Predictive Models for Acute Kidney Injury Following Cardiac Surgery

Article *in* American Journal of Kidney Diseases · December 2011

DOI: 10.1053/j.ajkd.2011.10.046 · Source: PubMed

7 authors, including:

Jesse D Schold
Cleveland Clinic
261 PUBLICATIONS **5,719** CITATIONS
SEE PROFILE

Jose L Navia
Cleveland Clinic
145 PUBLICATIONS **2,951** CITATIONS
SEE PROFILE

Tara M Mastracci
Cleveland Clinic
91 PUBLICATIONS **1,620** CITATIONS
SEE PROFILE

AJKD
Original Investigation

Predictive Models for Acute Kidney Injury Following Cardiac Surgery

Sevag Demirjian, MD,[1] Jesse D. Schold, PhD,[2] Jose Navia, MD,[3] Tara M. Mastracci, MD,[4] Emil P. Paganini, MD,[1] Jean-Pierre Yared, MD,[5] and Charles A. Bashour, MD[5]

Background: Accurate prediction of cardiac surgery–associated acute kidney injury (AKI) would improve clinical decision making and facilitate timely diagnosis and treatment. The aim of the study was to develop predictive models for cardiac surgery–associated AKI using presurgical and combined pre- and intrasurgical variables.

Study Design: Prospective observational cohort.

Settings & Participants: 25,898 patients who underwent cardiac surgery at Cleveland Clinic in 2000-2008.

Predictor: Presurgical and combined pre- and intrasurgical variables were used to develop predictive models.

Outcomes: Dialysis therapy and a composite of doubling of serum creatinine level or dialysis therapy within 2 weeks (or discharge if sooner) after cardiac surgery.

Results: Incidences of dialysis therapy and the composite of doubling of serum creatinine level or dialysis therapy were 1.7% and 4.3%, respectively. Kidney function parameters were strong independent predictors in all 4 models. Surgical complexity reflected by type and history of previous cardiac surgery were robust predictors in models based on presurgical variables. However, the inclusion of intrasurgical variables accounted for all explained variance by procedure-related information. Models predictive of dialysis therapy showed good calibration and superb discrimination; a combined (pre- and intrasurgical) model performed better than the presurgical model alone (C statistics, 0.910 and 0.875, respectively). Models predictive of the composite end point also had excellent discrimination with both presurgical and combined (pre- and intrasurgical) variables (C statistics, 0.797 and 0.825, respectively). However, the presurgical model predictive of the composite end point showed suboptimal calibration ($P < 0.001$).

Limitations: External validation of these predictive models in other cohorts is required before wide-scale application.

Conclusions: We developed and internally validated 4 new models that accurately predict cardiac surgery–associated AKI. These models are based on readily available clinical information and can be used for patient counseling, clinical management, risk adjustment, and enrichment of clinical trials with high-risk participants.

Am J Kidney Dis. 59(3):382-389.

INDEX WORDS: Acute kidney injury; cardiac surgery; predictive models.

Cardiac surgery–associated acute kidney injury (AKI) represents a devastating complication that portends significant morbidity and mortality.[1] Its incidence has been reported to be as high as 45%, depending on the definition used and the cohort studied, whereas severe AKI requiring dialysis has been observed in 1.7% of patients after cardiac surgery.[2,3] To date, AKI prevention and treatment ventures have been hindered by the lack of early diagnostic biomarkers that could reveal a window for effective therapeutic intervention. Traditionally, cardiac surgery has been a desirable clinical setting to study novel injury biomarkers and therapeutic interventions due to the vulnerability of the patient population, knowledge of the timing of injury, and availability of risk models predictive of cardiac surgery–associated AKI. Accurate predictive models are needed not only in the research arena, but also for patient counseling regarding risk-benefit comparisons, allocation of clinical resources, and comparison of observed-to-predicted adjusted outcomes for quality assurance. Previous models predictive of cardiac surgery–associated AKI have confined their variable selection to mostly presurgical risk factors, and the outcome, to kidney failure requiring dialysis, thus limiting their clinical utility.[2,4-6] Moreover, although simplified and parsimonious predictive models are user friendly and easily calculated

From the Departments of [1]Nephrology and Hypertension, [2]Quantitative Health Sciences, [3]Cardiothoracic Surgery, [4]Vascular Surgery, and [5]Cardiothoracic Anesthesiology, Cleveland Clinic, Cleveland, OH.

Received May 4, 2011. Accepted in revised form October 7, 2011. Originally published online December 30, 2011.

Address correspondence to Sevag Demirjian, MD, Department of Nephrology and Hypertension, Cleveland Clinic, 9500 Euclid Ave, Q7, Cleveland, OH 44195. E-mail: demirjs@ccf.org

0272-6386/$36.00
doi:10.1053/j.ajkd.2011.10.046

at the bedside, they are statistically compromised and sacrifice invaluable predictive aptitude.[7,8]

The purpose of this investigation is to develop and validate multivariable models based on presurgical and combined pre- and intrasurgical clinical information that predicts cardiac surgery–associated AKI. We examined 2 cardiac surgery–associated AKI outcomes, dialysis therapy and the composite end point of dialysis therapy or doubling of serum creatinine (SCr) level, in a large prospectively maintained registry of patients undergoing cardiac surgery at our institution.

METHODS

Study Participants

The study was approved by the Institutional Review Board at Cleveland Clinic. We studied 25,898 patients who underwent cardiac surgery at Cleveland Clinic between April 2000 and January 2008, obtained from the Anesthesiology Institute Patient Registry. Patient information is collected prospectively on a daily basis by research coordinators. Complementary laboratory data were retrieved from electronic medical records. We excluded patients with end-stage renal disease and those who required presurgical dialysis. We included only the first surgical episode for those who had multiple operations during the investigation period.

Explanatory Variables

We considered 47 clinically relevant pre- and intrasurgical variables for model development. Variables that captured redundant physiologic parameters, had prevalence rates $<5\%$, or had missing data of $\geq 10\%$ were excluded. Advanced medical procedures, such as presurgical intra-aortic balloon pump and extracorporeal membrane oxygenation, which are not universally available and are subject to varying practice patterns, also were excluded. Subsequently, 31 variables were used for multivariable analysis in pre- and intrasurgical–based models, and 27, in presurgical models. The most recent presurgical laboratory data were used. Baseline estimated glomerular filtration rate (eGFR) was calculated based on the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[9] Missing data for continuous variables were replaced by median values. Sensitivity analysis was performed for each imputed variable individually, with no significant influence on parameter estimates or *P* values.

Outcome Measures

We studied 2 main end points: AKI that required dialysis and a composite outcome of doubling of SCr level or dialysis therapy within 2 weeks of cardiac surgery (or hospital discharge).

Model Building

We summarized demographic, clinical, and laboratory data as median and interquartile range (IQR) for continuous variables and frequency for discrete variables. We examined continuous variables for a nonlinear relationship with the 2 binary end points individually; log transformation and higher order polynomials were used as deemed appropriate. We retained variables in the multivariable logistic regression model using backward selection with $P \leq 0.1$ and examined several interactions selected a priori on clinical grounds. Model comparisons were based on Akaike information criterion (AIC) minimization.

Model Validation

We assessed predictive accuracy by examining the discrimination and calibration of each model. Discrimination was evaluated using the concordance (C) statistic, which also represents the area under receiver operating characteristic curve (shown in Fig 1), and 95% confidence intervals (CIs). We constructed calibration plots using categories based on deciles of the entire cohort for each model (Fig S1, available as online supplementary material). Calibration was assessed by computing the Hosmer-Lemeshow statistic.[10]

We performed bootstrap validation of all 4 models using the entire cohort with 1,000 resampling runs to assess for bias due to overfitting.[11,12] Each bootstrap sample included backward elimination and tested the nonlinearity of certain variables. Optimism for the C statistic then was calculated by taking the difference between the bootstrap-generated mean C statistic of each model and the model applied to the original sample. Moreover, we obtained estimates of model optimism by calculating shrinkage factor (λ_{AIC}) using a heuristic linear shrinkage technique.[13] All statistical analyses were conducted using SAS, version 8.2 (SAS Institute Inc, www.sas.com).

Online Calculators

We constructed web-based calculators for each of the 4 models: presurgical variables/dialysis therapy end point (rcc.simpal.com/8IJJoG), pre- and intrasurgical variables/dialysis therapy end point (rcc.simpal.com/XA5TID), presurgical variables/composite of dialysis therapy or doubling of SCr level (rcc.simpal.com/i9G0ou), and pre- and intrasurgical variables/composite of dialysis therapy or doubling of SCr level (rcc.simpal.com/HURZeo).

RESULTS

Table 1 lists perisurgical characteristics of the entire cohort and participants who reached the study end points. Median age was 65 (IQR, 19) years, 67% were men, and 89% were white. The rates of AKI requiring dialysis therapy and the composite of doubling of SCr level or dialysis therapy were 1.7% (n = 429) and 4.3% (n = 1,113), respectively. Median time to dialysis therapy and peak SCr level were 4 (IQR, 6) and 3 (IQR, 2) days, respectively. Hospital median length of stay and mortality were 30 (IQR, 26) days and 48% (206 of 429) in patients who required dialysis therapy; 17 (IQR, 25) days and 10% (68 of 684) in patients with doubling of SCr level. Mortality was 0.2% (53 of 25,898) by postsurgical day 2 and 1.1% (297 of 25,898) within 2 weeks of cardiac surgery or hospital discharge. In the latter group, 31% (93 of 297) of participants had dialysis therapy and 45% (135 of 297) reached the composite end point of dialysis therapy or doubling of SCr level.

Model Building

Four new predictive models based on presurgical and combined (pre- and intrasurgical) variables for the 2 end points are listed in Tables 2 and 3, respectively. Intercept, β coefficient, standard error, and *P* value for each variable are listed in Table S1. Baseline eGFR was entered as a quadratic term in the compos-

Table 1. Baseline Clinical Characteristics and Operative Information for Patients Undergoing Cardiac Surgery

	Dialysis			Doubling of SCr or Dialysis			Entire Cohort
	Yes (n = 429)	No (n = 25,469)	*P*	Yes (n = 1,113)	No (n = 24,785)	*P*	(n = 25,898)
Age (y)	70 [15]	65 [19]	<0.001	69 [17]	65 [19]	<0.001	65 [19]
Men	255 (59)	17,122 (67)	0.001	665 (60)	16,712 (67)	<0.001	17,377 (67)
Race			0.002			<0.001	
White	362 (84)	22,634 (89)		948 (85)	22,048 (89)		22,996 (89)
Black	33 (7.7)	1,616 (6.3)		73 (6.6)	1,576 (6.3)		1,649 (6)
Other	34 (7.9)	1,219 (4.8)		92 (8.3)	1,161 (4.7)		1,253 (5)
Height (m)	170 [17]	172 [16]	<0.001	170 [17]	172 [16]	<0.001	172 [16]
Weight (kg)	80 [25]	81 [24]	<0.001	82 [26]	81 [24]	<0.001	81 [24]
Body mass index (kg/m^2)	27 [8]	27 [7]	<0.001	28 [8]	27 [7]	<0.001	27 [7]
Comorbid disease							
Diabetes mellitus	82 (19)	1,964 (7.7)	<0.001	194 (17)	1,852 (7.5)	<0.001	2,046 (7.9)
Hypertension	320 (75)	16,566 (65)	<0.001	837 (75)	16,049 (65)	<0.001	16,886 (65)
Cerebrovascular disease	66 (15)	1,847 (7.2)	<0.001	132 (12)	1,781 (7.2)	<0.001	1,913 (7.4)
Chronic kidney disease[a]	287 (67)	5,454 (21)	<0.001	496 (45)	5,245 (21)	<0.001	5,741 (22)
Congestive heart failure	268 (62)	7,626 (30)	<0.001	603 (54)	7,291 (29)	<0.001	7,894 (30)
Ejection fraction <35%	146 (34)	4,068 (16)	<0.001	339 (30)	3,875 (16)	<0.001	4,214 (16)
Pulmonary disease	86 (20)	2,536 (10)	<0.001	179 (16)	2,443 (9.9)	<0.001	2,622 (10)
Previous cardiac surgery	194 (45)	5,586 (22)	<0.001	423 (38)	5,357 (22)	<0.001	5,780 (22)
Emergent surgery	68 (16)	831 (3.2)	<0.001	166 (15)	733 (3)	<0.001	899 (3.5)
Baseline laboratory data							
SCr (mg/dL)	1.4 [1.0]	1.0 [0.4]	<0.001	1.1 [0.6]	1 [0.4]	<0.001	1.0 [0.4]
eGFR (mL/min/1.73 m^2)	48 [34]	77 [28]	<0.001	64 [39]	77 [28]	<0.001	76 [28]
SUN (mg/dL)	30 [27]	18 [8]	<0.001	22 [16]	18 [8]	<0.001	18 [8]
Sodium (mEq/L)	138 [6]	140 [5]	<0.001	139 [4]	140 [5]	<0.001	140 [5]
Potassium (mEq/L)	4.2 [0.6]	4.1 [0.5]	<0.001	4.1 [0.6]	4.1 [0.5]	<0.001	4.1 [0.5]
Bicarbonate (mEq/L)	25 [4]	26 [4]	<0.001	26 [5]	26 [4]	<0.001	26 [4]
Albumin (g/dL)	3.7 [1.0]	4.2 [0.6]	<0.001	3.9 [0.8]	4.2 [0.6]	<0.001	4.2 [0.6]
Bilirubin (mg/dL)	0.7 [0.7]	0.6 [0.4]	<0.001	0.6 [0.5]	0.6 [0.4]	<0.001	0.6 [0.4]
WBC count ($\times 10^3/\mu$L)	8.8 [4.1]	7.3 [3.2]	<0.001	8.2 [3.5]	7.3 [3.1]	<0.001	7.3 [3.0]
Hemoglobin (g/dL)	10.7 [3.7]	12.9 [2.9]	<0.001	11.4 [3.3]	12.9 [2.8]	<0.001	12.9 [2.7]
Platelets ($\times 10^3/\mu$L)	182 [72]	203 [78]	<0.001	195 [75]	203 [77]	<0.001	203 [73]
Surgical procedure			<0.001			<0.001	
CABG alone	73 (17)	8,318 (33)		244 (22)	8,147 (33)		8,391 (32)
Valve surgery alone	90 (21)	8,098 (32)		249 (22)	7,939 (32)		8,188 (32)
Combined CABG & valve surgery	141 (33)	4,782 (19)		294 (26)	4,629 (19)		4,923 (19)
Aortic surgery	79 (18)	2,650 (10)		200 (18)	2,529 (10)		2,729 (11)
Other[b]	46 (11)	1,621 (6)		126 (11)	1,541 (6)		1,663 (6)
Intrasurgical data							
CPB time (min)	143 [86]	95 [51]	<0.001	123 [73]	95 [50]	<0.001	96 [52]
Aorta cross-clamp time (min)	95 [55]	72 [40]	<0.001	87 [52]	72 [40]	<0.001	73 [40]
Vasopressor use	370 (86)	12,208 (48)	<0.001	814 (73)	11,764 (47)	<0.001	12,578 (49)
Packed RBC transfusion	345 (80)	7,753 (30)	<0.001	742 (67)	7,356 (30)	<0.001	8,098 (31)
Urine output (mL)	700 [750]	950 [650]	<0.001	800 [700]	950 [650]	<0.001	950 [650]

Note: Continuous variables are given as median [interquartile range]; categorical variables, as number (percentage). Conversion factors for units: SCr in mg/dL to mol/L, ×88.4; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; SUN in mg/dL to mmol/L, ×0.357; albumin and hemoglobin in g/dL to g/L, ×10; bilirubin in mg/dL to μmol/L, ×17.1. No conversion necessary for sodium, potassium, and bicarbonate in mEq/L and mmol/L; WBC and platelet counts in $\times 10^3/\mu$L and $\times 10^9$/L.

Abbreviations: CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; RBC, red blood cell; SCr, serum creatinine; SUN, serum urea nitrogen; WBC, white blood cell.

[a]Defined as eGFR <60 mL/min/1.73 m^2 based on the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[9]

[b]Includes cardiac aneurysm repair, myomectomy, and heart transplant.

Table 2. Predictive Models of Acute Kidney Injury Based on Presurgical Variables

	Doubling of SCr or Dialysis	*P*	Dialysis	*P*
Variable (reference group)				
Female	1.15 (1.00-1.32)	0.05		
Race (white)		0.003		<0.001
Black	1.36 (1.07-1.70)		1.69 (1.15-2.49)	
Other	1.38 (1.07-1.78)		1.91 (1.30-2.82)	
Body mass index	1.02 (1.01-1.03)	<0.001		
Pulmonary disease	1.25 (1.05-1.50)	0.01	1.63 (1.26-2.11)	<0.001
Congestive heart failure	1.43 (1.24-1.66)	<0.001	1.37 (1.08-1.73)	0.008
Diabetes mellitus	1.57 (1.30-1.88)	<0.001	1.38 (1.04-1.83)	0.03
Hypertension	1.26 (1.08-1.47)	0.003		
Surgical procedure (CABG)		<0.001		<0.001
Aortic surgery	2.39 (1.93-2.95)		3.14 (2.21-4.46)	
Valve surgery	1.10 (0.90-1.34)		1.04 (0.74-1.46)	
Combined CABG & valve	1.51 (1.25-1.83)		1.89 (1.38-2.59)	
Other surgery[a]	1.29 (0.98-1.70)		1.08 (0.68-1.73)	
Previous cardiac surgery	1.62 (1.42-1.86)	<0.001	1.99 (1.61-2.46)	<0.001
Emergent surgery	3.33 (2.66-4.18)	<0.001	3.36 (2.37-4.77)	<0.001
Estimated GFR[b]	0.97 (0.97-0.98)	<0.001	0.16 (0.12-0.21)[d]	<0.001
Estimated GFR[2,b,c]	1.0001 (1.0001-1.0002)	<0.001		
Albumin	0.59 (0.52-0.67)	<0.001	0.51 (0.43-0.62)	<0.001
Bicarbonate	0.96 (0.95-0.98)	<0.001		
Sodium	0.98 (0.96-0.99)	0.01	0.96 (0.94-0.98)	0.001
Serum urea nitrogen	1.01 (1.01-1.02)	<0.001	1.01 (1.01-1.02)	<0.001
Hemoglobin	0.92 (0.88-0.95)	<0.001		
Platelet count	0.99 (0.98-1.00)	0.001		
Bilirubin[d]	1.16 (1.03-1.30)	0.01	1.53 (1.29-1.81)	<0.001
Discrimination and calibration				
C statistic[e]	0.797 (0.784-0.810)		0.875 (0.859-0.891)	
Hosmer-Lemeshow *P*[f]		<0.001		0.2

Note: Values shown are odds ratio (95% confidence interval). Acute kidney injury is defined as doubling of SCr level or dialysis therapy within 2 weeks of cardiac surgery.

Abbreviations: CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; SCr, serum creatinine.

[a]Includes cardiac aneurysm repair, myomectomy, and heart transplant.

[b]Estimated GFR was calculated based on the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[9]

[c]Quadratic term.

[d]Natural logarithmic transformation used.

[e]Concordance statistic adjusted for optimism using bootstrap resampling; unity denotes perfect discrimination. The 95% confidence interval is given in parentheses.

[f]Significant *P* value for the Hosmer and Lemeshow statistic denotes significant deviation between predicted and observed events.

ite end point and log transformed in the dialysis-alone models.[14] We also explored the nonlinear effect of eGFR with both end points by fitting restricted cubic spline models (5 knots), which showed no further model improvement per AIC compared with the previously mentioned transformations. Participants with previous cardiac surgery or planned aortic surgery required longer cardiopulmonary bypass support, 123 ± 48 versus 96 ± 40 ($P < 0.001$) and 130 ± 50 versus 99 ± 41 minutes ($P < 0.001$), respectively. However, neither type of surgery nor history of previous cardiac surgery was retained in the models that incorporated intrasurgical information (Table 3). We also examined the effect of chronological year of cardiac surgery in each of the 4 models, which did not reach statistical significance (data not shown).

Model Validation

Summary statistics regarding the parameter weights and performance of the 4 models are listed in Tables 2 and 3. Models predictive of the dialysis therapy end point showed good calibration and superb discrimination; the combined (pre- and intrasurgical) model performed better than the presurgical model, C statistics of 0.910 (95% CI, 0.896-0.924) and 0.875 (95% CI, 0.859-0.891), respectively (Fig 1), whereas the models predictive of the composite end point (dialysis therapy or doubling of SCr level) had excellent discriminative capacity with both presurgical and combined (pre- and intrasurgical) variables, C statistics of 0.797 (95% CI, 0.784-0.810) and 0.825 (95% CI, 0.812-0.838), respectively (Fig 1). The incremental improvement in discrimination by the inclusion of

Table 3. Predictive Models of Acute Kidney Injury Based on Pre- and Intrasurgical Variables

	Doubling of SCr or Dialysis	*P*	Dialysis	*P*
Variable (reference)				
Race (white)		0.007		<0.001
Black	1.35 (1.06-1.72)		1.77 (1.20-2.62)	
Other	1.33 (1.03-1.73)		1.94 (1.31-2.89)	
Body mass index	1.03 (1.02-1.04)	<0.001		
Pulmonary disease	1.22 (1.02-1.47)	0.04	1.65 (1.26-2.15)	<0.001
Congestive heart failure	1.40 (1.22-1.62)	<0.001		
Diabetes mellitus	1.59 (1.32-1.91)	<0.001	1.50 (1.12-2.00)	0.006
Hypertension	1.23 (1.05-1.43)	0.003		
Emergent surgery	2.43 (1.97-3.00)	<0.001	1.95 (1.42-2.68)	<0.001
Estimated GFR[a]	0.98 (0.98-0.99)	<0.001	0.24 (0.18-0.32)[b]	<0.001
Estimated GFR[2,a,c]	1.0001 (1.00009-1.00013)	<0.001		
Albumin	0.71 (0.62-0.81)	<0.001	0.70 (0.58-0.84)	0.001
Potassium			1.29 (1.04-1.59)	0.02
Bicarbonate	0.97 (0.95-0.99)	0.002		
Sodium	0.98 (0.96-0.998)	0.06		
Serum urea nitrogen	1.01 (1.005-1.02)	<0.001	1.02 (1.01-1.02)	<0.001
Hemoglobin	0.97 (0.93-1.003)	0.08		
Platelet count	0.998 (0.997-0.999)	0.001		
Bilirubin[b]			1.45 (1.22-1.71)	<0.001
CPB time (≤80 min)		<0.001		<0.001
81-120 min	1.21 (0.997-1.48)		1.30 (0.89-1.90)	
121-150 min	1.34 (1.07-1.67)		1.52 (1.01-2.29)	
151-180 min	1.31 (1.01-1.71)		2.09 (1.36-3.21)	
>180 min	2.67 (2.07-3.43)		3.85 (2.54-5.82)	
Bypass not used	0.90 (0.66-1.24)		1.17 (0.68-2.00)	
Intrasurgical packed RBC transfusions (none)		<0.001		<0.001
1-2 units	1.48 (1.23-1.79)		1.75 (1.26-2.43)	
3-4 units	2.22 (1.80-2.74)		2.86 (2.05-3.99)	
5-6 units	3.25 (2.49-4.24)		4.18 (2.82-6.19)	
>6 units	6.53 (5.08-8.40)		9.24 (6.44-13.28)	
Intrasurgical vasopressor use	1.35 (1.16-1.58)	<0.001	2.22 (1.64-3.00)	<0.001
Intrasurgical urine output[b]	0.76 (0.71-0.81)	<0.001	0.76 (0.69-0.84)	<0.001
Discrimination and calibration				
C statistic[d]	0.825 (0.812-0.838)		0.910 (0.896-0.924)	
Hosmer-Lemeshow *P*[e]		0.09		0.2

Note: Values shown are odds ratio (95% confidence interval). Acute kidney injury is defined as doubling of SCr level or dialysis within 2 weeks of cardiac surgery. Conversion factors for units: eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; serum urea nitrogen in mg/dL to mmol/L, ×0.357.

Abbreviations: CBP, cardiopulmonary bypass; GFR, glomerular filtration rate; RBC, red blood cell; SCr, serum creatinine.

[a]Estimated GFR was calculated based on the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[9]

[b]Natural logarithmic transformation used.

[c]Quadratic term.

[d]Concordance statistic adjusted for optimism using bootstrap resampling; unity denotes perfect discrimination. The 95% confidence interval is given in parentheses.

[e]Significant *P* value for the Hosmer and Lemeshow statistic denotes significant deviation between predicted and observed events.

intrasurgical variables was 0.035 (95% CI, 0.023-0.047) for the dialysis therapy end point and 0.028 (95% CI, 0.021-0.036) for the composite end point. The presurgical model predictive of the composite end point showed suboptimal calibration per the Hosmer-Lemeshow test, $P < 0.001$ (Fig S1). The optimism correction for the C statistic was in the order of ≤0.002. λ_{AIC} ranged from 0.96-0.97 for our models, which precluded the need for applying shrinkage to any of the models; because λ_{AIC} is >0.9, a shrunken estimator or data reduction was not needed.[13]

Comparison to Previous Cleveland Clinic Risk Score

We applied the previously published Cleveland Clinic Risk score by Thakar et al[2] to the present cohort. It showed excellent discrimination, C statistic of 0.843 (95% CI, 0.825-0.861), but inadequate calibration (Hosmer-Lemeshow $P = 0.01$).

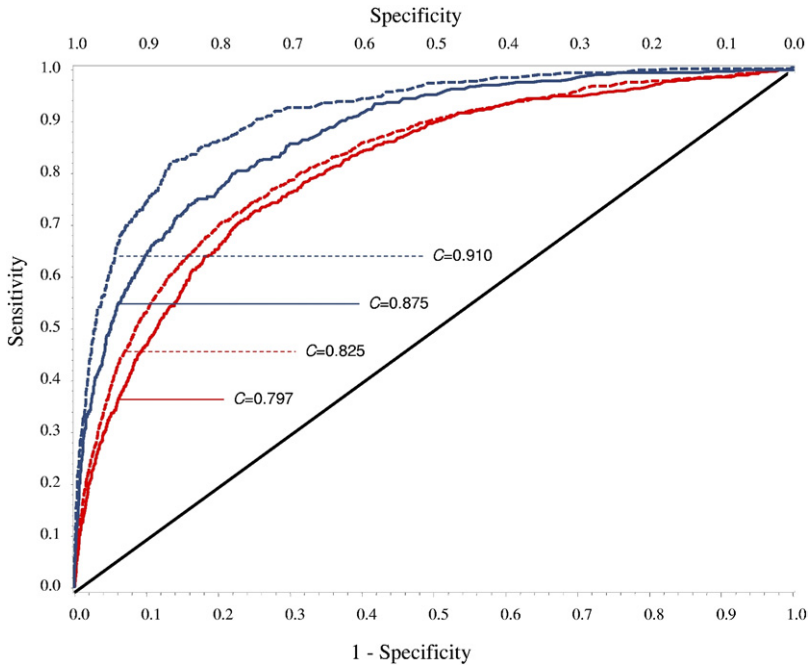

Figure 1. Receiver operating characteristic curves for the new predictive models. Red line represents models predictive of the composite end point of dialysis therapy or doubling of serum creatinine level, whereas the blue lines represent the dialysis therapy–only end point. Models that include both pre- and intraoperative variables are represented by broken lines, whereas solid lines represent models with preoperative only variables. C denotes concordance statistic, which also represents the area under the receiver operating characteristic curve.

DISCUSSION

We introduce 4 multivariable models predictive of cardiac surgery–associated AKI, defined as dialysis therapy alone and a composite of dialysis therapy or doubling of SCr level using presurgical or combined pre- and intrasurgical information. The 2 models predictive of the dialysis therapy end point using presurgical only or pre- and intrasurgical combined variables showed excellent discrimination and good calibration. The 2 models predictive of the composite end point (doubling of SCr level or dialysis therapy) showed good discrimination, but suboptimal calibration.

We compared the performance of the 2 models predictive of the dialysis therapy end point with the previously derived Cleveland Clinic ARF (acute renal failure) score, which in several external validation comparison studies has outperformed alternative risk algorithms.[2,6,15] In the new models, we introduce 2 major refinements in handling baseline kidney function, a major predictor of both outcomes. We replaced SCr level with eGFR, a superior marker of baseline kidney function.[9,16-18] We also explored the nonlinear relationship between baseline kidney function and outcome and avoided categorization of parameters that has been used often in the interest of model simplification.[2,6] Serum urea nitrogen is yet another marker for kidney function included in our models (also associated with poor outcome in patients with coronary artery disease).[19,20] During our variable selection process, we deliberately excluded procedure-based risk factors, such as presurgical use of intra-aortic balloon pump or extracorporeal membrane oxygenation, due to concerns about changing practice patterns and intercenter variability that might compromise external validity and model longevity. Unlike previous models, we included readily available baseline laboratory measurements, which reflect the functional status of various organ systems and the severity of illness. Previous researchers have taken a parsimonious approach for model building for simplicity and ease of use.[2,6] However, ironically, elimination of scientifically relevant variables (even if they do not reach statistical significance) is likely to lead to reduced predictive power.[7,21] Consequently, we opted to use a comprehensive model, but within the confines of proper event per variable ratio to avoid overfitting. We believe that the advantages of an unabridged model would sidestep the mentioned statistical drawbacks and remain end-user friendly when embedded to electronic medical records as automated calculators and accessible due to recent advances in mobile technology and its widespread use.[8]

As predicted, our new models that included intrasurgical information performed better than presurgical models. Prolonged cardiopulmonary bypass time and packed red blood cell transfusions reflect a complex procedure and complicated surgical course, whereas diminished intrasurgical urine output and use of diuretics are up-to-date markers of kidney function and injury. The improved predictive accuracy is invaluable for novel therapeutic interventions in the immediate postsurgical window in high-risk patients. Moreover, several new biomarkers of kidney injury have been evaluated for the early diagnosis of cardiac surgery–associated AKI, and a comprehensive model

would facilitate validation of their incremental predictive value.[22-25] We also introduced models predictive of a composite end point, which not only enrich the anticipated event rate required for clinical trials, but also circumvent potential bias introduced by a physician-driven intervention such as dialysis because certain presurgical characteristics such as baseline kidney function may influence the provision or timing of dialysis therapy after cardiac surgery.

Unfortunately, our presurgical model for the composite end point had inadequate calibration, as did the previous Cleveland Clinic Risk Score. This may illustrate different reasons for discordance between predicted versus observed probabilities across risk categories. Predictive models may lose predictive accuracy due to the inevitable change in patient characteristics, disease epidemiology, medical technology, and standards of care over time. This often is manifested as loss of calibration, which could be partially remedied through recalibration or structural model revisions (adding new variables).[26] The poor calibration noted in our presurgical model was driven mostly by overestimation of predicted risk in the highest risk category; the predictive value usually is low when the event rate is low even if the discriminatory test has high specificity and sensitivity. Despite poor calibration, a model could still discriminate patients who will incur a particular event.

Notwithstanding the advantages of the power and sample size of our prospectively collected large cohort, there are several limitations to consider before the application of these predictive models in clinical practice and/or clinical trials. The data are generated from a single center, which may limit generalizability; however, our cohort had balanced representation by race, sex, age, surgical procedure, and baseline chronic kidney disease stage. Moreover, the previously reported Cleveland Clinic Risk Score performed well when applied to external cohorts, which may reflect the quality of the underlying database.[6,15] The end points used in the present study, dialysis therapy and doubling of SCr level, are short-term in-hospital end points that may not reflect long-term outcomes. Nonetheless, these intermediate outcomes have been associated unequivocally with disease progression and mortality.[27-32]

In summary, we developed and internally validated 4 new models that accurately predict cardiac surgery–associated AKI. These models are based on readily available clinical information and can be used for patient counseling, clinical management, risk adjustment, and enrichment of clinical trials with high-risk participants. External validation of these predictive models in other cohorts will be required before wide-scale application.

ACKNOWLEDGEMENTS

We are thankful for the contribution of the research personnel from the Department of Cardiothoracic Anesthesiology at the Cleveland Clinic in maintaining the database and Sandra Bronoff for editorial assistance.

Support: Institutional funding was provided by the Cleveland Clinic.

Financial Disclosure: The authors declare that they have no relevant financial interests.

SUPPLEMENTARY MATERIAL

Table S1: Models of acute kidney injury: β coefficients and standard errors.

Figure S1: Calibration plots for the 4 risk prediction models.

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2011.10.046) is available at www.ajkd.org.

REFERENCES

1. Chertow GM, Levy EM, Hammermeister KE, et al. Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med*. 1998;104(4):343-348.

2. Thakar CV, Arrigain S, Worley S, et al. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol*. 2005;16(1):162-168.

3. Haase M, Bellomo R, Matalanis G, et al. A comparison of the RIFLE and Acute Kidney Injury Network classifications for cardiac surgery-associated acute kidney injury: a prospective cohort study. *J Thorac Cardiovasc Surg*. 2009;138(6):1370-1376.

4. Chertow GM, Lazarus JM, Christiansen CL, et al. Preoperative renal risk stratification. *Circulation*. 1997;95(4):878-884.

5. Mehta RH, Grab JD, O'Brien SM, et al. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. *Circulation*. 2006;114(21):2208-2216.

6. Wijeysundera DN, Karkouti K, Dupuis J-Y, et al. Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. *JAMA*. 2007;297(16):1801-1809.

7. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15(4):361-387.

8. Roques F, Michel P, Goldstone AR, et al. The logistic EuroSCORE. *Eur Heart J*. 2003;24(9):882.

9. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-470.

10. Lemeshow S, Hosmer DW. A review of goodness of fit statistics for use in the development of logistic regression model. *Am J Epidemiol*. 1982;115:92-106.

11. Efron BTR. *An Introduction to the Bootstrap.* New York, NY: Chapman & Hall; 1993.

12. Steyerberg EW, Harrell FE, Borsboom GM, et al. Internal validation of predictive models: Efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol*. 2001;54(8):774.

13. Steyerberg EW, Eijkemans MC, Habbema JD. Application of shrinkage techniques in logistic regression analysis: a case study. *Stat Neerl*. 2001;55(1):76-88.

14. Fang J, Austin PC, Jack VT. Test for linearity between continuous confounder and binary outcome first, run a multivariate regression analysis second. Poster presented at: SAS Global Forum; March 22-25, 2009; Washington, DC.

15. Candela-Toha A, Elias-Martin E, Abraira V, et al. Predicting acute renal failure after cardiac surgery: external validation

of two new clinical scores. *Clin J Am Soc Nephrol*. 2008; 3(5):1260-1265.

16. Wang F, Dupuis JY, Nathan H, et al. An analysis of the association between preoperative renal dysfunction and outcome in cardiac surgery: estimated creatinine clearance or plasma creatinine level as measures of renal function. *Chest*. 2003;124(5):1852-1862.

17. Noyez L, Plesiewicz I, Verheugt FW. Estimated creatinine clearance instead of plasma creatinine level as prognostic test for postoperative renal function in patients undergoing coronary artery bypass surgery. *Eur J Cardiothorac Surg*. 2006;29(4):461-465.

18. Silva J, Ridao-Cano N, Segura A, et al. Can estimated glomerular filtration rate improve the EuroSCORE? *Interact Cardiovasc Thorac Surg*. 2008;7(6):1054-1057.

19. Lubowitz H, Slatopolsky E, Shankel S, Rieselbach RE, Bricker NS. Glomerular filtration rate. Determination in patients with chronic renal disease. *JAMA*. 1967;199(4):252-256.

20. Kirtane AJ, Leder DM, Waikar SS, et al. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. *J Am Coll Cardiol*. 2005;45(11): 1781-1786.

21. Harrell FE Jr, Lee KL, Califf RM, et al. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984;3(2):143-152.

22. Go A, Parikh C, Ikizler TA, et al. The Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) Study: design and methods. *BMC Nephrol*. 2010; 11(1):22.

23. Ichimura T, Hung CC, Yang SA, et al. Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. *Am J Physiol Renal Physiol*. 2004; 286(3):F552-F563.

24. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet*. 2005;365(9466):1231-1238.

25. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157-172.

26. Peterson ED, DeLong DM, Muhlbaier LH, Hackett S, Mark DB. Comparing risk-adjustment methods for provider profiling. *Stat Med*. 1997;16(23):2645-2664.

27. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol*. 2004;15(6):1597-1605.

28. Brown JR, Cochran RP, MacKenzie TA, et al. Long-term survival after cardiac surgery is predicted by estimated glomerular filtration rate. *Ann Thorac Surg*. 2008;86(1):4-11.

29. Coca SG, Yusuf B, Shlipak MG, et al. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis*. 2009;53(6): 961-973.

30. Hobson CE, Yavas S, Segal MS, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*. 2009;119(18):2444-2453.

31. Hsu CY, Chertow GM, McCulloch CE, et al. Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol*. 2009;4(5):891-898.

32. Brown JR, Kramer RS, Coca SG, et al. Duration of acute kidney injury impacts long-term survival after cardiac surgery. *Ann Thorac Surg*. 2010;90(4):1142-1148.