

# Associations of Increases in Serum Creatinine with Mortality and Length of Hospital Stay after Coronary Angiography

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The absence of a universally accepted definition of radiocontrast nephropathy (RCN) has hampered efforts to characterize effectively the incidence and the clinical significance of this condition. The objective of this study was to identify a clinically relevant definition of RCN by assessment of the relationships between increases in serum creatinine (Scr) of varying magnitude after coronary angiography and clinical outcomes. An electronic medical database was used to identify all patients who underwent coronary angiography at the University of Pittsburgh Medical Center during a 12-yr period and abstract Scr levels before and after angiography, as well as demographic characteristics and comorbid conditions. Changes in Scr after angiography were categorized into mutually exclusive categories on the basis of absolute and relative changes from baseline levels, with a separate category denoting “unknown” change. Discrete proportional odds models were used to examine the association between increases in Scr and 30-d in-hospital mortality and length of stay. A total of 27,608 patients who underwent coronary angiography were evaluated. Small absolute (0.25 to 0.5 mg/dl) and relative (25 to 50%) increases in Scr were associated with risk-adjusted odds ratios for in-hospital mortality of 1.83 and 1.39, respectively. Larger increases in Scr generally were associated with greater risks for these clinical outcomes. Small increases in Scr after the administration of intravascular radiocontrast are associated with adverse patient outcomes. This observation will help guide the postprocedure care of patients who undergo coronary angiography and has important implications for future studies that investigate RCN.

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**R**adiocontrast nephropathy (RCN) is one of the most common forms of acute kidney injury (AKI) and has been linked to adverse health care outcomes, including increased in-hospital mortality and medical resource utilization (1–4). Whereas most patients who undergo procedures that use intravascular radiocontrast experience no deterioration in renal function, patients with underlying chronic kidney disease, particularly in the setting of diabetes or intravascular volume depletion, are at increased risk for the development of RCN (5–8). As with other forms of AKI, the initial and primary manifestation of RCN is an increase in the serum creatinine concentration (Scr), typically occurring within 1 to 3 d after the administration of radiocontrast medium (9,10). In the majority of patients, a transient rise in Scr is the sole manifestation of RCN. However, for a small proportion of patients, a more severe course may ensue, complicated by oliguria or other overt clinical manifestations of renal failure (3,5,10).

Multiple definitions of RCN, based on either relative or ab-

solute changes in Scr concentration that occur within variable time periods after the administration of radiocontrast medium, have been used in epidemiologic and intervention studies. These definitions have included relative increases in the Scr that range between 25 and 100% or absolute increases of 0.25 to 1.0 mg/dl that occur within 48, 72, or 96 h of radiocontrast administration (5,7,11–14). In some studies, even more complex definitions, based on both the magnitude of increase and threshold levels of Scr, have been used (1). The variability in definitions of RCN has made it difficult to determine precisely the incidence of this condition and has limited comparisons of the impact of preventive interventions across study populations.

There is a paucity of data on the correlation between the magnitude of change in renal function and patient outcomes in the setting of intravascular radiocontrast administration. Establishing a relationship between discrete levels of change in Scr and clinical outcomes would provide the basis for an evidence-based definition of RCN and would facilitate the design of adequately powered intervention trials to prevent this potentially avoidable iatrogenic condition. In this large electronic database analysis, we sought to evaluate the associations between discrete levels of change in Scr after radiocontrast administration during coronary angiography and

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the clinical outcomes of in-hospital mortality and length of stay (LOS).

## Materials and Methods

### Study Population

All patients who underwent diagnostic and/or therapeutic coronary angiography at the Oakland Campus of the University of Pittsburgh Medical Center between January 1, 1991, and January 1, 2003, were identified using the electronic Medical Archival System. This electronic database contains financial, administrative, and clinical data for all inpatient admissions and inpatient and outpatient procedures that have been performed at the University of Pittsburgh Medical Center since 1991 (15). Patients with ESRD based on *International Classification of Diseases, Ninth Revision, Clinical Modification* code 585 and/or V-Code (V45.1) at the time of angiography, patients who had undergone coronary artery bypass graft surgery within 14 d before angiography, and individuals who underwent angiography >2 d before hospital admission were excluded from the study cohort.

### Data Collection

The baseline level of renal function was defined as the Scr value that was performed most proximate to the time of angiography within the 42 d before the procedure. All Scr values that were performed within 3 d after angiography while patients were hospitalized also were abstracted. For patients with multiple Scr assessments on a given day, the earliest recorded value was used. Simultaneous replicate measurements were averaged; however, concurrent values that differed by >0.4 mg/dl were deemed unreliable and deleted. Demographic data including age, race, and gender as well as *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for conditions that compose the Charlson Comorbidity Index (CCI) and that were present at the time of the angiography also were abstracted (16).

Patients were categorized into four mutually exclusive groups on the basis of absolute changes in Scr from baseline of <0.25, 0.25 to 0.50, 0.51 to 1.0, and >1.0 mg/dl on each of the first 3 d after angiography. Similarly, patients were categorized into four mutually exclusive groups on the basis of relative changes in Scr of <25, 25 to 50, 51 to 100, and >100% at the same three time points. Patients who lacked a baseline Scr were categorized as having an unknown change in Scr, whereas patients who had a recorded baseline Scr but lacked a post-angiography Scr on a specific day were categorized as having an unknown change in Scr for that day.

### Statistical Analyses

We used discrete proportional odds models to assess the associations of absolute and relative changes in Scr on the first 3 d after angiography and in-hospital mortality and LOS within 30 d after angiography. This method takes into account that postprocedure Scr measurements were available and that patients were at risk for in-hospital mortality and potentially eligible for hospital discharge only while patients were hospitalized. Absolute and relative changes in Scr for the first 3 d after angiography were treated as time-dependent covariates. The appropriate dummy variable for categories of change in Scr were defined for days 1, 2, and 3, and the day 3 value was carried forward for the remainder of the hospital stay. This approach used the data that were available in real time. The odds for in-hospital mortality on day 1 were predicted as a function of the day 1 change in Scr, whereas the odds for in-hospital mortality on day 2 were predicted as a function of the day 2 change in Scr; the corresponding odds for day 3 and thereafter were predicted from the day 3 change. Patients who were in the hospital for longer than 30 d were censored at day 30. Patients whose index angio-

graphic procedure was performed on an outpatient basis and who were hospitalized within 2 d after the procedure were included in the analyses on the day of hospitalization. To minimize the inclusion of patients with causes of AKI other than RCN, patients who underwent coronary artery bypass graft surgery within 3 d after angiography were censored at the time of surgery.

The proportional odds models were adjusted for estimated GFR using the abbreviated four-variable Modification of Diet in Renal Disease study equation and clinical covariates that were believed to be associated with in-hospital mortality and LOS on the basis of administrative coding for the clinical conditions that make up the CCI (17,18). Individual adjustments were made for myocardial infarction, congestive heart failure, chronic pulmonary disease, diabetes, and a single indicator variable that denoted all of the remaining clinical conditions in the CCI (Table 1). Associations between levels of change in Scr and LOS are described using Kaplan-Meier curves and compared using log rank statistics. STATA version 9.0 (StataCorp LP, College Station, TX) was used for all statistical analyses. A two-sided  $P < 0.05$  was considered statistically significant. All study procedures were approved by the University of Pittsburgh's Institutional Review Board.

## Results

We identified 28,086 patients who underwent diagnostic and/or therapeutic coronary angiography during the study period. We excluded 478 patients from further analysis: 405 with ESRD, 71 who underwent coronary artery bypass graft surgery within 14 d before angiography, one who underwent angiography >2 d before hospital admission, and one for whom gender could not be confirmed from administrative data. The demographic and clinical characteristics of the re-

Table 1. Baseline patient characteristics<sup>a</sup>

Characteristic	<i>n</i>	%
Age ≥ 65 yr	13,565	49.1
Race		
white	24,293	88.0
black	1961	7.1
other	1354	4.9
Male gender	16,731	60.6
Comorbid conditions		
myocardial infarction	10,579	38.3
diabetes	6969	25.2
congestive heart failure	5639	20.4
chronic pulmonary disease	3742	13.6
peripheral vascular disease	1355	4.9
cerebrovascular disease	1230	4.5
renal disease	892	3.2
metastatic solid tumor	638	2.3
rheumatologic disease	457	1.7
peptic ulcer disease	339	1.2
mild liver disease	295	1.1
any malignancy including lymphoma and leukemia	160	0.6
dementia	36	0.1
AIDS	34	0.1

<sup>a</sup>Overall  $n = 27,608$ .

maining 27,608 patients are described in Table 1. The mean age was 63.5 yr, 60.6% were male, and 88% were white. Myocardial infarction, diabetes, congestive heart failure, and chronic pulmonary disease were the most prevalent comorbid conditions, whereas dementia and AIDS were the least common.

A baseline Scr was assessed in 14,188 (51.4%) patients (Table 2). Among these patients, 75% of baseline Scr measurements were within 1 d before angiography and 94% were performed within 4 d before angiography. Among the 13,420 (48.6%) patients with an unknown baseline Scr, the in-hospital mortality rate was 1.1%. Of the 14,188 patients with a known baseline Scr, 2705 (19.1%) had no postprocedure Scr performed; the mortality of this subgroup of patients was 4.4% (118 of 2705 patients). Of these 118 patients, 72% died within 24 h of the index angiogram, suggesting acute clinical decompensation after the cardiac procedure. The remaining 11,483 patients (81% of the patients with known baseline Scr) had at least one Scr value after angiography.

As shown in Table 3, <5% of patients demonstrated an absolute change in Scr of  $\geq 0.25$  mg/dl on any day of follow-up, and the frequency of patients decreased as the absolute level of change in Scr increased. With the exception of day 1 after radiocontrast administration, in-hospital mortality rates increased monotonically with progressively larger absolute changes in Scr. On day one, 44 (21.3%) of 207 patients with an increase in Scr of 0.51 to 1.0 mg/dl died compared with 21 (14.8%) of 142 patients with an increase in Scr of >1.0 mg/dl ( $P = 0.13$ ). Similar patterns were observed for relative changes in Scr, except that mortality increased monotonically with relative change in Scr on all 3 d after coronary angiography.

An absolute rise in Scr of 0.25 to 0.5 mg/dl within the first 3 d after angiography was associated with a statistically significant increased odds for in-hospital death within 30 d after adjustment for baseline estimated GFR (odds ratio [OR] 1.94; 95% confidence interval [CI] 1.44 to 2.61) and after additional adjustment for comorbid illness (OR 1.83; 95% CI 1.35 to 2.49;

Table 2. Assessment patterns of baseline and follow-up serum creatinine measurements and associated in-hospital mortality<sup>a</sup>

	Frequency <sup>b</sup>		Mortality <sup>c</sup>	
	<i>n</i>	%	<i>n</i>	%
Baseline Scr unknown	13,420	48.6	146	1.1
Baseline Scr known				
no follow-up Scr	2705	9.8	118	4.4
follow-up Scr on day 1	10,639	39	414	3.9
follow-up Scr on day 2	6500	24	323	4.9
follow-up Scr on day 3	4908	18	254	5.2

<sup>a</sup>Total does not sum to 14,188 because categories are day specific and not disjoint. Scr, serum creatinine.

<sup>b</sup>Number and percentage of patients with various Scr ascertainment patterns.

<sup>c</sup>Mortality rates based on corresponding Scr ascertainment patterns.

Table 4, Figure 1). Absolute changes in Scr of 0.51 to 1.0 mg/dl were associated with increased odds for in-hospital mortality, although the strength of association was less robust than that of smaller changes in Scr and was not statistically significant in the fully adjusted model. Relative increases in Scr of 25 to 50% were associated with increased odds for mortality in both partially adjusted (OR 1.44; 95% CI 1.04 to 2.00) and fully adjusted analyses (OR 1.39; 95% CI 1.00 to 1.93); these associations were of borderline statistical significance. Larger relative changes in Scr were strongly associated with increased odds for mortality in both models (Table 4, Figure 1). The wider CI for the relative change in Scr of >100% compared with the absolute change of >1.0 mg/dl reflects the smaller number of patients who were classified in the highest category of relative change ( $n = 230$ ) compared with the highest category of absolute change ( $n = 535$ ; Table 3). Patients with unknown change in Scr had no increased risk for mortality in any model considered.

Kaplan-Meier plots of LOS based on absolute and relative increases in Scr are shown in Figure 2. Patients in whom the change in Scr could not be calculated because of missing values had a significantly shorter LOS than patients with absolute changes in Scr <0.25 mg/dl or patients with relative changes in Scr of <25% ( $P < 0.01$  for each comparison). Hospital LOS increased with each sequential absolute or relative increase in Scr, and all were associated with longer hospitalization than the referent category ( $P \leq 0.01$  for each comparison). After multivariate adjustment, the relationships between changes in Scr of 0.25 to 0.5 mg/dl and 25 to 50% and extended LOS remained statistically significant ( $P < 0.02$ ).

## Discussion

In this large database analysis, we discovered that absolute and relative increases in Scr as small as 0.25 to 0.5 mg/dl and 25 to 50% after coronary angiography were linked to increased in-hospital mortality and prolonged hospital LOS. Progressively larger increases in Scr, particularly larger relative changes in Scr, were associated with even greater risk for death and longer LOS, although the number of patients who manifested more substantial changes in Scr was smaller.

Our observations are consistent with recent analyses of the relationship between change in Scr and patient outcomes in other clinical settings of AKI. In a retrospective analysis of 9205 hospitalized patients, Chertow *et al.* (19) found that an absolute increase in Scr of at least 0.3 mg/dl was associated with an approximate four-fold increased risk for hospital mortality, whereas a relative increase in Scr of 25% was associated with a two-fold increase in risk for mortality. Absolute increases in Scr of 0.3 to 0.4 mg/dl were associated with adjusted odds for death of 1.7 compared with patients with lesser changes in Scr. In another analysis, Lassnigg *et al.* (20) assessed mortality among cardiac and thoracic surgery patients on the basis of postoperative changes in Scr. Increases in the Scr of up to 0.5 mg/dl were associated with a nearly three-fold rise in 30-d postoperative mortality. Whereas the study by Chertow *et al.* included patients with heterogeneous causes of AKI and Lassnigg *et al.* focused on patients who had undergone cardiac and/or thoracic sur-

Table 3. Associations of day-specific absolute and relative changes in Scr and corresponding in-hospital mortality within 30 d of coronary angiography

	Timing of Serum Creatinine after Radiocontrast Administration <sup>a</sup>											
	Day 1				Day 2				Day 3			
	Frequency		Mortality		Frequency		Mortality		Frequency		Mortality	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Absolute $\Delta$ in Scr from baseline (mg/dl)												
<0.25	9513	35	278	2.9	5166	19.9	179	3.5	3545	14	134	3.8
0.25 to 0.50	700	2.6	64	9.1	647	2.5	47	7.3	471	1.9	33	7.0
0.51 to 1.0	207	0.8	44	21.3	264	1.0	31	11.7	204	0.8	22	10.8
>1.0	142	0.5	21	14.8	184	0.7	52	28.3	209	0.8	44	21.1
unknown	16,586	61.1	256	1.5	19,689	75.9	324	1.7	20,866	82.5	381	1.8
Relative $\Delta$ in Scr from baseline (%)												
<25	9660	35.6	314	3.3	5272	20.3	198	3.8	3630	14.4	150	4.1
25 to 50	703	2.6	54	7.7	690	2.7	45	6.5	490	1.9	22	4.5
51 to 100	168	0.6	31	18.5	201	0.8	34	16.9	208	0.8	33	15.9
>100	31	0.1	8	25.8	98	0.4	32	32.7	101	0.4	28	27.7
unknown	16,586	61.1	256	1.5	19,689	75.9	324	1.7	20,866	82.5	381	1.83

<sup>a</sup>Frequency indicates the number of patients who demonstrated the corresponding level of change in Scr on each day after angiography. Mortality indicates the 30-d mortality rate for patients who demonstrated the corresponding level of change in Scr on each day after angiography.

Table 4. Odds for in-hospital mortality by absolute and relative change in Scr concentration<sup>a</sup>

	Model 1 <sup>b</sup>		Model 2 <sup>c</sup>	
	OR	95% CI	OR	95% CI
Absolute $\Delta$ in Scr from baseline (mg/dl)				
0.25 to 0.50	1.94	1.44 to 2.61	1.83	1.35 to 2.49
0.51 to 1.0	1.62	1.03 to 2.55	1.42	0.90 to 2.25
>1.0	3.31	2.30 to 4.74	3.02	2.13 to 4.28
unknown	0.87	0.68 to 1.12	1.00	0.77 to 1.28
Relative $\Delta$ in Scr from baseline (%)				
25 to 50	1.44	1.04 to 2.00	1.39	1.00 to 1.93
51 to 100	3.05	2.16 to 4.30	2.68	1.89 to 3.81
>100	4.22	2.68 to 6.65	3.57	2.27 to 5.60
unknown	0.85	0.66 to 1.08	0.96	0.75 to 1.24

<sup>a</sup>OR, odds ratio; CI, confidence interval.

<sup>b</sup>Model 1 depicts OR adjusted for estimated GFR (eGFR) and relative to referent categories of change in Scr of <0.25 mg/dl and <25%.

<sup>c</sup>Model 2 depicts OR adjusted for eGFR, myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, diabetes, and indicator variable for all other conditions that compose the Charlson Comorbidity Index relative to referent categories of change in Scr of <0.25 mg/dl and <25%.

ger, our study demonstrates a similar relationship between small changes in Scr and adverse outcomes in a form of AKI that is considered to be relatively benign and usually is not associated with multiorgan failure. Although a retrospective study by Levy *et al.* (1) demonstrated a 5.5-fold increase in mortality among patients who developed RCN, this analysis used an increase in Scr of at least 25% to a value of at least 2 mg/dl to define RCN and did not stratify patients on the basis of the magnitude of increase in Scr. Our study demon-

strates that small increases in Scr after the administration of intravascular radiocontrast are independently associated with adverse patient outcomes.

Previous efforts to operationalize the definition of AKI provide a useful conceptual framework within which to interpret our findings. A recent consensus conference of the Acute Dialysis Quality Initiative proposed a broad, multidimensional definition of AKI on the basis of changes in Scr and/or urine output, stratifying AKI into three categories of acute change in

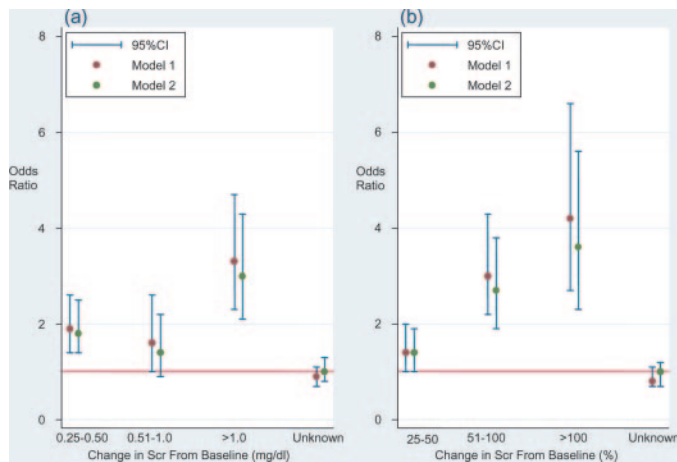


Figure 1. Odds for in-hospital mortality by absolute (A) and relative (B) changes in serum creatinine (Scr) after coronary angiography.

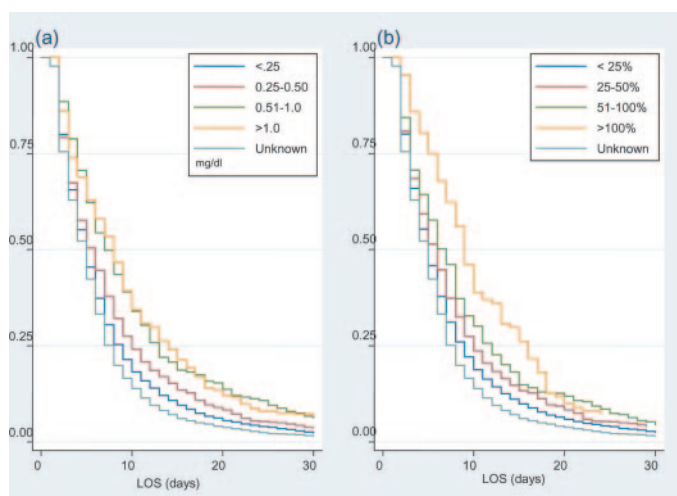


Figure 2. Kaplan-Meier estimated length of stay by absolute (A) and relative (B) changes in Scr after coronary angiography.

renal function—risk, injury, and failure—and two levels of outcome—loss and end-stage disease (RIFLE) (21). Applying our results to this model, which uses relatively small decrements in renal function to define “risk,” using small changes in Scr to identify the development of RCN provides a highly sensitive definition of this condition. Moreover, among a high-risk patient population, such a definition also has robust predictive value. Using larger magnitude changes in Scr to define RCN, as used in the RIFLE criteria to define more severe degrees of AKI, increases the specificity of the definition at the expense of its sensitivity, as the prevalence of patients with successive increments in Scr decreases.

This study has two major implications for clinical providers. First, our findings confirm a strong link between RCN and serious adverse patient outcomes, particularly death, underscoring the importance of implementing evidence-based preventive care in patients who are at high risk for this condition. Second, this study provides a basis for providers to interpret

nominal increases in Scr, 0.25 mg/dl or 25%, after radiocontrast administration as clinically germane and should facilitate the prompt institution of appropriate clinical follow-up. We believe that our finding that the mortality risk that is associated with an absolute increase in Scr of 0.51 to 1.0 mg/dl was lower than that of an absolute increase of 0.25 to 0.5 mg/dl was due to a substantially smaller number of patients who manifested the greater magnitude change. Accordingly, this finding should not reassure providers that such changes in Scr are of minimal clinical importance.

Our findings also are highly pertinent to the design of future clinical trials of strategies to prevent RCN. Using data from this study (Table 3), we performed *post hoc* calculations to determine the sample size that would be required to assess accurately a 40% reduction in the incidence of RCN from a hypothetical intervention, using a definition of RCN of an increase in Scr of  $\geq 0.25$  mg/dl on day 2 after radiocontrast administration, based on 90% power and an  $\alpha$  value of 0.05. We based these calculations on a reduction in the incidence of RCN of 40%, because this was the approximate effect size observed in several recent meta-analyses of the benefit of N-acetylcysteine in RCN (22–25). A total of 537 patients would be required in each of two study arms to observe a reduction in the incidence of RCN from 17.5 to 10.5%. Using an increase in Scr of  $>0.5$  mg/dl to define RCN, which we found to be associated with a 15% increase in the mortality risk compared with a change of  $\geq 0.25$  mg/dl,  $>1400$  patients per study arm would be required to observe the same effect size. It is important to note that these analyses are based on patients with all ranges of baseline renal function. However, by comparison, two relatively recent and highly cited studies that examined the impact of N-acetylcysteine on the incidence of RCN using an increase in Scr of at least 0.5 mg/dl to define this condition used a total of 79 and 83 patients, respectively (26,27). Our results help to validate the use of small changes in Scr to define RCN yet underscore the importance of enrolling adequate numbers of patients who are at significant risk for RCN in future trials of this condition to allow for a meaningful interpretation of the true effect of a particular intervention.

Our study has several limitations. First, our database was constructed using retrospectively collected data, and both Scr and mortality within 30 d were ascertained only while the patient remained hospitalized. A considerable proportion of patients had unknown baseline renal function, and many post-procedure Scr measurements were missing. We cannot reasonably assume that these measurements were missing at random, and excluding patients with missing Scr values and looking at changes in renal function only in patients with complete data would not have been justifiable. Second, missing Scr and out-of-hospital data precluded an assessment of the time point at which a rise in Scr should be considered most germane and of greatest prognostic value. Third, although we adjusted our analyses for comorbid illness, excluded patients who underwent coronary artery bypass graft surgery before angiography, and censored patients at the time of coronary artery bypass graft surgery after angiography, we cannot verify that the development of AKI was causally related to the administration of radiocontrast or that we accounted for all potential con-

founders of the study outcomes. It also is plausible that patients who underwent coronary artery bypass graft surgery were at increased risk for RCN, whereas we assumed independent censoring. Fourth, we recognize that the absolute number of patients who experienced in-hospital death after angiography was relatively small. Although the risk of in-hospital mortality clearly is increased with the development of RCN, the absolute risk remains relatively low. This underscores the importance of considering other outcomes such as LOS, need for renal replacement therapy, and medical resource utilization in studies of preventive interventions for and health care implications of RCN. We also note that our risk estimates for mortality in the setting of RCN are lower than have been reported in previous studies. This likely is due to our use of mutually exclusive categories of change in Scr to define RCN, whereas previous studies typically have used non-mutually exclusive categories of change in Scr to define RCN, which captures patients with very substantial levels of renal failure (1,3).

### Conclusion

Using a large retrospective database, we have demonstrated that small absolute and relative changes in Scr after coronary angiography are associated with an increased risk for mortality and extended LOS. These novel observations have significant implications for providers as well as ramifications for the design of interventional trials for the prevention of RCN. In the absence of clinically available and highly sensitive biomarkers to identify AKI in its incipient stages as the cardiac troponin does for myocardial infarction, changes in Scr remain the cornerstone of diagnosis of RCN. This study was the first effort to determine the threshold level of change in Scr after radiocontrast administration during coronary angiography that is associated with adverse clinical sequelae. Prospective studies with comprehensive Scr assessments and out of hospital follow-up are needed to validate our findings and to permit further refinement of an operational definition of RCN.

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