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Predictors of Postoperative Acute Renal Failure after Noncardiac Surgery in Patients with Previously Normal Renal Function

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Background: **The authors investigated the incidence and risk factors for postoperative acute renal failure after major noncardiac surgery among patients with previously normal renal function.**

Methods: **Adult patients undergoing major noncardiac surgery with a preoperative calculated creatinine clearance of 80 ml/min or greater were included in a prospective, observational study at a single tertiary care university hospital. Patients were followed for the development of acute renal failure (defined as a calculated creatinine clearance of 50 ml/min or less) within the first 7 postoperative days. Patient preoperative characteristics and intraoperative anesthetic management were evaluated for associations with acute renal failure. Thirty-day, 60-day, and 1-yr all-cause mortality was also evaluated.**

Results: **A total of 65,043 cases between 2003 and 2006 were reviewed. Of these, 15,102 patients met the inclusion criteria; 121 patients developed acute renal failure (0.8%), and 14 required renal replacement therapy (0.1%). Seven independent preoperative predictors were identified ($P < 0.05$): age, emergent surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy. Several intraoperative management variables were independent predictors of acute renal failure: total vasopressor dose administered, use of a vasopressor infusion, and diuretic administration. Acute renal failure was associated with increased 30-day, 60-day, and 1-yr all-cause mortality.**

Conclusions: **Several preoperative predictors previously reported to be associated with acute renal failure after cardiac surgery were also found to be associated with acute renal failure after noncardiac surgery. The use of vasopressor and diuretics is also associated with acute renal failure.**

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ACUTE renal failure (ARF) occurs in approximately 1–5% of all hospitalized patients and is increasingly prevalent.[1–3] The development of ARF is known to increase cost, duration of stay, and mortality.[1] There have been a variety of predictive models developed to risk stratify patients undergoing cardiac surgery.[4,5] The few published data regarding ARF in a noncardiac surgery population are limited to high-risk aortic procedures.[6,7] There are no large studies addressing renal dysfunction after noncardiac, nonvascular surgery. Cardiopulmonary bypass induces unique pathophysiology in cardiac surgery patients.[8] As a result, it is inappropriate to assume that the risk factors for ARF after noncardiac surgery are the same as those after cardiac surgery. In addition, no study has focused on patients with previously normal measured renal function.

The study of renal dysfunction is challenged by the wide variation in definitions. Clear endpoints such as renal replacement therapy underestimate the clinical impact of reduced glomerular filtration rate. Serum creatinine struggles to reflect variations due to rapidly changing renal status, ethnic background, sex, and age. Nevertheless, calculated creatinine clearance has been shown to be a more accurate measure of renal function that incorporates some interpatient variations.[9,10]

In this study, we sought to identify the incidence and risk factors for postoperative ARF after major noncardiac surgery among patients with previously normal renal function. Furthermore, we examined associations between ARF and intraoperative hemodynamic management, oliguria, and diuretic administration. We hypothesized that many of the comorbidities associated with ARF after cardiac surgery may also be preoperative predictors of ARF after noncardiac surgery.[4,5,10] In addition, we hypothesized that prolonged periods of intraoperative hypotension may be associated with ARF.

Materials and Methods

Institutional review board approval was obtained for this prospective, observational study at a large, tertiary care university hospital. Because no care interventions were mandated, signed patient consent was waived. All operations performed from July 1, 2003, to June 30, 2006, with an overnight admission were reviewed. Consistent with previous landmark studies by Lee *et al.*[11] evaluating predictors of perioperative cardiovascular events, "major" surgery was defined as a surgery with a

duration of stay of 2 or more days. Patients were included only if a preoperative serum creatinine within 30 days of the operative date was available. The most recent preoperative serum creatinine was used to derive an estimated creatinine clearance using the Cockcroft-Gault formula, ([(140 − age in years) × (weight in kilograms)]/[72 × serum creatinine in mg/dl]) × (0.85 for females).[12] Patients with a preoperative estimated creatinine clearance less than 80 ml/min were excluded. Additional exclusion criteria were cardiac, transplant, urology, and electroconvulsive therapy procedures; procedures involving a nephrectomy, ureteral manipulation, or suprarenal aortic cross-clamping; preoperative renal failure or renal dysfunction; or any radiology study using intravenous contrast within the first 7 postoperative days.

The primary outcome was ARF, defined as a calculated creatinine clearance of 50 ml/min or less within the first 7 postoperative days. This threshold was chosen because it represents an approximate 40% decrease from preoperative creatinine clearance and demands dosage adjustment for most renally excreted medications.[13] Estimated creatinine clearance has been demonstrated to be an accurate proxy for renal function in a steady state situation.[12] There are few data regarding its accuracy in the perioperative setting. Nevertheless, it remains the foundation for routine clinical care and dosing of medications in non–steady state situations.[13] There are data demonstrating its value in predicting postoperative ARF in a cardiac surgery population.[10] Secondary outcomes were the need for renal replacement therapy (extracorporeal hemodialysis, ultrafiltration, continuous venovenous hemofiltration, or continuous venovenous hemodialysis) within the first 7 postoperative days and all-cause mortality at 30 days, 60 days, and 1 yr. The study did not mandate or recommend any specific clinical decisions or therapies. Postoperative serum creatinine testing was ordered by the primary service according to their clinical judgment. If a patient met the inclusion criteria above but did not have a postoperative creatinine measured, he or she was presumed not to have postoperative ARF.

Preoperative, intraoperative, and postoperative data were collected from routine clinical documentation entered by anesthesiology residents, attending staff, and certified registered nurse anesthetists into the institution's perioperative clinical information system (Centricity®; General Electric Healthcare, Waukesha, WI). This documentation included a structured, electronic preoperative history and physical on every patient. This history and physical and its data storage were designed to serve not only clinical purposes, but also to collect data for observational research studies. Each clinical element (cardiac symptoms, history of coronary artery disease, *etc.*) is stored as a discrete database element. In addition, a structured, predefined pick-list is used by the clinician to enter information (appendix). Demographic and laboratory data were acquired *via* an automated, validated electronic interface from the hospital information system. Many of the preoperative variables evaluated (table 1) have been shown to be associated with ARF after cardiac surgery.[4,5,10] A surgery was defined as emergent if the anesthesiologist indicated an emergent code as part of the American Society of Anesthesiologists physical status code.[14] Based on previous cardiovascular risk stratification research, intrathoracic, intraperitoneal, suprainguinal vascular, and other surgeries with the potential for large fluid shifts or blood loss were defined as high risk (*i.e.*, multiple level spine fusions, intracranial aneurysm clipping, transhiatal esophagectomy, and pelvic exenteration).[11,15–17] A retrospective numeric cutoff for estimated blood loss or fluid administration was not used.

Intraoperative hemodynamic monitoring data were acquired *via* an automated, validated electronic interface from the physiologic monitors (Solar 9500®; General Electric Healthcare). The interface records one invasive arterial catheter blood pressure measurement each minute and all noninvasive blood pressure measurements. Each intraoperative anesthetic record was divided into consecutive 5-min epochs. The median systolic blood pressure (SBP) and median mean arterial pressure (MAP) for each 5-min epoch were calculated. The use of a median value over 5 min filters out monitoring artifacts and transient hypotension with limited clinical significance.[18] These median values were compared with absolute hypotension cutoff points: SBP less than 80, less than 70, and less than 60, and MAP less than 60, less than 50, and less than 40. In addition, the median values were also compared with the preoperative blood pressure documented in the history and physical to assess hypotension relative to this baseline blood pressure: SBP 30%, 40%, and 50% decrease, and MAP 30%, 40%, and 50% decrease. The number of epochs below these absolute and relative hypotension cutoff points was calculated for each case.

The total number of vasopressor boluses was calculated as a number of "equipotent" doses: phenylephrine (100 μg), ephedrine (5 mg), and epinephrine (10 μg). Administration of a vasopressor infusion was a separate clinical data element analyzed as a boolean variable. Additional intraoperative data recorded for each case included administration of mannitol or furosemide, urine output, and overall case duration measured in hours.

Mortality was derived by identifying patients in the Social Security Administration's Death Master File (US Department of Commerce, Springfield, VA). This publicly available database lists all deaths by social security number and is often used by financial institutions and healthcare researchers seeking all-cause mortality.[19] If the patient was found in the Death Master File, the date of death was compared with the date of operation to

Table 1. Preoperative Patient Characteristics

Risk Factor	Normal Postoperative Renal Function (n = 14,981)	Postoperative Acute Renal Failure (n = 121)	*P* Value†	% Cases with Complete Data
Male sex	7,743 (52)	68 (56)	0.32	100.0
Emergent surgery	1,798 (12)	25 (21)	<0.001	99.8
High-risk surgery*	2,012 (14)	37 (31)	<0.001	99.8
Coronary artery disease	1,194 (8)	23 (19)	<0.001	99.8
Cerebrovascular disease	710 (5)	8 (7)	0.34	100.0
Congestive heart failure	79 (1)	2 (2)	0.14	99.7
Chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy	871 (6)	19 (16)	<0.001	99.8
Dysrhythmia	601 (4)	11 (9)	0.01	99.8
Diabetes mellitus necessitating oral hypoglycemic therapy without insulin therapy	793 (5)	14 (12)	<0.001	99.4
Diabetes mellitus necessitating insulin therapy with or without oral hypoglycemic therapy	933 (6)	18 (15)	<0.001	100.0
Hypertension	4,412 (30)	59 (49)	<0.001	99.8
Previous coronary revascularization	577 (4)	10 (8)	0.01	99.3
Peripheral vascular occlusive disease	526 (4)	16 (13)	<0.001	99.8
Sleep apnea	540 (4)	8 (7)	0.08	99.0
Smoking	3,114 (21)	15 (13)	0.02	99.5
Valvular heart disease	398 (3)	6 (5)	0.12	99.8
History of vascular surgery	776 (5)	14 (12)	<0.001	99.3
Pulmonary hypertension	56 (0.4)	1 (1)	0.37	99.8
Liver disease	772 (5)	14 (12)	<0.001	100.0
Age, yr	47	59	<0.001	100.0
Body mass index, kg/m^2	29.5	33.8	<0.001	95.8
Baseline systolic blood pressure, mmHg	131	132	0.12	99.5
Baseline diastolic blood pressure, mmHg	74	71	0.01	99.5
Baseline mean arterial pressure, mmHg	92	91	0.47	99.5

Data are presented as n (%) unless otherwise indicated.

* Defined as intrathoracic, intraperitoneal, suprainguinal vascular, or involving large blood loss or fluid shifts. † *P* values calculated using Pearson chi-square or Fisher exact test for categorical variables and Student *t* test for continuous variables.

establish 30-day, 60-day, and 1-yr all-cause mortality. The Death Master File does not contain data regarding the specific cause of death. No analysis regarding specific causes of death was undertaken as part of the analysis.

Statistical Analysis

Statistical analysis was performed using SPSS® version 15 (SPSS Inc., Chicago, IL). Collinearity diagnostics were evaluated for all preoperative predictors. If any condition indexes were 30 or greater, a bivariate correlation matrix was constructed to evaluate pairwise correlations.[20] Groups of variables with a pairwise correlation of 0.70 or greater were deemed to demonstrate high levels of collinearity and were addressed by one of two options: collapsing the two variables into a single concept or removing one of the two variables from the model. The remaining variables were entered into a logistic regression full model fit. A propensity score for ARF based on this model was calculated for each patient.[21,22] A given patient's propensity score represents the predicted probability (ranging from 0 to 1) of the ARF outcome based on the preoperative characteristics. This propensity score was subsequently used for patient risk stratification and patient matching.[21,22] All variables deemed to be significant in the full model fit ($P < 0.05$) were established as independent predictors. Each variable was also assessed for effect size using hazard ratios comparing the likelihood of ARF among patients with and without the risk factor.[23] The resulting model's predictive value was evaluated using a receiver operating characteristic (ROC) area under the curve (AUC).[24]

In addition, an unweighted risk scale assigning one point to each risk factor was created using the independent risk factors (table 2). For purposes of the un-

Table 2. Independent Preoperative Predictors of Postoperative Acute Renal Failure

Preoperative Predictor	*P* Value	β Coefficient
Age, yr*	<0.001	0.055
Emergent surgery	<0.001	1.121
Liver disease	<0.001	1.047
Body mass index, kg/m^2*	<0.001	0.047
High-risk surgery†	0.001	0.589
Peripheral vascular occlusive disease	0.015	0.914
Chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy	0.045	0.589

Independent predictors of postoperative acute renal failure among patients with normal preoperative renal function were derived using full model fit logistic regression.

* Entered into full model fit as continuous variables. † Defined as intrathoracic, intraperitoneal, suprainguinal vascular, or involving large blood loss or fluid shifts.

weighted risk scale, continuous variables were transformed into dichotomous variables by identifying the maximal sum of sensitivity and specificity. Weighted and unweighted versions of the scale were compared using the ROC curve AUC.[24]

Intraoperative hemodynamic management and interventions were assessed by two different methods. First, the preoperative and intraoperative variables were combined into one comprehensive logistic regression full model fit. This comprehensive model's ROC curve AUC was compared with the preoperative predictor ROC curve AUC to assess for incremental predictive value. Second, patients were stratified into four equal ARF preoperative full model fit propensity score quartiles to create groups of patients with similar preoperative risk (quartile 1 = lowest risk, 2 = medium risk, 3 = medium–high risk, 4 = high risk).[21,25] After collinearity diagnostics and correlation adjustment, a logistic regression full model fit was performed within each quartile.

Finally, to compare mortality, we created two patient cohorts matched on their ARF preoperative full model fit propensity scores. ARF patients were matched using a five-digit matching algorithm to patients that did not experience ARF.[21,22] Mortality was compared using the Pearson chi-square test. Hazard ratios were used as an effect size measure.[23]

Results

A total of 65,043 cases were reviewed, and 15,102 patients met the inclusion criteria for the study. Exclusion reasons for the remaining patients are shown in figure 1. Of the 15,102 patients included in the analysis, 9,078 (60%) had a serum creatinine measured during the first 7 postoperative days. One hundred twenty-one patients developed ARF (0.8%), defined as an estimated creatinine clearance of 50 ml/min or less. Of the 121 patients who developed ARF, 14 patients required renal replacement therapy (0.1%). Vascular and general surgery procedures represented a significant proportion of the 121 patients (table 3).

Table 1 reflects the percentage of complete data for each variable evaluated. For all but two variables, the data completion rate was 99% or greater. Collinearity diagnostics revealed a condition index over 30, so a bivariate correlation matrix was used to identify variables with a high pairwise correlation of 0.70 or greater. Three pairs were identified: previous coronary revascularization and previous vascular surgery history, with previous vascular surgery history chosen because of a higher prevalence; preoperative baseline SBP and baseline MAP, with baseline SBP being chosen because of more common usage by clinicians; and baseline MAP and baseline diastolic blood pressure, with baseline MAP chosen. After these correlation adjustments, the largest correlation index was 14, and the highest pairwise correlation was 0.63.

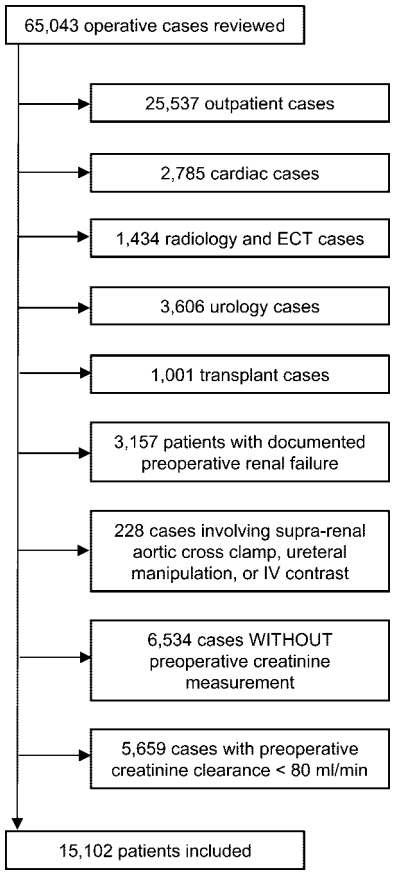

Fig. 1. Patient inclusions and exclusions. The number of patients excluded because of each exclusion criterion is shown.

The logistic regression full model fit was performed on the 14,066 patients (93.1%) who had a complete preoperative data set after pairwise correlation adjustment. Seven independent preoperative predictors were identified ($P < 0.05$): age, emergent surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy (table 2). The model was evaluated using the omnibus tests of model coefficients, which demonstrated a chi-square value of 141 with 21 degrees of freedom and a *P* value of

Table 3. Surgical Procedure Type among Patients with Postoperative Acute Renal Failure (n = 121)

Gastrointestinal	29 (24)
Vascular	21 (17)
Orthopedic	20 (17)
Thoracic	18 (15)
Trauma/burn	14 (12)
Neurosurgical	7 (6)
Gynecologic	5 (4)
Otorhinolaryngologic	5 (4)
Plastic and reconstructive	2 (2)

Data are presented as n (%).

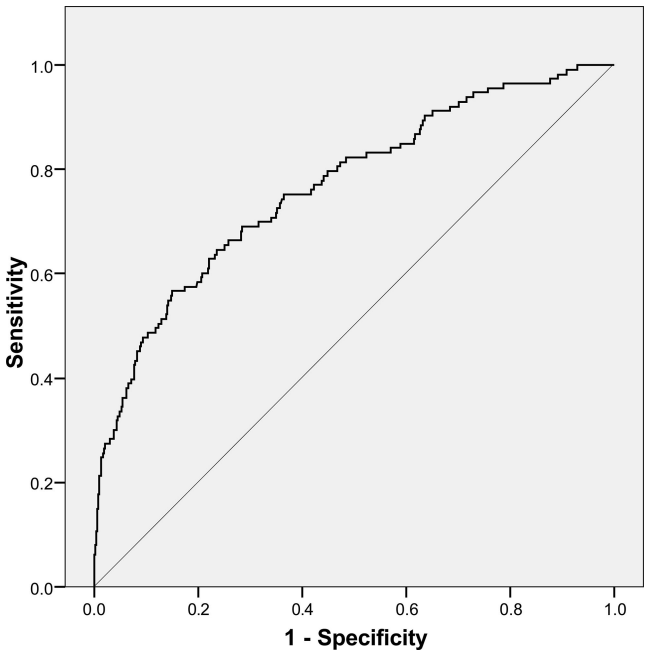

Fig. 2. A weighted receiver operating characteristic (ROC) curve evaluating the sensitivity and specificity of risk factors for acute renal failure is shown. Seven independent preoperative predictors were identified ($P < 0.05$): age, emergent surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy. The weighted ROC curve is based on the propensity score calculated for each patient using the logistic regression full model fit. The ROC curve assists practitioners in evaluating the value of a test. The area under the curve for the weighted preoperative predictor ROC curve was 0.77 ± 0.02.

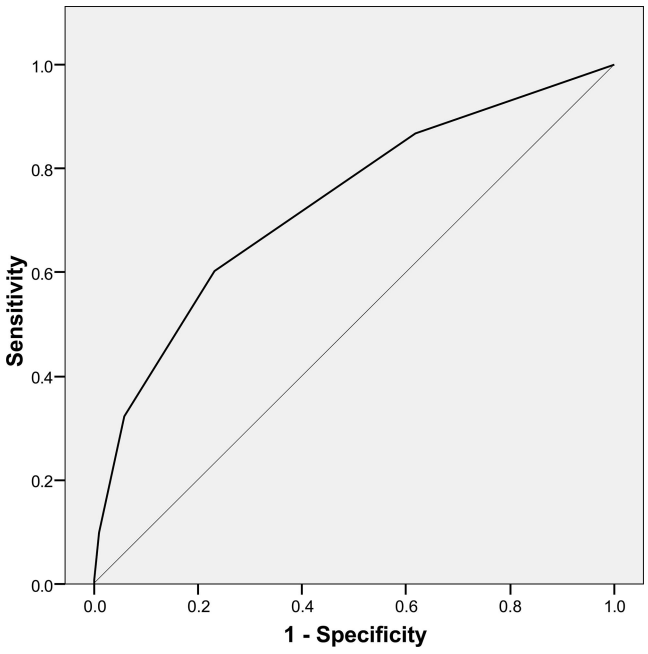

Fig. 3. An unweighted receiver operating characteristic (ROC) curve evaluating the sensitivity and specificity of risk factors for acute renal failure is shown. A patient was assigned one point for each of seven independent preoperative predictors: age ≥59 yr, emergent surgery, liver disease, body mass index ≥32 kg/m², high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy. A prediction score for acute renal failure was based on how many of these risk factors a patient possessed. The ROC curve assists practitioners in evaluating the value of a test and in establishing an appropriate cutoff for tests that posses a range of scores. The area under the curve for the unweighted preoperative predictor ROC curve was 0.73 ± 0.03.

less than 0.001. ROC curve analysis demonstrated an AUC of 0.77 ± 0.02 (fig. 2).

To improve clinical usability, an unweighted risk factor scale was created based on these risk factors. The two continuous variables identified in model, body mass index and age, were evaluated by ROC curves for a cutoff point and revealed an optimal sensitivity and specificity at a body mass index of 32 kg/m^2 or greater (sensitivity = 0.50 and specificity = 0.67) and age of 59 yr or greater (sensitivity = 0.56 and specificity = 0.77). Patients were assigned one point for each risk factor they possessed. ROC curve analysis demonstrated an AUC of 0.73 ± 0.03 (fig. 3). Hazard ratios for each risk factor were assessed (fig. 4). Patients were assigned to preoperative risk class I, II, III, or IV if they possessed exactly 0, exactly 1, exactly 2, or 3 or more risk factors, respectively. The incidence of ARF increased as the risk class increased, as did the hazard ratio for developing ARF: 0.3, 0.5, 1.3, and 4.3% (table 4).

The preoperative and intraoperative variables were combined into a single, comprehensive logistic regression full model fit to evaluate intraoperative predictors. This model included only 9,866 patients (65%) with complete data because only 10,569 patients (70%) had a documented intraoperative urine output. Given the large proportion of patients without urine output documentation, the full model fit was performed with and without urine output as a variable, yielding the same results. The model confirmed the predictive validity of the previously mentioned seven preoperative risk factors (table 2). It was evaluated using the omnibus tests of model coefficients, which demonstrated a chi-square value of 178

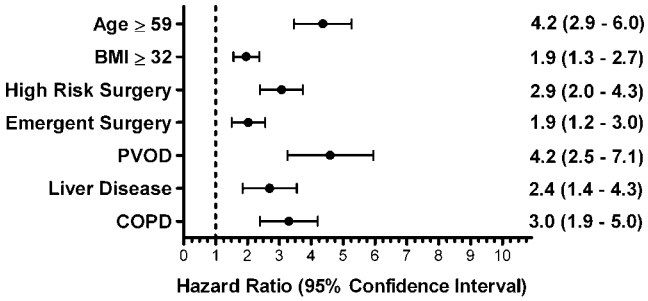

Fig. 4. Postoperative acute renal failure risk factors. Seven independent preoperative predictors of postoperative acute renal failure were identified using a full model fit logistic regression model. A hazard ratio (±95% confidence interval) for each risk factor was derived by comparing the odds of developing acute renal failure among patients with and without a given risk factor. COPD = chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy; PVOD = peripheral vascular occlusive disease.

Table 4. Frequency and Hazard Ratio of Acute Renal Failure Based on Number of Preoperative Risk Factors

Preoperative Risk Class	Acute Renal Failure, n (%)	Hazard Ratio (95% Confidence Interval)
Class I (0 risk factors), n = 5,728	16 (0.3)	
Class II (1 risk factor), n = 5,841	32 (0.5)	2.0 (1.1–3.6)
Class III (2 risk factors), n = 2,625	34 (1.3)	4.7 (2.6–8.5)
Class IV (3+ risk factors), n = 908	39 (4.3)	16.0 (8.9–28.8)

Seven independent preoperative predictors were identified ($P < 0.05$): age ≥59 yr, emergent surgery, liver disease, body mass index ≥32 kg/m^2, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy.

with 34 degrees of freedom and a P value of less than 0.001. In addition, this model also demonstrated significance ($P < 0.05$) for three intraoperative variables: use of a vasopressor infusion (2.2% among patients without ARF and 16% among patients with ARF), the mean number of vasopressor bolus doses administered (2.0 among patients without ARF and 5.3 among patients with ARF), and administration of furosemide or mannitol (5.8% among patients without ARF and 16% among those with ARF). This model had an ROC AUC of 0.79 ± 0.02. When compared with the ROC curve AUC of 0.77 ± 0.02 for the preoperative variables only, the inclusion of the intraoperative variables did improve the predictive value of the model, although the 95% confidence intervals did overlap.

A second intraoperative predictor analysis was performed after patients were divided into four equal ARF propensity score quartiles. After adjusting for collinearity among the blood pressure variables (data not shown), a logistic regression full model fit was performed within each quartile. Given the proportion of patients without a urine output documented, the full model fit was performed with and without inclusion of the urine output variable, yielding the same results. No significant predictors were observed for patients in quartiles 1 and 3. For quartile 2 patients, administration of furosemide or mannitol (4% among patients without ARF and 23% for patients with ARF) and the mean number of epochs with a MAP less than 40 mmHg (0.04 among patients without ARF and 0.14 among patients with ARF) were significant predictors. Among quartile 4 patients, the use of a vasopressor infusion (4% among patients without ARF and 18% among patients with ARF) was a significant predictor (table 5).

A propensity score based on the ARF preoperative predictor full model fit β coefficients was used to match patients experiencing ARF to those who did not. A five-digit matching algorithm allowed a 3:1 match. Comparison of these two matched groups shows that they were similar in most preoperative and operative respects (table 6) other than body mass index and frequency of chronic obstructive pulmonary disease. Chi-square test of 30-day, 60-day, and 1-yr all-cause mortality demonstrated a highly significant difference associated with the development of ARF (table 6).

Discussion

We report the incidence of postoperative ARF among patients with normal preoperative renal function undergoing noncardiac surgery to be 0.8%. This incidence is consistent with that reported among general hospitalized patients, ranging from 1% to 5%.[1–3,26,27] In the cardiac surgery population, ARF, defined as a 25% increase in creatinine, occurs in 17% of these high-risk surgical patients.[28] No previous study has considered noncardiac surgery patients as a whole when evaluating postoperative renal dysfunction.

Our analysis was restricted to patients with a documented normal preoperative Cockcroft-Gault estimated creatinine clearance of 80 ml/min or greater. This threshold was chosen because it is used by many living related kidney donor programs as evidence of "normal renal function."[29] The Cockcroft-Gault estimated creatinine clearance may be a more accurate reflection of glomerular filtration rate than serum creatinine.[9,10] Although estimated creatinine clearance has not been validated in a nonsteady state, the perioperative literature does demonstrate it has improved predictive value when compared with serum creatinine.[10] Although patients with preexisting renal dysfunction are at the highest risk of postoperative ARF,[5,10] patients with normal preoperative renal function were the focus of this study because of the lack of existing literature addressing this population.

In addition to describing the incidence of ARF in noncardiac surgery, we present a predictive model based on patient preoperative and operative characteristics (table 2). Most of the predictors are consistent with existing cardiac and vascular surgery ARF research: emergent surgery, chronic obstructive pulmonary disease, advanced age, peripheral vascular occlusive disease, and high-risk surgery.[4,5,10] However, these predictors have never been described for a broad general surgical patient population such as in this study. We have noted chronic liver disease to be an independent predictor of postoperative ARF. Historically, an association between obstructive jaundice and postoperative renal dysfunction has been noted.[30] We have also identified body mass index as an independent preoperative predictor of ARF. We are unaware of any existing literature demonstrating this relation for noncardiac surgery. Recent literature demonstrates an association between elevated body mass index and ARF after cardiac surgery and in a general medical population.[31–33] This association was

Table 5. Intraoperative Patient Characteristics

	Quartile 1,* Low Preoperative Risk (n = 3,596)			Quartile 2,* Medium Preoperative Risk (n = 3,595)			Quartile 3,* Medium–High Preoperative Risk (n = 3,595)			Quartile 4,* High Preoperative Risk (n = 3,595)		
	No ARF (n = 3,590)	ARF (n = 6)	*P* Value	No ARF (n = 3,581)	ARF (n = 14)	*P* Value	No ARF (n = 3,575)	ARF (n = 20)	*P* Value	No ARF (n = 3,522)	ARF (n = 73)	*P* Value
Mean case duration, h	4.0	3.0	NS	4.4	4.8	NS	4.7	4.3	NS	5.0	5.6	NS
No. of epochs <80 SBP	1.0	1.3	NS	1.4	2.4	NS	1.3	3.3	NS	1.4	2.9	0.04
No. of epochs <70 SBP	0.1	0.2	NS	0.2	0.7	NS	0.3	1.9	NS	0.3	1.7	NS
No. of epochs <60 SBP	0.0	0.0	NS	0.1	0.1	NS	0.1	0.6	NS	0.1	0.8	NS
No. of epochs <60 MAP	2.7	1.2	NS	2.5	2.4	NS	2.5	5.4	NS	3.0	6.5	0.00
No. of epochs <50 MAP	0.2	0.0	NS	0.3	0.4	NS	0.3	1.8	NS	0.4	1.4	0.01
No. of epochs <40 MAP	0.1	0.0	NS	0.0	0.1	NS	0.0	0.3	NS	0.1	0.3	NS
No. of epochs 30% ↓ SBP	4.2	2.5	NS	6.5	4.9	NS	8.7	12.7	NS	9.5	12.8	NS
No. of epochs 40% ↓ SBP	0.9	0.3	NS	1.8	0.7	NS	2.9	4.4	NS	3.3	6.8	0.03
No. of epochs 50% ↓ SBP	0.1	0.0	NS	0.3	0.0	NS	0.5	0.6	NS	0.7	2.2	NS
No. of epochs 30% ↓ MAP	4.7	2.5	NS	6.4	3.9	NS	7.6	9.6	NS	8.3	11.8	NS
No. of epochs 40% ↓ MAP	1.2	0.3	NS	1.7	0.6	NS	2.3	2.9	NS	2.6	4.5	0.05
No. of epochs 50% ↓ MAP	0.2	0.0	NS	0.2	0.2	NS	0.4	0.3	NS	0.5	0.9	NS
Vasopressor dosage total‡	0.7	0.0	NS	1.3	4.7	NS	2.0	3.4	NS	3.0	5.1	0.01
Vasopressor infusion†	22 (0.6%)	0 (0%)	NS	37 (1.0%)	0 (0%)	NS	64 (1.8%)	1 (5.3%)	NS	153 (4.4%)	13 (18%)	<0.001
Furosemide or mannitol administration†	134 (3.7%)	0 (0%)	NS	129 (3.6%)	3 (23.1%)	0.01	135 (3.8%)	3 (16%)	0.03	204 (5.8%)	8 (11%)	NS
Urine < 0.5 ml · $kg^{-1} \cdot h^{-1}$†	2,018 (92%)	3 (100%)	NS	2,207 (89%)	6 (75%)	NS	2,208 (85%)	11 (73%)	NS	2,279 (84%)	46 (74%)	0.04
Urine, mean, ml · $kg^{-1} \cdot h^{-1}$	2.1	3.4	NS	1.8	1.2	NS	1.4	1.0	NS	1.4	1.2	NS

* Patients were risk stratified into four propensity score quartiles. Statistical analysis of intraoperative management characteristics was performed within each quartile. After collinearity diagnostics and correlation adjustment, a logistic regression full model fit was performed within each quartile. † Cases with missing data are excluded from the percentage calculation. ‡ The total number of vasopressor boluses was calculated as a number of "equipotent" doses: phenylephrine (100 μg), ephedrine (5 mg), and epinephrine (10 μg).

ARF = acute renal failure; MAP = mean arterial pressure; NS = not significant; SBP = systolic blood pressure.

found independent of comorbidities such as diabetes and hypertension.

The unweighted preoperative model, using the independent predictors listed in table 2, has a modest accuracy given the ROC AUC of 0.73. This is similar to the c statistics for predictive models of renal replacement therapy in cardiac surgery described by Chertow and Thakar, 0.76 and 0.81, respectively.[4,5] The revised cardiac risk index described by Lee has a similar c statistic of 0.77 and remains the foundation for cardiac risk optimization nearly a decade after its debut.[11] Anesthesiologists may have used the postoperative cardiac event risk factors described by Lee as a proxy for postoperative renal failure risk stratification, assuming that both complications are based on ischemic injury to sensitive organs. According to our data, only high-risk surgery is an overlapping risk factor. Patients with three or more risk factors had an ARF incidence of 4.3% and hazard ratio of 16. As a result, we recommend that patients with three or more risk factors be considered as high risk.

Prerenal acute tubular necrosis has long been thought to be a prominent cause of postoperative ARF.[34] As a result, anesthesiologists attempt to maintain renal blood flow by a variety of strategies, such as intravenous hydration, tight control of blood pressure, and administration of vasoactive substances. Intraoperative urine output is watched closely as one measure of success with this goal.

Our data offer hypothesis-generating insight into each of these classically held tenets. By using a large data set, we were able to compare the intraoperative management of patients with a similar *a priori* risk of ARF. Specific levels of intraoperative hypotension have been associated with in-hospital and 1-yr mortality.[18,35] This

Table 6. Acute Renal Failure Propensity Score Matched Comparison of Mortality

Risk Factor	Normal Postoperative Renal Function (n = 352)	Postoperative Acute Renal Failure (n = 118)	*P* Value	Hazard Ratio
Emergent operation	68 (19)	23 (20)	NS	
High-risk surgery*	111 (32)	37 (31)	NS	
Case duration, h	4.9	5.2	NS	
Mean body mass index, kg/m^2	28.9	33.1	0.001	
Mean age, yr	56	59	NS	
Coronary artery disease	59 (17)	21 (18)	NS	
History of congestive heart failure	6 (1.7)	2 (1.7)	NS	
Chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy	30 (8.5)	18 (15)	0.03	
Diabetes mellitus†	82 (23)	34 (30)	NS	
Peripheral vascular disease	47 (13)	16 (14)	NS	
Liver disease	41 (12)	14 (12)	NS	
All-cause 30-day mortality	9 (2.7)	17 (15)	<0.001	6.5 (2.7–15)
All-cause 60-day mortality	17 (5.1)	19 (17)	<0.001	3.8 (1.9–7.6)
All-cause 1-yr mortality	39 (15)	29 (31)	0.001	2.6 (1.5–4.4)

Data are presented as n (%) unless otherwise indicated. An acute renal failure propensity score was calculated for all patients based on seven independent predictors (age, emergent surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy). Acute renal failure patients were matched using a five-digit matching algorithm to patients who did not experience acute renal failure. This resulted in approximately a 3:1 match. Mortality was compared between the two groups using the Pearson chi-square test.

* Defined as intrathoracic, suprainguinal vascular, or involving large blood loss or fluid shifts. † Diabetes mellitus documented in medical record, with or without diet control, oral hypoglycemic therapy, or insulin therapy.

NS = not significant.

study did not find any specific amount or duration of hypotension that was associated with ARF. However, ARF patients were more likely to receive vasopressor boluses or a vasopressor infusion during the operation. Both of these measures were independent predictors of ARF. The increased vasopressor administration is likely due to aggressive management of hypotension by the anesthesiologist. Despite extensive research, the clinical community remains uncertain whether aggressive vasopressor use, including dopamine, is harmful or helpful to the perioperative patient.[36,37] Among quartile 2 (medium-risk) patients, the number of epochs with a MAP less than 40 mmHg was a statistically significant independent predictor. Patients who developed ARF experienced a mean of 0.14 epochs, whereas patients without ARF experienced only 0.04 epochs. However, we are reticent to extrapolate any clinical significance to this finding. These data may warrant further prospective, randomized trials to identify the optimal blood pressure management strategy. Several options warrant further study: additional fluid resuscitation, vigilant cessation of preoperative antihypertensive regimens, decreased inhalational anesthetic concentrations, and aggressive vasopressor administration.

Intraoperative oliguria, defined as urine output less than 0.5 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}, was not associated with renal failure. Evaluation of urine output as a continuous variable demonstrated that patients with ARF had a lower rate of output within all quartiles. However, the mean urine output was greater than 1.0 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} for all patient groups, with or without renal failure (table 4). Administration of mannitol or furosemide was an independent predictor of ARF in quartile 2 (medium-risk) patients (table 5). In addition, it was also an independent predictor of ARF in the comprehensive logistic regression full model fit which included all 15,102 patients and preoperative and intraoperative variables. Diuretic administration may have been a proxy for oliguria. It is impossible to comment on the predictive role of oliguria or diuretics, given that our study did not mandate a specific diuretic or fluid administration protocol. There are existing data demonstrating the deleterious effects of furosemide and mannitol when administered in attempts to prevent ARF.[38,39]

Acute renal failure without the need for renal replacement therapy is associated with increased mortality in critically ill patients and postoperative cardiac surgery patients.[28,40] Our data are the first to suggest a similar and clinically important relation between ARF and increased postoperative mortality in noncardiac surgery. Detailed propensity score matching of ARF patients to non-ARF cohorts created two patient groups that were similar in regard not only to the ARF preoperative predictors, but also to other comorbidities such as coronary artery disease and operative characteristics such as case duration (table 6). Body mass index and chronic obstructive pulmonary disease did demonstrate a significant difference between the two groups despite propensity score matching. This is possible despite detailed five-digit propensity score matching. Nevertheless, the observed 30-day, 60-day, and 1-yr all-cause mortality were markedly higher in the ARF group and are difficult to attribute solely to these differences (table 6).

This study has several limitations. First, the data were collected as part of the clinical care delivered. As a result, the data reflect the electronic medical record, and

no additional detail is available. There were no rigorous processes to validate the entry of data. Although all the preoperative variables have excellent data entry rates (table 1), documentation of urine output was less reliable. In many cases, it was likely due to a lack of an indwelling urinary catheter. However, we cannot assume this to be the case. In fact, the absence of urine output documentation may have been linked to operative or patient characteristics and probably did not occur at random. Although selections were standardized as part of the clinical information system (appendix), users were not specifically trained on the definitions of the clinical terms. Second, the data are from a single tertiary care center which may not serve as a representative sample of general surgery patients throughout the world. We were unable to address the role of intravenous hydration in ARF because several data elements involved in the quantification of resuscitation volume were not accurately collected in the medical record (duration of fasting, losses due to bowel prep, preoperative hydration). This is an important aspect of renal failure pathophysiology and cannot be included in our analysis. In addition, the mortality data are based on all-cause mortality, and no additional detail regarding the proximate cause of death are available for review. This may limit the ability to interpret the 1-yr mortality data.

The observational nature of the study did not allow us to establish clinical controls or randomization. Clinicians were not mandated to adhere to a clinical protocol or describe reasoning for their intraoperative management. Prospective, randomized, controlled trials are necessary to evaluate a causal relation between aggressive blood pressure management and ARF. In addition, we may be overstating the incidence of ARF by excluding patients that did not have a preoperative creatinine measured. Presumably, higher-risk patients were more likely to be subjected to preoperative testing, and therefore, included in our study. Finally, although the intraoperative analysis was able to demonstrate several independent predictors of ARF across quartiles, we were not able to demonstrate a reliable predictor within quartiles or a "dose–response" curve for any of the hemodynamic variables studied. This may be due to variant ARF etiologies or lack of statistical power after the limited number of events was further subdivided. The intraoperative analysis is also challenged by the absolute number of variables evaluated. Because there is limited existing experimental literature suggesting a specific blood pressure nadir to avoid ARF, it was necessary to evaluate absolute and relative hypotension in MAP and SBP across a wide range of derangements. Nevertheless, this broad strategy does increase the likelihood of a type I error across the intraoperative analysis because the likelihood of such an error is additive.

Despite the aforementioned limitations, the study offers insight into previously unstudied areas. By identifying the risk factors for ARF after noncardiac surgery, we are now able to provide patients and their clinicians with an estimation of their risk of ARF; this may be critical during surgical planning, counseling, and consenting processes. In addition, the identification of high-risk patients enables prospective, randomized trials of specific intraoperative management techniques and therapies. Furthermore, we have identified an independent relation between the perioperative administration of vasopressor or diuretics and ARF, a finding that will demand further investigation regarding causation. Finally, we have been able to demonstrate that ARF is independently associated with increased mortality in noncardiac surgery.

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Appendix: Preoperative Predictor Pick-list Choices

Preoperative Predictor	Pick-list Choices
Coronary artery disease	Class: 0—asymptomatic
	Class: 1—Sx with strenuous activity
	Class: 2—Sx with moderate activity
	Class: 3—Sx with 1 flight of stairs or 2 blocks
	Class: 4—Sx with any activity or at rest
	Unstable angina
	New onset
	Stable
	Treatment: PCI
	Treatment: CABG
	Treatment: β-blocker
	Treatment: CCB
	Treatment: nitrates
	Previous myocardial infarction
Cerebrovascular disease	Transient ischemic attacks
	Carotid/vertebral disease
	Cerebrovascular accident
	Stroke
Congestive heart failure	Currently active CHF
	Class 1: no limitation of physical activity
	Class 2: ordinary symptoms produce cardiac symptoms
	Class 3: less than ordinary activity produces symptoms
	Class 4: symptoms at rest
Chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy	Severity: moderate (chronic bronchodilator use)
	Severity: severe (oxygen use)
	Severity: very severe (oxygen dependent)
Dysrhythmia	Ventricular tachycardia
	Atrial fibrillation
	Atrial flutter
	Sick sinus
	Irregular rhythm
	Pacemaker
	Dysrhythmia followed by a hand-typed rhythm
	SVT
Diabetes mellitus necessitating oral hypoglycemic therapy without insulin therapy*	Type 2 diabetes
	Oral hypoglycemic therapy

(continued)

Appendix: Continued

Preoperative Predictor	Pick-list Choices
Diabetes mellitus necessitating insulin therapy with or without oral hypoglycemic therapy†	Type 1 diabetes Type 2 diabetes with insulin therapy
Hypertension	Duration: unknown Duration: <1 yr Duration: 1–5 yr Duration: >5 yr
Previous coronary revascularization	Coronary artery bypass graft PCI
Peripheral vascular occlusive disease	PVOD Carotid/vertebral disease Visceral arterial disease Aortic aneurysm
Sleep apnea	Treated by BiPAP/CPAP Treated by surgery Symptomatic, untreated
Smoking	Current smoker
Valvular heart disease	Aortic stenosis Mitral regurgitation Tricuspid regurgitation Aortic insufficiency Tricuspid stenosis Mitral stenosis
Pulmonary hypertension	Etiology: idiopathic Etiology: valvular Etiology: primary pulmonary hypertension Etiology: embolic Etiology: lung disease (COPD, fibrosis)
Liver disease	Hepatitis Hepatoma Cirrhosis Portal hypertension Fatty liver Jaundice

This appendix lists structured anesthesia history and physical pick-list choices as they appear in the clinical information system user interface. Only choices that were used to define a patient as possessing the predictor are listed. All acronyms are listed as they appear in the clinical information system pick-list.

* Must be combined with documentation of oral hypoglycemic therapy in the diabetes or medications section and absence of insulin therapy documentation.
† Must be combined with documentation of insulin therapy in the diabetes or medications section.

BiPAP = bilevel positive airway pressure; CABG = coronary artery bypass graft; CCB = calcium channel blocker; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; PCI = percutaneous coronary intervention; PVOD = peripheral vascular occlusive disease; SVT = supraventricular tachycardia; Sx = symptoms.