Hospital-acquired Acute Kidney Injury: An Analysis of Nadir-to-Peak Serum Creatinine Increments Stratified by Baseline Estimated GFR

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Summary

Background and objectives Serum creatinine (sCr) increments currently used to define acute kidney injury (AKI) do not take into consideration the baseline level of kidney function. The objective of this study was to establish whether baseline estimated GFR (eGFR) provides additional risk stratification to sCr-based increments for defining AKI.

Design, setting, participants, & measurements 29,645 adults hospitalized at an acute care facility were analyzed. Hospital-acquired AKI was defined by calculating the difference between the nadir and subsequent peak sCr.

Results Different thresholds of nadir-to-peak sCr were found to be independently associated with increased in-hospital mortality according to baseline eGFR strata. A nadir-to-peak sCr minimum threshold of ≥0.2, ≥0.3, and ≥0.5 mg/dl was required to be independently associated with increased in-hospital mortality among patients with baseline eGFR ≥60 ml/min per 1.73 m^2 (odds ratio [OR] 1.67; 95% confidence interval [CI] 1.13 to 2.47), 30 to 59 ml/min per 1.73 m^2 (OR 2.69; 95% CI, 1.82 to 3.97), and <30 ml/min per 1.73 m^2 (OR 2.15; 95% CI 1.02 to 4.51), respectively. There was a significant interaction between the nadir-to-peak sCr and baseline eGFR for in-hospital mortality ($P < 0.001$). Using these thresholds, survivors of AKI episodes had an increased hospital length of stay and were more likely to be discharged to a facility rather than home. Sensitivity analyses showed a significant interaction between baseline eGFR strata and relative increases in sCr, as well as absolute and relative decreases in eGFR for in-hospital mortality ($P < 0.001$).

Conclusions This study suggests that future sCr-based definitions of AKI should take into consideration baseline eGFR.

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Introduction

Hospital-acquired acute kidney injury (AKI) is a relatively common and serious occurrence that is associated with increased mortality and resource consumption (1–9). Over the years, several definitions have been used to describe AKI (10). Because of the lack of consensus, the Acute Dialysis Quality Initiative group first published guidelines in 2003, defining AKI as either a 1.5-fold increase in serum creatinine (sCr), a decrease in GFR by >25%, or a decline in the urine output to <0.5 ml/kg/h over 6 hours (11). In 2008, the AKI Network (AKIN) group further modified this definition by adding an increase in sCr by ≥0.3 mg/dl (12). This additional criterion was on the basis of findings from two large single-center studies demonstrating an independent association between sCr increase of ≥0.3 mg/dl and in-hospital mortality (5,13).

Prior studies have formally tested for an interaction between the baseline kidney function level and the sCr-based AKI definition for the outcome of mortality (5,14). However, these reports have not further quantified whether different thresholds of sCr increases for defining AKI are required to optimize mortality risk stratification according to the baseline kidney function level. To address this knowledge gap, this analysis explores whether the magnitude of sCr increment that associates with adverse clinical outcomes varies by three categories of the baseline estimated GFR (eGFR).

Patients and Methods

Data Source

This was a single-center retrospective cohort study utilizing a data set that contained fully deidentified hospital discharges at a community-based tertiary acute care facility (St. Elizabeth's Medical Center, Boston, MA) over a 7-year period (October 1, 2000, to September 30, 2007). Discharge abstracts provided information on each patient's age, gender, race/eth-

nicity, dates of admission and discharge, hospital service type (medical, surgical, and other), up to 15 International Classification of Diseases-9th Edition-Clinical Modification (ICD-9-CM) diagnosis and procedural codes, discharge status (alive *versus* dead), and discharge disposition (home *versus* short-term/long-term care facility). Each discharge abstract was linked to the hospital's electronic laboratory database, from which we extracted all sCr values for the corresponding hospitalization, including the date and time of these measurements. Institutional Review Board approval was obtained.

Study Cohort Definition

The study sample included all adults (age, ≥18 years) who were hospitalized at least once and for whom there was an initial admission sCr measurement and at least one additional sCr measurement during hospitalization. These criteria were required to estimate the baseline level of kidney function and define hospital-acquired AKI. Patients with ESRD on maintenance dialysis were excluded, using a previously validated method (7,15,16). Hospitalizations with an absent or single sCr measurement, those where a change in sCr could not be calculated because of missing information on date/time of measurement, and those where discharge status was unknown were also excluded. For patients who were hospitalized more than once, one hospitalization per subject was randomly selected.

Assessment of Baseline Kidney-Function Level

Our intent was to focus on hospital-acquired AKI, not on community-acquired AKI or AKI that occurred before the hospitalization. We estimated the baseline kidney function level by calculating the eGFR using a baseline sCr, which was derived from the nadir (or lowest) value recorded in the first 3 days of hospitalization (Figure 1). Using this baseline sCr, we calculated the baseline eGFR using the four-variable Modification of Diet in Renal Disease study equation (17).

After the identification of the baseline sCr and corresponding eGFR, baseline kidney function was stratified according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification (eGFR of ≥60 ml/min per 1.73 m^2, eGFR of 30 to 59 ml/min per 1.73 m^2, and eGFR of <30 ml/min per 1.73 m^2) (18).

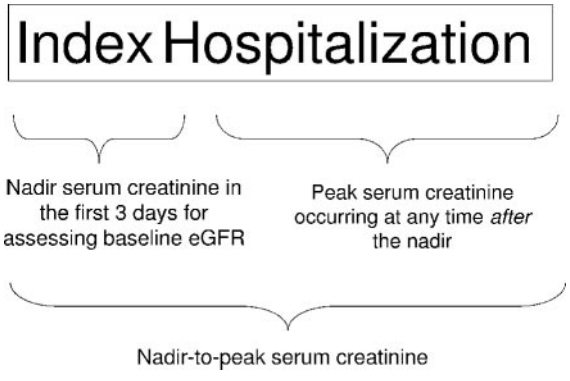

Figure 1. | Diagram of baseline assessment of kidney function/estimated GFR (eGFR) and acute kidney injury definition during the index hospitalization.

Definition of Hospital-acquired AKI

Hospital-acquired AKI was defined by calculating the difference between the lowest (or nadir) sCr during the first 3 days of hospitalization and the subsequent highest (or peak) sCr, in increments of 0.1 mg/dl, that would be independently associated with in-hospital mortality, a clinically important end point. The nadir sCr was used to calculate the baseline eGFR. If no increase in sCr occurred after the baseline assessment period, the nadir-to-peak sCr was considered to be zero.

Description of Covariates

Covariates included age, gender, race, hospital service type, and the Deyo-Charlson comorbidity index with its individual components (19,20). A Deyo-Charlson comorbidity index score of 0 to ≥3 was generated, with increasing numerical value reflecting greater comorbidity. Acute hospital-related variables of interest included sepsis, cardiac catheterization, abdominal surgery (21), coronary artery bypass grafting (CABG), and number of failed organs, as reflected by the acute organ system dysfunction (AOSD) score (7,22).

Description of Outcomes

The primary outcome of interest was in-hospital mortality. This end point was ascertained at the time of hospital discharge, and there was no loss of follow-up. Among patients who were discharged alive, secondary outcomes that are associated with resource consumption were analyzed mainly discharge disposition (to a facility *versus* home) and hospital length of stay (LOS).

Statistical Analyses

The continuous data are presented as means (with SD) or medians (with 25th and 75th percentiles) and categorical variables as frequencies (with percentages). For continuous variables, comparisons between groups were made by the *t* test and ANOVA for normally distributed data, by the Wilcoxon rank sum test and Kruskal–Wallis test for non-normally distributed data, and by the chi-squared test for categorical variables.

To determine whether the baseline eGFR was an effect modifier of the relationship of nadir-to-peak sCr to in-hospital mortality, we proceeded with *a priori* stratified multivariable logistic regression analyses, aimed at identifying thresholds of absolute sCr increases in 0.1-mg/dl increments where in-hospital mortality increased statistically within each baseline eGFR stratum. The models were adjusted incrementally for age, gender, race, the Deyo-Charlson comorbidity index, hospital service type, sepsis, cardiac catheterization, CABG, abdominal surgery, and the AOSD score. The smallest difference in the nadir-to-peak sCr that yielded an independent association with in-hospital mortality in the fully-adjusted model fulfilled our definition of hospital-acquired AKI within each baseline eGFR stratum. We used the modified Hosmer-Lemeshow test to assess for calibration and the tolerance test to assess for colinearity.

Using the operational definition of AKI identified within each eGFR stratum for the outcome of in-hospital mortality, we next examined in hospital survivors the independent association of AKI with hospital LOS and discharge to a short- or long-term care facility (*versus* home), using multivariable robust and logistic regression analyses, respectively. To explore the consistency of our findings, in the fully adjusted model, we formally checked for an interaction between nadir-to-peak sCr and baseline eGFR strata for the outcomes of in-patient mortality and discharge disposition.

For sensitivity analyses, we first tested for an interaction of the baseline eGFR strata with other AKI definitions for the outcome of in-hospital mortality, including the percentage of sCr increase as well as absolute and relative eGFR decrease. The change in eGFR was calculated using baseline and "nadir" eGFR that was derived from peak sCr. In another sensitivity analysis, we restricted the nadir-to-peak sCr time lag to 7 days or less to exclude outliers. Finally, in a subset of patients that had multiple hospitalizations, we used the lowest sCr from the prior hospitalization as a surrogate for an earlier baseline eGFR, which substituted the nadir sCr in the mortality analyses.

Results of the logistic and robust regression analyses are displayed as odds ratio (OR) and prolongation in average LOS (in days) with 95% confidence interval (CI). $P < 0.05$ was considered significant. All of the statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Derivation of the Analytical Data Set

The flow diagram describing the derivation of the study cohort is shown in Figure 2. In brief, there were 97,472 hospitalizations during the 7-year study period, representing 51,207 subjects. 6096 hospitalizations related to addiction medicine (representing 2747 subjects) were excluded upfront because of the anticipated absence or single sCr measurement. Of the remaining 91,376 hospitalizations, which represented 48,460 subjects, 31,498 subjects experienced a single hospitalization. For the remaining 16,962 subjects who were hospitalized more than once, a random hospitalization was selected. Among the 48,460 subjects, 18,815 were excluded. Reasons for exclusion were absence of sCr values (n = 9,261), presence of a single sCr value (n = 8,585), inability to determine the nadir-to-peak sCr (n = 588), and presence of end-stage renal disease ESRD (n = 381). The final analytic data set thus comprised 29,645 subjects. Eighty-three percent of subjects had four or fewer

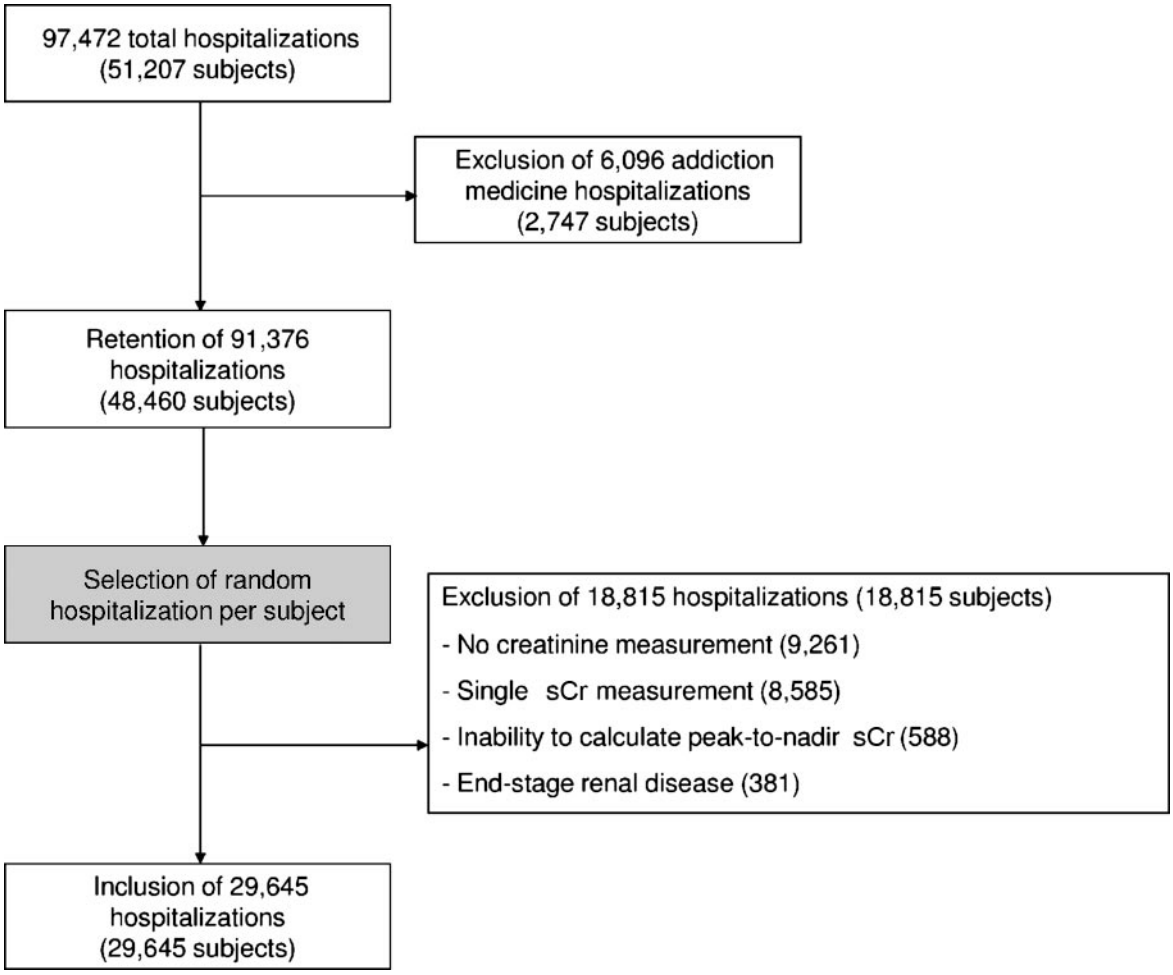

Figure 2. | Flow diagram describing the derivation of the study cohort.

sCr measurements in the first 3 days, which represented the baseline eGFR-assessment period.

Compared with the study cohort, the excluded cohort had fewer white subjects and more women; was overall healthier with a higher baseline eGFR, a lower Deyo-Charlson comorbidity index, and AOSD score; and was less likely to experience sepsis and undergo cardiac invasive and surgical procedures (Appendix 1; $P < 0.001$ for all comparisons).

Characteristics of the Cohort Stratified by Baseline eGFR

As shown in Table 1, patients with lower baseline eGFR tended to be older, were more likely to be women, and had a higher prevalence of individual comorbid conditions with a higher Deyo-Charlson comorbidity index. They were also more likely to suffer from sepsis and had a higher AOSD score. Finally, patients with lower baseline eGFR had higher in-hospital mortality rates, and among hospital survivors, they were more likely to experience a

Table 1. Baseline characteristics and selected outcomes of the hospitalized cohort stratified by baseline eGFR

	Baseline eGFR of <30 ml/min per 1.73 m^2 (n = 1546)	Baseline eGFR of 30 to 59 ml/min per 1.73 m^2 (n = 6560)	Baseline eGFR of ≥60 ml/min per 1.73 m^2 (n = 21,539)	P
Age, years	74.9 (13.7)	77.6 (11.6)	60.4 (19.2)	<0.001
Female gender, n (%)	878 (56.8)	3807 (58.0)	10749 (49.9)	<0.001
Race, n (%)				
white	1192 (77.1)	5703 (86.9)	17598 (81.7)	<0.001
black	75 (4.9)	186 (2.8)	1090 (5.1)	
other	279 (18.1)	671(10.2)	2851 (13.2)	
Baseline sCr, mg/dl	2.5 (2.0 to 3.4)	1.3 (1.1 to 1.4)	0.8 (0.7 to 0.9)	<0.001
Baseline eGFR, ml/min per 1.73 m^2	21.6 (15.1 to 26.4)	48.5 (41.0 to 54.3)	87.8 (74.1 to 105.4)	<0.001
Hospital service, n (%)				
medical	1429 (92.4)	5727 (87.3)	16928 (78.6)	<0.001
surgical	70 (4.5)	624 (9.5)	3072 (14.3)	
other	47 (3.0)	209 (3.2)	1539 (7.2)	
Coexisting conditions, n (%)				
diabetes mellitus	382 (24.7)	1628 (24.8)	3357 (15.6)	<0.001
myocardial infarction	302 (19.5)	1223 (18.6)	2889 (13.4)	<0.001
congestive heart failure	611 (39.5)	1943 (29.6)	2251 (10.5)	<0.001
peripheral vascular disease	165 (10.7)	460 (7.0)	751 (3.5)	<0.001
cerebrovascular disease	123 (8.0)	559 (8.5)	1166 (5.4)	<0.001
hemiplegia or paraplegia	3 (0.2)	17 (0.3)	104 (0.5)	0.02
dementia	35 (2.3)	212 (3.2)	296 (1.4)	<0.001
chronic obstructive pulmonary disease	328 (21.2)	1304 (19.9)	3510 (16.3)	<0.001
rheumatologic disease	30 (1.9)	155 (2.4)	358 (1.7)	0.001
peptic ulcer disease	28 (1.8)	132 (2.0)	384 (1.8)	0.49
liver disease	37 (2.4)	86 (1.3)	282 (1.3)	0.002
chronic kidney disease	311 (20.1)	373 (5.7)	75 (0.4)	<0.001
any malignancy	99 (6.4)	489 (7.5)	1497 (7.0)	0.23
AIDS	3 (0.2)	5 (0.1)	67 (0.3)	0.004
Deyo-Charlson comorbidity index, n (%)				
0	255 (16.5)	1704 (25.9)	10064 (46.7)	<0.001
1	373 (24.1)	1899 (29.0)	6205 (28.8)	
2	353 (22.8)	1515 (23.1)	2975 (13.8)	
≥3	565 (36.6)	1442 (22.0)	2295 (10.7)	
Acute hospital-related factors, n (%)				
sepsis	24 (1.6)	50 (0.8)	119 (0.6)	<0.001
cardiac catheterization	120 (7.8)	720 (11.0)	2672 (12.4)	<0.001
abdominal surgery	26 (1.7)	123 (1.9)	629 (2.9)	<0.001
CABG	30 (1.9)	327 (4.9)	1176 (5.5)	<0.001
AOSD score				
0	1331 (86.1)	6071 (92.6)	20442 (94.9)	<0.001
1 to 2	202 (13.1)	475 (7.2)	1076 (5.0)	
≥3	13 (0.8)	14 (0.2)	21 (0.1)	
Selected hospital outcomes				
discharge to facility, n (%)[a]	705 (53.2)	2843 (46.2)	6279 (29.8)	<0.001
hospital length of stay, days[a]	5 (3 to 9)	4 (2 to 8)	4 (2 to 6)	<0.001
in-hospital death, n (%)	220 (14.2)	406 (6.2)	478 (2.2)	<0.001

The data are presented as the means (SD), medians (25th to 75th percentile), or frequencies (percentages). sCr, serum creatinine; eGFR, estimated GFR; CABG, coronary artery bypass grafting; AOSD, acute organ system dysfunction.
[a]The discharge disposition and hospital length of stay refer only to patients who were discharged alive.

prolonged hospital LOS and be discharged to a short- or long-term care facility.

Nadir-to-Peak sCr and In-hospital Mortality Stratified by Baseline eGFR

The median time lag between the nadir and peak sCr was 1 (0 to 2) day. 77% and 96% of subjects had lag times of ≤2 days and ≤7 days, respectively. Using the AKIN criteria, the incidence of AKI (on the basis of nadir-to-peak sCr) was 15.3% (stage 1 AKI, 13%; stage 2 AKI, 1.5%; and stage 3 AKI, 0.8%) and was associated with a significantly higher in-hospital mortality rate (14.8% *versus* 1.7%; ($P <$ 0.0001) and prolonged median LOS (8 days [5 to 13 days] *versus* 4 days [2 to 6 days]; $P < 0.0001$) compared with those who did not develop AKI.

Table 2 displays the results of the logistic regression analyses examining the association of nadir-to-peak sCr increments, in intervals of 0.1 mg/dl, with in-hospital mortality, within each baseline eGFR stratum. In the fully adjusted model, among patients with a baseline eGFR ≥60 ml/min per 1.73 m^2, the ratio OR for in-hospital mortality became significant at a 0.2-mg/dl sCr increment, with an ratio OR of 1.67 (95% CI 1.13 to 2.47). Among patients with a lower baseline eGFR of 30 to 59 ml/min per 1.73 m^2, the ratio OR became significant at a 0.3-mg/dl sCr increment (OR 2.69; 95% CI 1.82 to 3.97). Finally, among patients with the lowest baseline eGFR of <30 ml/min per 1.73 m^2, the ratio OR did not become significant until the sCr increment reached 0.5 mg/dl (OR 2.15; 95% CI 1.02 to 4.51). Using the entire cohort, in the fully adjusted model, there was a significant interaction between the nadir-to-peak sCr and the baseline eGFR strata for in-hospital mortality (Figure 3; $P < 0.001$).

Nadir-to-Peak sCr and Resource Consumption Stratified by Baseline eGFR

We next examined the association of the identified eGFR specific nadir-to-peak sCr cutoff points with LOS and discharge disposition among hospital survivors (Tables 3 and 4). In the fully adjusted model, among patients with baseline eGFRs of ≥60, 30 to 59, and <30 ml/min per 1.73 m^2, hospital-acquired AKI was associated with an estimated prolongation of hospital LOS by 2.0 days (95% CI 1.9 to 2.1), 2.9 days (95% CI 2.7 to 3.1), and 2.8 days (95% CI 2.3 to 3.3) days, respectively.

Table 2. Logistic regression analyses examining the association of nadir-to-peak serum creatinine (sCr) increments and in-hospital mortality stratified by baseline eGFR

	Subjects	Deaths (%)	Adjusted Odds Ratio (95% Confidence Interval)
Baseline eGFR of ≥60 ml/min per 1.73 m^2			
total	21,539	478	
nadir-to-peak sCr increment (mg/dl)			
0	13,851	131 (0.9)	1.0
0.1	3,443	43 (1.3)	1.16 (0.82 to 1.64)
0.2	1,917	33 (1.8)	1.67 (1.13 to 2.47)
0.3	1,156	38 (3.3)	1.97 (1.31 to 2.95)
0.4	293	26 (9.2)	5.11 (3.14 to 8.32)
0.5	248	29 (10.1)	6.37 (3.89 to 10.43)
>0.5	631	155 (28.5)	16.71 (12.54 to 22.28)
Baseline eGFR of 30 to 59 ml/min per 1.73 m^2			
total	6,560	406	
nadir-to-peak sCr increment (mg/dl)			
0	3,468	94 (2.7)	1.0
0.1	1,241	35 (2.8)	0.97 (0.65 to 1.45)
0.2	314	15 (4.8)	1.53 (0.87 to 2.72)
0.3	516	43 (8.3)	2.69 (1.82 to 3.97)
0.4	119	8 (6.7)	2.02 (0.91 to 4.46)
0.5	205	29 (14.1)	4.69 (2.91 to 7.57)
>0.5	697	182 (26.1)	9.09 (6.75 to 12.24)
Baseline eGFR of <30 ml/min per 1.73 m^2			
total	1,546	220	
nadir-to-peak sCr increment (mg/dl)			
0	670	59 (8.8)	1.0
0.1	138	13 (9.4)	0.76 (0.36 to 1.53)
0.2	109	10 (9.2)	1.03 (0.49 to 2.12)
0.3	82	13 (15.9)	1.68 (0.82 to 3.44)
0.4[a]	35	0 (0.0)	
0.5	65	12 (18.5)	2.15 (1.02 to 4.51)
>0.5	447	113 (25.3)	2.65 (1.79 to 3.93)

The model is adjusted for age, gender, race, Deyo-Charlson comorbidity index, hospital service, sepsis, cardiac catheterization, coronary artery bypass grafting, abdominal surgery, and acute organ system dysfunction score. eGFR, estimated GFR.
[a]The odds ratio could not be calculated because there were no deaths in this group.

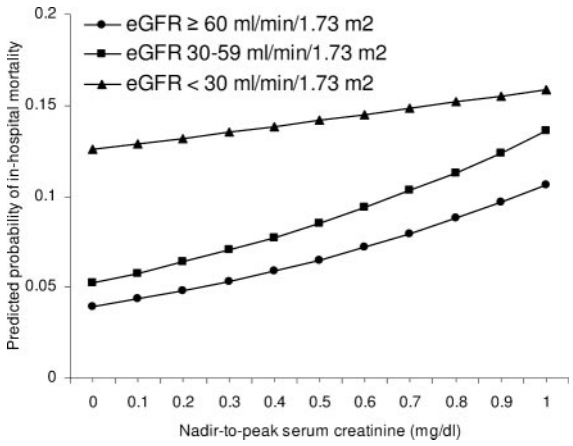

Figure 3. | Adjusted predicted probability of in-hospital mortality by nadir-to-peak serum creatinine increment stratified by baseline estimated GFR (eGFR). The analysis is adjusted for age, gender, race, the Deyo-Charlson comorbidity index, sepsis, cardiac catheterization, coronary artery bypass grafting, abdominal surgery, and the acute organ system dysfunction (AOSD) score. The analysis is on the basis of the final multivariate model with other covariates held constant near the cohort averages (*i.e.* a 60-year-old white woman with a Deyo-Charlson comorbidity index of 1 and an AOSD score of 1). $P < 0.001$ for the interaction term.

Similarly, in the fully adjusted model, among patients with baseline eGFRs of ≥60, 30 to 59, and <30 ml/min per 1.73 m^2, hospital-acquired AKI was associated with 1.57-fold (95% CI 1.44 to 1.70), 1.80-fold (95% CI 1.56 to 2.08), and 1.71-fold (95% CI 1.30 to 2.25) higher odds for discharge to another facility, respectively. Using the entire cohort, in the fully adjusted model, there was also a significant interaction between the nadir-to-peak sCr and the baseline eGFR strata for discharge disposition (Figure 4; $P < 0.001$).

Sensitivity Analyses

In sensitivity analyses, using fully-adjusted models, we found that the baseline eGFR remained a robust effect modifier of the independent association of the percentage increase in nadir-to-peak sCr, as well as the absolute and relative decrease in eGFR with in-hospital mortality ($P < 0.001$ for all interactions, data not shown). When the nadir-to-peak sCr assessment period was restricted to 7 days or less, the results from the fully adjusted mortality models revealed similar sCr increment thresholds of 0.2 mg/dl (OR 1.57; 95% CI 1.03 to 2.4), 0.3 mg/dl (OR 2.63; 95% CI 1.74 to 3.98), and 0.5 mg/dl (OR 2.43; 95% CI 1.13 to 5.24) in the baseline eGFR stratum ≥60, 30 to 59, and <30 ml/min per 1.73 m^2, respectively. Finally, in a sensitivity analysis restricted to patients with multiple hospitalizations ($n = 7104$), the median time between the index hospitalization and the nadir sCr value derived from a prior hospitalization was 3 months (1 to 12 months). In the basic model, we found a nonsignificant trend toward an interaction between the alternative nadir-to-peak sCr and eGFR for in-hospital mortality ($P = 0.08$), which was further attenuated in the fully adjusted model ($P = 0.67$).

Discussion

In our large hospitalized mixed patient population, we found that for different baseline eGFR strata, different-sized increments of nadir-to-peak sCr are independently associated with in-hospital mortality. A sCr increase of ≥0.2 mg/dl, ≥0.3 mg/dl, and ≥0.5 mg/dl was found to have an independent association with in-hospital mortality among patients with a baseline eGFR of ≥60, 30 to 59, and <30 ml/min per 1.73 m^2, respectively. These different levels of sCr changes for each baseline eGFR stratum represent our most important findings. These thresholds were also independently associated with resource consumption including an increase in hospital LOS and higher likelihood of discharge to a facility.

Table 3. Robust regression analyses examining the association of nadir-to-peak serum creatinine (sCr) increments and length of stay among hospital survivors stratified by baseline eGFR

	Subjects (%)	Adjusted Length of Stay Prolongation in Days (95% Confidence Interval)
Baseline eGFR of ≥60 ml/min per 1.73 m^2		
total	21,061	
nadir-to-peak sCr increment (mg/dl)		
<0.2	17,117 (81.3)	1.0
≥0.2	3,944 (18.7)	2.00 (1.91 to 2.09)
Baseline eGFR of 30 to 59 ml/min per 1.73 m^2		
total	6,154	
nadir-to-peak sCr increment (mg/dl)		
<0.3	4,879 (79.3)	1.0
≥0.3	1,275 (20.7)	2.86 (2.65 to 3.07)
Baseline eGFR of <30 ml/min per 1.73 m^2		
total	1,326	
nadir-to-peak sCr increment (mg/dl)		
<0.5	939 (70.8)	1.0
≥0.5	387 (29.2)	2.80 (2.29 to 3.31)

The model is adjusted for age, gender, race, Deyo-Charlson comorbidity index, hospital service, sepsis, cardiac catheterization, coronary artery bypass grafting, abdominal surgery, and acute organ system dysfunction score. eGFR, estimated GFR.

Table 4. Logistic regression analyses examining the association of nadir-to-peak serum creatinine (sCr) increments and discharge disposition among hospital survivors stratified by baseline eGFR

	Subjects (%)	Subjects Discharged to Facilities (%)	Adjusted Odds Ratio (95% Confidence Interval)
Baseline eGFR of ≥60 ml/min per 1.73 m^2			
total	21,061	6,279	
nadir-to-peak sCr increment (mg/dl)			
<0.2	17,117 (81.3)	4,653 (27.2)	1.0
≥0.2	3,944 (18.7)	1,626 (41.2)	1.57 (1.44 to 1.70)
Baseline eGFR of 30 to 59 ml/min per 1.73 m^2			
total	6,154	2,843	
nadir-to-peak sCr increment (mg/dl)			
<0.3	4,879 (79.3)	2,096 (42.9)	1.0
≥0.3	1,275 (20.7)	747 (58.6)	1.80 (1.56 to 2.08)
Baseline eGFR of <30 ml/min per 1.73 m^2			
total	1,326	705	
nadir-to-peak sCr increment (mg/dl)			
<0.5	939 (70.8)	473 (50.4)	1.0
≥0.5	387 (29.2)	232 (59.9)	1.71 (1.30 to 2.25)

The model is adjusted for age, gender, race, Deyo-Charlson comorbidity index, hospital service, sepsis, cardiac catheterization, coronary artery bypass grafting, abdominal surgery, and acute organ system dysfunction score. eGFR, estimated GFR.

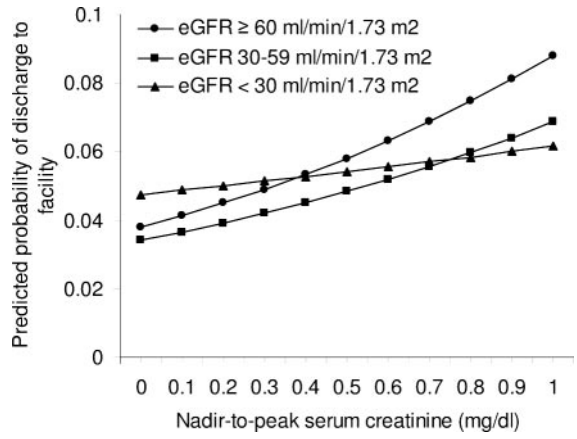

Figure 4. | Adjusted predicted probability of discharge to facility by nadir-to-peak serum creatinine increment stratified by baseline estimated GFR (eGFR). The analysis is adjusted for age, gender, race, the Deyo-Charlson comorbidity index, sepsis, cardiac catheterization, coronary artery bypass grafting, abdominal surgery, and the AOSD score. The analysis is on the basis of the final multivariate model with other covariates held constant near the cohort averages (*i.e.* a 60-year-old white woman with a Deyo-Charlson comorbidity index of 1 and an AOSD score of 1). $P < 0.001$ for the interaction term.

Statistical interactions between the nadir-to-peak sCr and the baseline eGFR strata for the outcomes of in-hospital mortality and discharge disposition were also significant. Our findings remained robust across several sensitivity analyses. Although our findings are consistent with prior studies demonstrating a strong association between small increases in sCr and in-hospital mortality, our study adds to the literature by showing that the association of sCr increments with in-hospital mortality is modified by baseline eGFR level. This suggests that sCr-based definitions of hospital-acquired AKI need to incorporate baseline kidney function level to optimize or refine risk stratification.

Several studies have explored the incidence of AKI and its associated adverse outcomes using various operational definitions (1–3,5,13). These definitions have traditionally used absolute or relative changes in sCr. Very few studies have taken into consideration the baseline level of kidney function to ascertain the magnitude of sCr increase. In 1983, Hou *et al.* (1) were the first to define AKI according to baseline level of kidney function by proposing a sCr increase of 0.5, 1.0, or 1.5 mg/dl from a baseline value of ≤1.9, 2.0 to 4.9, and ≥5 mg/dl, respectively. This definition has been adopted by others (2,5) and precedes the AKI classification and staging system proposed by the Acute Dialysis Quality Initiative and AKIN work groups (11,12). To examine the implications of the AKIN definitions, a simulation study of creatinine kinetics after AKI in the setting of normal baseline kidney function and various stages of chronic kidney disease found that the percentage rather than absolute change in sCr after AKI was highly dependent on baseline kidney function (23).

Studies identifying thresholds to define AKI have traditionally used in-hospital mortality as a patient-centered outcome (5,13,14,24,25) and have typically divided the study population by sequential increases in sCr to identify a threshold where mortality becomes significant. Using a data set of adults admitted to an acute care facility, Chertow *et al.* (5) demonstrated that patients who experienced a sCr increase of 0.3 to 0.4 mg/dl had 1.7-fold higher odds of in-hospital mortality relative to those who did not. Although these analyses were adjusted for pre-existing impaired kidney function, these authors did not explore interactions between nadir-to-peak sCr and baseline kidney function. Similarly, Lassnigg *et al.* (13) found that patients undergoing cardiac surgery who sustained postoperative absolute small sCr

Appendix 1. Baseline characteristics and selected outcomes of the excluded and included cohorts

	Excluded Cohort (n = 18,815)	Included Cohort (n = 29,645)	P
Age, years	45.0 (19.3)	64.9 (19.0)	<0.001
Female gender, n (%)	13,392 (71.2)	15,434 (52.1)	<0.001
Race, n (%)			
white	14,014 (74.5)	24,493 (82.6)	<0.001
black	1,067 (5.7)	1,351 (4.6)	
other	3,734 (19.9)	3,801 (12.8)	
Baseline serum creatinine, mg/dl	0.9 (0.7 to 1.0)	0.9 (0.7 to 1.1)	<0.001
Baseline eGFR, ml/min per 1.73 m^2	85.3 (68.8 to 103.7)	79 (58.8 to 98)	<0.001
Hospital service, n (%)			
medical	5,171 (27.5)	24,084 (81.2)	<0.001
surgical	3,712 (19.7)	3,766 (12.7)	
other	9,931 (52.8)	1,795 (6.1)	
Coexisting conditions, n (%)			
diabetes mellitus	1,424 (7.6)	5,367 (18.1)	<0.001
myocardial infarction	816 (4.3)	4,414 (14.9)	<0.001
congestive heart failure	649 (3.5)	4,805 (16.2)	<0.001
peripheral vascular disease	243 (1.3)	1,376 (4.6)	<0.001
cerebrovascular disease	404 (2.2)	1,848 (6.2)	<0.001
hemiplegia or paraplegia	30 (0.2)	124 (0.4)	<0.001
dementia	182 (1.0)	543 (1.8)	<0.001
chronic obstructive pulmonary disease	1,445 (7.7)	5,142 (17.4)	<0.001
rheumatologic disease	132 (0.7)	543 (1.8)	<0.001
peptic ulcer disease	59 (0.3)	544 (1.8)	<0.001
liver disease	59 (0.3)	405 (1.4)	<0.001
chronic kidney disease	230 (1.2)	759 (2.6)	<0.001
any malignancy	641 (3.4)	2,085 (7.0)	<0.001
AIDS	21 (0.1)	75 (0.3)	<0.001
Deyo-Charlson comorbidity index, n (%)			
0	14,222 (75.6)	12,023 (40.6)	<0.001
1	2,597 (13.8)	8,477 (28.6)	
2	1,190 (6.3)	4,843 (16.3)	
≥3	806 (4.3)	4,302 (14.5)	
Acute hospital related factors, n (%)			
sepsis	27 (0.1)	193 (0.7)	<0.001
cardiac catheterization	1,341 (7.1)	3,512 (11.9)	<0.001
abdominal surgeries	786 (4.2)	778 (2.6)	<0.001
CABG	29 (0.2)	1,533 (5.2)	<0.001
AOSD			
0	18,565 (98.7)	27,844 (93.9)	<0.001
1 to 2	248 (1.3)	1,753 (5.9)	
≥3	2 (<0.1)	48 (0.2)	
Select hospital outcomes			
hospital length of stay, days[a]	2 (1 to 4)	4 (2 to 7)	<0.001
discharged to facility, n (%)[a]	1,934 (10.4)	9,827 (34.4)	<0.001
in-hospital death, n (%)	210 (1.12)	1,104 (3.7)	<0.001

The data are presented as means (SD), medians (25th to 75th percentile) or frequencies (percentages).
[a]The discharge disposition and hospital length of stay refer only to patients who were discharged alive. CABG, coronary artery bypass grafting; AOSD, acute organ system dysfunction.

increases over the first 48 hours, defined by an increase of up to 0.5 mg/dl, had an increased 30-day mortality risk. These analyses were adjusted for the baseline sCr but did not explore an interaction. In another study of patients undergoing cardiac surgery, Thakar *et al.* (14) tested for an interaction between preoperative eGFR and postoperative decline in kidney function for its independent effect on mortality. At equivalent degrees of postoperative decreased kidney function, the risk of mortality was higher at lower preoperative eGFR levels. In their analyses, the reference group consisted of patients with preoperative eGFR >90 ml/min per 1.73 m^2 and no postoperative elevation in sCr. In our study, we opted to explore the optimal cutoff point where mortality became significant in each eGFR stratum to further refine the sCr-based AKI definition and optimize risk stratification.

Our study intentionally focused on hospital-acquired AKI rather than community-acquired AKI (26). The baseline kidney function estimate was on the basis of a nadir sCr registered over the first 3 days of hospitalization. The duration between the nadir and the peak sCr

was not limited but for most fell within 7 days. Prior studies have used variable methods to determine "baseline" kidney function and with variable time intervals to capture a peak sCr (5,13). In clinical practice, true baseline kidney function before hospital admission is often not precisely known. Reasons for this include fragmentation of medical records, variable time intervals to the last measured outpatient sCr, and uncertainty about rates of progression or acute changes in kidney function in the context of an illness leading to a hospitalization.

Strengths of our analysis include the use of a large, diverse, and mixed patient population with a wide range of comorbidities and complete outcome ascertainment. Limitations stem from a retrospective study design and use of administrative data including ICD-9-CM codes, which have variable diagnostic performance. To overcome this limitation, we used a well-validated comorbidity instrument, as well as surgical procedures codes and the AOSD scoring system to capture hospital-related factors (7,21,22). Nevertheless there may still remain some residual confounding. Our ascertainment of the end points is restricted to in-hospital mortality and discharge disposition and does not include longer-term outcomes. Furthermore, within each baseline eGFR stratum, the declining sample size might account for the wider confidence intervals around the effect estimates, and this uncertainty precludes definitive conclusions. This was particularly true for the eGFR group of <30 ml/min per 1.73 m^2. Finally, because our study was conducted at a single hospital, our findings apply most directly to a community-based tertiary care setting in the United States and require external validation. In particular, disposition plans might be susceptible to practices and prevailing conditions in our hospital and thus might not be extrapolated to other settings. In conclusion, in this study we provide support to the argument that baseline kidney function should be taken into account when using sCr increments to risk stratify individuals with hospital-acquired AKI.

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Disclosures

None.

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