Urine Alpha-1-Microglobulin Levels and Acute Kidney Injury, Mortality, and Cardiovascular Events following Cardiac Surgery

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Keywords

Acute kidney injury · Chronic kidney disease · Mortality · Biomarker · Alpha-1-microglobulin · Cardiac surgery

Abstract

Introduction: Urine alpha-1-microglobulin (Ua1m) elevations signal proximal tubule dysfunction. In ambulatory settings, higher Ua1m is associated with acute kidney injury (AKI), progressive chronic kidney disease (CKD), cardiovascular (CV) events, and mortality. We investigated the associations of pre- and postoperative Ua1m concentrations with adverse outcomes after cardiac surgery. **Methods:** In 1,464 adults undergoing cardiac surgery in the prospective multicenter Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury (TRIBE-AKI) cohort, we measured the pre- and postoperative Ua1m concentrations and calculated the changes from pre- to postoperative concentrations. Outcomes were postoperative AKI during index hospitalization and longitudinal risks for CKD incidence and progression, CV events, and all-cause mortality after discharge. We analyzed Ua1m continuously and categorically by tertiles using multivariable logistic regression and Cox

proportional hazards regression adjusted for demographics, surgery characteristics, comorbidities, baseline estimated glomerular filtration rate, urine albumin, and urine creatinine. **Results:** There were 230 AKI events during cardiac surgery hospitalization; during median 6.7 years of follow-up, there were 212 cases of incident CKD, 54 cases of CKD progression, 269 CV events, and 459 deaths. Each 2-fold higher concentration of preoperative Ua1m was independently associated with AKI (adjusted odds ratio [aOR] = 1.36, 95% confidence interval 1.14–1.62), CKD progression (adjusted hazard ratio [aHR] = 1.46, 1.04–2.05), and all-cause mortality (aHR = 1.19, 1.06–1.33) but not with incident CKD (aHR = 1.21, 0.96–1.51) or CV events (aHR = 1.01, 0.86–1.19). Postoperative Ua1m was not associated with AKI (aOR per 2-fold higher = 1.07, 0.93–1.22), CKD incidence (aHR = 0.90, 0.79–1.03) or progression (aHR = 0.79, 0.56–1.11), CV events (aHR = 1.06, 0.94–1.19), and mortality (aHR = 1.01, 0.92–1.11). **Conclusion:** Preoperative Ua1m concentrations may identify patients at high risk of AKI and other adverse events after cardiac surgery, but postoperative Ua1m concentrations do not appear to be informative.

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Published by S. Karger AG, Basel

Introduction

Kidney tubules are vital for fluid and electrolyte balance, neurohormonal regulation, and mineral metabolism, and kidney tubule injury can lead to severe kidney dysfunction and chronic kidney disease (CKD) [1, 2]. However, current clinical practice lacks tools to monitor kidney tubule health directly, and serum creatinine remains the dominant biomarker for the assessment of kidney function and diagnosis of kidney injury. Creatinine reflects glomerular clearance but not kidney tubule injury or dysfunction, making it ill-suited for timely recognition of many forms of acute kidney injury (AKI), particularly those due to kidney tubule damage [3–5]. Because AKI is responsible for substantial morbidity and mortality and also portends important long-term outcomes, including risk of subsequent CKD [6, 7], cardiovascular (CV) disease [8–10], and mortality [11, 12], there is an impetus to identify biomarkers of kidney tubule injury and dysfunction that could improve AKI risk assessment and early diagnosis. Furthermore, several of these kidney tubule health biomarkers have been shown to predict long-term kidney, CV, and mortality outcomes in multiple populations and may add an important dimension to the assessment of kidney health [13–17].

One promising biomarker is alpha-1-microglobulin ($\alpha 1m$), a low molecular weight protein synthesized by hepatocytes, freely filtered across the glomerulus, and then avidly reabsorbed by the proximal tubule [18, 19]. Because the concentration of urine $\alpha 1m$ (U $\alpha 1m$) is inversely proportional to proximal tubule resorptive capacity, it can signal proximal tubule dysfunction: higher U $\alpha 1m$ concentrations indicate impaired tubular reabsorption [20]. Small studies have previously shown that U $\alpha 1m$ concentrations increase in AKI, reflect severity of AKI, and are associated with the need for dialysis after nonoliguric AKI [21–23]. Elevated U $\alpha 1m$ correlates with interstitial fibrosis and tubular atrophy on kidney biopsy, representing chronic kidney damage [24]. Furthermore, U $\alpha 1m$ appears to predict kidney function decline and CKD progression [25, 26], AKI risk [27], CV events [28], and mortality [16, 28, 29].

To better define its diagnostic and prognostic utility, we investigated U $\alpha 1m$ in a multicenter prospective cohort of adults at high risk for AKI who underwent cardiac surgery as part of the Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury (TRIBE-AKI) study. Specifically, we measured preoperative and postoperative U $\alpha 1m$ concentrations and evaluated their associations with postoperative AKI, CKD in-

cidence and progression, CV events, and all-cause mortality after discharge. We hypothesized that higher pre- and postoperative levels of U $\alpha 1m$ would be associated with adverse outcomes after cardiac surgery.

Methods

Study Design and Participants

TRIBE-AKI is a prospective, multicenter cohort study of adults who underwent cardiac surgery at 6 North American academic medical centers. Overall study design and cohort selection have been presented in detail previously [13, 14, 30]. Between July 2007 and December 2010, 1,601 adults at high risk for AKI who were undergoing coronary artery bypass graft (CABG) and/or valve surgery were enrolled after informed consent. Risk of AKI was determined by the presence of one of the following characteristics: emergency surgery, preoperative serum creatinine >2.0 mg/dL, ejection fraction $<35\%$ or grade 3 or 4 left ventricular dysfunction, age >70 years, diabetes mellitus, concomitant CABG and valve surgery, or repeat revascularization. Patients undergoing multiple surgeries were enrolled in the study only once. Society of Thoracic Surgeon definitions were used for collection of preoperative characteristics, surgical characteristics, and postoperative complications [31]. To establish baseline kidney function, all participants had to have a documented value for serum creatinine within 2 months before surgery. This study complied with the Declaration of Helsinki, was approved by the institutional review board at each site, and all participants provided written informed consent.

Sample Collection and Biomarker Measurement

Sample collection and processing methods have been previously described in detail [13, 14]. Briefly, urine and blood samples were collected preoperatively and then daily for up to 5 days after surgery. The postoperative samples used in this analysis were collected during the first 12 h of postoperative day 1. All postoperative urine samples were collected before any form of dialysis was initiated. Fresh urine samples were obtained from the urimeter from participants with Foley catheters. Urine samples were centrifuged to separate cellular debris. Urine supernatant and plasma were stored at -80°C , until thawed for biomarker measurement. U $\alpha 1m$ was measured at the Kidney Health Research Collaborative laboratory based at the San Francisco VA Health Care System (San Francisco, CA) by immunonephelometry on the Siemens BNII instrument using the proprietary N $\alpha 1$ -Microglobulin Reagent Kit (Siemens Medical Solutions USA, Inc., Malvern, PA) with a lower limit of detection (LLD) at 5.4625 mg/L. Intra-assay coefficients of variation were not calculated because samples were run in a singlicate. A control sample provided by the manufacturer was run before batches of measurements to ensure validity of the assay. Values below the LLD were imputed as 5.4625 mg/L and included in the lowest tertile for categorical analyses.

Outcomes

Outcomes were defined and ascertained as they had been from the previous studies in the TRIBE-AKI cohort [30, 32–34]. AKI during index hospitalization was categorized as “at least mild AKI” defined as a serum creatinine increase $\geq 50\%$ or 0.3 mg/dL from the preoperative level, and “severe AKI” defined as at least doubling of serum creatinine or need for dialysis during the index hospitalization [35].

Table 1. Baseline characteristics of the study population overall and by tertile of preoperative Ua1m

	All	Tertile 1	Tertile 2	Tertile 3
Characteristic	<i>n</i> = 1,464	<i>n</i> = 507	<i>n</i> = 469	<i>n</i> = 488
Mean age at time of surgery, years	72 (10)	70 (10)	72 (10)	73 (9)
White race, <i>n</i> (%)	1,380 (94)	479 (94)	442 (94)	459 (94)
Male sex, <i>n</i> (%)	1,009 (69)	316 (62)	321 (68)	372 (76)
Diabetes, <i>n</i> (%)	565 (39)	192 (38)	173 (37)	200 (41)
Hypertension, <i>n</i> (%)	1,167 (80)	401 (79)	362 (77)	404 (83)
EF <35% or grade 3 or 4 LV dysfunction, <i>n</i> (%)	147 (10)	52 (10)	44 (9)	51 (10)
Myocardial infarction, <i>n</i> (%)	369 (25)	139 (27)	112 (24)	118 (24)
Congestive heart failure, <i>n</i> (%)	337 (23)	108 (21)	93 (20)	136 (28)
Median preoperative serum creatinine, mg/dL	1.00 (0.90, 1.20)	0.97 (0.80, 1.10)	1.00 (0.90, 1.20)	1.10 (0.90, 1.38)
Median preoperative eGFR, mL/min/1.73 m ²	69 (55, 83)	73 (61, 86)	69 (57, 83)	61 (48, 76)
eGFR ≤60 mL/min/1.73 m ² , <i>n</i> (%)	492 (34)	117 (23)	143 (30)	236 (48)
Median UACR, mg/g	15 (7, 46)	12 (6, 23)	14 (7, 45)	27 (10, 104)
Surgery type, <i>n</i> (%)				
CABG and valve	318 (22)	106 (21)	103 (22)	109 (22)
CABG only	712 (49)	255 (50)	232 (49)	225 (46)
Valve only	412 (28)	136 (27)	126 (27)	150 (31)
Other	22 (2)	10 (2)	8 (2)	4 (1)
Nonelective surgery	243 (17)	73 (14)	85 (18)	85 (17)

Ua1m ranges, tertile 1: 0–5.46 mg/L; tertile 2: 5.47–10.61 mg/L; and tertile 3: 10.63–285.02 mg/L. Values reported as mean (SD), *n* (%) or median (IQR). EF, ejection fraction; LV, left ventricular; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; CABG, coronary artery bypass graft; Ua1m, urine alpha-1-microglobulin; IQR, interquartile range.

Long-term outcomes among individuals who survived the index hospitalization were ascertained through patient phone calls, hospital records review (US sites), National Death Index search (US sites), and ICES data (Canadian site). CV events were defined as major adverse CV events: hospitalization for acute coronary syndrome, myocardial infarction, congestive heart failure, coronary bypass, and percutaneous coronary intervention. We identified CV events using administrative codes [36]. For US participants, CV events were obtained through linkages with Centers for Medicare and Medicaid Services databases. For Canadian participants, information was obtained from data held at ICES, linked using unique encoded identifiers, and analyzed at ICES.

CKD incidence and progression outcomes were available in participants from 2 study sites (Ontario, Yale). Follow-up serum creatinine values were obtained using the Ontario Laboratories Information System for Canadian participants and the Yale Joint Data Analytics Team's HELIX data repository for participants enrolled at Yale. Estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration Equation [37]. For participants with preoperative eGFR ≥60 mL/min/1.73 m², CKD incidence was defined as a 25% reduction in eGFR and a fall below 60 mL/min/1.73 m². In participants with preoperative eGFR <60 mL/min/1.73 m², CKD progression was defined as a 50% reduction in eGFR or a fall below 15 mL/min/1.73 m² [30, 38, 39].

Statistical Analyses

Descriptive statistics were reported using mean (standard deviation, SD) or median (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables. We

compared continuous variables using the Wilcoxon rank-sum test and categorical variables using the χ^2 test. Ua1m was modeled continuously (after log₂-transformation to represent per 2-fold higher levels) and categorically as tertiles. Logistic regression models were used to explore associations of (1) preoperative Ua1m, (2) postoperative Ua1m, and (3) relative change from pre- to postoperative Ua1m levels with postoperative AKI. These models were adjusted for age, sex, race, preoperative comorbidities abstracted from chart review (diabetes, hypertension, heart failure, and myocardial infarction), baseline eGFR, urine albumin, and urine creatinine at corresponding time point, cardiopulmonary bypass time >120 min (omitted from models of preoperative Ua1m), nonelective surgery, CABG versus valve replacement, and study site.

We used Cox proportional hazards regression to model the associations of (1) preoperative Ua1m, (2) postoperative Ua1m, and (3) relative change from pre- to postoperative Ua1m levels with longitudinal outcomes after discharge, including CKD incidence, CKD progression, CV events, and all-cause mortality. Kolmogorov-type supremum tests were used to evaluate proportional hazards assumptions for all models. Models of CKD incidence and progression after discharge were adjusted for the variables listed above in the AKI model except for the addition of AKI or dialysis during index hospitalization and the exclusion of myocardial infarction history and surgery type (CABG vs. valve replacement). Models for CV events and all-cause mortality were also adjusted for similar variables as noted in the AKI model except for the addition of baseline smoking history, baseline BMI, and AKI or dialysis during index hospitalization, the exclusion of surgery type.

Table 2. Association of preoperative Ua1m levels and risk of in-hospital AKI and longitudinal adverse outcomes following hospital discharge in the TRIBE-AKI cohort

	AKI ^a (n = 1,464)	All-cause mortality ^b (n = 1,449)	CKD incidence ^c (n = 602)	CKD progression ^c (n = 262)	CV events ^b (n = 1,449)
Events, n (%)	230 (16)	459 (32)	212 (35)	54 (21)	269 (19)
Preoperative Ua1m	aOR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Per 2-fold higher	1.34 (1.13, 1.60)	1.18 (1.06, 1.33)	1.20 (0.96, 1.50)	1.46 (1.04, 2.04)	1.02 (0.87, 1.19)
Tertile 1 (0–5.46 mg/L)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2 (5.47–10.61 mg/L)	0.64 (0.43, 0.95)	0.93 (0.71, 1.22)	1.36 (0.98, 1.88)	0.72 (0.30, 1.74)	0.83 (0.60, 1.14)
Tertile 3 (10.63–285.02 mg/L)	1.14 (0.76, 1.69)	1.40 (1.06, 1.83)	1.30 (0.85, 2.00)	1.47 (0.64, 3.37)	1.02 (0.73, 1.44)

Ua1m ranges, tertile 1: 0–5.46 mg/L; tertile 2: 5.47–10.61 mg/L; and tertile 3: 10.63–285.02 mg/L. Ua1m, urine alpha-1-microglobulin; AKI, acute kidney injury; TRIBE-AKI, Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury; CKD, chronic kidney disease; aOR, adjusted odds ratio; aHR, adjusted hazard ratio; CI, confidence interval. ^a Adjusted for age, sex, race, nonelective surgery, CABG versus valve replacement, diabetes, hypertension, congestive heart failure, myocardial infarction, baseline eGFR, urine albumin, urine creatinine, and site. ^b Adjusted for age, sex, race, nonelective surgery, diabetes, hypertension, congestive heart failure, myocardial infarction, smoking, BMI, AKI/dialysis during index hospitalization, baseline eGFR, urine albumin, urine creatinine, and site. ^c Adjusted for age, sex, race, nonelective surgery, diabetes, hypertension, congestive heart failure, AKI/dialysis during index hospitalization, baseline eGFR, urine albumin, urine creatinine, and site.

All tests of statistical significance were two-sided, and $p < 0.05$ was considered statistically significant. To investigate effect modification by heart failure, we tested for interactions between heart failure status with CV events and all-cause mortality. Analyses were performed in SAS (version 9.4; SAS Institute, Cary, NC, USA).

Results

The size of the analytic cohort differed by outcome (Tables 2–4). In the 1,464 participants with preoperative Ua1m measurements, mean age was 72 years, 69% were male, and 94% were White (Table 1). Surgery was non-elective in 17% and consisted of CABG alone in 49% of participants. The preoperative Ua1m level was below LLD in nearly 35% of participants. By tertile of preoperative Ua1m, there were 507 participants in tertile 1 (all of whom had levels below LLD), 469 participants in tertile 2, and 488 participants in tertile 3. In the highest Ua1m tertile compared to the lowest, participants were older (73 vs. 70 years), more likely to be male (76 vs. 62%), and had a higher prevalence of CKD, diabetes, hypertension, and heart failure.

Preoperative Ua1m Levels and Postoperative Outcomes

There were 230 AKI events during the index hospitalization, among which 67 were stage 2 or 3. Analyzed con-

tinuously, each 2-fold higher level of Ua1m was associated with significantly increased odds of postoperative AKI (Table 2; Fig. 1). In the categorical analysis, the association between the highest tertile of preoperative Ua1m and postoperative AKI was attenuated and not statistically significant. In stratified analysis by diabetes status, there was evidence that Ua1m was more strongly associated with postoperative AKI among participants without diabetes compared to those with diabetes (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/00010.1159/000518240). In unadjusted analyses, there were statistically significant associations between preoperative Ua1m and stage 2 or 3 AKI (unadjusted odds ratio [OR] = 1.36, 95% confidence interval [CI] 1.09–1.69), but these were no longer significant in the adjusted model (adjusted OR = 1.30, 95% CI 0.97–1.73).

There were 459 deaths over a median follow-up of 6.7 years (IQR 4.0, 7.9). Higher preoperative Ua1m levels were associated with increased risk of all-cause mortality when analyzed continuously and categorically (Table 2; Fig. 2). The highest tertile of Ua1m was associated with a 40% higher risk of all-cause mortality compared to the lowest tertile. However, this association was modified by heart failure (Ua1m and heart failure interaction $p = 0.009$ for continuous analysis, $p = 0.008$ for categorical analysis). Among those without heart failure, preoperative Ua1m was strongly associated with mortality

Table 3. Association of postoperative Ua1m levels and risk of in-hospital AKI and longitudinal adverse outcomes following hospital discharge in the TRIBE-AKI cohort

	AKI ^a (n = 1,445)	All-cause mortality ^b (n = 1,430)	CKD incidence ^c (n = 598)	CKD progression ^c (n = 258)	CV events ^b (n = 1,430)
Events, n (%)	226 (16)	450 (31)	210 (35)	53 (21)	262 (18)
Postoperative Ua1m	aOR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Per 2-fold higher	1.07 (0.93, 1.22)	1.01 (0.92, 1.11)	0.90 (0.79, 1.03)	0.79 (0.56, 1.11)	1.06 (0.94, 1.19)
Tertile 1 (5.46–8.05 mg/L)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2 (8.06–23.03 mg/L)	0.75 (0.47, 1.17)	0.97 (0.73, 1.30)	1.02 (0.66, 1.57)	2.16 (0.93, 5.05)	1.55 (1.05, 2.27)
Tertile 3 (23.20–651.36 mg/L)	0.98 (0.61, 1.58)	1.14 (0.83, 1.59)	0.84 (0.52, 1.38)	0.74 (0.22, 2.45)	1.56 (1.01, 2.39)

Postoperative samples collected on postoperative day 1. Ua1m, urine alpha-1-microglobulin; AKI, acute kidney injury; TRIBE-AKI, Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury; CKD, chronic kidney disease; aOR, adjusted odds ratio; aHR, adjusted hazard ratio; CI, confidence interval. ^aAdjusted for age, sex, race, cardiopulmonary bypass time >120 min, nonelective surgery, CABG versus valve replacement, diabetes, hypertension, congestive heart failure, myocardial infarction, baseline eGFR, urine albumin, urine creatinine, and site. ^bAdjusted for age, sex, race, cardiopulmonary bypass time >120 min, nonelective surgery, diabetes, hypertension, congestive heart failure, myocardial infarction, smoking, BMI, AKI/dialysis during index hospitalization, baseline eGFR, urine albumin, urine creatinine, and site. ^cAdjusted for age, sex, race, cardiopulmonary bypass time >120 min, nonelective surgery, diabetes, hypertension, congestive heart failure, AKI/dialysis during index hospitalization, baseline eGFR, urine albumin, urine creatinine, and site.

Table 4. Association of per 100% change in preoperative to postoperative day 1 Ua1m levels and risk of in-hospital AKI and longitudinal adverse outcomes following hospital discharge in the TRIBE-AKI cohort

	AKI ^a (n = 1,444)	All-cause mortality ^b (n = 1,429)	CKD incidence ^c (n = 598)	CKD progression ^c (n = 258)	CV events ^b (n = 1,429)
Events, n (%)	226 (16)	450 (31)	210 (35)	53 (21)	262 (18)
Change in Ua1m	aOR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
per 100% change	1.00 (0.97, 1.02)	0.98 (0.96, 1.00)	0.98 (0.95, 1.01)	0.79 (0.65, 0.97)	0.99 (0.97, 1.02)
Tertile 1 (–96.9% to 0.0%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2 (0.0–152.9%)	0.74 (0.49, 1.11)	0.83 (0.65, 1.06)	0.62 (0.42, 0.94)	0.55 (0.26, 1.17)	1.02 (0.73, 1.43)
Tertile 3 (154.1–840.7%)	0.95 (0.61, 1.47)	0.78 (0.58, 1.04)	0.69 (0.43, 1.09)	0.32 (0.11, 0.92)	1.03 (0.70, 1.50)

Ua1m, urine alpha-1-microglobulin; AKI, acute kidney injury; TRIBE-AKI, Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury; CKD, chronic kidney disease; aOR, adjusted odds ratio; aHR, adjusted hazard ratio; CI, confidence interval. ^aAdjusted for age, sex, race, cardiopulmonary bypass time >120 min, nonelective surgery, CABG versus valve replacement, diabetes, hypertension, congestive heart failure, myocardial infarction, baseline eGFR, urine albumin, urine creatinine, and site. ^bAdjusted for age, sex, race, cardiopulmonary bypass time >120 min, nonelective surgery, diabetes, hypertension, congestive heart failure, myocardial infarction, smoking, BMI, AKI/dialysis during index hospitalization, baseline eGFR, urine albumin, urine creatinine, and site. ^cAdjusted for age, sex, race, cardiopulmonary bypass time >120 min, nonelective surgery, diabetes, hypertension, congestive heart failure, AKI/dialysis during index hospitalization, baseline eGFR, urine albumin, urine creatinine, and site.

(adjusted hazard ratio [aHR] = 1.28, 95% CI 1.12–1.47), whereas the association was weaker among those with heart failure (aHR = 1.06, 95% CI 0.84–1.32). Categorical analyses yielded similar findings (online suppl. Table 2).

There were 212 incident CKD diagnoses and 54 events of CKD progression over a median follow-up of 5.8 years (IQR 4.2, 7.1 years). There were no significant associations between preoperative Ua1m and CKD incidence (Table 2). However, there was a significant in-

Fig. 1. Adjusted associations of preoperative Ua1m levels with risk of in-hospital AKI and longitudinal adverse outcomes following hospital discharge in the TRIBE-AKI cohort. Squares represent model-adjusted estimates of OR (for AKI) or HR (longitudinal outcomes) for each 2-fold higher preoperative Ua1m concentration. Brackets represent 95% CIs. *For AKI, measure of association is aOR. OR, odds ratio; aOR, adjusted odds ratio; Ua1m, urine alpha-1-microglobulin; AKI, acute kidney injury; TRIBE-AKI, Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury; CI, confidence interval; HR, hazard ratio.

Fig. 2. Kaplan-Meier curves depicting survival probability by tertile of preoperative Ua1m. Ua1m, urine alpha-1-microglobulin.

teraction on diabetes status, whereby preoperative Ua1m was associated with incident CKD among participants with diabetes (aHR = 1.73, 95% CI 1.30–2.31) but not among those without diabetes (aHR = 0.87, 95% CI 0.61–1.25; online suppl. Table 3). Higher preoperative Ua1m concentrations were associated with significantly greater risk of CKD progression when analyzed as a continuous predictor, though this association was not statistically significant when Ua1m was analyzed in tertiles (Table 2; Fig. 1).

There were 269 CV events over a median follow-up of 6.3 years (IQR 3.1, 7.7). Preoperative Ua1m levels were not associated with CV events in continuous or categorical analyses.

Postoperative Day 1 Ua1m Levels and Postoperative Outcomes

In the unadjusted analyses, postoperative day 1 Ua1m levels were associated with higher odds of AKI (OR =

1.28, 95% CI 1.16–1.41) and severe AKI (OR = 1.50, 95% CI 1.27–1.76), but these associations were attenuated and no longer significant after multivariable adjustment (Table 3; online suppl. Table 1). Postoperative Ua1m was not associated with CKD incidence or CKD progression. In contrast, higher postoperative Ua1m concentrations were associated with increased risk of CV events. Though the strength of this association was attenuated by multivariable adjustment, the categorical estimates remained significant and directionally consistent in the multivariable model (Table 3). Heart failure status did not modify the association of postoperative Ua1m with CV events. Postoperative Ua1m levels were not associated with all-cause mortality (Table 3).

Relative Changes from Preoperative to Postoperative Ua1m Levels and Postoperative Outcomes

The median (IQR) change from preoperative Ua1m level to postoperative day 1 Ua1m level was 43.9%

Fig. 3. a Frequency distribution of preoperative Uα1m (red line) and postoperative Uα1m (blue line) concentrations in mg/L. Uα1m, urine alpha-1-microglobulin. **b** Histogram of relative (%) change from preoperative to postoperative Uα1m concentration. Uα1m, urine alpha-1-microglobulin.

(−12.2%, 256.9%) (Fig. 3a, b). Larger increases from preoperative to postoperative day 1 levels were associated with marginally increased risk of AKI, but these associations disappeared with adjustment (Table 4). Larger increases in Uα1m were not associated with CKD incidence but were associated with lower risk of CKD progression (for each 100% increase in Uα1m aHR = 0.79, 95% CI 0.65–0.97). Compared to the lowest tertile, the highest tertile of change in Uα1m levels was also associated with decreased risk of CKD progression (aHR = 0.32, 95% CI 0.11–0.92; Table 4). There were no significant associations between the percent change of Uα1m and CV events. Associations between changes in Uα1m and all-cause mortality were marginal and attenuated with adjustment (Table 4).

Discussion

In this large, well-described cohort of high-risk patients undergoing cardiac surgery, we found that higher preoperative Uα1m levels were significantly associated with increased risk of AKI during index hospitalization as well as with CKD progression and all-cause mortality. Postoperative Uα1m levels and the relative change between pre- and postoperative Uα1m were not strongly associated with post-discharge outcomes. Our findings underscore the potential value of Uα1m as an ambulatory marker of tubular function that can risk-stratify as well as prognosticate kidney and nonkidney outcomes but did not support the use of Uα1m as an early indicator of in-hospital AKI.

Ua1m levels reflect proximal tubule dysfunction and have been reported to increase in AKI and to correlate with pathologic changes of CKD, making Ua1m an attractive surrogate for kidney damage [18, 22, 24]. However, the finding that preoperative Ua1m was more consistently and strongly associated with AKI, CKD, and death compared with postoperative Ua1m was unexpected. Perhaps due to the unique kinetics of α 1m, preoperative (baseline) and immediate postoperative (stressed) levels appear to represent distinct physiologies and should be interpreted differently based on our findings. Because α 1m is filtered across the glomerulus, it is susceptible to hemodynamic variation during and after cardiac surgery and may be unreliable in the early postoperative period compared to the steady state preoperative levels. Though postoperative levels of Ua1m increased in most participants, some of these elevations may have quickly declined as normal tubular function was restored, but we measured Ua1m only on the first postoperative day and thus could not observe normalization. Transient elevations Ua1m might not capture clinically important AKI in contrast to the tubule injury markers that we have previously studied in this cohort, such as IL-18 and KIM-1, in which the median levels rise approximately 10-fold in AKI cases compared to non-cases [13, 40–42]. In contrast, Ua1m may be most informative of underlying kidney health when measured in the absence of acute stressors.

Our finding that higher preoperative Ua1m was associated with 36% higher odds of postoperative AKI is consistent with previously published estimates. Among ambulatory SPRINT trial participants with CKD, each 2-fold higher baseline Ua1m level was associated with 20% higher risk of subsequent in-hospital AKI, independent of baseline eGFR, albuminuria, and other kidney tubule biomarkers [27]. Likewise, higher Ua1m appears to portend worsening kidney function. We found that higher baseline Ua1m levels indicated a significantly greater risk of CKD progression in participants with prevalent CKD and demonstrated a directionally consistent, though nonsignificant, association with incident CKD. These results agree with findings from ambulatory settings in which Ua1m predicted faster kidney function decline in healthy and chronically ill populations [25, 26]. Furthermore, we found some evidence that the association between preoperative Ua1m levels and kidney outcomes might differ depending on baseline diabetes status, which warrants investigation in future studies. In sum, the results of our analysis, in addition to those from prior studies, suggest that baseline Ua1m levels might indicate the kidney's sus-

ceptibility to insults and risk of functional decline independent of baseline eGFR and albuminuria.

Unexpectedly, larger Ua1m elevations in the immediate postoperative period were associated with significantly lower risk of CKD progression among participants with prevalent CKD. However, we did not find significant associations between postoperative Ua1m levels alone and AKI or CKD incidence; rather, this association was observed when we analyzed the relative changes in the Ua1m level from before to after surgery. Few studies have evaluated associations of changes in Ua1m with subsequent CKD risk. One recent study in ambulatory HIV-infected women observed that rising Ua1m concentrations were associated with higher risk of incident CKD [43]. Additionally, among SPRINT trial participants assigned to the usual care arm, rising Ua1m concentrations were associated with incident CKD, whereas declining Ua1m concentrations were associated with incident CKD in the intensive antihypertensive therapy arm [44]. These findings suggest that changes in Ua1m may disclose risk of CKD, but also that Ua1m concentrations are susceptible to hemodynamic changes. This issue may be particularly relevant to the period immediately after cardiac surgery. The degree of perioperative change may be further confounded by underlying kidney health, as demonstrated by a study comparing Ua1m levels before and after cardiac surgery between individuals with creatinine clearances above and below 60 mL/min [21]. In this study, the relative change from preoperative to postoperative levels was greater among those with creatinine clearance >60 mL/min [21]. Thus, it is conceivable that larger relative increases in Ua1m levels after surgery are an indicator of individuals with healthier kidneys before surgery. Acute variations in Ua1m warrant further exploration to clarify their potential significance.

Higher preoperative Ua1m levels in this cohort were independently associated with all-cause mortality, which is consistent with findings across a variety of populations. In kidney transplant recipients, Ua1m was associated with a 51% increased risk of death per 2-fold higher level [45]. Among 2,948 Framingham Heart Study participants, each standard deviation increase of log-transformed Ua1m was associated with 26% higher risk of all-cause mortality [29]. In a case-cohort study of ambulatory older adults, each 2-fold higher baseline Ua1m was associated with a 1.29-fold greater risk of all-cause mortality over a median follow-up of 12 years [16]. Similarly, Garimella et al. [28] demonstrated that each 2-fold higher Ua1m level was

associated with a 25% increase in the adjusted hazard of all-cause mortality among patients with CKD and hypertension.

The association of Ua1m with mortality risk in this study was much stronger in participants without heart failure than in those with heart failure. The physiology of Ua1m may render it less reliable in patients with heart failure. Heart failure can cause neurohormonally mediated reductions in GFR [46], which could decrease the amount of α 1m filtered into the tubule and ultimately excreted in urine irrespective of reabsorption – in essence, mimicking intact reabsorption. However, this was unlikely to be the case in the TRIBE-AKI cohort, given that participants with baseline heart failure were more likely to be in the highest tertile of preoperative Ua1m. Alternatively, mortality risk in individuals with heart failure may be influenced by pathways that are less related to kidney tubule dysfunction [36].

Previously reported associations between Ua1m and heart disease have been inconsistent, and we found only weak evidence for an association between Ua1m and CV events in this cohort. Similarly, the aforementioned analysis from the Framingham Heart Study found no association between Ua1m and CV events despite a strong association with mortality [29]. Jotwani et al. [16] found that higher baseline Ua1m was associated with significantly higher risk of CV events but not incident heart failure in older adults. Similarly, Park et al. [45] found that higher Ua1m was associated with CV events in kidney transplant recipients. Among TRIBE-AKI participants, those with severe postoperative AKI were more likely to experience CV events or death during a median 3.8 years of follow-up; however, only postoperative cardiac biomarkers – not kidney injury biomarkers – were associated with this outcome, suggesting against an independent kidney pathway in this relationship [36].

Though this study benefited from a well-characterized, large, multicenter cohort, its observational design is susceptible to residual confounding despite comprehensive multivariable adjustment. TRIBE-AKI did not record information on the severity and control of some comorbidities that could conceivably obfuscate the association between Ua1m and postoperative outcomes. However, we presume that comorbidities were perioperatively optimized for elective surgeries, which comprised the majority (83%) of procedures. Furthermore, only 10% of participants had severe heart failure at baseline as defined by left ventricular ejection fraction <35% or grade 3 or 4 left ventricular dysfunction. The unique

clinical characteristics of the participants limit generalizability, particularly to populations with lower burdens of CVD and lower risk of AKI. Furthermore, the sample was overwhelmingly White and male, highlighting the need for future studies to include participants more representative of the general population. Postoperative Ua1m levels were available only from the first postoperative day, so it is unknown whether or not Ua1m fluctuations later in the hospitalization would be informative for kidney and CV prognosis. In spite of these limitations, the validity of our findings is supported by their consistency with results from studies of Ua1m in other populations.

In conclusion, preoperative Ua1m was independently associated with postoperative AKI, CKD progression, and all-cause mortality in this cohort of adults undergoing cardiac surgery. Contrary to our *a priori* hypothesis, associations of postoperative Ua1m or changes in pre- to postoperative Ua1m concentrations with these outcomes were weak and inconsistent. These results contribute to growing evidence that Ua1m levels have important associations with adverse outcomes and suggest that kidney tubule dysfunction is an important risk factor for kidney disease and mortality. Future studies should better characterize short-, medium-, and long-term variations in Ua1m levels and investigate whether these associations generalize to more diverse populations.

Acknowledgements

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed in the material are those of the authors and not necessarily those of CIHI.

Statement of Ethics

This study was performed in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the institutional review board at each study site. All study participants provided written informed consent.

Conflict of Interest Statement

C.R.P. serves on the advisory boards of Renalytix AI, LLC, and GENFIT Pharmaceuticals. M.M.E. and M.G.S. have received funding from Bayer Healthcare Pharmaceuticals, Inc. M.G.S. discloses consulting income from Intercept Pharmaceuticals, Inc. and Cricket Health. The remaining authors did not declare relevant financial interests.

Funding Sources

J.G.A. is supported by National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award No. F32DK126381. CRP is supported by NIH Grants under Award No. R01HL085757, U01DK082185, and the P30DK079310 O'Brien Kidney Center Grant.

Author Contributions

J.G.A., M.M.E., C.R.P., and M.G.S. contributed to research question and study design; C.R.P., A.X.G., and M.G.S. contributed to data acquisition; J.G.A., M.M.E., A.X.G., S.G.C., H.T.P., E.M., C.R.P., and M.G.S. contributed to data analysis and interpretation; H.T.P. and E.M. contributed to statistical analysis; M.M.E., C.R.P., and M.G.S. contributed to supervision and mentorship. Each author contributed to important intellectual content during manuscript drafting and revision.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (M.G.S.) upon reasonable request.

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