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Acute Kidney Injury Is Associated With Increased Long-Term Mortality After Cardiothoracic Surgery

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Background—Long-term survival after acute kidney injury (AKI) is poorly studied. We report the relationship between long-term mortality and AKI with small changes in serum creatinine during hospitalization after various cardiothoracic surgery procedures.

Methods and Results—This was a retrospective study of 2973 patients with no history of chronic kidney disease who were discharged from the hospital after cardiothoracic surgery between 1992 and 2002. AKI was defined by the RIFLE classification (Risk, Injury, Failure, Loss, and End stage), which requires at least a 50% increase in serum creatinine and stratifies patients into 3 grades of AKI: Risk, injury, and failure. Patient survival was determined through the National Social Security Death Index. Long-term survival was analyzed with a risk-adjusted Cox proportional hazards regression model. Survival was worse among patients with AKI and was proportional to its severity, with an adjusted hazard ratio of 1.23 (95% CI 1.06 to 1.42) for the least severe RIFLE risk class and 2.14 (95% CI 1.73 to 2.66) for the RIFLE failure class compared with patients without AKI. Survival was worse among all subgroups of cardiothoracic surgery with AKI except for valve surgery. Patients with complete renal recovery after AKI still had an increased adjusted hazard ratio for death of 1.28 (95% CI 1.11 to 1.48) compared with patients without AKI.

Conclusions—The risk of death associated with AKI after cardiothoracic surgery remains high for 10 years regardless of other risk factors, even for those patients with complete renal recovery. Improved renal protection and closer postdischarge follow-up of renal function may be warranted. **(*Circulation*. 2009;119:2444-2453.)**

Key Words: kidney ■ outcomes ■ surgery ■ complications

Acute kidney injury (AKI) is a serious complication after cardiothoracic surgery and is associated with increased short-term mortality.[1] AKI develops in 5% to 30% of patients who undergo cardiothoracic surgery, depending on the definition used for AKI.[2,3] Most previous studies have focused on severe AKI, defined either as a need for dialysis or a substantial increase in serum creatinine (sCr).[1] However, studies reporting the association of small changes in sCr with adverse short-term outcomes are emerging in the literature.[2–4]

Clinical Perspective on p 2453

The Acute Dialysis Quality Initiative Group introduced a new classification system for AKI in 2004 named RIFLE (Risk, Injury, Failure, Loss, and End stage) to provide a standardized definition of AKI.[5] Since then, the RIFLE classification has been validated and widely accepted.[6] The RIFLE classification defines 3 grades of AKI severity (RIFLE-R, risk; RIFLE-I, injury; and RIFLE-F, failure) based on changes in sCr relative to the baseline condition. Recent studies have reported a higher prevalence of RIFLE-defined AKI in cardiothoracic surgery patients and confirmed the association of AKI with short-term mortality.[7–9] The few studies focused on long-term survival after AKI have been limited by heterogeneous cohorts of patients and have often included patients with preexisting chronic kidney disease (CKD). In addition, most of these studies included only severe AKI and lacked an adequate control group.[10–13] Recently, we have reported in a large cohort of surgical patients that RIFLE-defined AKI is associated with a significant risk for long-term mortality.[14] To date, no study has assessed the association of less severe AKI, as defined by RIFLE, with long-term survival in cardiothoracic surgery. The goals of the present study were to evaluate the long-term mortality risk associated with RIFLE-defined AKI after cardiothoracic surgery in a large, single-center cohort of patients with no history of CKD who required at least a 24-hour admission to an intensive care unit (ICU) and to determine whether that risk varied with type of surgery.

Methods

Patient Population

The present study was approved by the Institutional Review Board of the University of Florida as a retrospective cohort study. A total of 11 080 adult patients who were admitted to a surgical ICU for at least 24

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hours after any kind of general/gastrointestinal, vascular, cardiothoracic, or neurosurgical operative procedure and who survived to discharge from the hospital were identified through a search of the billing database between the years 1992 and 2002, as reported previously.[14] Among this cohort, we selected 3240 patients who underwent any kind of cardiothoracic procedure with subsequent admission to a cardiothoracic surgery ICU for inclusion in the present study.

Patients with a history of CKD of any stage were excluded. History of CKD was established through review of all relevant clinical notes and sCr values before surgery and by analysis of ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes for end-stage renal disease and CKD. Patients were classified by type of operative procedure: Isolated CABG, valve surgery (including valve surgery combined with other procedures), aortic surgery (including aortic procedures combined with other procedures), heart transplant, and thoracic surgery (including lung transplant). Need for renal replacement therapy (RRT) was recorded for each patient.

Definition of AKI

AKI was defined by the RIFLE classification by the change in sCr during hospitalization compared with baseline sCr. For the baseline sCr, we used the lowest of 2 values: The lowest measured sCr at the hospital admission or the expected sCr value (Cr_{MDRD}), calculated with the abbreviated Modification of Diet in Renal Disease (MDRD) equation.[5] Patients who met the RIFLE criteria for AKI were classified as "AKI," whereas those who did not were classified as "no AKI." Patients with AKI were stratified according to the maximum RIFLE class ($RIFLE_{max}$) reached during the hospital admission. RIFLE-R corresponds to a 100% increase in sCr, RIFLE-I to a 200% increase in sCr, and RIFLE-F to a 3-fold increase in sCr. $RIFLE_{max}$ was determined by comparing the highest sCr during hospitalization with the baseline sCr. Renal outcome at the time of discharge was evaluated by comparing the discharge sCr to the baseline sCr. Complete renal recovery existed if the sCr returned to a level less than 50% above baseline sCr, whereas partial renal recovery existed if there was an sCr $>50\%$ above baseline sCr but no need for RRT. No renal recovery implied there was a need for RRT at the time of hospital discharge.

Definition of Outcomes and Covariates

Comorbidities and surgical complications were identified by ICD-9-CM codes on the basis of previously published criteria.[15–17] The billing codes for acute renal failure were ICD-9-CM diagnostic codes 584.XX or 997.5. Disposition at the time of discharge was determined from the discharge summaries. Patient survival after discharge was determined through a 1-day search in 2006 of the National Social Security Death Index.

Statistical Analysis

Results are expressed as means (SD) for variables with normal distribution. The Shapiro-Wilk W test and distribution plots were used to test normality of distribution. For data that did not meet normality assumptions, median and interquartile ranges were displayed, and the Kruskal-Wallis test was used to evaluate the independence of group levels. For categorical variables, the Pearson χ^2 test or Fisher's exact test was applied as appropriate.

Survival probabilities were estimated with the product-limit method (Kaplan–Meier algorithm). Survival differences between groups were analyzed with log-rank tests. Adjusted hazard ratios (AHRs) were generated by Cox proportional hazard modeling with adjustment for factors potentially associated with patient survival. These factors were chosen a priori, based on both the literature on AKI in surgery patients and on our clinical experience with AKI in these patients. Survival models were initiated at the time of hospital discharge and followed until death or last follow-up time. Adjusted survival curves were also generated that demonstrated the impact of AKI by individual surgery type based on the mean level of model covariates. A double-sided probability value less than 0.05 was considered statistically significant for all tests. Statistical analyses were performed with Statistica (version 8.0; StatSoft, Inc, Tulsa, Okla) and SAS (version 9.1.3; SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 2973 patients with no history of CKD who were admitted to the cardiothoracic surgery ICU for >24 hours after a cardiothoracic surgical procedure survived to be discharged from the hospital. Of these patients, 1265 (43%) had an episode of AKI during hospitalization: 637 (22%) had $RIFLE_{max}$-R, 386 (13%) had $RIFLE_{max}$-I, and 242 (8%) had $RIFLE_{max}$-F (Table 1). There was significant variability in the proportion of patients who developed AKI among the different types of surgery, ranging from 33% for patients with thoracic surgery to 59% for patients with aortic surgery (Table 2).

Patients with AKI were older and more likely to have associated comorbid conditions (Table 1) and postoperative complications (Table 3). The average baseline sCr and estimated glomerular filtration rate for all patients were 0.90 ± 0.16 mg/dL and 87 ± 20 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}, respectively, with no difference between patients with and without AKI. Only 75 (6%) of the patients with AKI required any RRT: 34 (45%) were hemodialysis dependent, 25 (33%) had partial renal recovery, and 16 (21%) had complete renal recovery at the time of hospital discharge.

Kaplan-Meier plots illustrated that patients with AKI had significantly worse long-term survival over the follow-up period ($P<0.001$). The proportion of survivors among patients with AKI was 89% at 1 year and 44% at 10 years, whereas the proportion of survivors among patients without AKI was 95% at 1 year and 63% at 10 years (Figure 1). The 10-year survival rates among patients with AKI according to $RIFLE_{max}$ class were 51% for RIFLE-R, 42% for RIFLE-I, and 26% for RIFLE-F (Figure 2).

The Cox proportional hazards model for patient mortality demonstrated that AKI (AHR 1.39, 95% CI 1.23 to 1.57) was an independent predictor of mortality. Other factors associated with an increased risk for death included older age, diabetes mellitus, chronic heart failure, chronic pulmonary disease, prolonged length of hospital stay, and discharge to a site other than home (Table 4). Patients with valve, aortic, and thoracic surgery had an increased risk of death compared with patients undergoing CABG. Furthermore, severity of AKI was associated with a progressively increased hazard for death. Patients with the least severe $RIFLE_{max}$ classification ($RIFLE_{max}$-R) had an AHR of 1.23 (95% CI 1.06 to 1.42); patients with $RIFLE_{max}$-I had an AHR of 1.45 (95% CI 1.22 to 1.72), and patients with the most severe $RIFLE_{max}$ ($RIFLE_{max}$-F) had an AHR of 2.14 (95% CI 1.73 to 2.66).

In the subgroup analysis, AKI was associated with decreased survival among patients undergoing all types of cardiothoracic surgery except for valve surgery (Figure 3B). Among valve surgery patients, only RIFLE-F class had a significantly higher mortality risk (AHR 1.63, CI 1.02 to 2.59). For all other types of surgery, AKI was associated with increased risk for long-term mortality (Table 4; Figure 4), which was highly significant for patients undergoing aortic and thoracic surgery. Other factors associated with long-term mortality varied with type of surgery, although AKI, congestive heart failure, diabetes mellitus, pro-

Table 1. Demographic and Clinical Characteristics of Patients

		AKI					
	No AKI (n=1708; 57%)	All AKI (n=1265; 43%)	$\text{RIFLE}_{\text{max}}$-R (n=637; 22%)	$\text{RIFLE}_{\text{max}}$-I (n=386; 13%)	$\text{RIFLE}_{\text{max}}$-F (n=242; 8%)	*P**	*P†*
Demographics							
Age, y	60 (13)	64 (13)	64 (12)	64 (13)	64 (13)	<0.001	0.84
Female sex (n=1019, 34%)	552 (32%)	467 (37%)	205 (32%)	162 (42%)	100 (41%)	0.009	0.002
Black ethnicity (n=174, 6%)	105 (6%)	69 (5%)	19 (3%)	33 (9%)	17 (7%)	0.46	0.006
Baseline renal function							
Baseline sCr level, mg/dL	0.90 (0.16)	0.89 (0.16)	0.91 (0.15)	0.89 (0.18)	0.90 (0.17)	0.45	0.001
Baseline GFR, $\text{mL} \cdot \text{min}^{-1} \cdot 1.73\ \text{m}^{-2}$	89 (20)	85 (20)	83 (17)	87 (24)	85 (22)	0.09	0.001
Highest sCr level, mg/dL	0.93 (0.26)	2.27 (1.62)	1.40 (0.38)	1.98 (0.55)	4.11 (2.18)	<0.001	<0.001
Comorbidities							
Hypertension (n=1410, 47%)	762 (45%)	648 (51%)	314 (49%)	207 (54%)	127 (52%)	<0.001	0.47
Diabetes mellitus (n=602, 20%)	309 (18%)	293 (23%)	150 (24%)	97 (25%)	50 (21%)	<0.001	0.42
Atrial fibrillation (n=628, 21%)	285 (17%)	343 (27%)	151 (24%)	115 (30%)	77 (32%)	<0.001	0.02
Congestive heart failure (n=699, 24%)	294 (17%)	405 (32%)	175 (27%)	122 (32%)	108 (45%)	<0.001	<0.001
Chronic pulmonary disease (n=504, 17%)	268 (16%)	236 (19%)	103 (16%)	78 (20%)	55 (23%)	0.02	0.07
Chronic liver disease (n=41, 1%)	15 (1%)	26 (2%)	9 (1%)	4 (1%)	13 (5%)	0.006	0.001
IABP (n=143, 5%)	58 (3%)	85 (7%)	43 (7%)	18 (5%)	24 (10%)	<0.001	0.04
CPB (n=2122, 71%)	1217 (71%)	905 (72%)	485 (76%)	271 (70%)	149 (62%)	0.86	0.001

GFR indicates glomerular filtration rate; IABP, intra-aortic balloon pump; and CPB, cardiopulmonary bypass.

Continuous variables are presented as mean (SD) or as median (interquartile range) when not normally distributed. Categorical variables are presented as No. (percentages within the columns).

*Comparing patients without AKI to all patients with AKI.

†Comparing patients within the 3 subgroups of AKI patients.

longed hospital stay (>21 days), and older age (>61 years) remained the most consistent factors associated with a risk of dying. A formal analysis of any possible interaction between type of surgery and effect of AKI on mortality did not find any statistically significant interaction terms.

Patients with complete and partial renal recovery after AKI had significantly higher risk of dying than patients with no AKI (Table 5). The 10-year survival rate for patients with AKI and complete and partial renal recovery at discharge was 44% compared with 63% for patients with no AKI (Figure 4). Too few patients with no recovery of renal function survived to calculate a 10-year survival rate.

We collected data on the cause of death and progression of kidney disease in a small subgroup of 41 patients with billing codes for AKI. Cardiovascular death (54%) and sepsis (24%) were the 2 most common reported causes of death in this subgroup. Forty-six percent of patients in this subgroup were hemodialysis dependent at the time of death, and 24% were reported to have some degree of CKD.

Discussion

In a large, single-center cohort of patients with no history of CKD who survived to discharge after cardiothoracic surgery, AKI characterized by small changes in sCr level during

Table 2. AKI by Type of Surgery

		AKI					
Type of surgery	No AKI (n=1708; 57%)	All AKI (n=1265; 43%)	$\text{RIFLE}_{\text{max}}$-R (n=637; 22%)	$\text{RIFLE}_{\text{max}}$-I (n=386; 13%)	$\text{RIFLE}_{\text{max}}$-F (n=242; 8%)	*P**	*P†*
Isolated CABG (n=1423, 48%)	901 (63%)	522 (37%)	328 (23%)	136 (10%)	58 (4%)	<0.001	<0.001
Valve surgery (n=640, 22%)	324 (51%)	316 (49%)	151 (24%)	99 (15%)	66 (10%)		
Aortic surgery (n=475, 16%)	213 (45%)	262 (55%)	86 (18%)	92 (19%)	84 (18%)		
Thoracic surgery (n=401, 14%)	268 (67%)	133 (33%)	63 (16%)	49 (12%)	21 (5%)		
Heart transplant (n=34, 1%)	2 (6%)	32 (94%)	9 (26%)	10 (29%)	13 (38%)		

Categorical variables are presented as No. (percentages within the rows).

*Comparing patients without AKI to all patients with AKI.

†Comparing patients within the 3 subgroups of AKI patients.

Table 3. Complications and Short-Term Outcomes

		AKI					
	No AKI (n=1708; 57%)	All AKI (n=1265; 43%)	RIFLE$_{\text{max}}$-R (n=637; 22%)	RIFLE$_{\text{max}}$-I (n=386; 13%)	RIFLE$_{\text{max}}$-F (n=242; 8%)	*P**	*P†*
Complications							
Stroke (n=227, 7%)	96 (6%)	131 (10%)	70 (11%)	32 (8%)	29 (12%)	<0.001	0.19
Mechanical ventilation (n=394, 13%)	89 (5%)	305 (24%)	84 (13%)	89 (23%)	132 (55%)	<0.001	<0.001
Tracheostomy (n=118, 4%)	16 (1%)	102 (8%)	17 (3%)	24 (6%)	61 (25%)	<0.001	<0.001
Sepsis (n=103, 3%)	11 (1%)	92 (7%)	16 (3%)	27 (7%)	49 (20%)	<0.001	<0.001
Renal outcomes							
Highest sCr level, mg/dL	0.93 (0.26)	2.27 (1.62)	1.40 (0.38)	1.98 (0.55)	4.11 (2.18)	<0.001	<0.001
RRT		75 (6%)	0 (0%)	0 (0%)	75 (31%)		<0.001
Renal recovery at discharge							<0.001
Complete recovery		754 (60%)	469 (74%)	199 (52%)	86 (36%)		
Partial recovery		476 (37%)	168 (26%)	187 (48%)	121 (50%)		
No recovery		35 (3%)	0 (0%)	0 (0%)	35 (14%)		
Days in hospital	9 (7–12)	15 (10–26)	12 (9–18)	16 (11–27)	29 (19–51)	<0.001	<0.001
Days in ICU	3 (2–4)	6 (3–12)	4 (2–7)	7 (4–13)	17 (7–33)	<0.001	<0.001
Discharge to home (n=2392, 80%)	1531 (90%)	861 (68%)	513 (81%)	260 (67%)	93 (38%)	<0.001	<0.001
Billing code for acute renal failure‡		159 (13%)	5 (1%)	32 (8%)	122 (50%)		<0.001

Continuous variables are presented as mean (standard deviation) or as median (interquartile interval) when not normally distributed. Categorical variables are presented as No. (percentages within the columns).

*Comparing patients without AKI to all patients with AKI.

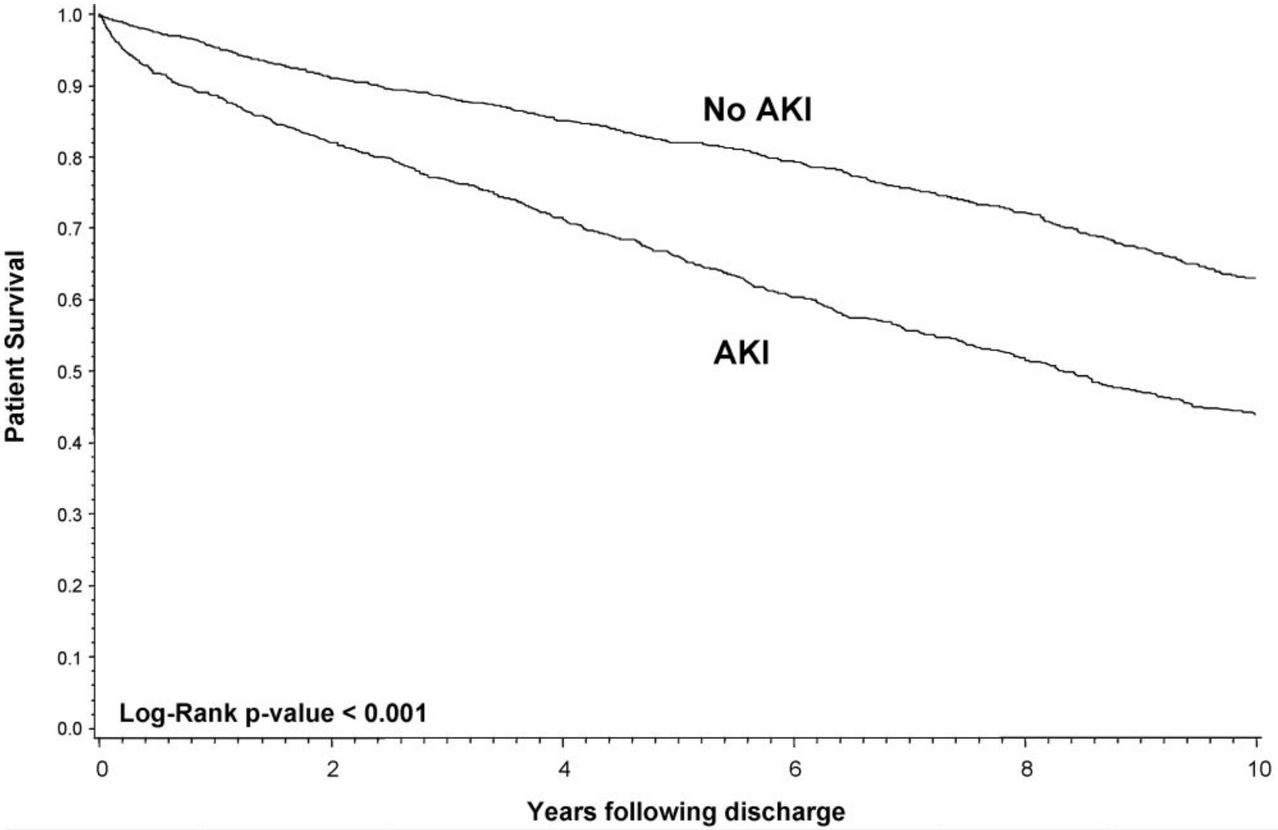
†Comparing patients within the 3 subgroups of AKI patients.

‡ICD-9 codes 584.XX or 997.5.

hospitalization was associated with a long-term risk of death. Even patients who had complete recovery of renal function by the time of hospital discharge had an increased risk of death for up to 10 years compared with patients with no AKI. This risk of death was independent of other postoperative complications and comorbidities. Ten years after surgery, only 44% of patients with AKI were alive compared with 63% of patients without kidney injury.

RIFLE is a now widely accepted and validated classification for AKI that emphasizes the importance of less severe grades of AKI.[6] Recent studies have reported that RIFLE-defined AKI occurs in 20% to 48% of cardiothoracic surgery patients and is associated with worse in-hospital outcomes.[7–9] Most of the studies that have reported long-term survival after AKI in cardiothoracic surgery have defined AKI by the need for RRT, have included patients with CKD, and have not included an adequate control group without AKI.[10–13] Five-year survival in these studies, which ranged from 36% to 63%,[10–12] corresponds to the 5-year survival of 63% for the RIFLE-I group and 47% for the RIFLE-F group in the present study. Two recent studies addressed long-term outcome in cardiothoracic surgery patients who sustained less severe AKI.[18,19] Loef et al[19] reported 62% survival at 8 years for mainly post-CABG patients with AKI defined as greater than a 25% increase in sCr, a more sensitive criteria for AKI than RIFLE-R. They also reported that elevated risk for long-term mortality was independent of renal function recovery at discharge. In a recent study of 13 593 patients with isolated CABG stratified by postoperative estimated glomerular filtration rate,[18] the 5-year mortality rate for the group with estimated glomerular filtration rate of 30 to 59 mL · min^{-1} · 1.73 m^{-2} was 90% compared with 75% for the present RIFLE-R group. The difference in survival may be due to case mix, because that study included only patients with an isolated CABG procedure, and ICU admission was not a requirement for inclusion. Nevertheless, even a small decline in postoperative estimated glomerular filtration rate was associated with a sex- and age-adjusted hazard ratio that ranged between 1.76 and 7.03, depending on the severity of AKI. Patients without AKI in the present study have long-term survival comparable to that reported in the literature for patients undergoing CABG surgery,[20] aortic surgery,[21] and valve surgery.[22] Therefore, it is unlikely that any difference in mortality risk was solely due to surgical technique.

The present report is the first detailing the association between long-term mortality after cardiothoracic surgery and AKI defined by RIFLE. The RIFLE classification uses the relative change in sCr from baseline to define AKI. This is particularly important for patients with normal renal function and low baseline sCr who develop AKI: They may have a significant relative change in sCr without ever reaching a high absolute sCr. The Society of Thoracic Surgeons National Cardiac Surgery database, the largest clinical database in the field, defines new postoperative renal failure as an sCr >2.0 mg/dL, a doubling of peak postoperative sCr from preoperative creatinine, or a requirement for RRT.[23] Of the 1265 patients with AKI in the present study, 50% had less than a 2-fold increase in sCr, 81% had a maximum sCr <2 mg/dL, and 94% did not require dialysis. This implies that postoperative AKI in the cardiothoracic surgery patient is currently



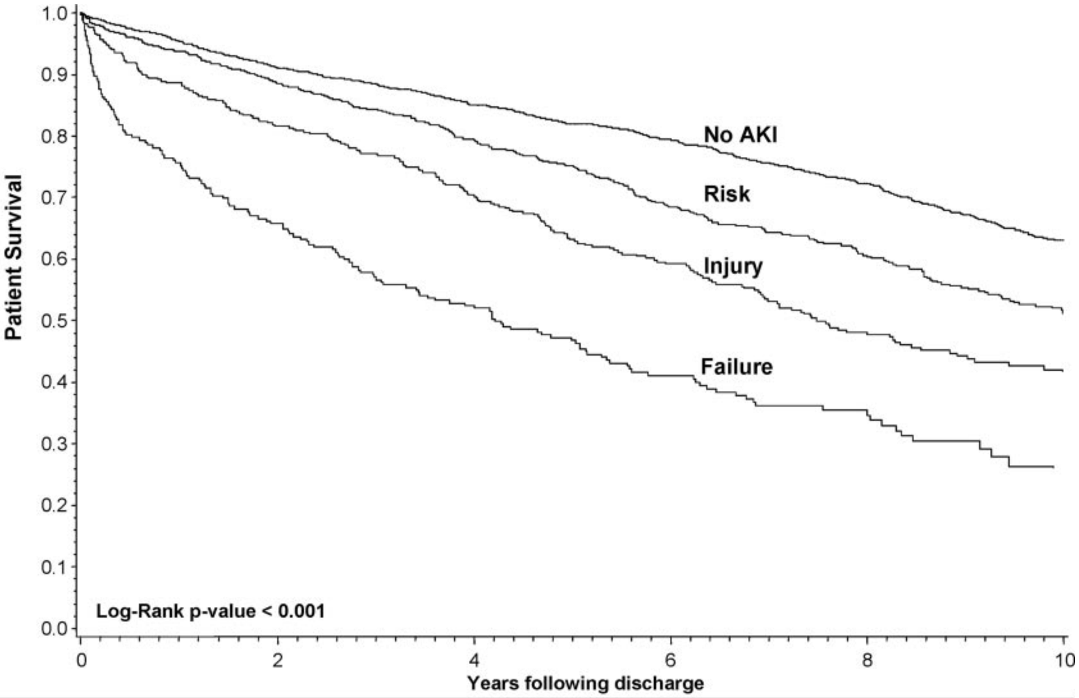
Follow Up (years)		T=0	T=2	T=4	T=6	T=8	T=10
At risk (n)	No AKI	1708	1555	1454	1075	770	465
	AKI	1265	1038	894	624	422	241

Figure 1. Long-term survival of patients with and without an AKI during hospitalization.

going unrecognized. In the present study cohort, 43% of discharged patients had an episode of RIFLE-defined AKI, and only 6% of them required RRT. That only 13% of patients with RIFLE-defined AKI in the present study had an ICD-9-CM code for acute renal failure emphasizes that the prevalence of AKI may also be underestimated when based solely on ICD-9-CM codes for acute renal failure.

The stratification of patients into surgical procedure subgroups and the exclusion of patients with documented CKD provided well-defined and homogeneous study populations. Patients undergoing different procedures may have different risks for long-term mortality, and preoperative CKD is a well-recognized risk factor for in-hospital and postdischarge mortality.[7,13,24] In the present study, less severe AKI was associated with long-term mortality risk for the subgroups of patients undergoing CABG, aortic, and thoracic surgery but not valve surgery. Among valve patients, only those with RIFLE-F class had a significantly higher mortality risk. There was a very high prevalence of congestive heart failure in the valve surgery subgroup (48%), and congestive heart failure was independently associated with long-term mortality in the multivariate model. It is possible that there is overlap between the effects of AKI and congestive heart failure in this group of patients. It is also plausible that the cause of AKI in valve patients is different from that in CABG patients. The factors associated with risk for long-term mortality in the Cox regression model varied among different surgery subgroups, which implies that some of them might be procedure specific.

We can only speculate about possible cause-and-effect relationships between AKI and long-term mortality. In some patients, the operative procedure may have unmasked a latent kidney injury due to hypertension, focal renal artery obstruction, or generalized atherosclerotic disease. This may explain why there was less difference in survival after AKI for patients undergoing valve surgery, because atherosclerosis is a much less important cause of valve disease than of coronary ischemia.[25] It is important to recognize that AKI can be a reflection of the general insult of critical illness on the body, while also being an independent contributor to that critical illness. It is well known that a postoperative systemic inflammatory response syndrome can result after complex cardiothoracic surgery[26,27] and, in a patient with a complicated recovery or with significant comorbid conditions, may contribute to a secondary postoperative AKI. Conversely, perioperative insults may cause AKI that then results in a primary renal inflammatory state with diverse negative distal effects.[28] Although AKI may be viewed as a marker of systemic illness in some patients, it is becoming clear that it can exhibit important independent effects on outcome that extend well beyond discharge from hospital.[29] Seminal early studies



Follow Up (years)		T=0	T=2	T=4	T=6	T=8	T=10
At risk (n)	No AKI	1708	1555	1454	1075	770	465
	Risk	637	564	504	364	259	165
	Injury	386	315	265	181	121	61
	Failure	242	159	125	79	42	15

Figure 2. Long-term survival of patients stratified by AKI severity.

demonstrated that renal blood flow and clearance function can remain impaired for a prolonged period of time after an episode of AKI, despite apparent normalization of sCr.[30] This may account for the intriguing finding that the risk of death remained higher even for those patients whose sCr returned to baseline levels. Several studies have indicated that there is ongoing progressive damage after AKI that results in a decrease in the capillary density of peritubular capillaries, a process known as "rarefaction."[31] This process may be linked to the development of CKD, often with a delayed increase in sCr. Ishani et al[32] reported that elderly individuals with AKI and no previous history of CKD had an AHR of 13 (95% CI 10.6 to 16.0) for the development of end-stage renal disease. The study by Ishani et al[32] was a retrospective analysis of the Medicare database that used ICD-9-CM codes to define AKI among beneficiaries and then linked the occurrence of AKI with the development of end-stage renal disease reported in the United States Renal Data System database. Nonetheless, the Ishani study is the first study to report this association in a large cohort of patients.

The present study has several limitations. First, it is a retrospective observational analysis from which causal inference cannot be derived and which is subject to bias from unmeasured factors. Although we attempted to control for selection bias with multivariate statistical methods and risk adjustment for factors that affect postoperative mortality, we could not completely eliminate the potential for residual confounding. In the absence of a comparable prospective database of AKI, a retrospective study with compensatory statistical methods is a reasonable approach. Second, we did not have data on severity of illness at the time of admission to the ICU (eg, APACHE score [Acute Physiology And Chronic Health Evaluation]). Nevertheless, our model included length of stay in the ICU, as well as the most common ICU complications, thereby accounting for differences in severity of illness. Third, we relied on the assessment of preexisting comorbidities and other postoperative complications using ICD-9-CM codes, based on previously validated criteria.[15–17] Studies based on administrative databases rely on accurate coding, and subtle differences in coding definitions may exist between different institutions. Furthermore, it is possible that the incidence of complications for which the diagnosis was dependent on physician judgment (eg, sepsis) rather than on documentation of a procedure (eg, tracheostomy) might be undercoded and thus underrepresented. Therefore, our risk estimates might represent the lower limit of the true risk for these complications. Although errors and variance in the data may exist, we have assumed that these are randomly distributed and should not lead to significant bias in our conclusions. Fourth, we did not have access to information related to subsequent medical care; however, the risks of mortality associated with sCr change were constant over time, which suggests that events subsequent to hospitalization had little impact on a patient's future event risk. Fifth, our analysis addressed the relationship between all-cause sCr increase and subsequent mortality. The cause of AKI in the postoperative period is usually multifactorial, and the strong

Table 4. Cox Proportional Hazards Model for Patient Mortality After Hospital Discharge

Parameter (Reference Level)	Level	All Patients (n=2973), AHR (95% CI)	Isolated CABG (n=1423; 48%), AHR (95% CI)	Valve Surgery (n=640; 22%), AHR (95% CI)	Aortic Surgery (n=475; 16%), AHR (95% CI)	Thoracic Surgery (n=401; 14%), AHR (95% CI)
AKI (No AKI)		1.38 (1.18–1.52)	1.28 (1.05–1.54)	1.11 (0.84–1.47)	1.79 (1.27–2.51)	1.60 (1.18–2.17)
		P=0.001	*P*=0.01	*P*=0.45	*P*<0.001	*P*=0.002
Type of surgery (CABG)	Valve surgery	1.20 (1.02–1.42)				
		P=0.03				
	Aortic surgery	1.49 (1.24–1.80)				
		P<0.001				
	Thoracic surgery	2.74 (2.19–3.43)				
		P<0.001				
	Heart transplant	0.95 (0.56–1.60)				
		P=0.84				
Demographics						
Age group (18–45 y)	46–60 y	1.54 (1.20–1.98)	1.67 (0.81–3.43)	1.35 (0.81–2.27)	0.97 (0.51–1.81)	1.84 (1.19–2.82)
		P<0.001	*P*=0.17	*P*=0.25	*P*=0.91	*P*=0.005
	61–70 y	2.26 (1.77–2.90)	2.16 (1.06–4.41)	1.92 (1.17–3.16)	1.46 (0.82–2.60)	2.65 (1.68–4.17)
		P<0.001	*P*=0.03	*P*=0.01	*P*=0.19	*P*<0.001
	≥71 y	3.53 (2.75–4.53)	3.20 (1.56–6.54)	3.46 (2.14–5.60)	3.14 (1.75–5.60)	2.86 (1.72–4.75)
		P<0.001	*P*=0.001	*P*<0.001	<0.001	*P*<0.001
Gender (male)	Female	0.92 (0.81–1.03)	0.86 (0.71–1.04)	0.94 (0.73–1.21)	0.83 (0.61–1.13)	0.88 (0.67–1.15)
		P=0.15	*P*=0.12	*P*=0.62	*P*=0.24	*P*=0.37
Ethnicity (white)	Black	0.99 (0.77–1.28)	0.82 (0.48–1.40)	1.30 (0.78–2.15)	1.38 (0.83–2.29)	0.89 (0.49–1.63)
		P=0.96	*P*=0.47	*P*=0.32	*P*=0.22	*P*=0.71
	Other*	0.92 (0.71–1.18)	0.79 (0.53–1.17)	1.10 (0.65–1.83)	1.08 (0.62–1.87)	1.60 (0.64–4.10)
		P=0.50	*P*=0.24	*P*=0.75	*P*=0.78	*P*=0.31
Comorbidities						
Diabetes mellitus (none)	Yes	1.40 (1.22–1.61)	1.43 (1.19–1.73)	1.50 (1.09–2.01)	1.75 (1.08–2.81)	1.18 (0.75–1.85)
		P<0.001	*P*<0.001	*P*=0.01	*P*=0.02	*P*=0.47
Congestive heart failure (none)	Yes	1.34 (1.17–1.53)	1.57 (1.28–1.92)	1.37 (1.04–1.80)	0.93 (0.66–1.32)	1.24 (0.70–2.21)
		P<0.001	*P*<0.001	*P*=0.02	*P*=0.69	*P*=0.45
Chronic pulmonary disease (none)	Yes	1.29 (1.12–1.49)	1.19 (0.94–1.50)	1.25 (0.89–1.77)	2.16 (1.51–3.09)	1.19 (0.89–1.62)
		P<0.001	*P*=0.14	*P*=0.21	*P*<0.001	*P*=0.23
Hypertension (none)	Yes	0.93 (0.83–1.05)	0.96 (0.81–1.15)	0.93 (0.71–1.22)	0.73 (0.55–0.98)	0.93 (0.67–1.28)
		P=0.23	*P*=0.65	*P*=0.61	*P*=0.04	*P*=0.65
Atrial fibrillation (none)	Yes	1.14 (0.99–1.31)	1.18 (0.94–1.47)	1.14 (0.89–1.48)	1.08 (0.78–1.51)	1.14 (0.89–1.48)
		P=0.07	*P*=0.16	*P*=0.30	*P*=0.64	*P*=0.30
IABP (none)†	Yes	1.18 (0.91–1.53)	0.81 (0.57–1.16)	2.08 (1.34–3.25)		
		P=0.21	*P*=0.25	*P*=0.001		
CPB (none)†	Yes	0.88 (0.75–1.03)	1.04 (0.79–1.39)	0.72 (0.50–1.02)	0.97 (0.72–1.31)	
		P=0.11	*P*=0.78	*P*=0.07	*P*=0.86	
Complications						
Mechanical ventilation >96 h (none)	Yes	1.15 (0.97–1.37)	1.63 (1.18-2.25)	1.10 (0.77-1.58)	1.35 (0.96-1.89)	0.86 (0.54–1.37)
		P=0.12	*P*=0.003	*P*=0.26	*P*=0.09	*P*=0.53
Stroke (none)	Yes	1.15 (0.94–1.40)	1.23 (0.94–1.63)	0.82 (0.53–1.27)	1.22 (0.75–1.97)	3.17 (1.13–8.90)
		P=0.18	*P*=0.14	*P*=0.38	*P*=0.43	*P*=0.03
Sepsis (none)	Yes	0.98 (0.71–1.36)	0.87 (0.47–1.68)	1.04 (0.56–1.83)	0.86 (0.50–1.48)	0.92 (0.40–2.10)
		P=0.91	*P*=0.67	*P*=0.89	*P*=0.58	*P*=0.84

(*Continued*)

Table 4. Continued

Parameter (Reference Level)	Level	All Patients (n=2973), AHR (95% CI)	Isolated CABG (n=1423, 48%), AHR (95% CI)	Valve Surgery (n=640, 22%), AHR (95% CI)	Aortic Surgery (n=475; 16%), AHR (95% CI)	Thoracic Surgery (n=401, 14%), AHR (95% CI)
Discharge site (home)	Other‡	1.20 (1.04–1.40)	1.47 (1.14–1.90)	1.45 (1.10–1.92)	1.18 (0.86–1.63)	0.89 (0.55–1.45)
		P=0.02	*P*=0.003	*P*=0.009	*P*=0.29	*P*=0.65
Hospital LOS (0–7 d)	8–11 d	1.11 (0.93–1.33)	1.34 (1.04–1.73)	1.63 (0.93–2.85)	1.02 (0.56–1.88)	0.98 (0.68–1.42)
		P=0.24	*P*=0.25	*P*=0.09	*P*=0.94	*P*=0.92
	12–19 d	1.23 (1.02–1.48)	1.44 (1.09–1.90)	1.76 (0.99–3.07)	1.32 (0.73–2.39)	0.74 (0.49–1.13)
		P=0.03	*P*=0.009	*P*=0.06	*P*=0.36	*P*=0.16
	≥20 d	1.38 (1.11–1.72)	1.96 (1.35–2.85)	2.33 (1.29–4.19)	1.44 (0.77–2.69)	0.89 (0.55–1.45)
		P=0.004	*P*<0.001	*P*=0.004	*P*=0.25	*P*=0.64

IABP indicates intra-aortic balloon pump; CPB, cardiopulmonary bypass; and LOS, length of stay.

*Other includes Asian, Hispanic, and unknown.

†IABP was not included in the model for aortic and thoracic surgery (<1% patients), whereas CPB was not included for thoracic patients (<1% patients).

‡Other includes discharge to in-patient rehabilitation facility, nursing home, and other acute care facilities.

association of mild AKI with hospital mortality was demonstrated regardless of the cause of AKI. Lastly, we were not able to collect information on the cause of death and progression of kidney disease, except with regard to a small subgroup of 41 patients with AKI. Remarkably, 46% of these patients were hemodialysis dependent at the time of death, and 24% were reported to have some degree of CKD. We can only postulate that the development of CKD after discharge is one of the potential mechanisms that exposes these patients to increased cardiovascular morbidity and mortality.[33] We are actively addressing this hypothesis through a newly initiated study to link our database with the United States Renal Data System database.

In conclusion, in a single-center cohort of 2973 cardiothoracic surgery patients with no previous history of CKD who

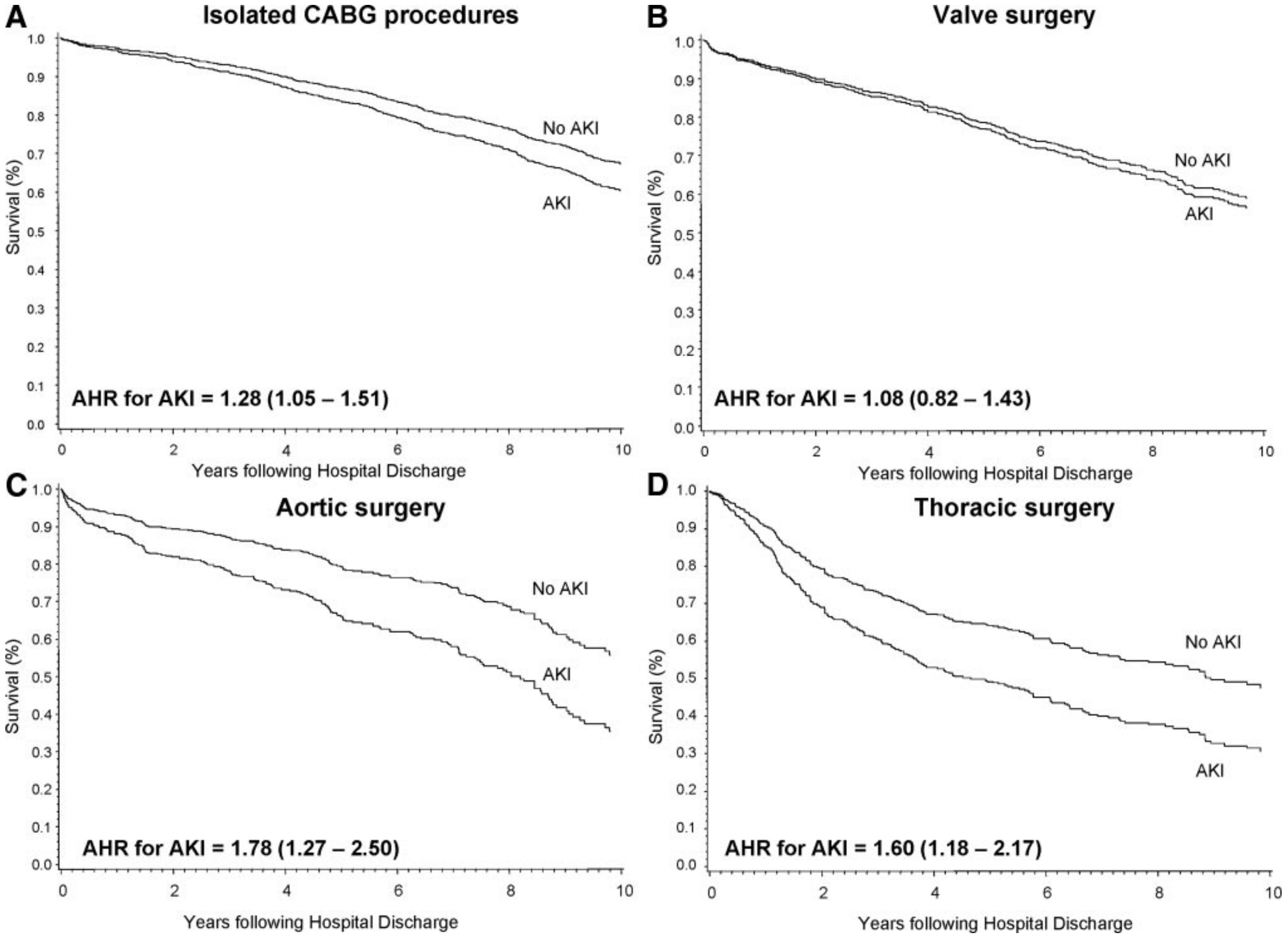
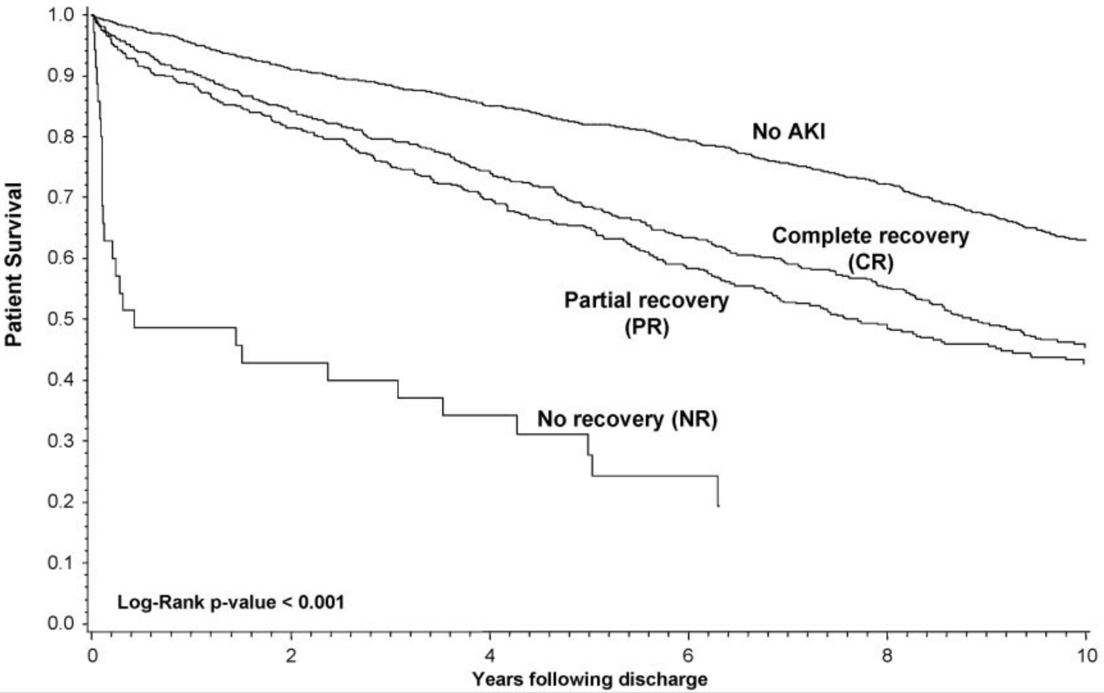


Figure 3. Long-term survival of patients with and without an AKI during hospitalization, stratified by individual surgery type. AKI group includes all patients with AKI, regardless of severity. Survival curves are adjusted for the mean level of model covariates listed in Table 2.



Follow Up (years)		T=0	T=2	T=4	T=6	T=8	T=10
At risk (n)	No AKI	1708	1555	1454	1075	770	465
	CR	754	635	555	380	259	141
	PR	476	388	327	238	160	100
	NR	35	15	12	6	3	0

Figure 4. Long-term survival of patients with and without an AKI during hospitalization, stratified by degree of renal recovery.

required at least a 24-hour admission to a cardiothoracic surgery ICU, we demonstrated an independent association between RIFLE-defined AKI and long-term mortality risk. This risk was consistent, dose responsive, and present during 10 years of follow-up. Although we cannot statistically conclude that the type of surgery modifies the effect of AKI on mortality, the present results suggest that further follow-up of the specific role of AKI in different surgical groups is warranted. Even for patients with complete renal recovery at the time of discharge, the risk of dying was higher than for patients with no AKI.

The present study confirmed that the RIFLE classification provides a useful tool for identifying patients with AKI in the perioperative setting and may also identify patients with increased risk for long-term mortality. In doing so, the present study may prompt closer monitoring after discharge of the patient who sustains perioperative AKI, given that follow-up for mild AKI currently is almost nonexistent in clinical practice. AKI may result in ongoing progressive renal damage beyond the acute episode, despite apparent normalization of sCr. This is an important insight for all physicians who care for postoperative cardiothoracic surgery patients, and future studies will need to determine the optimal post-discharge follow-up of renal function for patients with small perioperative increases in sCr, regardless of renal recovery at the time of discharge. This is especially important given that even mild CKD is a significant risk factor for cardiovascular disease and death.

Table 5. Cox Proportional Hazards Model for Patient Mortality Stratified by Renal Recovery at the Time of Discharge*

Parameter (Reference Level)	Level	AHR†	95% CI	*P*
Renal recovery at time of discharge (no AKI)	Complete recovery	1.28	1.11–1.48	<0.001
	Partial recovery	1.49	1.27–1.74	<0.001
	No recovery	3.76	2.46–5.74	<0.001

*Model additionally adjusted for all variables listed in Table 2.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In a single-center cohort of 2973 patients with no previous history of kidney disease who were discharged from the hospital after cardiothoracic surgery, acute kidney injury (AKI) with even small changes in serum creatinine level during hospitalization was associated with an independent long-term risk of death. Most importantly, even patients with complete renal recovery had an increased risk of death for up to 10 years compared with patients without AKI. Although AKI may be a marker of severe systemic illness in some patients, it is becoming clear that severe kidney injury can exhibit important independent effects on outcome that may extend well beyond discharge from the hospital. The effect of less severe AKI on long-term outcomes is less well understood, and in fact, the finding that patients with complete recovery after AKI had long-term outcomes comparable to those patients with only partial recovery may point toward some still unknown independent effect of mild AKI on long-term longevity. The findings of the present study promote efforts to identify and minimize renal-injurious interventions before surgery. Perhaps more important is follow-up for patients who sustain mild to moderate postoperative AKI, which is almost nonexistent in current clinical practice. This study may prompt closer monitoring of the patient who sustains postoperative AKI, as well as more aggressive attempts to protect this patient from any further injury to the kidney. This is especially important given that even mild chronic kidney disease is a significant risk factor for cardiovascular disease and death.

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