Predicting kidney disease progression in patients with acute kidney injury after cardiac surgery

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ABSTRACT

Objective: The study objective was to identify patients who are likely to develop progressive kidney dysfunction (acute kidney disease) before their hospital discharge after cardiac surgery, allowing targeted monitoring of kidney function in this at-risk group with periodic serum creatinine measurements.

Methods: Risks of progression to acute kidney disease (a state in between acute kidney injury and chronic kidney disease) were modeled from acute kidney injury stages (Kidney Disease: Improving Global Outcomes) in patients undergoing cardiac surgery. A modified Poisson regression with robust error variance was used to evaluate the association between acute kidney injury stages and the development of acute kidney disease (defined as doubling of creatinine 2-4 weeks after surgery) in this observational study.

Results: Acute kidney disease occurred in 4.4% of patients with no preexisting kidney disease and 4.8% of patients with preexisting chronic kidney disease. Acute kidney injury predicted development of acute kidney disease in a graded manner in which higher stages of acute kidney injury predicted higher relative risk of progressive kidney disease (area under the receiver operator characteristic curve = 0.82). This correlation persisted regardless of baseline kidney function ($P < .001$). Of note, development of acute kidney disease was associated with higher mortality and need for renal replacement therapy.

Conclusions: The degree of acute kidney injury can identify patients who will have a higher risk of progression to acute kidney disease. These patients may benefit from close follow-up of renal function because they are at risk of progressing to chronic kidney disease or end-stage renal disease. (J Thorac Cardiovasc Surg 2018;155:2455-63)

Central Message

AKI definitions can be used to predict AKD, a disease state between AKI and CKD in patients undergoing cardiac surgery.

Perspective

Patients with AKI may sustain further worsening of kidney function that is subchronic (AKD), and some of these patients may progress to CKD. There is no reliable method to predict who with AKI is at risk for developing progressive kidney disease. This study presents a serum creatinine-based predictive model for such at-risk patients.

See Editorial Commentary page 2464.

Acute kidney injury (AKI) is a common disorder associated with increased morbidity and mortality.¹⁻⁴ In cardiac surgery, AKI complicates up to 30% of operations, and 1% to 2% of patients may require postoperative renal replacement therapy (RRT).^{2,4} Although AKI may be reversible, some patients develop subclinical or sub-acute

kidney disease (AKD) that can lead to progressive kidney disease (Figure 1 and Video 1).

Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines termed this subchronic kidney injury as “AKD and disorders.” They defined AKD as kidney damage for less than 3 months after AKI, glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² for less than 3 months, or a decrease in glomerular filtration rate 35% or more or increase in sCr by more than 50% for less than 3 months⁵ (Figure 1 and Table E1).

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Scanning this QR code will take you to the supplemental tables and video for this article.

Abbreviations and Acronyms

AKD	= acute kidney disease
AKI	= acute kidney injury
AUC _{ROC}	= area under the receiver operator characteristic curve
CABG	= coronary artery bypass grafting
CKD	= chronic kidney disease
eGFR	= estimated glomerular filtration rate
KDIGO	= Kidney Disease: Improving Global Outcomes
NKD	= no known kidney disease
RRT	= renal replacement therapy
sCr	= serum creatinine

Although serum creatinine (sCr) is not an ideal biomarker for diagnosing AKI, it is an established marker of chronic kidney disease (CKD), a disease that can be clinically silent and asymptomatic until later stages. Unfortunately, current clinical practice does not require periodic sCr measurements in all postoperative patients after discharge because it is neither clinically indicated nor fiscally prudent. Therefore, our main objective was to determine whether early postoperative changes in sCr (AKI) during the index hospital admission after cardiac surgery could identify a subset of at-risk patients who will progress to CKD or end-stage renal disease via AKD. Identification of such patients before they are discharged from the hospital after cardiac surgery will enable targeted periodic sCr measurements in this at-risk patient group.

We hypothesized that sCr-based AKI stages can predict clinically significant decline in kidney function (development of AKD), defined as doubling of sCr from baseline by 2 to 4 weeks after surgery in patients with no kidney disease and patients with preexisting CKD. Doubling of sCr was used as our outcome because it represents a significant ($\geq 50\%$) decrease in kidney function and is part of the KDIGO AKD definition. Our primary objective was to investigate whether the degree of AKI (AKI stages) can predict the development of AKD. Our secondary objective was to investigate whether patients who developed AKD had higher mortality and need for RRT after surgery.

MATERIALS AND METHODS**Data Sources, Data Collection, and Patient Characteristics**

All patients who underwent cardiopulmonary bypass at Brigham and Women's Hospital from 2006 to 2014 were enrolled in the study. The data for this retrospective study were extracted from our electronic patient medical records using the RPDR query system (Partners Research, Boston, Mass). The authors' institutional review board approved this study, and the need for patient consent was waived.

Patients were divided into 2 groups: those with preoperative normal kidney function (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/

1.73 m²) and those with preexisting CKD (eGFR < 60 mL/min/1.73 m²). Preoperative eGFR was estimated by the isotope dilution mass spectrometry traceable Modification of Diet in Renal Disease study equation.⁶ Baseline sCr was defined as the closest sCr before surgery within 2 weeks of the operation.

Outcomes of Interest

The primary outcome of interest was development of postoperative AKD. AKD, a subchronic kidney injury state, was defined as doubling of sCr using the peak sCr value during the 2- to 4-week postoperative period relative to preoperative baseline. We did not include AKI as part of the definition of AKD or urine output (Table E1). The highest sCr value available during this specific time period was used rather than the mean because we valued sensitivity at the expense of including false-negatives. Doubling of sCr was used because it met the functional criteria for AKD in the AKI guidelines and represents significant (50% or potentially $> 50\%$) loss of renal function.⁵ Mortality and need for RRT were secondary outcomes. Alternately, we also defined AKD as a decrease in eGFR 35% or more at the 2- to 4-week postoperative period. This definition was included as part of the functional criteria for AKD in the guidelines. Data using the eGFR criteria are presented in Tables E2 to E4.

According to the guidelines, AKD is defined as kidney injury less than 3 months.⁵ We chose this 2- to 4-week time after the surgery because we wanted to predict the development of sustained kidney injury closer to the acute period (ie, possibly during a reversible period) than a more chronic time point (ie, possibly irreversible period). We considered this 2- to 4-week postoperative period a point in time that reflects a period beyond the acute injury phase but before the chronic disease state, thus subchronic. We also chose this specific time because we previously found that early changes in sCr predicted progression of AKI to sustained kidney disease occurring 2 to 4 weeks after surgery in patients undergoing mesothelioma surgery.⁷

Statistical Analysis

Continuous baseline characteristics of patients with no known kidney disease (NKD) and with preexisting CKD were summarized as mean $\pm$ standard deviation and compared using Student *t* tests. Categorical variables were reported as absolute numbers (percentage) and analyzed using Fisher exact tests.

After univariate analyses, a multivariate prediction model including age, gender, and surgical type was generated rather than a propensity score-matching model to maintain the generalizability of the prediction model. Surgery type was categorized as the following: coronary artery bypass grafting (CABG); CABG and aortic or mitral valve surgery; valve surgery (without CABG); heart failure surgery (heart transplantation and mechanical assist device); and other (mainly congenital and surgery on the aorta). Other covariates known to be associated with increased risk of renal injury in patients undergoing cardiac surgery, as reoperations, emergency surgery, need for intra-aortic balloon pump, history of diabetes, and hypertension, did not show significance with univariate analysis and were not included in the multivariate prediction model.

A modified Poisson regression with robust error variance was used to estimate the cumulative relative risk of the association between the stages of KDIGO AKI and the development of AKD.⁸ The modified Poisson regression was used because it allowed us to obtain cumulative risk ratios directly. Receiver operator characteristic curves were generated to examine the ability of the multivariate regression model using KDIGO AKI definitions to predict the development of AKD.

To evaluate the trend of AKI rates during the study period (2006-2014), patients with no AKI were compared with patients with AKI stage 1 and stages 2 and 3 combined. Linear regression was used to test for linear trend in AKI rates. All statistical analyses were performed using R software version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

FIGURE 1. Phases of kidney disease progression from normal kidney function through AKI, AKD, and CKD to end-stage renal disease. After the initial episode of AKI, patients with NKD at baseline may (1) recover or progress to AKD, (2) progress to CKD, or (3) progress to ESRD. Patients who developed AKD may (1) progress to CKD or ESRD after other AKI events or (2) recover to baseline AKD. Likewise, patients with CKD who are exposed to AKI may (1) recover to their baseline CKD or (2) progress further to ESRD. *AKI*, Acute kidney injury; *AKD*, acute kidney disease; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease.

RESULTS

From 2006 to 2014, 10,491 patients underwent cardiac surgery under cardiopulmonary bypass at Brigham and Women's Hospital. After excluding patients aged less than 18 years ($n = 10$), patients with preexisting RRT or history of kidney transplantation ($n = 133$), and those who died within 2 days of surgery ($n = 114$), we

enrolled 10,234 patients in our observational study (Figure 2).

In our cohort of 10,234 patients, 68% ($n = 6952$) had NKD and 32% ($n = 3282$) had preexisting CKD. We found that 20.5% ($n = 2095$) had sCr values between 2 and 4 weeks. This included 1194 patients with NKD and 901 patients with preexisting kidney disease. When we compared patients with 2- to 4-week sCr values ($n = 2095$) with those missing their 2- to 4-week sCr data ($n = 8139$), we found that patients missing their data were healthier, as noted by their significantly lower mortality, lower need for RRT, and lower AKI rates (Table E5). For all of the studies except for the evaluation of AKI rates over the time (2006-2014), we analyzed the data for patients who had sCr measured during the 2- to 4-week period after surgery ($n = 2095$) as opposed to using their last sCr available after hospital discharge as a surrogate for their 2- to 4-week postoperative sCr values (Tables E6 and E7).

Baseline characteristics revealed that patients with preexisting CKD were older by 9 years (71 vs 64; $P < .001$), and there were more women (absolute numbers) in that group (40.7% vs 34.5%; $P = .004$) than those with NKD (Table 1). However, when we evaluated the percentage of men and women with AKD, they were similar (Table 2). The AKI rate (stages 1-3) was lower in patients with normal preoperative kidney function ($n = 303$; 25.4%) compared with patients with preexisting CKD ($n = 299$; 33.2%) (Table 1).

Predicting Kidney Disease Progression in Patients with Acute Kidney Injury after Cardiac Surgery

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VIDEO 1. This narrated video discusses the significance of AKI in cardiac surgery and the definitions of AKI, AKD, and CKD. This video also discusses the importance of predicting the progression of AKI to CKD before kidney injury is irreversible. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(18\)30399-4/fulltext](http://www.jtcvsonline.org/article/S0022-5223(18)30399-4/fulltext).

FIGURE 2. Flow diagram of study patients shows 10,234 patients were enrolled in the study after exclusions. Patients were divided into normal kidney function and preexisting CKD by glomerular filtration rate criteria. Only patients with 2- to 4-week postoperative sCr data ($n = 1194$ for normal kidney function and $n = 901$ with preexisting CKD) were included in the prediction studies. *RRT*, Renal replacement therapy; *CKD*, chronic kidney disease; *sCr*, serum creatinine.

AKD occurred in 4.4% ($n = 53$) of patients with NKD and 4.8% ($n = 43$) of patients with preexisting CKD (Table 1). Patients who developed AKI during their hospital admission were more likely to progress to AKD than those who did not (Table 2).

Effect of Acute Kidney Disease on Mortality and Need for Renal Replacement Therapy

Patients with preexisting CKD had significantly higher in-hospital (7.77% vs 2.35%) and 30-day mortality (5.11% vs 1.76%) than patients with NKD (Table 1). Among the patients who developed AKD with NKD, the in-hospital (15.1% vs 1.75%; $P < .001$) and 30-day (7.6% vs 1.49%; $P = .006$) mortality rates were more than 4 times higher than those who did not develop AKD (Table 2). Likewise, patients with preexisting CKD who developed AKD had higher in-hospital (44.2% vs 5.9%; $P < .001$) and 30-day mortality (20.9% vs 4.3%; $P < .001$) than those who did not develop AKD.

Patients with preexisting CKD were more than 3 times more likely to require RRT postoperatively than patients

with NKD (6.77% vs 1.76%; $P < .001$) (Table 1). More patients with NKD who developed AKD required postoperative RRT than those who did not develop AKD (22.6% vs 0.79%; $P < .001$) (Table 2). Likewise, patients with preexisting CKD who developed AKD required postoperative RRT more often than the patients who did not develop AKD (51.2% vs 4.6%; $P < .001$) (Table 2).

Stages of Acute Kidney Injury Predict the Development of Acute Kidney Disease in a Graded Manner

Although the stages of AKI have distinct definitions, the guidelines state they are not explicitly graded (ie, higher stages of AKI do not necessarily predict worse outcomes). After adjusting for age, gender, and surgical type, we found that stages of AKI predicted AKD in a graded manner (area under the receiver operator characteristic curve [AUC_{ROC}] = 0.82-0.84) (Table 3). Patients who developed KDIGO AKI stages 1, 2, and 3 had a 2.3, 9.4, and 22.9 times higher relative risk of developing AKD, respectively, regardless of their baseline kidney function, compared with those patients who did not develop AKD (Table 3).

TABLE 1. Outcomes of patients with no known prior kidney disease and patients with preexisting chronic kidney disease after cardiac surgery

n = 2095	NKD (n = 1194)	Preexisting CKD (n = 901)	P value
Preoperative characteristics			
Age (y), mean (SD)	64 (14.9)	71 (12.3)	<.001
Gender (male), n (%)	782 (65.5%)	534 (59.3%)	.004
Preoperative sCr, mean (SD)	0.88 (0.16)	1.48 (0.57)	<.001
Preoperative eGFR, mean (SD)*	89.8 (28.8)	41.2 (12.7)	<.001
Type of surgery			
CABG only	279 (23.4%)	171 (19.0%)	<.001
CABG+AV or MV	137 (11.5%)	136 (15.1%)	
Valve surgery	335 (28.1%)	244 (27.1%)	
Heart Tx or VAD	69 (5.78%)	103 (11.4%)	
Other†	374 (31.3%)	247 (27.4%)	
Outcomes			
Incidence of AKD			
Doubling of sCr; 2-4 wk after surgery	53 (4.4%)	43 (4.8%)	.798
Other outcomes			
In-hospital mortality	28 (2.35%)	70 (7.77%)	<.001
30-d mortality, %	21 (1.76%)	46 (5.11%)	<.001
Need for RRT after surgery, %	21 (1.76%)	61 (6.77%)	<.001
Incidence of KDIGO AKI stages			
No AKI	891 (74.6%)	602 (66.8%)	<.001
Stage 1	210 (17.6%)	199 (22.1%)	
Stage 2	57 (4.8%)	26 (2.9%)	
Stage 3	36 (3.0%)	74 (8.2%)	

NKD, No known kidney disease; CKD, chronic kidney disease; SD, standard deviation; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting; AV, aortic valve; MV, mitral valve; Tx, transplant; VAD, ventricular assist device; AKD, acute kidney disease; RRT, renal replacement therapy; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury. *eGFR was calculated using the MDRD formula. †Other mainly included congenital and surgery on the aorta.

This graded response persisted whether patients had NKD or preexisting CKD ($AUC_{ROC} = 0.84$ for both) (Table 3).

AKI Incidence Over Time

For this segment of our study, we used the entire cohort ($n = 10,234$) because all patients had sCr values to evaluate AKI. We found that most of the patients did not develop AKI (>80% with no AKI since 2006) (Figure 3). By 2014, the percentage of patients with no AKI increased to 89%. There also seemed to be a progressive decline in the number of patients who developed AKI. This trend was noted for both patients with NKD and preexisting CKD ($P < .001$ for trends of decreasing AKI stage 1 and stages 2+3 over time). Specifically, by 2014, the percentage of patients with AKI stages 2 or 3 decreased by 50% in both cohorts compared with data from 2006.

DISCUSSION

Patients undergoing cardiac surgery are at risk for developing AKI, and although some patients recover from AKI, other patients develop subclinical or sub-AKD that places them at risk for developing progressive kidney disease.⁵ Although several novel biomarkers are showing promise as a better method of diagnosing AKI, sCr is still the established method of tracking disease progression. However, it is impractical and currently not clinically indicated to follow

sCr levels in all patients who undergo cardiac surgery after they are discharged. Therefore, we were interested in identifying the subset of patients who would truly benefit from periodic sCr measurements after discharge.

We hypothesized that the degree of AKI (AKI stages) predicts the development of AKD (defined as doubling of sCr present 2-4 weeks after surgery) in patients with NKD and preexisting CKD. We confirmed our initial hypothesis and found that the degree of AKI can be used to predict risk of subsequent development of AKD for patients with NKD and patients with preexisting CKD. We also found that KDIGO AKI stages predicted the development of AKD in a graded manner in which patients classified with higher stages of AKI had a higher risk of developing AKD (Table 3). This is likely the first report demonstrating that AKI stages can predict disease progression from AKI to AKD in a graded manner.

As in our clinical experience, we found that patients with preexisting CKD had worse outcomes compared with patients with normal kidney function in regard to mortality and need for RRT. Patients with preexisting CKD had a higher incidence of AKI and AKD. Therefore, this confirms prior observations that patients with preexisting CKD are at higher risk for perioperative morbidities (including progressive kidney dysfunction) than those with normal baseline kidney function.

TABLE 2. Outcomes of patients with acute kidney disease

	Patient characteristics					
	NKD (n = 1194)			Preexisting CKD (n = 901)		
	AKD (n = 53)	No AKD (n = 1141)	P value	AKD (n = 43)	No AKD (n = 858)	P value
Age (y), mean (SD)	64 (17.5)	64 (14.8)	.83	72.1 (12.2)	70.7 (12.3)	.459
Gender (male)	38 (71.1%)	744 (65.2%)	.41	24 (55.8%)	510 (59.4%)	.754
% male with AKD*	4.9% (38/782)			4.5% (24/534)		
% female with AKD*	3.6% (15/412)			5.2% (19/367)		
Preoperative sCr, mean (SD)	0.86 (0.18)	0.88 (0.16)	.56	1.4 (0.42)	1.39 (0.45)	.729
Preoperative eGFR, mean (SD)†	96.1 (35.5)	89.6 (28.4)	.2	42.4 (11.8)	43.8 (11.8)	.34
Type of surgery						
CABG only	11 (20.75%)	268 (23.5%)	.011	6 (14.0)	165 (19.2%)	.725
% CABG only with AKD‡	3.9% (11/279)			3.5% (6/172)		
CABG+AV or MV	5 (9.43%)	132 (11.6%)		7 (16.3%)	129 (15.0)	
% CABG+AV/MV with AKD§	3.6% (5/137)			5.1% (7/136)		
Valve surgery	12 (22.6%)	323 (28.3%)		14 (32.6%)	230 (26.8%)	
% Valve with AKD	3.6% (12/335)			5.7% (14/244)		
Heart Tx or VAD	9 (16.98%)	60 (5.26%)		3 (6.98%)	100 (11.7%)	
% Heart Tx/VAD with AKD¶	13% (9/96)			2.9% (3/103)		
Other#	16 (30.2%)	358 (31.4%)		13 (30.2%)	234 (27.3)	
% Other with AKD**	4.3% (16/374)			5.3% (13/247)		
Outcomes						
Mortality						
In hospital	8 (15.1%)	20 (1.75%)	<.001	19 (44.2%)	51 (5.9%)	<.001
30-d	4 (7.6%)	17 (1.49%)	.006	9 (20.9%)	37 (4.3%)	<.001
Need for RRT after surgery	12 (22.6%)	9 (0.79%)	<.001	22 (51.2%)	39 (4.6%)	<.001
KDIGO AKI stages			<.001			<.001
No AKI	17 (32.1%)	874 (76.6%)		8 (18.6%)	594 (69.2%)	
Stage 1	6 (11.3%)	204 (17.9%)		10 (23.3%)	189 (22.0%)	
Stage 2	11 (20.8%)	46 (4.0%)		2 (4.7%)	24 (2.8%)	
Stage 3	19 (35.9%)	17 (1.5%)		23 (53.5%)	51 (5.9%)	
Patients with AKI stages (1-3) who developed AKD#	36 (67.9%)	N/A		35 (81.4%)	N/A	

NKD, No known kidney disease; CKD, chronic kidney disease; AKD, acute kidney disease; SD, standard deviation; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting; AV, aortic valve; MV, mitral valve; Tx, transplant; VAD, ventricular assist device; RRT, renal replacement therapy; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury; N/A, not applicable. *Denotes the AKD rate (%) in patients who were male or female. †eGFR was calculated using the MDRD formula. ‡Denotes the AKD rate (%) in patients who had a CABG only. §Denotes the AKD rate (%) in patients who had a CABG+AV or MV. ||Denotes the AKD rate (%) in patients who had valve surgery. ¶Denotes the AKD rate (%) in patients who had heart transplant or VAD surgery. #This was calculated by adding the patients who developed AKD with stages 1 to 3 AKI divided by all patients who developed AKD. **Denotes the AKD rate (%) in patients who had other surgery (mainly congenital and surgery on the aorta).

We also found that patients who developed AKD had a higher risk of death and need for RRT. This finding can be valuable because it reaffirms the importance of following these patients closely, even after hospital discharge.

As noted in our study, our initial cohort consisted of 10,234 patients, but only 20.5% (n = 2095) of these patients had sCr values during this 2- to 4-week period. The most plausible explanation for why these patients were missing their sCr values after hospital discharge was that they had normal or stable kidney function at hospital discharge that did not warrant further clinical follow-up.

On the contrary, the patients who had their 2- to 4-week sCr values were likely patients who were at risk of kidney injury and had sCr values followed closely. In a separate analysis in which we used the last sCr value available as a surrogate for the missing 2- to 4-week sCr values, we found that the AKD rates, mortality, and need for RRT after surgery were lower in the cohort in whom we used surrogate values (total cohort) compared with those with sCr values during the 2- to 4-week postoperative period. This suggests the true incidence of AKD in patients with NKD and CKD is approximately between 1% and 4.4% and 2% and 4.8%, respectively (Table E7). Of note, when we used the

TABLE 3. Kidney Disease: Improving Global Outcomes acute kidney injury staging for patients with normal preoperative renal function and patients with preexisting chronic kidney disease predicts development of acute kidney disease (defined as doubling of serum creatinine by 2-4 wk after surgery)

	Total cohort (n = 2095)			NKD (n = 1194)			Preexisting CKD (n = 901)		
	RR [95% CI]	P value	AUC _{ROC} *	RR (95% CI)	P value	AUC _{ROC}	RR (95% CI)	P value	AUC _{ROC}
No AKI	Ref		0.82 (0.77-0.87)	Ref		0.84 (0.78-0.90)	Ref		0.84 (0.77-0.91)
Stage 1	2.31 [1.23-4.33]	.009		1.36 [0.53-3.47]	.522		4.0 [1.59-10.2]	.003	
Stage 2	9.36 [4.74-18.5]	<.001		9.57 [4.42-20.7]	<.001		6.0 [1.25-29.1]	.003	
Stage 3	22.9 [13.9-37.6]	<.001		25.7 [13.2-50.1]	<.001		27.6 [12.2-62.8]	.003	

NKD, No known kidney disease; CKD, chronic kidney disease; RR, relative risk; CI, confidence interval; AUC_{ROC}, area under the receiver operating characteristic curve; AKI, acute kidney injury. *Adjusted for age, gender, and surgical type.

FIGURE 3. Trend of decreasing AKI over time (2006-2014) for patients undergoing cardiopulmonary bypass ($P < .001$ for trend of decreasing incidence of AKI). A, AKI trend in the entire cohort. B, AKI trend in patients with NKD. C, AKI trend in patients with preexisting CKD. The x-axis is represented by year; y-axis on the left of the graph represents the percentage of patients with stage 1 or stage 2+3 AKI, and the y-axis on the right of the graph represents the percentage of patients with no AKI. AKI, Acute kidney injury; CKD, chronic kidney disease.

surrogate sCr values, we found that 41 additional patients (17 with NKD and 24 with CKD) would have been classified as developing AKD using this surrogate analysis (Table E7). Therefore, it is possible that these patients may have benefited from periodic sCr measurements even though they did not appear to be at risk.

Early identification of patients who progress to AKD is important, especially in cardiac surgery because these patients often return for other cardiac surgical or transcatheter procedures that may involve intravenous radiographic contrast administration or other hemodynamic insults that may increase their risk for developing subsequent, repeated AKI episodes. Therefore, we believe in the future, our prediction may be helpful in identifying patients who should be followed after discharge.

To predict the development of AKD, we used sCr because we were interested in using a universally available biomarker rather than a novel biomarker because we believe identification of patients who develop progressive disease is important for patient care now. Although sCr is not an ideal biomarker for an acute process because it increases 24 to 72 hours after renal injury and sCr changes are not seen until 50% of renal function is lost, it is suitable for following CKD.^{9,10} By using novel biomarkers, it is possible that we could have identified more at-risk patients.^{11,12} We also chose to follow early changes in sCr (stages of KDIGO AKI) to predict the risk of progression to AKD because we believe this will allow development of large-scale collaborative studies targeted at this at-risk cohort.

We also evaluated the incidence of AKI over time and found that the overall incidence of AKI has steadily declined in both patients with NKD and CKD (Figure 3). Specifically, when we combined patients with AKI stages 2 and 3, and compared them with patients with AKI stage 1, the incidence of AKI declined by approximately 50% from 2006 to 2014. This is interesting because the rate of AKI is increasing worldwide, and there is an initiative by the International Society of Nephrology to eliminate preventable deaths due to AKI by 2025.¹³ Although our study did not examine the possible causes of this improvement, it is noteworthy that our use of blood transfusions has significantly decreased during this period.

Our study has several strengths. First, we showed in a cohort of cardiac surgery patients that sCr-based AKI stages can predict the development of AKD after cardiopulmonary bypass for patients with no known preexisting kidney disease and with preoperative CKD. We also showed that patients with higher AKI stages were more likely to develop AKD in a graded manner. In patients with normal preoperative renal function and preexisting CKD, the ability of AKI stages to predict the development of AKD had a good predictive/diagnostic value with an $AUC_{ROC} = 0.84$ (Table 3).

Study Limitations

As a retrospective observational study, we were unable to determine whether other important perioperative variables predict AKD. By classifying patients with normal glomerular filtration rate as patients with NKD, we assumed their normal eGFR reflected their true baseline. However, it is possible that patients classified as NKD may have been misclassified because they may have already had subacute AKI or AKD (not reflected by their creatinine value). It is also possible that a more sensitive biomarker would have helped determine whether these patients were accurately classified with normal kidney function at baseline.

Second, unadjusted crude estimates are presented except when we adjusted for 3 variables: age, gender, and surgery type. Future prospective studies designed to adjust for other confounders and variables such as blood transfusions and hemodynamic instability could both refine and validate our approach.

Third, many of our patients were missing their 2- to 4-week sCr data. We believe the majority of patients missing their 2- to 4-week sCr values were missing these values because clinically they had no indication to have sCr values checked after discharge because their sCr values returned to normal or to their baseline. Therefore, we studied only those patients with 2- to 4-week sCr values available. By doing this, our selection bias exaggerated the incidence of AKD, in-hospital and 30-day mortality, and need for RRT after surgery (Table E7).

CONCLUSIONS

Although the results are not generalizable to the entire cohort, we believe we found a meaningful method of identifying patients who may benefit from serial sCr measurements after discharge: patients who develop AKI stages 1 to 3 during their index admission. In addition, it is possible that an automated, real-time electronic alert system (as described by Porter and colleagues¹⁴) could send e-alerts to care providers when patients meet the AKI criteria. This could lead to increased awareness and recognition of those at risk for developing AKD and subsequent progression to CKD or end-stage renal disease.¹⁴

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: kidney disease progression, acute kidney injury, AKI, cardiac surgery, acute kidney disease, KDIGO AKI, predicting kidney disease progression, chronic kidney disease

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TABLE E1. Definitions of stages of kidney disease progression⁵

Definition	Criteria
NKD	GFR ≥ 60 mL/min/1.73 m ²
AKI	sCr increase by 50% within 7 d or 0.3 mg/dL within 2 d or oliguria Stage 1: sCr increase 1.5-1.9 times baseline or ≥ 0.3 mg/dL increase; urine output < 0.5 mL/kg/h for 6-12 h Stage 2: sCr increase 2-2.9 times baseline; urine output < 0.5 mL/kg/h for ≥ 12 h Stage 3: sCr increase 3 times baseline or increase in sCr ≥ 4 mg/dL or initiation of RRT or in patients < 18 y, decrease in eGFR < 35 mL/min/1.73 m ² ; anuria ≥ 12 h
AKD	AKI or GFR < 60 mL/min/1.73 m ² < 3 mo or Decrease in GFR 35% or increase in sCr $> 50\%$ < 3 mo Structural kidney damage < 3 mo
CKD	GFR < 60 mL/min/1.73 m ² > 3 mo Structural kidney damage > 3 mo

NKD, No known kidney disease; GFR, glomerular filtration rate; AKI, acute kidney injury; sCr, serum creatinine; RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate; AKD, acute kidney disease; CKD, chronic kidney injury.

TABLE E2. Development of acute kidney disease (defined by doubling of serum creatinine or by decrease in estimated glomerular filtration rate $\geq 35\%$) in patients with no known prior kidney disease (n = 2095)

Definition of AKD	Patient characteristics					
	Doubling of sCr			Decrease in eGFR $\geq 35\%$		
	AKD (n = 53)	No AKD (n = 1141)	P value	AKD (n = 237)	No AKD (n = 957)	P value
Age (y), mean (SD)	64 (17.5)	64 (14.8)	.83	67 (14.1)	63 (15.0)	<.001
Gender (male)	38 (71.1%)	744 (65.2%)	.41	160 (67.5%)	622 (65.0%)	.514
% male with AKD*	4.9% (38/782)			20.5% (160/782)		
% female with AKD*	3.6% (15/412)			36% (77/412)		
Preoperative sCr, mean (SD)	0.86 (0.18)	0.88 (0.16)	.56	0.85 (0.17)	0.88 (0.16)	.022
Preoperative eGFR, mean (SD)†	96.1 (35.5)	89.6 (28.4)	.2	94.2 (31.6)	88.8 (28.0)	.017
Type of surgery						
CABG only	11 (20.75%)	268 (23.5%)	.011	73 (30.8%)	206 (21.53%)	.011
%AKD in CABG only‡	3.9% (11/279)			26.2% (73/279)		
CABG+AV or MV	5 (9.43%)	132 (11.6%)		27 (11.39%)	110 (11.49%)	
%AKD in CABG+AV/MV§	3.6% (5/137)			19.7 (27/137)		
Valve surgery	12 (22.6%)	323 (28.3%)		51 (21.52%)	284 (29.68%)	
%AKD in valve	3.6% (12/335)			15.2% (51/335)		
Heart Tx or VAD	9 (16.98%)	60 (5.26%)		17 (7.17%)	52 (5.43%)	
%AKD in Tx or VAD¶	13% (9/69)			24.6% (17/69)		
Other	16 (30.2%)	358 (31.4%)		69 (29.11%)	305 (31.87%)	
% AKD in other#	4.3% (16/374)			18.4% (69/374)		
Outcomes						
Mortality						
In hospital	8 (15.1%)	20 (1.75%)	<.001	22 (9.28%)	6 (0.63%)	<.001
30-d	4 (7.6%)	17 (1.49%)	.006	12 (5.06%)	9 (0.94%)	<.001
Need for RRT after surgery	12 (22.6%)	9 (0.79%)	<.001	17 (7.17%)	4 (0.42%)	<.001
KDIGO AKI Stages			<.001			<.001
No AKI	17 (32.1%)	874 (76.6%)		104 (43.88%)	787 (82.24%)	
Stage 1	6 (11.3%)	204 (17.9%)		77 (32.49%)	133 (13.9%)	
Stage 2	11 (20.8%)	46 (4.0%)		28 (11.81%)	29 (3.03%)	
Stage 3	19 (35.9%)	17 (1.5%)		28 (11.81%)	8 (0.84%)	
Patients with AKI stages (1-3) who developed AKD	36 (67.9%)*	N/A		133 (56.1%)*	N/A	

AKD, Acute kidney disease; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; SD, standard deviation; CABG, coronary artery bypass grafting; AV, aortic valve; MV, mitral valve; Tx, transplant; VAD, ventricular assist device; RRT, renal replacement therapy; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury; N/A, not applicable. *Denotes the AKD rate (%) in patients who were male or female. †eGFR was calculated using the MDRD formula. ‡Denotes the AKD rate (%) in patients who had a CABG only. §Denotes the AKD rate (%) in patients who had a CABG+AV or MV. ||Denotes the AKD rate (%) in patients who had valve surgery. ¶Denotes the AKD rate (%) in patients who had heart transplant or VAD surgery. #Denotes the AKD rate (%) in patients who had other surgery (mainly congenital and surgery on the aorta). **This was calculated by adding the patients who developed AKD with stages 1 to 3 AKI divided by all patients who developed AKD.

TABLE E3. Development of acute kidney disease (defined by doubling of serum creatinine or by decrease in estimated glomerular filtration rate $\geq 35\%$) in patients with preexisting chronic kidney disease (n = 901)

Definition of AKD	Patient characteristics					
	Doubling of sCr			Decrease in eGFR $\geq 35\%$		
	AKD (n = 43)	No AKD (n = 858)	P value	AKD (n = 174)	No AKD (n = 727)	P value
Age (y), mean (SD)	73 (12.2)	71 (12.3)	.459	72.21 (12.15)	70.39 (12.32)	.078
Gender (male)	24 (55.8%)	510 (59.4%)	.754	100 (57.47%)	434 (59.7%)	.652
% male with AKD*	(24/534)			(100/534)		
% female with AKD*	(19/367)			(74/367)		
Preoperative sCr	1.4 (0.39)	1.48 (0.58)	.247	1.46 (0.48)	1.49 (0.59)	.455
Preoperative eGFR [†]	42.6 (11.52)	41.1 (12.73)	.415	41.06 (12.05)	41.25 (12.82)	.854
Type of surgery						
CABG only	6 (13.95%)	165 (19.23%)	.725	33 (18.97%)	138 (18.98%)	.197
%AKD in CABG only [‡]	3.5% (6/171)			19.3% (33/171)		
CABG+AV or MV	7 (16.28%)	129 (15.03%)		33 (18.97%)	103 (14.17%)	
%AKD in CABG +AV/MV [§]	5.1% (7/136)			24.3% (33/136)		
Valve surgery	14 (32.56%)	230 (26.81%)		43 (24.71%)	201 (27.65%)	
%AKD in valve	5.7% (14/244)			17.6% (43/244)		
Heart Tx or VAD	3 (6.98%)	100 (11.66%)		13 (7.47%)	90 (12.38%)	
%AKD in Tx or VAD [¶]	2.9% (3/103)			12.6% (13/103)		
Other*	13 (30.2%)	234 (27.3%)		52 (29.89%)	195 (26.82%)	
% AKD in other [#]	5.3% (13/247)			21% (52/247)		
Mortality						
In hospital	19 (44.2%)	51 (5.9%)	<.001	45 (25.86%)	25 (3.44%)	<.001
30-d	9 (20.9%)	37 (4.3%)	<.001	27 (15.52%)	19 (2.61%)	<.001
Need for RRT after surgery	22 (51.2%)	39 (4.6%)	<.001	42 (24.14%)	19 (2.61%)	<.001
KDIGO AKI stages			<.001			.197
No AKI	8 (18.6%)	594 (69.2%)		33 (18.97%)	138 (18.98%)	
Stage 1	10 (23.3%)	189 (22.0%)		33 (18.97%)	103 (14.17%)	
Stage 2	2 (4.7%)	24 (2.8%)		43 (24.71%)	201 (27.65%)	
Stage 3	23 (53.5%)	51 (5.9%)		13 (7.47%)	90 (12.38%)	
Patients with AKI stages (1-3) who developed AKD**	35 (81.4%)	N/A		89 (51.1%)	N/A	

AKD, Acute kidney disease; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; SD, standard deviation; CABG, coronary artery bypass grafting; AV, aortic valve; MV, mitral valve; Tx, transplant; VAD, ventricular assist device; RRT, renal replacement therapy; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury; N/A, not applicable. *Denotes the AKD rate (%) in patients who were male or female. [†]eGFR was calculated using the MDRD formula. [‡]Denotes the AKD rate (%) in patients who had CABG only. [§]Denotes the AKD rate (%) in patients who had CABG+AV or MV. ^{||}Denotes the AKD rate (%) in patients who had valve surgery. [¶]Denotes the AKD rate (%) in patients who had heart transplant or VAD surgery. [#]Denotes the AKD rate (%) in patients who had other surgery (mainly congenital and surgery on the aorta). **This was calculated by adding the patients who developed AKD with stages 1 to 3 AKI divided by all patients who developed AKD.

TABLE E4. Ability of Kidney Disease: Improving Global Outcomes acute kidney injury stages to predict the development of acute kidney disease (defined as decrease estimated glomerular filtration rate $\geq 35\%$ present 2-4 wk after surgery) for both patients with normal preoperative renal function or with preexisting chronic kidney disease

	Total cohort (n = 2095)			NKD (n = 1194)			Preexisting CKD (n = 901)		
	RR [95% CI]	P value	AUC _{ROC} *	OR (95% CI)	P value	AUC _{ROC}	OR (95% CI)	P value	AUC _{ROC}
No AKI	Ref		0.754 (0.73-0.78)	Ref		0.764 (0.73-0.798)	Ref		0.759 (0.72-0.8)
Stage 1	2.73 [2.2-3.5]	<.001		3.16 [2.35-4.25]	<.001		2.28 [1.57-3.32]	<.003	
Stage 2	4.4 [3.1-6.2]	<.001		4.36 [2.86-6.66]	<.001		4.21 [2.25-7.89]	<.003	
Stage 3	6.49 [4.95-8.5]	<.001		6.91 [4.53-10.53]	<.001		6.74 [4.62-9.83]	<.003	

NKD, No known kidney disease; CKD, chronic kidney disease; RR, relative risk; CI, confidence interval; AUC_{ROC}, area under the receiver operating characteristic curve; OR, odds ratio; AKI, acute kidney injury. *Adjusted for age, gender, and surgical type.

TABLE E5. Comparison of patients with 2- to 4-week serum creatinine data available with those without

	2- to 4-wk data available (n = 2095)	Missing 2- to 4-wk data (n = 8139)	P value
Preoperative characteristics			
Age (y), mean (SD)	66.97 (14.23)	66.77 (13.27)	.576
Gender (male), n (%)	1316 (62.82%)	5417 (66.56%)	<.001
Preoperative sCr, mean (SD)	1.14 (0.49)	1.02 (0.33)	<.001
Preoperative eGFR, mean (SD)*	68.92 (33.49)	75.65 (29.06)	<.001
Preexisting CKD	901 (43.01%)	2381 (29.25%)	<.001
Type of surgery			<.001
CABG only	450 (21.48%)	2719 (33.41%)	
CABG+AV or MV	273 (13.03%)	1004 (12.34%)	
Valve surgery	579 (27.64%)	2500 (30.72%)	
Heart Tx or VAD	172 (8.21%)	10 (0.12%)	
Other†	621 (29.64%)	1906 (23.42%)	
Outcomes			
In-hospital mortality	98 (4.68%)	96 (1.18%)	<.001
30-d mortality, %	67 (3.2%)	112 (1.38%)	<.001
Need for RRT after surgery, %	82 (3.91%)	37 (0.45%)	<.001
Incidence of KDIGO AKI stages			
No AKI	1493 (71.26%)	7306 (89.77%)	<.001
Stage 1	409 (19.52%)	704 (8.65%)	
Stage 2	83 (3.96%)	63 (0.77%)	
Stage 3	110 (5.25%)	66 (0.81%)	

SD, Standard deviation; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CABG, coronary artery bypass grafting; AV, aortic valve; MV, mitral valve; Tx, transplant; VAD, ventricular assist device; RRT, renal replacement therapy; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury.

*eGFR was calculated using the MDRD formula. †Other mainly included congenital and surgery on the aorta.

TABLE E6. Comparison of acute kidney injury rates

Cohort	AKI (stages 1-3)	No AKI
Total cohort*		
Total cohort (n = 10,234)	1435 (14%)	8799 (86%)
No prior kidney disease (n = 6952)	736 (10.6%)	6216 (89.4%)
Preoperative CKD (n = 3282)	699 (21.3%)	2583 (78.7%)
Cohort with 2-4 wk postoperative sCr available		
2-4 wk sCr available (n = 2095)	602 (28.7%)	1493 (71.3%)
No prior kidney disease (n = 1195)	303 (25.4%)	891 (74.6%)
Preoperative CKD (n = 901)	299 (33.2%)	602 (66.8%)

AKI, Acute kidney injury; CKD, chronic kidney injury; sCr, serum creatinine. *Total cohort represents the cohort missing their 2- to 4-week sCr values and where their last sCr available before discharge was used as a surrogate. For a separate analysis for patients who did not have sCr values during the 2- to 4-week period, we used their latest available sCr before hospital discharge. We assumed that the last discharge sCr values represented the patients' stable kidney function and confirmed this by comparing the last sCr value available before discharge (used for our analysis) with sCr values available beyond the fourth postoperative week (obtained during follow-up visits).

TABLE E7. Comparison of outcomes between cohort with 2- to 4-week postoperative serum creatinine available (n = 2095) versus total cohort (n = 10,234)

Outcomes*			
Incidence of AKD			
Cohort	NKD	Preexisting CKD	P value
Cohort with 2-4 wk postoperative sCr available†	53 (4.4%)	43 (4.8%)	.798
Total cohort‡	70 (1%)	67 (2.0%)	<.001
Other outcomes			
Cohort with 2-4 wk postoperative sCr available			
In-hospital mortality	28 (2.35%)	70 (7.77%)	<.001
30-d mortality, %	21 (1.76%)	46 (5.11%)	<.001
Need for RRT after surgery, %	21 (1.76%)	61 (6.77%)	<.001
Total cohort			
In-hospital mortality	65 (0.93%)	129 (3.93%)	<.001
30-d mortality, %	63 (0.9%)	116 (3.5%)	<.001
Need for RRT after surgery, %	34 (0.5%)	85 (2.6%)	<.001

AKD, Acute kidney disease; NKD, no known kidney disease; CKD, chronic kidney injury; sCr, serum creatinine; RRT, renal replacement therapy. *Because we chose to analyze data for patients who had their 2- to 4-week sCr postoperative values available, we likely overestimated incidence of outcomes. Therefore, we also ran a separate analysis in which for patients who did not have sCr values during the 2- to 4-week period, we used their latest available sCr before hospital discharge. We assumed that the last discharge sCr values represented the patients' stable kidney function and confirmed this by comparing the last sCr value available before discharge (used for our analysis) with sCr values available beyond the fourth postoperative week (obtained during follow-up visits). We have noted this cohort as the total cohort here. We found that when we analyzed the data for patients who had sCr measured during the 2- to 4-week postoperative period, the incidence of AKD among patients was higher in both those with NKD and preexisting CKD (4.4% and 4.8%, respectively) versus the total cohort in both those with NKD and preexisting CKD (1% and 1.7%, respectively). Therefore, by analyzing only the patients with their 2- to 4-week sCr values available, we overestimated the outcome, whereas if we used surrogate sCr values (as in the total cohort), we would have underestimated the true outcome. †Represents cohort with 2- to 4-week postoperative sCr available. The number of patients in each group is noted: NKD (n = 1194) and preexisting CKD (n = 901). ‡Represents cohort for patients missing their 2- to 4-week sCr values. The last sCr available before discharge was used as a surrogate. The number of patients in each group is noted: NKD (n = 6952) and preexisting CKD (n = 3282).