ORIGINAL CLINICAL RESEARCH REPORT

Associations Between Preoperative Biomarkers and Cardiac Surgery–Associated Acute Kidney Injury in Elderly Patients: A Cohort Study

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BACKGROUND: Acute kidney injury (AKI) is associated with mortality after cardiac surgery. Novel risk factors may improve identification of patients at risk for renal injury. The authors evaluated the association between preoperative biomarkers that reflect cardiac, inflammatory, renal, and metabolic disorders and cardiac surgery–associated AKI (CSA-AKI) in elderly patients.
METHODS: This was a secondary analysis of the 2-center prospective cohort study "Anesthesia Geriatric Evaluation." Twelve biomarkers were determined preoperatively in 539 patients. Primary outcome was CSA-AKI. The association between biomarkers and CSA-AKI was investigated with multivariable logistic regression analysis. Secondary outcomes were 1-year mortality and patient-reported disability and were assessed with relative risks (RR) between patients with and without CSA-AKI.
RESULTS: CSA-AKI occurred in 88 (16.3%) patients and was associated with increased risk of mortality (RR, 6.70 [95% confidence interval {CI}, 3.38–13.30]) and disability (RR, 2.13 [95% CI, 1.53–2.95]). Preoperative concentrations of N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitive C-reactive protein (hs-CRP), hemoglobin, and magnesium had the strongest association with CSA-AKI. Identification of patients with CSA-AKI improved when a biomarker panel was used (area under the curve [AUC] 0.75 [95% CI, 0.69–0.80]) compared to when only clinical risk factors were used (European System for Cardiac Operative Risk Evaluation [EuroSCORE II] AUC 0.67 [95% CI, 0.62–0.73]).
CONCLUSIONS: Preoperative cardiac, inflammatory, renal, and metabolic biomarkers are associated with CSA-AKI and may improve identification of patients at risk. (Anesth Analg 2021;133:570–7)

KEY POINTS

- **Question:** Are preoperative cardiac, inflammatory, renal, and metabolic biomarkers associated with cardiac surgery–associated acute kidney injury (CSA-AKI) in elderly patients?
- **Finding:** Preoperative N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitive C-reactive protein (hs-CRP), hemoglobin, and magnesium concentrations are associated with CSA-AKI and could improve risk stratification.
- **Meaning:** A panel with cardiac, inflammatory, renal, and metabolic biomarkers can be used to better identify older patients at risk for renal injury after cardiac surgery.

GLOSSARY

AGE = Anesthesia Geriatric Evaluation; **AUC** = area under the curve; **CABG** = coronary artery bypass graft; **CI** = confidence interval; **CKD-EPI** = Chronic Kidney Disease Epidemiology Collaboration; **CSA-AKI** = cardiac surgery–associated acute kidney injury; **eGFR** = estimated glomerular filtration rate; **EuroSCORE** = European System for Cardiac Operative Risk Evaluation; **GDF-15** = growth differentiation factor-15; **Glu** = glucose; **Hb** = hemoglobin; **hs-CRP** = high-sensitive C-reactive protein; **hs-cTnT** = high-sensitive cardiac troponin T; **IL-6** = interleukin-6; **IQR** = interquartile range; **LVEF** = left ventricular ejection fraction; **Mg** = magnesium; **NA** = not applicable; **NT-proBNP** = N-terminal pro B-type natriuretic peptide; **NYHA** = New York Heart Association; **OR** = odds ratio; **RR** = relative risk; **STROBE** = STrengthening the Reporting of OBservational studies in Epidemiology; **TIA** = transient ischemic attack; **WBC** = white blood cell count; **WHODAS** = World Health Organization Disability Assessment Schedule

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Conflicts of Interest: See Disclosures at the end of the article.

Cardiac surgery–associated acute kidney injury (CSA-AKI) occurs in 10% to 30% of patients.[1–5] Postoperative renal injury is a risk factor for chronic kidney disease and reduces short- and long-term survival after cardiac surgery.[2,6] Even when renal function returns to baseline at the time of hospital discharge, long-term mortality risk remains increased.[4,6] One year after cardiac surgery, patients who experienced CSA-AKI report a lower health-related quality of life than patients without renal injury.[7] In addition, loss of renal function increases hospital costs.[8] Age is an important risk factor for CSA-AKI.[1,5,9] Depending on the type of surgery, the odds for long-term mortality are 3-fold higher for patients age >70 years compared to younger patients.[6]

The pathophysiology of CSA-AKI is complex. Multiple perioperative determinants, such as cardiopulmonary bypass, systemic inflammation, hypotension, and blood loss contribute to a compromised glomerular blood flow and renal hypoxemia.[10,11] Preoperative assessment can be used to identify patients at risk for renal injury and to initiate preventive measures. However, clinical risk factors (ie, comorbidity, age, and sex) are not sufficient to accurately distinguish patients at risk for CSA-AKI.[12] Chronic disease, low-grade inflammation, and endothelial dysfunction are key pathways in the pathogenesis of renal injury in cardiac patients before surgery (Figure 1).[13] Biomarkers that represent these pathways may be used as novel risk markers for CSA-AKI.[14,15]

In this study, we aimed to evaluate the associations between preoperative cardiac, inflammatory, renal, and metabolic biomarkers and CSA-AKI. In addition, we investigated the relation of CSA-AKI to 1-year mortality and self-reported disability in older cardiac surgery patients.

METHODS

Design and Participants

This is a prospectively designed substudy of the Anesthesia Geriatric Evaluation (AGE) study (clinicaltrials.gov no NCT02535728). The AGE study was a 2-center observational cohort study of the association of frailty with 1-year functional outcome after cardiac surgery in elderly patients. Eligible patients were aged ≥70 years and were scheduled for elective open cardiac surgery. Inclusion took place from July 2015 until August 2017. An elaborate description of the design and analysis of the AGE study was previously reported.[16] In short, standard preanesthesia assessment was supplemented with a comprehensive geriatric assessment. Further perioperative care was performed according to local standardized operating procedures. The local Research Ethics Committee approved the study protocol on June 30, 2015, and all patients provided written informed consent. This article adheres to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. Preoperative data were extracted from electronic medical records and included comorbidities, medication use, European System for Cardiac Operative Risk Evaluation (EuroSCORE II), and echocardiography results, which were available at the time of preoperative screening or on the day before surgery.

Biomarkers

Selection of biomarkers was based on clinical reasoning and previous reports on the pathophysiology of CSA-AKI (Figure 1), availability in clinical practice, and costs. Twelve biomarkers were stratified into 4 categories (cardiac, inflammatory, renal, and metabolic). Cardiac biomarkers consisted of high-sensitive cardiac troponin T (hs-cTnT), N-terminal pro B-type natriuretic peptide (NT-proBNP), and growth differentiation factor-15 (GDF-15), because of the association between cardiovascular disease, heart failure, and AKI.[14,17,18] Inflammatory biomarkers included hs-C-reactive protein (hs-CRP), interleukin-6 (IL-6), and white blood cell count (WBC). These biomarkers reflect the association between inflammation and endothelial and tubular cell injury in AKI.[10] Renal biomarkers were hemoglobin (Hb) and estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[19] Hb was considered a renal biomarker because it might reflect anemia caused by renal insufficiency. Metabolic biomarkers included glucose, albumin, phosphate, and magnesium. Magnesium deficiency, glucose intolerance, and low albumin concentrations are associated with endothelial dysfunction and a pro-inflammatory state, which has been associated with AKI.[10,20,21] Phosphate dysregulation is common in patients with chronic kidney disease. Blood samples for Hb, WBC, and creatinine/eGFR were collected at the outpatient clinic as part of routine care and directly analyzed on a Sysmex 9000 system (Sysmex) or a Sapphire system (Abbott Laboratories) (for WBC and Hb), and a Cobas platform (Roche Diagnostics) or an Atellica system (Siemens Healthcare) for creatinine. For the remaining markers, blood samples were collected in the operating room from the arterial catheter, after induction of anesthesia and before surgical incision. Plasma was stored in cryogenic tubes at −80 °C

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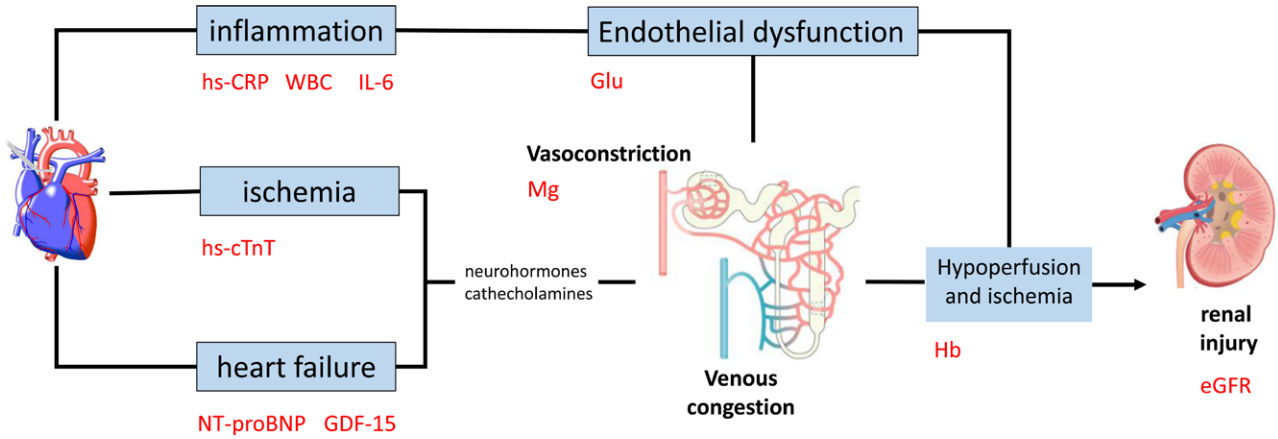

Figure 1. Potential pathways of the biomarker panel in the pathogenesis of preoperative renal injury in cardiac patients. eGFR indicates estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; Glu, glucose; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; Mg, magnesium; NT-proBNP, N-terminal pro B-type natriuretic peptide; WBC, white blood cell count.

until batch analysis was performed. The plasma biomarkers were analyzed on an automated Cobas 8000 platform (Roche Diagnostics) by the following assays: Elecsys cTnT hs assay (fifth-generation assay); Elecsys IL-6, Elecsys GDF-15, Elecsys proBNP II, and CRPL3 (third-generation CRP assay); ALBT2 (Tina-quant albumin second generation assay); GLUC3 (glucose HK assay); MG2 (magnesium second-generation assay); and PHOS2 (inorganic phosphate assay version 2). Cutoff values for all biomarkers were set according to the manufacturer's manual (Roche Diagnostics), were locally determined (WBC), or were set according to international guidelines (Hb and eGFR) and represented the 95th percentile (and 99th percentile in the case of hs-cTnT): hs-cTnT ≥14 µg/L; NT-proBNP ≥486 pg/mL for women and ≥470 pg/mL for men; GDF-15 ≥ 2199 pg/mL; CRP ≥5 mg/L; IL-6 ≥7 pg/mL; WBC ≥10.8 × 10^9/L for women and ≥10.6 × 10^9/L for men; glucose ≥6.38 mmol/L; albumin ≤35 g/L; phosphate ≥1.45 mmol/L; and magnesium ≤0.66 mmol/L. The cutoff values for Hb were ≤7.45 mmol/L for women and ≤8.07 mmol/L for men.[22] Cutoff value for eGFR was ≤60 mL/min/1.73 m^2.[23] All analyses were performed using standardized diagnostic methods.

Outcomes

The primary outcome was CSA-AKI, defined as an absolute increase of serum creatinine ≥26.5 µmol/L within 48 hours after surgery or 1.5 times the baseline value within the first 5 days.[23] Postoperative serum creatinine values were routinely determined on the first and second day after surgery and on clinical indication on postoperative days 3 and 5, using an automated Cobas 8000 platform (Roche Diagnostics) or an Atellica system (Siemens Healthcare). Missing creatinine values were considered normal. Secondary outcomes were mortality and self-reported disability 1 year after surgery. Vital status, including date of death in case of mortality, was assessed by consulting the national personal records database. Disability was measured according to the self-assessment 36-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) and reported as a percentage score of limitations in functioning over the past 4 weeks. Scores ranged from 0% (no disability) to 100% (fully disabled). In our study, disability was defined as a score ≥25%.[16] Deceased patients were excluded from the analysis regarding postsurgical disability.

Missing Data

Multiple imputation was used to handle missing data regarding disability questionnaires. This reduces bias by creating multiple datasets in which the missing values are estimated using information from the same source population. Pre- and postoperative missing values, including disability data, were imputed in 30 datasets.[24] Biomarker assays were performed after imputation analyses. Because only a small number of biomarker values were missing (16 of 555 patients, 2.9%), and missing values were completely at random, we excluded these patients from the analyses. Results obtained from each imputed dataset were pooled using Rubin's rules.[25]

Statistical Analysis

Differences between patients with or without CSA-AKI were presented as frequencies, with percentages for dichotomous and categorical data and medians with interquartile ranges (IQR) for continuous data. Significance was tested with a χ^2 test or Mann-Whitney *U* test, as appropriate. Unadjusted relative risks (RR) with 95% confidence interval (CI) were calculated for the association between CSA-AKI and 1-year

mortality and self-reported disability. Mortality was further analyzed by Kaplan-Meier curves and log-rank tests. Early mortality (within 5 days) precluded CSA-AKI diagnosis. Therefore, the Kaplan-Meier curve was limited to those alive after 5 days. Correlations between biomarkers were analyzed with Spearman's rho. Associations of preoperative biomarkers with CSA-AKI were assessed with logistic regression analyses. In univariable analyses, biomarkers were tested as continuous variables according to the aforementioned predefined cutoff points. To improve the readability of our results, we refer to biomarker values above or below the cutoff value as "elevated" or "decreased," respectively. Thereafter, multivariable logistic regression analyses were conducted for the association between CSA-AKI and each biomarker separately, with adjustments for age, sex, and type of surgery. To assess the association between each of the biomarkers and CSA-AKI, we used multivariable logistic regression analysis and included all continuous biomarker values in the model. Continuous biomarker values were standardized to enable direct comparison. Standardization was performed by subtracting the mean from the patient-specific value and dividing it by the standard deviation of that particular variable. Therefore, the highest standardized odds ratio (OR) implied the strongest association in the multivariable model. Because clinical interpretation is difficult after standardization, the unstandardized values were also analyzed in multivariable analysis. Biomarkers with a negative association (ie, Hb, eGFR, albumin, and magnesium) were added as an inverse value. Multicollinearity was checked using the variance inflation factor. The area under the curve (AUC) was calculated to express the discriminative ability for CSA-AKI based on a biomarker panel and clinical risk factors in terms of the EuroSCORE II. Differences between model fit were compared with the likelihood ratio test. A $P < .05$ was considered statistically significant. Data were analyzed using SPSS v24 for Windows (IBM Corp) and R version 3.5.1 for Windows.

RESULTS

Patient Population

The AGE study cohort consisted of 555 patients. Preoperative blood samples were missing in 16 patients (2.9%); the remaining 539 patients were included in the analysis. Serum creatinine values were available for all patients on day 1 or 2, and for 426 (79.0%) patients on day 3 or 5. Median age was 75 years (IQR, 72–77), and 181 patients (33.6%) were women. Eighty-eight patients (16.3%) developed CSA-AKI. Patients with CSA-AKI had higher rates of hypertension, diabetes mellitus, and chronic renal failure; a higher New York Heart Association (NYHA) class; and higher EuroSCORE II, and they underwent more complex surgery (Table 1). The overall mortality rate was 2.8% (n = 15) during hospital stay and 5.6% (n = 30) after 1 year. Patients with CSA-AKI had a nearly 7-fold increased risk for 1-year mortality (RR, 6.70 [95% CI, 3.38–13.30]). Survival for patients with and without CSA-AKI is presented in Figure 2. Of the 509 surviving patients, 116 (22.8%) reported disabilities at 1 year after surgery. Patients with CSA-AKI were at increased risk for disability (RR, 2.13 [95% CI, 1.53–2.95]).

Cardiac Biomarkers

Preoperative cardiac biomarker concentrations were higher in patients with CSA-AKI (Table 2). The correlation between hs-cTnT and GDF-15 concentrations was moderate ($r = .50$; Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/D591). An elevated GDF-15 or NT-proBNP concentration was present in 35.2% and 64.8% of patients with CSA-AKI compared to 17.3% and 45.5% of patients without CSA-AKI ($P < .001$ and $P = .001$, respectively). Of all cardiac biomarkers, GDF-15 and NT-proBNP had the strongest association with CSA-AKI (Table 3).

Inflammatory Biomarkers

Patients with CSA-AKI had significantly higher preoperative concentrations of CRP and IL-6 (Table 2).

Table 1. Baseline Characteristics

Characteristic	No CSA-AKI n = 451	CSA-AKI n = 88	*P*
Age, median [IQR]	74 [72–77]	75 [72–78]	.925
Female sex, n (%)	150 (33.3)	31 (35.2)	.721
Current smoker, n (%)	32 (7.1)	9 (10.2)	.311
Hypertension, n (%)	366 (81.2)	82 (93.2)	.006
Hypercholesterolemia, n (%)	278 (61.6)	63 (71.6)	.077
Angina, n (%)	169 (37.5)	32 (36.4)	.844
NYHA class, n (%)			.003
1	72 (16.0)	7 (8.0)	
2	238 (52.8)	45 (51.1)	
3	133 (29.5)	29 (33.0)	
4	8 (1.8)	7 (8.0)	
LVEF ≤50%, n (%)	95 (21.1)	20 (22.7)	.735
Diabetes, n (%)	82 (18.2)	28 (31.8)	.004
Chronic renal failure, n (%)	53 (11.8)	20 (22.7)	.006
Preoperative creatinine (μmol/L)	81 [68–98]	91 [75–110]	<.001
Peripheral vascular disease, n (%)	50 (11.1)	15 (17.0)	.116
Stroke/TIA, n (%)	60 (13.3)	14 (15.9)	.516
Atrium fibrillation, n (%)	131 (29.0)	32 (36.4)	.172
EuroSCORE II, median [IQR]	1.7 [1.2–3.0]	2.6 [1.9–4.4]	<.001
Frailty, n (%)	95 (21.1)	22 (25.0)	.324
Type of surgery, n (%)			.001
Single CABG or maze	161 (35.7)	21 (23.9)	
Single valve	134 (29.7)	18 (20.5)	
Combined surgery	126 (27.9)	38 (43.2)	
Aortic surgery	30 (6.7)	11 (12.5)	

Values are frequencies n (%) or medians [IQR].

Abbreviations: CABG, coronary artery bypass graft; CSA-AKI, cardiac surgery–associated acute kidney injury; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TIA, transient ischemic attack.

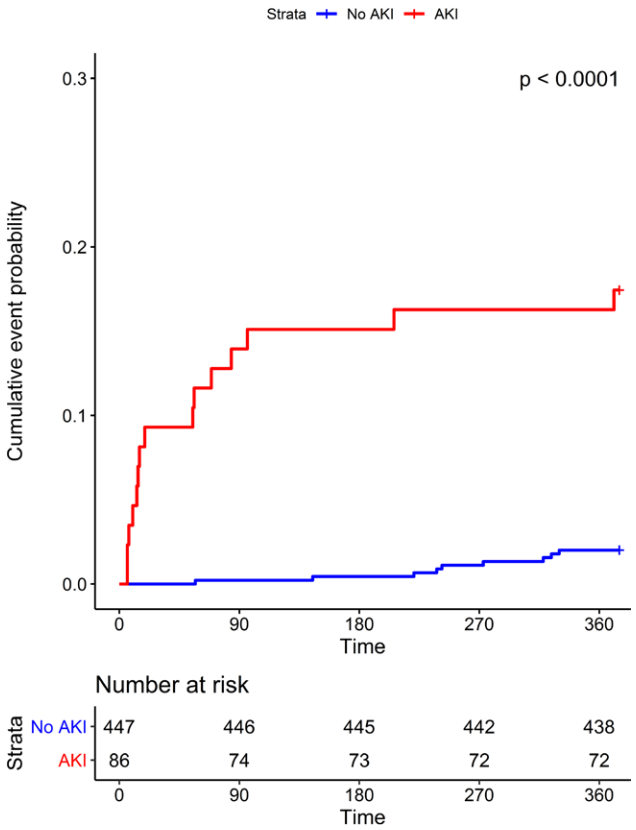

Figure 2. Kaplan-Meier curve for mortality according to CSA-AKI. CSA-AKI indicates cardiac surgery–associated acute kidney injury.

Table 2. Preoperative Biomarker Concentrations

Biomarker	No CSA-AKI n = 451	CSA-AKI n = 88	*P*
Cardiac			
hs-cTnT (μg/L)	14 (10–21)	16 (12–25)	.026
NT-proBNP (pg/mL)	420 (187–1005)	732 (341–1660)	.002
GDF-15 (pg/mL)	1333 (1003–1867)	1757 (1264–2583)	.001
Inflammatory			
hs-CRP (mg/L)	1.2 (1.0–2.6)	2.1 (1.0–5.01)	.001
IL-6 (pg/mL)	3.1 (2.1–4.5)	4.2 (2.7–8.3)	.003
WBC (10^9/L)	7.2 (6.3–8.6)	7.5 (4.4–8.9)	.504
Renal			
Hb (mmol/L)	8.8 (8.2–9.4)	8.2 (7.4–8.9)	<.001
eGFR (mL/min/ 1.73 m2)	69 (58–82)	63 (50–75)	.002
Metabolic			
Glucose (mmol/L)	5.9 (5.4–6.6)	6.1 (5.4–7.1)	.071
Albumin (g/L)	38.6 (36.2–40.7)	38.5 (36.1–40.7)	.922
Phosphate (mmol/L)	0.98 (0.87–1.10)	1.03 (0.91–1.13)	.383
Magnesium (mmol/L)	0.78 (0.74–0.83)	0.76 (0.68–0.82)	.303

All values are median concentrations with interquartile range.

Abbreviations: CSA-AKI, cardiac surgery–associated acute kidney injury; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; NT-proBNP, N-terminal pro B-type natriuretic peptide; WBC, white blood cell count.

The correlation between CRP and IL-6 concentrations was strong (r = .62). Hs-CRP and IL-6 concentrations were elevated in 25.0% and 27.3% of patients with CSA-AKI compared to 10.2% and 13.1% of patients without CSA-AKI, respectively (P < .001 for both). An elevated hs-CRP or IL-6 concentration was associated with increased odds for CSA-AKI (Table 3).

Renal Biomarkers

Preoperative concentrations of renal biomarkers were lower in patients with CSA-AKI (Table 2). Lower eGFR before surgery was related to higher cardiac biomarker concentrations (Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/D591). Preoperative anemia was more common in patients with CSA-AKI (15.9% compared to 4.2% of patients without CSA-AKI, P < .001). The odds for CSA-AKI were higher in patients with preoperative anemia (Table 3).

Metabolic Biomarkers

Impaired fasting glucose concentrations and decreased magnesium concentrations were common and occurred in 40.9% and 18.2% of patients with CSA-AKI compared to 29.0% and 6.7% of patients without CSA-AKI (P = .0038 and P < .001, respectively). Both biomarkers were associated with increased odds for CSA-AKI (Table 3).

Multivariable Analysis

Figure 3 presents standardized effect estimates of a multivariable model including all biomarkers. Based on the highest standardized ORs, the biomarkers with the strongest associations were NT-proBNP, hs-CRP, Hb, and magnesium. Identification of patients with CSA-AKI improved when a preoperative biomarker panel was used (AUC, 0.75 [95% CI, 0.69–0.80]) compared to when only clinical risk factors were used (EuroSCORE II AUC, 0.67 [95% CI, 0.62–0.73]), and model fit improved significantly (P = .016). Results for unstandardized associations of all biomarkers are shown in Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/D592.

DISCUSSION

In elderly patients undergoing cardiac surgery, CSA-AKI occurred in 16% and was associated with 1-year mortality and disability. Preoperative cardiac, inflammatory, renal, and metabolic biomarkers were associated with CSA-AKI. The biomarkers with the strongest associations were NT-proBNP, hs-CRP, Hb, and magnesium.

Our results confirmed that preoperative biomarkers are associated with the occurrence of CSA-AKI.[3,14,15,17,18,26] Another study that associated multiple preoperative biomarkers with CSA-AKI focused on inflammation, compromised renal blood flow, and ischemia-reperfusion injury.[15] Preoperative inflammatory biomarkers (soluble tumor necrosis factor receptor 1 and 2) had the highest discrimination for CSA-AKI

Table 3. Associations Between Biomarkers and CSA-AKI

	Continuous		Cutoff[a]	
Biomarker	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Cardiac				
hs-cTnT (per µg/L)	1.02 (1.00–1.03)	.014	1.72 (1.02–2.90)	.042
NT-proBNP (per 100 pg/mL)	1.02 (1.01–1.04)	<.001	2.04 (1.24–3.36)	.005
GDF-15 (per 100 pg/mL)	1.04 (1.02–1.06)	<.001	2.54 (1.51–4.27)	<.001
Inflammatory				
hs-CRP (per mg/L)	1.05 (1.02–1.08)	.004	2.81 (1.56–5.07)	.001
IL-6 (per pg/mL)	1.0 (1.0–1.06)	.053	2.12 (1.21–3.73)	.009
WBC (per 10^9/L)	0.92 (0.76–1.12)	.760	1.06 (0.45–2.52)	.887
Renal				
Hb[b] (per mmol/L)	1.03 (1.01–1.04)	<.001	2.00 (1.23–3.24)	.005
eGFR[b] (per mL/min/1.73 m2)	2.00 (1.53–2.61)	<.001	4.65 (2.17–9.95)	<.001
Metabolic				
Glucose (per mmol/L)	1.20 (1.04–1.38)	.011	1.82 (1.12–2.95)	.016
Albumin[b] (per g/L)	1.01 (0.94–1.09)	.837	1.36 (0.74–2.49)	.322
Phosphate (per 0.1 mmol/L)	1.21 (1.03–1.43)	.018	NA	NA
Magnesium[b] (per 0.1 mmol/L)	1.56 (1.18–2.07)	.002	3.08 (1.57–6.03)	.001

NA: none of the patients had a phosphate concentration below the clinical cutoff value of 1.45 mmol/L.

Abbreviations: CI, confidence interval; CSA-AKI, cardiac surgery–associated acute kidney injury; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; NA, not applicable; NT-proBNP, N-terminal pro b-type natriuretic peptide; OR, odds ratio; WBC, white blood cell count.

[a]Cutoff levels for all biomarkers are described in the Methods section. All associations were adjusted for age, sex, and type of surgery.

[b]Inverse association.

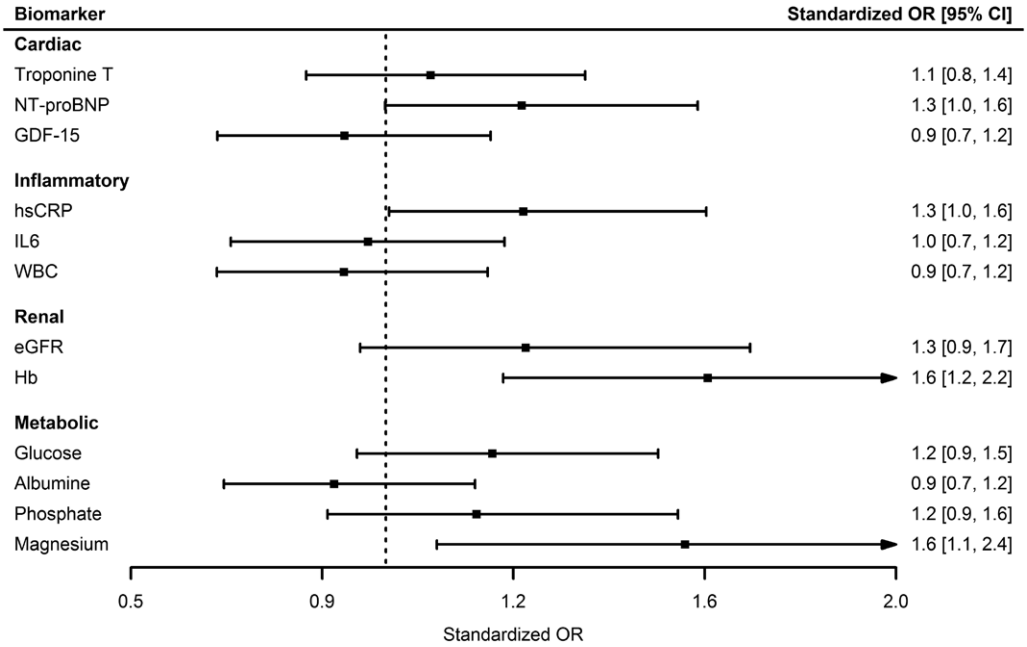

Figure 3. Multivariable analysis for the standardized association between a preoperative biomarker panel and CSA-AKI, independent of age, sex, and type of surgery. Biomarkers with a negative association (ie, Hb, eGFR, albumin, and magnesium) were added as an inverse value. This means that lower values of these biomarkers indicate higher associations. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; NT-proBNP, N-terminal pro B-type natriuretic peptide; WBC, white blood cell count.

(AUC, 0.75 [95% CI, 0.68–0.81]).[15] Both biomarkers have been associated with progression of renal disease, indicating that existing renal failure is an important risk factor for CSA-AKI.[27,28] In addition, our results showed that chronic cardiac disease contributes to the development of CSA-AKI and that its presence can be used to improve risk stratification. Heart failure is an important prognosticator in cardiac disease and is associated with chronic kidney disease.[29] EuroSCORE II contains detailed clinical information on preoperative heart failure (ie, left ventricular function and NYHA functional classification), which can be used to accurately predict postoperative mortality. In addition to preoperative echocardiography results and clinical symptoms, use of NT-proBNP increased the accuracy of preoperative risk assessment for CSA-AKI in our study. NT-proBNP

remained associated with CSA-AKI in our full model, which included 11 other biomarkers.

The results of our study suggest that different pathophysiological processes are involved in the pathogenesis of renal injury in cardiac disease. Preoperative concentrations of NT-proBNP, hs-CRP, Hb, and magnesium had the strongest association with CSA-AKI. Chronic cardiac disease is characterized by episodes of myocardial ischemia, heart failure, and a systemic hormonal and inflammatory response.[1,10] Depending on disease severity, these processes impair renal oxygenation by cardiac and endothelial dysfunction (Figure 1). High levels of circulating neurohormones induce renal sodium and water retention, which reduces glomerular blood flow (venous congestion) and impairs renal microcirculation.[29] Local edema and inflammation lead to areas with impaired renal oxygenation and trigger systemic inflammation.[26] Renal hypoxemia is exacerbated by coexisting anemia. Furthermore, endogenous catecholamines increase vascular tone and reduce glomerular perfusion. Homeostasis of the renal microcirculation is dependent on endothelium-derived nitric oxide–mediated vasodilation. Magnesium naturally counteracts vasoconstriction and potentiates the action of endogenous vasodilators.[20] Hypomagnesemia may lead to renal vasoconstriction and impair glomerular blood flow. High glucose levels have been associated with changes in the function of the glomerular endothelial glycocalyx, reducing its function as a protein-restrictive layer and aggravating endothelial dysfunction.[21]

Preoperative biomarkers can be used to diagnose new diseases and assess the progress of previously diagnosed comorbidity. Targeted preoperative interventions based on biomarker results to improve outcome after cardiac surgery are scarce.[30] Future research that aims to reduce the incidence of CSA-AKI should consider the use of a preoperative biomarker panel to identify patient-specific risks that are suitable for targeted preoperative interventions.

This study has several limitations. First, the definition of AKI includes a 7-day measurement of eGFR and urine output. In our study, full data on eGFR were available during the first 2 days after surgery and in 79% of the patients between day 3 and 5. Urine output was not measured. Several patients with CSA-AKI may have been missed due to missing creatinine or urine measurements. However, the incidence of CSA-AKI in our study is comparable to that of previous reports.[3–5] Second, preoperative blood samples were missing in 16 patients. Because missing blood samples were not related to patient characteristics or outcome, the risk of bias was low. In 73 patients, disability questionnaires were missing. We performed multiple imputation in an attempt to limit bias.[25] However, this could have influenced the association between CSA-AKI and disability at 1 year. A major strength of our study was the use of 12 preoperative biomarkers, which represented the multifactorial pathogenesis of renal injury in cardiac patients. We realize that there are many other biomarkers that are potentially associated with CSA-AKI. For practical reasons, we chose a biomarker panel that can be routinely assessed in clinical care. Although GDF-15 and IL-6 panels are less common, they are available from Roche, Abbott, Siemens, and Beckman Coulter Diagnostics for IL-6, and from Roche and Abbott for GDF-15. Because these systems are widely used, this allows for reproducibility and comparison of our results by others and facilitates clinical implementation. Other strengths of this study include the thorough preoperative screening of all patients and data availability. In addition, the focus on elderly patients increases the accuracy of the results for this specific population.

CONCLUSIONS

CSA-AKI is common in elderly patients and is associated with higher risk for 1-year mortality or disability. Preoperative cardiac, inflammatory, renal, and metabolic biomarkers are associated with CSA-AKI, and their use could improve identification of patients at risk.

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REFERENCES

1. O'Neal JB, Shaw AD, Billings FT IV. Acute kidney injury following cardiac surgery: current understanding and future directions. *Crit Care*. 2016;20:187.
2. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephrol*. 2006;1:19–32.
3. Enger TB, Pleym H, Stenseth R, Greiff G, Wahba A, Videm V. A preoperative multimarker approach to evaluate acute kidney injury after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2017;31:837–846.
4. Loef BG, Epema AH, Smilde TD, et al. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. *J Am Soc Nephrol*. 2005;16:195–200.
5. Lopez-Delgado JC, Esteve F, Torrado H, et al. Influence of acute kidney injury on short- and long-term outcomes in patients undergoing cardiac surgery: risk factors and prognostic value of a modified RIFLE classification. *Crit Care*. 2013;17:R293.
6. Hobson CE, Yavas S, Segal MS, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*. 2009;119:2444–2453.
7. Mishra PK, Luckraz H, Nandi J, et al. Long-term quality of life postacute kidney injury in cardiac surgery patients. *Ann Card Anaesth*. 2018;21:41–45.
8. Lau D, Pannu N, James MT, et al. Costs and consequences of acute kidney injury after cardiac surgery: a cohort study. *J Thorac Cardiovasc Surg*. Published online March 3, 2020. DOI: 10.1016/j.jtcvs.2020.01.101.
9. Mårtensson J, Bellomo R. Perioperative renal failure in elderly patients. *Curr Opin Anaesthesiol*. 2015;28:123–130.
10. Ostermann M, Liu K. Pathophysiology of AKI. *Best Pract Res Clin Anaesthesiol*. 2017;31:305–314.
11. Fuhrman DY, Kellum JA. Epidemiology and pathophysiology of cardiac surgery-associated acute kidney injury. *Curr Opin Anaesthesiol*. 2017;30:60–65.
12. Kiers HD, van den Boogaard M, Schoenmakers MC, et al. Comparison and clinical suitability of eight prediction models for cardiac surgery-related acute kidney injury. *Nephrol Dial Transplant*. 2013;28:345–351.
13. Berl T, Henrich W. Kidney-heart interactions: epidemiology, pathogenesis, and treatment. *Clin J Am Soc Nephrol*. 2006;1:8–18.
14. Patel UD, Garg AX, Krumholz HM, et al; Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) Consortium. Preoperative serum brain natriuretic peptide and risk of acute kidney injury after cardiac surgery. *Circulation*. 2012;125:1347–1355.
15. McBride WT, Kurth MJ, McLean G, et al. Stratifying risk of acute kidney injury in pre and post cardiac surgery patients using a novel biomarker-based algorithm and clinical risk score. *Sci Rep*. 2019;9:16963.
16. Verwijmeren L, Peelen LM, van Klei WA, et al. Anaesthesia geriatric evaluation to guide patient selection for preoperative multidisciplinary team care in cardiac surgery. *Br J Anaesth*. 2020;124:377–385.
17. Guenancia C, Kahli A, Laurent G, et al. Pre-operative growth differentiation factor 15 as a novel biomarker of acute kidney injury after cardiac bypass surgery. *Int J Cardiol*. 2015;197:66–71.
18. Heringlake M, Charitos EI, Gatz N, et al. Growth differentiation factor 15: a novel risk marker adjunct to the EuroSCORE for risk stratification in cardiac surgery patients. *J Am Coll Cardiol*. 2013;61:672–681.
19. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
20. Barbosa EB, Tomasi CD, de Castro Damasio D, et al. Effects of magnesium supplementation on the incidence of acute kidney injury in critically ill patients presenting with hypomagnesemia. *Intensive Care Med*. 2016;42:1084–1085.
21. Singh A, Fridén V, Dasgupta I, et al. High glucose causes dysfunction of the human glomerular endothelial glycocalyx. *Am J Physiol Renal Physiol*. 2011;300:F40–F48.
22. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2011 (WHO/NMH/NHD/MNM/11.1). Accessed June 9, 2020. http://www.who.int/vmnis/indicators/haemoglobin. pdf.
23. KDIGO AKI Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Inter Suppl*. 2012;17:1–138.
24. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9:57.
25. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59:1087–1091.
26. Zelt JGE, Mielniczuk LM, Liu PP, et al. Utility of novel cardiorenal biomarkers in the prediction and early detection of congestive kidney injury following cardiac surgery. *J Clin Med*. 2018;7:E540.
27. Barr ELM, Barzi F, Hughes JT, et al. High baseline levels of tumor necrosis factor receptor 1 are associated with progression of kidney disease in indigenous australians with diabetes: the eGFR follow-up study. *Diabetes Care*. 2018;41:739–747.
28. Parodis I, Ding H, Zickert A, et al. Serum soluble tumour necrosis factor receptor-2 (sTNFR2) as a biomarker of kidney tissue damage and long-term renal outcome in lupus nephritis. *Scand J Rheumatol*. 2017;46:263–272.
29. Rangaswami J, Bhalla V, Blair JEA, et al; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e840–e878.
30. Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. *Lancet*. 2019;393:2201–2212.