Serum Creatinine Trajectories for Community- versus Hospital-Acquired Acute Kidney Injury

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Key Words

Baseline serum creatinine · Serum creatinine ·
Multivariable regression models · Creatinine trajectory

Abstract

Background: Patterns of acute kidney injury (AKI) can be distinguished by the rate of changes in the serum creatinine concentrations during hospitalizations. We hypothesized that the timing and values of minimum and maximum serum creatinine (sCr) could be used to distinguish between transient hospital-associated AKI (THA-AKI) and hospital-acquired AKI (HA-AKI). **Materials and Methods:** We evaluated adults admitted to 2 regionally distinct academic medical centers. Peak sCr during the hospitalization was used to define AKI, using absolute changes and timing from the minimum sCr. sCr trajectories were derived based on the rate of change between the minimum and peak creatinine concentrations. **Results:** Peak creatinine followed the minimum creatinine for HA-AKI, while the peak creatinine preceded the minimum creatinine for THA-AKI. There were 82,403 patients included in the analyses, and 53,882 (65%) did not have AKI during the index hospitalization. There were 2,611 inpatient deaths; HA-AKI had a 4.8-fold increased risk relative to those

without AKI ($p < 0.01$), and transient AKI had a 1.6-fold increased risk for inpatient mortality relative to inpatients without AKI ($p < 0.01$). **Conclusions:** Patients with hospital-associated AKI are at an increased risk for inpatient mortality. Creatinine trajectories can be used to describe the rate of development as well as recovery from inpatient AKI. The 24- and 48-hour interval slopes may be early indicators of developing AKI.

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Introduction

Acute kidney injury (AKI) is defined by changes in serum creatinine (sCr) from a baseline value [1, 2]. The time course of changes in sCr concentrations has been referred to as the creatinine ‘trajectory’ [3–7], and is discussed in the current KDIGO AKI staging criteria [8].

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We used datasets from 2 large academic medical centers (University of Alabama Hospital (UAH) and University of California at San Diego (UCSD)) to examine inpatient sCr trajectories and hypothesized that the timing and values of minimum and maximum sCr could be used to distinguish between transient hospital-associated AKI (THA-AKI) and hospital-acquired AKI (HA-AKI). Our objectives were to (1) describe the time course of sCr trajectories, using the temporal relationships between the minimum and peak sCr values, and (2) determine the associations between the patterns of AKI defined by the creatinine trajectories and inpatient mortality.

Materials and Methods

Description of Cohorts and Definitions

We examined adults admitted to UAH between October 1, 2009 and September 30, 2013, and UCSD Medical Center between January 1, 2011 and December 31, 2012, obtaining demographic information, admission and discharge dates, discharge diagnoses, procedure codes, and vital status. The Institutional Review Boards at both sites approved the use of de-identified patient information for this study.

The index admissions from UAH ($n = 67,019$) and UCSD ($n = 15,384$) were limited to 30 days. Patients were excluded who received chronic dialysis or kidney transplantation, or had <2 inpatient sCr values, or maximum estimated glomerular filtration rates (eGFR) <15 ml/min/1.73 m².

AKI was defined by comparing the peak sCr value to the minimum sCr for each admission [9], with the additional criteria that the elapsed time between the peak sCr and the minimum sCr was >6 h. We omitted patients with sCr values <0.4 mg/dl and used AKI threshold criteria that reflected the minimum sCr: 0.3 mg/dl change for minimum sCr <1.0 mg/dl, and 0.5 mg/dl change for minimum sCr ≥ 1.0 mg/dl [10, 11]. Patients without significant changes in the sCr comprised the reference group (No-HA-AKI). HA-AKI was defined by the minimum sCr preceding the peak sCr, and an increased sCr above the AKI threshold. The peak preceding the minimum sCr, with a significant decrease in sCr, defined THA-AKI.

Other Adjustments and Statistical Analysis

The baseline sCr (cr-min0) for HA-AKI was defined by the timing and magnitude of the last sCr that still remained within the AKI threshold following the minimum sCr. The average minimum sCr for HA-AKI (0.96 mg/dl) was observed 43 h following admission, and the cr-min0 (1.02 mg/dl) averaged 62 h after admission. Maximal sCr values were calculated at 24-hour intervals after cr-min0 for describing the sCr trajectory. Similarly, minimal sCr values were calculated at 24-hour intervals after the peak sCr values for describing recovery from the peak sCr.

We compared baseline characteristics of patients using chi-square tests and analysis of variance. The Dunnett test was used for multiple comparisons, with minimal statistical significance set at $p \leq 0.05$. Mean values are presented as ± 1 SD, and medians with

25th and 75th-centiles. Incident rates and incident rate ratios were obtained with Poisson regression models and presented with 95% CIs. Statistical analyses were performed with Stata version 14.1 (StataCorp, College Station, Tex., USA).

Results

The baseline characteristics are shown in table 1. Patients with AKI were older, more likely to be male, longer lengths of stay, and to receive intensive than the reference group. The proportion with maximum eGFR <60 ml/min/1.73 m² was similar for THA-AKI and HA-AKI, and greater than the reference group. HA-AKI was associated with 13%, THA-AKI with 4.0% and No-HA-AKI with 1.3% inpatient mortality rates.

Figure 1 illustrates the sCr trajectories for HA-AKI (8,465 patients; closed symbols) and THA-AKI (20,056 patients; open symbols). Also shown is the time course for No-HA-AKI (53,882 patients; gray symbols), with a shorter length of stay than either THA-AKI or HA-AKI. The time-course is distinct for THA-AKI compared to HA-AKI, with marked separation between the timing of the minimum and maximum sCr values.

Figure 2 shows the sCr trajectory for HA-AKI, with the minimum, peak and last sCr values. The cr-min0 was the baseline sCr used to define the sCr trajectory. On average, sCr increased by 0.89 ± 1.02 mg/dl over 95 ± 81 h from the baseline sCr for HA-AKI. Also shown are the highest sCr values recorded during the indicated 24-hour intervals following the cr-min0. This slope of the sCr trajectory was steeper for the first 24- or 48-hour interval than that calculated using the peak sCr.

Recovery from HA-AKI compared the last sCr and the peak sCr values, and was 0.33 ± 0.59 mg/dl over 28 ± 29 h following the peak sCr value.

The minimum, peak and last sCr are shown along with the minimal sCr values in each of the indicated time intervals for THA-AKI in figure 3. On average, sCr decreased by 0.89 ± 1.21 mg/dl to the minimum sCr at 95 ± 81 h following the peak sCr. The initial rate of recovery was more rapid and then it attenuated over subsequent days.

Discussion

We have previously described patterns of inpatient AKI [9], and now extend these descriptions to index admissions for another academic medical center. De-

Table 1. Characteristics and mortality rates for inpatients without, or with AKI (82,403 patients; 2,611 inpatient deaths (3.2%))

	No-HA-AKI: 53,683 (65%) ^a	THA-AKI: 20,255 (25%) ^a	HA-AKI: 8,465 (10%) ^a
Demographic characteristics, time course and changes in sCr			
Age, years ^b	56 (42–68)	58 (44–69)	59 (48–70)^c
Male sex, n (%)	27,287 (51)	12,077 (60)	4,521 (53)^c
Whites, other patients, n (%)	37,574 (70)	13,564 (67)	5,690 (67)
Black patients ^d , n (%)	12,772 (24)	5,924 (29)	2,440 (29)
Hispanic patients, n (%)	3,337 (6.2)	767 (3.8)	335 (4.0)
Length of stay, days	3.1 (2.0–5.1)	6.2 (4.0–11.0)	7.1 (4.1–12.0)^c
Intensive care unit stay, n (%)	9,278 (17)	7,969 (39)	3,691 (44)^c
Max-eGFR, ml/min/1.73 m ²	99 (80–116)	98 (73–117)	93 (69–111)^c
Max-eGFR <60 ml/min/1.73 m ² (60), n (%)	5,998 (11)	3,529 (17)	1,666 (20)^c
Inpatient mortality, 30 day length of stay			
Inpatient deaths, n (%)	673 (1.3)	817 (4.0)	1,121 (13)^c
Incident rate for deaths (per 30-patient days)	0.093 (0.086–0.100)	0.149 (0.139–0.159)	0.442^c (0.417–0.469)
Incident rate ratios for deaths	1.00 (reference)	1.60 (1.44–1.77)	4.75 (4.32–5.23)^c

Values are given as number (percentage), means $\pm$ 1 SD, medians with (25th–75th centile), or means (95% CI) for incident rates and incident rate ratios.

Max-eGFR = Maximum eGFR for admission, based on minimum sCr for the admission.

^a Row percentages; all others are column percentages.

^b $p < 0.001$ for comparisons of characteristics between each group by analysis of variance for means, signed rank test for me-

dians, and chi-square test for proportions; shown as bold text, relative to No-AKI which served as the reference group.

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

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

spite differences in demographics and case mix, the AKI patterns and sCr trajectories were similar at both sites.

The definition of AKI is based on changes in sCr from a reference value [8]. The magnitude and timing of the peak and sCr with respect to the reference point are needed for characterizing sCr trajectories and AKI patterns: sCr is a vector with both magnitude (mg/dl) and time dimension, defined as the elapsed time after admission. Ambulatory sCr values obtained before admission have been used as a baseline sCr for characterizing AKI in the hospital setting [1, 2, 12], but these scalars lack the relevant time dimension required to define sCr trajectories. Creatinine kinetics and trajectories have been explicitly considered in some analyses of AKI [5, 7, 10, 13, 14], and addressed in the KDIGO AKI criteria [8], but most studies have not considered sCr trajectories, and have only used the scalar differences between maximum and baseline sCr.

We do not equate the minimum sCr value for a given admission to the ‘baseline’ sCr value. While the minimum sCr has evident utility for separating THA-AKI from HA-AKI, it may not be the optimal reference point for defin-

Fig. 1. Creatinine trajectories by AKI types, combined cohort (82,402 patients). AKI patterns were defined by the temporal sequence of the minimum (Min) and maximum (Peak) inpatient sCr values. Also shown are the first (#1) and last sCr values. Squares indicate the discharge date.

Fig. 2. Creatinine trajectory for HA-AKI (8,453 patients). HA-AKI was defined by the minimum (Min) sCr preceding the maximum (Peak) sCr during the admission. Also shown are the first (#1) and last sCr values, and the discharge date. The intervening time points represent the minimum sCr values during the indicated intervals in hours after the peak value, and the maximum sCr values during the indicated intervals in hours after the minimum value. The dashed upward diagonal line is an estimate of the slope of the creatinine trajectory from min 0 value to peak value (0.89 mg/dl/95 h). The dashed downward diagonal line is an estimate of the recovery from peak sCr (0.33 mg/dl over 28 h).

Fig. 3. Creatinine trajectory for THA-AKI (20,255 patients). THA-AKI was defined by the maximum (Peak) sCr preceding the minimum (Min) sCr during the admission. Also shown are the first (#1) and last sCr values, and the discharge date. The intervening time points represent the maximum sCr values during the indicated intervals (hours) following the peak sCr. The dashed downward diagonal line is an estimate of the recovery from peak to minimum sCr (0.89 mg/dl within 95 h).

ing sCr trajectories, assessing recovery from AKI, or staging of the severity of HA-AKI. For example, the delay after the minimum sCr before the HA-AKI threshold is reached suggests that the timing and magnitude of the last sCr before a significant increase in sCr, which we term cr-min0 in figure 2, constitute a better baseline sCr than the minimum sCr for HA-AKI. Further work is needed to define the baseline or reference sCr values especially for the staging of HA-AKI, but this approach may be helpful in defining a baseline sCr for patients who lack pre-admission data. The creatinine trajectory (heavy dashed line) for HA-AKI is curvilinear (fig. 2), and may not be accurately represented by the simple rise and run of sCr between the minimum and peak sCr values, which can be considered to be a minimal estimation of the slope of the creatinine trajectory.

A notable strength of the current analysis is the use of sCr trajectories, rather than discharge codes to define AKI [15, 16]. Nevertheless, our study has several limitations. We could not determine the etiology of AKI, urine output, fluid administration or other medications from

the current inpatient datasets. The frequency and timing of inpatient sCr determinations are dependent on local clinical practices, which could be a source of residual confounding [17, 18]. Follow-up status after discharge and pre-hospitalization sCr values are not currently available.

Changes in sCr depend on factors that modify creatinine generation (body composition, muscle wasting, and acute muscle injury) [19]. Changes in the volume of distribution of creatinine (dehydration or volume expansion) may occur, especially in the elderly [20] and critically ill patients with prolonged hospitalizations [21–23], which could lead to false-negative ascertainment. To address these limitations, we have excluded patients with minimum sCr values <0.4 mg/dl, or with a maximal eGFR (based on the minimum sCr) <15 ml/min/1.73 m² throughout the duration of hospitalization. In addition, we limited the length of stay to 30 days, and acknowledge that outcome misclassification is inherent in the use of vital status administrative coding at the time of discharge or other deposition [24].

In conclusion, we have described the patterns of AKI based on their creatinine trajectories, and have illustrated the value of defining patterns of AKI based on the timing and magnitude of changes in sCr values for each subject during a single admission. Patients with hospital-associated AKI are at increased risk for inpatient mortality. Creatinine trajectories can be used to describe the rate of development as well as recovery from inpatient AKI. The 24- and 48-hour interval slopes may be early indicators of developing AKI. Further work is needed, but the use of creatinine trajectories may support the development of real-time, dynamic tools for assessing the risks associated with evolving AKI, which is a pressing need for current AKI research [25–27].

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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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