for final variable retention.

To assess the accuracy of uNGAL as a predictor for AKI and severe AKI, receiver operating characteristic (ROC) curves were created, using the best uNGAL-related predictor of both outcomes as test statistic and the absence or presence of AKI, severe AKI, and RRT as binary status variables. From these, areas under the curve (AUC) were calculated to determine the variable's value as a predictor for AKI, severe AKI, and potential RRT, and then the optimum cutoff values for the tested variable were identified to optimize accuracy, the latter was defined as the best balance of sensitivity and specificity. All tests were two-tailed and performed using the IBM Statistical Package for Social Sciences (SPSS) version 23 (SPSS, Chicago, IL, USA).

Results

Over the 13-month recruitment, a total of 75 patients met our eligibility criteria and were followed. Their baseline data are summarized in Table 1. There was a wide range in age (18–89 years) and a relatively equal gender distribution across the subgroups. All patients had at least 1 major risk factor for AKI, including septic shock in 34 patients, cardiogenic shock in 20, severe and postoperative hypotension in 16, and trauma in 5 patients. The patients underwent different surgical procedures including neurological, cardiovascular, major abdominal, and gynecological procedures, ranging from 3 to 6 procedures per patient. Table 2 summarizes the outcomes across the whole sample, namely in terms of death and

Table 1. Baseline characteristics of the patients

Patients	75
Mean age (range), years	51.6 (18–89)
Male gender, *n* (%)	38 (50.7)
Baseline mean arterial pressure (range), mm Hg	56.4 (43–69)
1 vasopressor required, *n* (%)	44 (58.7)
>1 vasopressor required, *n* (%)	28 (37.3)
Inotrope required, *n* (%)	46 (61.3)
Mean APACHE II score (range)	24.6 (10–47)
Mean SOFA score (range)	9.8 (4–16)
Major risk factor for AKI, *n* (%)	75 (100.0)
Septic shock	34 (45.3)
Cardiogenic shock	20 (26.7)
Trauma	5 (6.7)
Postoperative hypotension	16 (21.3)

APACHE II, Acute Physiology and Chronic Health Evaluation, version II; SOFA, Sepsis-Related Organ Failure Assessment; AKI, acute kidney injury.

Table 2. Clinical outcomes for all patients (level of kidney injury and mortality)

Final measured RIFLE grade[1]	
Normal kidney function	25 (33.3)
Kidney function at risk (R)	29 (38.7)
Acute kidney injury (I)	18 (24.0)
Kidney failure (F)	3 (4.0)
Kidney loss (L)	n/a (0)
End-stage renal disease (E)	n/a (0)
Worst kidney injury[2]	
Normal cystatin level	14 (18.7)
Mild injury	18 (24.0)
Moderate injury	25 (33.3)
Severe injury	16 (21.3)
Kidney failure	2 (2.7)
Mortality	
Required RRT	17 (22.7)
Died in ICU	16 (21.3)
Died in hospital	40 (53.3)

Values are shown as *n* (%). n/a, no patient in this group because excluded from the start. RRT, renal replacement therapy; ICU, intensive care unit. [1] Kidney status categorized using RIFLE criteria. [2] Worst kidney injury categorized according to maximum serum cystatin C level.

renal injury. Since renal function was assessed only during hospital stay, we could not present any data here on long-term renal loss or ESRD. The latter requires 1 and 3 months of loss of function, as per RIFLE criteria.

In our sample, there was a very strong association between the level of injury, as indicated by the cystatin C level, and the RIFLE grade ($\chi^2 = 47.9$, $p < 0.001$). In total, 16 of the total patients (21.3%) died during their ICU stay. Out of 16 patients who died, the admission diagnosis was septic shock in 12, trauma in 3, and cardiogenic shock in 1 patient (Fig. 1). The ICU mortality rate was 52.5% among those with AKI and 55.6% among those with severe AKI compared with rates of 9.3% ($\chi^2 = 16.8$, $p < 0.001$) and 10.5% ($\chi^2 = 16.5$, $p < 0.001$) among

Table 3. Comparison of patients with AKI and those without (RIFLE grade)

	AKI (n = 21)	No AKI (n = 54)	Test statistic	Significance (p value)
Mean age, years	51.6	51.6	t = 0.003	0.997
Male, %	38.1	55.6	χ^2 = 1.84	0.17
Mean baseline APACHE II score	32.2	21.6	t = 5.40	<0.001
Mean baseline SOFA score	12.9	8.6	t = 5.46	<0.001
MAP, mm Hg				
Baseline	52.1	58.1	t = 4.63	<0.001
Maximum	65.3	69.5	t = 4.78	<0.001
Minimum	52.0	58.0	t = 4.65	<0.001
Mean	59.4	64.3	t = 5.78	<0.001
Improvement in MAP (1st 24 h)	8.4	7.8	t = 0.59	0.55
Mean baseline creatinine, μmol/L	165.6	99.7	t = 5.29	<0.001
Mean baseline cystatin C level, μg/L	2,338.6	1,401.1	t = 2.42	0.018
Maximum uNGAL, ng/mL				
Day 0	747.6	376.4	t = 2.50	0.015
Day 1	1,020.0	428.8	t = 3.78	<0.001
Day 0–1	999.9	534.7	t = 3.97	<0.001
Death, %	52.4	9.3	χ^2 = 16.75	>0.001

APACHE II, Acute Physiology and Chronic Health Evaluation, version II; SOFA, Sepsis-Related Organ Failure Assessment; MAP, mean arterial pressure; AKI, acute kidney injury; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

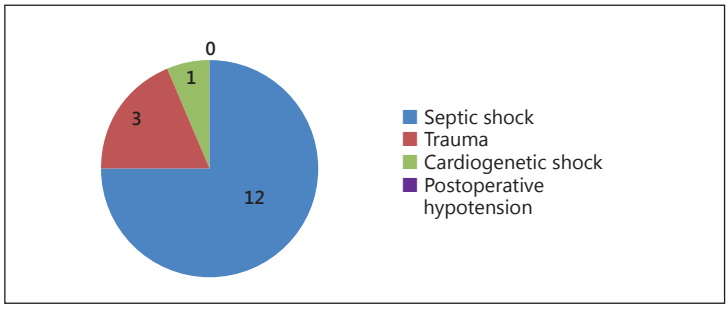

Fig. 1. Causes of death in the ICU.

those without AKI or severe AKI, respectively. Eighty-one percent of those who experienced at least some level of AKI in the ICU died prior to hospital discharge, and 83.3% of those suffered from severe AKI.

Twenty-one of the total patients fulfilled the RIFLE criteria for AKI during their ICU stay. Bivariate comparisons of these 21 patients and the remaining 54 patients are summarized in Table 3. Note that both groups did not differ in patient age or gender, but most other clinical measures differed between the two groups, while maintaining a Bonferroni-adjusted threshold for statistical significance of p = 0.001. This included mean scores for both scales assessing the overall health status (the SOFA and APACHE II scales), all measures of MAP (baseline and the mean, minimum, and maximum MAP over the first 72 h in the ICU), the mean serum creatinine level, and lastly the maximum levels of uNGAL over the first 2 ICU days, and specifically over the second 24 h. The mean baseline serum cystatin C and uNGAL levels over the first 24 h in the ICU failed to meet the adjusted level of significance (both p ~ 0.02), and there was no intergroup difference in the mean improvement in MAP over the first 72 h in the ICU (p = 0.55).

Table 4. Comparison of patients with severe AKI/failure and those without (cystatin grade)

	Severe AKI (n = 18)	No severe AKI (n = 57)	Test statistic	Significance (p value)
Mean age, years	53.8	50.9	t = 0.57	0.57
Male, %	38.9	61.1	χ^2 = 1.31	0.25
Mean baseline APACHE II score	32.2	22.2	t = 4.68	<0.001
Mean baseline SOFA score	13.1	8.8	t = 6.15	<0.001
MAP, mm Hg				
Baseline	52.8	57.5	t = 3.21	0.002
Maximum	66.6	68.8	t = 2.24	0.03
Minimum	52.8	57.4	t = 3.20	0.002
Mean	60.3	63.7	t = 3.40	0.001
Improvement in MAP (1st 24 h)	7.9	8.0	t = 0.14	0.89
Mean baseline creatinine, μmol/L	182.7	97.8	t = 8.12	<0.001
Mean baseline cystatin C level, μg/L	2,968.7	1,251.5	t = 4.61	<0.001
Maximum uNGAL, ng/mL				
Day 0	923.4	346.1	t = 3.88	<0.001
Day 1	1,079.5	462.3	t = 3.65	<0.001
Day 0–1	1,079.0	444.0	t = 4.35	<0.001
Death, %	55.6	10.5	χ^2 = 16.50	<0.001

APACHE II, Acute Physiology and Chronic Health Evaluation, version II; SOFA, Sepsis-Related Organ Failure Assessment; MAP, mean arterial pressure; AKI, acute kidney injury; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

Similar results were observed comparing patients with AKI when defined according to cystatin C levels (n = 18, Table 4). This counted 18 patients who suffered from renal failure compared to those remaining. Again, age and gender were not different between the groups, but a significant difference was detected for most clinical variables. In this instance, variables that failed to meet the adjusted p value threshold of 0.001 were the baseline MAP as well as the maximum and minimum MAP over the first 72 h in the ICU. As with AKI, the 2 groups exhibited no difference at all in the level of improvement (i.e., increase in MAP) over the first 72 h in the ICU.

When we compared the 17 patients who required RRT with the remaining 58 who did not (Table 5), and as with AKI and severe AKI, the 2 groups were statistically different in every clinical variable of interest, except for maximum MAP over the first 24 h in the ICU, which remained borderline (p = 0.057). Yet, again, the degree of improvement in MAP over the first 72 h showed no significant difference (p = 0.26). Females accounted for a disproportionate percentage on RRT and showed a significant association (χ^2 = 3.97, p = 0.046), but the almost 4-year difference between the 2 subgroups in mean age (those on RRT were older, 54.5 vs. 50.8 years) was not statistically significant.

A final series of bivariate comparisons was done by combining the outcomes, severe kidney injury and death, into a single outcome called "poor outcome" (Table 6). We compared the 24 patients who met the criteria for "poor outcome" with the 51 patients who did not, and again there was no significant difference in either age or gender. On the other hand, there were detectable differences for every clinical variable (all p < 0.001), except for the mean increase in the MAP over the patients' first 72 h in the ICU (p = 0.49).

On hierarchical binary logistic regression, the only statistically significant predictor of AKI was the mean MAP over the first 72 h in the ICU (p < 0.001, Table 7), while the only predictor of severe AKI, including renal failure, was the SOFA score (p = 0.037, Table 8).

Table 5. Comparison of patients on RRT with those not on RRT

	RRT (n = 17)	No RRT (n = 58)	Test statistic	Significance (p value)
Mean age, years	54.5	50.8	t = 0.73	0.47
Male, %	29.4	56.9	χ^2 = 3.97	0.046
Mean baseline APACHE II score	34.5	21.7	t = 6.40	<0.001
Mean baseline SOFA score	13.2	8.8	t = 5.28	<0.001
MAP, mm Hg				
Baseline	50.9	58.0	t = 5.28	<0.001
Maximum	66.5	68.8	t = 1.94	0.057
Minimum	50.9	58.0	t = 5.31	<0.001
Mean	59.6	63.9	t = 4.35	<0.001
Improvement in MAP (1st 24 h)	8.9	7.7	t = 1.14	0.26
Mean baseline creatinine, μmol/L	163.5	104.9	t = 4.14	<0.001
Mean baseline cystatin C level, μg/L	3,288.2	1,257.2	t = 3.77	<0.001
Maximum uNGAL, ng/mL				
Day 0	1,068.6	304.6	t = 5.60	<0.001
Day 1	1,350.1	347.2	t = 7.87	<0.001
Day 0–1	1,339.5	347.2	t = 7.78	<0.001
Death, %	82.4	3.4	χ^2 = 14.69	<0.001

RRT, renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation, version II; SOFA, Sepsis-Related Organ Failure Assessment; MAP, mean arterial pressure; AKI, acute kidney injury; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

Table 6. Comparison of patients with a poor outcome (severe AKI and/or death in ICU) and those with a good outcome

	Good outcome (n = 51)	Poor outcome (n = 24)	Test statistic	Significance (p value)
Mean age, years	51.1	52.6	t = 0.33	0.75
Male, %	58.8	33.3	χ^2 = 4.24	0.04
Mean baseline APACHE II score	20.7	32.9	t = 7.10	<0.001
Mean baseline SOFA score	8.2	13.1	t = 7.20	<0.001
MAP, mm Hg				
Baseline	58.2	52.5	t = 4.55	<0.001
Maximum	69.5	65.8	t = 3.88	<0.001
Minimum	58.2	52.5	t = 4.55	<0.001
Mean	64.3	59.9	t = 5.15	<0.001
Improvement in MAP (1st 24 h)	7.8	8.5	t = 0.70	0.49
Mean baseline creatinine, μmol/L	95.4	166.6	t = 6.26	<0.001
Mean baseline cystatin C level, μg/L	1,241.3	2,561.0	t = 3.71	<0.001
Maximum uNGAL, ng/mL				
Day 0	275.2	927.0	t = 5.17	<0.001
Day 1	318.4	1,163.4	t = 6.54	<0.001
Day 0–1	334.7	1,152.6	t = 7.09	<0.001

APACHE II, Acute Physiology and Chronic Health Evaluation, version II; SOFA, Sepsis-Related Organ Failure Assessment; MAP, mean arterial pressure; AKI, acute kidney injury; uNGAL, urinary neutrophil gelatinase-associated lipocalin.

Table 7. Hierarchical logistic regression to identify AKI

	B	SE	Wald	df	Significance	Exp(B)
Step 1[a]						
MAP_Mean	–0.452	0.129	12.362	1	0.000	0.636
Age	–0.021	0.020	1.144	1	0.285	0.979
Gender	0.265	0.699	0.144	1	0.704	1.304
uNGAL_Day0_MEAN	0.000	0.001	0.044	1	0.833	1.000
Constant	27.636	8.662	10.178	1	0.001	1,004,776,629,432.010

[a] Variable(s) entered in step 1: MAP_Mean, age, gender, uNGAL_Day0_MEAN. AKI, acute kidney injury; MAP_ Mean, mean arterial pressure over the first 72 h in the intensive care unit (ICU); uNGAL_Day0_MEAN, mean urinary neutrophil gelatinase-associated lipocalin level (2–4 measurements) over the first 24 h in the ICU.

Table 8. Hierarchical logistic regression to identify severe kidney injury or renal failure risk

	B	SE	Wald	df	Significance	Exp(B)
Step 1[a]						
MAP_Mean	–0.081	0.130	0.386	1	0.534	0.922
AdmissionDx2	–0.284	0.391	0.527	1	0.468	0.753
SOFA	0.329	0.157	4.365	1	0.037	1.389
uNGAL_max_D1	0.000	0.001	0.087	1	0.768	1.000
Constant	0.511	8.755	0.003	1	0.953	1.667

[a] Variable(s) entered in step 1: MAP_Mean, AdmissionDx2, SOFA, and uNGAL_max_D1. MAP_Mean, mean arterial pressure over the first 72 h in the intensive care unit (ICU); SOFA, Sequential Organ Failure Assessment score; AdmissionDx2, reason for admission to the ICU; uNGAL_Max_D1, maximum urinary neutrophil gelatinase-associated lipocalin level on the second hospital day.

Table 9. Hierarchical logistic regression to identify the need for RRT

	B	SE	Wald	df	Significance	Exp(B)
Step 1[a]						
AdmissionDx2	–1.714	0.697	6.042	1	0.014	0.180
uNGAL_Day0_MAX	0.002	0.001	10.610	1	0.001	1.002
Constant	–0.070	0.956	0.005	1	0.941	0.932

[a] Variable(s) entered in step 1: AdmissionDx2 and uNGAL_Day0_MAX. RRT; renal replacement therapy; AdmissionDx2, admission diagnosis; uNGAL_Day0_MAX, maximum recorded level of urinary neutrophil gelatinase-associated lipocalin in the first 24 h in the intensive care unit.

However, when severe kidney injury and death were combined, 5 variables remained in the final predictor model: SOFA score (p = 0.016), baseline cystatin C level (p = 0.035), patient gender (p = 0.036), admission diagnosis (p = 0.049), and baseline serum creatinine (p = 0.052), and that is with the maximum level of uNGAL over the first 24 h in the ICU borderline (p = 0.105) (Table 9). Interestingly, the maximum measured level of uNGAL over the first

Table 10. Hierarchical logistic regression to identify the probability of a "poor outcome" (i.e., severe renal injury or death)

	B	SE	Wald	df	Significance	Exp(B)
Step 1[a]						
Gender	2.255	1.075	4.405	1	0.036	9.540
AdmissionDx2	–1.272	0.647	3.861	1	0.049	0.280
SOFA	0.564	0.235	5.761	1	0.016	1.757
CystatinC_D1_t0	0.001	0.000	4.443	1	0.035	1.001
SerumCre_1	0.022	0.012	3.776	1	0.052	1.023
uNGAL_Day0_MAX	0.001	0.001	2.628	1	0.105	1.001
Constant	–13.195	4.241	9.681	1	0.002	0.000

[a] Variable(s): gender, AdmissionDx2, SOFA, CystatinC_D1_t0, SerumCre_1, uNGAL_Day0_MAX. Admission Dx, reason for admission to the ICU; SOFA, Sequential Organ Failure Assessment score; CystatinC_D1_t0, cystatin C level roughly 24 h into the intensive care unit stay; SerumCre_1, serum creatinine on the second hospital day; uNGAL_Max_D1, maximum urinary neutrophil gelatinase-associated lipocalin level on the second hospital day.

24 h in the ICU was the best predictor of the ultimate need for RRT ($p = 0.001$), and admission diagnosis ($p = 0.014$) was the only other variable to remain in the multivariate predictive model (Table 10).

Since both in bivariate and multivariate analysis, the maximum level of uNGAL for the first and second 24 h in the ICU were similar, particularly in terms of their association with the outcomes, both variables were used for the ROC curves for the 3 outcomes of interest (AKI, severe AKI, and RRT). For the maximum level of uNGAL over the first 24 h in the ICU, the AUC was 0.79 (95% confidence interval 0.68, 0.91; $p < 0.001$) for AKI, indicating a fair to good value as a measure of immediate AKI risk. For the maximum level of uNGAL over the second 24 h in the ICU, the AUC was 0.77 (95% confidence interval 0.66, 0.87; $p = 0.001$), indicating a fair value as a measure of immediate AKI risk. For severe AKI, corresponding values for the first 24-h and second 24-h maximum level of uNGAL were: AUC 0.80 (0.69, 0.90; $p < 0.001$) and AUC 0.78 (0.67, 0.90; $p = 0.001$); and for RRT they were: AUC 0.84 (0.75, 0.95; $p < 0.001$) and AUC 0.93 (0.87, 0.998; $p < 0.001$). Figures 2–4 demonstrate the sensitivity and specificity for each of these 3 measures at thresholds 150, 200, 500, and 1,000 ng/mL for each of the 3 main outcomes. It should be noted that for the first 2 outcomes (AKI and severe AKI), the day 1 threshold for maximum uNGAL at which sensitivity and specificity were closest was 200 ng/mL (sensitivity 79 and 75%; specificity 70 and 66%, respectively). Conversely, for the maximum uNGAL measured on ICU day 2, the corresponding threshold was 500 ng/mL (sensitivity 73 and 75%; specificity 73 and 66%, respectively). For RRT, the thresholds at which sensitivity and specificity were closest were 500 ng/mL maximum uNGAL for day 1 (sensitivity 75%; specificity 80%) and 1,000 ng/mL for day 2 levels (sensitivity 87.5%; specificity 88%).

Discussion

The incidence of AKI is both high and rapidly increasing in ICU settings for reasons not entirely understood [8, 34]. Most common in patients with sepsis [8, 35, 36], a seemingly essential underlying mechanism of AKI is renal ischemia followed by reperfusion [34] in an organ that has a limited capacity for repair. The consequences of AKI can be severe, including

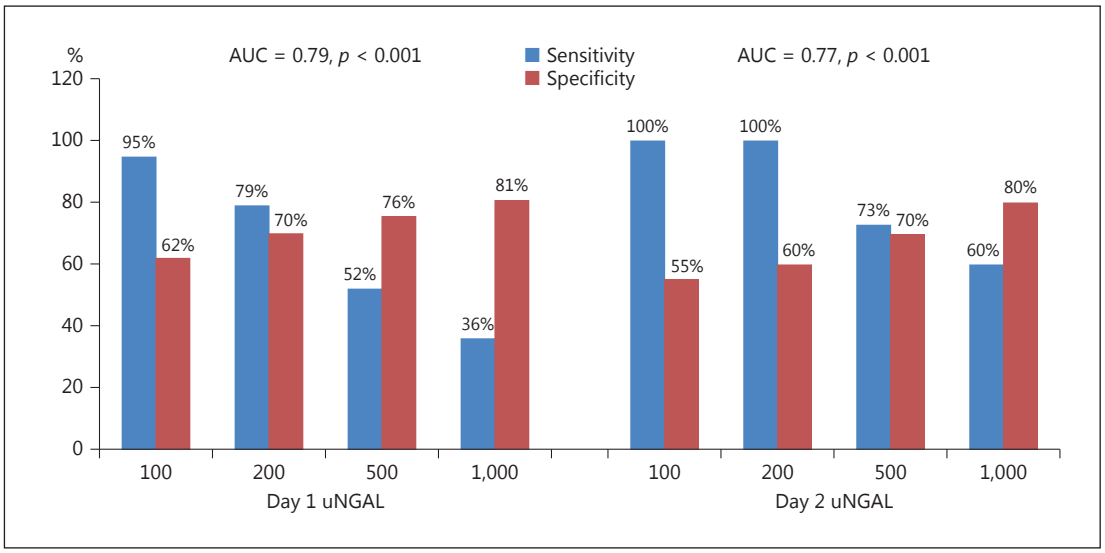

Fig. 2. Sensitivity and specificity of maximum urinary neutrophil gelatinase-associated lipocalin (uNGAL; ng/mL), ICU day 1 versus day 2, for acute kidney injury.

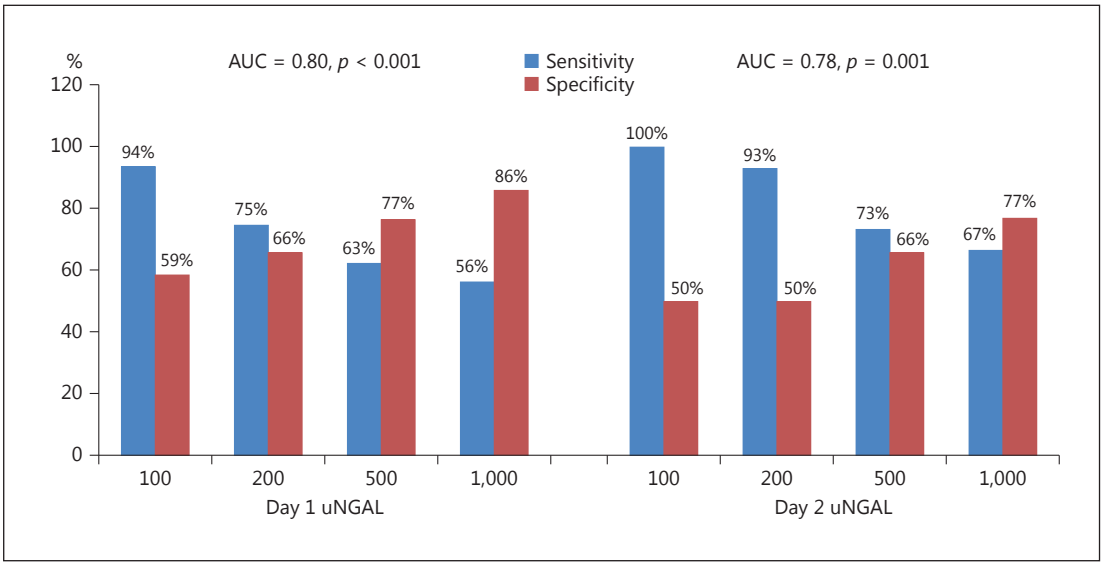

Fig. 3. Sensitivity and specificity of maximum urinary neutrophil gelatinase-associated lipocalin (uNGAL; ng/mL), ICU day 1 versus day 2, for severe acute kidney injury.

renal failure, ESRD requiring long-term RRT, and even death, with studies indicating that AKI itself is an independent predictor of mortality [37]. In previously published papers, mortality rates have been reported as high as 60% prior to discharge from the hospital [5]. In our sample, which included patients with septic, traumatic, and cardiogenic shock, as well as postoperative shock, the mortality rate prior to hospital discharge among those with documented AKI was an alarming 81%, with 50% of them dying during their initial ICU stay.

Since the treatment of AKI is far less than satisfactory [38–40], there is a general agreement that current emphasis should be on (1) AKI prevention among those at risk, and (2) its early

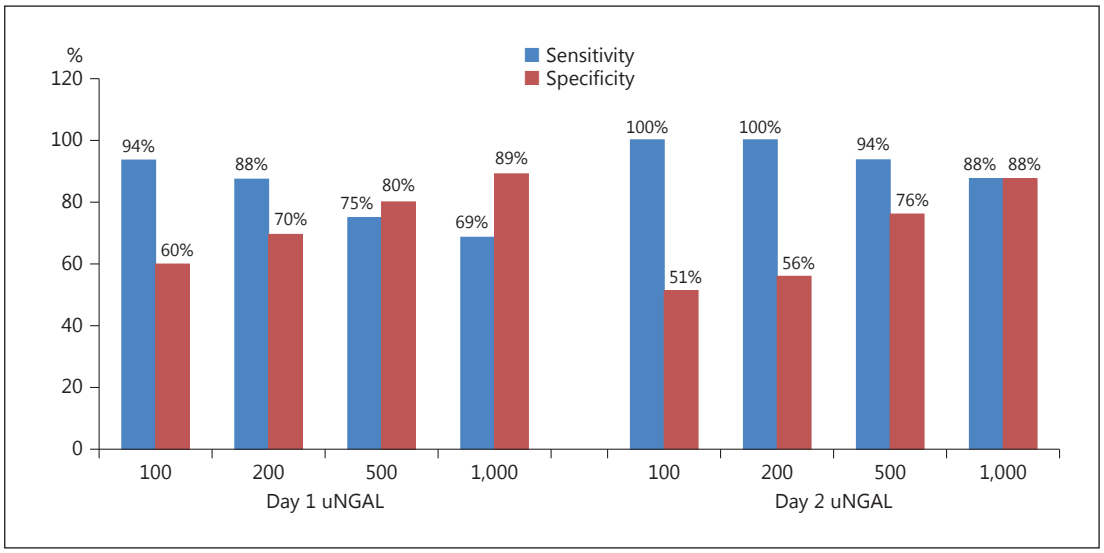

Fig. 4. Sensitivity and specificity of maximum urinary neutrophil gelatinase-associated lipocalin (uNGAL; ng/mL), ICU day 1 versus day 2, for renal replacement therapy.

detection, before the onset of irreversible tissue injury [7, 41, 42]. The challenge has been to accurately identify those who are at meaningful risk. One problem with traditional markers of renal function, such as serum creatinine and blood urea nitrogen levels, is that they are late indicators of renal injury, only becoming elevated once the injury is already established [6]. A distinct advantage of markers like uNGAL, cystatin C, and kidney injury molecule-1 (KIM-1) is that levels often become elevated prior to elevations in serum creatinine or blood urea nitrogen, hence earlier in the course of renal injury. In fact, this phenomenon of uNGAL increasing prior to creatinine was observed amongst our patients, where the level of uNGAL was greater than our predefined normal threshold of 150 ng/mL in 94.7% of patients who were later diagnosed with AKI. On the other hand, serum creatinine measured on that same day was elevated in less than two-thirds of patients (61.9%; $\chi^2 = 61.16$, $p = 0.01$) and only minimally in most. What this suggests is that, at least for our sample, uNGAL was an earlier predictor of renal injury than serum creatinine.

The early detection of subclinical renal injury using uNGAL was reported in animal models, and it appears to be both sensitive and fairly specific [19, 43]. In a study in mice, this was particularly true of the uNGAL to plasma NGAL ratio [19]. Two recently published meta-analyses assessed its accuracy in the early detection of AKI [7] and in early detection of AKI among patients with sepsis [8]. In the 2009 meta-analysis, Haase et al. [7] analyzed data from 19 studies incorporating 2,538 patients, of whom 487 patients (19.2%) ultimately developed AKI. For their analysis, AKI was defined as an increase in serum creatinine level to above 50% from the baseline and within 7 days, or contrast-induced nephropathy (this, in turn, was defined as an increase within 48 h of contrast administration in serum creatinine of over 25%, or a concentration >0.5 mg/dL in adults, or an increase of more than 50% in children). Other outcomes of interest were the initiation of RRT and the in-hospital mortality. Both uNGAL and serum/plasma NGAL were assessed. Though the identified range of cutoffs maximizing the accuracy of AKI detection, and that across the 19 studies spanned from 100 to 270 ng/mL, there was a general agreement that the NGAL threshold of normal (i.e., ≤150 ng/mL) was best. Using this threshold, an overall AUC of 0.815 (95% CI 0.732, 0.892) was calculated for NGAL in general, with an overall AUC for uNGAL of 0.837 (95% CI 0.762, 0.906), i.e., slightly

higher than for plasma NGAL (0.775; 95% CI 0.679, 0.869) [7]. The investigators also detected differences in AUC between patients defined as "critically ill" (0.728; 95% CI 0.615, 0.834), postoperative cardiac surgery patients (0.775; 95% CI 0.669, 0.867), and patients who developed AKI after the infusion of contrast (0.894; 95% CI 0.826, 0.950) [7].

More recently, in 2016, Zhang et al. [8] published the results of their meta-analysis of 15 studies, all published between 2010 and 2015, encompassing 1,478 patients with sepsis. Out of the 15 studies, 9 examined uNGAL alone, 3 plasma NGAL alone, and 3 both. As opposed to the meta-analysis by Haase et al. [7], no uniform criteria for AKI were used. Instead, all means or criteria any of the 15 studies adopted were included. The latter included (but not exclusively) the RIFLE scale (n = 3), the Acute Kidney Injury Network (AKIN) scale (n = 8), or both (n = 2), and the Kidney Disease Improving Global Outcomes (KDIGO) scale was used in the final two studies. Of the total of 1,478 patients, 592 cases (40.1%) had an elevated level of either uNGAL or plasma NGAL or both. Plasma NGAL was measured in 433 patients across 6 studies, in which the pooled AUC was 0.86, the sensitivity was 83%, and the specificity was 57%. Urine levels of NGAL were measured in 12 studies, encompassing 1,263 patients, among whom the pooled estimates for AUC, sensitivity, and specificity were 0.90, 80%, and 80%, respectively [8].

We evaluated the association between levels of uNGAL and ultimate renal injury in 3 different ways. (1) Via bivariate analysis, comparing patients who did have AKI with those who did not, those who did acquire severe AKI with those who did not, and those who ultimately required RRT with those who did not, all across a range of demographic and clinical variables, including the different measures and timing of uNGAL. (2) Via multivariate analysis, entering uNGAL and our other variables into 3 different models, one for each of the 3 main study outcomes, AKI, severe AKI, and the need for RRT, and using hierarchical binary logistic regression. Finally, (3) using ROC curves, and calculating AUC for all 3 renal outcomes, thus determining the best thresholds for the predictor variables of interest, namely in terms of optimizing accuracy (defined as the best balance of sensitivity and specificity).

On bivariate analysis for these 3 outcomes, we identified statistically significant differences in most clinical parameters, including global measures of systemic illness severity (SOFA and APACHE II), baseline creatinine, cystatin C, uNGAL, and MAP, as well as several measures of both uNGAL and MAP, and even when adjusting for multiple comparisons. On the other hand, on multivariate analysis, all but one of these clinical variables – including uNGAL and baseline serum creatinine – dropped out of binary regression models predicting AKI and severe AKI. The sole predictors that remained in the models were the average MAP over the first 72 h in the ICU for AKI and the SOFA score, thus indicating sequential organ failure for severe injury. However, when the outcomes of severe AKI and patient mortality were combined, (i.e., a patient either had severe AKI or died), 5 parameters remained as predictors: the SOFA score, baseline cystatin C level, patient gender, admission diagnosis, and baseline serum creatinine, with the maximum level of uNGAL over the first 24 h in the ICU borderline.

The need for RRT was the outcome best predicted by urine levels of NGAL, with uNGAL remaining as the stronger of the 2 remaining predictors in the final model, and whether the maximum level for day 1, day 2, or across both days was used. The best of these 3 uNGAL measures, as a predictor of RRT, was the maximum level recorded over the first 24 h in the ICU.

Based upon our bivariate and multivariate results, we then elected to assess the accuracy of 2 different measurements of uNGAL: the maximum level measured over the first 24 h in the ICU and the maximum level measured over the second 24 h in the ICU. Both were identified as fair to good indicators of AKI, and of fair value for future severe AKI, with AUC ranging from 0.77 to 0.80. The latter was consistent with the calculations reported in the meta-analysis published by Haase et al. [7] for critically ill patients (AUC ~0.73). The uNGAL

threshold at which the optimum balance of sensitivity and specificity was achieved differed between the 2 measures. However, with ICU day 1 uNGAL levels >200 ng/mL, 79% were sensitive and 70% specific for AKI and 75% were sensitive and 66% specific for potential severe AKI. Similar but slightly lower levels of sensitivity and specificity (73 and 70%; 73 and 66%, respectively) were achieved with day 2 levels >500 ng/mL. In other words, the threshold that maximized diagnostic accuracy was 200 ng/mL when uNGAL was measured on the first ICU day but 500 ng/mL when measured on ICU day 2. This is consistent with the considerably higher levels of uNGAL we recorded on the second ICU day. What this further means is that, while urine levels of NGAL measured in the first 24 h of an ICU stay were both sensitive and specific for AKI and pending severe AKI, and using the threshold of 200 ng/mL was superior to the 150 ng/mL cutoff used by others [7, 8], the same cannot be said for day 2 levels, for which using a threshold of even 200 ng/mL was highly sensitive but barely more specific than flipping a coin.

Another interesting finding was how excellent a predictor uNGAL is for future RRT need, and especially the day 2 maximum level of uNGAL. In general, AUC values >0.90 are considered an excellent value, and the AUC we calculated for day 2 uNGAL was 0.93. However, it was the higher levels of day 1 and 2 uNGAL that best balanced sensitivity and specificity (thereby optimizing accuracy), with day 1 levels of uNGAL >500 ng/mL 75% sensitive and 80% specific, and day 2 levels >1,000 ng/mL 87.5% sensitive and 88% specific. This means that not only the timing of uNGAL measurement is important, but also the threshold used as a positive test varies, depending on the renal outcome of interest.

The following limitations must be acknowledged. First, the relatively small patient population, which prohibited any subgroup analysis, for example comparing the AUC for AKI in patients with sepsis versus cardiogenic, traumatic, or postoperative shock. Also, we were not entirely consistent in the number of daily measurements of uNGAL undertaken from patient to patient, though it was generally measured 3 times for each patient, and all patients' levels were measured at least twice on ICU days 1 and 2. On the other hand, we feel that our study showed notable strengths, among them is the fact that we measured NGAL multiple times each day. Our study is one of the few to specifically assess patients with traumatic and postoperative shock, and although we were not able to conduct subgroup analysis for sensitivity, specificity, and AUC, we did perform a stepwise binary logistic regression. The latter concluded that, while the distribution of admission diagnoses did differ between those with AKI and those without, and those developing severe AKI and those who did not on bivariate analysis, other variables came into play to eliminate admission diagnosis in the final models. Yet, admission diagnosis did remain in a model for RRT, and in a model combining the 2 outcomes of severe AKI and death. Another strength of this study is the serial measurement of MAP, where we assessed different levels of renal injury. The latter was neither done nor reported in other studies. Our study is also the only study reporting data collected in Saudi Arabia.

In summary, our series included 75 ICU patients admitted over a 13-month period with risk factors for AKI and severe AKI, both were common and occurring in more than 1 in every 4 patients. They were associated with markedly elevated mortality rates up to 50% in the ICU and an additional 30% who died later during their hospital stay. Beside the increased risk of in-house mortality, those with AKI were also different in almost all baseline clinical and laboratory characteristics, including elevated uNGAL, especially over the second 24 h in the ICU. We also found that, as did others, urine levels of NGAL were of value as predictors and indicators of renal outcomes. While most prior analyses have focussed on AKI, we found that uNGAL is also valuable as a predictor for more severe renal disease, including failure leading to RRT. Our results also raised questions on the current "threshold of normal" used for urine levels of NGAL. Our findings suggest that using higher thresholds, and using different thresholds for different purposes, can enhance the diagnostic accuracy of this test.

Conclusion

Maximum uNGAL measured over the first and second 24 h of an ICU admission is a highly accurate predictor of renal injury, with a potential future need for RRT. Yet, they are less accurate predictors of early and severe AKI. Different thresholds should be used when assessing different outcomes. More research is needed to validate the latter.

Disclosure Statement

The authors declare no conflicts of interests.

References

1 Bell M, Granath F, Schon S, Ekbom A, Martling CR: Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med 2007; 33:773–780.
2 Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, Macleod A: Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 2007;18:1292–1298.
3 Pickering JW, James MT, Palmer SC: Acute kidney injury and prognosis after cardiopulmonary bypass: a meta-analysis of cohort studies. Am J Kidney Dis 2015;65:283–293.
4 Coca SG, Singanamala S, Parikh CR: Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012;81:442–448.
5 Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294:813–818.
6 Yang CH, Chang CH, Chen TH, Fan PC, Chang SW, Chen CC, Chu PH, Chen YT, Yang HY, Yang CW, Chen YC: Combination of urinary biomarkers improves early detection of acute kidney injury in patients with heart failure. Circ J 2016;80:1017–1023.
7 Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A: Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009;54:1012–1024.
8 Zhang A, Cai Y, Wang PF, Qu JN, Luo ZC, Chen XD, Huang B, Liu Y, Huang WQ, Wu J, Yin YH: Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis. Crit Care 2016;20:41.
9 Isshiki R, Asada T, Sato D, Sumida M, Hamasaki Y, Inokuchi R, Matsubara T, Ishii T, Yahagi N, Nangaku M, Noiri E, Doi K: Association of urinary neutrophil gelatinase-associated lipocalin with long-term renal outcomes in ICU survivors: a retrospective observational cohort study. Shock 2016;46:44–51.
10 Camou F, Oger S, Paroissin C, Guilhon E, Guisset O, Mourissoux G, Pouyes H, Lalanne T, Gabinski C: Plasma neutrophil gelatinase-associated lipocalin (NGAL) predicts acute kidney injury in septic shock at ICU admission. Ann Fr Anesth Reanim 2013;32:157–164.
11 Trof RJ, Di MF, Leemreis J, Groeneveld AB: Biomarkers of acute renal injury and renal failure. Shock 2006; 26:245–253.
12 Devarajan P: Neutrophil gelatinase-associated lipocalin – an emerging troponin for kidney injury. Nephrol Dial Transplant 2008;23:3737–3743.
13 Flower DR, Attwood TK, North AC: Structure and sequence relationships in the lipocalins and related proteins. Protein Sci 1993;2:753–761.
14 Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P: Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003;14:2534–2543.
15 Almalky MA, Hasan SA, Hassan TH, Shahbah DA, Arafa MA, Khalifa NA, Ibrahim RE: Detection of early renal injury in children with solid tumors undergoing chemotherapy by urinary neutrophil gelatinase-associated lipocalin. Mol Clin Oncol 2015;3:1341–1346.
16 Delfino Duarte PA, Fumagalli AC, Wandeur V, Becker D: Urinary neutrophil gelatinase-associated lipocalin in critically ill surgical cancer patients. Indian J Crit Care Med 2015;19:251–256.
17 Kesik V, Demirkaya E, Buyukpamukcu M: Urinary neutrophil gelatinase associated lipocalin as a biomarker in ifosfamide induced chronic renal failure. Eur Rev Med Pharmacol Sci 2015;19:4851–4857.
18 Seker MM, Deveci K, Seker A, Sancakdar E, Yilmaz A, Turesin AK, Kacan T, Babacan NA: Predictive role of neutrophil gelatinase-associated lipocalin in early diagnosis of platin-induced renal injury. Asian Pac J Cancer Prev 2015;16:407–410.

19 Mishra J, Mori K, Ma Q, Kelly C, Barasch J, Devarajan P: Neutrophil gelatinase-associated lipocalin: a novel early urinary biomarker for cisplatin nephrotoxicity. Am J Nephrol 2004;24:307–315.
20 Dede O, Dagguli M, Utangac M, Yuksel H, Bodakcı MN, Hatipoğlu NK, Sancaktutar AA, Penbegül N: Urinary expression of acute kidney injury biomarkers in patients after RIRS: it is a prospective, controlled study. Int J Clin Exp Med 2015;8:8147–8152.
21 Ramirez-Sandoval JC, Herrington W, Morales-Buenrostro LE: Neutrophil gelatinase-associated lipocalin in kidney transplantation: a review. Transplant Rev (Orlando) 2015;29:139–144.
22 Mishra J, Ma Q, Kelly C, Mitsnefes M, Mori K, Barasch J, Devarajan P: Kidney NGAL is a novel early marker of acute injury following transplantation. Pediatr Nephrol 2006;21:856–863.
23 Garcia-Alvarez M, Glassford NJ, Betbese AJ, Ordoñez J, Baños V, Argilaga M, Martínez A, Suzuki S, Schneider AG, Eastwood GM, Victoria Moral M, Bellomo R: Urinary neutrophil gelatinase-associated lipocalin as predictor of short- or long-term outcomes in cardiac surgery patients. J Cardiothorac Vasc Anesth 2015;29:1480–1488.
24 Ho J, Tangri N, Komenda P, Kaushal A, Sood M, Brar R, Gill K, Walker S, MacDonald K, Hiebert BM, Arora RC, Rigatto C: Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: a meta-analysis. Am J Kidney Dis 2015;66:993–1005.
25 McIlroy DR, Farkas D, Matto M, Lee HT: Neutrophil gelatinase-associated lipocalin combined with delta serum creatinine provides early risk stratification for adverse outcomes after cardiac surgery: a prospective observational study. Crit Care Med 2015;43:1043–1052.
26 Souza DF, Reis SS, Botelho RV, Ferreira-Filho SR: Relative and absolute changes in urinary neutrophil gelatinase-associated lipocalin and correlation with small increases in serum creatinine levels after coronary angiography: an observational study. Nephron 2015;129:84–90.
27 Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, Lee HT: Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology 2006;105:485–491.
28 Cruz DN, Virzi GM, Brocca A, Ronco C, Giavarina D: A comparison of three commercial platforms for urinary NGAL in critically ill adults. Clin Chem Lab Med 2016;54:353–362.
29 Vanmassenhove J, Glorieux G, Lameire N, Hoste E, Dhondt A, Vanholder R, Van Biesen W: Influence of severity of illness on neutrophil gelatinase-associated lipocalin performance as a marker of acute kidney injury: a prospective cohort study of patients with sepsis. BMC Nephrol 2015;16:18.
30 Nasioudis D, Witkin SS: Neutrophil gelatinase-associated lipocalin and innate immune responses to bacterial infections. Med Microbiol Immunol 2015;204:471–479.
31 Lichosik M, Jung A, Jobs K, Mierzejewska A, Zdanowski R, Kalicki B: Interleukin 18 and neutrophil-gelatinase associated lipocalin in assessment of the risk of contrast-induced nephropathy in children. Cent Eur J Immunol 2016;40:447–453.
32 Schley G, Koberle C, Manuilova E, Rutz S, Forster C, Weyand M, Formentini I, Kientsch-Engel R, Eckardt KU, Willam C: Comparison of plasma and urine biomarker performance in acute kidney injury. PLoS One 2015;10:e0145042.
33 Fanning N, Galvin S, Parke R, Gilroy J, Bellomo R, McGuinness S: A Prospective study of the timing and accuracy of neutrophil gelatinase-associated lipocalin levels in predicting acute kidney injury in high-risk cardiac surgery patients. J Cardiothorac Vasc Anesth 2016;30:76–81.
34 Vanmassenhove J, Veys N, Van BW: Prevention and conservative management of acute kidney injury. Minerva Urol Nefrol 2016;68:58–71.
35 Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol 2007;2:431–439.
36 Alobaidi R, Basu RK, Goldstein SL, Bagshaw SM: Sepsis-associated acute kidney injury. Semin Nephrol 2015;35:2–11.
37 Umbro I, Gentile G, Tinti F, Muiesan P, Mitterhofer AP: Recent advances in pathophysiology and biomarkers of sepsis-induced acute kidney injury. J Infect 2016;72:131–142.
38 Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J: Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000;356:2139–2143.
39 Lauschke A, Teichgraber UK, Frei U, Eckardt KU: "Low-dose" dopamine worsens renal perfusion in patients with acute renal failure. Kidney Int 2006;69:1669–1674.
40 Allgren RL, Marbury TC, Rahman SN, Weisberg LS, Fenves AZ, Lafayette RA, Sweet RM, Genter FC, Kurnik BR, Conger JD, Sayegh MH: Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. N Engl J Med 1997;336:828–834.
41 Kellum JA, Mehta RL, Levin A, Molitoris BA, Warnock DG, Shah SV, Joannidis M, Ronco C; Acute Kidney Injury Network (AKIN): Development of a clinical research agenda for acute kidney injury using an international, interdisciplinary, three-step modified Delphi process. Clin J Am Soc Nephrol 2008;3:887–894.
42 Kellum JA, Levin N, Bouman C, Lameire N: Developing a consensus classification system for acute renal failure. Curr Opin Crit Care 2002;8:509–514.
43 Kaucsar T, Godo M, Revesz C, Kovács M, Mócsai A, Kiss N, Albert M, Krenács T, Szénási G, Hamar P: Urine/plasma neutrophil gelatinase associated lipocalin ratio is a sensitive and specific marker of subclinical acute kidney injury in mice. PLoS One 2016;11:e0148043.