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Small increases in serum creatinine are associated with prolonged ICU stay and increased hospital mortality in critically ill patients with cancer

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Abstract

Purpose—Declining kidney function has been associated with adverse hospital outcome in cancer patients. ICU literature suggests that small changes in serum creatinine are associated with poor outcome. We hypothesized that reductions in renal function previously considered trivial would predict a poor outcome in critically ill patients with malignant disease. We evaluated the effects on hospital mortality and ICU length of stay of small changes in creatinine following admission to the intensive care unit.

Methods—We conducted a retrospective cohort study utilizing clinical, laboratory and pharmacy data collected from 3,795 patients admitted to the University of Texas M.D. Anderson Cancer Center's Intensive Care Unit. We conducted univariate and multivariate regression analysis to determine those factors associated with adverse ICU and hospital outcome.

Results—Increases in creatinine as small as 10% (0.2 mg/dl) were associated with prolonged ICU stay (5 days vs 6.6 days, $p<0.001$) and increased mortality (14.6% vs 25.5%, $p<0.0001$).

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Conflict of Interest None of the authors has any significant conflict of interest to report.

Patients with a 25% rise in creatinine during the first 72 h of ICU admission were twice as likely to die in the hospital (14.3% vs 30.1%, $p<0.001$). RIFLE criteria were accurate predictors of outcome, though they missed much of the risk of even smaller increases in creatinine.

Conclusions—Even small rises in serum creatinine following admission to the ICU are associated with increased morbidity and mortality in oncologic patients. The poor outcome in those with rising creatinine could not be explained by severity of illness or other risk factors. These small changes in creatinine may not be trivial, and should be regarded as evidence of a decline in an individual patient's condition.

Keywords

Acute kidney injury; Cancer; Critical care; Creatinine; Outcome

Introduction

Acute kidney injury (AKI) is a major cause of morbidity and mortality in hospitalized patients [1], particularly in the critically ill [2,3]. For patients admitted to the ICU, the incidence of AKI is reportedly as high as 25%, with a hospital mortality of 86% [4]. Classically published definitions of AKI include (1) the need for dialysis, (2) a doubling of serum creatinine, (3) a 50% rise in serum creatinine, or (4) a prolonged period of oliguria. There is a growing consensus that even small changes in serum creatinine adversely affect outcome in hospitalized patients [5–7] or following surgical procedures [8–10]. It has been well documented that acute kidney injury requiring dialysis is associated with poor outcomes in patients with malignancy [11–16]. Newer definitions of acute kidney injury include smaller changes in creatinine than were previously considered significant.[17,18] However, the prognostic implication of minor increases in serum creatinine in critically ill patients with cancer remains uncertain. As is the case for other critically ill populations, in patients with malignancy it is likely that small changes in serum creatinine reflect a reduction in glomerular filtration rate, and thus renal function per se. This may actually be more serious for cancer patients, who frequently receive multiple nephrotoxic drugs, yet rely heavily on their kidneys' ability to clear toxins from their blood compartment [19]. Therefore, we hypothesized that small changes in serum creatinine would be associated with adverse outcome in these patients.

Methods

We developed a clinical research database to analyze demographic, clinical, and laboratory variables for all patients admitted to the ICU at The University of Texas M.D. Anderson Cancer Center. In order to include only those patients who were critically ill, we excluded patients who remained in the ICU for less than 24 h, and in order to avoid survival bias we included first time admissions only. This study was approved by the Institutional Review Board, and a waiver of informed consent was obtained before the database was queried.

Study population

The analysis population is from the 53-bed medical and surgical oncology intensive care unit at the University of Texas M. D. Anderson Cancer Center. All patients admitted to the ICU between September 1, 2001 and December 31, 2003 and remaining there at least 24 h were considered for this study.

Data collection

The study database was populated with demographic, administrative, laboratory, pharmacologic, and other clinical data, integrating these from independent data sources.

(See Table 1) Due to limitations of the electronic records at the time, details of physical examinations and therefore Glasgow Coma Score values and individual vital signs were not included in the database. All pharmacy dispensed medications were classified as potential nephrotoxins by class of agent. We defined five categories of nephrotoxic agent: antibiotic, non-steroidal anti-inflammatory drug, angiotensin-converting enzyme (ACE) inhibitor, diuretic, or chemotherapeutic agent.

Analysis

For the purposes of this analysis, the lowest creatinine value within 48 h after ICU admission was used as the baseline measurement, and the subsequent peak creatinine within 10 days was used as the maximum. Need for dialysis was determined by the consulting nephrologist. The severity of illness score developed in our ICU was modified from the Sequential Organ Failure Assessment (SOFA) score[20], has been reported elsewhere and includes data relating to cardiovascular, respiratory, hematologic, hepatic and renal function[21].

Statistics

The statistical analyses were performed using the Statistical Package for Social Sciences, SPSS 12 for Windows (SPSS Inc, Chicago, IL, USA) and STATA 8 (Statacorp, College Station, TX USA). Figures and graphs were constructed using GraphPad Prism 5 for Windows. Continuous variables are described as mean (SD) where appropriate. Categorical variables are described as proportions. Serum creatinine value was treated as either a continuous variable or an ordinal categorical variable depending on the analysis performed. Following basic descriptive analysis and univariate assessment, logistic regression was used to analyze the relation between changes in creatinine and hospital mortality, and for calculation of the odds ratios for increased risk of dying. Although stepwise analysis was undertaken, demographic variables such as age and gender were forced into the model because of their known clinical relevance for outcome.

Results

A total of 6,372 patients were admitted to the ICU during the study period. Excluding readmissions and patients staying less than 24 h, the study population comprised 3,795 medical and surgical patients. There were eight patients who did not have a serum creatinine checked within 3 days of ICU admission and, though all survived, these patients were excluded from the analysis. Despite the uniform diagnosis of malignancy and critical illness in this population, overall hospital mortality for the group was only 17.2% (653/3,787). Overall, the mean serum creatinine level on admission to the ICU was 0.9±0.6 mg/dl. The baseline creatinine was higher in patients who died (1.2±0.9 mg/dl) than in those who survived (0.9±0.5 mg/dl), as was peak creatinine during the first week following ICU admission (1.9±1.4 mg/dl for those who died vs 1.1±0.9 mg/dl for survivors). (See Table 2) Patients whose creatinine did not rise more than 0.1 mg/dl after admission had a mean (SD) length of ICU stay of 5 days (8.6 days). Those with any increase in creatinine of 0.2 mg/dl or more during the first 3 days of ICU admission remained in the ICU for a significantly longer period (Fig. 1).

Hospital mortality was significantly higher in those who experienced increases in creatinine. Patients with an increase in creatinine as little as 10% above the admission value (with a minimum rise of 0.2 mg/dl) experienced double the hospital mortality compared to those without a rise in creatinine. Those with an increase of more than 50% on the day after ICU admission had a mortality rate of 44%, and were three times more likely to die than those

without an increase. (See Fig. 2) These changes in mortality began with the earliest changes in serum creatinine and appeared additive the higher the creatinine rose (Figures 3 and 4).

Confirming the effect on outcome of an early increase in creatinine during the first 24 h after ICU admission, we found that patients whose creatinine increased by at least 25% within 3 days of ICU admission stayed longer in the ICU (7.8 days vs 4.8 days, $p<0.0001$) and had significantly higher hospital mortality (30.1% vs 14.3%, OR 2.6, $p<0.0001$) than patients who did not experience this increase in creatinine. These findings were consistent in subgroups defined by gender, age, and type of admission (medical and surgical). Medical patients were more likely than surgical patients to experience a rise in creatinine of 25% (OR=1.3, 95% CI 1.08–1.55).

A recently described classification system for AKI makes use of the Risk, Injury, and Failure; Loss and End-stage kidney disease (RIFLE) nomenclature. [17,22] We categorized the degree of elevation in serum creatinine using the RIFLE definitions of Risk, Injury and Failure. In this patient population, 2,962 subjects had creatinine values that remained in the "normal" range. "Risk" occurred in 474 patients, while 184 and 167 experienced "Injury" and "Failure", respectively. Hospital mortality rose steadily with increasing RIFLE classification (See Fig. 5). ICU stay was also significantly prolonged.

We next examined these effects in multivariate analysis, attempting to control for other potential factors that might affect mortality and ICU stay. Factors examined included patient age, gender, severity of illness at time of ICU admission, use of diuretics, number and type of nephrotoxins dispensed on day of ICU admission, need for mechanical ventilation, and dialysis during ICU stay. Other than age and gender, all of these variables remained highly significantly associated with increased mortality in our multivariate model, and were therefore independently predictive of outcome. Importantly, the deleterious effect of even a small change in creatinine remained significant when controlling for each of these other factors. Corrected for the above factors, a 10% increase in creatinine (average increase only 0.2 mg/dl) was associated with a 35% increase in hospital mortality (See Table 3).

In order to explore the effect of a sustained rise in serum creatinine, we compared patients who experienced a rise in creatinine of 25% for 48 h or longer with those who did not. Mortality rates were 36% and 15% respectively, $p<0.0001$.

Discussion

This study examines the deleterious effects of small changes in serum creatinine following admission to the intensive care unit of a cancer hospital. Using lowest creatinine early during ICU admission as a baseline, patients with any rise in creatinine greater than 0.1 mg/dl had an increase in both hospital mortality and ICU length of stay. In this population, the higher their rise in creatinine, the longer was the ICU stay and the higher the mortality. This finding confirms the work of others who have reported similar adverse outcomes in patients with only a small rise in serum creatinine, but represents the first report of such an effect in a large series of cancer patients. This finding holds whether considering absolute changes in creatinine or when utilizing an ordinal approach such as that employed by the RIFLE or AKIN criteria. We believe that acutely, changes in creatinine may be more accurate than calculated estimates of creatinine clearance (Cockroft Gault) or glomerular filtration rate (MDRD equation), as these equations were developed for drug dose adjustment in patients with chronic kidney disease, and they have not been validated in patients whose renal function is not at steady state. Any acute change in serum creatinine must reflect a reduction in GFR, and thus changes in this parameter either continuously recorded (absolute or percent

change in creatinine) or in ordinal fashion (RIFLE) better represent the changing state of acute kidney function.

While many studies have shown a relationship between the need for acute dialysis and mortality, relatively few have demonstrated the association of smaller changes in creatinine and deleterious outcomes. Those that have examined this have done so in specialized populations such as post CABG or abdominal surgery. This is the largest study to analyze the outcomes of patients with neoplastic disorders, and it demonstrates that the increased mortality in patients with small increases in creatinine is likely independent of severity of illness, dialysis rate and presence of other measured co-morbidities.

As a retrospective study, there are many limitations of the current and conclusions must be tempered. Using large databases such as these may introduce unknown biases into the analysis. We still lack firm data on patient's daily vital signs, as these were not recorded in the electronic records at the time this database was established. The patient population is not homogenous and included patients who had multiple sites and types of malignancy. Though all subjects carry a diagnosis of cancer, we are unable to assess outcomes based on type or duration of malignancy. Additionally, there are likely multiple co-morbid conditions present which our modified severity of illness scale (M-SOFA) did not capture. Conditions such as diabetes and hypertension have significant effects on outcome in patients with chronic kidney disease and are not included in the current analysis. Whether such medical conditions exert a similar effect in acute kidney injury is less clear. It is interesting that baseline creatinine was not found to be significantly associated with hospital mortality in this study, as is it generally considered that patients with chronic kidney disease have an overall worsened prognosis when critically ill, but a better prognosis with acute creatinine rise.

While there is still no generally accepted definition of acute kidney injury, consensus is being attempted, and data such as those presented in the current study potentially support even more inclusive limits than those currently suggested.

Conclusion

We have shown that in this population of critically ill patients with cancer, small changes in serum creatinine are independently predictive of adverse outcome. Whether such small changes in creatinine are also associated with poor outcome in a wider population is unclear, but we believe that traditional suggested definitions of AKI may not be sufficiently inclusive for all critically ill populations, and that newer, more inclusive definitions, may be more appropriate. Independent validation in additional populations may be required before a general consensus on AKI definition may be reached.

Acknowledgments

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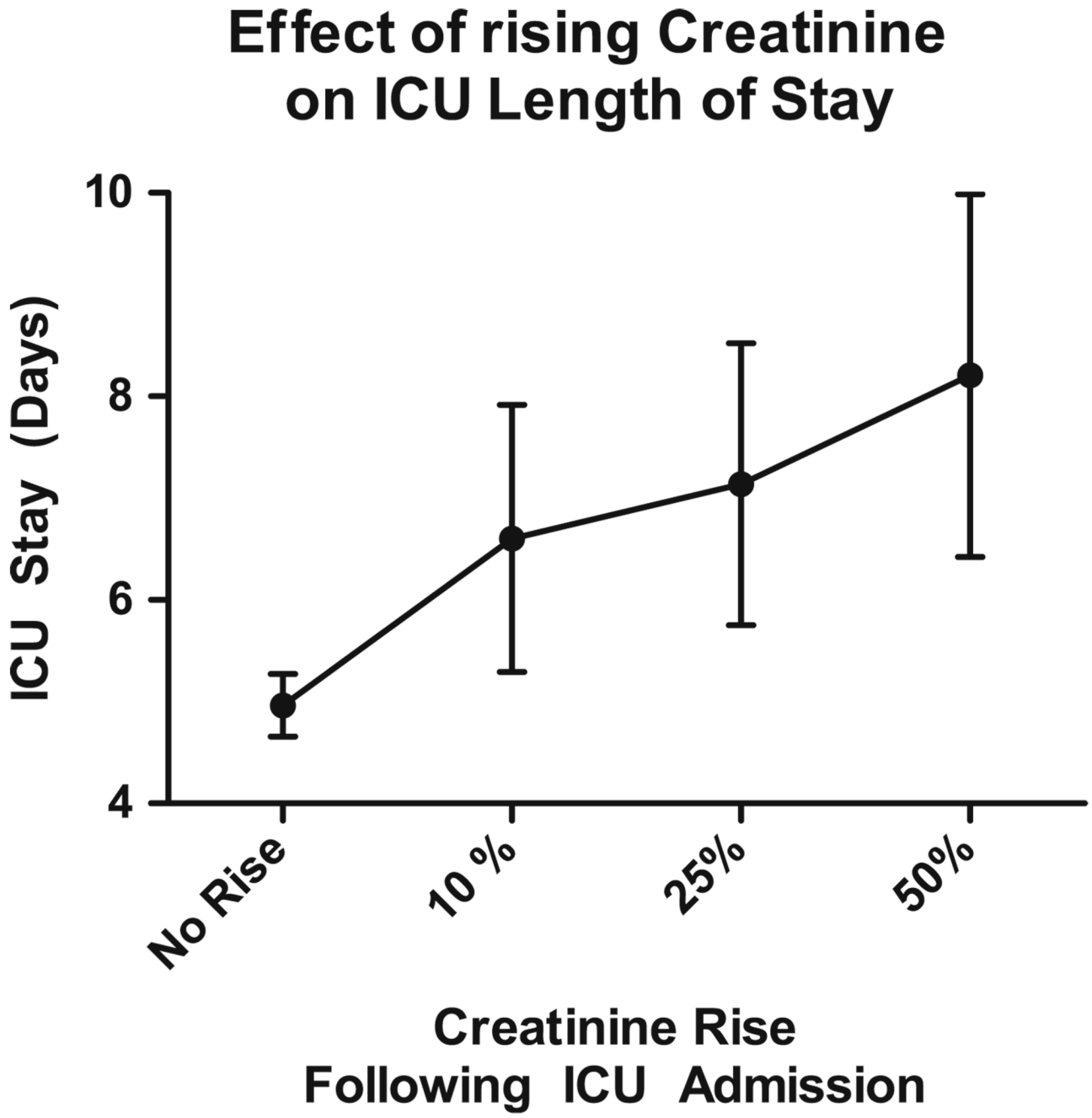

Fig. 1.
Effect of rising creatinine on ICU length of stay

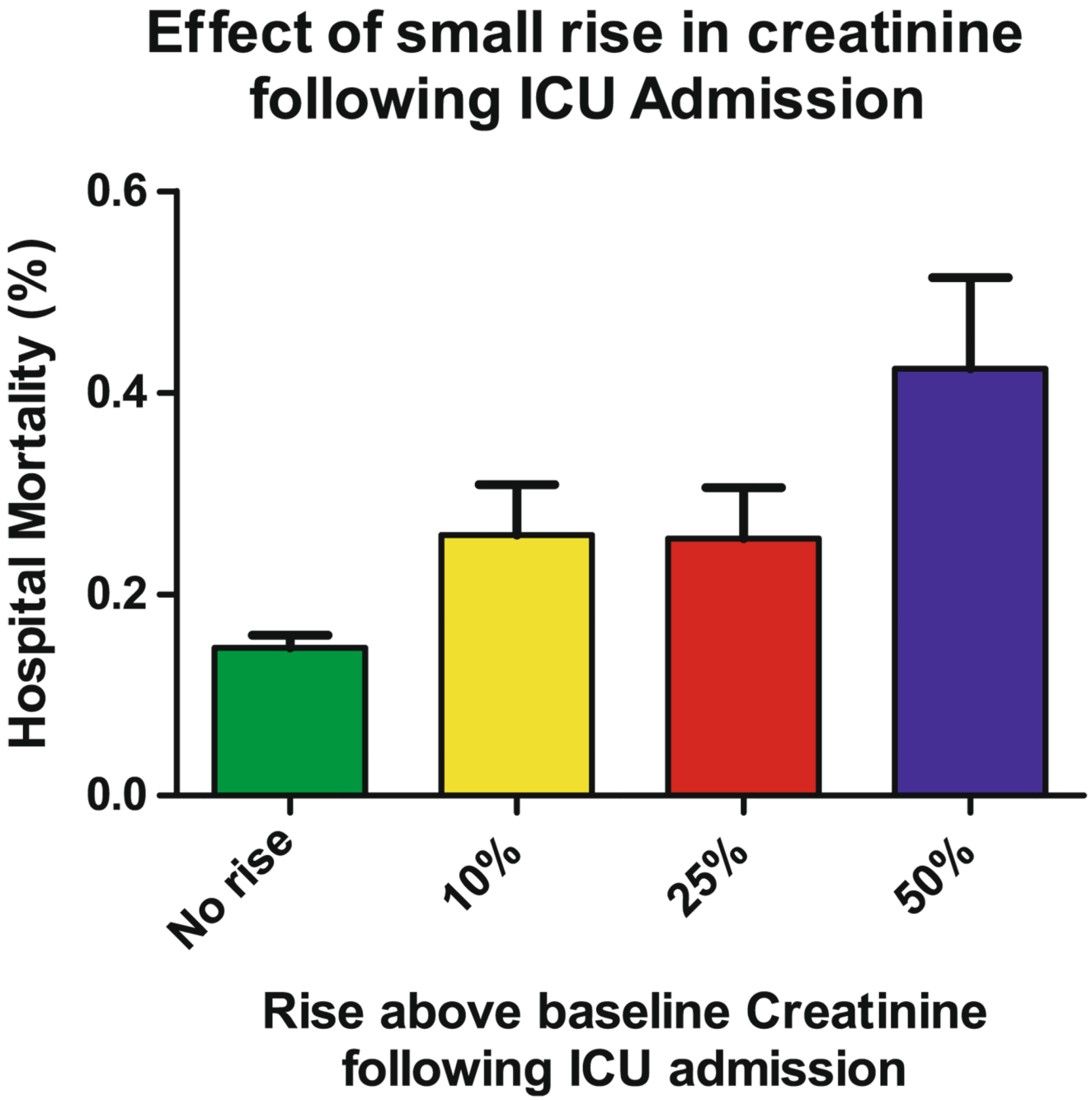

Fig. 2.
Effect of small rise in creatinine following ICU admission

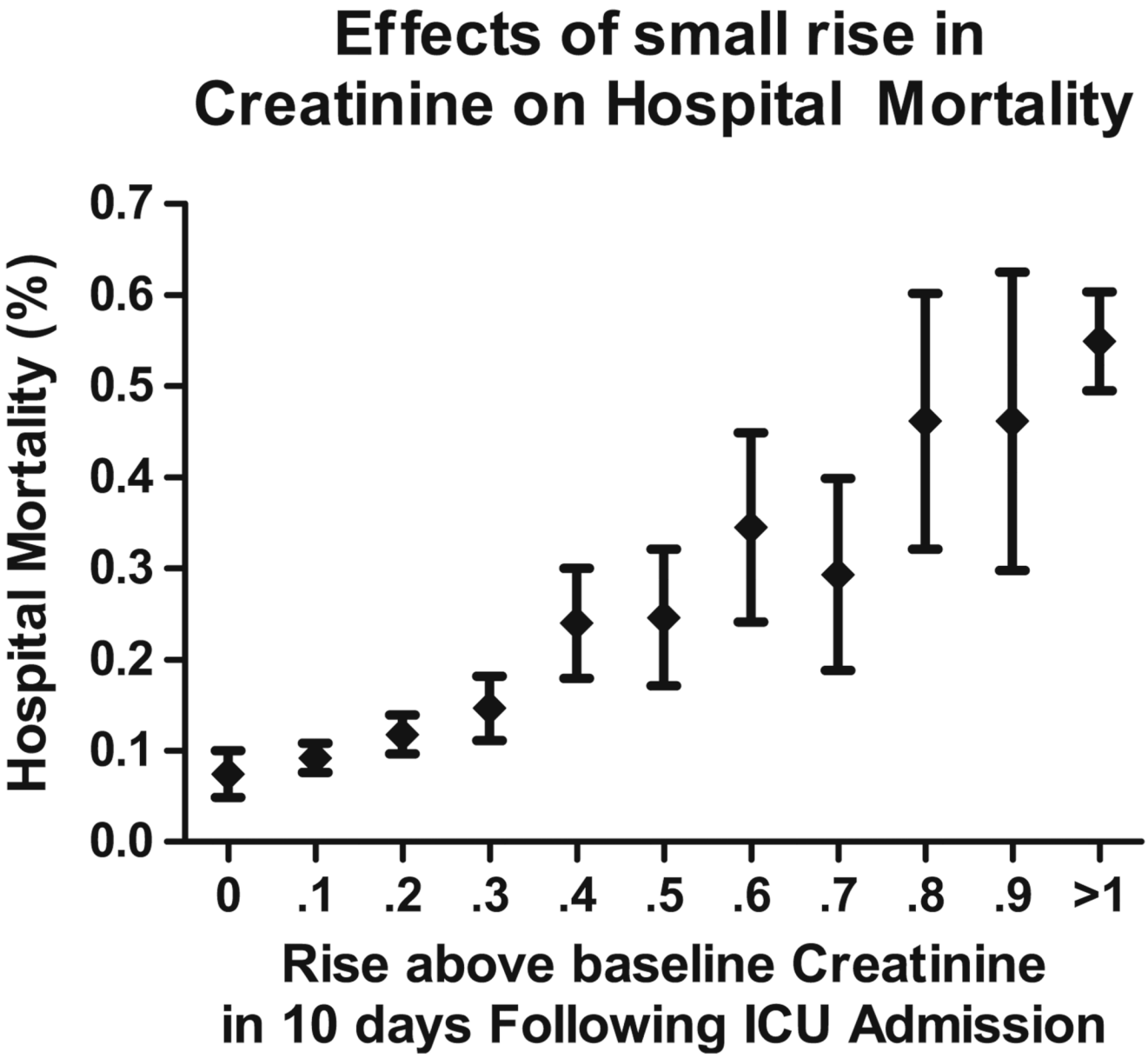

Fig. 3.
Effects of small rise in creatinine on hospital mortality

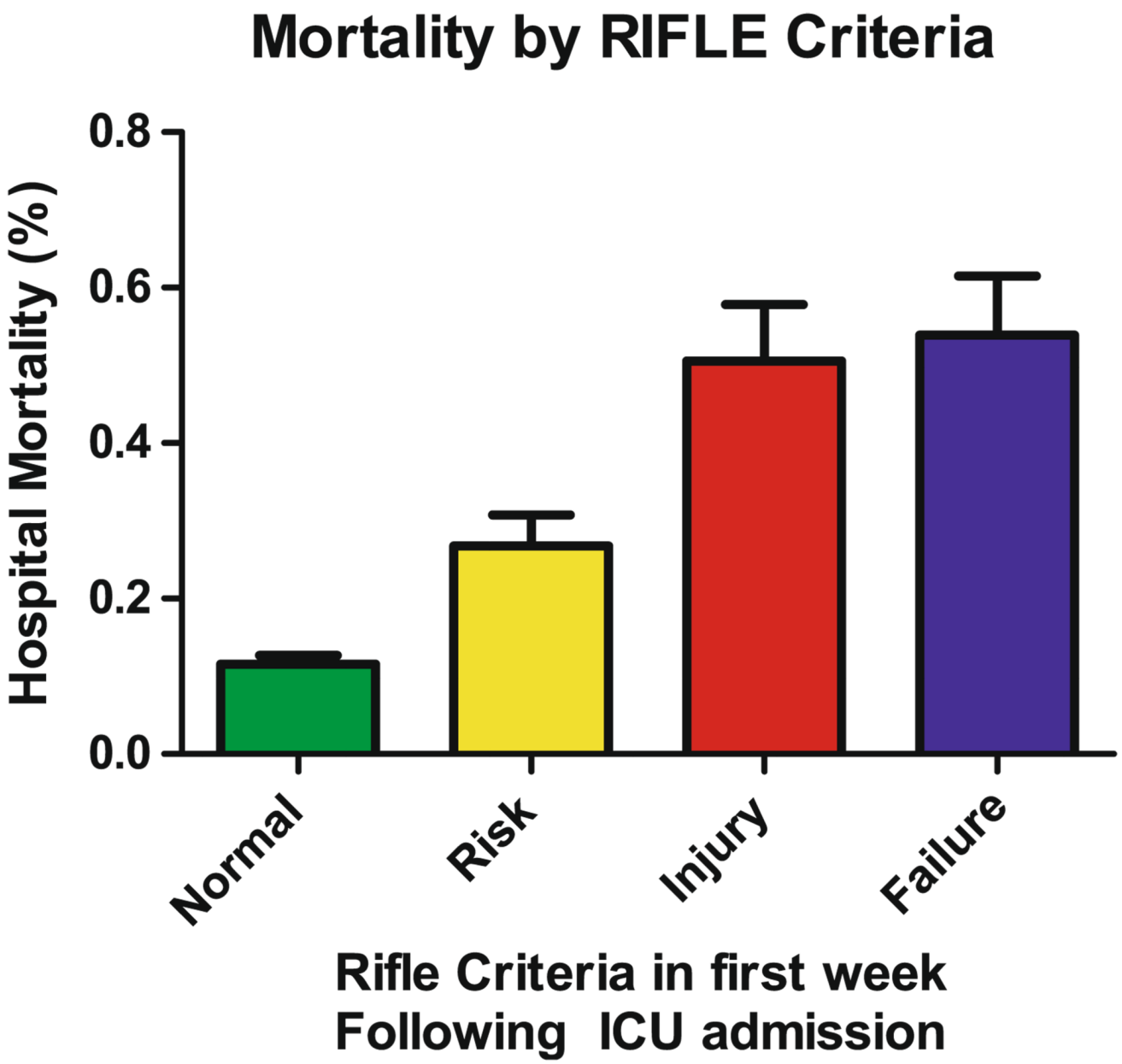

Fig. 4.
Mortality by RIFLE criteria

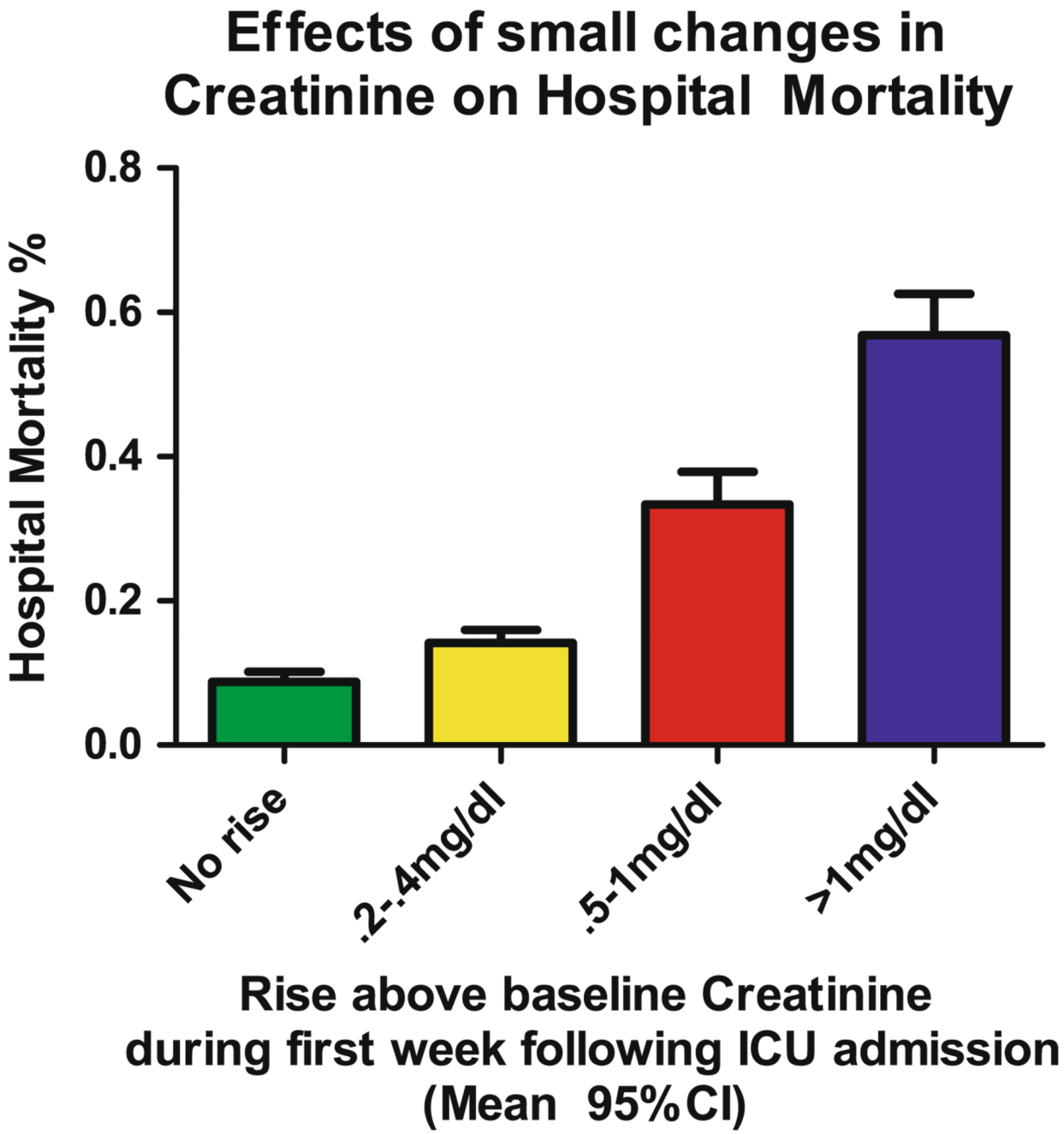

Fig. 5.
Effects of small changes in creatinine on hospital mortality

Table 1

Clinical variables included in database analysis

Age	Serum creatinine	Hemoglobin
Gender	Serum BUN	WBC
Race	Serum potassium	Platelet
Medical vs Surgical	Serum sodium	IV contrast exposure
Days in ICU before AKF	Serum pH	Antibiotic exposure
Surgery before admit	Change in Cr	Diuretic exposure
Pressor use	Change in BUN	Chemotherapy exposure
Intubation/ventilation	Need for dialysis	ACE inhibitor exposure
Modified SOFA score	CT scan ± contrast	

Table 2

Differences in risk factors between survivors and non-survivors

Risk factor	Non-survivors (*n*=653)	Survivors (*n*=3142)	*p* value
Age	56.4 (16.9)	56.0 (16.6)	0.58
Males	60.0%	57.6%	0.2534
M-SOFA at admission	5.5 (3.2)	2.2 (2.3)	<0.0001
Creatinine on admission	1.2 (0.9)	0.85 (0.5)	<0.0001
Peak ICU creatinine	1.9 (1.4)	1.1 (0.9)	<0.0001
# Nephrotoxins at admission	2.1 (2.5)	0.7 (1.3)	<0.0001
Dialysis in ICU	19.0%	1.6%	<0.0001
Assisted ventilation	9.6%	1.7%	<0.0001

Table 3

Multivariate analysis of risk factors for mortality

Risk factor	Odds ratio	95% CI	*p*-value
Creatinine rise of 10%	1.36	1.08–1.71	<0.010
Age	1.00	0.99–1.01	0.919
Gender	0.97	0.79–1.19	0.745
Baseline creatinine	1.09	0.95–1.26	0.220
M-SOFA at admission	1.33	1.28–1.40	<0.001
Use of diuretics	1.78	1.42–2.20	<0.001
Nephrotoxin use	1.50	1.22–1.85	<0.001
Dialysis in ICU	3.35	2.24–4.99	<0.001
Assisted ventilation	2.59	1.95–3.45	<0.001