Original Article

Urinary neutrophil gelatinase-associated lipocalin as an early predictor of prolonged intensive care unit stay after cardiac surgery

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ABSTRACT

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein of lipocalin family highly expressed in various pathologic states and is an early biomarker of acute kidney injury in cardiac surgery. We performed an observational study to evaluate the role of NGAL in predicting postoperative intensive care stay in high-risk patients undergoing cardiac surgery. We enrolled 27 consecutive patients who underwent high-risk cardiac surgery with cardiopulmonary bypass. Urinary NGAL (uNGAL) was measured before surgery, at intensive care unit (ICU) arrival and 24 h later. Univariate and multivariate predictors of ICU stay were performed. uNGAL was 18.0 (8.7–28.1) ng/mL at baseline, 10.7 (4.35–36.0) ng/mL at ICU arrival and 29.6 (9.65–29.5) 24 h later. The predictors of prolonged ICU stay at the multivariate analysis were body mass index (BMI), uNGAL 24 h after surgery, and aortic cross-clamp time. The predictors of high uNGAL levels 24 h after at a multivariate analysis were preoperative uNGAL and logistic European System for Cardiac Operative Risk Evaluation. At a multivariate analysis the only independent predictors of prolonged ICU stay were BMI, uNGAL 24 h after surgery and aortic cross-clamp time.

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INTRODUCTION

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein belonging to the lipocalin superfamily. Lipocalins are composed of 8 beta-strands that form a beta-barrel enclosing a calyx. The calyx binds and transports low molecular weight chemicals. These proteins interact with cell-surface receptors.[1]

Human NGAL is expressed by neutrophils and various epithelial cells. Variable degree of NGAL gene expression is demonstrated in human tissues, such as uterus, prostate, salivary glands, lung, trachea, stomach, colon, and kidney.[2]

The recent findings that NGAL binds siderophores (iron-chelating molecules secreted by micro-organisms) and is highly expressed in various pathological states, such as acute kidney injury (AKI), have prompted a large number of studies. NGAL gene was found to be one of the seven genes that were highly upregulated in mouse models of renal ischemia reperfusion injury. NGAL was detected in the very first urine samples within 2 h after ischemia and its levels correlated with the duration of ischemia.[3]

Further experiments validated NGAL as one of the earliest and most robustly induced proteins in kidneys following ischemic and nephrotoxic insults. NGAL can be measured both in plasma

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and urine samples. NGAL gene upregulation occurs in two major areas in the early phase of AKI, kidney, and other systemic organs, such as liver and lungs. The NGAL synthesized in the distal tubules of the kidney is efficiently excreted in urine and that synthesized in other organs constitute the systemic pool.[4]

Both serum and urinary NGAL (uNGAL) have been found to be reliable predictors of AKI in cardiac surgical patients.[5-9] uNGAL measurements are probably more reflective of local renal injury, since it is noninvasive and relatively free of interfering proteins.

Previous clinical studies investigated the role of NGAL in predicting postoperative AKI in the specific setting of cardiac surgery.[5-9]

We performed this study to evaluate the role of NGAL in predicting postoperative intensive care stay in high-risk patients undergoing cardiac surgery.

MATERIALS AND METHODS

After Ethical Committee approval and patients' written consent, 27 patients who underwent high-risk cardiac surgery in a single hospital were enrolled in this observational study. Inclusion criteria were age>18 years, elective surgery, and one of the following: Reintervention or combined surgery, defined as multiple valvular surgery or valvular surgery associated to coronary artery bypass grafting (CABG) or ascending aorta replacement. Exclusion criteria were emergent operation, lack of consent, inclusion in other protocols, and chronic renal failure on renal replacement therapy.

All patients underwent preoperative clinical evaluation, routine blood tests (cell blood count, coagulation, electrolytes, liver and renal function, enzymes of tissue necrosis), resting ECG, chest radiograph and transesophageal echocardiography.

Patients older than 40 years or with history suggestive of ischemic heart disease underwent coronary angiography before surgery. Preoperative therapy was administered until the day of surgery with the exception of aspirin suspended a week before the procedure, and ACE inhibitors suspended on the day of surgery.

All patients received a standardized anesthetic management. Premedication (morphine 0.1 mg/kg intramuscularly; scopolamine 0.003 mg/kg intramuscularly) was administered 1 h before surgery; general anesthesia was induced with fentanyl (10–20 μg/kg) and propofol (2 mg/kg). To facilitate endotracheal intubation, rocuronium 0.5 mg/kg was administered. Anesthesia was maintained with propofol (2–4 mg/kg/h), sevofluorane (end-tidal concentration <1 MAC), and additional doses of fentanyl when required. An intraoperative infusion of tranexamic acid (1 g over 20 min followed by 400 mg/h) was used for all patients. All the patients received colloid solutions. All the operations were performed by one of the six surgeons. All the patients underwent median sternotomy.

The standard cardiopulmonary bypass (CPB) technique was used with ascending aortic and two-stage venous cannulation in all the patients. During CPB, moderate hemodilution (hematocrit 20%–25% with mild systemic hypothermia (32°C–34°C) was utilized. A bolus of 300 U/kg of heparin was administered to achieve an activated clotting time greater than 480 s for aortic and caval cannulation. The extracorporeal device consisted of a centrifugal pump (BP80 Medtronic, Minneapolis, MN, USA). The circuit priming consisted of 1500 mL Ringer's lactate containing 0.5 g/kg mannitol 18%, 0.5 g tranexamic acid, 5000 IU of heparin. The pump flows were adjusted to maintain a flow ≥4.5 L/min. Protamine reversal was performed at the end of operation. According to the needs, the patients were infused fluids administered diuretics, and inotropic drugs.

Monitoring included arterial and central venous blood pressure, ECG (leads II and V_5) with ST-segment analysis, temperature, pulse oximeter, end-tidal carbon dioxide, and urine output.

After surgery, all the patients were transferred to the intensive care unit (ICU). For each of them, vital signs, hourly diuresis, and biochemical signs (serum creatinine, plasma electrolytes, and gas analysis parameters), and clinical course in intensive care and treatments, were collected.

uNGAL was measured before anesthesia induction, at the arrival to the ICU after surgery and 24 h after surgery.

Decision to transfer the patient from the ICU to the ward was based on these criteria: Pulse oximetry ≥94% at an FiO_2≤0.5 by facemask, adequate cardiac stability with no hemodynamically significant arrhythmias, chest tube drainage <50 mL/h, urine output >0.5 mL/kg/h, no

intravenous inotropic or vasopressor agent in excess of dopamine 5 μg/kg/min, and no seizure activity. Criteria for hospital discharge were hemodynamic and cardiac rhythm stability, presence of clean and dry incisions, afebrile, normal bowel movement, and independent ambulation and feeding.

uNGAL was measured on Architect i1000 (Abbott Diagnostici, Roma, Italy), the Architect uNGAL assay is a chemiluminescent microparticle immune assay for the quantitative detection in human urine.

Statistics

Data were analyzed using SAS 1999–2001 program (release 8.2 by SAS Institute Inc., Cary, NC, USA). Continuous measures are expressed as mean±SD or as median (25^{th}–75^{th} percentile), whereas categorical variables are reported as number (percent). The Pearson's correlation coefficient was used to explore the linear relationship between two variables. We used a multivariate general linear model to assess the effect of independent variables on ICU. Variables with univariate significance (<0.05) were entered into the regression's model. We present the parameter estimate and *P* value at a 95% confidence level for each analyzed variables.

RESULTS

All our patients underwent surgery with CPB. Thirteen patients (48%) underwent multiple valvular surgery, 8 (30%) combined valvular surgery and CABG, and 6 (22%) combined valvular surgery and ascending aorta replacement.

Seventeen patients (63%) had perioperative need for inotropic drugs, and 2 of these patients (7.4%) needed also intra-aortic balloon pump. Diuretics were used in 11 patients (41%). Four patients (15%) received red blood cell transfusions. Six (22%) patients had AKI, according to R of RIFLE criteria, no one required renal replacement therapy or died. Median ICU stay was 1 day (1–3 days) and length of hospital stay was 10 days (7–10 days).

uNGAL was 18 (8.7–28.1) ng/mL at baseline, 10.7 (4.4–36.1) ng/mL at ICU arrival, and 29.6 (9.6–39.5) 24 h later. uNGAL was not associated with the development of AKI.

Perioperative data are illustrated in Table 1 together with their univariate and multivariate association with prolonged ICU stay.

Table 1: Perioperative data of 27 patients who underwent high-risk cardiac surgery together with their univariate and multivariate association to postoperative intensive care unit stay

Perioperative data	Values (%)	*P* value univariate analysis	*P* value multivariate analysis
Age, years	65 ± 13.0	0.4	
Females, *n* (%)	10 (37)	0.07	
Body Mass Index, kg/m^2	25.5 ± 4.13	0.006	0.006
Ejection fraction, %	56 ± 11.2	0.007	
End-diastolic diameter, mm	57 ± 9.4	0.03	
Serum creatinine at baseline, mg/dL	1.0 ± 0.29	0.3	
uNGAL at baseline, ng/mL	18 (8.7–28.1)	0.5	
Logistic EUROscore	4.9 ± 3.11	0.6	
Previous cardiac surgery	3 (11)	0.2	
Hypertension, *n* (%)	16 (59)	0.13	
Previous myocardial infarction, *n* (%)	4 (15)	0.08	
Atrial fibrillation, *n* (%)	7 (26)	0.07	
Cardio-pulmonary by-pass time, min	109 ± 37.2	0.022	
Aortic cross-clamp time, min	83 ± 27.5	0.041	0.008
Inotropic drugs, *n* (%)	17 (63)	0.044	
Diuretics, *n* (%)	11 (41)	0.2	
Transfusion of red blood cells, *n* (%)	4 (15)	0.3	
Intra aortic balloon pump, *n* (%)	2 (7.4)	0.039	
Serum creatinine at ICU arrival, mg/dL	1.0 ± 0.28	0.14	
Serum creatinine 24 h after surgery, mg/dL	1.2 ± 0.43	0.13	
Troponine T at ICU arrival, *ng/mL*	0.54 (0.41–0.80)	0.7	
Troponine T 8 h after surgery, ng/mL	1.00 (0.62–1.41)	0.9	
Troponine T 24 h after surgery, ng/mL	0.84 (0.62–1.16)	0.5	
uNGAL ICU arrival, ng/mL	10.7 (4.4–36.1)	0.6	
uNGAL 24 h after surgery, ng/mL	29.6 (9.6–39.5)	0.02	0.03

uNGAL - Neutrophil gelatinase-associated lipocalin; ICU - Intensive care unit; EUROscore - European System for Cardiac Operative Risk Evaluation. Data are expressed as mean±standard deviation, median (interquartile range), or number (percentage)

The predictors of prolonged ICU stay at the univariate analysis were the followings: Body mass index (BMI), preoperative ejection fraction and end-diastolic diameter, uNGAL 24 h after surgery, CPB time, aortic cross-clamp time and intraoperative need for inotrops or IABP. At a multivariate analysis the only independent predictors of prolonged ICU stay were the following: BMI, uNGAL 24 h after surgery, and aortic cross-clamp time.

We made another set of analysis to understand which perioperative factors were related to high uNGAL levels 24 h after surgery [Table 2]. The predictors of higher uNGAL levels 24 h after surgery at the univariate analysis were the following: Preoperative ejection fraction, preoperative uNGAL, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), preoperative atrial fibrillation, perioperative need for IABP, and serum creatinine at ICU arrival. At a multivariate analysis the only independent predictors of higher uNGAL levels 24 h after surgery were preoperative uNGAL and logistic EuroSCORE.

Table 2: Perioperative data of 27 patients who underwent high-risk cardiac surgery together with their univariate and multivariate association to uNGAL 24 h after surgery

Perioperative data	Values (%)	*P* value univariate analysis	*P* value multivariate analysis
Age, years	65 ± 13.0	0.2	
Females, *n* (%)	10 (37)	0.18	
Body mass index, kg/m^2	25.5 ± 4.13	0.5	
Ejection fraction, %	56 ± 11.2	0.014	
End-diastolic diameter, mm	57 ± 9.4	0.058	
Serum creatinine at baseline, mg/dL	1.0 ± 0.29	0.5	
uNGAL at baseline, ng/mL	18 (8.7–28.1)	0.005	0.001
Logistic EUROscore	4.9 ± 3.11	0.06	0.03
Previous cardiac surgery	3 (11%)	0.08	
Hypertension, *n* (%)	16 (59)	0.8	
Previous myocardial infarction, *n* (%)	4 (15)	0.7	
Atrial fibrillation, *n* (%)	7 (26)	0.035	
Cardiopulmonary bypass time, min	109 ± 37.2	0.2	
Aortic cross-clamp time, min	83 ± 27.5	0.8	
Inotropic drugs, *n* (%)	17 (63)	0.7	
Diuretics, *n* (%)	11 (41)	0.3	
Transfusion of red blood cells, *n* (%)	4 (15)	0.9	
Intra aortic balloon pump, *n* (%)	2 (7.4)	0.039	
Serum creatinine at ICU arrival, mg/dL	1.0 ± 0.28	0.006	
Troponine T at ICU arrival, ng/mL	0.54 (0.41–0.80)	0.5	
Troponine T 8 h after surgery, ng/mL	1.00 (0.62–1.41)	0.4	
uNGAL ICU arrival, ng/mL	10.7 (4.4–36.1)	0.6	

uNGAL - Neutrophil gelatinase-associated lipocalin; ICU - Intensive care unit; EUROscore - European system for cardiac operative risk evaluation. Data are expressed as mean±standard deviation, median (interquartile range), or number (percentage)

DISCUSSION

The most important result of this study is to suggest that uNGAL at 24 h after cardiac surgery is a predictor of prolonged ICU stay.

uNGAL was the only biomarker predicting prolonged ICU stay: Neither serum creatinine nor serum troponine T were significant predictors of prolonged ICU stay at multivariate analysis. Among the other predictors of prolonged ICU stay at multivariate analysis we found BMI and aortic cross-clamp time.

It is interesting to note that an important predictor of high uNGAL 24 h after surgery is the EuroSCORE. The EuroSCORE identifies a number of risk factors that help to predict mortality in cardiac surgery:[10,11] Age, female sex, preoperative ejection fraction, serum creatinine >200 μmol/L, previous cardiac surgery, recent myocardial infarct or unstable angina, emergency operation, critical preoperative state, type of surgery, and other copathologies (extracardiac arteriopathy, pulmonary disease, and neurologic dysfunction).

Furthermore, we also suggest that NGAL immediately after cardiac surgery (10.7; 4.4–36.1 ng/mL) is not increased when compared to preoperative values (18; 8.7–28.1 ng/mL). This finding is in contrast with that of other authors. Mishra *et al*.[5] demonstrated that postoperative NGAL measured both in urine and in plasma samples peaked 2 h postoperatively in 71 children undergoing cardiac surgery with CPB. Bennet confirmed these findings in 191 children undergoing the same kind of surgery.[6]

Also Xin *et al*.[10] and Tuladhar *et al*.,[11] studying, respectively, 33 and 50 adults undergoing cardiac surgery with CPB, confirmed that both plasma and uNGAL peaked 2 h after surgery. In a large prospective study, Wagener *et al*.[9] studied 426 adult patients undergoing cardiac surgery and found that uNGAL peaked immediately after surgery and remained high for 24 h. Our hypothesis to explain the late rise in uNGAL levels is that our patients had uneventful intraoperative period with short surgical time and hemodilution; furthermore, since they were high-risk patients undergoing complex surgery, they had a postoperative course characterized by low cardiac output syndrome and use of inotropic agents.

This was a small pilot study and the results should be confirmed in a large population before including uNGAL among the established predictors of prolonged ICU stay. The small sample size was probably the reason why we did not find an association between uNGAL and AKI in our population.

We conclude that uNGAL could predict prolonged ICU stay after high-risk cardiac surgery.

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