Categories of Hospital-Associated Acute Kidney Injury: Time Course of Changes in Serum Creatinine Values

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Key Words

Serum creatinine · Multivariable regression models · Epidemiology

Abstract

Hospital-associated acute kidney injury (HA-AKI) is associated with increased inpatient mortality. Our objective was to categorize HA-AKI based on the timing of minimum and peak inpatient serum creatinine (sCr) and describe the association with inpatient mortality. **Materials and Methods:** This study is a retrospective analysis of an administrative data set for adults admitted to a single medical center for over 4 years. Changes and timing of the minimum and peak sCr were used to define HA-AKI categories. **Results:** Peak creatinine followed minimum creatinine for HA-AKI, and preceded the minimum value for transient HA-AKI (THA-AKI). A subset of patients developed HA-AKI after recovering from THA-AKI. Multivariable Cox regression analyses examined the association between these categories and 28-day inpatient mortality, adjusting for age, sex, race, Charlson comorbidity index, baseline kidney function, AKI recovery and renal replacement therapy. There were 50,601 patients included in the analyses, and 29,996 (59%) did not have AKI. There were 2,440 deaths; HA-AKI had a 2.24-fold (95% CI 1.99–2.51) increased risk, while THA-AKI group (12,101) had a 1.23-fold

(95% CI 1.09–1.40) increased risk for inpatient mortality. THA-AKI patients who recovered and then developed HA-AKI had the same mortality risk as THA-AKI (1.27-fold [95% CI 1.07–1.51]) but longer hospitalization and less recovery from AKI. **Conclusions:** Risk of short-term inpatient mortality is associated with AKI, and this risk is attenuated with recovery of kidney function in the hospital. Systematic surveillance with repeated inpatient sCr values is needed to assess the short- and long-term consequences of HA-AKI.

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Introduction

Acute kidney injury (AKI) has significant sequelae including increased inpatient mortality, and long-term risk of renal and cardiovascular events and death [1]. AKI is common among critically ill patients [2–5]. Once AKI was ascertained based on changes in serum creatinine (sCr) values rather than diagnostic-related groups, the striking incidence of AKI became apparent [6].

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The definition of AKI is based on a change in sCr from baseline values or a surrogate value if baseline values are not available [7, 8]. Hospital-associated AKI (HA-AKI) is characterized by maximal ('peak') sCr values compared to the baseline value [3, 9]. 'Transient azotemia' has been used to describe elevated sCr that normalizes within 3 days of admission without renal replacement therapy (RRT) [10] in contrast to patients with HA-AKI who often have persistently elevated sCr at the time of discharge [10–12]. Transient HA-AKI (THA-AKI) has been described an independent predictor of hospital mortality (OR 2.3 compared to patients without AKI), while persisting AKI was associated with a 6.1-fold risk for inpatient mortality [10].

We retrospectively analyzed an administrative data set from a single large referral center (University of Alabama Hospital at Birmingham (UAHB)) to examine the classification of AKI and its association with inpatient mortality, using the minimum sCr during the admission as the surrogate for baseline sCr. We hypothesized that the timing of minimum sCr relative to the peak sCr could distinguish between THA-AKI and HA-AKI. Accordingly, our objectives were to (1) distinguish between AKI categories, using the temporal relation between minimum and peak sCr, and (2) describe the associations of the AKI categories with inpatient mortality.

Materials and Methods

We examined hospital discharges from UAHB, a 1,121-bed academic healthcare center between October 1, 2009, and September 30, 2013, using demographic information, admissions and discharge dates, admission site location code, hospital inpatient service location, discharge diagnoses and procedure codes and discharge vital status. Each admission was linked to UAHB's central laboratory, and sCr values were extracted with date-time stamps and service locations. The Institutional Review Board at UAHB approved the use of de-identified patient information for this study and waived the requirement for informed consent at the patient level.

There were 109,456 patients (age ≥ 18 years) discharged from UAHB (181,574 admissions), with 5,452 inpatient deaths (3.0%) during the ascertainment interval. Patients with chronic dialysis or kidney transplantation or those having less than 2 sCr measurements were excluded from the analysis. Cases were excluded for sCr < 0.3 mg/dl, estimated glomerular filtration rates (eGFRs) < 10 ml/min/1.73 m² and length of stay (LOS) < 1 day [4]. Four cases were excluded with apparent miscoding of inpatient RRT based on < 0.2 mg/dl difference between first sCr, peak sCr, minimum sCr and last sCr.

Admission point of origin was determined from the site location code included in the discharge summary [13]. There were 11,065 patients transferred to the UAHB from other hospitals and 939 from other healthcare facilities (HCFs; e.g., skilled nursing

homes, hospice units, psychiatry unit, rehabilitation unit, etc.); these 12,004 patients are defined as admissions originating from HCFs. There were 38,576 patients admitted to the UAHB from community locations (including 20,931 from home or office, 12,821 from outpatient physician offices or clinics and 4,725 patients from UAHB Emergency Department). There were 122 patients with unknown points of origin who were excluded from analysis. The follow-up period was limited to 28-day maximum LOS. The final analytic data set included 50,580 patients who were admitted once during the evaluation period.

The admission date-time stamp was assigned to that of the first sCr and was adjusted by 24 h for each day that the first sCr measurement was obtained after the admission date. HA-AKI was defined as cases where the minimum sCr preceding the highest measured ('peak') sCr value for the admission. We used an increment of 0.3 mg/dl as the criteria for AKI based on prior studies of the minimum increment independently associated with risk of 28-day inpatient mortality [3, 9, 14]. THA-AKI was defined with the highest ('peak') sCr preceding the minimum sCr, with a subsequent sCr decrease of ≥ 0.3 mg/dl from the peak sCr. Some THA-AKI patients subsequently developed HA-AKI following recovery to the minimum sCr value and were then classified as 2HA-AKI. Patients without a clinically significant change (± 0.3 mg/dl) between peak and minimum sCr were classified as not having AKI (No-AKI).

For time-to-event regression analysis, AKI category was the effect variable, and the exposure period was LOS (> 1 and ≤ 28 days). The covariates included age stratified at the median value of 55 years, gender, black or non-black race, Charlson comorbidity index [15] and eGFR (stratified at 60 ml/min/1.73 m², where the CKD-EPI eGFR [16] was calculated from the minimum inpatient sCr, provision of RRT and covariates that described the extent of recovery from peak sCr). The outcome measure was inpatient mortality, ascertained as vital status at time of discharge or at the 28th day of stay. We calculated the hazard ratios (HRs) and 95% confidence intervals for inpatient mortality among cases with no AKI (reference) and among AKI categories. We compared baseline characteristics of patients using chi-square test and analysis of variance. Dunnett tests were used for multiple comparisons, with minimal statistical significance set at $p \leq 0.05$. Mean values are presented as ± 1 standard deviation, and medians with 25th and 75th centiles. Survivor functions for multivariable-adjusted Cox analysis with point-wise confidence intervals were generated as described [17]. Relative integrated discrimination improvement (IDI) was used with an a priori criterion for clinical significance of 10% [18, 19]. Statistical analyses were performed with Stata version 13.1 (Stata Corp, College Station, Tex., USA) using the following functions: group, IDIsurv, median test, pwmean, prtest, stcox (with tvco option) and survci.

Results

The patient characteristics, classified by AKI category, are shown in table 1: 29,989 (59%) did not develop AKI (No-AKI); 12,101 (24%) had THA-AKI; 2,243 (4.4%) developed HA-AKI after recovering from THA-AKI (2HA-AKI) and 6,247 (12%) developed HA-AKI. Compared to the No-AKI reference group, patients with AKI were old-

Table 1. Characteristics of 50,580 inpatients (2,500 deaths, 4.9%) without or with AKI, including discharge diagnosis groups

	AKI category			
	No-AKI: 29,989 (59)	THA-AKI: 12,101 (24)	2HA-AKI: 2,243 (4.4)	HA-AKI: 6,247 (12)
Age, years	53±18	55±18	56±18^a	58±17^a
Male sex	15,028 (50)	7,270 (60)	1,408 (63)	3,408 (55)^a
Black race ^b	8,673 (29)	3,933 (33)	465 (36)	1,998 (32)^a
Baseline eGFR ^c	100±27	94±35	95±40	87±34^a
HCF transfers	6,336 (21)	2,941 (24)	722 (32)	2,005 (32)^a
LOS, days	3.7±3.2	6.9±5.2	12±6.5	8.1±6.1
Charlson score	1.2±1.7	1.6±1.9	2.0±2.1	2.1±2.1^a
Diabetes	5,089 (17)	2,697 (22)	466 (21)	1,553 (25)^a
COPD	4,459 (15)	1,875 (16)	397 (18)	1,140 (18)^a
CHF	2,104 (7.0)	1,429 (12)	434 (19)	1,312 (21)^a
Stroke	2,534 (8.5)	994 (8.2)	241 (11)	631 (10)^a
Renal disease	1,139 (3.8)	1,681 (14)	492 (22)	970 (16)
AMI	1,893 (6.3)	1,057 (8.7)	265 (12)	842 (14)
Cancer	2,263 (7.6)	854 (7.1)	154 (6.9)	549 (8.8)^a
Met cancer	1,394 (4.7)	590 (4.9)	87 (3.8)	361 (5.8)^a
Inpatient RRT	0	287 (2.4)	246 (11)	256 (4.1)
Ever in ICU	5,280 (18)	4,564 (38)	1,425 (64)	3,028 (49)^a
Inpatient deaths	506 (1.7)	606 (5.1)	267 (12)	1,121 (18)^a

Unless otherwise indicated, values are given as number (percentage) or means ± SD; medians are given with (25th–75th centile).

SIRR = Incident rate ratio (incident rates express as events per 28 patient-days).

p < 0.001 for comparisons of characteristics between each group by ANOVA for means, signed-rank test for medians and chi-square test for proportions; shown as bold text, relative to 'No-AKI', which served as the reference group.

^a p < 0.05 for comparison between THA-AKI, 2HA-AKI and HA-AKI (Dunnett test for multiple comparisons) or chi-square test for proportions.

^b Race or ethnic group was self-reported, and further classified as black or non-black.

^c eGFR calculated with minimum sCr.

COPD = Chronic obstructive pulmonary disease; CHF = congestive heart failure; AMI = acute myocardial infarction.

er, more likely to be male, black, had longer LOS, higher Charlson comorbidity scores, more likely to spend at least 1 day in an intensive care unit (ICU) and more likely to be transferred from another HCF to UAHB.

There were differences in the Charlson comorbidities between AKI subgroups, especially for diabetes, congestive heart failure and acute myocardial infarction. The prevalence of chronic renal disease was higher, which was reflected in lower baseline eGFR values for each patient. The inpatient mortality rates were 1.7% for No-AKI, 5.1% for THA-AKI, 12% for 2HA-AKI and 18% for HA-AKI.

Figure 1 illustrates the time course of sCr changes for the AKI categories. HA-AKI, 2HA-AKI and THA-AKI were defined based on the timing of the peak and mini-

mum sCr; the peak sCr preceded the minimum sCr for THA-AKI (blue) and 2HA-AKI (purple), while the minimum sCr preceded the peak sCr for HA-AKI (red). The inset shows elapsed time (hours) relative to the estimated time of admission.

For THA-AKI and 2HA-AKI, the peak sCr was recorded at 38 ± 47 and 30 ± 36 h after admission, while the minimum sCr values were observed at for 115 ± 88 and 136 ± 97 h after admission, respectively. The peak sCr for HA-AKI occurred at 127 ± 105 h, and followed the minimum sCr recorded at 42 ± 59 h. For all AKI categories, the discharge time was 7–10 h after the last recorded sCr (fig. 1inset).

The distinguishing characteristic of the 2HA-AKI patients was progression to a secondary peak sCr (peak 2)

Fig. 1. Time course for AKI types. The analysis pertains to 50,601 patients with a single admission to the University of Alabama at Birmingham Hospital between October 1, 2009 and September 30, 2013; first, peak, minimum and last sCr values, connected by dashed lines, stratified by AKI type. #1, first sCr recorded for admission; 2HA-AKI, transient hospital associated AKI that resolves, followed by a second episode of AKI; THA-AKI defined as peak sCr ≥ 0.3 mg/dl above the minimum sCr with peak sCr preceding the minimum sCr; HA-AKI defined as peak sCr ≥ 0.3 mg/dl above the minimum sCr with minimum sCr preceding the peak sCr; last, last sCr recorded for admission; No-AKI defined as peak sCr < 0.3 mg/dl above the minimum sCr. The elapsed hours relative to admission are listed in the inset.

that occurred after they had recovered from the initial elevation of sCr present at admission (purple line; fig. 1). The peak 2 sCr values needed for classification as 2HA-AKI were defined as ≥ 0.3 mg/dl above the individual minimum sCr and occurred at 219 ± 126 h (136 ± 97 h) for the 2HA-AKI patients. As seen in table 1, the baseline characteristics of these patients were more similar to the HA-AKI patients than to the THA-AKI patients, and they were more likely to receive inpatient RRT, had longer LOS and spent more days in an ICU than the other categories. Despite these differences, the 2HA-AKI patients had better short-term mortality outcomes than the HA-AKI patients (table 2).

Table 2 summarizes recovery for patients with THA-AKI, 2HA-AKI and HA-AKI. By definition, 100% of the 2,243 2HA-AKI patients recovered from the initial peak sCr to the minimum sCr, and thereafter developed a subsequent elevation of sCr that was ≥ 0.3 mg/dl above their individual minimum sCr value. Of the 12,101 THA-AKI patients, 80% had $>75\%$ decrease from the peak sCr compared to their last sCr, and $<1\%$ had $<33\%$ improvement from their peak sCr value. In contrast, the improvement from the secondary peak sCr for 2HA-AKI patients, and from peak sCr for HA-AKI patients was blunted, with $<20\%$ of these patients showing 75% improvement from their peak sCr values. The majority

of 2HA-AKI (71%) and HA-AKI (52%) patients had less than modest improvement ($>33\%$) from their peak sCr values.

The relevant sCr values for each AKI category are summarized in table 2, as well as other baseline characteristics and inpatient mortality comparisons. For those patients who received care in an ICU, the average number of days in those units was 4.8 ± 3.6 days for patients with no AKI, compared to >9 days for patients with AKI. The inpatient mortality rates (No-AKI, 1.7%; THA-AKI, 5%; 2HA-AKI, 12%; HA-AKI, 18%) increased in parallel with the number of ICU days, as well as LOS across the AKI categories. The last row in table 2 shows the HRs for the AKI categories, obtained with Cox multivariable regression analysis.

Table 3 summarizes the Cox proportional hazard models for inpatient mortality, with sequential addition of covariates and analysis of their time dependence, as reflected in the correlation (ρ) of the smoothed Schoenfeld residuals with time and the significant interactions with $\ln(\text{LOS})$. When the time-dependent covariates were included in the Cox model, the HR for THA-AKI was 1.088 (95% CI 0.952–1.242; $p = 0.217$) and the HR for 2HA-AKI was 1.015 (95% CI 0.84–1.223; $p = 0.868$). The HR for HA-AKI remained significantly different from zero and the other AKI HRs (table 3). Even though the time-aver-

Table 2. Characteristics of 50,580 inpatients (2,500 deaths, 4.9%) without or with AKI, including sCr values (mg/dl)

	AKI category			
	No-AKI: 29,989 (59)	THA-AKI: 12,101 (24)	2HA-AKI: 2,243 (4)	HA-AKI: 6,247 (12)
LOS, days	3.7±3.2	6.9±5.2	12±6.5	8.1±6.1
Age > median (55 years)	14,262 (48)	6,666 (55)	1,268 (57)^a	3,798 (61)
HCF transfers	6,336 (21)	3,237 (25)	426 (33)	2,005 (32)^a
Baseline eGFR <60 ^b	2,494 (8.3)	2,290 (19)	469 (21)	1,447 (23)^a
First sCr	0.9±0.3	1.7±1.6	2.1±2.4^a	1.2±0.8^a
Minimum sCr	0.8±0.3	1.0±0.7	1.1±1.0^a	1.1±0.7^a
Peak sCr	1.0±0.3	1.9±1.7	2.3±2.6^a	2.0±1.5^a
2nd peak sCr		0.9±0.4	1.7±1.5	
Last sCr	0.9±0.3	1.0±0.7	1.5±1.4^a	1.6±0.3^a
sCr: number/day	1.4±0.7	1.5±0.8	1.6±0.9	1.4±0.9
Percent recovery ^c	N/A	88±18	100	35±35
>75% recovery	N/A	9,643 (80)	100	1,140 (18)
<33% recovery	N/A	66 (0.6)	0	3,232 (52)
>75% recovery 2	N/A		108 (4.8)	
<33% recovery 2	N/A		1,594 (71)	
Charlson index	1 (0–2)	1 (0–2)	1 (0–2)	2 (0–2)
Inpatient RRT	0	287 (2.4)	246 (11)	256 (4.1)
Total ICU days	4.8±3.6	9.2±6.0	13±6.6^a	9.8±6.6^a
Inpatient deaths	506 (1.7)	606 (5.0)	267 (12)	1,121 (18)^a
IR: death	0.128 (0.117–0.140)	0.205 (0.189–0.222)	0.278 (0.247–0.314)	0.622 (0.587–0.660)
IRR: deaths	1.00 (reference)	1.60 (1.42–1.80)	2.18 (1.88–2.52)	4.86 (4.38–5.40)^a
HR for death ^d	1.00 (reference)	1.23 (1.09–1.40)	1.27 (1.07–1.51)^a	2.24 (1.99–2.51)^a

Unless otherwise indicated, values are given as number (percentage) or means ± 1 SD, medians are given with (25th–75th-percentile).

Baseline eGFR <60, baseline eGFR calculated from minimal sCr; risk category defined by patients with baseline eGFR <60 ml/min/1.73 m²; IRR = incident rate ratio (incident rates express as events per 28 patient-days).

p < 0.001 for comparisons of characteristics between each group by ANOVA for means, signed-rank test for medians, and chi-square test for proportions; shown as bold text, relative to 'No-AKI', which served as the reference group.

^a p < 0.05 for comparison between THA-AKI and HA-AKI (Dunnett test for multiple comparisons) or chi-square test of proportions.

^b eGFR calculated with minimum sCr.

^c Percent recovery calculated as 100*(peak sCr – minimum sCr)/(peak sCr – last sCr).

^d HR for inpatient mortality (Cox model; adjusted for median age, gender, race, Charlson comorbidity index, admission source, eGFR <60, percent recovery to 75%, percent recover <35%, and RRT).

aged HRs for THA-AKI and 2HA-AKI were not significantly from the reference category (No-AKI), there was a significant interaction between 2HA-AKI and elapsed time in the hospital.

Figure 2 shows the survival functions for the AKI categories with point-wise 95% CI for the survival curves [17]. While the survival curve for HA-AKI clearly separated from the other categories early during the course of hospitalization, the survival curves for THA-AKI and 2HA-AKI only became evident for patients with prolonged LOSs. The curves for THA-AKI and 2HA-AKI were similar over time.

Discussion

We describe a retrospective analysis with 4 years ascertainment of all initial admissions to a single large academic referral medical center, and have used the timing of peak and minimal sCr values to distinguish between transient and more prolonged AKI during the hospital course. Over 40% of the admissions presented with AKI at the time of admission, or developed AKI after being admitted UAHB. The 24% of all qualifying admissions classified as TH-AKI (including the subset (4%) of patients who presented with TH-AKI, but experienced re-

Table 3. Cox multiple regression models: univariate analysis

Univariate analysis	HR	Lower 95% CI	Upper 95% CI	p value	Rho (p value)	Relative IDI, %
No-AKI	1.00	–	–			
THA-AKI	1.38	1.22	1.55	<0.001	0.03 (0.102)	
2HA-AKI	1.56	1.34	1.82	<0.001	0.06 (0.003)	
HA-AKI	3.86	3.45	4.30	<0.001	–0.05 (0.006)	
Age > median	1.91	1.76	2.08	<0.001	0.06 (0.006)	22.5
Male gender	1.03	0.95	1.12	0.431	–0.01 (0.818)	–0.1
Black race	0.98	0.90	1.07	0.684	0.02 (0.301)	0.1
HCF transfer	1.70	1.57	1.84	<0.001	–0.16 (<0.001)	8.3
eGFR <60	3.59	3.31	3.90	<0.001	–0.22 (<0.001)	18.2
Charlson index	1.82	1.72	1.92	<0.001	0.03 (0.205)	13.3
Recovery <75%	1.76	1.63	1.91	<0.001	–0.12 (<0.001)	5.1
Recovery 2 <75%	0.49	0.24	0.97	0.042	0.04 (0.039)	0.1
Inpatient RRT	3.44	3.06	3.87	<0.001	–0.02 (0.221)	–5.9

Time-dependent HR analysis	Main analysis				Interactions with ln(time)		p value
	HR	lower 95% CI	upper 95% CI	p value	HR	95% CI	
AKI	1.29	1.21	1.39	<0.001	1.00	0.96–1.03	0.860
Age > median	0.78	0.65	0.93	0.006	1.32	1.20–1.45	<0.001
Male gender	1.12	0.96	1.33	0.139	0.96	0.88–1.04	0.285
Black race	0.92	0.77	1.10	0.378	1.02	0.93–1.12	0.647
HCF transfer	2.42	2.06	2.84	<0.001	0.76	0.70–0.82	<0.001
eGFR <60	6.86	5.69	8.26	<0.001	0.51	0.47–0.57	<0.001
Charlson index	1.02	0.92	1.14	0.705	1.20	1.13–1.28	<0.001
Recovery <75%	2.49	2.09	2.95	<0.001	0.79	0.72–0.86	<0.001
Recovery 2 <75%	0.02	0.01	1.40	0.072	3.45	0.8–14.9	0.095
Inpatient RRT	1.18	0.87	1.61	0.282	1.30	1.14–1.49	<0.001

Adjusted for time-dependent covariates	HR	Lower 95% CI	Upper 95% CI	p value	Rho (p value)
No-AKI	1.00	Reference			
THA-AKI	1.088	0.952	1.242	0.217	0.031 (0.123)
2HA-AKI	1.015	0.844	1.223	0.868	0.055 (0.004)
HA-AKI	2.120	1.881	2.389	<0.001	–0.021 (0.286)

Age > median, risk category for age >55 years (median value for entire cohort); eGFR <60, baseline eGFR calculated from minimal sCr, risk category defined by patients with baseline eGFR <60 ml/min/1.73 m²; HCF transfer, patient admitted to the University of Alabama Hospital to another HCF; IRR = incident rate ratio (incident rates express as events per 28 patient-days); Rho = correlation coefficient for smoothed Schoenfeld residuals with time.

p < 0.001 for comparisons of characteristics between each group by ANOVA for means, signed-rank test for medians, and chi-square test for proportions; shown as bold text, relative to 'No-AKI', which served as the reference group.

Percent recovery calculated as 100*(peak sCr – minimum sCr)/(peak sCr – last sCr).

Criteria for inclusion of covariates: age, race, gender and others with: univariate HR >3.0; significant correlation coefficient (rho) for Schoenfeld residual (p < 0.05); or rIDI >10%.

onset of HA-AKI) accounted for 70% of all cases with AKI during the ascertainment interval.

Overall, our findings confirm the previous description of 'transient azotemia' [10]. We also describe a subset of patients with THA-AKI who have developed a second episode of AKI during the same admission, which we have

termed '2HA-AKI'. This subgroup had increased inpatient mortality rates compared to THA-AKI patients who returned and remained at the minimum sCr, but lower mortality rates than the larger group of patients with HA-AKI. When adjusted for LOS and other covariates, the hazard rates for inpatient mortality were identical for the

Fig. 2. Survival curves for AKI types. The analysis pertains to 50,601 patients with a single admission to the University of Alabama at Birmingham Hospital between October 1, 2009 and September 30, 2013. The survival curves were generated from Cox regression models, using point-wise confidence intervals for the covariate-adjusted survivor functions generated from Cox regression analysis [17]. #1, first sCr recorded for admission; 2HA-AKI defined by second peak sCr ≥ 0.3 mg/dl above the minimum sCr with second peak sCr following the minimum sCr; HA-AKI defined as peak sCr ≥ 0.3 mg/dl above the minimum sCr with minimum sCr preceding the peak sCr; last, last sCr recorded for admission; No-AKI defined as peak sCr < 0.3 mg/dl above the minimum sCr; THA-AKI defined by peak sCr ≥ 0.3 mg/dl above the minimum sCr with peak sCr preceding the minimum sCr. The patients at risk for each category relative to admission date are listed in the inset.

THA-AKI and 2HA-AKI groups, and significantly less than the HA-AKI group. The mortality risk for the 2HA-AKI group may reflect the case-mix, comorbidities and other baseline characteristics and needs to be assessed in other independent data sets.

The subgroup with 2HA-AKI was not addressed in the previous description of transient azotemia, although a group with THA-AKI who had not improved by the third hospital day was noted and reclassified as ‘persisting ATN’ [10]. We suspect that this group with poor recovery from THA-AKI may well have been the group we now characterized as 2HA-AKI. In future studies, it may be informative to evaluate these classifications of inpatient AKI and the risks for developing AKI as well as all-cause mortality during subsequent hospitalizations [20].

There are different assumptions that may account for the difference in apparent incidence of AKI and the ex-

tent of improvement from peak sCr. Uchino et al. [10] defined transient azotemia as resolving within 3 days without RRT, while patients receiving RRT were classified as persisting ATN. We have not used extent of recovery in the present definitions of THA-AKI, 2HA-AKI and HA-AKI, and observed that 17% of patients with HA-AKI had significant improvement ($\geq 80\%$) from their peak sCr values before hospital discharge and thus did not have persisting AKI. Sensitivity analysis showed that exclusion of patients receiving RRT did not change the estimates of recovery from AKI (data not shown); rather than reclassifying these patients as HA-AKI, we simply included RRT as a covariate in the time-to-event regression model. The major reason for the apparent increased incidence of AKI in our series was the use of a lower threshold (0.3 mg/dl) for diagnosing AKI [9, 14], rather than the higher 0.5 mg/dl used by Uchino et al. [10]. Neither study used prior measurements of sCr as baseline values; we used the minimal sCr for each admission, and Uchino et al. [10] imputed the baseline sCr based on an estimated eGFR of 75 ml/min/1.73 m² for two-thirds of their patients, an approach likely to overestimate that incidence of AKI [7, 8], and thus does not account for the increased incidence of AKI that we describe in the present analysis.

The definition of baseline kidney function is somewhat controversial even with the availability of previous ambulatory determinations of sCr [9, 21, 22]. Using a pre-admission ambulatory sCr as the baseline has been advocated, with a number of surrogates considered when ambulatory data is not available [21]. Siew et al. [7, 8] defined the most recent ambulatory sCr measurement as the baseline sCr and found AKI incidence rates were underestimated for adults when the first admission sCr was used for the baseline (14%), compared to the AKI incidence rate of 26% based on the last pre-admission sCr. The minimum sCr during admission performed better as a surrogate baseline sCr than the first measured sCr, which may reflect a number of cases with THA-AKI included in their analyses. The misclassification and overestimation of the incidence of AKI that occurred when the minimum sCr was used as the surrogate baseline sCr was most evident in the mildest stages of AKI (i.e., stage 1).

There are 2 limitations of the current definitions of baseline sCr that are worth considering [23]: (1) AKI is a global health issue [24, 25], and the majority of patients with AKI in developing countries have never had a previous sCr measurement and (2) pre-hospitalization sCr values, when available, are only relevant to the magnitude of

the baseline sCr, but do not address the timing of the baseline sCr, which is the distinctive feature of the current analysis. Not only was the elapsed time from admission to the minimum sCr measurement significantly different, but there was also a statistically significant difference in the magnitude of the minimum sCr for patients with THA-AKI compared to HA-AKI. This observation questions whether there is a single baseline creatinine that is appropriate for all forms of AKI.

Finally, we report that there is only a modest risk for inpatient mortality associated with THA-AKI and 2HA-AKI (fig. 2). If the regression analyses used time-averaged covariates, then the significance of the association of inpatient mortality with THA-AKI and 2HA-AKI was greatly attenuated (table 3). The time dependence of hazards associated with AKI has been described in several recent publications [26–28]. Even though the HR for inpatient mortality was identical for THA-AKI and 2HA-AKI, the long-term outcomes may diverge, especially noting that the THA-AKI had nearly complete recovery from AKI, while the 2HA-AKI group had severely reduced recovery from AKI, similar to the HA-AKI group.

Other reports have described AKI acquired before admission, which resolved in the hospital setting as ‘community-acquired’ AKI [22, 29–33]. We have operationally defined THA-AKI as cases where the peak sCr values precede the subsequent minimal sCr for that admission, and surmise that the rapid decrease in sCr may have reflected dehydration prior to admission that was promptly and appropriately corrected with fluid administration. Of the 14,344 patients with THA-AKI and 2HA-AKI in our analysis, 10,681 (75%) were admitted to the UAHB from a community-based setting, but 25% were transferred/admitted to the UAHB from other hospitals and HCFs; so THA-AKI and community-acquired AKI are not entirely synonymous. In contrast, a higher percentage of HA-AKI patients (32%) were transferred to the UAHB from other HCFs.

Others have described inpatient recovery of AKI but the criteria for recovery have not been standardized [34]. Recovery to the baseline sCr measured before AKI developed has been used [5], often with the focus on severely ill patients in the critical care setting [35]. We report that the average improvement in elevated sCr for patients with THA-AKI was $88 \pm 18\%$, with 80% achieving 75% improvement from the peak sCr before hospital discharge. In contrast, only 4.8% of the 2HA-AKI and 17% of the HA-AKI achieved a 75% reduction from the peak sCr before hospital discharge.

Our study has several limitations and is based on retrospective analyses of an administrative data set reflecting the 4-year experience at a single tertiary academic referral medical center. Information about pre-hospitalization sCr was not available, and neither can the etiology of AKI nor urine output nor fluid administration be determined from the administrative data set. Follow-up status after discharge was not included, and many patients, especially those with HA-AKI and 2HA-AKI, were discharged before they may have had more complete recovery of their renal function. We cannot describe their subsequent course due to the limitations of our data set. The density and timing of inpatient sCr data reflect case ascertainment that is dependent on clinical decision-making and laboratory testing ordering practices [3], which introduces several sources of potential confounding and bias [36].

Changes in sCr depend on factors that modify creatinine generation (body composition, muscle wasting and acute muscle injury) [37] and changes in the volume of distribution of creatinine (dehydration or volume expansion) may occur, especially in elderly [11] and critically ill patients with prolonged hospitalizations [38, 39]. Most admissions were not associated with significant changes (≤ 0.3 mg/dl) in sCr; these admissions were defined as the reference group with ‘No-AKI’ for these analyses. We do not attribute the observed decreases in sCr to changes in creatinine generation rate because we censored each case at 28 days LOS, and the majority of the cases of THA-AKI were not exposed to an intensive care setting. Nevertheless, there is certainly a subset of critically ill patients who may have decreased creatinine generation rates, and net cumulative fluid balance, which could dilute their sCr values [40].

The approach described herein is readily applicable to retrospective analyses of large administrative inpatient data sets, and does not use diagnosis-related groups to define AKI categories. Further work is needed to directly compare the minimum inpatient sCr with previous values, to determine if the minimum inpatient sCr value can be used as a real-time tool in assessing the development and recovery from AKI during an acute hospitalization and to compare the minimum inpatient sCr value to sCr values obtained for patients with previous hospital admissions.

In conclusion, we conducted a retrospective analysis of a large administrative set from a single academic medical center, and described 3 unique subgroups of AKI that were differentiated by the time course of the changes in sCr with reference to the minimal and maximal values

obtained during a single hospitalization. While the associate risk for inpatient mortality was attenuated for THA-AKI and 2HA-AKI, the finding that approximately 20% of patients initially classified as THA-AKI experienced a second episode of AKI suggests that continued surveillance of inpatient sCr even after 'complete' recovery from THA-AKI would be informative and could potentially lead to clinical initiatives targeted at improving outcomes for this high risk group of patients. Finally, approximately 20% of patients with HA-AKI have significant improvement from their peak sCr values during the hospitalization. More information is needed to better characterize recovery from peak sCr in patients with AKI, with the goals of better surveillance and implementation of pro-active treatment programs that could positively impact patient outcomes and LOS [23].

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Authorship

All authors participated in the study design, analysis and writing of the manuscript. No other persons participated in the analyses, drafting or revision of the manuscript.

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Disclosure Statement

None of the authors disclose any conflicts of interest relevant to this report.

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