Urinary NGAL in patients with and without acute kidney injury in a cardiology intensive care unit

ABSTRACT

Objective: To assess the diagnostic and prognostic efficacy of urine neutrophil gelatinase-associated lipocalin in patients admitted to an intensive care unit.

Methods: Longitudinal, prospective cohort study conducted in a cardiology intensive care unit. The participants were divided into groups with and without acute kidney injury and were followed from admission to the intensive care unit until hospital discharge or death. Serum creatinine, urine output and urine neutrophil gelatinase-associated lipocalin were measured 24 and 48 hours after admission.

Results: A total of 83 patients admitted to the intensive care unit for clinical reasons were assessed, most being male (57.8%). The participants were divided into groups without acute kidney injury (N=18), with acute kidney injury (N=28) and with severe acute kidney injury (N=37). Chronic diseases, mechanical ventilation and renal replacement therapy were more common in the groups with acute kidney injury and severe acute kidney injury, and those groups exhibited longer intensive care unit stay and hospital stay and higher mortality. Serum creatinine did not change significantly in the group with acute kidney injury within the first 24 hours of admission to the intensive care unit, although, urine neutrophil gelatinase-associated lipocalin was high in the groups with acute kidney injury and severe acute kidney injury (p<0.001). Increased urine neutrophil gelatinase-associated lipocalin was associated with death.

Conclusion: An increase in urine neutrophil gelatinase-associated lipocalin precedes variations in serum creatinine in patients with acute kidney injury and may be associated with death.

Keywords: Acute kidney injury; Lipocalins; Creatinine; Intensive care units

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication among patients with or without previous history of kidney disease, especially in severe cases. The incidence of AKI in intensive care units (ICU) varies from 1 to 25% according to the definition of AKI that is applied.¹,²

In 2004, a new definition and classification for AKI was formulated: the RIFLE criteria. The RIFLE criteria is based on the serum creatinine or glomerular filtration rate and urine output. It classifies AKI into
three severity classes - Risk, Injury and Failure - and two outcome classes, Loss of kidney function and End-stage kidney disease.\(^{(3)}\) Later, the less detailed Acute Kidney Injury Network (AKIN) classification was formulated, according to which AKI severity is classified into stages 1, 2 and 3 according to serum creatinine and urine output. Stage 3 corresponds to the most severe cases, requiring renal replacement treatment (RRT).\(^{(4)}\)

These two classification systems were united by the Kidney Diseases Improving Global Outcomes (KDIGO) Clinical Practice Guidelines Workgroup. According to KDIGO, AKI is defined as an increase in serum creatinine by 0.3mg/dL or more within 48 hours or a 1.5-fold increase in serum creatinine relative to the baseline (known or pre-established) or urine output less than 0.5mL/kg/h for six hours. KDIGO also formulated a new staging system for the severity of AKI, as follows: stage 1, serum creatinine increase \(\geq 0.3\, \text{mg/dL (1.5-1.9 times baseline)}\) or urine output \(< 0.5\, \text{mL/kg/h for 6-12 hours};\) stage 2: serum creatinine \(2-2.9\) times baseline or urine output \(< 0.5\, \text{mL/kg/h for \(\geq 12\) hours};\) and stage 3: serum creatinine \(3\) times baseline or increase in serum creatinine to \(\geq 4\, \text{mg/dL},\) initiation of RRT or urine output \(< 0.3\, \text{mL/kg/h for \(\geq 12\) hours.}\(^{(5)}\)

Although the KDIGO guidelines represent an advance in the clinical interpretation of AKI, they are still based on the serum creatinine and urine output levels. Serum creatinine and urine output are the most widely used parameters in the clinical setting, but, their sensitivity and specificity as indicators of kidney function are low. Serum creatinine increases too slowly and thus does not reflect the dynamic changes in glomerular filtration rate, limiting its use as an early marker of AKI.\(^{(6,7)}\) The imprecision in the use of serum creatinine as a marker is due to several extrarenal factors, such as volume distribution, tubular secretion and use of medication, in addition to the patient’s gender, age, muscle mass and type of diet.\(^{(8)}\)

Accurate and early diagnosis of AKI is needed to start treatment in a timely manner or to neutralize potentially reversible causes and to prevent or limit the progression of kidney injury.\(^{(9)}\) In AKI, as in any cell-exposure situation, injury begins by induction of molecular disturbances that result in cell death. The cells produce markers of injury that may be detected in the earliest stages of disease. The use of molecular markers may allow early diagnosis of AKI, even before the onset of clinical manifestations, and consequently early therapeutic interventions. The ideal markers should be easily detectable in serum or urine samples at either the bedside or the laboratory with few or non-invasive techniques, and having low cost.\(^{(8)}\)

This unfavorable scenario has triggered efforts to detect and establish sensitive markers of kidney injury. In addition to the above-mentioned biochemical characteristics, neutrophil gelatinase-associated lipocalin (NGAL), a member of the lipocalin superfamily also known as lipocalin-2, is a 25-kDa protein compound with 178-amino-acid covalently bound to gelatinase from neutrophils.\(^{(7)}\)

Urine NGAL (uNGAL) exhibits satisfactory discriminatory performance at the injury site, is relatively free from interference by proteins and is measurable noninvasively.\(^{(8,10)}\) Thus, the objective of the present study was to assess the diagnostic and prognostic efficacy of uNGAL in individuals admitted to an ICU.

**METHODS**

The present longitudinal, prospective, quantitative cohort study was conducted at the clinical ICU of a cardiology hospital. Data were collected from November 2010 to June 2011.

The sample included individuals (N=83) admitted to the ICU, who were followed up from 24 hours after admission until outcome (hospital discharge or death). Patients younger than 18 years old, pregnant, with chronic kidney disease under dialysis or under long-term use of corticoids were excluded from the study. The study was approved by the ethics committee of Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (ruling n° 0467/10). Patients or relatives were requested to sign an informed consent form, including authorization for collection of blood and urine samples. The participants were selected on
their first day in the ICU and followed up every day until the outcome.

Participants were classified as without AKI, with AKI or with severe AKI according to KDIGO guidelines. Serum creatinine, 24-hour urine output and uNGAL in a single sample were measured at two time-points: within the first 24 hours after admission to the ICU and between 24 and 48 hours after admission to ICU. To measure uNGAL, urine samples were centrifuged and stored at -80°C and then analyzed using a commercial kit (Human Lipocalin-2/NGAL ELISA, BioVendor).

The continuous variables are expressed as the mean, standard deviation, median and interquartile range. The categorical variables are expressed as absolute (N) and relative (%) frequencies. Means were compared between two groups by Student’s t-test and between three groups by one-factor analysis of variance (ANOVA) with the non-parametric Kruskal-Wallis test. The non-parametric Wilcoxon test was used to compare two periods, and the chi-squared or Fisher’s exact test to investigate the homogeneity between proportions. Correlations were assessed by Spearman’s coefficient. Death prognostic factors were assessed through a multivariate linear regression model. Statistical analysis was performed using the software Statistical Package for the Social Sciences (SPSS) 15.0 for Windows. The significance level was set at 5%.

RESULTS

A total of 83 patients admitted to the ICU for clinical reasons were assessed. The participants’ age varied from 20 to 89 years (mean: 61±13 years); most were male (57.8%) and white (73.5%).

The participants were divided into three groups: without AKI (patients who did not develop AKI during their stay at ICU), with AKI (patients who developed AKI during their stay at ICU) and severe AKI (patients with AKI upon admission to ICU).

Table 1 shows that 21.7% of the participants did not develop AKI, 33.7% developed AKI during their stay at the ICU, and 44.6% had severe AKI upon admission. The main cause of AKI in the group with severe AKI was cardiorenal syndrome (p<0.041). Patients with AKI exhibited higher prevalences of diabetes mellitus (DM) (p<0.036) and congestive heart failure (CHF) (p<0.002). The life support measure most frequently required by the patients with AKI was mechanical ventilation (MV) (p<0.001). The participants with severe AKI had greater need for RRT compared to the ones without AKI (p<0.032). As a result, the length of stay at the ICU (p<0.012) and at the hospital (p<0.007) of the participants with AKI was longer, and their mortality rate was significantly higher (p<0.001).

Table 2 shows that only the group with severe AKI exhibited higher serum creatinine compared to the other groups at the 24-hour (p<0.001) and 48-hour assessments (p<0.001). The groups did not differ in urine output at either assessment time-point. uNGAL was higher in the AKI and severe AKI groups at the 24-hour (p<0.001) and 48-hour assessments (p<0.006) compared to the group without AKI. However, no significant difference was found in uNGAL at the two time-points among the three groups. In group AKI, uNGAL was negatively correlated (p<0.001) with urine output at the 24-hour assessment (Table 3). In the group with severe AKI, uNGAL was positively correlated with serum creatinine (p<0.001) at the 24- and 48-hour assessments.

Table 4 describes the variables that were associated with the outcome death in the total sample. Among all the participants who died, only one belonged to the group without AKI. Univariate analysis showed that the factors associated with death for the participants with AKI were Chagas’ disease (p<0.030), low ejection fraction (p<0.010), high serum creatinine (p<0.019), low urine output (p<0.001), high uNGAL at 24 hours (p<0.001), use of vasoactive drugs (p<0.013), use of MV (p<0.001), need for an intra-aortic balloon pump (IABP, p<0.001) and need for RRT (p<0.001).
Table 1 - Demographic and clinical characteristics

| Characteristic          | Without AKI | AKI | Severe AKI | p value |
|-------------------------|-------------|-----|------------|---------|
| **Age (years)**         | 58.8±7.9    | 60.7±6.6 | 61.7±12.1 | NS*     |
| **Male gender**         | 11 (61.1)   | 15 (53.6) | 22 (59.5) | NS*     |
| **Ethnicity**           |             |       |            |         |
| White                   | 11 (61.1)   | 22 (78.6) | 28 (75.7) | NS*     |
| Black                   | 2 (11.1)    | 4 (14.3)  | 4 (10.8)  | NS*     |
| Mixed                   | 5 (27.8)    | 2 (7.1)   | 15 (13.5) | NS*     |
| **AKI cause**           |             |       |            |         |
| Sepsis*                 | -           | 13 (46.4) | 16 (43.2) | NS*     |
| Cardiorenal syndrome*   | -           | 11 (39.3) | 24 (64.9) | 0.041*  |
| **Comorbidities**       |             |       |            |         |
| SAH                     | 15 (83.3)   | 19 (67.9) | 26 (70.3) | NS*     |
| Chagas                  | 2 (11.1)    | 6 (21.4)  | 6 (16.2)  | NS*     |
| DM                      | 4 (22.2)    | 6 (21.4)  | 18 (48.7) | 0.036*  |
| CHF                     | 4 (22.2)    | 15 (53.6) | 27 (73.0) | 0.002*  |
| EF (%)                  | 0.46±0.17   | 0.38±0.18 | 0.38±0.16 | NS*     |
| VD use                  | 12 (66.7)   | 25 (89.3) | 33 (89.2) | NS*     |
| MV                      | 1 (5.6)     | 17 (60.7) | 20 (54.1) | <0.001* |
| IABP                    | 1 (5.6)     | 4 (14.3)  | 5 (13.5)  | NS*     |
| RRT*                    | -           | 7 (25)    | 19 (51.4) | 0.032*  |
| ICU stay (days)         | 9.4±5.8     | 21.7±23.1 | 18.1±14.3 | 0.017*  |
| Hospital stay (days)    | 18.0±10.9   | 41.7±30.7 | 31.9±31.3 | 0.007*  |
| Death                   | 1 (5.6)     | 9 (32.1)  | 22 (59.5) | <0.001* |

AKI - acute kidney injury; NS - non-significant; SAH - systemic arterial hypertension; DM - diabetes mellitus; CHF - congestive heart failure; EF - ejection fraction; VD - vasoactive drugs; MV - mechanical ventilation; IABP - intra-aortic balloon pump; RRT - renal replacement therapy; ICU - intensive care unit; * descriptive probability level of the one-factor analysis of variance; # descriptive probability level of the chi-squared test; & descriptive probability level of Fisher's exact test; * AKI versus severe AKI. Results expressed as absolute number (%).

Table 2 - Characterization of renal function based on serum creatinine, urine output and urine neutrophil gelatinase-associated lipocalin

| Time-point (hours) | Without AKI | AKI | Severe AKI | p value |
|-------------------|-------------|-----|------------|---------|
| **Serum creatinine (mg/dL)** | Median [IQR] | Mean±standard deviation | Median [IQR] | p value |
| 24                | 1.04 [0.84-1.24] | 1.08±0.53 | 0.91 [0.72-1.25] | 4.66 [1.35-12.12] |
| **Urine output (ml/kg/h)** | Median [IQR] | p value |
| 24                | 1.33 [1.01-1.47] | 0.89±0.60 | 0.80 [0.65-1.00] | NS | 13.38 [6.76-24.44] | <0.001* |
| **Serum creatinine (mg/dL)** | Median [IQR] | p value |
| 48                | 3.43 [2.71-4.04] | <0.001* | 0.96±0.78 | 0.78 [0.34-1.36] | 30.14 [15.02-70.78] | <0.001* |
| **Urine output (ml/kg/h)** | Median [IQR] | p value |
| 48                | 1.07 [1.04-1.24] | 1.11±0.44 | 1.01 [0.73-1.27] | NS | 4.09 [2.35-8.58] |
| **Serum creatinine (mg/dL)** | Median [IQR] | p value |
| 24                | 1.20 [1.02-1.32] | 1.00±0.54 | 0.28 [0.65-1.00] | NS | 14.79 [5.76-29.42] | 0.006* |
| **Urine output (ml/kg/h)** | Median [IQR] | p value |
| 24                | 2.64 [2.24-3.98] | <0.001* | 1.02±0.67 | 0.08 [0.59-1.30] | 17.25 [6.29-49.87] | 0.007* |

NGAL - neutrophil gelatinase-associated lipocalin; IQR - interquartile range; AKI - acute kidney injury; NS - non-significant. Descriptive probability level of non-parametric Wilcoxon test; * versus without AKI. Results expressed as the mean±standard deviation and median [interquartile range].

Table 3 - Values of Spearman's coefficient of correlation of urine neutrophil gelatinase-associated lipocalin with serum creatinine and urine output at different time-points

| Time-point (hours) | AKI | Severe AKI | p value |
|-------------------|-----|------------|---------|
| **Urine output**  | r   | 0.601      | 0.150   | r       | -0.501 | 0.660 |
|                   | p   | 0.001      | 0.446   | p       | 0.002  | <0.001 |
| **Serum creatinine** | r   | -0.215     | 0.284   | r       | -0.376 | 0.578 |
|                   | p   | 0.301      | 0.170   | p       | 0.058  | 0.002 |

AKI - acute kidney injury; r - value of Spearman coefficient; p - levels of correlation significance.
Table 4 - Univariate analysis of clinical and laboratory characteristics associated with death

| Characteristic          | No (N=51) | Death (N=32) | p value |
|-------------------------|-----------|--------------|---------|
| Age (years)             | 61.6±12.2 | 59.3±14.4    | 0.436   |
| Male gender             | 27 (52.9) | 21 (65.6)    | 0.255   |
| Ethnicity               |           |              |         |
| White                   | 39 (76.5) | 22 (68.8)    |         |
| Black                   | 4 (7.8)   | 6 (18.8)     | 0.353   |
| Mixed                   | 8 (15.7)  | 4 (12.5)     |         |
| Comorbidities           |           |              |         |
| SAH                     | 38 (74.5) | 22 (68.8)    | 0.568   |
| Chagas                  | 5 (9.8)   | 9 (28.1)     | 0.030   |
| DM                      | 17 (33.3) | 11 (34.4)    | 0.922   |
| CHF                     | 25 (51.0) | 11 (34.4)    | 0.139   |
| Clinical variables      |           |              |         |
| Creatinine baseline     | 1.28±0.48 | 1.28±0.40    | 0.970   |
| EF (%)                  | 0.44±0.17 | 0.34±0.16    | 0.010   |
| Serum creatinine        | 2.06±1.68 | 2.68±1.74    | 0.019   |
| Urine output 24 hours   | 1.15±0.63 | 0.67±0.64    | <0.001  |
| Urine NGAL 24 hours     | 22.97±33.45 | 43.44±38.78 | 0.001   |
| VD use                  | 39 (76.5) | 31 (96.9)    | 0.013   |
| MV                      | 15 (29.4) | 23 (71.9)    | <0.001  |
| IABP                    | 1 (2.0)   | 9 (28.1)     | <0.001  |
| RRT                     | 5 (9.8)   | 21 (65.6)    | <0.001  |

SAH - systemic arterial hypertension; DM - diabetes mellitus; CHF - congestive heart failure; EF - ejection fraction; VD - vasoactive drugs; MV - mechanical ventilation; IABP - intra-aortic balloon pump; RRT - renal replacement therapy; * descriptive probability level of one-factor analysis of variance; # descriptive probability level of the chi-squared test; & descriptive probability level of Fisher’s exact test. Results expressed as absolute number (%) or mean±standard deviation.

**DISCUSSION**

AKI is a complex syndrome associated with a wide variety of situations in the intensive care setting, with manifestations that range from minimal increases in serum creatinine to kidney failure with anuria. Early detection of AKI in severely ill patients is a therapeutic strategy with high impact on the patients' clinical progression, as well as on the socioeconomic scenario. Among the most sensitive and specific markers of kidney injury, NGAL stands out as a specific, sensitive and early predictor of AKI after cardiac surgery, in septic shock, during administration of iodinated contrast, and in kidney transplantation.

NGAL is present in low concentrations in several biological fluids. The plasma concentration of NGAL is close to 20ng/mL, being most likely derived from neutrophil activity. Under physiological conditions, the circulating NGAL is freely filtered through the renal glomeruli (as a protein with low-molecular-weight and positive charge) and reabsorbed in the proximal tubule. Thus, low plasma NGAL is expected in the absence of kidney disease. Under such conditions, the NGAL concentration in both serum and urine is close to 20ng/mL. In AKI, NGAL expression is induced in the proximal and distal tubule epithelial cells, resulting in increased concentrations of NGAL in plasma and urine.

In AKI, NGAL release starts by expression of the corresponding messenger RNA (mRNA) in the thick ascending limb of the loop of Henle and collecting duct, which induces NGAL synthesis in the nephron distal area and its secretion into urine. Kidney injury, even when undetected based on serum creatinine, triggers NGAL release, metabolism and excretion, with consequent increase
Clinical studies show that increases in serum and urine NGAL are an independent predictor of AKI compared to serum creatinine.\(^{17,18}\)

The participants of the present study, namely, individuals admitted to our ICU for clinical reasons, with an average age of 60 years, mostly male and white, were divided into three groups: without AKI, with AKI (stages 1 and 2) and with severe AKI (stage 3). The prevalence of AKI was highest among the participants with chronic diseases, such as DM and CHF. Pre-existent diseases can reduce the estimated glomerular filtration rate or cause proteinuria, which are the main risk factors for AKI.\(^{19}\)

The participants with AKI and severe AKI required life support measures, such as vasoactive drugs, MV, IABP and RRT, in addition to having the longest ICU stays and hospital stays and the highest mortality rates, which are conventionally known to represent severity factors in patients admitted to the ICU. Because kidney dysfunction only seldom occurs as an isolated phenomenon, the risk of death in this group of patients is frequently associated with extrarenal complications and multiple-organ dysfunction.\(^{20,21}\)

The present study found that high uNGAL within the first 24 hours after admission to the ICU predicted the occurrence of AKI before the serum creatinine increase in individuals with KDIGO stage 1 or 2. Because serum creatinine did not exhibit significant variations in the AKI group at the same time-point, it is safe to conclude that uNGAL was able to detect AKI earlier than serum creatinine. Other studies corroborate the ability of uNGAL to indicate AKI earlier than serum creatinine.\(^{22,23}\) An observational prospective study conducted with patients admitted to the ICU found high serum NGAL in the patients who developed AKI on admission and during the first week in the ICU.\(^{23}\)

The uNGAL concentration was positively correlated with serum creatinine in the participants with AKI, i.e., the highest serum creatinine corresponded to a higher uNGAL value. However, small increases in NGAL represent minimal kidney injury, a situation in which no changes are detected in serum creatinine. This finding can demonstrate the ability of NGAL to detect AKI early, even when it is underreported by the usual methods, such as serum creatinine and urine output.\(^{5,6}\)

The correlation of uNGAL with the urine output was negative in the AKI and severe AKI groups, i.e., the higher the urine output, the lower uNGAL. This finding confirms that urine output may be considered a sensitive indicator of variations in the kidney hemodynamics.\(^{24}\) In addition, low NGAL in patients diagnosed with AKI based on the urine output criterion point to possible prerenal azotemia in the absence of tubular injury, in which case, rapid fluid replacement or administration of vasoactive drugs may restore renal perfusion, with consequent improvement of urine output.\(^{25}\)

Chagas’ disease, low ejection fraction, low urine output, need for life support measures (vasoactive drugs, MV, IABP and RRT), high serum creatinine and high uNGAL were correlated with death and thus may reflect the severity of disease. A prospective study conducted with patients subjected to cardiac surgery found a correlation between high uNGAL and the severity and duration of AKI, longer hospital stay, need for RRT and death.\(^{11}\)

Despite the existence of several results that emphasize the predictive value of NGAL for AKI, future studies are needed to establish the quantitative relationship between NGAL expression in the kidney tissue and its urine excretion. The data obtained in the present study corroborate the satisfactory discriminatory performance of NGAL in AKI, especially when it is measured on admission to or within the first 24 hours in the ICU, in addition to being predictive of unfavorable outcomes, such as death.

The KDIGO Acute Kidney Injury Workgroup recommends performing studies with the new biomarkers allowing for early identification, differential diagnosis and establishing the prognosis of individuals with AKI. For this purpose, more precise and earlier markers of AKI compared to the ones currently used (serum creatinine and urine output) should be developed in clinical practice that are also able to behave as predictors of AKI risk or progression.\(^{5}\)

Inpatients, especially those with acute or chronic comorbidities, should be subjected to monitoring
Objetivo: Avaliar a eficácia diagnóstica e prognóstica da lipocalina associada à gelatinase neutrofílica urinária em pacientes de unidade de terapia intensiva.

Métodos: Estudo do tipo coorte, prospectivo, longitudinal desenvolvido em uma unidade de terapia intensiva clínica especializada em cardiologia. Os pacientes foram estratificados segundo os grupos sem e com lesão renal aguda, acompanhados a partir das primeiras 24 horas de internação até a alta hospitalar ou óbito. A creatinina sérica, o fluxo urinário e a lipocalina associada à gelatinase neutrofílica urinária foram coletadas em dois períodos: 24 horas e 48 horas de admissão.

Resultados: Foram avaliados 83 pacientes clínicos da unidade de terapia intensiva, com predomínio do gênero masculino (57,8%). Os pacientes foram agrupados em sem lesão renal aguda (N=18), com lesão renal aguda (N=28) ou com lesão renal aguda grave (N=37). Entre os pacientes com lesão renal aguda e lesão renal aguda grave, foram prevalentes os portadores de doenças crônicas, em uso de ventilação mecânica e em terapia de substituição renal, além daqueles com maiores taxas de permanência na unidade de terapia intensiva e hospitalar, e maior mortalidade. O grupo com lesão renal aguda não apresentou alteração significativa da creatinina sérica nas primeiras 24 horas na unidade de terapia intensiva, apesar dos níveis elevados de lipocalina associada à gelatinase neutrofílica urinária demonstrados nos grupos com lesão renal aguda e lesão renal aguda grave (p<0,001). Níveis elevados de lipocalina associada à gelatinase neutrofílica urinária na amostra foram associados ao óbito.

Conclusão: A elevação nos níveis de lipocalina associada à gelatinase neutrofílica urinária antecede as variações da creatinina sérica em pacientes com lesão renal aguda e pode ser associada ao óbito.

Descritores: Lesão renal aguda; Lipocalinas; Creatinina; Unidades de terapia intensiva

RESUMO

CONCLUSION

Urine neutrophil gelatinase-associated lipocalin within the first 24 hours after admission in the intensive care unit precedes the increase of serum creatinine in acute kidney injury patients and it can be associated with death.

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