Research Article

Urinary neutrophil gelatinase-associated lipocalin in critically ill surgical cancer patients

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Abstract

Background and Aims: Neutrophil gelatinase-associated lipocalin (N-GAL) is an early biomarker of acute kidney injury (AKI) due to various etiologies. On the other hand, N-GAL is also elevated in patients with acute inflammatory conditions and in several solid neoplasms. The goal of this study was to assess the efficacy of N-GAL as a predictor of AKI and mortality in oncological surgical patients postoperatively in the intensive care unit (ICU). **Methods:** This was a prospective cohort observation study on adult cancer patients submitted to elective or emergency surgeries and admitted in the ICU. Urinary N-GAL was measured at the first 2 h after admission. AKI incidence and other complications were assessed, including hospital mortality. **Results:** A total of 22 patients were assessed (77% male, age 52.8 years, Acute Physiology and Chronic Health Evaluation II [APACHE II] 17.3) in whom the most frequent site of cancer was the gastrointestinal tract. AKI incidence was 13.6%. Urinary N-GAL was a predictor of AKI (22.0 ng/ml in patients without AKI vs. 239.1 ng/ml in patients with AKI, $P < 0.001$). Multivariate analysis showed that the main predictors of AKI were age, APACHE II, and N-GAL. N-GAL was also higher, although not statistically significant in patients who died in the hospital. **Conclusions:** In oncological postoperative patients admitted to the ICU, urinary N-GAL was an independent predictor of AKI; moreover, its level was higher in the deceased patients.

Keywords: Acute kidney injury, inflammation, neoplasms, postoperative

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Introduction

The perioperative period of major oncological surgery is marked by several potential causes for renal injury such as hypotension, volume depletion, self-regulation disorders of the kidney, surgical trauma and drug-induced nephrotoxicity.[1-3] On the other hand, patients with oncological malignancies are susceptible to various kidney insults that are associated to complications from the disease itself or from its treatment, such as chemotherapy and radiotherapy.[4-6] Thus, surgical stress would potentiate various risk factors to kidney injury previously present in the carriers of malignancies, resulting in increased length of hospitalization, infectious complications, and mortality rates.[4-9]

In the last few years, several researchers have been trying to find serum and urinary biomarkers that could detect earlier or even predict the evolution to acute kidney injury (AKI)/failure in patients at risk. Neutrophil gelatinase-associated lipocalin (N-GAL) is a widely studied early biomarker of ischemia and kidney injury, which allows the identification of patients at a higher risk of kidney injury 48 h before traditional detection methods, thereby allowing the implementation of preventive/protective strategies before renal damage becomes irreversible.[10-13]

Considering the negative impact of AKI among oncology patients,[8,14] this study intended to assess the

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efficacy of urinary N-GAL as an early biomarker of AKI immediately after major oncological surgeries in patients admitted to the intensive care unit (ICU).

Methods

This was a prospective cohort study on consecutive patients diagnosed with solid neoplasia, submitted to elective or emergency surgeries, and admitted in the ICU of a cancer Hospital.

All adult patients (aged >18 years) submitted to major oncological surgeries (abdominal, pelvic, thoracic, or head/neck) were included, since they previously had a normal renal function. The exclusion criteria were: Patients with a previous diagnosis of kidney injury or failure (with or without renal replacement therapy), pregnant women, and terminal patients under exclusive palliative support.

Acute kidney injury diagnosis was defined in accordance with the AKI network definition of injury criteria.[15]

Descriptive statistical analysis of the obtained data was performed. Univariate analysis was applied to identify the risk factors for AKI. Selected variable data (age, Acute Physiology and Chronic Health Evaluation II [APACHE II], N-GAL, C-reactive protein-immediate postoperative [CRP-IPO], serum creatinine-IPO, serum creatinine 1st PO, serum urea-immediate PO and 1st PO, length of hospitalization, operation time, and serum lactate-IPO) were standardized using Z function and later analyzed by principal component analysis (PCA), after verification of the data quality using Kaiser-Meyer-Olkin (KMO) test. Correlation between matrix of variables was assessed using Bartlett spherical test. Using PCA, it was possible to determine the explanatory variables for each of the patients, with *a priori*–defined outcome (0–normal; AKI).

Urinary N-GAL was measured at the time of admission in the ICU using Quantitative Architect® Abbott (chemiluminescent microparticle immunoassay) method.

The study was approved by the Local Ethical Committee.

Results

A total of 22 patients submitted to major oncological surgeries were assessed. Most of the patients (77%) were males, with a mean age of 52.8 years. Gastrointestinal tract was the most common site of neoplasia.

Demographic and clinical characteristics of the patients are shown in Table 1. Patients with elevated urinary N-GAL had higher APACHE II score at admission, with a trend toward higher mean age compared with those with reduced N-GAL. There were no differences in gender, site of cancer, or related diseases [Table 1].

Overall incidence of PO AKI was 13.6%. Patients with lower levels of urinary N-GAL had lower incidence of AKI (lower levels serum urea and creatinine) and shorter length of hospitalization in the ICU.

When patients with or without the development of AKI were compared, the urinary N-GAL levels were found to be a strong outcome predictor of AKI incidence [Table 2]. The occurrence of AKI increased the length of hospitalization in the ICU, although it did not increase the mortality rate.

Multivariate analysis

When the KMO test value was >0.5 (KMO = 0.695), it was possible to verify that the variables post oncological surgeries were in accordance with the PCA application assumptions, after removing the variables creatinine 1st PO, urea 1st PO, length of hospitalization, duration of surgery, and lactate-IPO. Correlation between matrix of variables was assessed using Bartlett spherical test ($c^2 = 53.097$, $P < 0.0001$).

Using canonical analysis (axes F1 and F2), it was confirmed that age, N-GAL, and APACHE II score were the primary variables associated with AKI outcome [Figure 1].

Discussion

This study showed that in the context of oncological surgery, the urinary N-GAL level assessed at admission to the ICU was a strong predictor of AKI, and patients with higher values of N-GAL showed a trend toward higher hospital mortality.

Neutrophil gelatinase-associated lipocalin, as well as other lipocalins, is expressed biologically in various tissues, such as lungs, spleen, kidney, liver, brain, heart, and testicles, under healthy conditions in humans. But under stress conditions, it is produced by neutrophils and performs complementary functions, by transporting inflammatory substances (such as prostaglandins and arachidonic acid) and mediating the action of iron during inflammatory process. Therefore, N-GAL has possible immunological action during severe acute situations, such as sepsis and trauma.

Table 1: Demographic characteristics and clinical outcome of the patients according to urinary N-GAL levels

	Total	Urinary N-GAL, ng/ml			*P*	
		<10.0	10.0–100	>100.0	<10.0 versus >10.0	>100.0 versus <100.0
N	22	14	04	04		
Demographic and clinical data						
Male, *n* (%)	17 (77.3)	10 (71.4)	4 (100)	3 (75)	0.736	0.588
Age, years, mean±SD	52.8±15.4	48.3±17.2	56.5±4.4	65.0±7.1	0.068	0.081
APACHE II, mean±SD	17.3±8.6	13.1±5.7	20.2±6.8	29.2±7.1	<0.001	<0.001
Tumor site, *n* (%)						
Head-neck	03 (13.6)	02 (14.2)	1 (25)	0	0.319	0.361
Gastrointestinal tract	15 (68.2)	08 (57.1)	3 (75)	04 (100)		
Thorax	01 (4.5)	01 (7.1)	0	0		
Others	03 (13.6)	03 (21.4)	0	0		
Previous diseases, *n* (%)						
COPD	03 (13.6)	02 (14.2)	1 (25)	0	0.738	0.590
Obesity	04 (18.2)	01 (7.1)	0	01 (25)		
Chronic kidney failure	0	0	0	0		
Kind of surgery, *n* (%)						
Elective	21 (95.5)	13 (92.9)	4 (100)	04 (100)	0.768	0.402
Emergency	01 (4.5)	01 (7.1)	0	0		
Duration of surgery, min, mean±SD	228.7±94.7	214.1±106.8	256.2±105.7	245.0±40.4	0.405	0.711
Outcome/evolution						
Length of hospitalization in ICU, days, mean±SD	3.2±3.0	2.3±2.3	2.0±0.8	7.2±3.8	0.093	0.003
Length of hospitalization, days, mean±SD	12.2±11.4	11.3±13.2	10.5±8.0	17.0±7.2	0.647	0.368
MV >24 h, *n* (%)	1 (4.5)	1 (7.1)	0	0	0.768	0.394
Vasoactive drugs >6 h, *n* (%)	5 (22.7)	2 (22.2)	1 (25)	02 (50)	0.614	0.434
Highest serum creatinine postoperative, mg/dl, mean±SD	1.2±0.9	0.8±0.2	0.9±0.2	2.6±1.6	0.024	<0.001
Highest serum urea postoperative, mg/dl, mean±SD	47.1±45.3	34.7±30.7	32.7±6.6	104.7±69.5	0.090	0.002
Dialysis need, *n* (%)	1 (4.5)	0	0	1 (25)	0.772	0.398
Hospital mortality, *n* (%)	06 (27.3)	3 (21.4)	0	03 (75)	0.750	0.080

MV: Mechanical ventilation, SD: Standard deviation, ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease, APACHE II: Acute Physiology and Chronic Health Evaluation II, N-GAL: Neutrophil gelatinase-associated lipocalin

Table 2: Univariate analysis of the risk factors and outcomes among patients with or without the development of AKI

	Total	AKI		*P*
		No	Yes	
n	22	19	03	
Risk factors				
Male, *n* (%)	17 (77.27)	15 (78.94)	02 (66.6)	0.789
Age, years, mean±SD	52.8±15.4	50.6±15.3	66.7±7.6	0.096
APACHE II, mean±SD	17.3±8.6	15.2±6.8	30.3±8.3	0.002
Tumor site, *n* (%)				
Head-neck	03 (1.6)	3 (15.8)	0	NS
Gastrointestinal tract	15 (68.2)	12 (63.1)	03 (100)	
Thorax	01 (4.5)	01 (5.3)	0	
Others	03 (13.7)	3 (15.8)	0	
Previous disease, *n* (%)				
COPD	03 (13.6)	03 (15.8)	0	NS
Obesity	04 (18.2)	03 (15.8)	01 (33.3)	
CKD	0	0	0	
Kind of surgery, *n* (%)				
Elective	21 (95.5)	18 (94.7)	03 (100)	NS
Emergency	01 (4.5)	01 (5.3)	0	
Duration of surgery, min, mean±SD	22.7±94.7	228.1±99.2	233.3±40.4	0.930
Lactate-IPO, mg/dl, mean±SD	2.1±1.2	2.1±1.3	2.4±0.9	0.692
CRP-IPO, mg/dl, mean±SD	3.1±4.6	2.2±3.1	8.8±9.2	0.019
VAD need >6 h postoperative, *n* (%)	5 (22.7)	03 (15.7)	02 (66.6)	0.224
Aminoglycoside use, *n* (%)	02 (9.09)	01 (5.26)	01 (33.3)	NS
Radiological contrast use, *n* (%)	0	0	0	-
Urinary N-GAL, mean±SD	106.2±291.5	22.0±51.2	639.1±612.6	<0.001
N-GAL <10.0, *n* (%)	14 (63.63)	15 (78.94)	0	0.039

Contd...

Table 2: Contd...

	Total	AKI		P
		No	Yes	
Length of hospitalization in ICU, days, mean±SD	3.2±3.0	2.4±2.0	8.3±3.8	<0.001
Length of hospitalization, days, mean±SD	12.2±11.4	11.6±11.8	16.3±8.7	0.516
Hospital mortality, *n* (%)	06 (27.27)	04 (21.05)	02 (66.6)	0.343

AKI: Acute kidney injury, VAD: Vasoactive drugs, ICU: Intensive care unit, SD: Standard deviation. N-GAL: Neutrophil gelatinase-associated lipocalin, CRP: C-reactive protein, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, APACHE II: Acute Physiology and Chronic Health Evaluation II, NS: Not significant, IPO: Immediate postoperative

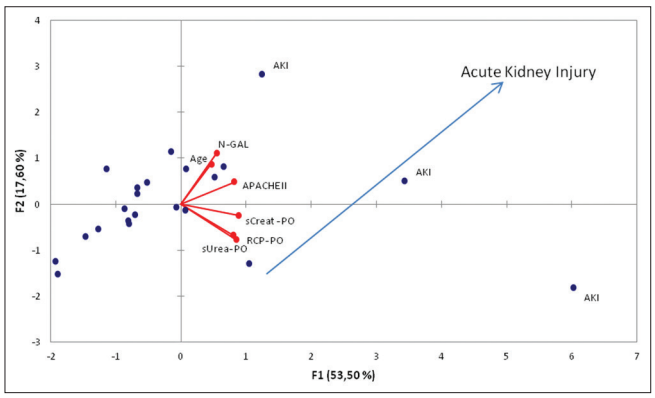

Figure 1: Relationship between variables and risk of developing acute kidney injury (*n* = 22)

On the other hand, specifically in the kidney tissue, N-GAL is upregulated in injuries (particularly ischemic and by the use of contrast). Therefore, it is possible to say that plasma N-GAL acts like a neutrophil activation biomarker and urinary N-GAL acts like a tubular injury marker. However, because of its small size and resistance to degradation, N-GAL is easily detected in the blood and urine. Therefore, increased urinary N-GAL detection could be affected by a kidney process (AKI) or it might reflect a severe acute systemic inflammatory process (e.g., sepsis or trauma).[15,16] During differentiation of various human tissues, N-GAL may play a role in the genesis and, probably, the growth, proliferation, and diffusion of human neoplasms.[10-12,17-19]

Major surgeries can themselves result in severe systemic inflammatory process,[20,21] which intrinsically would lead to higher mortality. N-GAL has been shown to be increased during the PO period of major cardiac and noncardiac surgeries, correlating with the severity of inflammatory process and mortality,[22,23] and even in other chronic and acute inflammatory conditions, such as extracorporeal circulation[24] and inflammatory bowel disease.[25]

Acute kidney injury is common in the PO period of major surgeries, with a strong impact on morbi-mortality, particularly in patients with cancer.[1,2,26-30] Despite its multifactorial nature, a characteristic feature of AKI related to PO period is its association with systemic inflammation processes.[31,32] In the present study, urinary N-GAL showed a strong correlation to kidney dysfunction and a tendency toward increase in mortality (possibly not significant due to an insufficient number of patients).

In this study, urinary N-GAL, besides being clearly an AKI predictor, was increased (although without statistical significance) in patients who died. N-GAL has been associated with unfavorable outcome in critical patients, particularly (but not exclusively) in sepsis and Systemic Inflammatory Reaction Syndrome (SIRS) patients.[33]

Inflammation has an important role in cellular biology and cancer pathophysiology, either in the development and emergence of oncogenic mutations and metastasis formation or host reaction and eventual secondary immunosuppression.[34] Moreover, secondary to major surgeries, particularly in patients with cancer, a systemic inflammatory process is triggered, including an immunosuppressive anti-inflammatory response[21] – an activity that could be mediated by N-GAL. In the current study, all patients were submitted to moderate to high-risk surgery, with severe PO inflammation, as shown by the elevated CRP levels.

In the current study, age >65 years was related to higher levels of N-GAL. This could only be associated with the intrinsic higher severity of disease in these patients, with higher number of comorbidities and higher AKI risk. However, although the literature is not clear regarding the correlation between age and N-GAL levels, elderly patients with SIRS/sepsis present greater inflammatory activity (determined by biomarkers) than younger patients.[35] Hence, N-GAL could hypothetically be a biomarker of age-related inflammatory activity in these patients.

The incidence rate of AKI (13.6%) and need for renal replacement therapy (4.5%) in this study were compatible with literature. AKI incidence varying from 6.8% (lung cancer) and 17.3% (pancreatectomy) to 38.3% (esophageal cancer) has been described in

hospitalized oncology patients, with a strong correlation to hospital mortality.[8,14,27-30] In this study, there was a small increase of AKI incidence in gastrointestinal surgeries, although without statistical difference.

The main predictors of AKI were older age, APACHE II score, urinary N-GAL, and CRP, and the first three parameters maintained their predictability when subjected to multivariate analysis. In PO patients, it has been shown that AKI is correlated with disease severity, previous diseases (such as chronic heart failure [CHF] and diabetes), and abdominal surgery.[1,2] The CRP level in critically ill sepsis cancer patients shows a strong correlation with the course of acute disease, thereby being a good marker of inflammatory process.[36]

This study has some limitations, primarily because of a single center design and limited number of subjects. Thus its generalizability is limited. In addition, N-GAL serum level was not measured, which could better differentiate between systemic inflammatory process and kidney injury. It has also been shown that urinary N-GAL has a strong correlation with mortality and inflammatory process, independent of the presence of AKI.[22,23] The serial measurement of N-GAL was not performed, which could increase the predictability of the diagnostic test. In addition, because two variables were studied (oncological and at PO status) it would be difficult to arrive at conclusions on the relative impact of each one of the parameters involved in the development of AKI.

Conclusions

In a small cohort of cancer patients submitted to major surgery and admitted to the ICU, initial urinary N-GAL was a predictor of PO AKI. Patients with elevated urinary N-GAL also showed a trend toward higher hospital mortality.

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