Urinary Biomarkers of AKI and Mortality 3 Years after Cardiac Surgery

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ABSTRACT

Urinary biomarkers of AKI provide prognostic value for in-hospital outcomes, but little is known about their association with longer-term mortality after surgery. We sought to assess the association between kidney injury biomarkers and all-cause mortality in an international, multicenter, prospective long-term follow-up study from six clinical centers in the United States and Canada composed of 1199 adults who underwent cardiac surgery between 2007 and 2009 and were enrolled in the Translational Research in Biomarker Endpoints in AKI cohort. On postoperative days 1–3, we measured the following five urinary biomarkers: neutrophil gelatinase-associated lipocalin, IL-18, kidney injury molecule-1 (KIM-1), liver fatty acid binding protein, and albumin. During a median follow-up of 3.0 years (interquartile range, 2.2–3.6 years), 139 participants died (55 deaths per 1000 person-years). Among patients with clinical AKI, the highest tertiles of peak urinary neutrophil gelatinase-associated lipocalin, IL-18, KIM-1, liver fatty acid binding protein, and albumin associated independently with a 2.0- to 3.2-fold increased risk for mortality compared with the lowest tertiles. In patients without clinical AKI, the highest tertiles of peak IL-18 and KIM-1 also associated independently with long-term mortality (adjusted hazard ratios [95% confidence intervals] of 1.2 [1.0 to 1.5] and 1.8 [1.4 to 2.3] for IL-18 and KIM-1, respectively), and yielded continuous net reclassification improvements of 0.26 and 0.37, respectively, for the prediction of 3-year mortality. In conclusion, urinary biomarkers of kidney injury, particularly IL-18 and KIM-1, in the immediate postoperative period provide additional prognostic information for 3-year mortality risk in patients with and without clinical AKI.

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In many studies, the development of AKI, defined by acute changes in serum creatinine, associates with a higher risk of long-term mortality.[1,2] Acute changes in serum creatinine, however, may not fully reflect the severity of kidney injury due to the influence of age, sex, muscle mass, changes in hydration, nutritional status, and medications on creatinine kinetics. Moreover, serum creatinine may abruptly rise in hospitalized settings due to functional processes such as altered hemodynamics, without any true nephron damage. Several urinary biomarkers of structural kidney injury have been investigated in human cohorts in an effort to identify AKI earlier, improve the diagnosis of AKI, and to aid in risk stratification.[3] It is largely unknown, however,

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whether kidney injury biomarkers associate with long-term outcomes, including mortality, and whether these biomarkers add useful prognostic information beyond the standard measure to detect AKI (*e.g.,* peak change in serum creatinine). Some data suggest that "subclinical AKI," as evidenced by elevations in urinary kidney injury biomarkers in the absence of a rise in serum creatinine, associates with worse in-hospital clinical outcomes.[4] Few studies have examined whether kidney injury biomarkers associate with long-term mortality after hospital discharge.[5]

To address the current knowledge gaps, we conducted this study to characterize the association between kidney injury biomarkers and long-term mortality and to assess whether these biomarkers provide any incremental prognostic information for long-term mortality beyond that of serum creatinine changes and other clinical variables.

RESULTS

Baseline characteristics are presented in Table 1 for the overall population and by survival status. During a median follow-up of 3.0 years (interquartile range, 2.2–3.6), 139 participants died (55 deaths per 1000 person-years). Patients who died were older; were more likely to have a history of congestive heart failure, reduced estimated GFR, and microalbuminuria; were more likely to have undergone a combined coronary artery bypass graft (CABG) and valve repair; and were more likely to have longer perfusion and cross-clamp times. Participants who died also had more clinical AKI, more nonrenal complications postsurgery, longer intubation time, and longer intensive care unit (ICU) and in-hospital length of stay. Of the 407 patients with AKI, 68 (17%) died (mortality rate, 80 per 1000 person-years). Of the 792 patients without AKI, 71 (9%) died (mortality rate, 40 per 1000 person-years).

Peak Postoperative Urinary Biomarkers and Risk of Mortality

Mortality rates increased monotonically by tertile of urinary biomarker in the AKI and non-AKI strata (Figure 1). The mortality rate in the highest tertile of urinary biomarkers of kidney injury in those without clinical AKI approximated the mortality rate in the lowest tertile of biomarkers in those with clinical AKI (except for urinary liver fatty acid binding protein [L-FABP]; Figure 1). In multivariable-adjusted analyses, stratified by clinical AKI status, higher peak urinary biomarker levels had consistently stronger associations with the relative risk of mortality in those with clinical AKI than those without AKI (Figure 2). The adjusted hazard ratios (HRs) for the highest versus lowest tertiles for all five biomarkers ranged from 2.0 to 3.2 (Figure 3) in patients with clinical AKI. In patients without clinical AKI, the upper tertiles of the peak concentrations of urinary IL-18 (HR, 1.2; 95% confidence interval [95% CI], 1.0 to 1.5) and kidney injury molecule-1 (KIM-1) (HR, 1.8; 95% CI, 1.4 to 2.3) were independently associated with increased mortality risk. In participants without AKI, urine L-FABP was inversely associated with mortality (for highest versus lowest tertile: HR, 0.7; 95% CI, 0.5 to 0.9).

Incremental Value in Risk Prediction

Addition of peak biomarkers to the clinical model did not change the area under the curve (AUC) for death (AUC for biomarkers plus the clinical model ranged from 0.69 to 0.71). The addition of the peak urinary biomarker concentration to the clinical model yielded a continuous net reclassification index (NRI) that ranged from 0.18 for KIM-1 to 0.44 for both neutrophil gelatinase–associated lipocalin (NGAL) and IL-18 in patients with AKI. In patients without AKI, the continuous NRI ranged from 0.04 for L-FABP to 0.37 for KIM-1 (Table 2). IL-18 predominantly correctly reclassified those that died (continuous NRI, 0.36), whereas KIM-1 improved reclassification in patients who ultimately died or survived (0.17 and 0.20, respectively).

Secondary Analyses

Urinary biomarkers were weakly associated with serum creatinine concentrations, and urinary KIM-1 was completely uncorrelated with serum creatinine (Table 3). Associations between the injury biomarkers varied and were moderate in strength. Urine NGAL and IL-18 were the most strongly correlated of any of the biomarkers (r=0.61; $P<0.001$).

The associations between the first postoperative biomarker concentrations (at 0–6 hours after surgery) were generally weaker than that observed for peak biomarker concentrations in patients with AKI. In patients without clinical AKI, there were no statistically significant associations for any of the five biomarkers at 0–6 hours (Supplemental Table 1). When the cumulative concentrations of biomarkers were considered as the primary exposure variable, the point estimates for the adjusted HRs, AUCs, and NRIs approximated those seen for the peak concentrations in the first 3 postoperative days for patients with and without AKI (Supplemental Figure 1, Supplemental Table 2).

DISCUSSION

Elevated levels of urinary kidney injury biomarkers in the postoperative period are independently associated with an increased risk for long-term mortality over a median 3-year follow-up in a population of patients that were at high risk for AKI and underwent cardiac surgery. The associations were strongest when the absolute value of the peak postoperative concentrations were considered compared with the first postoperative value. The relationships were minimally confounded by preoperative and perioperative factors known to influence mortality, and were independently associated with mortality even in patients without clinically apparent AKI. These results indicate that urinary biomarkers not only provide added prognostic information in those with clinical AKI, but potentially

Table 1. Baseline characteristics of TRIBE-AKI participants by survival status at 3 years of follow-up

Characteristic	Overall (*N*=1199)	Nonsurvivors (*n*=139)	Survivors (*n*=1060)	*P* Value
Demographics				
Age at the time of surgery (yr) (SD)	71.4 (10.1)	74 (9.5)	71 (10.1)	0.001
Men	817 (68)	95 (68)	722 (68)	0.96
White race	1122 (94)	130 (94)	992 (94)	0.98
Medical history (time of surgery)				
Diabetes	475 (40)	65 (47)	410 (39)	0.70
Hypertension	946 (79)	108 (78)	838 (79)	0.71
Congestive heart failure	307 (26)	56 (40)	251 (24)	<0.001
Left ventricular ejection fraction <40%	119 (10)	19 (14)	100 (9)	0.12
Previous myocardial infarction	306 (26)	38 (29)	268 (26)	0.46
eGFR (ml/min per 1.73 m^2) (SD)	68 (19.3)	62 (21.3)	68 (18.9)	0.001
<60 (μmol/L per 1.73 m^2)	411 (34)	62 (44)	349 (32)	0.001
>60	788 (66)	77 (55)	711 (67)	0.001
30–60	375 (31)	52 (37)	323 (30)	
<30	36 (3)	10 (7)	26 (2)	
SCr (mg/dl)[a]	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)	0.001
Microalbuminuria[b]	392 (33)	62 (48)	330 (32)	<0.001
Urine albumin to creatinine ratio				<0.001
≤10.0	401 (35)	25 (19)	376 (37)	
10.0–30	347 (30)	42 (33)	305 (30)	
30–300	323 (28)	46 (36)	277 (27)	
≥300	69 (6)	16 (12)	53 (5)	
Surgical characteristics				
Elective surgery	953 (79)	112 (81)	841 (79)	0.73
Surgery				0.004
CABG or valve	948 (79)	97 (70)	851 (80)	
CABG plus valve	250 (21)	42 (30)	208 (20)	
Off-pump	155 (13)	21 (15)	134 (13)	0.38
Reoperation	20 (2)	2 (2)	18 (2)	0.83
Perfusion time (min) (SD)	113.4 (59.5)	124.1 (64.7)	112 (58.7)	0.03
Cross-clamp time (min) (SD)	77.4 (44.4)	86.8 (49.1)	76.1 (43.6)	0.01
Diseased coronary vessels (*n*)				0.86
None	312 (26)	38 (27)	274 (26)	
1	156 (13)	17 (12)	139 (13)	
2	224 (19)	23 (17)	201 (19)	
3	497 (42)	61 (44)	436 (42)	
Left main disease ≥50%	423 (36)	51 (38)	372 (36)	0.69
Postoperative complications				
Clinical AKI[c]				<0.001
ΔSCr (%)				
≥50 (or ≥0.3 mg/dl)	359 (30)	52 (37)	307 (29)	
≥100	30 (3)	9 (6)	21 (2)	
≥200	18 (2)	7 (5)	11 (1)	
Acute dialysis	11 (1)	5 (4)	6 (1)	
Oliguria in first day[d]	15 (1)	2 (1)	13 (1)	0.50
Peak ΔSCr[e] (SD)	0.2 (0.4)	0.3 (0.5)	0.2 (0.4)	<0.001
Nonrenal complications (*n*)[f]				<0.001
0	730 (61)	67 (48)	663 (63)	
1–2	363 (30)	46 (33)	317 (30)	
>2	106 (9)	26 (19)	80 (8)	
Ventilator >48 h	45 (4)	14 (10)	31 (3)	0.001

Table 1. Continued

Characteristic	Overall (*N*=1199)	Nonsurvivors (*n*=139)	Survivors (*n*=1060)	*P* Value
Length of stay (d)				
ICU	2 (1, 3)	3 (1, 5)	2 (1, 3)	<0.001
Hospital	6 (5, 8)	8 (6, 13)	6 (5, 8)	<0.001

Data are presented as the mean (SD), *n* (%), or median (interquartile range) unless otherwise specified. eGFR, estimated GFR; SCr, serum creatinine.
[a]To convert serum creatinine values to millimoles per liter, multiply by 88.4.
[b]Microalbuminuria is defined as a urine albumin to creatinine ratio>30 μg/mg.
[c]Clinical AKI is defined as a change in serum creatinine of ≥50% or ≥0.3 mg/dl from before surgery to the peak postoperative value.
[d]Oliguria is defined as a patient who had <125 ml or <500 ml urine output in 6 or 24 hours, respectively.
[e]Peak indicates the highest biomarker value through the third postoperative day.
[f]Nonrenal complications are defined as reoperation, infection, neurologic, pulmonary, vascular, and other.

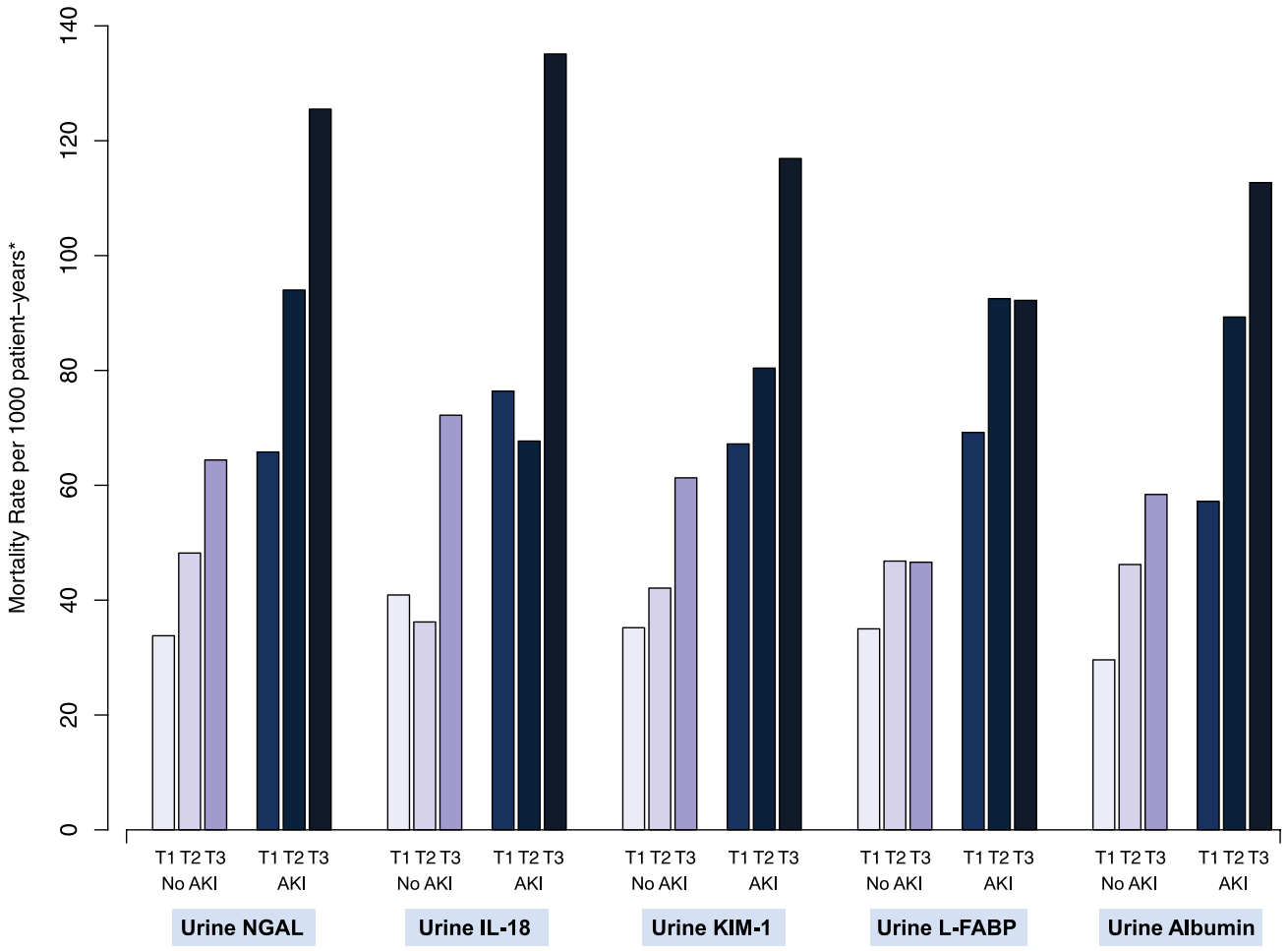

Figure 1. Peak urinary biomarker tertiles and mortality rates. *Mortality rate per 1000 patient-years adjusted for site. Biomarker tertiles are based on the peak biomarker percentiles on postoperative days 1–3. Biomarker tertile cut-off values and adjusted mortality HRs are presented in Figure 2.

support a revised paradigm in which even subclinical AKI may confer increased risk for adverse outcomes. The absolute mortality rate for patients in the upper tertiles of urinary biomarkers of kidney injury that had no apparent clinical AKI approximated that of those in the first tertile of urinary injury biomarker concentrations with clinical AKI. Thus, if validated in future studies, our results suggest that definitions of kidney injury should be based on changes in urinary biomarkers in addition to changes in serum creatinine.

This study is one of the few to show a sustained association of urinary kidney injury biomarkers with outcomes long after the time of hospitalization. Most studies of urinary biomarkers have only focused on short-term outcomes.[3,4,6] Ralib *et al.*

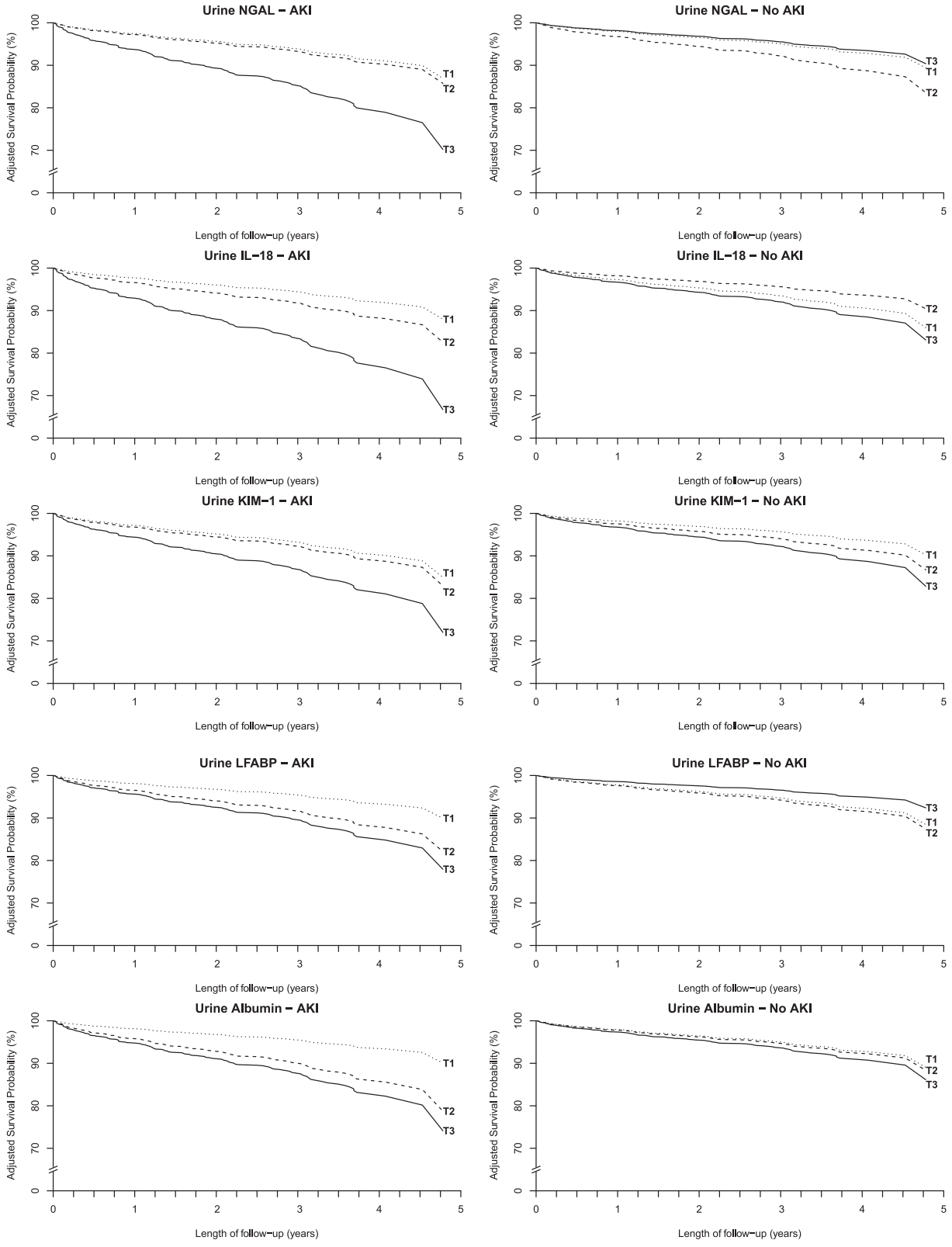

Figure 2. Multivariable-adjusted survival curves by peak biomarker concentration tertiles. Survival curves are adjusted for age (per year), sex, white race, cardiopulmonary bypass time>120 minutes, nonelective surgery, diabetes, hypertension, congestive heart failure, myocardial infarction, preoperative estimated GFR (eGFR), preoperative urine albumin to creatinine ratio, type of surgery (CABG or valve versus all others), and clinical site. T1, tertile 1; T2, tertile 2; T3, tertile 3.

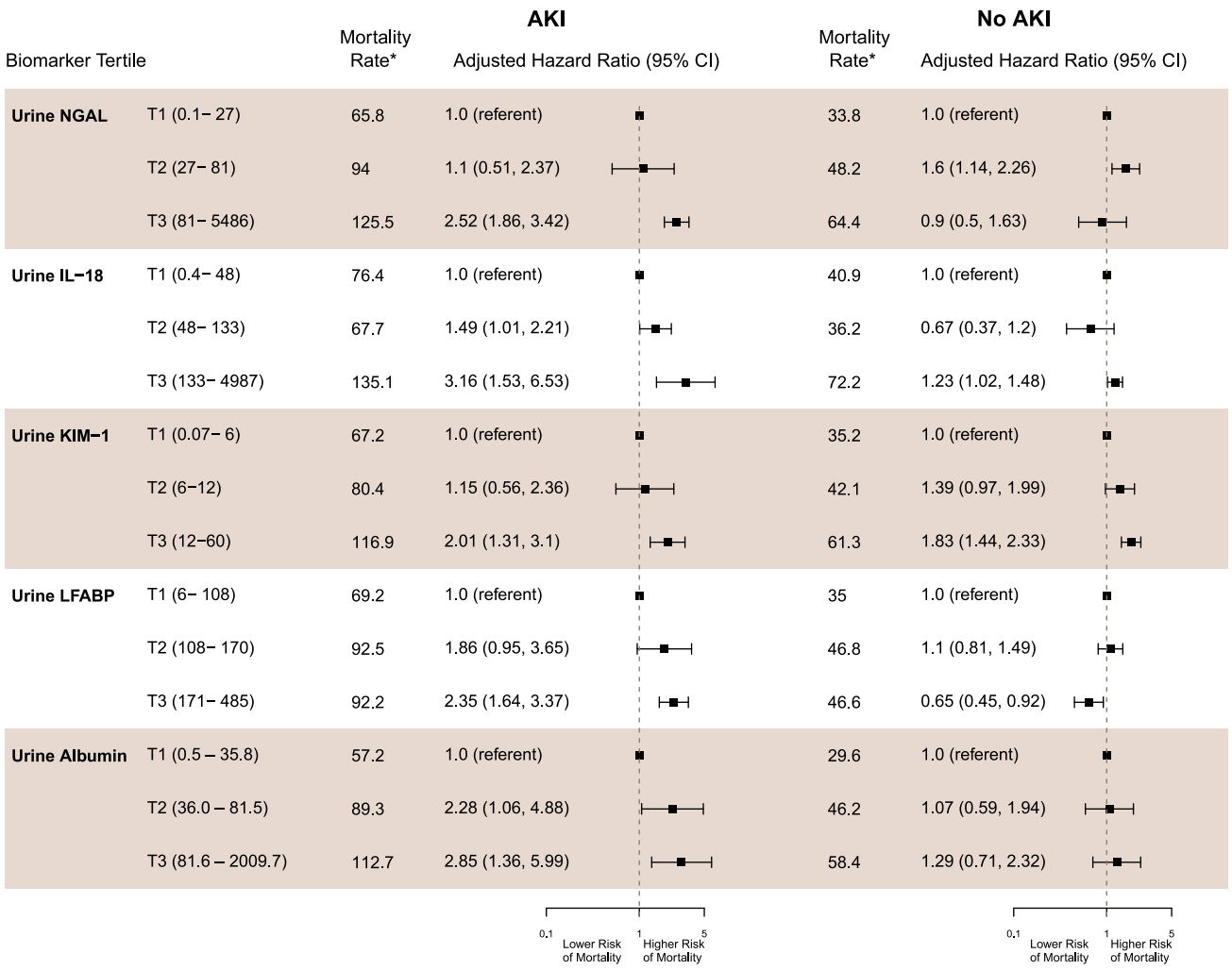

Figure 3. Analyses of tertiles of peak urinary biomarkers with risk of death, stratified by clinical AKI status. *Mortality rate per 1000 patient-years adjusted for site. Biomarker tertiles based on the peak biomarker percentiles on postoperative days 1–3. Cox proportional hazards regression models are used to examine the relationship between each biomarker and mortality. The models include an interaction term between biomarker tertile and AKI and are adjusted for age (per year), sex, white race, cardiopulmonary bypass time>120 minutes, nonelective surgery, diabetes, hypertension, congestive heart failure, myocardial infarction, preoperative estimated GFR (eGFR), preoperative urine albumin to creatinine ratio, type of surgery (CABG or valve versus all others), and clinical site. *P* values for interaction are as follows: urine NGAL, 0.01; urine IL-18, 0.07; urine KIM-1, 0.80; urine L-FABP, 0.02; and urine albumin, 0.18. AKI defined by serum creatinine≥0.3 mg/dl or ≥50% from baseline (preoperative) to peak postoperative creatinine value.

examined the association between several urinary kidney injury biomarkers and survival at 1 year in a cohort of 528 patients in the ICU.[5] They found mild to modest discrimination for the absolute concentrations of NGAL, IL-18, and KIM-1 and 1-year survival (AUC, 0.56–0.60). In a fully adjusted model, the 24-hour excretion rate of urinary NGAL provided similar results to our findings; the adjusted HR for the highest tertile versus the lowest tertile for mortality at 1 year was 2.1 (95% CI, 1.2 to 3.7). However, the highest tertiles of urinary IL-18 (adjusted HR, 1.2; 95% CI, 0.7 to 2.0) and KIM-1 (adjusted HR, 0.7; 95% CI, 0.4 to 1.2) were not independently associated with 1-year mortality in their cohort, after adjusting for age, sex, sepsis, erythropoietin treatment, and Acute Physiology, Age, Chronic Health Evaluation II and Sequential Organ Failure Assessment scores. Our findings build upon those reported by Ralib *et al.* in several ways. Our study included the following: a larger cohort (1199 versus 528 participants), longer follow-up time (3 years versus 1 year), and standardized collection of urinary biomarkers after the known timing of occurrence of kidney injury (postoperative setting versus mixed ICU population). Another study of 153 deceased donor kidney transplant recipients found that the first postoperative values of urinary NGAL and IL-18 were associated with adjusted odds ratios of 6.0 and 5.5, respectively, for poor allograft function at 1 year after transplantation.[7] Thus, our results, along with the data from previously published studies,[5,7] demonstrate

that the paradigm of using AKI biomarkers for risk stratification for posthospitalization outcomes is feasible and valid.

The mechanisms that underlie the association between elevated levels of urinary kidney injury biomarkers and mortality are unclear. One possibility is that urinary biomarkers of kidney injury quantify additional signals of kidney injury above and beyond those captured by serum creatinine (glomerular filtration). The weak associations we observed between the urinary biomarkers and serum creatinine confirm that they are capturing a different dimension of kidney physiology. Changes in serum creatinine can occur for a multitude of reasons, from either true kidney injury or from changes in renal perfusion due to abnormal cardiac output or vascular tone. Because the urinary biomarkers are more specific for identification of true kidney injury, they may be better at capturing the effect of AKI on subsequent CKD[8–11] or the effect of AKI on subsequent injury of nonrenal organs such as the heart, lungs, brain, and liver.[12–14] The biomarker elevations, however, may reflect more kidney injury but not be on the causal pathway to long-term mortality. For example, patients who manifest more severe AKI may be at greater risk for long-term complications such as death because of worse functioning of other organs rather than the episode of AKI.

Table 2. Continuous NRI for peak urinary biomarkers patients with and without AKI

Biomarker	Patients with AKI			Patients without AKI		
	Death	No Death	Overall	Death	No Death	Overall
Urine NGAL	0.22	0.22	0.44	−0.23	0.28	0.05
Urine IL-18	0.37	0.07	0.44	0.36	−0.10	0.26
Urine KIM-1	0.13	0.05	0.18	0.17	0.20	0.37
Urine L-FABP	0.59	0.28	0.30	0.18	−0.13	0.05
Urine albumin	0.46	0.26	0.2	−0.23	0.35	0.13

Data are presented as continuous NRI values. Clinical model comprised of age (per year), sex, white race, cardiopulmonary bypass time>120 minutes, nonelective surgery, diabetes, hypertension, congestive heart failure, myocardial infarction, preoperative estimated GFR, preoperative urine albumin to creatinine ratio, type of surgery (CABG or valve versus all others), and clinical site.

Our study has some limitations. First, our data are specific to patients at high risk for AKI who underwent cardiac surgery, and may not generalize as well to other patient populations. Second, we lacked data on cause of death and long-term kidney function, although a greater risk of CKD is likely given the known association between AKI and subsequent CKD.[15] Third, we did not study other biomarkers, such as troponin T and B-type brain natriuretic peptide, which have been associated with adverse outcomes in cardiac surgery. Fourth, we used spot urine samples rather than 24-hour collections. However, a previous study found that the 24-hour excretion of NGAL did not fare better in predicting 1-year survival compared with the absolute concentration of NGAL obtained on a spot sample.[5] In addition, the regimen of daily biomarker collection postoperatively used in this study was for research purposes, and may be quite onerous for use in routine care. We also did not fully explore combinations of biomarkers; the statistical methods for optimal combination are still being developed. Finally, we examined several biomarkers and did not adjust statistical significance for multiple comparisons. This study does have several strengths. It is the largest study to date of kidney biomarkers with assessment of long-term outcomes. Multiple clinical centers participated, the processes used to collect and store the biospecimens were standardized across sites, and we used validated assays for all biomarker measurements.

In conclusion, we provide new evidence that higher urinary kidney injury biomarkers are independently associated with death in a large prospective cohort of adults who underwent cardiac surgery. The additional prognostic information provided by the kidney injury biomarkers suggests that subclinical AKI may have prognostic importance, in addition to traditional predictor variables, including change in serum creatinine. With further validation, our results suggest that novel definitions of kidney injury that also consider urinary biomarker concentrations may be preferable to current definitions that are limited to changes in serum creatinine alone. Additional studies are also needed to evaluate whether therapeutic or preventative strategies that also prevent subclinical AKI postoperatively can improve long-term outcomes.

Table 3. Pearson correlation coefficients for peak biomarker concentrations

Biomarker	Serum Creatinine	Urine Albumin	Urine IL-18	Urine NGAL	Urine KIM-1	Urine L-FABP
Serum creatinine						
r (*P*)	—	0.14 (<0.001)	0.08 (0.01)	0.17 (<0.001)	0.003 (0.92)	0.11 (<0.001)
Urine albumin						
r (*P*)	0.14 (<0.001)	—	0.45 (<0.001)	0.46 (<0.001)	0.32 (<0.001)	0.27 (<0.001)
Urine IL-18						
r (*P*)	0.08 (0.01)	0.45 (<0.001)	—	0.61 (<0.001)	0.45 (<0.001)	0.46 (<0.001)
Urine NGAL						
r (*P*)	0.17 (<0.001)	0.46 (<0.001)	0.61 (<0.001)	—	0.34 (<0.001)	0.51 (<0.001)
Urine KIM-1						
r (*P*)	0.003 (0.92)	0.32 (<0.001)	0.45 (<0.001)	0.34 (<0.001)	—	0.16 (<0.001)
Urine L-FABP						
r (*P*)	0.11 (<0.001)	0.27 (<0.001)	0.46 (<0.001)	0.51 (<0.001)	0.16 (<0.001)	—

—, unable to calculate correlation coefficient.

CONCISE METHODS

Study Population

The Translation Research Investigating Biomarker Endpoints for Acute Kidney Injury (TRIBE-AKI) study is a prospective cohort of 1219 adults who underwent cardiac surgery (CABG or valve surgery) and had a high risk for AKI. Participants were enrolled at six academic medical centers in North America from July 2007 through December 2009.[16] Full study details, including sample collection and processing, were previously described.[16,17] In brief, we collected urine and plasma specimens preoperatively and daily for up to 5 days after surgery. We stopped specimen collection on postoperative day 3 in patients who were transferred to a hospital ward from the ICU without evidence of an increase in serum creatinine. Patients who died during the index hospitalization for surgery (n=20) were excluded from this analysis.

Measurement of Kidney Injury Biomarkers

The primary measures were the peak concentrations of five urinary biomarkers (NGAL, IL-18, KIM-1, L-FABP, and albumin) 1–3 days after surgery. In secondary analyses, the primary exposure was varied to consider biomarker concentrations from the first postoperative sample (0–6 hours after surgery) and the cumulative concentration of each biomarker across the first 3 postoperative days. To estimate the cumulative concentration, we first calculated the percentiles of each biomarker on each of the first 3 postoperative days and then averaged the three percentile values for each of the five biomarkers. For each participant, these cumulative concentration values approximated the AUC for each biomarker. Patients with only one biomarker measurement were excluded from analyses of the cumulative concentration (n=14–20 depending on the biomarker). For patients with only two biomarker measures, we carried forward the last available biomarker value (n=76–114 depending on the biomarker). The assays for NGAL, IL-18, L-FABP, KIM-1, and albumin were previously described,[16–18] and all biomarker measurements were completed before ascertainment of vital status. The personnel measuring the biomarkers were blinded to clinical outcomes, including AKI and vital status.

Measurement of Covariates

We recorded serum creatinine values obtained in routine clinical care for every patient throughout the hospital stay. All preoperative creatinine values were measured within 2 months before surgery. The preoperative and postoperative serum creatinine level measurements were performed in the same clinical laboratory for each patient at all sites. For adults, we estimated the preoperative GFR using the Chronic Kidney Disease Epidemiology Collaboration equation.[19] We defined AKI clinically by a change in serum creatinine of $\geq$50% or $\geq$0.3 mg/dl from before surgery to the peak postoperative value.[20] We collected preoperative characteristics, operative details, and postoperative complications using Society of Thoracic Surgeons definitions.[16]

Mortality

We obtained vital status after discharge through various mechanisms (and cross-referenced when possible). For those living in the United States, we performed phone calls to patients' homes, searched the National Death Index, and reviewed hospital records. For Canadian participants (those enrolled into the TRIBE-AKI study in London, ON, Canada), we used data held at the Institute for Clinical Evaluative Sciences to acquire vital status. The death status and date of death were recorded. Participants still alive on February 21, 2012 were considered censored for death.

Statistical Analyses

We used Cox proportional hazards regression with robust sandwich variance estimators (accounting for clustering within centers) to examine the association between biomarkers and time to death from the date of surgery. Peak biomarker concentrations were expressed as tertiles, with the lowest tertile as the reference group. Primary analyses were adjusted for the following variables: age (per year), sex, race (white versus nonwhite), nonelective surgery, diabetes, hypertension, congestive heart failure, myocardial infarction, type of surgery (CABG alone or valve repair alone versus both), preoperative estimated GFR (in milliliters per minute per 1.73 m^2), preoperative urine albumin to creatinine ratio, cardiopulmonary bypass time ($>$120 minutes versus $\leq$120 minutes or no cardiopulmonary bypass time), and clinical center. We used Schoenfeld residuals to confirm the proportional hazards assumption. To explore the influence of clinical AKI on the relationship between biomarkers and mortality, we included an interaction term between clinical AKI (yes versus no) and biomarker tertiles in the models. Because there was evidence of effect modification by clinical AKI, all results are presented separately by the presence or absence of clinical AKI.

To determine the ability of the biomarkers to discriminate survival risk, we calculated AUCs.[21] Instead of looking at the change in AUC to evaluate if the biomarkers provided incremental value beyond the clinical model, we examined the significance level of the biomarkers adjusted for the factors in the clinical model. Completing a second test of the change in AUC has been argued as redundant and may have statistical issues leading to overly conservative findings.[22–24] We quantified the improvement in 3-year risk prediction after the addition of biomarkers to the clinical model with the continuous NRI and the integrated discriminative index.[25–27] All analyses were performed in SAS (version 9.2; SAS Institute, Cary, NC) and R 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria) software.

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DISCLOSURES

C.R.P. is a named coinventor on the IL-18 patent. H.M.K. reports that he chairs a cardiac scientific advisory board for United Healthcare and is the recipient of a research grant from Medtronic, Inc. through Yale University.

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