The Pattern of Longitudinal Change in Serum Creatinine and 90-Day Mortality After Major Surgery

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Objective: Calculate mortality risk that accounts for both severity and recovery of postoperative kidney dysfunction using the pattern of longitudinal change in creatinine.

Background: Although the importance of renal recovery after acute kidney injury (AKI) is increasingly recognized, the complex association that accounts for longitudinal creatinine changes and mortality is not fully described.

Methods: We used routinely collected clinical information for 46,299 adult patients undergoing major surgery to develop a multivariable probabilistic model optimized for nonlinearity of serum creatinine time series that calculates the risk function for 90-day mortality. We performed a 70/30 cross validation analysis to assess the accuracy of the model.

Results: All creatinine time series exhibited nonlinear risk function in relation to 90-day mortality and their addition to other clinical factors improved the model discrimination. For any given severity of AKI, patients with complete renal recovery, as manifested by the return of the discharge creatinine to the baseline value, experienced a significant decrease in the odds of dying within 90 days of admission compared with patients with partial recovery. Yet, for any severity of AKI, even complete renal recovery did not entirely mitigate the increased odds of dying, as patients with mild AKI and complete renal recovery still had significantly increased odds for dying compared with patients without AKI [odds ratio: 1.48 (95% confidence interval: 1.30–1.68)].

Conclusions: We demonstrate the nonlinear relationship between both severity and recovery of renal dysfunction and 90-day mortality after major surgery. We have developed an easily applicable computer algorithm that calculates this complex relationship.

Keywords: acute kidney injury, epidemiology and outcomes, machine learning, 90-day mortality, postoperative complications, renal recovery, serum creatinine, time series

(*Ann Surg* 2015;00:1–9)

Acute kidney injury (AKI) is one of the most common and serious postoperative complications.[1–4] The consensus classification for AKI, RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney), introduced a simple approach that uses the magnitude of change in routinely measured serum creatinine (sCr) to define 3 severity stages. The presence of AKI was based on at least a 50% change in sCr relative to the reference value,[5] but the recent KDIGO (Kidney Disease: Improving Global Outcomes) consensus has expanded the criteria to include sCr changes as small as 0.3 mg/dL.[6] Although RIFLE introduced the concept of renal recovery, estimated using the ratio of discharge and reference sCr, most of the initial epidemiological studies using the RIFLE criteria have focused on the effect of AKI severity rather than on renal recovery and rarely the combination of the two.[7]

The importance of renal recovery after AKI, and recognition that the risk associated with AKI may vary not only with severity but also with subsequent recovery of kidney function, has been shown in several recent studies.[8–12] Most of these studies focused on either discharge residual renal function or staging of renal recovery on the basis of the continuing need for renal replacement therapy (RRT) and a decrease in sCr below an arbitrary cutoff value as defining elements. By considering sCr as a physiological signal, and using it in automated pattern analysis with machine learning, a time series model may better capture the complex association between sCr changes over time and various adverse outcomes. Recently, Saria et al[13] have described a machine learning method that produces a probability score for illness severity using physiological signals including blood pressure, heart rate, and oxygen saturation. Using a similar computational approach, we have developed a probabilistic model that captures the nonlinear relationship between sCr change over time and postoperative mortality. In a large single-center cohort of 46299 patients undergoing major surgery, we have trained and validated this probabilistic model for postoperative 90-day mortality using the pattern in longitudinal change of sCr in addition to preoperative risk factors.

MATERIALS AND METHODS

Study Subjects

Using the University of Florida Health Integrated Data Repository, we have integrated perioperative clinical, administrative, and laboratory databases containing information related to routine clinical care for all patients aged 18 years or older and admitted to the hospital for longer than 24 hours after any type of inpatient operative procedure between January 1, 2000, and November 30, 2010. We excluded patients with no sCr measurements (n = 6636), patients with history of end-stage renal disease before admission (n = 1935) identified by the previously validated *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic and procedure codes,[14] and patients who had undergone surgery for more than 14 days after the admission date (n = 1406). Patients with extreme changes in sCr value (n = 94) were excluded on the basis of 2 criteria: (a) patients with 3 consequent sCr measurements where the third value deviated from the first by no more than by 20% and the second value is either 5 times greater or smaller than the first one; (b) patients with either a 10-fold increase or decrease in 2 consecutive sCr measurements. For patients with multiple surgical procedures, we chose the first procedure. The final cohort consisted

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Disclosure: Azra Bihorac was supported by a Vision Grant from the Society of Critical Care Medicine (SCCM) and Center for Sepsis and Critical Illness Award P50 GM-111152 from the National Institute of General Medical Sciences and has received research grants from Astute Medical, Inc. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or SCCM. The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

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ISSN: 0003-4932/15/00000-0001
DOI: 10.1097/SLA.0000000000001362

of 46299 patients. We obtained institutional review board approval through the University of Florida Health Science Center Institutional Review Board and University of Florida Privacy Office (#5-2009).

Covariates and Outcomes

Patient survival status was determined using hospital discharges, the Social Security Death Index and Florida Bureau of Statistics. We defined 90-day mortality as death due to any cause within 90 days of the date of admission. The primary exposure variable was a time series of longitudinal sCr measurements taken during index hospitalization. For each patient, we determined additional preoperative risk factors on the basis of clinical availability and univariate analysis: emergent surgery status, type of surgical procedure, age, race, sex, intensive care unit admission, Charlson-Deyo Comorbidity Index (a measure of the severity of comorbid illness ranging from 0 to 16, with higher scores indicating more comorbidities),[15] RRT, time of surgery (days elapsed between admission and the surgical operation), and operating surgeons' unique identifier.

Serum Creatinine Time Series

For all calculations, we defined baseline sCr as the minimum of the sCr values available within 6 months of admission including the admission day value. The approach using the minimum and mean of the sCr values available within 7 days before admission including the admission day sCr used for sensitivity analyses did not yield any difference in results.[16] Using baseline sCr value and sex, race, and age[17] for each patient, we calculated baseline estimated glomerular filtration rate (eGFR) by applying the Chronic Kidney Disease Epidemiology Collaboration equation.[18] We considered 3 models on the basis of different representations of sCr time series. The model 1 included the absolute values for the maximum sCr and the last measured sCr during index hospitalization. The last measured creatinine for more than 95% of the patients was on the day of discharge whereas 5% of the patients had values within 2 days of discharge. The model 2 included differences between maximum sCr, last measured sCr and baseline sCr values during index hospitalization. The model 3 included ratios of maximum sCr and last measured sCr values relative to baseline sCr value during index hospitalization. In addition, we considered a model that included only preoperative data (no sCr time series) referenced as model 0.

We identified a subcohort of 7766 patients with either history of chronic kidney disease (CKD) before admission (determined using previously validated ICD-9-CM diagnostic codes),[14] or with the baseline eGFR of less than 60 mL/min/1.73 m^2. Because these patients may have different sCr kinetics, we performed a separate analysis using models with sCr time series for this cohort.[18] The remaining cohort of 38533 patients included patients whose baseline eGFR was 60 mL/min/1.73 m^2 or greater.

We applied KDIGO consensus definitions for AKI severity and recovery categories using sCr changes only without urine output criteria. KDIGO defines AKI as either 0.3 mg/dL increase within 48 hours or 50% increase above baseline sCr.[6] For all calculations, we defined baseline sCr as described for sCr time series. Patients were stratified according to the maximum KIDGO stage reached during the hospital admission by comparing the highest sCr during hospitalization with the baseline sCr. Stage 1 corresponds to a 50% change in sCr, stage 2 to a doubling in sCr, and stage 3 to a tripling in sCr or increase in sCr to 4.0 mg/dL or greater or initiation of RRT. Need for RRT was determined using daily hospital charges in the billing database. Complete renal recovery was considered if the sCr returned to a level less than 50% above baseline sCr, whereas partial renal recovery existed if there was a persistent increase in sCr more than 50% above baseline sCr but no need for RRT. No renal recovery implied that there was a need for RRT at the time of hospital discharge.[5,6] For the subgroup of patients without history of CKD but with baseline eGFR of less than 60 mL/min/1.73 m^2 that could have represented with early AKI or undiagnosed CKD, we defined complete recovery as return of discharge creatinine values to the level that corresponds to GFR of 60 mL/min/1.73 m^2 or greater.

Statistical Analysis

The analytical plan followed the STROBE recommendations for observational cohort studies[19] and was performed using SAS software (v.9.3, Cary, NC), R software and MATLAB (v 7.12, Natick, MA, The MathWorks Inc., 2003) by D.K., P.M., P.T., T.O.B., and A.B. (see Supplemental Digital Content, Methods, available at http://links.lww.com/SLA/A811). We have developed R code for the final algorithm that is available from authors upon request. The algorithm can utilize clinical data obtained in routine clinical care using variables described in our cohort and can be trained in local environment.

Using a 70/30 cross validation procedure, the data were randomly split into 70% used for training and 30% used for validation. Models were learned using the training set only. The reported results were obtained by applying the model to the validation data set only. Multivariable modeling of the association between the sCr pattern and 90-day mortality was performed using generalized additive models with logistic link function and a backward stepwise selection method based on Akaike information criterion (see Supplemental Digital Content, Methods, available at http://links.lww.com/SLA/A811).[20,21] All variables were tested for univariate association before inclusion in the model, but the final feature selection was performed using a backward selection process applied to all variables. The performance of all models was optimized using separate approaches for continuous, nominal, and categorical variables. All models were adjusted for nonlinearity of all covariates using nonlinear risk functions f_i estimated with cubic splines.[21] The degrees of freedom for each spline were estimated by maximizing the restricted likelihood function.[22] Degrees of freedom characterize a curvature of a spline, with values greater than 1 corresponding to a nonlinear function where higher values indicate functions with more deviation from linearity. Categorical variables were modeled with conditional probabilities for a patient to have a particular variable value conditioning on the outcome. The type of surgical procedure (a nominal variable with >2000 discrete values) was modeled on the basis of *ICD-9-CM* codes for primary procedure with a forest structure, where each node represents a group of procedures, with roots representing most general groups of procedures and leaf nodes representing specific procedures (see Supplemental Digital Content, Methods, available at http://links.lww.com/SLA/A811). In addition, we performed multivariable analysis using same approach described previously for all variables but sCr time series. Instead, we used KDIGO AKI stage groups stratified by renal recovery to determine odds ratios (ORs) and 95% confidence intervals (CI) for 90-day mortality while considering patients without AKI as the reference group.

The accuracy of the models was assessed separately for training and validation data sets using area under the receiver operating characteristic curves (AUCs) with 95% prediction intervals. For each of the models, we performed 100 iterations of 70/30 cross validation procedure. For each iteration, the data set was randomly split into 70% training and 30% validation sets. Mean and 95% prediction intervals were calculated using AUCs obtained from 100 iterations. Model fit was tested using Hosmer-Lemeshow goodness-of-fit test. We used Vuong's closeness test for nonnested models as the statistical measure of the "closeness" between models using the pscl package in R software.[23,24] Large negative or positive test statistics yielding small *P* values indicate statistical significance of the difference between models.

Sensitivity Analyses

We performed multiple sensitivity analyses. Because patients with baseline eGFR less than 60 mL/min/1.73 m^2 or CKD before admission may have different sCr kinetics, we performed separate analyses using models with sCr time series for this cohort.[18] Furthermore, as RRT can artificially change sCr, all analyses were also performed before and after exclusion of patients requiring RRT. The change in sCr toward the end of index hospitalization was important modifier of the effect of the maximum creatinine in time series analyses. Approximately 99.6% of the cohort had hospital discharge before day 90 when primary outcome was assessed and approximately 50% of all deaths occurred after hospital discharge. Because the last measured creatinine for more than 95% of the patients was on the day of discharge, to exclude the fixed effect of discharge creatinine on 90-day mortality for patients who died in hospital, we considered 2 approaches for sensitivity analyses. To account for entire cohort, we performed a sensitivity analysis using the creatinine value before discharge day as the "last measured creatinine" for the model calculations. In the second approach, we performed a sensitivity analyses by running models after exclusion of patients who died in hospital before day 90 when outcome was assessed.

RESULTS

Optimal Model Selection and Model Performance

Among 46299 patients, 83% (38533/46299) had baseline eGFR of 60 mL/min/1.73 m^2 or greater whereas 17% (7766/46299) had either history of CKD before admission or baseline eGFR of less than 60 mL/min/1.73 m^2. The overall 90-day mortality was 4% in cohort with eGFR of 60 mL/min/1.73 m^2 or greater and 11% in cohort with CKD or eGFR of less than 60 mL/min/1.73 m^2. Majority of patients stayed in the hospital for less than 7 days. About 43% of the all cohort had intensive care unit admission, with 41% and 52% in eGFR of 60 mL/min/1.73 m^2 or greater and eGFR of less than 60 mL/min/1.73 m^2 cohorts, respectively. Using KDIGO consensus criteria, the prevalence of AKI was 33% in patients with eGFR of 60 mL/min/1.73 m^2 or greater and 69% among those with CKD or baseline eGFR of less than 60 mL/min/1.73 m^2. Nonsurvivors were more likely to be older, male, and to undergo emergent surgery but did not differ in baseline renal function compared with survivors in cohort with eGFR of 60 mL/min/1.73 m^2 or greater (Table 1). After excluding 270 and 735 patients requiring RRT in each cohort, the characteristics of the cohort were not significantly changed.

Using backward stepwise selection for each model, we selected sets of significant variables and estimated the degrees of freedom to determine their nonlinear risk function for 90-day mortality (see Supplemental Digital Content, Methods, available at http://links.lww.com/SLA/A811). All longitudinal sCr time series and most of the other continuous risk factors exhibited nonlinear risk functions (see Supplemental Digital Content Table S1, available at http://links.lww.com/SLA/A812) in relation to mortality. Overall, all models had better performance among patients with baseline eGFR of 60 mL/min/1.73 m^2 or greater (Table 2). The addition of longitudinal sCr time series provided an improvement to the model discriminatory ability (AUC: 0.865 vs AUC: 0.837, $P < 0.05$ for patients with eGFR of $\geq$60 mL/min/1.73 m^2 and 0.809 vs 0.768, $P < 0.05$ for patients with CKD or baseline eGFR of <60 mL/min/1.73 m^2) and model fit when compared using Vuong's test for nonnested models ($P < 0.0001$) for 90-day mortality (Table 2). All 3 models with sCr time series had very similar discrimination and model fit for 90-day mortality, likely reflecting the fact that sCr time series in all 3 models contained similar information. For each patient, we calculated mortality probabilities with 95% prediction intervals, using each of the sCr models separately, to determine the number of patients for whom these intervals do not overlap. For the entire cohort, this number was less than 0.5%, indicating that all 3 models produce similar probabilities for 90-day mortality.

The results of sensitivity analyses are summarized in Table 2. For all analyses, the results were not significantly changed when performed in cohorts that included patients requiring RRT, regardless of baseline eGFR. No significant difference in model performance was observed after using the creatinine value before discharge day as the "last measured creatinine" for the model calculations or after exclusion of the patients who died in hospital.

Pattern of Longitudinal Creatinine Change and 90-Day Mortality

The risk factors describing sCr time series represent 4 separate properties of renal function: baseline renal function (as measured by baseline sCr and baseline eGFR), severity of AKI (defined either using ratio or absolute difference between highest and baseline sCr), degree of renal recovery (defined either using ratio or absolute difference between last measured and baseline sCr), and discharge renal function (as measured by last measured sCr). To illustrate the relationship and degree to which severity and renal recovery for any degree in longitudinal change in creatinine are associated with mortality, we used model 3 to compute adjusted ORs as functions of the ratio of highest and baseline sCr (maxCr/baseCr) and the ratio of the last measured and baseline sCr (lastCr/baseCr) while adjusting for other preoperative risk factors. Model 3 was selected as it was the simplest, while providing accuracy and model fit equal to the other two models (baseline sCr was eliminated during feature selection as a separate variable in this model). An OR of 1 corresponds to a patient with no longitudinal change in sCr during hospitalization.

Figures 1 and 2 illustrate the unadjusted and adjusted nonlinear functions f_i for the association between 90-day mortality and sCr changes, age, and Charlson Comorbidity Index after exclusion of RRT patients, calculated separately for the cohort with baseline eGFR of 60 mL/min/1.73 m^2 or greater and the cohort including patients with CKD and those with eGFR of less than 60 mL/min/1.73 m^2, respectively. In adjusted analyses, for any given value of sCr change, both severity and recovery of renal dysfunction contributed to the associated increased risk of 90-day mortality in nonlinear and nonadditive fashion. Furthermore, the increase in last measured sCr compared with baseline creatinine reflecting lack of renal recovery was important modifier of the magnitude of the adverse effect of the maximum change in creatinine that was not evident in unadjusted analysis. Any degree of incomplete renal recovery as manifested by the persistent increase in the last measured creatinine above the baseline value contributed to increased risk for associated mortality over the whole spectrum of severity of AKI (Figs. 1–3).

To illustrate common clinical scenarios, we imposed cutoffs proposed for KDIGO severity stages and renal recovery categories (Table 3). For any given severity of AKI, those patients who had more complete renal recovery, as manifested by the return of the last measured creatinine to the baseline value, experienced a significant decrease in the odds of dying up to 90 days after admission. The most dramatic difference was for patients with the most severe stage 3 AKI. Patients who remained dialysis dependent throughout the hospitalization and those with persistent increase in sCr but no initiation of RRT had comparable increase in the odds of dying compared with patients with no AKI (OR: 14.73, 95% CI: 12.10–17.94 for patients on RRT, and OR: 16.36, 95% CI: 13.58–19.71 for group with persistent creatinine increase and no RRT initiation). However, for patients with stage 3 AKI who had complete renal recovery, the odds of dying, although still high, were improved (OR: 5.73, 95% CI: 4.74–6.93). However, for any stage of AKI, even complete

TABLE 1. Baseline Patients' Characteristics Stratified by 90-Day Mortality

	Baseline eGFR <60 mL/min/1.73 m^2 (n = 7766)		Baseline eGFR ≥60 mL/min/1.73 m^2 (n = 38,533)	
	Nonsurvivors (n = 848)	Survivors (n = 6918)	Nonsurvivors (n = 1597)	Survivors (n = 36,936)
Patients' characteristics				
Age in years, median (25th, 75th)	73 (63, 80)	67 (55, 75)*	64 (52, 74)	54 (41, 65)*
Female sex, n (%)	360 (42)	3135 (45)	700 (44)	18,509 (50)*
Race, n (%)				
White	699 (82)	5617 (81)	1319 (83)	29,860 (81)
African American	88 (10)	876 (13)	168 (11)	4339 (12)
Hispanic	14 (2)	154 (2)	32 (2)	1195 (3)†
Other	14 (2)	136 (2)	30 (2)	810 (2)
Missing	33 (4)	135 (2)*	48 (3)	732 (2)†
Charlson Comorbidity Index, median (25th, 75th)	3 (1, 4)	2 (1, 4)*	2 (1, 4)	1 (0, 2)*
Operative characteristics				
Emergent surgery, n (%)	603 (71)	3346 (48)*	1086 (68)	15,211 (41)*
Operating surgeon (448 physician IDs), n (%)				
First rank	70 (8)	403 (6)	110 (7)	1656 (4)
Second rank	49 (6)	277 (4)	63 (4)	1292 (4)
Third rank	41 (5)	264 (4)	57 (4)	1267 (3)
Surgery type, n (%)				
Cardiothoracic surgery	237 (28)	1518 (22)*	234 (15)	4152 (11)*
Noncardiac general and vascular surgery	201 (24)	1537 (22)	308 (19)	8097 (22)‡
Neurological surgery	107 (13)	568 (8)*	534 (33)	6811 (18)*
Specialty surgical procedures§	164 (19)	2063 (30)*	259 (16)	11,725 (32)*
Other surgical procedures‖	139 (16)	1232 (18)	262 (16)	6151 (17)
Time of surgery in days, median (25th, 75th)	1 (0, 4)	1 (0, 2)*	1 (0, 3)	0 (0, 1)*
Number of ICU admissions, median (25th, 75th)	1 (1, 2)	0 (0, 1)*	1 (0, 1)	0 (0, 1)*
ICU admissions, n (%)				
0	148 (17)	3553 (51)*	407 (25)	22,209 (60)*
1	459 (54)	2614 (38)*	825 (52)	12,398 (34)*
2	163 (19)	528 (8)*	247 (15)	1791 (5)*
≥3	78 (9)	223 (3)*	118 (7)	538 (1)*
Hospital length of stay, median (25th, 75th)	13 (7, 25)	8 (5, 15)*	11 (6, 21)	6 (4, 10)*
Renal function				
Baseline serum creatinine, median (25th, 75th)	1.5 (1.2, 2.0)	1.4 (1.2, 1.8)*	0.8 (0.6, 0.9)	0.8 (0.6, 0.9)
Baseline estimated glomerular filtration rate, mL/min/1.73 m^2, median (25th, 75th)	43 (29, 53)	48 (36, 56)*	91 (78, 105)	98 (84, 111)*
Acute kidney injury (KDIGO), n (%)				
No AKI	118 (14)	2274 (33)*	497 (31)	25,420 (69)*
Stage 1	261 (31)	2837 (41)*	458 (29)	8406 (23)*
Stage 2	119 (14)	677 (10)*	275 (17)	2259 (6)*
Stage 3	350 (41)	1130 (16)*	367 (23)	851 (2)*
Renal replacement therapy, n (%)	224 (26)	511 (7)*	153 (10)	117 (0.3)*

All percentage values refer to column percentage.
*$P < 0.001$ for comparison between survivors and nonsurvivors.
†$P < 0.01$ for comparison between survivors and nonsurvivors.
‡$P < 0.05$ for comparison between survivors and nonsurvivors.
§Specialty surgical procedures include orthopedic, urology, ear-nose-throat, and gynecological surgeries.
‖Other surgical procedures include trauma, burn, and transplant surgeries.
ICU indicates intensive care unit.

renal recovery did not entirely mitigate the increased odds of dying. Patients with mild AKI (KDIGO stage 1) with complete renal recovery had significantly increased odds for dying compared with patients with no AKI (OR: 1.48, 95% CI: 1.30–1.68). Age, Charlson Comorbidity Index, operating surgeon, emergent surgery status, and type of surgical procedure were all associated with increased risk for mortality, in addition to sCr factors, although the magnitude of the association was the highest for sCr time series.

DISCUSSION

The pattern of longitudinal change in sCr during hospitalization in a large single-center cohort of postoperative patients is

TABLE 2. Model Accuracy for Training and Validation Cohorts for Generalized Additive Models for 90-Day Mortality

	Area Under the Receiver Operating Curve (95% Prediction Intervals)			
	Preoperative Model Without Serum Creatinine Time Series (Model 0*)		Preoperative Model With Serum Creatinine Time Series (Model 3†)	
	Training Cohort	Validation Cohort	Training Cohort	Validation Cohort
Baseline eGFR ≥60 mL/min/1.73 m^2				
Excluding RRT patients (N = 38,263)	0.856 (0.850, 0.862)	0.837 (0.823, 0.852)	0.881 (0.875, 0.886)	0.865 (0.852, 0.879)‡
Using sCr before discharge day as the last measured creatinine	0.856 (0.850, 0.862)	0.837 (0.823, 0.852)	0.877 (0.871, 0.883)	0.861 (0.847, 0.876)‡
Excluding hospital deaths (N = 37,484)	0.883 (0.875, 0.891)	0.845 (0.824, 0.867)	0.885 (0.877, 0.894)	0.847 (0.824, 0.870)
Including RRT patients (N = 38,533)	0.866 (0.860, 0.872)	0.851 (0.837, 0.866)	0.888 (0.883, 0.893)	0.876 (0.864, 0.888)‡
Excluding hospital deaths (N = 37,594)	0.883 (0.875, 0.892)	0.845 (0.821, 0.869)	0.886 (0.877, 0.894)	0.847 (0.823, 0.871)
Baseline eGFR <60 mL/min/1.73 m^2 or chronic kidney disease before admission				
Excluding RRT patients (N = 7031)	0.813 (0.802, 0.824)	0.768 (0.740, 0.795)	0.847 (0.836, 0.859)	0.809 (0.782, 0.836)‡
Using sCr before discharge day as the last measured creatinine	0.813 (0.802, 0.824)	0.768 (0.740, 0.795)	0.840 (0.828, 0.852)	0.804 (0.778, 0.831)‡
Excluding hospital deaths (N = 6645)	0.817 (0.797, 0.838)	0.744 (0.694, 0.794)	0.819 (0.802, 0.837)	0.747 (0.703, 0.790)
Including RRT patients (N = 7766)	0.828 (0.818, 0.839)	0.795 (0.773, 0.818)	0.854 (0.842, 0.866)	0.823 (0.796, 0.850)‡
Excluding hospital deaths (N = 7168)	0.805 (0.791, 0.820)	0.737 (0.698, 0.776)	0.810 (0.790, 0.829)	0.737 (0.688, 0.785)

All models showed sufficient fit using Hosmer-Lemeshow goodness-of-fit test.
* Model 0 included only preoperative data and no serum creatinine time series data.
†Model 3 included ratios of maximum serum creatinine and last measured serum creatinine values relative to baseline serum creatinine during index hospitalization.
‡$P < 0.05$ compared with area under the receiver operating curve of model 0 fit on validation cohort.

significantly associated with 90-day mortality, independently of other clinical factors. We have developed an algorithm that calculates a complex nonlinear function on the basis of both the magnitude of longitudinal change in sCr during hospitalization and its return to a baseline value for any given set of sCr time series data adjusted for other clinical factors. The two-dimensional graphical representation of this relationship demonstrates that the increased risk for mortality is a function not only of how severe AKI is when it occurs but also of how complete is renal recovery after AKI. This relationship is continuous and nonlinear and can be implemented in real time on serial creatinine values through a computer algorithm. Our study expands previous findings of the association between the severity of AKI in surgical patients with postoperative complications, hospital mortality, and cost by adding the dimension of renal recovery into consideration.

This study demonstrates for the first time that the risk-adjusted association between longitudinal change in postoperative sCr and 90-day mortality is continuous over the whole spectrum of measured creatinine values and duration of time series and is independent of the need for RRT after AKI.[6] Using empirical cutoffs for renal recovery proposed in the consensus criteria, we have demonstrated that complete renal recovery at the time of discharge significantly lessens the risk for mortality even among patients with the most severe AKI whereas lack of complete recovery maintains the increased risk for patients with the least severe AKI. Recent study in cohort of patients with pneumonia has reported similar findings.

Most of the studies of renal recovery after AKI have focused on the liberation from RRT during or after hospitalization.[25] It has long been recognized that the severity of AKI, reflecting the magnitude of decline in glomerular filtration rate, is determinant of adverse outcomes associated with AKI. We confirm the importance of renal recovery, estimated either by the degree of successful renal recovery[8–12] or by the estimated residual renal function at discharge[9–11,26–28] in minimizing adverse outcomes associated with AKI. Recently, Engoren et al[29] combined RIFLE AKI stage with discharge creatinine to demonstrate a strong association with adverse outcomes for the interaction of these two factors. This study integrates all 3 dimensions—severity of functional decline, renal recovery, and discharge residual renal function while accounting for colinearity and nonlinearity between these measurements and confirms that patients without complete renal recovery have worse survival for any level of renal functional decline. More importantly, even patients with complete renal recovery at the time of discharge have increased mortality over both the short and long term.[9,11,26,27,30,31] In the cohort of 32,045 critically ill patients, Kellum et al[32] demonstrated that short- and long-term risk of death or RRT is greatest when patients meet both the sCr level and urine output criteria for AKI and when these abnormalities persist. Consensus clinical guidelines use a categorical cutoff to define renal recovery, but they also utilize the unfortunate label of "partial renal recovery" for patients with a persistent increase in sCr but no need for RRT, when in fact their sCr likely does not reflect true recovery of renal function.[5,6] For elderly patients with longer hospitalizations, even normal creatinine values may overestimate actual glomerular filtration rate because of the multifactorial decrease in creatinine generation in acute illness.[33]

In contemporary clinical practice, the awareness for AKI is low and only 20% of patients with AKI carry this diagnosis in their discharge summary.[26] Not surprisingly, any follow-up of creatinine within the first 3 months of hospitalization occurs in less than 50% of patients with the most severe AKI, and one can assume even less frequently after less severe AKI.[34] Among AKI survivors with persistent renal dysfunction at discharge, the referral rates for outpatient nephrology consultation are as low as 11%.[34,35] We provide a simple graphic representation of the association between multiple creatinine measurements and 90-day mortality that may help identify patients with the highest risk of adverse outcome who may benefit from timely nephrology follow-up and repeat creatinine measurements after discharge. Importantly, most of the patients who would have an increased risk by this algorithm would not be picked up by their age, comorbidities, or surgery type alone or by isolated measurement of creatinine.

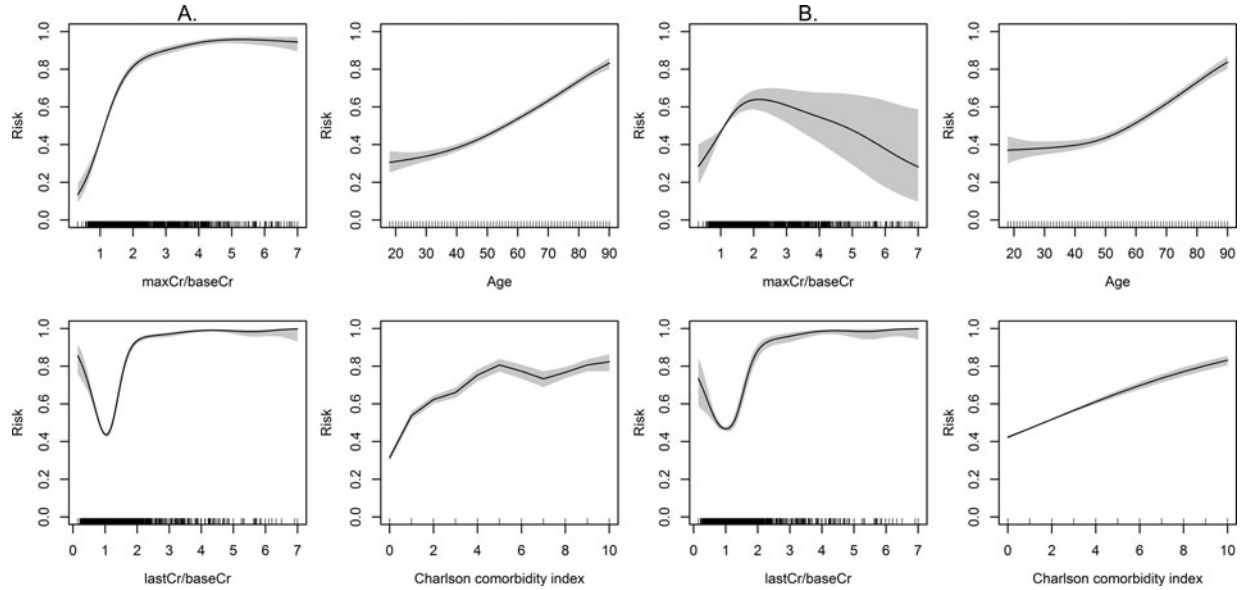

FIGURE 1. Nonlinear functions for the association between maximum creatinine and baseline creatinine ratio (maxCr/baseCr), last measured creatinine and baseline creatinine ratio (lastCr/baseCr), age, and Charlson Comorbidity Index, and 90-day mortality for the patients with baseline estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or greater after excluding patients on renal replacement therapy. Panels (A) and (B) show unadjusted and adjusted nonlinear functions, respectively. The *Y* axis represents risk probability for 90-day mortality ranging from 0 to 1. The shaded areas represent 95% prediction intervals for the function values.

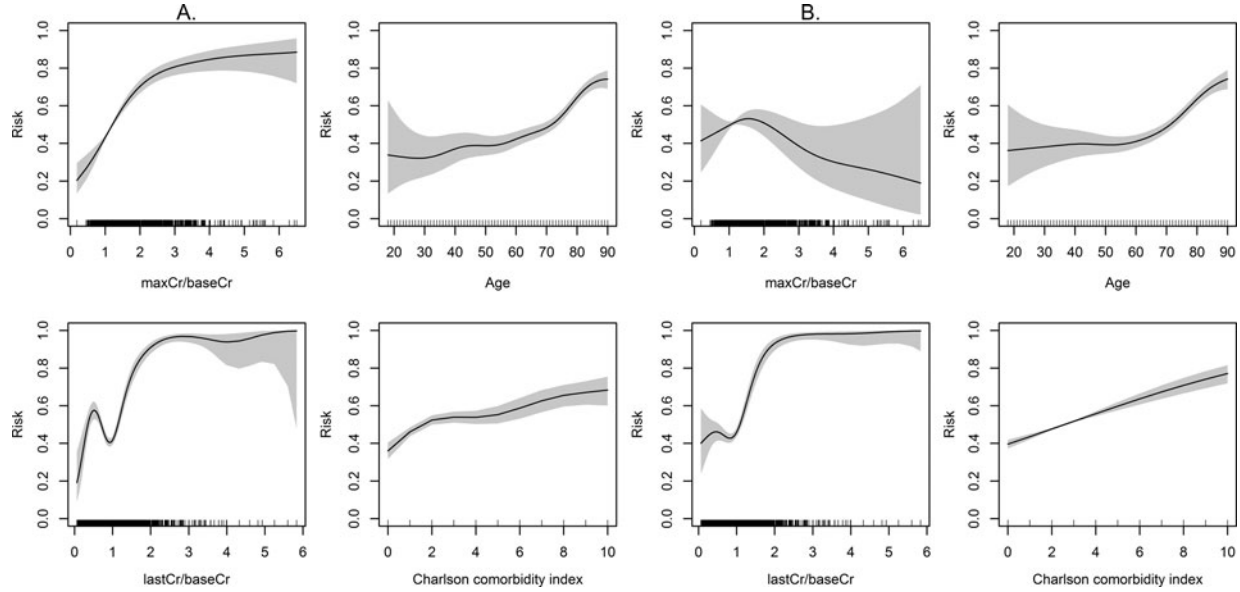

FIGURE 2. Nonlinear functions for the association between maximum creatinine and baseline creatinine ratio (maxCr/baseCr), last measured creatinine and baseline creatinine ratio (lastCr/baseCr), age, and Charlson Comorbidity Index, and 90-day mortality for the patients with chronic kidney disease or baseline estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 after excluding patients on renal replacement therapy. Panels (A) and (B) show unadjusted and adjusted nonlinear functions, respectively. The *Y* axis represents risk probability for 90-day mortality ranging from 0 to 1. The shaded areas represent 95% prediction intervals for the function values.

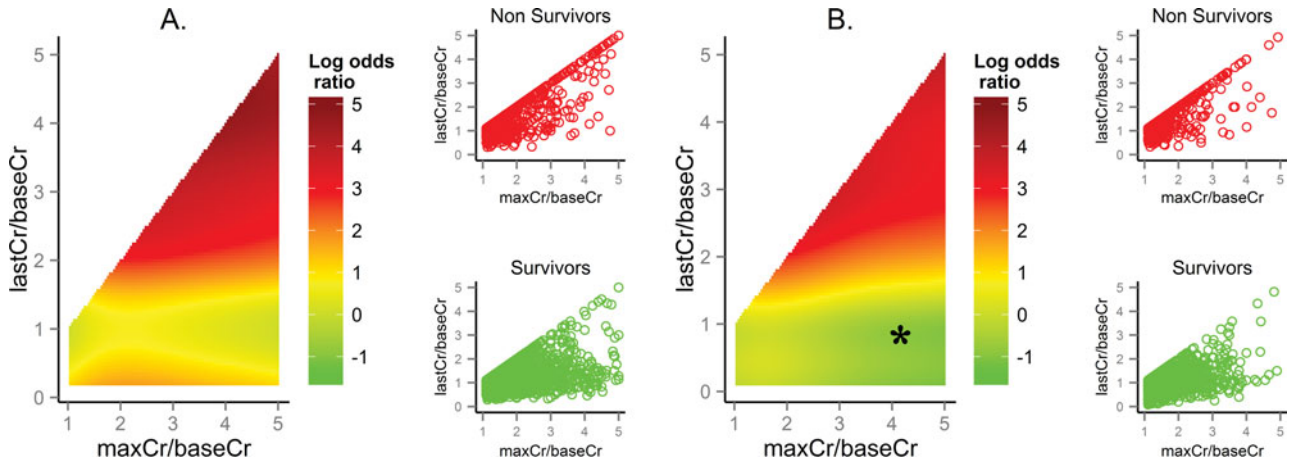

FIGURE 3. Association between pattern in serum creatinine change and 90-day mortality adjusted for preoperative clinical factors among (A) patients with baseline estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or greater and (B) patients with chronic kidney disease or baseline estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2. Left panel: The log odds ratios for 90-day mortality based on adjusted nonlinear functions for maximum creatinine and baseline creatinine ratio (maxCr/baseCr) and last measured creatinine and baseline creatinine ratio (lastCr/baseCr) with respect to a pattern with no change in serum creatinine. Right panel: Distribution of maxCr/baseCr and lastCr/baseCr values for nonsurvivors and survivors. *There were no patients in the data set with the combination of the maxCr/baseCr and lastCr/baseCr in the marked range.

TABLE 3. Patterns of Renal Recovery and 90-Day Mortality

	Number of Patients, N	Crude Mortality, n (%)	Adjusted Odds Ratios (95% CI)
No AKI	28,309	615 (2)	1 (reference)
Complete recovery			
Stage 1 AKI	9441	481 (5)	1.48 (1.30–1.68)*
Stage 2 AKI	2613	214 (8)	2.16 (1.81–2.56)*
Stage 3 AKI	1193	199 (17)	5.73 (4.74–6.93)*
Partial recovery			
Stage 1 AKI	2521	238 (9)	2.73 (2.31–3.23)*
Stage 2 AKI	717	180 (25)	8.81 (7.17–10.82)*
Stage 3 AKI	792	283 (36)	16.36 (13.58–19.71)*
No recovery	713	235 (33)	14.73 (12.10–17.94)*

Adjusted odds ratios for 90-day mortality were obtained in all cohort of 46,299 patients, including the patients with renal replacement therapy and using general additive models while adjusting for age, sex, race, Charlson Comorbidity Index, emergent surgery status, type of surgical procedure, operating surgeon, and intensive care unit admission.
*$P < 0.001$ for comparison with respect to no AKI group.

We attempted to control for selection bias with multivariable statistical methods and risk adjustment, but the retrospective design precludes any conclusion on causal inference. The major strength of our study was the ability to use mathematically optimized sCr time series rather than relying on previously established cutoffs for severity and recovery of renal function or use of statistical methods that do not account for nonlinearity of creatinine measurements. Furthermore, our analyses demonstrate that all continuous variables had nonlinear associations with an increased risk of 90-day mortality. This analysis required the use of generalized additive models, as commonly used logistic regression models would be inadequate to demonstrate such associations. The performance of all models was optimized using separate approaches for continuous, nominal, and categorical variables. We assessed comorbidities using previously validated criteria.[15] This approach relies on accurate coding leading to potential risk underassessment. Although this is a single institution report, it comprises a large cohort of patients with morbidity and mortality that is comparable with other reports in the literature for the same procedures. The administration of intravenous fluids during surgery may have influenced sCr through dilution, but we do not have data on overall fluid balance to further examine this potential effect. The performance of the model depends on the initial training of the model using the institutional distribution of surgical procedures and operating surgeons. The internal validity of analyses is ensured by our use of the methodology recommended by the STROBE guidelines including the use of a validation cohort and sensitivity analyses addressing missing data, selection bias, and effect of baseline creatinine.[19]

The recovery of renal function after an episode of AKI is dependent upon both the structural changes in the kidney that occur after AKI and the repair potential of the kidney. Both adaptive and maladaptive cellular changes persist for weeks after the induction of kidney injury.[36] A beneficial adaptation is acquired cytoresistance that protects the kidney against repeated injury, whereas a maladaptive adaptation includes tubular upregulation of toll-like receptor responses with resulting exaggerated cytokine production and increased susceptibility to recurrent infections.[37] Persistent upregulation of proinflammatory, profibrotic, and vasoconstrictive genes leads to progressive renal injury. Thus, the important period between injury induction and the onset of renal repair can ultimately impact renal functional recovery, extrarenal injury, and the possible transition of AKI into progressive renal disease.[36,38]

With the recent emergence of validated urinary biomarkers to detect early AKI, clinicians now have the prospect of interventions to reduce the effects of AKI.[39,40] Prevention of new AKI and mitigation of injury from newly detected AKI are logical goals for primary and secondary prevention in surgical patients and will likely depend on the development and adoption of clinical guidelines and "kidney protective strategies" by intensivists, surgeons, and anesthesiologists as the primary caregivers for these patients.[6,40] Successful renal recovery emerges as a key goal for the management of patients with established AKI that will fundamentally affect their chances for survival and long-term recovery and will require synergistic action between primary surgical caregivers and nephrologists and must extend beyond the hospital discharge.[41,42] Available evidence from

randomized controlled trials, large observational studies, and comparative analysis of their results suggest that the avoidance of intermittent hemodialysis and of a cumulative positive fluid balance is likely to increase the speed of renal recovery and may prevent end-stage renal failure in selected high-risk patients with AKI.[43–46]

CONCLUSIONS

Our results expand upon previous findings to demonstrate the nonlinear relationship between the severity and recovery of renal dysfunction and 90-day mortality after major surgery. We have developed an algorithm that calculates this complex relationship. Even complete recovery to baseline renal function in patients with the smallest change in sCr does not mitigate the risk for adverse outcomes. The development of clinical guidelines for standardized primary and secondary prevention of postoperative AKI using clinical risk stratification and urinary biomarkers is urgently needed.

ACKNOWLEDGMENTS

The authors thank Gigi Lipori, Christine Bono, and Yue Du for assistance with data retrieval.

Momcilovic and Bihorac contributed equally as senior authors of the manuscript. Korenkevych, Ozrazgat-Baslanti, and Thottakkara contributed equally as the first authors of the manuscript.

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