AKI Superimposed On CKD After Cardiac Surgery Needs Different Cutoff Value Of Plasma NGAL

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Background and Purpose

Plasma neutrophil gelatinase-associated lipocalin (NGAL) is a recently developed new acute kidney injury (AKI) biomarker and its performance for pediatric and adult post-cardiac surgery AKI has been reported. However, previous clinical evaluations focused mostly on AKI occurred in patients without chronic kidney disease (CKD). It is still unclear whether plasma NGAL can predict acute-on-chronic kidney injury after cardiac surgery, because CKD significantly increases plasma NGAL levels in stable condition and may hamper the prediction of AKI by plasma NGAL measurement.

The present study was aimed at evaluating plasma NGAL as an AKI biomarker with adult post-cardiac surgery patients with or without preoperative complication by CKD.

Materials and Methods

Patient population

A total of 143 adult patients undergoing scheduled cardiac surgery at Tokyo University Hospital (Tokyo, Japan) and Itabashi Chuo Medical Center (Tokyo, Japan) were studied prospectively. Patients with end-stage renal disease or renal transplant were excluded. The study protocol was approved by the Institutional Review Board of each hospital. The presence of AKI was assessed daily by calculating the change in serum creatinine from the baseline (before surgery) to the maximum serum creatinine until postoperative day (POD) 3; AKI was defined as an absolute increase in serum creatinine of more than 0.3 mg/dl or a 50% increase from the baseline. The AKI severity was categorized according to the AKIN criteria. Pre-existing chronic kidney disease (CKD) was determined by estimated GFR lower than 60 ml/min per 1.73 m^2, as calculated using the MDRD equation with a known baseline creatinine value.

Plasma NGAL measurement

For each patient, eight blood samples were obtained, which corresponded to presurgery, 0 hr (ICU arrival), and 2, 4, 12, 24, 36, and 60 hr after ICU arrival. Plasma NGAL was determined using an NGAL test (Triage; Alere, San Diego, CA, USA). The test is a point-of-care, fluorescence-based immunoassay designed for rapid quantitative measurement of NGAL in EDTA-anticoagulated whole blood.

Statistical analyses

Data were expressed as mean ± standard deviation and continuous variables were compared using t-test or Wilcoxon rank-sum tests when the normality assumption does not hold. Categorical variables were compared using the Pearson χ^2 or Fisher's exact test. The performance of urinary biomarkers was determined using receiver operating characteristic (ROC) curve analysis. These calculations were performed using software (JMP ver. 8.0; SAS Institute Inc.). A conventional criterion of alpha level 0.05 was used to determine statistical significance.

Discussion

An AKI biomarker that can detect both de novo AKI and AKI superimposed on CKD will be useful in a clinical setting. More than 40% patients in this cohort were complicated with CKD before surgery (Table 1). Results of the present study show a significant and negative correlation between eGFR and plasma NGAL measured before surgery. These data suggest that de novo AKI and AKI superimposed on CKD have different cutoff values.

When we classified the patients into four groups using AKI and pre-existing CKD, the CKD(-)AKI(+) group and the CKD(+)AKI(-) group showed virtually equal plasma NGAL levels at all perioperative sampling points (Fig. 2). This result suggests that the magnitude of AKI-induced increase of plasma NGAL from the baseline (i.e. before surgery) was in the same range of increase of plasma NGAL by reduced GFR in CKD. Therefore, plasma NGAL levels should be interpreted with the existence of preoperative CKD.

ROC analysis in this study revealed that the cutoff values of plasma NGAL for AKI in the non-CKD patients were approximately 100 ng/ml, whereas results obtained with the CKD patients showed cutoff values of 120–180 ng/ml (Table 4).

Limitations; 1) the number of patients (n = 143), although the patients were enrolled at two general hospitals, might be insufficient to determine the reliability and generalizability of plasma NGAL. 2) AKI was diagnosed only with serum creatinine. 3) AKI diagnosis based on serum creatinine might underestimate renal injury. It has been suggested that a composite endpoint by clinical events other than a short-term change in serum creatinine should be regarded as a major adverse kidney event.

Conclusion

Plasma NGAL can detect post-cardiac surgery AKI occurring in CKD and non-CKD patients. The baseline plasma NGAL was negatively correlated with the estimated GFR before surgery. Therefore, determining different cutoff values for de novo AKI and AKI superimposed on CKD was required for accurate AKI diagnosis.

Results

Table 1. Patient characteristics

	Non-AKI (n = 89)	AKI (n = 54)	P value
Age (y.o.)	67.9 ± 11.4	66.3 ± 11.0	0.4265
Male, n (%)	56 (62.9%)	32 (59.3%)	0.7241
Diabetes, n (%)	31 (34.8%)	16 (29.6%)	0.5841
Hypertension, n (%)	56 (62.9%)	36 (66.7%)	0.7203
CKD, n (%)	33 (37.1%)	34 (63.0%)	0.0033
Serum Cre (mg/dl)	0.88 ± 0.34	1.26 ± 0.64	< 0.0001
eGFR (ml/min/1.73 m^2)	67.0 ± 21.6	51.1 ± 24.7	< 0.0001
Plasma NGAL (ng/ml)	71.1 ± 38.1	105.6 ± 65.4	0.0001
Operation			
Operation time (min)	308.5 ± 85.0	384.2 ± 182.6	0.0010
OPCAB, n (%)	17 (19.1%)	12 (22.2%)	0.6725
CPB, n (%)	72 (80.9%)	42 (77.8%)	0.6725
CPB time (min)	160.1 ± 59.1	209.3 ± 142.2	0.0111
Valve surgery, n (%)	33 (37.1%)	17 (31.5%)	0.5882
CABG surgery, n (%)	8 (9.0%)	7 (13.0%)	0.5748
Valve + CABG, n (%)	9 (10.1%)	7 (13.0%)	0.5964
Aortic graft replacement, n (%)	18 (20.2%)	11 (20.4%)	1.0000
Other, n (%)	5 (5.6%)	4 (7.4%)	0.7296
Postoperative			
Need for RRT, n (%)	0 (0.0%)	10 (18.5%)	< 0.0001
ICU stay (day)	3.5 ± 2.2	8.4 ± 10.3	< 0.0001

This study prospectively analyzed 143 adult patients who had cardiac surgery at two general hospitals. Severity of AKI; AKIN stage 1, n = 36; stage 2, n = 7; stage 3, n=11 A significant correlation was found between estimated GFR and plasma NGAL measured before surgery (R = −0.36, p < 0.0001).

Table 2. Plasma NGAL values at various time points

		Non-AKI (n=89)	AKI (n=54)	P value
Plasma NGAL (ng/ml)	pre	71.1 ± 38.1	105.6 ± 65.4	0.0001
	0 h	126.2 ± 78.8	199.4 ± 103.0	<0.0001
	2 h	125.2 ± 77.1	206.5 ± 112.9	<0.0001
	4 h	115.4 ± 76.5	216.2 ± 128.7	<0.0001
	12 h	102.1 ± 67.5	215.6 ± 142.9	<0.0001
	24 h	93.4 ± 57.4	205.0 ± 145.7	<0.0001
	36 h	87.5 ± 50.9	200.3 ± 153.3	<0.0001
	60 h	75.7 ± 40.2	165.8 ± 132.8	<0.0001

Figure 1. Plasma NGAL values grouped by AKI severity
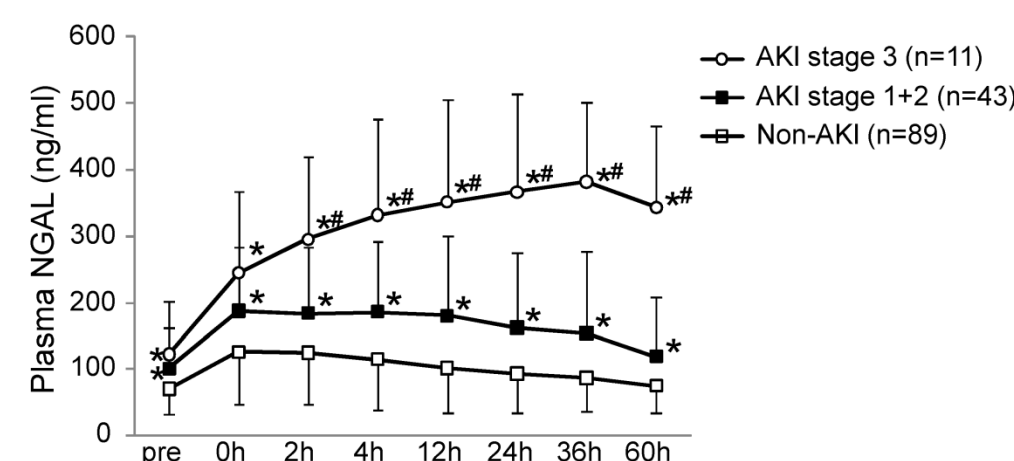
Table 3. Multiple logistic regression analysis

Variable	Regression Coefficient (95% confidence interval)	P value
CKD	0.411 (0.026–0.803)	0.037
Operation time (min)	0.005 (0.002–0.009)	0.011
Plasma NGAL before surgery (ng/ml)	0.010 (0.002–0.020)	0.018

A multiple logistic regression analysis incorporating the parameters with univariate p value < 0.05 revealed that plasma NGAL before surgery was independently associated with post-surgery AKI occurrence.

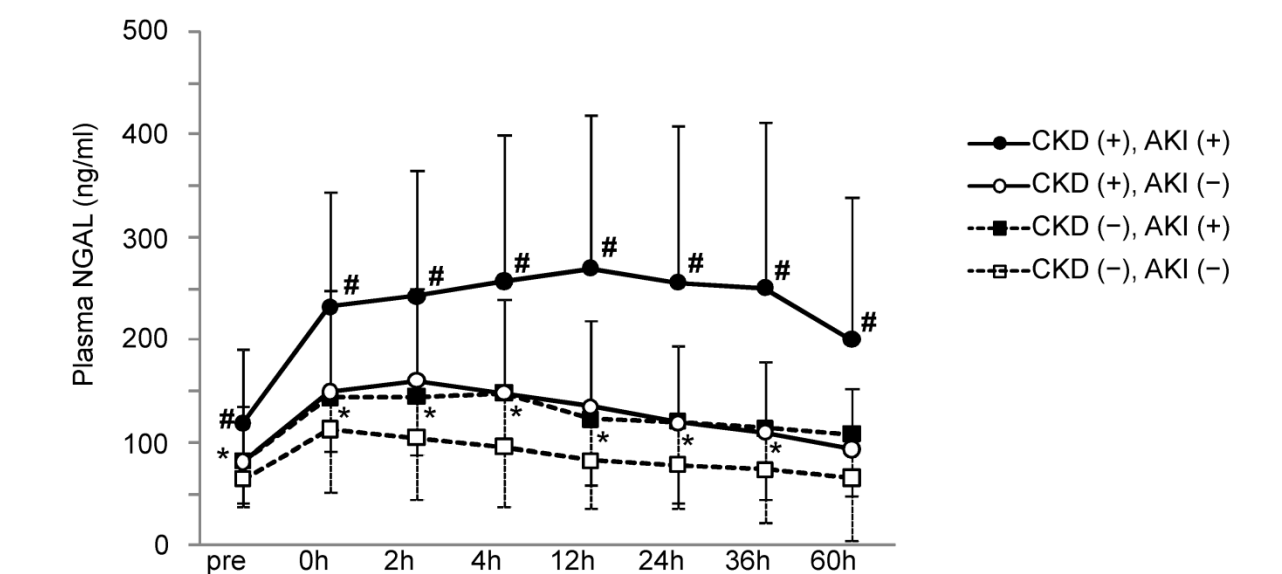### Figure 2. Plasma NGAL values in de novo AKI and AKI superimposed on CKD

Table 4. ROC analysis for plasma NGAL in de novo AKI and AKI superimposed on CKD

	Non-CKD AUC-ROC (95% CI)	Cutoff (ng/ml)	Sensitivity/ Specificity (%)	CKD AUC-ROC (95% CI)	Cutoff (ng/ml)	Sensitivity/ Specificity (%)
pre	0.62 (0.50 − 0.73)	67	35.0/80.9	0.72 (0.57 − 0.82)	65	70.6/69.7
0 hr	0.68 (0.55 − 0.79)	103	80.0/60.7	0.76 (0.62 − 0.86)	122	85.3/54.5
2 hr	0.73 (0.60 − 0.84)	97	85.0/66.1	0.74 (0.60 − 0.84)	142	82.4/51.5
4 hr	0.80 (0.68 − 0.89)	97	85.0/75.0	0.74 (0.59 − 0.85)	158	78.8/69.7
12 hr	0.72 (0.56 − 0.83)	107	60.0/84.6	0.80 (0.66 − 0.89)	186	73.5/78.8
24 hr	0.68 (0.53 − 0.80)	68	70.0/64.3	0.78 (0.64 − 0.88)	172	75.8/81.2
36 hr	0.67 (0.53 − 0.79)	64	65.0/68.9	0.81 (0.68 − 0.90)	161	67.7/78.8
60 hr	0.57 (0.45 − 0.83)	207	20.0/100.0	0.79 (0.66 − 0.88)	127	63.6/80.6

ROC analysis in this study revealed that the cutoff values of plasma NGAL for AKI in the non-CKD patients were approximately 100 ng/ml, whereas results obtained with the CKD patients showed cutoff values of 120–180 ng/ml.