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Modest serum creatinine elevation affects adverse outcome after general surgery

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Background. Modest preoperative serum creatinine elevation (1.5 to 3.0 mg/dL) has been recently shown to be independently associated with morbidity and mortality after cardiac surgery. It is important to know if this association can be applied more broadly to general surgery cases.

Methods. Multivariable logistic regression analyses of 46 risk variables in 49,081 cases from the Veterans Affairs National Surgical Quality Improvement Program, undergoing major general surgery from 10/1/96 through 9/30/98.

Results. Thirty day mortality and several cardiac, respiratory, infectious and hemorrhagic morbidities were significantly ($P < 0.001$) higher in patients with a serum creatinine >1.5 mg/dL. With multivariable analysis, the adjusted odds ratio for mortality for patients with a serum creatinine of 1.5 to 3.0 mg/dL was 1.44 [95% confidence interval (95% CI) 1.22 to 1.71] and for creatinine >3.0 mg/dL was 1.93 (95% CI 1.51 to 2.46). The adjusted odds ratio for morbidity (one or more postoperative complications) for patients with a serum creatinine of 1.5 to 3.0 mg/dL was 1.18 (95% CI 1.06 to 1.32) and for creatinine >3.0 mg/dL was 1.19 (95% CI 0.99 to 1.43). Further stratification and recursive partitioning of creatinine levels revealed that a serum creatinine level >1.5 mg/dL was the approximate threshold for both increased morbidity and mortality.

Conclusions. Modest preoperative serum creatinine elevation (>1.5 mg/dL) is a significant predictor of risk-adjusted morbidity and mortality after general surgery. A preoperative serum creatinine of 1.5 mg/dL or higher is a readily available marker for potential adverse outcomes after general surgery.

More than 30 million patients undergo non-cardiac surgery annually in the United States. In patients undergoing general surgery, preoperative assessment seeks to determine if both inherent and modifiable risk factors for adverse operative outcomes are present. Preoperative risk stratification may improve clinical care, as well as the process of informed consent. In addition, identification of risk factors for adverse outcome can lead to better risk-adjustment models for examining variation in quality of care [1–4].

Most attention has focused on preoperative evaluation designed to detect risk for cardiac or pulmonary complications [5–12]. Such factors as surgical priority, type of surgery, and cardiopulmonary and functional status have served as the basis for assessing postoperative cardiac complication risk [5–12]. Analyses of several widely used existing methods to predict postoperative cardiac risk suggest a need for improved risk prediction models [10, 11]. For example, modest serum creatinine elevation (1.5 to 3.0 mg/dL) has been recently shown to be independently associated with cardiac complication risk, as well as other postoperative complications and mortality after cardiac surgery [13, 14]. Currently, at least 3 million Americans are estimated to have a serum creatinine of 1.7 mg/dL or higher [15, 16]. The association between modest creatinine elevations and poor outcomes from cardiac surgery may be related to the intensity of the operation. The present analysis was done to determine whether the findings that modest serum creatinine elevation is a predictor of adverse outcomes following cardiac surgery can be applied more broadly to general surgery. To test this hypothesis, we examined operative outcomes of 49,081 patients undergoing major general surgical procedures at 100 Department of Veterans Affairs (VA) medical centers across the United States.

METHODS

Study population

Based on the Continuous Improvement in Cardiac Surgery Program [17] (CICSP) and the National VA Surgical Risk Study [1–3], the VA National Surgical Quality Improvement Program (NSQIP) was established in 1994. For non-cardiac surgery, this is the first validated, com-

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prehensive, national outcome-based, and peer-controlled program for measuring and improving quality of surgical care [18]. NSQIP surgical nurse reviewers collect extensive preoperative, intraoperative, and postoperative data on patients undergoing non-cardiac operations at 123 VA medical centers across the United States. More detailed information about the NSQIP study has been published previously [1–3, 18].

All patients undergoing major general surgery operations in the NSQIP database between October 1, 1996 and September 30, 1998 were eligible for this study, as it contained the most recent data available [1]. In order to reduce confounding effects to increase poor outcome and to be consistent with NSQIP analytic practices, cases with a subsequent general surgical procedure performed within 30 days of the index procedure (3640 cases) were excluded. Of 62,231 cases identified, 13,129 (21%) were eliminated from further analysis because they lacked documentation of a preoperative serum creatinine level. An additional 21 cases were eliminated due to missing more than 50% of the preoperative risk variables. The final study population consisted of 49,081 cases.

End points and preoperative risk factors

Two major outcomes were analyzed in this study: (*1*) death due to any cause within 30 days of the operation (30-day mortality), and (*2*) the occurrence of one or more of 21 major morbidities within 30 days of the operation (30-day morbidity). The use of a binary outcome (none vs. one or more morbidities) to assess risk-adjusted morbidity has been validated previously [3, 19].

Prior to data analysis, cases were stratified by three levels of preoperative serum creatinine concentration: (*1*) less than 1.5 mg/dL (normal value for most hospital laboratories), (*2*) 1.5 to 3.0 mg/dL inclusive (consistent with mild to moderate renal insufficiency, usually asymptomatic), and (*3*) greater than 3.0 mg/dL (indicative of advanced renal insufficiency) [20, 21]. No data on creatinine clearance were obtained, and a more detailed analysis (such as use of the Cockcroft-Gault nomogram) of renal function was not available from the database.

There were 46 preoperative risk factors in the study data, details of which have been previously published [1]. Seven neurologically-based risks were combined into one variable indicating any neurologic dysfunction. Others were eliminated because of high numbers of missing (test not done) values (alkaline phosphatase, bilirubin, BUN, prothrombin time, partial thromboplastin time, SGOT), unreliability documented by NSQIP (redo operation), close relationship with wound infection (wound classification), and collinearity with creatinine (preoperative dialysis, acute renal failure). American Society of Anesthesiologists (ASA) class also was eliminated because it represents a composite ranking based on other preoperative risk factors also in initial study models. All risk variables included in the analyses were missing in less than 1.6% of cases, except for platelet count (3.8% missing) and serum albumin (38.5% missing). Cases missing either of these latter values were first categorized by their serum creatinine value, and then the respective median value for the missing lab result was assigned to that case. Since all other risk variables were missing in very few cases (<1.6%), these missing values were imputed to their respective reference group values.

Statistical analysis

To examine possible bias due to omitting cases with missing serum creatinine, comparisons of preoperative risk factors and outcomes were made between cases with a documented preoperative serum creatinine and cases missing creatinine, using either a chi-square test (categorical variables) or a nonparametric Kruskal-Wallis test (continuous variables) [22].

Statistical analyses were performed to compare differences in preoperative risks, mortality, and morbidity between the three groups of cases categorized by serum creatinine concentration. For risk model development, the data were randomly and evenly split into a learning set (for building a model) and test set (to test the model), one for each of the two outcomes. Employing stepwise selection, multivariate logistic regression [23] was performed on each learning dataset (for mortality and morbidity), allowing all preoperative risk variables other than serum creatinine, to be candidate variables since the number of outcomes was sufficiently large [24]. The models were then applied to the test data, where the risk of death and risk of morbidity were calculated for every case. C-indices [25] were calculated on test data for these models, and minus two log likelihood (−2LL) values were noted [26].

The three-level serum creatinine variable was subsequently added to each risk model (using test data) to evaluate the independent effect on mortality and morbidity. The logistic transformation of the mortality/morbidity risk estimate was used as an offset so that initial risk parameters would not be re-estimated, leaving the originally estimated probability of risk intact. The −2LL was noted and the likelihood ratio test [26] was used to assess improvement in the full models (with creatinine) over the reduced models (without creatinine), since it is the preferred method of assessing statistical significance of creatinine in a nested model [24–26]. C-indices also were calculated for each model.

To estimate the threshold value of preoperative serum creatinine that increases risk-adjusted mortality and morbidity, recursive partitioning was performed using CART software (Version 3.63; Salford Systems, San Diego, CA, USA) on all 49,081 cases, using observed outcomes [27, 28]. To confirm these thresholds, Cramer's V [29] tests and further regression analyses were performed. Cramer's V is a chi-square measure that reflects the strength of association between two variables, ranging in value from 0 (no association) to 1 (perfect association). Further regression analyses were done by additional stratification of creatinine when added to the reduced model, and the use of contrast statements [30] to directly compare groupings of creatinine concentration.

Since renal failure results in physiologic abnormalities that have been shown to predispose patients to postoperative complications of bleeding, infections, cardiac complications, and respiratory complications [15, 16], further analyses were performed for these individual morbidities. Separate models were built for individual morbidity outcomes of cardiac arrest, respiratory complications (reintubation or ventilator use for more than 48 hours postoperatively), infections (pneumonia, urinary tract infection, or deep wound infection), bleeding (requiring >4 units of packed red blood cells postoperatively), and systemic sepsis. Serum creatinine was added to each risk model with the logistic transformation of the risk estimate as an offset, to assess its independent effect. Further regression analyses were again utilized in an attempt to better understand the respective threshold effect of creatinine.

All analyses in this study other than recursive partitioning were performed using SAS (Version 6.12; SAS Institute Inc., Cary, NC, USA) software.

RESULTS

In evaluating differences between those cases with documented preoperative serum creatinine and those without creatinine documented (cases excluded from study), patient risk factors and outcomes were analyzed. Compared to the study population, excluded cases were significantly younger (58.9 vs. 61.5 years; $P < 0.001$) and less likely to have general anesthesia (69 vs. 77%). Excluded cases also had less frequent (all with $P < 0.005$) emergency surgery (8 vs. 15%), neurologic disorder (4 vs. 13%), history of severe COPD (11 vs. 15%), and history of congestive heart failure in the month prior to surgery (1 vs. 3%). Excluded cases also had significantly lower unadjusted mortality (1.8 vs. 4.4%) and morbidity (6.3 vs. 14.2%; $P < 0.001$) rates than included cases. Clearly, cases excluded due to a lack of preoperative serum creatinine were less severely ill than the cohort of cases included in our analysis.

In the study population, 87% of cases had a preoperative serum creatinine level less than 1.5 mg/dL, 10% between 1.5 and 3.0 mg/dL inclusively, and 3% greater than 3.0 mg/dL. Table 1 depicts selected preoperative patient risks and outcomes in cases stratified by preoperative serum creatinine concentration. Cases with higher preoperative serum creatinine were older, more often male, of non-white race and more often underwent emergent surgery. Cases with higher serum creatinine also presented more often with ascites, bleeding disorders, pneumonia, neurologic deficits, diabetes, dependent functional status, recent congestive heart failure, a history of COPD, corticosteroid use, and ventilator dependence, as well as an abnormal serum albumin, hematocrit, platelet count, white blood cell count and sodium concentrations, than those with a preoperative serum creatinine concentration of <1.5 mg/dL. Mortality and morbidity, as well as individual postoperative complications, were also more prevalent in cases with a preoperative serum creatinine concentration >1.5 mg/dL.

Multivariate modeling performed on the learning data set showed that three preoperative risk factors (ETOH use, steroid use, and transfusions of >4 units) out of 28 were not statistically significant for predicting 30-day mortality, and five risk factors (pneumonia, disseminated cancer, DNR order, ventilator dependent, and serum sodium) were not statistically significant for predicting 30-day morbidity. Table 2 shows the significant risk variables for both initial models and their respective odds ratio with a 95% confidence interval (95% CI).

The three-level serum creatinine variable was subsequently added to the mortality risk model and the morbidity risk model, using the logistic transformation of the previously derived respective risk estimates as an offset. In both models, creatinine was statistically significant ($P < 0.01$). The adjusted odds ratio for mortality for patients with a serum creatinine of 1.5 to 3.0 mg/dL was 1.44 (95% CI 1.22 to 1.71) and for creatinine >3.0 mg/dL was 1.93 (95% CI 1.51 to 2.46). The adjusted odds ratio for morbidity for patients with a serum creatinine of 1.5 to 3.0 mg/dL was 1.18 (95% CI 1.06 to 1.32) and for creatinine >3.0 mg/dL was 1.19 (95% CI 0.99 to 1.43). The c-index for the full models (with creatinine) was 0.906 for mortality and 0.765 for morbidity, which was marginally increased from the reduced models (0.905 and 0.764 for mortality and morbidity), although the difference was statistically significant for mortality. The likelihood ratio was significant for both mortality and morbidity ($P < 0.01$), indicating that the inclusion of serum creatinine added significantly to each respective original risk model.

To explore the threshold at which an increase in preoperative serum creatinine is associated with an increase in mortality and morbidity, additional analyses were conducted on the entire data. Recursive partition analysis, Cramer's V test, and further regression analyses each yielded a level of 1.5 mg/dL for morbidity, while the threshold levels yielded for mortality were 1.5, 1.7, and 1.4 mg/dL, respectively, for each method. Figure 1 depicts unadjusted mortality and morbidity odds ratios for 0.1 mg/dL increments of preoperative serum creatinine levels. A steeper slope is noted at approximately 1.6 to 1.7 mg/dL for mortality odds ratios, and rises significantly

Table 1. Characteristics of study patients grouped by pre-operative serum creatinine concentration

Variable	Pre-operative serum creatinine concentration *mg/dL* <1.5 (*N* = 42,822)	1.5–3.0 (*N* = 4945)	>3.0 (*N* = 1314)	*P* value
Patient risks				
Mean creatinine *mg/dL*	1.0	1.9	6.0	<0.001
Median creatinine *mg/dL*	1.0	1.7	5.1	<0.001
Mean age *years*	60.7	68.4	64.1	<0.001
Non-white race %	28	31	44	0.001
Male gender %	96	99	98	0.001
ASA class III or IV %	9	28	51	0.001
Ascites %	1	4	5	0.001
Bleeding disorder %	2	4	8	0.001
Chronic dialysis therapy %	<1	1	49	0.001
Congestive heart failure[a] %	2	9	14	0.001
Corticosteroid use %	3	5	6	0.001
Functionally dependent %	11	24	28	0.001
Diabetes mellitus %	15	27	31	0.001
Do not resuscitate order %	1	3	5	0.001
Dyspnea %	15	26	27	0.001
Emergency surgery %	13	28	36	0.001
Neurologic deficit %	11	23	27	0.001
Pneumonia %	1	4	7	0.001
Severe COPD[b] history %	14	21	18	0.001
Smoker within 1 year %	37	28	30	0.001
Ventilator dependent %	1	5	10	0.001
Weight loss >10%/6 months %	7	7	8	0.009
>2 alcoholic drinks/day[c] %	12	8	8	0.001
Serum albumin <3.5 %	34	54	73	0.001
Hematocrit <35 or >45 %	42	53	73	<0.001
Platelets <150 or >400,000 %	19	26	31	<0.001
White blood cells <4000 or >10,000 %	17	41	57	<0.001
Serum sodium <135 %	10	15	20	0.001
Post-operative outcomes				
30-day mortality %	3.1	11.4	19.9	<0.001
30-day morbidity %	12.4	25.2	31.0	<0.001
Median postop LOS[d] *days*	5.0	7.0	9.0	<0.001
Cardiac arrest %	0.8	2.5	4.5	0.001
On ventilator >48 hours %	2.0	7.3	11.0	0.001
Re-intubation %	1.7	4.3	4.6	0.001
Pulmonary embolism %	0.1	0.2	0.1	0.836
>4 units blood transfused %	0.5	1.4	3.0	0.001
Superficial infection %	2.5	3.0	2.1	0.083
Sepsis %	1.2	3.6	6.5	0.001
Pneumonia %	2.5	4.9	5.7	0.001

[a] Congestive heart failure (CHF) in the month before surgery
[b] COPD, chronic obstructive pulmonary disease
[c] >2 alcoholic drinks/day for 2 weeks before surgery
[d] LOS, length of stay

after 1.9 mg/dL, while the morbidity odds ratio curve rises at a much slower rate after an increase in the slope between 1.3 to 1.4 and 1.6 to 1.7 mg/dL.

To assess whether modest elevation of serum creatinine was associated with specific postoperative complications previously reported with renal insufficiency, multivariate models were tested for risk of hemorrhage, cardiac arrest, infection, pulmonary complication, and sepsis. Serum creatinine added significantly to the preoperative risk models for each of the five individual outcomes except for infections. As with overall morbidity and mortality, regression analyses of further stratification of creatinine levels were employed to assess the approximate threshold of serum creatinine that changes its effect on individual morbidities (Table 3). The respective thresholds found were approximately 1.5 mg/dL for respiratory complications, 2.0 mg/dL for sepsis, 2.5 mg/dL for cardiac arrest and 3.0 mg/dL for bleeding complications.

Because of the potential concern that including dialysis patients in this analysis could bias results, all analyses were repeated after eliminating 729 cases reporting preoperative dialysis therapy. While *P* values and odds ratios were not identical, the results were consistent throughout all analyses, and the approximate threshold values of 1.5 mg/dL for both mortality and morbidity remained unchanged.

DISCUSSION

The results of the present study suggest that modest preoperative serum creatinine elevation (1.5 to 3.0 mg/dL)

Table 2. Significant risk variables with adjusted odds ratio for mortality or morbidity, without serum creatinine

Risk variable	Adjusted odds ratio (95% confidence interval)	
	Mortality model	Morbidity model
Age	1.046 (1.039, 1.053)	1.023 (1.020, 1.027)
Female gender	0.410 (0.213, 0.791)	0.698 (0.540, 0.901)
Emergency surgery	2.331 (1.992, 2.729)	1.928 (1.746, 2.128)
Severe COPD[a] history	1.308 (1.104, 1.550)	1.219 (1.097, 1.354)
CHF in month before surgery	1.400 (1.102, 1.778)	1.322 (1.111, 1.574)
Dependent functional status	1.436 (1.219, 1.693)	1.361 (1.225, 1.512)
Ascites	3.542 (2.660, 4.716)	1.467 (1.155, 1.863)
Corticosteroid use	NS ($P > 0.05$)	1.305 (1.088, 1.565)
Neurologic deficit	1.613 (1.371, 1.896)	1.305 (1.175, 1.449)
>2 alcoholic drinks/day for 2 weeks	NS ($P > 0.05$)	1.147 (1.016, 1.295)
Bleeding disorder	1.492 (1.124, 1.981)	1.325 (1.066, 1.647)
Anesthesia type		
General	reference	reference
Epidural/spinal	0.581 (0.458, 0.737)	0.320 (0.279, 0.367)
Other	0.081 (0.020, 0.329)	0.113 (0.070, 0.184)
Pneumonia	1.470 (1.127, 1.916)	NS ($P > 0.05$)
Disseminated cancer	3.137 (2.463, 3.994)	NS ($P > 0.05$)
"Do not resuscitate" order	2.451 (1.857, 3.236)	NS ($P > 0.05$)
Dyspnea	1.220 (1.030, 1.444)	1.300 (1.173, 1.440)
>4 units RBC pre-operatively	NS ($P > 0.05$)	1.618 (1.320, 1.983)
Ventilator dependent	1.730 (1.325, 2.260)	NS ($P > 0.05$)
Weight loss >10% last 6 months	1.648 (1.360, 1.997)	1.368 (1.206, 1.551)
Hematocrit *%*		
Normal (35–45)	reference	reference
Mildly low (30–35)	1.462 (1.215, 1.759)	1.303 (1.168, 1.454)
Severely low (<30)	1.708 (1.398, 2.086)	1.380 (1.209, 1.575)
Mildly high (45–50)	0.969 (0.725, 1.296)	0.788 (0.694, 0.895)
Severely high (>50)	1.260 (0.755, 2.104)	0.812 (0.622, 1.061)
Platelet count *1000/mm³*		
Normal (150–400)	reference	reference
Mildly low (50–150)	1.591 (1.315, 1.925)	0.921 (0.812, 1.045)
Severely low (<50)	5.512 (2.990, 10.161)	0.971 (0.574, 1.642)
Mildly high (400–600)	0.774 (0.592, 1.011)	1.070 (0.919, 1.247)
Severely high (>600)	0.549 (0.281, 1.072)	0.567 (0.380, 0.845)
White blood cell count *1000/mm³*		
Normal (4–10)	reference	reference
Mildly low (2–4)	1.188 (0.804, 1.756)	1.192 (0.949, 1.496)
Severely low (<2)	1.966 (0.682, 5.666)	1.163 (0.531, 2.544)
Mildly high (10–15)	1.227 (1.024, 1.471)	1.068 (0.962, 1.185)
Severely high (>15)	1.823 (1.492, 2.227)	1.397 (1.225, 1.594)
Serum sodium *mmol/L*		
Normal (≥135)	reference	NS ($P > 0.05$)
Mildly abnormal (130–135)	1.326 (1.103, 1.594)	
Severely abnormal (<130)	1.404 (0.984, 2.001)	
Serum albumin *g/dL*		
Normal (>3.5)	reference	reference
Mildly abnormal (3.0–3.5)	1.733 (1.413, 2.124)	1.420 (1.275, 1.582)
Severely abnormal (≤3.0)	2.836 (2.343, 3.433)	1.698 (1.513, 1.906)

[a] COPD is chronic obstructive pulmonary disease

is significantly and independently associated with increased morbidity and mortality after general surgery. These study results also provide new information as to threshold levels of preoperative serum creatinine that are associated with adverse operative outcome. Three statistical analytic methods (recursive partitioning, Cramer's V, and further regression analyses) all yielded a threshold serum creatinine value of approximately 1.5 mg/dL for excess morbidity and mortality. Moreover, we found a "hierarchy of susceptibility" as to the magnitude of elevation of preoperative serum creatinine and type of postoperative complication. For example, respiratory complications appeared to occur with only slight elevation of serum creatinine while values >3.0 mg/dL were required for an independent association with postoperative hemorrhage to be demonstrated.

Our results are consistent with studies from smaller, more selected patient populations. Browner et al found that a reduced estimated creatinine clearance was a significant (odds ratio 6.8; 95% CI 2.8 to 16.0), independent predictor of postoperative mortality in 474 male veterans undergoing non-cardiac surgery [31]. An analysis of nearly 3000 patients undergoing non-cardiac surgery found that a preoperative serum creatinine of >2.0 mg/dL was the

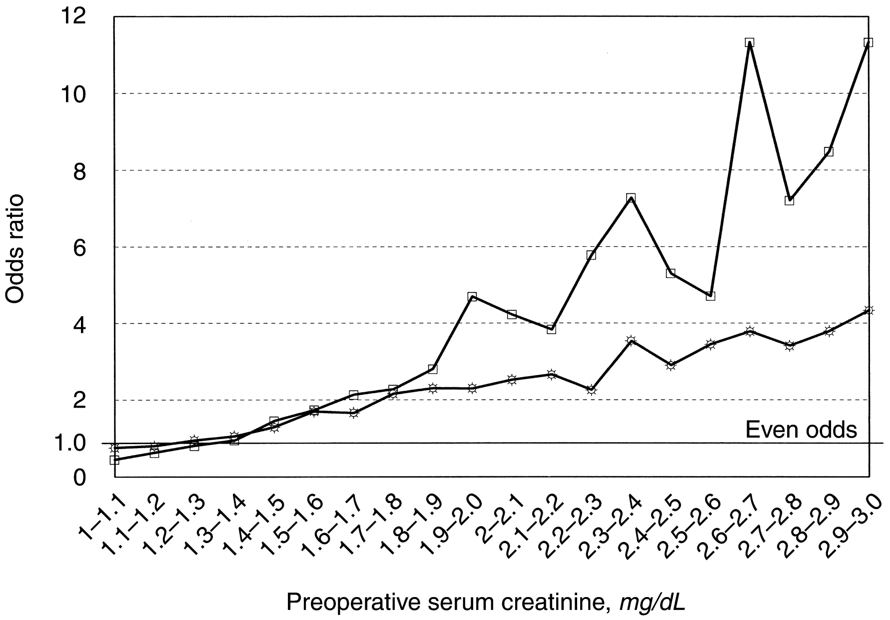

Fig. 1. Mortality (□) and morbidity (○) odds ratios for serum creatinine levels between 1.0 mg/dL and 3.0 mg/dL.

Table 3. Multivariate risk-adjusted odds ratios (95% confidence interval) for preoperative serum creatinine concentrations relative to serum creatinine <1.5 mg/dL, for selected post-operative morbidities

	Post-operative morbidity			
Pre-operative serum creatinine	Sepsis	Respiratory complications	Cardiac arrest	Hemorrhage
1.5–2.0 mg/dL	1.14 (0.90, 1.44)	1.42 (1.22, 1.64)	1.00 (0.76, 1.32)	1.34 (0.94, 1.91)
2.0–2.5 mg/dL	1.62 (1.18, 2.22)	1.39 (1.11, 1.75)	1.28 (0.87, 1.88)	1.57 (0.97, 2.54)
2.5–3.0 mg/dL	2.14 (1.53, 2.99)	1.60 (1.23, 2.07)	1.52 (1.01, 2.29)	1.18 (0.63, 2.21)
>3.0 mg/dL	1.83 (1.43, 2.33)	1.58 (1.31, 1.89)	1.56 (1.16, 2.08)	1.71 (1.20, 2.45)

single variable associated with the greatest likelihood of a major cardiac complication [5]. In two recent studies, we have found that a serum creatinine between 1.5 and 3.0 mg/dL was significantly and independently associated with excess mortality and morbidity, similar to those observed in the present study, after coronary artery bypass grafting and other types of cardiac surgery [13, 14].

We should note some of the limitations of our analyses. First, our results may not be generalizable to non-VA populations, particularly women. Also, our results are exclusively observational in nature. This observational nature of our study, however, provides a more representative view of the population undergoing major surgical procedures within the VA population than reported with other study designs, such as randomized controlled trials in which patients are often highly selected.

Second, the use of a discretionary definition to categorize the presence and degree of renal failure may have resulted in the inclusion of some patients with a serum creatinine concentration less than 1.5 mg/dL that in fact had mild to moderate renal failure. Dependent on the number of cases for which this may hold true, the magnitude of our observed association of mild renal insufficiency with adverse operative outcome could be underestimated. Unfortunately, weight information was not available so we could not more precisely estimate glomerular filtration rate by published formulas. Also, our results do not provide any pathophysiologic insights as to why modest creatinine elevation is independently associated with operative mortality and several postoperative morbidities. It is tempting to speculate that such factors known to be associated with impaired renal function, such as decreased excretion of volume loads and pharmacologic agents and impaired platelet function, could contribute to enhanced respiratory complications and bleeding respectively. Further studies are required to ascertain the precise mechanism(s) underlying the association of renal dysfunction and operative mortality and morbidity.

Finally, the inclusion criteria of having a preoperative baseline serum creatinine concentration available appears to have resulted in selection of a higher risk population for study. Approximately 21% of eligible patients, excluded for no baseline serum creatinine determination, demonstrated preoperative co-morbidity as well as postoperative morbidity and mortality that were significantly lower than the included patients. Also, the percentage of our patients in higher risk categories appears to be significantly higher than in other studies [11]. Thus, our results may not be applicable to all VA patients undergoing general surgery.

This study supplies evidence to support a significant relationship between modest serum creatinine elevations and postoperative complications and death. First, risk-adjusted mortality and morbidity rates in patients with a serum creatinine between 1.5 and 3.0 mg/dL (10.1 and 21.6%, respectively) were substantially higher than in patients with a creatinine <1.5 mg/dL (3.5 and 12.1%, respectively). Second, we found a dose response relationship in which higher preoperative serum creatinine concentrations were associated with greater risk of 30-day mortality, with statistically significant differences noted between the two higher creatinine groups (1.5 to 3.0 mg/dL and >3.0 mg/dL, $P = 0.04$). To our knowledge, this is the first documentation of such a dose-response relationship for patients undergoing general surgery. Third, we observed specificity of association of creatinine levels with specific morbidities that are known to be associated with renal insufficiency (sepsis, respiratory complications, cardiac arrest, and hemorrhage).

A single measure of serum creatinine does not distinguish between reversible, hemodynamically mediated creatinine elevation and chronic, intrinsic renal disease [20, 21], which could potentially affect our conclusions in either direction. Moreover, as demonstrated in Table 3, there appears to be a differential sensitivity for renal failure to be associated with selected postoperative morbidities. For example, only moderate elevations of serum creatinine (1.5 to 2.0 mg/dL) are independently associated with respiratory complications, while more advanced renal failure (serum creatinine >3.0 mg/dL) was required to demonstrate an independent association with postoperative hemorrhage.

In summary, our results demonstrate that modest elevations of serum creatinine concentrations (>1.5 mg/dL) identifies a cohort of general surgery patients at increased risk of postoperative death and complications in a VA patient population. Efforts to measure and improve the quality of postoperative care should consider including modest elevations of serum creatinine in risk-adjusted models. Prospective studies to examine strategies of either enhanced clinical surveillance or of specific interventions for patients with modest creatinine elevations could potentially improve outcome in these patients.

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