学位論文

Renal Biomarkers in the Early Detection of Acute Kidney Injury After Off-Pump Coronary Artery Bypass Grafting
（オフポンプ冠動脈バイパス術後の急性腎障害に対する腎バイオマーカーの早期発見能について）

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ORIGINAL ARTICLE

Renal Biomarkers in the Early Detection of Acute Kidney Injury After Off-Pump Coronary Artery Bypass Grafting

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Background: Cardiac surgery-associated (CSA) acute kidney injury (AKI) is a severe postoperative complication in patients undergoing off-pump coronary artery bypass grafting (OPCAB). Early detection of postoperative CSA-AKI may be key to improving patient outcomes. This study explored the use of renal biomarkers measured immediately after surgery for the early detection of CSA-AKI in patients undergoing OPCAB.

Methods and Results: In all, 111 patients who underwent OPCAB at Kumamoto University Hospital between June 2020 and October 2022 were included in this study. Urinary neutrophil gelatinase-associated lipocalin, liver-type fatty acid-binding protein, and *N*-acetyl-*β*-D-glucosaminidase (NAG) were measured upon arrival in the intensive care unit (ICU) after surgery. AKI was diagnosed using KDIGO criteria. Of the 111 patients, 32 (28.8%) developed postoperative AKI. Regarding AKI staging, 19 (59.4%), 11 (34.4%), and 2 (6.3%) patients had Stage 1, 2, and 3 AKI, respectively. There were significant differences in chronic kidney disease, preoperative estimated glomerular filtration rate (eGFR), and NAG between the AKI and non-AKI groups. Multivariate analysis showed that preoperative eGFR (odds ratio [OR] for 5-mL/min/1.73 m^2 increase in eGFR 0.75; 95% confidence interval [CI] 0.63–0.89) and increasing urinary NAG concentrations at ICU admission (OR 2.44; 95% CI 1.30–4.60) were significant risk factors for CSA-AKI in OPCAB patients.

Conclusions: NAG and eGFR may be valuable biomarkers for the early detection of CSA-AKI in patients undergoing OPCAB.

Key Words: Acute kidney injury; Urine biomarker

In Japan, the number of patients with cardiovascular disease is increasing as the population ages, and the number of cardiac surgeries continues to rise. Although cardiac surgery is an effective treatment for cardiovascular diseases, it is associated with several complications.

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a severe complication in cardiac surgery patients, affecting approximately 25–30% of these patients.[1,2] CSA-AKI is associated with increased operative mortality, as well as prolonged intensive care unit (ICU) stay, hospital stay, and duration of ventilator use.[3] Although several risk factors for CSA-AKI have been reported, the risks have not yet been clearly elucidated; thus, there are limited active treatments for CSA-AKI.[4] The UK acute kidney injury (AKI) guidelines state that although there is no specific treatment for AKI because of the wide variety of causes, it is advisable to start treatment (e.g., supplemental fluids and inotropic drugs) as soon as a diagnosis of AKI is made to improve prognosis.[4]

Although the UK guidelines recommend starting treatment, such as infusion, as soon as possible after the diagnosis of CSA-AKI, in actual clinical practice it often takes time to reach a diagnosis due to elevated serum creatinine (SCr) or decreased urine output. In addition, Barrera-Chimal et al reported that mineralocorticoid receptor antagonists such as spironolactone are effective in treating CSA-AKI, and early administration of these drugs may improve the prognosis of CSA-AKI.[5] In short, early detection of the onset of CSA-AKI is crucial for appropriate therapeutic intervention.[5] In particular, it would be clinically helpful to have an indicator that can detect the onset of CSA-AKI at the time of ICU admission when clinical evaluation is focused on the first stage of postoperative management. At present, there is no such helpful indicator because potential biomarkers have not been sufficiently investigated.

Recently, several urinary biomarkers have attracted

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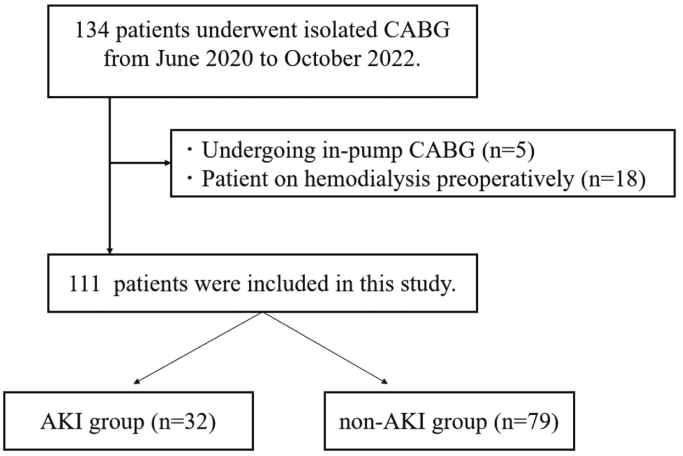


Figure 1. Study cohort description. In all, 134 patients underwent isolated coronary artery bypass grafting (CABG) at Kumamoto University Hospital between June 2020 and October 2022. Patients who underwent preoperative hemodialysis or on-pump CABG were excluded. The 111 patients included in the study were divided into 2 groups according to the presence or absence of postoperative acute kidney injury (AKI).

attention owing to their usefulness in the early diagnosis of AKI.[6–8] Of these, neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid-binding protein (L-FABP), and *N*-acetyl-*β*-D-glucosaminidase (NAG) have been approved for use in diagnostic tests for AKI.[6–8] However, the usefulness of these urinary biomarkers for CSA-AKI remains unclear. If AKI could be evaluated by a single measurement using spot urine samples at the time of ICU admission, rapid diagnosis and risk assessment would be possible.

This study was conducted to explore detection of the early occurrence of CSA-AKI after off-pump coronary artery bypass grafting (OPCAB) in adult patients using urinary biomarkers collected at the time of ICU admission. In addition, the association between clinical parameters and the occurrence of CSA-AKI from the preoperative period to immediately after ICU admission was also investigated.

Methods

Study Patients

This was a single-center observational study conducted at Kumamoto University Hospital (Kumamoto, Japan). Patients who underwent isolated coronary artery bypass grafting (CABG) between June 2020 and October 2022 were enrolled in the study. Overall, 134 patients underwent isolated CABG at Kumamoto University Hospital. Patients undergoing on-pump CABG (n=5), and those receiving maintenance hemodialysis at study enrollment (n=18) were excluded. The remaining 111 patients (82.8%) were divided into 2 groups according to the presence or absence of postoperative AKI for analysis. The study flowchart is shown in **Figure 1**.

After admission to the ICU, urine samples were collected from all patients, and NGAL, L-FABP, and NAG concentrations were measured. Patients were followed up postoperatively for 7 days, and AKI diagnosis was based on the KDIGO criterion.[9]

The study protocol was reviewed and approved by the Research Ethics Committee of Kumamoto University Hospital, following the principles of the revised Declaration of Helsinki. Informed consent was obtained from all participating patients.

Surgical Procedure

The procedure was performed via median sternotomy in all patients. Our strategy for isolated CABG was directed towards achieving complete myocardial revascularization using an off-pump technique, whenever feasible. Details of our operative techniques for off-pump CABG have been described previously.[10] All arterial grafts were harvested in a skeletonized matter using an ultrasonic scalpel (Harmonic Synergy; Ethicon Endosurgery Inc., Blue Ash, OH, USA). All significantly stenosed coronary arteries (those with at least a 75% reduction in diameter) >1 mm in diameter were bypassed. Our strategy for graft selection in isolated CABG has been previously described.[10] When distal anastomosis was performed, a bloodless field was obtained using a proximal silicone elastic snare suture and a carbon dioxide blower. Postoperatively, aspirin (100 mg/day) and clopidogrel (75 mg/day) were administered after initiating oral intake. Aspirin was continued indefinitely, and clopidogrel was discontinued 1 year after surgery.

Definitions

We used the KDIGO definition as our diagnostic criterion for AKI, which reflects an abrupt (within 48 h) decline in renal function. AKI was defined as an absolute increase in SCr concentrations of ≥0.3 mg/dL within 48 h or a ≥1.5-fold increase within 7 days, or a reduction in urine output (documented oliguria of <0.5 mL/kg/h for >6 h).

AKI was staged according to Levin et al.[9] Stage 1 was defined as an increase in SCr ≥0.3 mg/dL within 48 h or to 1.5- to 1.9-fold the baseline value within 7 days, or a reduction in urine output <0.5 mL/kg/h for 6–12 h; Stage 2 was defined as an increase in SCr to 2.0- to 2.9-fold of the baseline value, or a reduction in urine output <0.5 mL/kg/h for ≥12 h; and Stage 3 was defined as an increase in SCr to 3-fold the baseline value, an absolute increase in SCr to ≥3-fold the baseline value, an absolute increase in SCr of ≥4.0 mg/dL, the initiation of renal replacement therapy (RRT), a reduction in urine output <0.3 mL/kg/h for ≥24 h, or anuria for ≥12 h.[9]

Clinical Evaluation and Laboratory Testing

Age (years) and sex were also evaluated. Smoking history was defined as a current or past smoking status. Hypertension was defined as history of hypertension, systolic blood

Table 1. Preoperative Variables

	Overall (n=111)	AKI group (n=32)	Non-AKI group (n=79)	P value
Age (years)	70 [61–74]	69 [60.5–75]	70 [62–74]	0.899
Female sex	25 (22.5)	3 (9.4)	22 (27.9)	0.044
Body surface area (m^2)	1.68 [1.55–1.78]	1.70 [1.63–1.82]	1.66 [1.52–1.78]	0.121
Hypertension	104 (93.7)	31 (96.9)	73 (92.4)	0.671
Diabetes	71 (64.0)	25 (78.1)	46 (58.2)	0.053
Dyslipidemia	103 (92.8)	31 (96.9)	72 (91.1)	0.435
Smoking history	79 (71.2)	25 (78.1)	54 (68.4)	0.361
Old myocardial infarction	22 (19.8)	7 (21.9)	15 (19.0)	0.794
History of cerebrovascular disease	18 (16.2)	7 (21.9)	11 (13.9)	0.394
Chronic kidney disease	21 (18.9)	14 (43.8)	7 (8.9)	<0.001
eGFR (mL/min/1.73 m^2)	59 [49–71]	49 [35–62]	62 [52–74]	<0.001
BUN (mg/dL)	17.9 [14.9–21.5]	18.9 [15.6–24.8]	17.7 [14.9–20.6]	0.146
Cr (mg/dL)	0.92 [0.78–1.08]	1.13 [0.93–1.60]	0.86 [0.74–1.03]	<0.001
Na (mEq/L)	139 [138–141]	139 [137–141]	140 [138–141]	0.409
K (mEq/L)	4.2 [4.0–4.5]	4.3 [4.0–4.6]	4.2 [3.9–4.4]	0.360
Cl (mEq/L)	105 [102–107]	104 [101–107]	105 [102–107]	0.402
Pre-operative systolic pressure (mmHg)	127.0 [118.0–139.0]	131.5 [122.0–143.5]	125.0 [117.0–137.0]	0.596
Pre-operative diastolic pressure (mmHg)	70.0 [62.0–78.0]	69.5 [64.0–78.5]	71.0 [60.0–78.0]	0.596
Pre-operative MAP (mmHg)	90.0 [81.3–97.3]	89.5 [83.8–102.3]	90.0 [78.7–96.7]	0.219

Unless indicated otherwise, values are presented as the median [interquartile range] or n (%). AKI, acute kidney injury; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure that is the average arterial pressure throughout one cardiac cycle, systole, and diastole.

Table 2. Operative and Postoperative Data

	Overall (n=111)	AKI group (n=32)	Non-AKI group (n=79)	P value
No. anastomoses	4 [3–5]	4 [3–4]	4 [3–5]	0.733
Operation time (min)	245 [212–268]	253 [225.5–274]	239 [205–267]	0.200
Bleeding (mL)	791 [486–1,215]	790.5 [497.5–1,314.5]	805 [480–1,193]	0.848
Blood transfusion	45 (40.5)	18 (56.3)	27 (34.2)	0.032
Maximum creatinine after operation (mg/dL)	1.01 [0.87–1.29]	1.57 [1.21–2.37]	0.94 [0.86–1.17]	<0.001
Intubation time (h)	6.5 [5.0–15.5]	9.2 [5.0–15.8]	6.0 [5.0–15.0]	0.524
Intensive care unit stay (days)	2.0 [1.0–2.0]	1.5 [1.0–2.0]	2.0 [1.0–2.0]	0.701
Stroke	3 (2.7)	1 (3.1)	2 (2.5)	1.000
Respiratory failure	0	0	0	–
Pneumonia	2 (1.8)	2 (6.3)	0	0.081
Required hemodialysis	2 (1.8)	2 (6.3)	0	0.081
Re-exploration due to bleeding	0	0	0	–
Mediastinitis	1 (0.9)	1 (3.1)	0	0.288
Atrial fibrillation	22 (19.8)	7 (21.9)	15 (19.0)	0.794
Minimum operative systolic pressure (mmHg)	80.0 [70.0–80.0]	80.0 [75.0–90.0]	80.0 [70.0–80.0]	0.752
Minimum operative diastolic pressure (mmHg)	50.0 [40.0–60.0]	60.0 [40.0–60.0]	50.0 [40.0–60.0]	0.059
Lowest operative MAP (mmHg)	56.7 [53.3–66.7]	66.7 [56.7–66.7]	56.7 [53.3–66.7]	0.131
ΔMAP (mmHg)	27.7 [20.0–37.3]	28.0 [20.7–37.5]	27.3 [19.0–37.3]	0.880
Maximum intraoperative CVP (mmHg)	17 [14–20]	17 [15–21]	17 [14–19]	0.149
Minimum intraoperative CVP (mmHg)	8 [6–10]	9 [7–10]	8 [6–9]	0.052

Unless indicated otherwise, values are presented as the median [interquartile range] or n (%). CVP, central venous pressure; ΔMAP, difference between preoperative and intraoperative minimum MAP. Other abbreviations as in Table 1.

pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg. Diabetes, dyslipidemia, previous myocardial infarction, and a history of cerebrovascular disease, peripheral artery disease, and chronic obstructive pulmonary disease were defined as a past history of the disease. Atrial fibrillation was defined as paroxysmal or persistent atrial fibrillation. Chronic kidney disease (CKD) was defined as a past history of the condition or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Mean arterial pressure (MAP) was defined as the average arterial pressure

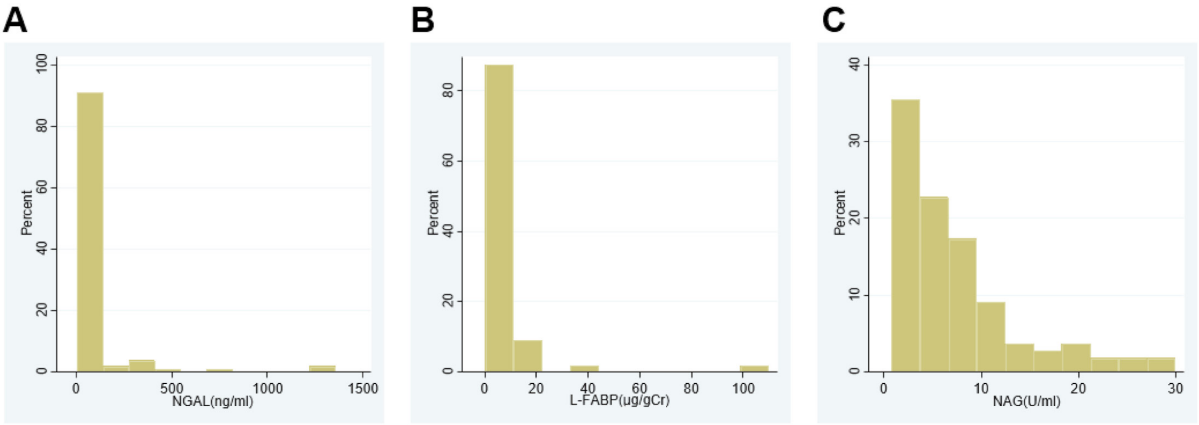


Figure 2. Distributions of measurements for the 3 biomarkers: (**A**) neutrophil gelatinase-associated lipocalin (NGAL); (**B**) liver-type fatty acid-binding protein (L-FABP); and (**C**) *N*-acetyl-β-D-glucosaminidase (NAG). Cr, creatinine.

Table 3. Urinary Biomarker Data

	All (n=111)	AKI group (n=32)	Non-AKI group (n=79)	P value
NGAL (ng/mL)	30.8 (16.4–63.0)	35.7 (21.9–61.4)	28.5 (15.6–63.6)	0.390
L-FABP (μg/mL)	2.1 (0.8–5.2)	3.8 (1.4–6.4)	1.5 (0.7–3.8)	0.130
NAG (U/L)	5.6 (2.7–9.5)	8.5 (5.6–15.5)	5.2 (2.5–7.6)	<0.001

Unless indicated otherwise, values are presented as the median (interquartile range). AKI, acute kidney injury; L-FABP, liver-type fatty acid-binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

throughout one cardiac cycle, systole, and diastole. Central venous pressure (CVP) was defined as the blood pressure in the venae cavae near the right atrium of the heart. We also evaluated blood urea nitrogen, SCr, serum sodium (Na), serum potassium (K), and serum chloride (Cl) concentrations.

Statistical Analysis

Continuous variables are summarized as the median with interquartile range (IQR) and categorical variables are presented as numbers and percentages. Comparisons between the AKI and non-AKI groups were performed using Wilcoxon's test for continuous variables and Fisher's exact test for categorical variables. Univariate logistic regression models were first used to assess associations between each candidate's risk factors and AKI outcome (≥Stage 1). Then, for variable selection, we considered variables with P<0.1 in univariate logistic regression models as candidate risk factors for the multivariate logistic regression model. We also included variables that are clinically important as candidate risk factors regardless of whether they had P>0.1 in the univariate analysis. Then, we performed a multivariate logistic regression analysis and subsequent backward variable selection analysis (P<0.05) using the candidate risk factors chosen as described above. We then used a multivariate ordinal logistic regression model to evaluate the associations between the risk factors and the severity of CSA-AKI. Notably, univariate and multivariate logistic regression models using robust standard errors of estimates were used to evaluate associations between each clinical parameter and AKI events. In the analyses of the area under the receiver operating characteristic curve (AUROC), 10,000 bootstrap replications were performed to estimate the median value and 95% confidence intervals (CIs). To evaluate the performance of the final multivariate logistic regression model, we compared AUROCs between the final model and the univariate logistic regression model of a single explanatory variable, such as eGFR or log(NAG) for each. Finally, the Hosmer-Lemeshow test was used to evaluate the goodness of fit of the multivariate logistic regression model. In this test, the clinical risk score for CSA-AKI was used a decile and the discrepancy between estimated CSA-AKI events and actual recorded CSA-AKI events was evaluated.

All statistical analyses were performed using Stata 15.0 (StataCorp, College Station, TX, USA). All P values are 2-tailed, and statistical significance was set at P<0.05.

Results

Patient Characteristics and Operative and Postoperative Data

Baseline clinical data are presented in **Table 1** and the surgical procedures and outcomes are presented in **Table 2** for patients enrolled in this study.

According to the KDIGO classification, 32 (28.8%) patients developed postoperative AKI. In terms of AKI staging, 19 (59.4%), 11 (34.4%), and 2 (6.3%) patients had

Table 4. Univariate and Multivariate Logistic Regression Analyses for AKI

Variable	Univariate models			Multivariate Model 1			Multivariate Model 2		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age (per 1-year increase)	1.00	0.96–1.04	0.867	1.03	0.97–1.09	0.353			
Female sex	0.27	0.07–0.98	0.046	0.27	0.05–1.51	0.137			
Diabetes	2.56	0.99–6.65	0.053	2.37	0.72–7.77	0.155			
Chronic kidney disease	8.00	2.8–22.83	<0.001						
eGFR (per 5-mL/min/1.73 m^2 increase)	0.75	0.64–0.87	<0.001	0.77	0.63–0.93	0.007	0.75	0.63–0.89	0.001
Operation time (per 10-min increase)	1.05	0.95–1.16	0.299						
Log(Bleeding volume)	0.93	0.47–1.82	0.825						
Blood transfusion	1.17	1.01–1.35	0.032	1.14	0.88–1.47	0.325			
Log(NGAL)	1.05	0.75–1.48	0.782						
Log(L-FABP)	1.45	1.05–2.01	0.024	1.01	0.61–1.67	0.963			
Log(NAG)	2.54	1.33–4.85	0.005	2.48	1.31–4.70	0.003	2.44	1.30–4.60	0.006
Minimum operative systolic pressure (per 5-mmHg increase)	1.01	0.96–1.05	0.761						
Minimum operative diastolic pressure (per 5-mmHg increase)	1.04	1.00–1.09	0.062	1.45	1.06–1.97	0.018			
ΔMAP (per 5-mmHg increase)	1.04	0.89–1.21	0.635						
Maximum operative CVP (per 1-mmHg increase)	1.10	0.99–1.23	0.087	1.14	0.92–1.40	0.228			
Minimum operative CVP (per 1-mmHg increase)	1.17	0.99–1.38	0.062	0.95	0.72–1.24	0.695			

Univariate logistic regression analysis was performed to assess associations between each candidate risk factor and AKI outcome (≥Stage 1). Next, a multivariate logistic regression analysis was performed using candidate risk factors with P<0.1 in the univariate logistic regression analysis or those that were considered clinically meaningful (Model 1). The final logistic regression model (Model 2) used stepwise variable selection analysis. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1–3.

Stage 1, 2, and 3 AKI, respectively. Of the patients with AKI, 2 required temporary hemodialysis after the operation. No patients died within 30 days.

No statistically significant differences were found between the AKI and non-AKI groups in terms of age, body surface area, or comorbidities such as hypertension and dyslipidemia. In contrast, female sex, patients with lower eGFR, and those who received intraoperative blood transfusions were significantly more common in the AKI group (**Tables 1**,**2**).

Urinary NGAL, L-FABP, and NAG Concentrations in AKI

The distribution of concentrations of the 3 biomarkers was right-skewed (**Figure 2**). Urinary NGAL and L-FABP concentrations were not significantly different between the AKI and non-AKI groups (**Table 3**). In contrast, urinary NAG levels at the time of ICU admission were significantly higher in the AKI than non-AKI group (**Table 3**).

Detectors of Postoperative AKI

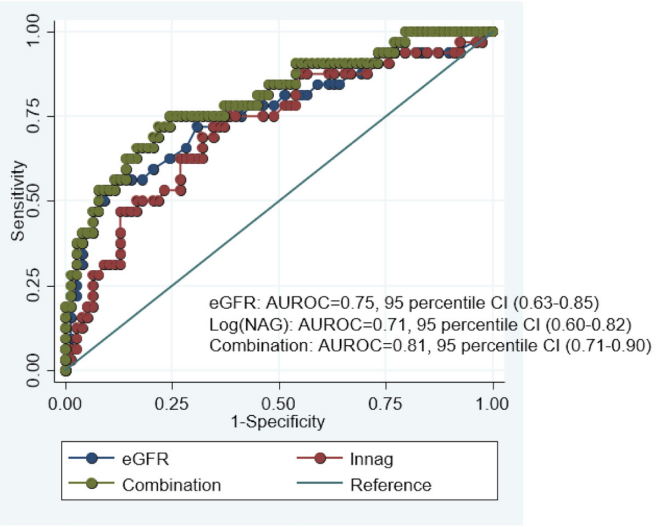
To evaluate the association between the clinical information collected at the time of ICU admission and CSA-AKI in patients undergoing OPCAB, we performed univariate logistic regression analysis for each clinical parameter. As a result, female sex (odds ratio [OR] 0.27; 95% CI 0.07–0.98), the presence of CKD (OR 8.00; 95% CI 2.80–22.83), decreased eGFR (OR for 5-mL/min/1.73 m^2 increase in eGFR 0.75; 95% CI 0.64–0.87) in the preoperative state, blood transfusion during operation (OR 1.17; 95% CI 1.00–1.35), minimum operative diastolic pressure (OR 1.04; 95% CI 1.00–1.09), maximum operative CVP (OR 1.10; 95% CI 0.99–1.23), minimum operative CVP (OR 1.17; 95% CI 0.99–1.38), elevation in urinary L-FABP concentrations (OR 1.45; 95% CI 1.05–2.01) and NAG concentrations (OR 2.54, 95% CI 1.33–4.85) at the time of ICU admission after cardiac surgery were significantly associated with the onset of CSA-AKI (**Table 4**).

Based on the results of the univariate analyses, we considered the clinical adequacy of these parameters as risk factors for CSA-AKI after OPCAB and concluded that age, female sex, decreased eGFR, blood transfusion, increased urinary L-FABP and NAG concentrations, minimum operative diastolic pressure, and maximum and minimum operative CVP pressure were candidate risk factors because the presence of CKD overlapped with decreasing eGFR levels. We subsequently performed multivariate logistic regression analysis to assess relationships between these candidate risk factors and CSA-AKI; subsequent backward variable selection analysis revealed that decreased eGFR in the preoperative state (OR for 5-mL/min/1.73 m^2 increase in eGFR 0.75; 95% CI 0.63–0.89) and elevation of urinary NAG concentrations at the time of ICU admission (OR 2.44; 95% CI 1.30–4.60) were significant risk factors for CSA-AKI in patients who underwent OPCAB (**Table 4**). Thus, we concluded that eGFR and urinary NAG concentrations were significant variables for the early detection of CSA-AKI and generated a detection score comprising eGFR and urinary NAG concentrations for the early detection of CSA-AKI onset, which we have named the CSA-AKI score:

$$\text{CSA-AKI score} = -0.0601754 \times \text{eGFR} + 0.9718174 \times \log_e(\text{NAG})$$

Interestingly, this score was significantly associated with

A



B

	delta AUC (95 percentile CI)	delta IDI (95 percentile CI)	Delta NRI (95 percentile CI)
Combination vs eGFR	0.07 (0.01-0.16)	0.06 (0.01-0.16)	0.39 (0.07-0.65)
Combination vs log(NAG)	0.10 (0.02-0.22)	0.12 (0.03-0.25)	0.39 (0.13-0.63)

Figure 3. Receiver operating characteristic (ROC) curves for estimated glomerular filtration rate (eGFR) and log-transformed *N*-acetyl-β-D-glucosaminidase (NAG) concentrations. (**A**) ROC curves were generated for eGFR and log(NAG), with areas under the ROC curve (AUROC) of 0.75 and 0.71, respectively, indicating acceptable predictive performance for both. (**B**) Log(NAG) and eGFR were evaluated in combination; the combined AUROC of 0.81 was higher than the delta AUROC, delta integrated discrimination increment (IDI), and delta net reclassification index (NRI), compared with the AUROC alone. Combined AUROC is more useful than each of these evaluations alone.

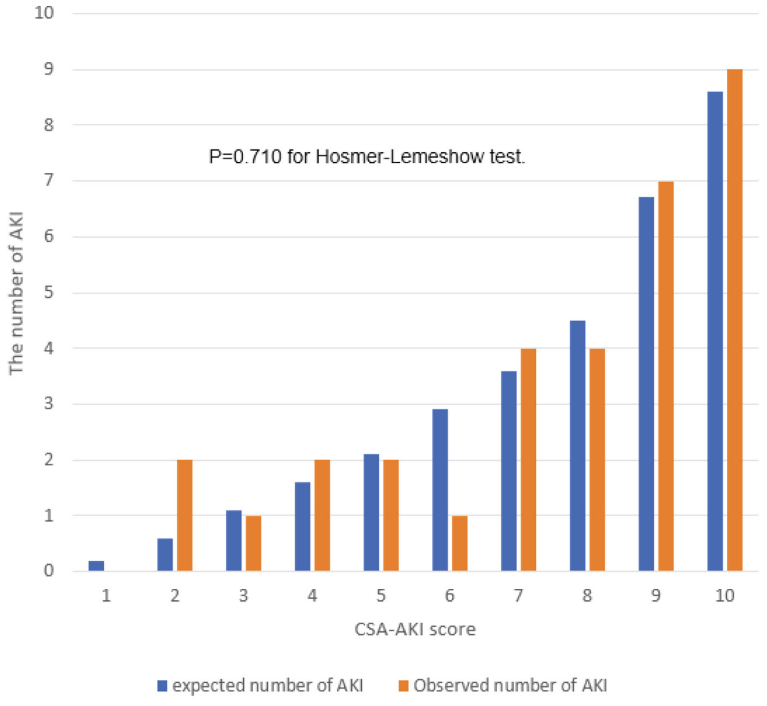


Figure 4. Hosmer-Lemeshow test of this study. The Hosmer-Lemeshow test revealed that the predictive probability for the occurrence of postoperative cardiac surgery-associated acute kidney injury (CSA-AKI) did not show a significant discrepancy between the observed and actual events in the present study.

the severity of CSA-AKI (OR 2.85; 95% CI 1.82–4.46).

In evaluating model performance, the AUROC for the final model was estimated to be 0.81 (95% CI 0.71–0.90), and the Hosmer-Lemeshow test revealed that the predictive probability for the occurrence of postoperative CSA-AKI did not show a significant discrepancy between observed and actual CSA-AKI events in the present study (P=0.7097; **Figures 3**,**4**). In addition, we confirmed that the predictive ability, evaluated by the integrated discrimination increment and net reclassification index, was significantly improved in the final model compared with the univariate model using the 2 risk factors of eGFR and NAG.

Discussion

This study explored the risk factors for AKI development after OPCAB using preoperative, intraoperative, and immediate ICU admission data. In all, 111 patients who underwent isolated OPCAB were included in this study. Elevated NAG concentrations in spot urine samples after ICU admission and low preoperative eGFR were risk factors for the development of AKI, as defined by the KDIGO criteria. Furthermore, the combination of these 2 factors improved the accuracy of detecting the development of AKI compared with the use of each factor alone. The results for blood loss, diabetes, NGAL, and L-FABP, commonly used markers, were not significant.

Unexpectedly, NGAL and L-FABP concentrations were not useful for the detection of postoperative AKI, with only NAG identified as a significant biomarker. Previous reports have suggested that biomarkers such as NGAL and L-FABP are useful for the early detection of AKI by capturing peak values through multiple measurements.[6–8,11,12] However, in the present study, the timing of risk assessment was based on the assessment of spot urine samples at the time of ICU admission, which may have resulted in the peak values of NGAL and L-FABP not being captured.

Considering the pathological conditions reflected by the biomarkers, NGAL and L-FABP are proteins secreted from the distal tubules into the blood and urine. Their production and urinary excretion are reported to increase when the kidneys and tubules are stressed and reabsorption from the proximal tubules is inhibited.[13,14] Conversely, NAG is a lysosomal enzyme that is highly localized in proximal tubular epithelial cells (among others) and is reportedly an absconding enzyme that leaks out of cells having increased membrane permeability due necrosis (i.e., when proximal tubular cells are severely damaged).[15] These reports suggest more severe tubular damage in patients with elevated urinary NAG concentrations than in those with increased urinary NGAL or L-FABP excretion.

Furthermore, urinary NAG may be a cost-effective test for detecting CSA-AKI in many centers because it is covered by insurance in Japan, can be performed at any medical facility, is less expensive than NGAL or L-FABP, and requires less time to perform.

In addition, as reported in other studies,[16] reduced preoperative eGFR was an independent risk factor for the development of AKI in the present study. A 5-year cohort study of more than 920,000 people in the general population of Alberta, Canada, reported that 6,520 (0.7%) were diagnosed with AKI and that a low eGFR was an independent risk factor.[16] AKI is generally considered to be caused by tubular damage, such as in acute tubular necrosis. Peritubular interstitial blood flow is easily destabilized by surgical invasion or reperfusion ischemia owing to shunt blood flow between the microvessels in the kidney.[17] Furthermore, chronic renal failure with reduced eGFR is associated with chronic tubular dysfunction due to various causes.[17] Therefore, hemodynamic changes, such as cardiac decompensation, are likely to cause further deterioration of tubular dysfunction, which, in turn, is likely to cause further deterioration of renal function. Considering that low eGFR was also a risk factor for the development of CSA-AKI in the present study, our results are consistent with previous reports and ideas.

A limitation of the present study is that it was a single-center study in Japan, and there may have been information bias. Thus, extrapolation needs to be examined before generalizing our conclusions to other non-Asian populations. In addition, the present study did not examine the effect of using cardiopulmonary bypass surgery. Future studies have to explore the impact of the use of cardiopulmonary bypass in CABG.

In conclusion, NAG may be a useful biomarker for the early detection of CSA-AKI after OPCAB. Our results also suggest that reduced preoperative eGFR is a risk factor for the development of CSA-AKI in patients undergoing OPCAB. Furthermore, the combined risk assessment of NAG and eGFR is an effective method for early detection of CSA-AKI. This combination may lead to early therapeutic intervention and improved prognosis for patients with CSA-AKI after OPCAB.

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Disclosures

The authors declare no conflicts of interest. All authors met the 4 ICMJE authorship criteria.

IRB Information

This study was approved by the Ethics Committee of Kumamoto University (Approval no. Kumamoto University 2251).

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