

Improving the Identification of Patients at Risk of Postoperative Renal Failure after Cardiac Surgery

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Background: Preoperative renal insufficiency is an important predictor of the need for postoperative renal replacement therapy (RRT). Serum creatinine (sCr) has a limited ability to identify patients with preoperative renal insufficiency because it varies with age, sex, and muscle mass. Calculated creatinine clearance (CrCl) is an alternative measure of renal function that may allow better estimation of renal reserve.

Methods: Data were prospectively collected for consecutive patients who underwent cardiac surgery requiring cardiopulmonary bypass at a tertiary care center. The relation between CrCl (Cockcroft-Gault equation) and RRT was initially described using descriptive statistics, logistic regression, and receiver operating curve analysis. Based on these analyses, preoperative renal insufficiency was defined as CrCl of 60 ml/min or less. Preoperative renal function was classified as moderate insufficiency (sCr > 133 μ M), mild insufficiency (100 μ M < sCr \leq 133 μ M), occult insufficiency (sCr \leq 100 μ M and CrCl \leq 60 ml/min), or normal function (sCr \leq 100 μ M and CrCl > 60 ml/min). The independent association of preoperative renal function with RRT was subsequently determined using multiple logistic regression.

Results: Of the 10,751 patients in the sample, 137 (1.2%) required postoperative RRT. Approximately 13% of patients with normal sCr had occult renal insufficiency. Occult renal insufficiency was independently associated with RRT (odds ratio, 2.80; 95% confidence interval, 1.39–5.33). The magnitude of this risk was similar to patients with mild renal insufficiency ($P = 0.73$).

Conclusions: The inclusion of a simple CrCl-based criterion in preoperative assessments may improve identification of patients at risk of needing postoperative RRT.

ACUTE renal failure necessitating renal replacement therapy (RRT) is a severe complication of cardiac surgery. Although no causative relation has been proven, the need for postoperative RRT is independently associated with increased mortality.^{1,2} Prognostic risk stratification for RRT, therefore, is an important component of the preoperative assessment of cardiac surgery patients.

Numerous studies have consistently identified preexisting renal insufficiency as an independent predictor of the need for postoperative RRT.^{2–8} Most of these studies, however, did not specify thresholds for defining clinically important preoperative renal insufficiency; furthermore, any specified thresholds were chosen in an arbitrary manner.^{2–8} In addition, most defined thresholds estimated renal function using serum creatinine concentration (sCr).^{2,5,8} Creatinine concentration has important limitations because it varies with factors aside from renal function: age, sex, muscle mass, metabolism, and hyperhydration. Consequently, the glomerular filtration rate (GFR) may be reduced by 75% before sCr becomes abnormal.⁹

Creatinine clearance (CrCl) is an alternative measure of preoperative renal reserve that approximates GFR. Although the direct accurate measurement of CrCl over short time periods is possible in the research setting, it is not a feasible option in clinical practice or larger clinical studies.¹⁰ A more practical solution is to estimate CrCl using sCr-based prediction equations that estimate GFR with moderate accuracy and precision.^{11,12}

To better understand the role of estimated CrCl in prognostic stratification for RRT, we undertook a retrospective cohort observational study of cardiac surgical patients. Creatinine clearance was estimated using the Cockcroft-Gault equation.¹¹ This prediction equation was chosen because it is calculated using readily available clinical data and is reasonably correlated with measured creatinine clearance in cardiac patients.¹³ The association between CrCl and RRT was first examined to determine an optimal CrCl-based cutoff for defining preoperative renal insufficiency. This definition was subsequently applied among patients with normal sCr values to determine whether it was independently associated with the need for postoperative RRT.

Materials and Methods

Data Sources

After approval by the institutional research ethics board was obtained, preoperative, intraoperative, and postoperative data on individuals undergoing cardiac surgery at the Toronto General Hospital (Toronto, Ontario, Canada) were prospectively collected in a clinical registry. This database has been previously described.¹⁴ Attending anesthesiologists, surgeons, and perfusionists collected all preoperative and intraoperative data. A full-time research nurse, who was blinded to the details of this study, adjudicated all outcomes from patients' med-

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ical records. Database accuracy was measured by reabstracting the medical records of 200 randomly selected patients.

Study Sample

The study sample consisted of adults (aged ≥ 18 yr) who underwent cardiac surgery under cardiopulmonary bypass between May 1999 and July 2004. Exclusion criteria included severe preoperative renal dysfunction (preoperative dialysis dependence or $sCr > 300 \mu M$) and infrequent procedures (heart transplantation, ventricular assist device insertion). Missing data values were imputed. An unknown left ventricular ejection fraction was considered equal to a normal value ($> 60\%$).¹⁵ Missing values for dichotomous variables were assigned the most frequent value, whereas continuous variables were assigned the median value.¹⁶ Using sample size recommendations for 10 or more outcome events per predictor variable, a sample of 10,000 patients was deemed sufficient to allow unbiased fitting of up to 10 predictor variables in multiple logistic regression (estimated 1% incidence of postoperative RRT).¹⁷

General Analysis Issues

Statistical analyses were performed using SAS Version 8.20 (SAS Institute, Cary, NC). All *P* values were two tailed, with statistical significance defined by $P \leq 0.05$. The dependent variable was the need for postoperative RRT (intermittent hemodialysis or continuous venovenous hemodiafiltration). Decisions about implementing RRT were made by consulting nephrologists. The common indications for RRT at our institution are fluid overload, metabolic abnormalities (acidosis, hyperkalemia), and anuria.

The principal predictor variable for this study was preoperative renal function. Preoperative renal function was estimated using both sCr and $CrCl$. The sCr concentrations of patients undergoing cardiac surgery at the Toronto General Hospital are routinely measured before surgery (within 30 days). The preoperative sCr was defined as the value closest to surgery. The preoperative $CrCl$ was calculated using the Cockcroft-Gault equation.¹¹ Several other preoperative factors that are associated with RRT were considered as potential confounders in multivariable analyses (table 1).^{2-8,18}

Unadjusted Relation between $CrCl$ and Postoperative RRT

To determine the optimum $CrCl$ -based definition of preoperative renal insufficiency, the unadjusted relation between $CrCl$ and postoperative RRT was analyzed using descriptive statistics, logistic regression, and receiver operating characteristic (ROC) curve analysis. Patients were divided into six strata based on $CrCl$: 20 or less, 21-40, 41-60, 61-80, 81-100, and more than 100 ml/min. The proportion of individuals requiring RRT within

each stratum was subsequently determined. Exact binomial 95% confidence intervals (CIs) were calculated for these proportions. The relation between $CrCl$ (continuous variable) and RRT was subsequently analyzed using logistic regression. Given that logistic regression assumes a linear relation between $CrCl$ and the probability of RRT (logit transformation), restricted cubic spline analyses were used to derive more accurate estimates of this relation.¹⁹ Finally, the relation between $CrCl$ and RRT was evaluated further using ROC curve analysis. An ROC curve was used to identify an optimal $CrCl$ -based threshold for predicting RRT (minimum distance to ideal sensitivity and specificity values of 1). Based on these analyses, preoperative renal insufficiency was defined as a $CrCl$ of 60 ml/min or less (Results). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of this threshold were calculated with associated exact binomial 95% CIs. Accuracy was defined as the sum of concordant cells divided by the sum of all cells in a two-by-two table.

Adjusted Relation between Preoperative Renal Function and Postoperative RRT

The unadjusted associations between potential predictor variables and RRT were initially determined using appropriate tests (*t* test, Mann-Whitney U test, chi-square test, Fisher exact test). Patients were divided into four categories on the basis of preoperative renal function. Moderate renal insufficiency (class 4) was defined as a preoperative sCr greater than $133 \mu M$ (1.5 mg/dl). This degree of preoperative renal insufficiency is independently associated with perioperative mortality and morbidity after cardiac surgery.^{8,20,21} Mild renal insufficiency (class 3) was defined as $100 \mu M < sCr \leq 133 \mu M$. The $100\text{-}\mu M$ value was chosen because it is the upper limit of the normal sCr range at our institution; furthermore, it is the threshold above which many clinicians would interpret renal function as being abnormal. Occult renal insufficiency (class 2) was defined as a normal sCr ($\leq 100 \mu M$) with an abnormal $CrCl$ (≤ 60 ml/min). Normal renal function (class 1) included all individuals with both normal sCr ($\leq 100 \mu M$) and $CrCl$ (> 60 ml/min).

The independent association of preoperative renal function (classes 1-4) with postoperative RRT was determined using multiple logistic regression. The reference group against which other levels of renal function were compared was class 1 (normal renal function). In addition to preoperative renal function, we considered 13 other variables, which were previously identified as independent predictors of postoperative RRT, as potential confounders. These variables were age, sex, diabetes mellitus requiring insulin or oral hypoglycemic agents, systemic hypertension (requiring medication), chronic obstructive pulmonary disease (requiring daily oral or inhaled medication), vascular disease (history of stroke,

Table 1. Characteristics of Study Sample and Subgroups (Stratified by Preoperative Renal Function)

	Entire Sample, n = 10,751	Class 1 (sCr ≤ 100 μM and CrCl > 60 ml/min), n = 6,743 (63%)	Class 2 (sCr ≤ 100 μM and CrCl ≤ 60 ml/min), n = 1,008 (9%)	Class 3 (100 μM < sCr ≤ 133 μM), n = 2,357 (22%)	Class 4 (sCr > 133 μM), n = 643 (6%)
Characteristics					
Age, yr	62 ± 12	59 ± 12	73 ± 7	66 ± 11	68 ± 10
Female sex	2,787 (26)	1,641 (24)	700 (69)	324 (14)	122 (19)
Weight, kg	79 ± 16	81 ± 15	61 ± 9	81 ± 15	79 ± 16
Renal function					
Creatinine concentration, μM	92 ± 26	80 ± 13	85 ± 10	112 ± 9	164 ± 33
Creatinine clearance, ml/min	82 ± 31	97 ± 27	51 ± 7	64 ± 19	42 ± 14
Comorbid disease					
Diabetes mellitus requiring medication	2,381 (22)	1,446 (21)	183 (18)	552 (23)	200 (31)
Hypertension	5,891 (55)	3,410 (51)	605 (60)	1,400 (59)	476 (74)
Chronic obstructive pulmonary disease	427 (4)	237 (4)	42 (4)	115 (5)	33 (5)
Cerebrovascular disease	968 (9)	492 (7)	96 (10)	270 (11)	110 (17)
Peripheral vascular disease	1,421 (13)	689 (10)	152 (15)	399 (17)	181 (28)
Cerebrovascular and/or peripheral vascular disease	2,066 (19)	1,035 (15)	219 (22)	561 (24)	251 (39)
Left ventricular ejection fraction					
> 60%	4,864 (45)	3,262 (48)	501 (50)	914 (39)	187 (29)
41–60%	3,748 (35)	2,321 (34)	319 (32)	859 (36)	249 (39)
21–40%	1,831 (17)	1,005 (15)	171 (17)	486 (21)	169 (26)
≤ 20%	308 (3)	155 (2)	17 (2)	98 (4)	38 (6)
Surgical details					
Coronary angiography within 72 h before surgery	779 (7)	477 (7)	85 (8)	178 (8)	39 (6)
Active endocarditis	88 (0.8)	42 (0.6)	8 (0.8)	22 (0.9)	16 (2.5)
Previous cardiac surgery	856 (8)	525 (8)	66 (7)	193 (8)	72 (11)
Preoperative intraaortic balloon pump	217 (2)	124 (2)	22 (2)	50 (2)	21 (3)
Operative procedure					
CABG or ASD repair alone	7,005 (65)	4,434 (66)	603 (60)	1,574 (67)	394 (61)
Valve repair alone	1,755 (16)	1,164 (17)	172 (17)	332 (14)	87 (14)
Complex procedures	1,991 (19)	1,145 (17)	233 (23)	451 (19)	162 (25)
Timing of surgery					
Elective	6,392 (59)	4,322 (64)	539 (53)	1,240 (53)	291 (45)
Urgent	4,158 (39)	2,303 (34)	452 (45)	1,073 (46)	33 (51)
Emergent	201 (2)	118 (2)	17 (2)	44 (2)	22 (3)
Outcomes					
In-hospital mortality	180 (1.7)	66 (1.0)	34 (3.4)	48 (2.0)	32 (5.0)
Need for renal replacement therapy	137 (1.2)	29 (0.4)	13 (1.3)	37 (1.6)	58 (9.0)

Data are presented as mean ± SD or number of patients (%).

ASD = atrial septal defect; CABG = coronary artery bypass graft; CrCl = creatinine clearance; sCr = serum creatinine.

transient ischemic attacks, carotid disease, aortoiliac disease, or femoropopliteal disease), left ventricular ejection fraction (four classes: > 60, 41–60, 21–40, and ≤ 20%), recent coronary angiography (within 72 h of surgery), active endocarditis, previous cardiac surgery, preoperative intraaortic balloon pump use, procedure type (three classes: coronary artery bypass or atrial septal defect repair, valve surgery alone, and other procedures), and timing of surgery.^{2–8,18} The timing of surgery was classified into three categories: elective, urgent (cannot leave hospital without surgery), and emergent (surgery required within 12 h of presentation). To conform to the underlying assumptions of logistic regression, age was transformed to a continuous variable restricted between 60 to 80 yr.¹⁹ Thus, ages below 60 yr were considered equal to 60 yr; similarly, ages above 80 yr were considered equivalent to 80 yr. Backward stepwise variable selection was used to construct the final regres-

sion model (criterion for selection: $P \leq 0.05$). The associations of independent predictors with RRT in the final model were expressed as odds ratios with 95% CIs. The variation in the dependent variable (RRT) attributable to each independent predictor was estimated by the likelihood ratio chi-square statistic; a larger chi-square statistic implied a more important role in explaining variation in the dependent variable. Model discrimination was measured using the *c* statistic, which is equivalent to the area under the ROC curve. Model calibration was estimated using the Hosmer-Lemeshow statistic (higher *P* values imply that the model fit the observed data better).

The validity of the final model was further described using bootstrap techniques. Initially, 1,000 computer-generated samples, each including 10,571 individuals, were derived from the study sample by random selection with replacement. The bootstrap samples were used to estimate the 95% CI for the *c* statistic of the final model.

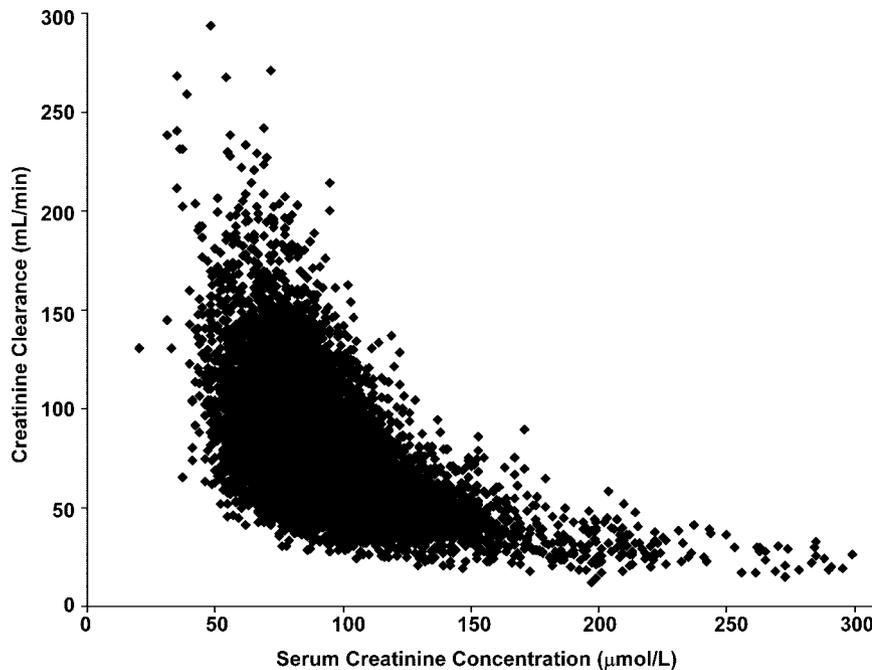


Fig. 1. Scatter plot showing the correlation between preoperative serum creatinine concentration and creatinine clearance. Despite a moderate negative correlation ($R = -0.56$; $P < 0.0001$), the range of creatinine clearance is wide among patients with creatinine concentrations below $100 \mu\text{M}$.

The reliability of the independent predictors included in the final model was also described using bootstrap bagging.²² In summary, 1,000 bootstrap samples were generated as described above. Within each bootstrap sample, forward stepwise variable selection (criterion for inclusion: $P \leq 0.05$) was employed using all 14 potential independent variables. The reliability of predictor variables in the final regression model was estimated by how often they were retained as independent predictors in the bootstrap samples. Reliable predictors were expected to be retained in a higher proportion of bootstrap samples.

Results

During the study period, 10,940 patients underwent cardiac surgical procedures under cardiopulmonary bypass. A total of 189 patients were excluded because of preoperative dialysis dependence, severe preoperative renal insufficiency ($\text{sCr} > 300 \mu\text{M}$), or ineligible procedures. The final sample consisted of 10,751 individuals. Within this sample, 54 patients (0.5%) had missing values in one or more data elements. All missing values were replaced using imputation, as described previously. Exclusion of patients with missing data did not alter the magnitude or significance of the results. Database accuracy exceeded 95%.

Overall rates of in-hospital mortality and RRT were 1.7% ($n = 180$) and 1.2% ($n = 137$), respectively (table 1). Among patients requiring postoperative RRT, 47% ($n = 65$) died in the hospital. Despite a moderate negative correlation between sCr and CrCl (Pearson correlation coefficient $R = -0.56$; $P < 0.001$), the range of CrCl

values among patients with normal sCr ($\leq 100 \mu\text{M}$) was wide (fig. 1). When the study sample was classified into six strata based on CrCl , the rate of RRT remained below 1% until the preoperative CrCl decreased below 60 ml/min (fig. 1). Similarly, when restricted cubic splines and logistic regression were used to analyze the relation between CrCl (continuous variable) and RRT, the risk of RRT seemed to increase appreciably when CrCl was 60 ml/min or less (fig. 2). In ROC curve analyses, the area under the curve for the relation between CrCl and RRT was 0.77 (95% CI, 0.73–0.82). The optimal threshold for predicting RRT was a CrCl of 60 ml/min or less, with a sensitivity and specificity of 0.64 (95% CI, 0.56–0.72) and 0.76 (95% CI, 0.75–0.76), respectively. Clinically important preoperative renal dysfunction was therefore defined as a CrCl of 60 ml/min or less. This threshold had an overall accuracy of 0.76 (95% CI, 0.75–0.76). Given the low prevalence of RRT in our sample, the threshold had a relatively low positive predictive value (0.03; 95% CI, 0.03–0.04) but high negative predictive value (0.99; 95% CI, 0.99–1.00).

The prevalence of occult renal dysfunction ($\text{sCr} \leq 100 \mu\text{M}$ and $\text{CrCl} \leq 60$ ml/min) was 9% ($n = 1,008$). Approximately 13% of individuals with normal sCr were subsequently found to have occult renal dysfunction ($\text{CrCl} \leq 60$ ml/min). These individuals were more likely to be elderly females with low body weights (table 1). In comparison with individuals with normal renal function, patients with occult renal dysfunction experienced more than a threefold increased risk of mortality and RRT (table 1).

In unadjusted analyses, the following variables had significant associations with RRT: sex, age, weight, sCr ,

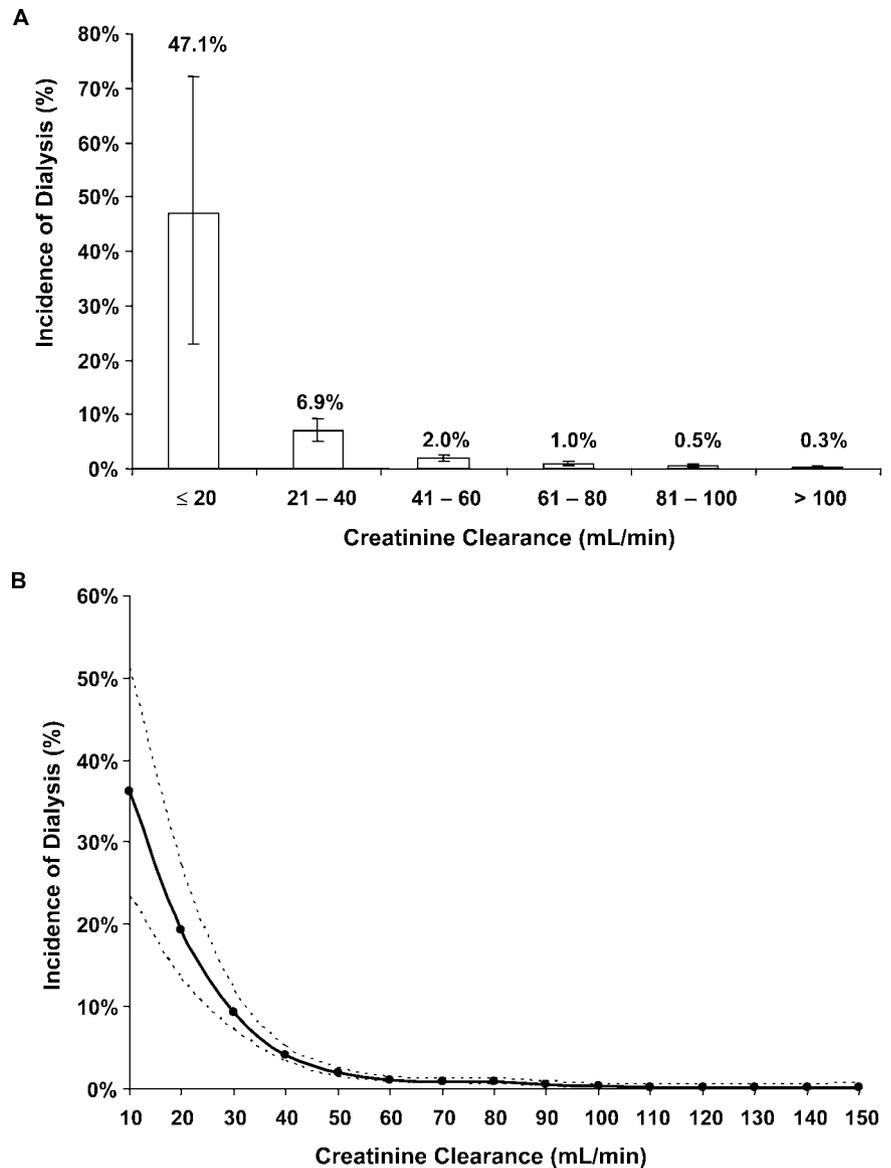


Fig. 2. Association between preoperative creatinine clearance and postoperative renal replacement therapy as determined by descriptive statistics (A) and logistic regression analyses (B). The 95% confidence intervals for this association are denoted by error bars in A and dotted lines in B.

CrCl, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, vascular disease, left ventricular ejection fraction, recent coronary angiography, previous cardiac surgery, preoperative intraaortic balloon pump use, procedure type, and timing of surgery (table 2).

In multiple logistic regression analyses, preoperative renal function, diabetes mellitus, left ventricular ejection fraction, previous cardiac surgery, procedure type, and timing of surgery were independently associated with RRT (table 3). All predictor variables that were included in the final model were also retained in more than 50% of 1,000 bootstrap samples (table 3). The final model had good discrimination (*c* statistic, 0.87; 95% CI, 0.83–0.89) and calibration (Hosmer-Lemeshow statistic, 7.33; $P = 0.50$). Occult renal dysfunction (class 2) was independently associated with RRT (odds ratio, 2.80; 95% CI, 1.39–5.33; $P = 0.003$). The magnitude of this increased risk was similar to that of patients with mild renal dysfunction (odds ratio, 3.14; 95% CI, 1.92–5.19; $P <$

0.001). There was no significant difference between occult and mild renal dysfunction with regard to risk of RRT ($P = 0.73$).

Discussion

This study found that the risk of postoperative RRT increases appreciably when CrCl decreases below 60 mL/min, even if sCr is normal. If this criterion is incorporated into preoperative assessments, 13% of individuals with normal sCr values ($\leq 100 \mu\text{M}$) would be identified as being at increased risk of needing perioperative RRT. Patients with occult renal dysfunction were disproportionately elderly women with low body weights. Occult renal dysfunction has an important impact on perioperative outcomes. It is associated with a greater than threefold increase in the unadjusted risk of perioperative mortality and RRT. Furthermore, it is independently as-

Table 2. Characteristics of Patients Who Did or Did Not Require Postoperative Renal Replacement Therapy

Characteristics	No Renal Replacement Therapy, n = 10,614	Renal Replacement Therapy, n = 137	P Value
Characteristics			
Age, yr	62 ± 12	65 ± 13	0.003
Female sex	2,741 (26)	46 (34)	0.04
Weight, kg	79 ± 16	76 ± 18	0.03
Renal function			
Creatinine concentration, μM	92 ± 25	138 ± 56	< 0.001
Creatinine clearance, ml/min	82 ± 31	54 ± 26	< 0.001
Comorbid disease			
Diabetes mellitus requiring medication	2,328 (22)	53 (39)	< 0.001
Hypertension	5,805 (55)	86 (63)	0.06
Chronic obstructive pulmonary disease	424 (4)	3 (2)	0.38
Cerebrovascular disease	949 (9)	19 (14)	0.05
Peripheral vascular disease	1,389 (13)	32 (23)	< 0.001
Cerebrovascular and/or peripheral vascular disease	2,022 (19)	44 (32)	< 0.001
Left ventricular ejection fraction			
> 60%	4,826 (45)	38 (28)	
21–60%	5,496 (52)	83 (61)	< 0.001
≤ 20%	292 (3)	16 (12)	
Surgical details			
Coronary angiography within 72 h before surgery	759 (7)	20 (15)	< 0.001
Active endocarditis	85 (0.8)	3 (2)	0.07
Previous cardiac surgery	833 (8)	23 (17)	< 0.001
Preoperative intraaortic balloon pump	204 (2)	13 (9)	< 0.001
Operative procedure			
CABG or ASD repair alone	6,949 (65)	56 (41)	
Valve repair alone	1,376 (13)	12 (9)	< 0.001
Complex procedures	2,289 (22)	69 (50)	
Timing of surgery			
Elective	6,343 (60)	49 (36)	
Urgent	4,088 (39)	70 (51)	< 0.001
Emergent	183 (2)	18 (13)	

Data are presented as mean ± SD or number of patients (%).

ASD = atrial septal defect; CABG = coronary artery bypass graft.

sociated with perioperative RRT to the same extent as mild renal dysfunction ($100 \mu\text{M} < \text{sCr} \leq 133 \mu\text{M}$). These findings confirm the importance of including an estimate of GFR in both clinical practice and research.

The current study has important strengths. First, a large accurate prospectively collected database was used. Second, the outcome of interest (need for RRT) was clear and clinically relevant. Third, the logistic re-

Table 3. Independent Predictors of the Need for Postoperative Renal Replacement Therapy

	Odds Ratio	95% Confidence Interval	P Value	Likelihood Ratio Chi-square Statistic (P Value)	Reliability, %
Preoperative renal function					
sCr ≤ 100 μM and CrCl > 60 ml/min	1*	—	—		
sCr ≤ 100 μM and CrCl ≤ 60 ml/min	2.80	1.39–5.33	0.003	131.3 (P < 0.001)	100
100 $\mu\text{M} < \text{sCr} \leq 133 \mu\text{M}$	3.14	1.92–5.19	< 0.001		
sCr > 133 μM	15.23	9.57–24.71	< 0.001		
Comorbid disease					
Diabetes mellitus requiring medication	2.46	1.67–3.60	< 0.001	20.1 (P < 0.001)	100
Left ventricular ejection fraction					
> 60%	1*	—	—		
21–60%	1.48	0.99–2.25	0.06	8.4 (P = 0.02)	70
≤ 20%	2.61	1.32–4.95	0.004		
Operative details					
Previous cardiac surgery	1.71	1.02–2.79	0.04	4.1 (P = 0.04)	54
Operative procedure					
CABG or ASD repair alone	1*	—	—		
Valve repair alone	1.58	0.77–3.02	0.19	38.8 (P < 0.001)	100
Complex procedures	3.52	2.37–5.24	< 0.001		
Timing of surgery					
Elective	1*	—	—		
Urgent	1.76	1.19–2.60	0.005	42.0 (P < 0.001)	100
Emergent	9.91	5.22–18.11	< 0.001		

* Reference group.

ASD = atrial septal defect; CABG = coronary artery bypass graft; CrCl = creatinine clearance; sCr = serum creatinine.

gression analyses adhered to sample size recommendations for 10 or more outcome events per predictor variable.¹⁷ Fourth, the regression analyses were further strengthened by internal bootstrap validation. Finally, our analyses clearly demonstrate that the use of the CrCl threshold of 60 ml/min or less would enable clinicians to identify approximately 10% of the surgical population that would otherwise be misclassified as low risk for requiring postoperative RRT.

Our finding that CrCl has important advantages over sCr is consistent with previous research. The ability of sCr to identify outpatients with impaired renal function is limited.^{23,24} In the perioperative setting, the association of preoperative renal function with outcomes is strengthened by the use of CrCl, as opposed to sCr.^{7,25,26} The definition of clinically significant preoperative renal impairment (CrCl \leq 60 ml/min) identified in the current study is also in accord with the literature.^{3,25-27}

Limitations

There are several limitations to be considered when interpreting our results. First, the use alternative prediction equations (e.g., Modification of Diet in Renal Disease equation) may have improved correlation between estimated CrCl and GFR.¹² The Modification of Diet in Renal Disease equation was not applied in the current study because the prospective clinical registry did not capture all required variables. It is unlikely that this limitation significantly affected our results, given that our analyses focused on the association between estimated CrCl and clinical outcomes, not GFR. Second, the Cockcroft-Gault equation introduces more complexity to the preoperative assessment than sCr alone. Nonetheless, its use may be facilitated through the use of nomograms or personal digital assistant software. Third, given that these data originated from a single center, further external validation is still needed. Fourth, as opposed to calculating CrCl, clinicians could simply interpret sCr in light of sex, age, and weight. However, this process would entail that clinicians consider different sCr cutoffs for a 60-yr-old, 50-kg man; a 70-yr-old, 100-kg woman; and a 45-yr-old, 50-kg man. Such a strategy would introduce considerably more complexity to the preoperative assessment process than simply calculating CrCl and comparing it against a single threshold (60 ml/min). Finally, given that our clinical registry is limited to in-hospital data, the long-term implications of postoperative RRT after hospital discharge remain unknown.

Clinical Implications

The assessment of preoperative renal function involves interplay between sCr, age, sex, and muscle mass. The current study suggests that clinicians should estimate the CrCl of all cardiac surgery patients using their closest preoperative sCr. Individuals with CrCl values below 60 ml/min should be deemed to have clinical important

preoperative renal insufficiency, regardless of their sCr concentration. This strategy would allow clinicians to readily identify 10% of the surgical population who are at increased risk of perioperative renal insufficiency despite having normal sCr values.

The incorporation of a CrCl threshold (\leq 60 ml/min) in the preoperative assessment would therefore facilitate identification of high-risk patients for potential renal-protective interventions. Although vasoactive agents seem to have limited efficacy in preserving renal function, therapies targeting other pathogenic mechanisms (ischemia-reperfusion injury, suboptimal hematocrit) may hold promise.^{14,28-30} In addition, these same high-risk patients may be ideal candidates for recruitment into clinical trials of novel new renal-protective therapies.

References

- Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J: Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med* 1998; 104:343-8
- Thakar CV, Worley S, Arrigain S, Yared JP, Paganini EP: Influence of renal dysfunction on mortality after cardiac surgery: Modifying effect of preoperative renal function. *Kidney Int* 2005; 67:1112-9
- Chertow GM, Lazarus JM, Christiansen CL, Cook EF, Hammermeister KE, Grover F, Daley J: Preoperative renal risk stratification. *Circulation* 1997; 95: 878-84
- Conlon PJ, Stafford-Smith M, White WD, Newman MF, King S, Winn MP, Landolfo K: Acute renal failure following cardiac surgery. *Nephrol Dial Transplant* 1999; 14:1158-62
- Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT: Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. *Ann Intern Med* 1998; 128:194-203
- Thakar CV, Liangos O, Yared JP, Nelson D, Piedmonte MR, Hariachar S, Paganini EP: ARF after open-heart surgery: Influence of gender and race. *Am J Kidney Dis* 2003; 41:742-51
- Wang F, Dupuis JY, Nathan H, Williams K: 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; 124:1852-62
- Weerasinghe A, Hornick P, Smith P, Taylor K, Ratnatunga C: Coronary artery bypass grafting in non-dialysis-dependent mild-to-moderate renal dysfunction. *J Thorac Cardiovasc Surg* 2001; 121:1083-9
- Kellen M, Aronson S, Roizen MF, Barnard J, Thisted RA: Predictive and diagnostic tests of renal failure: A review. *Anesth Analg* 1994; 78:134-42
- Cittanova ML, Zubicki A, Savu C, Montalvan C, Nefaa N, Zaier K, Riou B, Coriat P: The chronic inhibition of angiotensin-converting enzyme impairs postoperative renal function. *Anesth Analg* 2001; 93:1111-5
- Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31-41
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: 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; 130:461-70
- Spinler SA, Nawarskas JJ, Boyce EG, Connors JE, Charland SL, Goldfarb S: Predictive performance of ten equations for estimating creatinine clearance in cardiac patients. Iohexol Cooperative Study Group. *Ann Pharmacother* 1998; 32:1275-83
- Karkouti K, Beattie WS, Wijeyesundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karski J, David TE: Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. *J Thorac Cardiovasc Surg* 2005; 129:391-400
- Pierpont GL, Kruse M, Ewald S, Weir EK: Practical problems in assessing risk for coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 1985; 89: 673-82
- Ferguson TB, Jr., Coombs LP, Peterson ED: Preoperative beta-blocker use and mortality and morbidity following CABG surgery in North America. *JAMA* 2002; 287:2221-7
- Concato J, Feinstein AR, Holford TR: The risk of determining risk with multivariable models. *Ann Intern Med* 1993; 118:201-10
- Provenchere S, Plantefeve G, Hufnagel G, Vicaut E, DeVaumas C, Lecharny JB, Depoix JP, Vrtochnik F, Desmonts JM, Philip I: Renal dysfunction after cardiac

- surgery with normothermic cardiopulmonary bypass: Incidence, risk factors, and effect on clinical outcome. *Anesth Analg* 2003; 96:1258-64
19. Harrell Jr, FE Lee KL, Pollock BG: Regression models in clinical studies: Determining relationships between predictors and response. *J Natl Cancer Inst* 1988; 80:1198-202
20. Anderson RJ, O'Brien M, Ma Whinney S, Villa Nueva CB, Moritz TE, Sethi GK, Henderson WG, Hammermeister KE, Grover FL, Shroyer AL: Renal failure predisposes patients to adverse outcome after coronary artery bypass surgery. VA Cooperative Study #5. *Kidney Int* 1999; 55:1057-62
21. Anderson RJ, O'Brien M, Ma Whinney S, Villa Nueva CB, Moritz TE, Sethi GK, Henderson WG, Hammermeister KE, Grover FL, Shroyer AL: Mild renal failure is associated with adverse outcome after cardiac valve surgery. *Am J Kidney Dis* 2000; 35:1127-34
22. Breiman L: Bagging predictors. *Mach Learn* 2005; 24:123-40
23. Duncan L, Heathcote J, Djurdjev O, Levin A: Screening for renal disease using serum creatinine: Who are we missing? *Nephrol Dial Transplant* 2001; 16:1042-6
24. Swedko PJ, Clark HD, Paramsothy K, Akbari A: Serum creatinine is an inadequate screening test for renal failure in elderly patients. *Arch Intern Med* 2003; 163:356-60
25. Kertai MD, Boersma E, Bax JJ, van den Meiracker AH, van Urk H, Roelandt JR, Poldermans D: Comparison between serum creatinine and creatinine clearance for the prediction of postoperative mortality in patients undergoing major vascular surgery. *Clin Nephrol* 2003; 59:17-23
26. Walter J, Mortasawi A, Arnrich B, Albert A, Frerichs I, Rosendahl U, Ennker J: Creatinine clearance versus serum creatinine as a risk factor in cardiac surgery. *BMC Surg* 2003; 3:4
27. Wijeyesundera DN, Rao V, Beattie WS, Ivanov J, Karkouti K: Evaluating surrogate measures of renal dysfunction after cardiac surgery. *Anesth Analg* 2003; 96:1265-73
28. Julier K, da Silva R, Garcia C, Bestmann L, Frascarolo P, Zollinger A, Chassot PG, Schmid ER, Turina MI, von Segesser LK, Pasch T, Spahn DR, Zaugg M: Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebo-controlled, multicenter study. *ANESTHESIOLOGY* 2003; 98:1315-27
29. Lee HT, Ota-Setlik A, Fu Y, Nasr SH, Emala CW: Differential protective effects of volatile anesthetics against renal ischemia-reperfusion injury *in vivo*. *ANESTHESIOLOGY* 2004; 101:1313-24
30. Friedrich JO, Adhikari N, Herridge MS, Beyene J: Meta-analysis: Low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005; 142:510-24