Minor Postoperative Increases of Creatinine Are Associated with Higher Mortality and Longer Hospital Length of Stay in Surgical Patients

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ABSTRACT

Background: Surgical patients frequently experience postoperative increases in creatinine levels. The authors hypothesized that even small increases in postoperative creatinine levels are associated with adverse outcomes.

Methods: The authors examined the association of postoperative changes from preoperative baseline creatinine with all-cause in-hospital mortality and hospital length of stay (HLOS) in a retrospective analysis of surgical patients at a single tertiary care center between January 2006 and June 2012.

Results: The data of 39,369 surgical patients (noncardiac surgery n = 37,345; cardiac surgery n = 2,024) were analyzed. Acute kidney injury (AKI)—by definition of the Kidney Disease: Improving Global Outcome group—was associated with a five-fold higher mortality (odds ratio [OR], 4.8; 95% CI, 4.1 to 5.7; $P < 0.001$) and a longer HLOS of 5 days ($P < 0.001$) after adjusting for age, sex, comorbidities, congestive heart failure, preoperative hemoglobin, preoperative creatinine, exposure to radiocontrast agent, type of surgery, and surgical AKI risk factors. Importantly, even minor creatinine increases (Δcreatinine 25 to 49% above baseline but < 0.3 mg/dl) not meeting AKI criteria were associated with a two-fold increased risk of death (OR, 1.7; 95% CI, 1.3 to 2.4; $P < 0.001$) and 2 days longer HLOS ($P < 0.001$). This was more pronounced in noncardiac surgery patients. Patients with minor creatinine increases had a five-fold risk of death (OR, 5.4; 95% CI, 1.5 to 20.3; $P < 0.05$) and a 3-day longer HLOS ($P < 0.01$) when undergoing noncardiac surgery.

Conclusions: Even minor postoperative increases in creatinine levels are associated with adverse outcomes. These results emphasize the importance to find effective therapeutic approaches to prevent or treat even mild forms of postoperative kidney dysfunction to improve surgical outcomes. **(Anesthesiology 2015; 123:1301-11)**

A WORLD Health Organization–funded study estimates that approximately 230 million surgical procedures are undertaken every year worldwide.[1] Although various efforts are associated with declining surgical mortality rates, organ injury remains an important cause for adverse postoperative outcomes.[2] With an estimated incidence of approximately 1% in noncardiac surgery patients, acute kidney injury (AKI) is one of the leading causes for postoperative organ failure,[3,4] with a similar occurrence rate as myocardial infarction.[5,6]

Acute kidney injury has been associated with higher mortality, morbidity, and costs in hospitalized patients.[7–9] However, its impact on morbidity and hospital length of stay (HLOS) in surgical patients is unclear. Perioperatively,

What We Already Know about This Topic

- Acute kidney injury (AKI) is a common form of postoperative organ failure. Recently, even minor kidney function impairment below AKI criteria has been linked to higher surgical morbidity and mortality.
- This study is a single-center, retrospective cohort study that investigated the impact of AKI on in-hospital mortality and hospital length of stay after noncardiac and cardiac surgery.

What This Article Tells Us That Is New

- Even minor creatinine increases not meeting acute kidney injury criteria were associated with an increased risk of death and hospital length of stay, and this risk was more pronounced in noncardiac compared with cardiac surgical patients.

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numerous events can occur that each by itself may impair kidney function: exposure to radiocontrast agent or other nephrotoxic medicaments,[10–12] hypovolemia and hypotension including reperfusion injury,[13,14] cardiopulmonary bypass (CPB),[8,15,16] and postoperative infection or inflammation with possible sepsis.[17–19]

Whereas postoperative AKI is a common and thus well-investigated complication in cardiac surgery patients, the significance of AKI in the many times larger population of noncardiac surgery patients is less evident. Recently, even minor kidney function impairment below AKI criteria has been linked to higher morbidity and mortality in hospitalized patients.[20–22] Similarly, other studies suggested in the context of myocardial injury that minor increases in troponin T values—only detectable by high-sensitivity cardiac troponin assays—are associated with postoperative myocardial injury and long-term mortality after noncardiac surgery.[23] In contrast, the impact of AKI and particularly of minor kidney function impairment on outcomes in undistinguished noncardiac surgery populations is unknown.

On the basis of the studies suggesting that minor postoperative myocardial injury could be associated with adverse outcomes in surgical patients,[23,24] we hypothesized, before data collection and analysis, that also minor increases in postoperative creatinine values—indicating subclinical postoperative kidney dysfunction not meeting AKI criteria—could be associated with adverse outcomes in surgical patients. Therefore, we conducted a single-center retrospective cohort study to investigate the impact of AKI on in-hospital mortality and HLOS in a broad population of surgical patients. Particularly, we also examined minor creatinine increases not fulfilling AKI criteria and their impact on mortality and morbidity. In an additional *post hoc* analysis based on the examinations of the data, we compared the influence of AKI on patients' outcome after noncardiac surgery compared with cardiac surgery.

Materials and Methods

Patients

The institutional ethics committee (Ethikkommission, Charité–Universitätsmedizin Berlin, Berlin, Germany) approved the study and waived the requirement for informed consent (EA1/303/11). The trial was registered before data collection at ClinicalTrials.gov (NCT01522313) on January 23, 2012 (principle investigator: C.D.S.). All patients undergoing surgical procedures between January 2006 and June 2012 at the *Campus Charité Mitte* and *Campus Virchow-Klinikum*, Charité–Universitätsmedizin Berlin, Berlin, Germany, were considered eligible for inclusion if they had at least one preoperative creatinine measurement within 28 days before the procedure. Patients with end-stage renal disease, preoperative need of renal replacement therapy, or undergoing nephrectomy or kidney transplantation were excluded. End-stage renal disease and respective procedures were obtained from administrative data that store diagnoses and procedures in codes based on the *International Statistical Classification of Diseases and Related Health Problems,* Tenth Revision (ICD-10; *e.g.*, N18.6 signifies end-stage renal disease and is applicable for chronic kidney disease requiring renal replacement therapy) and the German procedure classification codes (*Operationen- und Prozedurenschlüssel* [OPS; *e.g.*, 5–502.1 signifies right hemihepatectomy], an adaptation of the International Classification of Procedures in Medicine).

Data Collection

We extracted patients' data from two sources and combined them in one MySQL database (MySQL Community Server, USA). From the hospital data management system (SAP, Germany), we acquired age, sex, ICD-coded diagnoses, OPS-coded procedures, creatinine (Cr) levels, postoperative intensive care unit stay, HLOS (interval between surgery and discharge or death), and in-hospital mortality. From the electronically archived anesthesia protocols (Medlinq Softwaresysteme, Germany), we acquired the surgical discipline, priority and location of the surgery, and intraoperative transfusions. For patients undergoing more than one surgical procedure during their stay, only data of the first surgical procedure were analyzed. The Charlson Comorbidity Index[25] with all its items (including congestive heart failure) was abstracted from the ICD diagnoses as described by Quan *et al.*,[26] and whether the patient received any radiocontrast agent before the surgery was abstracted from the OPS codes.

Definition of AKI and AKI Severity

Acute kidney injury was diagnosed by the definition of the Kidney Disease: Improving Global Outcome (KDIGO) group,[27] considering the maximum increase during the first 7 postoperative days (PODs):

$$\Delta Cr = \text{Maximum}\left(Cr_{POD1}, Cr_{POD2}, \ldots, Cr_{POD7}\right) / Cr_{preop}.$$

The KDIGO AKI classification is the most recently published AKI classification,[27] merged Risk, Injury, Failure, Loss of kidney function, End-stage renal disease (RIFLE) and Acute Kindney Injury Network (AKIN) criteria,[28–30] and leads to the most frequent diagnosis of AKI.[31] Based on the maximum value of available postoperative creatinine, patients were categorized in mutually exclusive categories of creatinine change and corresponding stages of AKI according to the KDIGO definition,[27] including no follow-up (no F/U), no measured increase ($\Delta Cr \leq 0\%$), slight increase (ΔCr 1 to 24%), minor increase (ΔCr 25 to 49%), KDIGO stage 1 (ΔCr 50 to 99%, corresponding to RIFLE R or AKIN 1), KDIGO stage 2 (ΔCr 100 to 199%, RIFLE I or AKIN 2), and KDIGO stage 3 ($\Delta Cr \geq 200\%$, RIFLE F or AKIN 3).[27,29,30] According to KDIGO guidelines, patients were categorized to the highest category possible.[27] Creatinine

increases below KDIGO AKI criteria were dichotomized according to previous studies.[20–22,32–34] The estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease formula.[35]

In routine clinical practice, not all patients have postoperative creatinine follow-up measurements on a daily basis, hence leading to missing data. Categorizing patients by creatinine increase in mutually exclusive categories as described in the paragraph above resulted in a data set without any missing values for the analyses. This approach was considered unlikely to create substantial bias because it took the worst kidney function impairment into account that was measured postoperatively. However, we did perform additional sensitivity analyses to evaluate the stability of our findings.

Statistical Analyses

Sample size was not calculated beforehand as common in retrospective cohort studies. Assuming the effect size of small creatinine increases on in-hospital mortality to be small, a convenience sample as big as possible was obtained being limited by the availability of electronic data from the machine-readable anesthesia protocols starting January 2006.

Frequencies are reported as numbers and percentages with 95% CIs when appropriate, and continuous variables are presented as median with interquartile range (IQR) if normality was ruled out by histograms or Q-Q-plots. Categorical data were compared using the chi-square test, continuous data using the Mann–Whitney U test, and the Kruskal–Wallis test as indicated.

For all regression models including Cox proportional hazard models, covariate selection was based on clinical assessment, factors described in previous studies, and availability from our databases. Age, sex, and variables associated with bivariate association ($P < 0.1$) were introduced to the final models. We considered patient-attributed risks for AKI (age, preoperative kidney function, and comorbidities), surgery-attributed risks (intrathoracic surgery, abdominal surgery, need for transfusion, and emergency surgery), cardiac surgery, preoperative exposure to radiocontrast agent, and postoperative intensive care unit admission as potential confounders.

Modeling HLOS was conducted using a multiple robust regression model with Huber function. Usual linear multiple regression models may be incorrect for not normally distributed dependent variables and lead to incorrect variances, covariances, and hence incorrect CIs and Wald tests. For this case, Huber provided a robust sandwich estimator for the covariance matrix, which was used for the extremely skewed distribution of HLOS.

For Kaplan–Meier curves and corresponding Cox proportional hazard models, time to event was considered as interval between surgery and discharge or death. When analyzing in-hospital death as dependent variable, patients were censored at hospital discharge; when analyzing discharge as dependent variable, patients were censored at the time of death.

To evaluate for bias, we performed sensitivity analyses limited to subgroups with limited/no missing daily creatinine values, as well as limiting the analyses to early creatinine values (POD 1 or POD 2) for greater uniformity.

Binary logistic regression models, Cox proportional hazard regression models, and all other calculations were conducted using IBM SPSS Statistics version 22, robust regression using R 3.0 (The R Foundation for Statistical Computing, Austria; http://www.R-project.org/). Figures were created using GraphPad Prism 6 (GraphPad, USA). Exact testing was conducted whenever applicable. The probability of a type I error less than 5% was considered to be statistically significant.

Results

Study Population

During the study period, preoperative creatinine was measured in 42,078 of 241,931 patients (17.4%). Out of those 42,078 patients, 2,718 patients were excluded because of preexisting end-stage renal disease (1,677 patients), because of preoperative renal replacement therapy (610 patients), or because they had a nephrectomy or kidney transplantation as surgical intervention (431 patients). The data of 39,369 patients were analyzed (fig. 1A).

Patients had a median age of 60 yr (IQR, 45 to 72), 48% were female, and had a median Charlson Comorbidity Index of 3 (IQR, 1 to 5). The most frequent comorbidities were malignancies (31%), diabetes without complications (17%), and metastatic solid tumor (11%; table 1). In the 39,369 patients analyzed, overall all-cause in-hospital mortality was 2.2%, and patients stayed in the hospital for a median of 5 ays (IQR, 3 to 10). The frequencies of different types of surgeries are displayed in figure 1B. AKI rate was highest in cardiac surgery patients with 35.2% and second highest with 9.3% in general surgery patients (for postoperative course of creatinine and glomerular filtration rate as well as frequency of creatinine assessments, see Supplemental Digital Content 1, http://links.lww.com/ALN/B200).

Association of AKI and Postoperative Mortality and HLOS

Among the patients analyzed in the study (39,369 patients), a total of 2,465 patients (6.3%; 95% CI, 6.0 to 6.5%) developed postoperative AKI. Patients with AKI experienced higher mortality rates (410 of 2,465 [16.6%; 95% CI, 15.2 to 18.2%] *vs.* 442 of 36,904 [1.2%; 95% CI, 1.1 to 1.3%]; $P < 0.001$) and stayed longer in the hospital (15 days [IQR, 8 to 29] *vs.* 5 days [IQR, 3 to 9]; $P < 0.001$). These findings remained highly significant after multivariable adjustment for age, sex, comorbidities, congestive heart failure, preoperative hemoglobin, preoperative creatinine, preoperative administration of radiocontrast agent, cardiac surgery, intraoperative risk factors, and postoperative intensive care unit admission: postoperative AKI was independently associated with a five-fold risk of all-cause in-hospital death (odds ratio

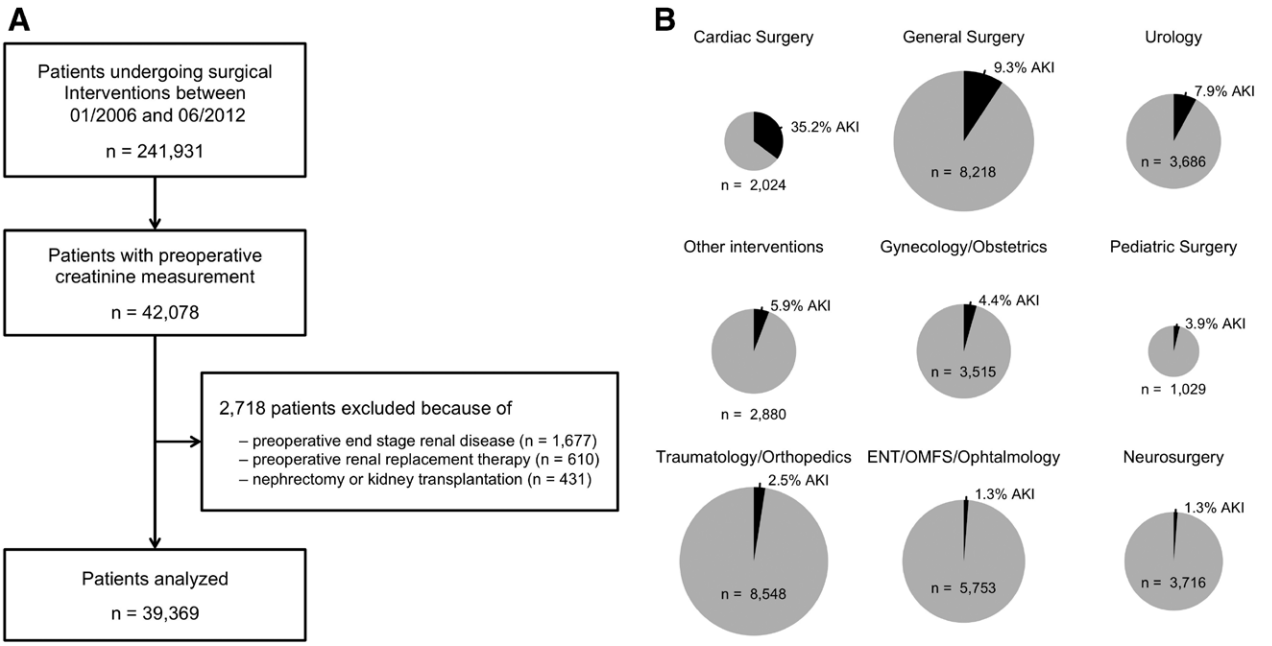

Fig. 1. Study cohort. (*A*) Flow chart of the composition of the study population. (*B*) Study population by surgical discipline with corresponding rates of acute kidney injury (AKI) by definition of the Kidney Disease: Improving Global Outcome group[27]; areas within and between pie charts correspond to the number of cases. ENT = ear–nose–throat; OMFS = oral and maxillofacial surgery.

[OR], 4.8; 95% CI, 4.1 to 5.7; $P < 0.001$) and a longer HLOS of 5 days (β = 4.8; 95% CI, 4.5 to 5.0; $P < 0.001$).

Association of AKI Severity and Postoperative Outcome

Mortality. Mortality was higher in patients with more severe AKI. Interestingly, even patients with only minor creatinine increases (ΔCr 25 to 49%, not meeting AKI criteria) experienced higher mortality rates compared with patients without creatinine increases (5.5 *vs.* 2.3%; $P < 0.001$; fig. 2A). Minor creatinine increases remained significantly associated after multivariable adjustment with a two-fold risk for in-hospital death (OR, 1.7; 95% CI, 1.3 to 2.4; $P < 0.001$; table 2). A Kaplan–Meier analysis and a corresponding Cox proportional hazard model confirmed these findings. The more severe AKI, the greater the hazard ratio (HR) for in-hospital death, already present at minor creatinine increases below AKI criteria (ΔCr 25 to 49%: HR, 1.4; 95% CI, 1.0 to 1.8; $P < 0.05$; fig. 2B and table 2).

We additionally performed sensitivity analyses to rule out possible bias due to missing creatinine follow-up measurements. First, we analyzed the subgroup of patients with creatinine measurements during at least 6 of the first 7 PODs (n = 3,338). The multivariable binary logistic regression confirmed our original findings: a minor creatinine increase was associated with a similar risk of death (ΔCr 25 to 49%: OR, 1.6; 95% CI, 1.0 to 2.5; $P < 0.05$) as in the entire study population (n = 39,369). Second, we conducted a binary logistic regression in the entire study population (n = 39,369), but this time only considered creatinine measurements of POD1 and POD2 when categorizing creatinine increase (ΔCr = maximum [Cr_{POD1}, Cr_{POD2}] / Cr_{preop}). The results showed an association of minor creatinine increases with in-hospital death (ΔCr 25 to 49%: OR, 1.5; 95% CI, 1.0 to 2.2; $P < 0.05$) similar to the association when considering creatinine measurements of all 7 PODs.

Hospital Length of Stay. Similar to the above findings on in-hospital mortality, HLOS was longer in patients with more severe AKI ($P < 0.001$; fig. 2C). Patients with only minor increases of creatinine (ΔCr 25 to 49%; not meeting AKI criteria) experienced longer HLOSs compared with patients without creatinine increases (12 days [IQR, 8 to 21] *vs.* 9 days [IQR, 5 to 14], $P < 0.001$; fig. 2C). After multivariable adjustment, a minor creatinine increase below AKI criteria remained associated with a longer hospital stay of 2 days (β = 2.4; 95% CI, 2.1 to 2.7; $P < 0.001$; table 2). Kaplan–Meier analysis and a corresponding Cox proportional hazard regression confirmed that the more severe degree of AKI, the longer the patient stayed in the hospital, including patients with minor creatinine increases (HR, 0.80; 95% CI, 0.75 to 0.86; $P < 0.001$; fig. 2D and table 2).

Association of AKI Severity and Postoperative Outcome in Noncardiac versus Cardiac Surgery Patients

The characteristics of the study population separated into noncardiac and cardiac surgery patients are presented in Supplemental Digital Content 2, http://links.lww.com/ALN/B201. Analyzing all patients from the study population, noncardiac surgery was associated with a higher risk of in-hospital death (OR, 1.9; 95% CI, 1.5 to 2.6; $P < 0.001$) and a longer HLOS (β = 2.3; 95% CI, 2.0 to 2.5; $P < 0.001$; table 2). Due to the fact that previous studies had found AKI in cardiac surgery patients associated with increased morbidity and mortality, we performed subgroup analyses according to the severity of

Table 1. Characteristics of the Study Cohort

Characteristics	n = 39,369
Age, median (IQR), yr	60 (45–72)
Sex	
Female, No. (%)	18,814 (47.8)
Male, No. (%)	20,555 (52.2)
Charlson Comorbidity Index, median (IQR)	3 (1–5)
Any malignancy, No. (%)	12,115 (30.9)
Diabetes without chronic complication, No. (%)	6,743 (17.1)
Metastatic solid tumor, No. (%)	4,446 (11.3)
Chronic pulmonary disease, No. (%)	3,354 (8.5)
Peripheral vascular disease, No. (%)	3,074 (7.8)
Congestive heart failure, No. (%)	2,972 (7.5)
Renal disease, No. (%)	2,706 (6.9)
Cerebrovascular disease, No. (%)	1,972 (5.0)
Myocardial infarction, No. (%)	1,918 (4.9)
Mild liver disease, No. (%)	1,891 (4.8)
Hemiplegia or paraplegia, No. (%)	1,673 (4.3)
Diabetes with chronic complication, No. (%)	698 (1.8)
Rheumatic disease, No. (%)	516 (1.3)
Dementia, No. (%)	387 (1.0)
Peptic ulcer disease, No. (%)	316 (0.8)
Moderate or severe liver disease, No. (%)	284 (0.7)
AIDS/HIV, No. (%)	80 (0.2)
Preoperative hemoglobin, median (IQR), mg/dl	13.5 (12.2–14.6)
Preoperative creatinine, median (IQR), mg/dl*	0.84 (0.70–1.01)
Severity of postoperative AKI†	
No F/U, No. (%)	22,689 (57.6)
ΔCr ≤ 0%, No. (%)	7,904 (20.1)
ΔCr 1–24%, No. (%)	5,159 (13.3)
ΔCr 25–49%, No. (%)	1,152 (2.9)
KDIGO stage 1, No. (%)	1,464 (3.7)
KDIGO stage 2, No. (%)	337 (0.9)
KDIGO stage 3, No. (%)	664 (1.7)
All-cause in-hospital mortality, No. (%)	852 (2.2)
Hospital length of stay, median (IQR)‡	5 (3–10)

* International Systems of Units conversion factor: to convert creatinine to μM, multiply values by 76.3. † Mutually exclusive categories of AKI severity by definition of the KDIGO group.[27] ‡ Interval between operation and discharge or death.

AIDS = acquired immune deficiency syndrome; AKI = acute kidney injury; Cr = creatinine; F/U = follow-up; HIV = human immunodeficiency virus; IQR = interquartile range; KDIGO = Kidney Disease: Improving Global Outcome.

AKI comparing the impact of noncardiac to cardiac surgery on mortality and HLOS. Supplemental Digital Content 3, http://links.lww.com/ALN/B202, presents four models describing the association of AKI severity on postoperative outcome in the cardiac surgery patients of the study population.

The impact of minor creatinine increases (ΔCr 25 to 49%) on mortality was more pronounced in noncardiac surgery patients compared with cardiac surgery patients. Patients with minor creatinine increases died more often after noncardiac surgery compared with patients after cardiac surgery (6.4 *vs.* 1.4%, $P < 0.01$; fig. 3A). These findings were confirmed by multivariable adjustment. Noncardiac surgery was associated with a five-fold risk of in-hospital death in patients with minor creatinine increase ($OR_{noncardiac}$, 5.4; 95% CI, 1.5 to 20.3; $P < 0.05$; fig. 3B). Similar to mortality, noncardiac surgery was associated with a 3-day longer HLOS in patients with minor creatinine increases after multivariable adjustment ($\beta_{noncardiac} = 2.87$; 95% CI, 1.07 to 4.68; $P < 0.01$; fig. 3, C and D).

Discussion

In this single-center retrospective cohort study, we investigated the impact of AKI on in-hospital mortality and HLOS in a broad population of surgical patients. We found that AKI was independently associated with a six-fold increased risk of in-hospital death. Patients with more severe AKI experienced higher rates of mortality and a longer HLOS. Surprisingly, we also found that even minor postoperative creatinine increases not fulfilling AKI criteria were independently associated with a two-fold risk of in-hospital death and a 3-day longer hospital stay. We were also surprised by the finding that noncardiac surgery patients with milder forms of AKI had a higher risk of in-hospital death and longer HLOS compared with cardiac surgery patients with corresponding AKI severity. Together, these findings highlight that even mild forms of AKI significantly impact the outcome of surgical patients.

Acute kidney injury occurred in 6% of this study population that was selected by preoperative creatinine measurement. Assuming that patients without preoperative creatinine measurement did not develop AKI and considering all 241,931 patients undergoing surgery during the study period (including those without preoperative creatinine measurement; fig. 1A), a total of 2,465 patients developing AKI in this surgical population would result in an incidence of 1.0%. This concurs with previous studies in similar populations of noncardiac surgery patients.[3,4] Similarly, the much higher AKI incidence (35%) in cardiac surgery patients corresponds with previous studies.[8] Moreover, our findings indicate that the manifestation of more severe forms of AKI occurs less frequently in surgical patients. However, the risk of death gradually increased dependent on the severity of AKI. This epidemiology in surgical patients is consistent with previous studies in other cohorts of hospitalized patients.[7–9,18,20,22,32]

In contrast, the association of minor creatinine increases not fulfilling AKI criteria with adverse outcome has not been shown in noncardiac surgical patients before. Some studies have linked minor creatinine increases to higher mortality in small subsets of cardiac surgery patients. These studies categorized patients by absolute creatinine increases,[21,34,36] by relative creatinine increase[32,37] or by AKI stages.[38,39] Although explicitly accounting for minor creatinine changes, the patients identified as "at risk" were either likely to be diagnosed as stage 1 AKI by current AKI definition or the study failed to identify all patients at risk. Our findings decisively contrast these studies by demonstrating for the first time in a large and broad surgical patient sample that even minor creatinine increases below the current AKI criteria—*i.e.*, ΔCr 25 to 49% but not ≥ 0.3 mg/dl—are independently

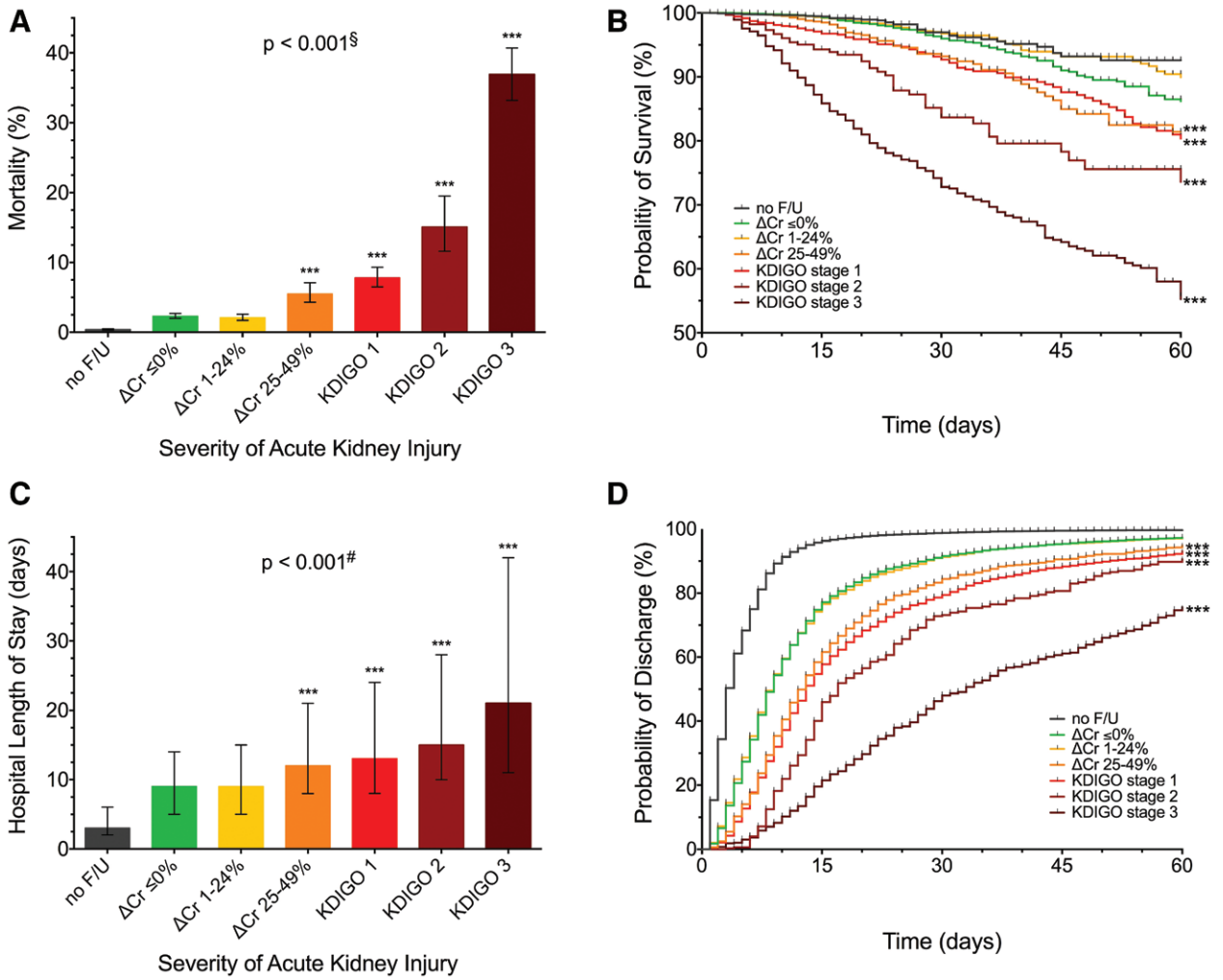

Fig. 2. Postoperative outcome by severity of acute kidney injury. (*A*) In-hospital mortality (95% CI) gradually increases the more severe the acute kidney injury; §global chi-square test; ***$P < 0.001$ compared with ≤ 0% increase in creatinine (chi-square tests). (*B*) Probability of survival gradually decreases the higher the postoperative creatinine increase (Kaplan–Meier survival curves); ***$P < 0.001$ compared with ≤ 0% increase in creatinine (generalized Wilcoxon tests). (*C*) Hospital length of stay (median and quartiles) gradually increases the higher the postoperative creatinine increase; #Kruskal–Wallis test; ***$P < 0.001$ compared with ≤ 0% increase in creatinine (Mann–Whitney U tests). (*D*) Probability of discharge gradually decreases the higher the postoperative creatinine increase (Kaplan–Meier response curves); ***$P < 0.001$ compared with ≤ 0% increase of creatinine increase (generalized Wilcoxon tests). Cr = creatinine; KDIGO = Kidney Disease: Improving Global Outcome; no F/U = no follow-up.

associated with a two-fold risk of in-hospital death and a longer hospital stay. Although we dichotomized creatinine increases below AKI criteria at arbitrary 25% because this was used in previous studies,[20–22,32–34] a receiver operating characteristic curve and a Youdon's J statistic support these findings. The best cutoff for predicting in-hospital mortality was a postoperative creatinine increase of 19%.

Despite the impact on morbidity and mortality shown in the current study, minor creatinine increases may frequently be overlooked in routine clinical practice. Just as increased postoperative creatinine measurements, even small increases within the reference range were associated with higher mortality and longer HLOS. In fact, 44% of the outcome-relevant minor creatinine increases in our sample had an increase to a maximum that was within the laboratory reference range (0.5 to 0.9 mg/dl for women and 0.7 to 1.2 mg/dl for men), making it even harder to spot these changes in clinical routine. Clinicians—before this study—were likely not aware of the potential impact that mild kidney function impairment could have on outcomes, *i.e.*, KDIGO stage 1 AKI and in particular minor creatinine increases below AKI criteria. Recently, automatic alert systems have been reported to be helpful in timely AKI diagnosis.[40,41] However, as those systems use current AKI criteria, they will fail to alert clinicians about patients who are at risk for postoperative complications due to increased creatinine levels below AKI criteria, as were identified in our study. The KDIGO clinical practice guideline for AKI recommends a number of measures to undertake in patients at risk of and with AKI, *i.e.*, discontinuation of nephrotoxic agents when possible, ensuring

Table 2. Four Models Describing the Association of AKI Severity with Postoperative Outcome

	Mortality				Morbidity			
	In-hospital Death		Survival*		Hospital Length of Stay†		Discharge‡	
	P Value	OR (95% CI)	*P* Value	HR (95% CI)§	*P* Value	β (95% CI)	*P* Value	HR (95% CI)‖
Constant#	<0.001	—	—	—	<0.001	9.75 (9.21–10.30)	—	—
Age, yr	0.002	0.99 (0.99 to 1.00)	0.39	1.00 (0.99 to 1.01)	0.30	−0.00 (−0.01 to 0.00)	<0.001	1.00 (1.00 to 1.00)
Sex, female *vs.* male	0.19	0.90 (0.77 to 1.05)	0.67	0.97 (0.84 to 1.12)	0.08	0.09 (−0.01 to 0.20)	0.27	0.99 (0.97 to 1.01)
Charlson Comorbidity Index	<0.001	1.18 (1.16 to 1.21)	<0.001	1.13 (1.11 to 1.15)	<0.001	0.17 (0.16 to 0.19)	<0.001	0.96 (0.96 to 0.96)
Congestive heart failure	<0.001	2.15 (1.77 to 2.61)	<0.001	1.61 (1.36 to 1.89)	<0.001	1.12 (0.91 to 1.33)	<0.001	0.85 (0.81 to 0.89)
Preoperative hemoglobin, mg/dl	<0.001	0.79 (0.76 to 0.86)	<0.001	0.87 (0.84 to 0.90)	<0.001	−0.38 (−0.40 to −0.35)	<0.001	1.09 (1.08 to 1.10)
Preoperative creatinine, mg/dl**	0.08	0.90 (0.80 to 1.01)	0.55	0.97 (0.88 to 1.07)	<0.001	−1.11 (−1.24 to −0.98)	<0.001	1.20 (1.17 to 1.24)
Radiocontrast agent††	<0.001	1.90 (1.61 to 2.25)	<0.001	1.48 (1.28 to 1.72)	<0.001	0.72 (0.55 to 0.89)	<0.001	0.87 (0.84 to 0.90)
Noncardiac *vs.* cardiac surgery	<0.001	1.94 (1.48 to 2.55)	0.002	1.43 (1.14 to 1.78)	<0.001	2.27 (1.99 to 2.54)	0.003	0.92 (0.87 to 0.97)
Risk factors of surgical AKI‡‡								
1 risk factor	0.93	1.01 (0.83 to 1.23)	0.69	1.04 (0.97 to 1.49)	0.86	−0.01 (−0.13 to 0.11)	0.14	1.02 (0.99 to 1.05)
2 risk factors	0.09	1.23 (0.97 to 1.58)	0.10	1.20 (0.97 to 1.49)	<0.001	1.04 (0.79 to 1.28)	0.15	0.96 (0.92 to 1.01)
≥ 3 risk factors	<0.001	3.27 (2.28 to 4.69)	<0.001	1.98 (1.49 to 2.63)	<0.001	4.25 (3.55 to 4.96)	<0.001	0.65 (0.56 to 0.74)
Postoperative ICU admission	<0.001	2.54 (2.09 to 3.09)	0.004	1.31 (1.09 to 1.58)	<0.001	4.83 (4.69 to 4.98)	<0.001	0.57 (0.56 to 0.59)
Severity of AKI§§								
No F/U	0.001	0.60 (0.45 to 0.81)	0.35	0.87 (0.65 to 1.16)	<0.001	−2.27 (−2.42 to −2.13)	<0.001	1.70 (1.65 to 1.75)
ΔCr 1–24%	0.49	0.92 (0.71 to 1.17)	0.19	0.85 (0.67 to 1.08)	0.001	0.28 (0.11 to 0.45)	0.81	1.00 (0.97 to 1.04)
ΔCr 25–49%	<0.001	1.74 (1.28 to 2.38)	0.04	1.36 (1.02 to 1.82)	<0.001	2.44 (2.12 to 2.75)	<0.001	0.80 (0.75 to 0.86)
KDIGO stage 1	<0.001	2.21 (1.69 to 2.87)	<0.001	1.55 (1.22 to 1.98)	<0.001	2.88 (2.58 to 3.17)	<0.001	0.77 (0.72 to 0.82)
KDIGO stage 2	<0.001	3.82 (2.65 to 5.52)	<0.001	2.24 (1.62 to 3.09)	<0.001	5.12 (4.52 to 5.71)	<0.001	0.65 (0.58 to 0.73)
KDIGO stage 3	<0.001	15.64 (12.07 to 20.28)	<0.001	4.46 (3.57 to 5.56)	<0.001	10.87 (10.36 to 11.37)	<0.001	0.38 (0.34 to 0.42)

On the left, a binary logistic regression model estimating the OR and a corresponding Cox proportional hazard regression model estimating the HR for all-cause in-hospital death; on the right, a robust regression model estimating the coefficients for hospital length of stay and a corresponding Cox proportional hazard model calculating the HR for hospital discharge.

* A total of 37,772 cases were censored due to hospital discharge; † $R^2 = 0.35$; ‡ 842 cases were censored due to in-hospital death; § HR for in-hospital death; ‖ HR for discharge from hospital; # not applicable for Cox proportional hazard regression models; ** International Systems of Units conversion factor: to convert creatinine to μM, multiply values by 76.3; †† administered within 1 week before surgery; ‡‡ as described by Kheterpal *et al.*[3]; §§ mutually exclusive categories of AKI severity by definition of the KDIGO group.[27]

AKI = acute kidney injury; Cr = creatinine; HR = hazard ratio; ICU = intensive care unit; KDIGO = Kidney Disease: Improving Global Outcome; no F/U = no follow-up; OR = odds ratio; SE = standard error.

volume status and perfusion pressure, considering functional hemodynamic monitoring, monitoring creatinine and urine output, avoiding hyperglycemia, and considering alternatives to radiocontrast procedures.[27] It is critical for future interventional studies to examine whether applying these nephroprotective measures in patients with minor creatinine increases can improve kidney function and consequently reduce mortality. Such studies will eventually resolve whether small increases in serum creatinine have a causal and modifiable association with adverse outcome.

Minor creatinine increases or mild forms of AKI in noncardiac surgery patients were associated with higher mortality compared with cardiac surgery patients in our patient sample. This may be due to the different underlying pathophysiology for AKI in the setting of CPB surgery. Indeed, besides the multiple nephrotoxic agents and events that can injure the kidney during a surgical hospital stay, cardiac surgery patients uniquely distinguish themselves by the intraoperative exposure to CPB. The fact that the blood comes into contact with the surface of the bypass machine, oxygenator, and tubing leads to the activation of multiple inflammatory pathways, vascular deregulation, and ultimately a worsened organ perfusion.[17,42,43] The duration of intraoperative CPB has thus been linked to the incidence and severity of postcardiac surgery AKI.[8,15,44–47] However, the fact that AKI in noncardiac surgery patients has a more profound impact on

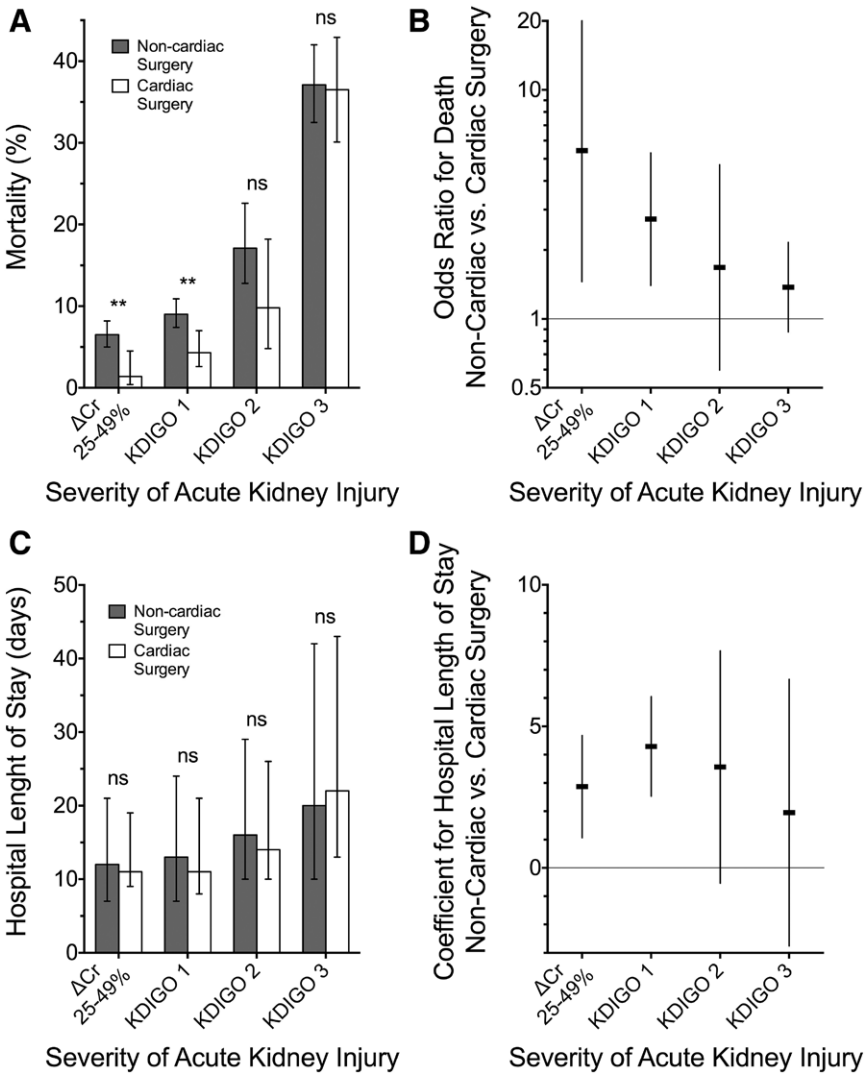

Fig. 3. Postoperative outcome by severity of acute kidney injury (AKI) in noncardiac compared with cardiac surgery patients. (*A*) Mortality in noncardiac surgery compared with cardiac surgery patients is higher in subgroups with less severe AKI, $^{**}P < 0.01$ (chi-square tests). (*B*) After multivariable adjustment, noncardiac surgery is associated with higher risk of in-hospital death in patients with less severe AKI; data from four multivariable binary logistic regression models, one for each subgroup of AKI severity (odds ratios and 95% CIs). (*C*) Hospital length of stay is not longer in noncardiac surgery patients compared with cardiac surgery patients in subgroups with less severe AKI (Mann–Whitney U tests). (*D*) After multivariable adjustment, noncardiac surgery is associated with longer hospital stay in patients with less severe AKI; coefficients from four robust regression models, one for each subgroup of AKI severity (βs and 95% CIs). Cr = creatinine; KDIGO = Kidney Disease: Improving Global Outcome; ns = not significant.

mortality and HLOS suggests that "low-grade AKI" caused by CPB is likely an event that the kidneys can recover from in most instances, whereas "low-grade AKI" without the use of CPB indicates a more severe form of intrinsic injury to the kidneys. Indeed, these findings alert to the fact that clinicians should take subclinical increases of creatinine levels in general surgery patients very seriously.

One of the key challenges for the field of anesthesiology is to find novel preventive or therapeutic approaches that are targeted to prevent postoperative organ injury.[2,48–51] Although there are measures to treat pre- and postrenal AKI, intrinsic AKI caused by drugs (antibiotics or contrast agents), inflammation, hypoxia–reperfusion injury (*e.g.*, due to prerenal injury), or any other noxa is not treatable till today. Most approaches are indeed limited to strategies that prevent the underlying cause or are focused on protecting the kidneys from additional insults.[52,53] Although numerous and mainly preventive strategies have been trialed, *e.g.*, remote ischemic preconditioning as well as pharmacotherapeutic options, growing evidence is still inconclusive, and many potential drugs have been shown to be ineffective.[2,27,54] Patients at risk of AKI should be managed according to their susceptibilities and exposures, say the current KDIGO guidelines. In most instances, patients admitted for surgery present themselves with a normal kidney function. Based on proper risk and exposure assessment, physicians should draw their attention to intra- and postoperatively preserving patients' kidney function. In addition, it is generally accepted that there is a small therapeutic window for the treatment of AKI. In fact, both animal studies and early phase clinical trial indicate that preventive strategies for kidney protection are probably more effective than treating already established AKI.[55] As such, our findings highlight the need for additional preventive approaches that could protect the kidney in surgical patients.

Limitations

Including patients only with preoperative creatinine measurement may have introduced selection bias to our study. The patients analyzed in our study are rather comorbid and may be more likely to have had a prior history of renal tubular insult and recovery and may therefore have been susceptible for future renal injury. Generalizability of our results may therefore be limited to patients with similar comorbidities and may not be transferable to healthier surgical patients. Our design may have biased the incidence rate of AKI but—with high probability—not the effect we were able to show. If a minor creatinine increase below AKI stage 1 criteria does occur, it is associated with a two-fold risk of in-hospital death.

Due to the study design using clinical routine data, our results are further limited by the uncontrolled nonsystematic creatinine follow-up measurements. Because we conducted a retrospective analysis, not every patient in our study had a postoperative creatinine measurement on every POD. Missing values may have introduced bias to our study by misclassifying patients as having a minor creatinine increase (ΔCr 25 to 49%) when they in fact had KDIGO stage 1 AKI. Although this may have consequently led to an overestimation of the association of minor increases with mortality and morbidity, our sensitivity analyses indicate that the findings are robust and unlikely affected by the missing values. The data presented in this study depict real-life postoperative kidney function monitoring (*i.e.*, data that would be available to the treating clinician) and suggest that either postoperative kidney function monitoring or the current AKI definitions may need revision.

Due to the observational design of this study, we were unable to demonstrate causality of minor creatinine increases and adverse outcome. However, basic research shows that AKI *per se* is an important cause for multiorgan failure. For example, a study in mice demonstrates dose-dependently that AKI causes increases in intestinal permeability and inflammatory mediator release from Paneth cells, thereby triggering multiorgan failure.[56] Moreover, the dose-dependent relation between creatinine increases and outcome parameters (mortality and HLOS) in the current study provides an additional indication that creatinine increases and AKI could potentially play a functional role in causing perioperative organ injury.[2] In addition, the resemblance of our study's results to those of previous studies in smaller patient samples and in elect surgical subpopulations further supports our conclusions.[20–22,34,36,57]

Conclusions

Acute kidney injury is a relevant complication in surgical patients and affects more patients than identified by current AKI criteria. Our results underscore the need for improving the identification of patients at risk and the need for causal and effective preventive as well as therapeutic options for this multifactorial and multicausal disease continuum in order to improve surgical patients' outcome.

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Competing Interests

All the authors declare no competing interests for the submitted work. Outside the submitted work, Dr. Kork received grants from the German Academic Exchange Service (Bonn, Germany) and the German Federal Ministry of Commerce (Berlin, Germany). Outside the submitted work, Dr. Spies received grants from the Ethical Committee Vienna Faculty

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