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Permalink
https://escholarship.org/uc/item/5cd9j6ct

Journal
Kidney international reports, 3(1)

ISSN
2468-0249

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Publication Date
2018

DOI
10.1016/j.ekir.2017.08.011

Peer reviewed
Acute Kidney Injury Ascertainment Is Affected by the Use of First Inpatient Versus Outpatient Baseline Serum Creatinine

To the Editor: An important methodological issue concerning acute kidney injury (AKI) definitions is the choice of “baseline” serum creatinine (SCR). The most recent consensus definition proposes a rolling 48-hour window for AKI ascertainment during hospitalization, or the use of a baseline value that is “known or presumed to have occurred in the past 7 days.” However, significant misclassification in assigning AKI status can occur when admission or nadir inpatient SCR (as has been done in a number of studies) is used rather than a predmission outpatient baseline. A well-recognized concern with the use of admission SCR to define baseline kidney function is that it will be higher than a patient’s true baseline if community-acquired AKI is present, and therefore community-acquired AKI will be missed if the admission SCR is used to define baseline. However, animal and human studies have recently shown that creatinine generation can also quickly fall with acute illness, so falsely low readings may result. It is unknown whether changes in creatinine generation affect AKI ascertainment. Therefore, to quantify variation in first inpatient SCR level and the impact on AKI ascertainment, we compared predmission baseline and first inpatient SCR in a large, population-based, hospitalized cohort. We also identified predictors of lower first inpatient SCR.

We identified all hospitalized adults without end-stage renal disease at 21 Kaiser Permanente Northern California hospitals between 2006 and 2011 (Supplementary Figure S1): only the first eligible hospitalization per subject was included. Kaiser Permanente Northern California is a large integrated health care delivery system caring for > 4.1 million persons in the San Francisco Bay Area that is highly representative of the statewide population. The study was approved by the institutional review boards of the Kaiser Foundation Research Institute and the University of California, San Francisco.

Baseline SCR was the most recent outpatient SCR from a maximum of 365 days and a minimum of 7 days pre-admission. We selected this as the gold standard because this definition has been used in prior studies examining the impact of baseline SCR on AKI ascertainment, including the prospective Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) study. A peak inpatient SCR ≥ 50% relative, ≥ 0.3 mg/dl absolute increase from the outpatient baseline, or need for acute dialysis defined AKI for this analysis. Covariates included demographics, comorbidities, severity of illness, predmission estimated glomerular filtration rate (eGFR), and proteinuria. Comorbidities (diabetes, hypertension, cancer, coronary disease, chronic heart failure, prior ischemic stroke) were ascertained for up to 5 years before hospitalization using previously validated methods based on inpatient and ambulatory diagnoses and procedures, laboratory results, and pharmacy databases (codes available upon request). We identified coronary revascularization, sepsis, and acute heart failure occurring during the index hospitalization using relevant diagnosis and procedure codes. To further describe acute severity of illness, we determined whether patients were admitted to the intensive care unit during their stay and calculated the Laboratory-Based Acute Physiology Score (LAPS) and COMorbidity Point Score (COPS), along with a validated predicted mortality score based on automated inpatient, outpatient and laboratory data.
Among all patients, and chronic kidney disease (51.6% vs. 28.8%) (all (40.3% vs. 26.3%), hypertension (79.5% vs. 65.5%), prevalence of sepsis (20% vs. 7%), diabetes mellitus met our AKI criteria. AKI was associated with a higher NC).

Conducted using SAS version 9.3 (SAS Institute, Cary, baseline SCr stratification. Among all patients, 21.7% had a first inpatient SCr that was ≥ 110% above outpatient baseline (Table 1 and Figure 2). Not surprisingly, a greater proportion of patients with AKI (74.6%) experienced this pattern.

In all, 45% of the patients had a first inpatient SCr that was < 90% of the outpatient baseline; 9.4% of those with AKI experienced this pattern. Regardless of AKI status, older age, history of cancer, and intensive care unit admission were associated with a first inpatient SCr that was < 90% of outpatient baseline SCr (Table 2). Patients with diabetes mellitus, hypertension, sepsis, and greater severity of illness (measured by predicted mortality) were less likely to have a low first inpatient SCr, reflecting the fact that many of these patients present with AKI in evolution. It should be noted that several of these factors (e.g., sepsis and acute illness) are associated with acute reductions in creatinine generation, so the severity of AKI may be difficult to ascertain based on changes in SCr alone. In the future, novel biomarkers or real-time measurement of GFR may better define AKI severity.

Preadmission eGFR (in ml/min per 1.73 m²) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation12 and baseline SCr information described previously. We ascertained proteinuria based on a urine dipstick result of 1+ or greater (in the absence of a concomitant urinary tract infection).10 The first inpatient SCr was expressed as a percentage change compared with baseline SCr. We used multivariable logistic regression to identify predictors of a first inpatient SCr that was < 90% of baseline SCr stratified by AKI status. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Of 214,802 eligible hospitalizations, 37,827 (17.6%) met our AKI criteria. AKI was associated with a higher prevalence of sepsis (20% vs. 7%), diabetes mellitus (40.3% vs. 26.3%), hypertension (79.5% vs. 65.5%), and chronic kidney disease (51.6% vs. 28.8%) (all P < 0.001) (Supplementary Table S1). Among all patients, 21.7% had a first inpatient SCr that was ≥ 110% above outpatient baseline (Table 1 and Figure 2). Not surprisingly, a greater proportion of patients with AKI (74.6%) experienced this pattern.

In all, 45% of the patients had a first inpatient SCr that was < 90% of the outpatient baseline; 9.4% of those with AKI experienced this pattern. Regardless of AKI status, older age, history of cancer, and intensive care unit admission were associated with a first inpatient SCr that was < 90% of outpatient baseline SCr (Table 2). Patients with diabetes mellitus, hypertension, sepsis, and greater severity of illness (measured by predicted mortality) were less likely to have a low first inpatient SCr, reflecting the fact that many of these patients present with AKI in evolution. It should be noted that several of these factors (e.g., sepsis and acute illness) are associated with acute reductions in creatinine generation, so the severity of AKI may be difficult to ascertain based on changes in SCr alone. In the future, novel biomarkers or real-time measurement of GFR may better define AKI severity.

Table 1. Distribution of change between baseline and first inpatient serum creatinine (SCr) concentration, overall and stratified by acute kidney injury (AKI) status

| Ratio between first inpatient and outpatient baseline SCr | Overall (N = 214,802) | AKI (n = 37,827) | No AKI (n = 176,975) |
|----------------------------------------------------------|-----------------------|------------------|---------------------|
| < 0.70                                                   | 17,573 (8.2)          | 488 (1.3)        | 17,085 (9.7)        |
| 0.70–0.79                                                | 32,351 (15.1)         | 1056 (2.8)       | 31,295 (17.7)       |
| 0.80–0.89                                                | 47,202 (22.0)         | 1978 (5.3)       | 45,224 (25.6)       |
| 0.90–0.99                                                | 40,338 (18.8)         | 2618 (6.9)       | 37,720 (21.3)       |
| 1.00–1.09                                                | 30,745 (14.3)         | 3455 (9.1)       | 27,290 (15.4)       |
| 1.10–1.19                                                | 15,379 (7.2)          | 3459 (9.1)       | 11,920 (6.7)        |
| 1.20–1.29                                                | 8876 (4.1)            | 4015 (10.6)      | 4861 (2.7)          |
| 1.30–1.39                                                | 5119 (2.4)            | 3828 (10.1)      | 1291 (0.7)          |
| 1.40–1.49                                                | 3472 (1.6)            | 3183 (8.4)       | 289 (0.2)           |
| 1.50–1.99                                                | 7283 (3.4)            | 7283 (19.3)      | 0 (0.0)             |
| ≥ 2.00                                                  | 6464 (3.0)            | 6464 (17.1)      | 0 (0.0)             |

*Overall P value < 0.001.

*It should be noted that among those with AKI, a ratio between first inpatient and outpatient baseline SCr > 1.1 may or may not meet criteria for AKI. For example if the baseline SCr is 1.6 mg/dl, 110% of baseline would be 1.76 mg/dl and would not meet criteria for AKI; such an individual might have evolving AKI and a subsequent rise in SCr that meets criteria for AKI. In contrast, if the baseline SCr is 3.1 mg/dl, 110% of baseline would be 3.41 mg/dl, and this individual would meet criteria for AKI, which would be community acquired.
Figure 2. Change between baseline and first inpatient serum creatinine (Scr) concentration, overall and stratified by acute kidney injury (AKI) status. Each column represents the proportion of individuals meeting those criteria.

Our results have important implications for AKI ascertainment. Of the patients, 45% had a first inpatient Scr that was <90% of the outpatient baseline. Consequently, using the first inpatient Scr in place of the outpatient baseline may misclassify some individuals as having AKI when no AKI is, in fact, present (as the Scr rises back to the actual baseline) (Figure 1b). In fact, in our study population, 6605 individuals would have met AKI criteria, had the first inpatient Scr been used in place of the outpatient baseline (Figure 3). The inclusion of patients without actual AKI because of this misclassification can bias associations between AKI and true AKI risk factors towards the null. Even among those who met our criteria for AKI, nearly 1 in 12 had a first inpatient Scr that was <90% of outpatient baseline; here, using an inpatient Scr that is lower than outpatient baseline may lead to misclassification of AKI severity. In contrast, using the outpatient baseline Scr identified 21,864 individuals who were not identified as having AKI using the first inpatient Scr, likely due to the presence of community-acquired AKI. A total of 15,963 individuals were identified as having AKI using either the outpatient baseline or first inpatient Scr. Thus, the overall incidence of AKI was higher when the outpatient baseline Scr was used (37,827 vs. 22,568).

We note that, in some populations (i.e., those of older age and with cancer), the first inpatient Scr was more likely to be <90% of preadmission baseline, as might be expected, as these conditions are more likely to be associated with reductions in muscle mass over time. Further studies are needed to better understand whether these differences reflect ongoing malnutrition due to chronic illness, and, if so, how best to estimate baseline Scr in these populations. In clinical practice, careful evaluation of both the outpatient baseline Scr and first inpatient Scr in these populations who are more likely to have a first inpatient Scr is warranted to help with the clinical ascertainment of AKI. Due to the presence of community-acquired AKI at admission, a significant proportion of patients who met our AKI definition would not have met criteria for AKI had the first inpatient Scr been used as baseline (Figure 3).

Study strengths include the large number of patients with outpatient baseline Scr measurements.

### Table 2. Correlates of having a first inpatient serum creatinine (Scr) value <90% of outpatient baseline

| Characteristic                        | AKI (n = 37,827) | No AKI (n = 176,975) |
|---------------------------------------|------------------|---------------------|
| Age, yr                               |                  |                     |
| < 45                                  | REF              | REF                 |
| ≥ 45–74                               | 1.53 (1.28–1.84) | 1.33 (1.28–1.37)    |
| ≥ 75                                  | 2.06 (1.71–2.50) | 1.37 (1.32–1.43)    |
| Male gender                           | 0.95 (0.88–1.02) | 0.85 (0.83–0.87)    |
| Race/ethnicity                        |                  |                     |
| White                                 | REF              | REF                 |
| Black/African American                 | 1.03 (0.92–1.16) | 0.88 (0.85–0.91)    |
| Asian/Pacific Islander                | 1.12 (1.00–1.26) | 0.97 (0.94–1.00)    |
| Other/unknown                         | 199 (0.5)        | 891 (0.5)           |
| Medical history                       |                  |                     |
| Diabetes mellitus                     | 0.82 (0.76–0.89) | 0.93 (0.91–0.95)    |
| Hypertension                          | 0.90 (0.82–0.99) | 0.92 (0.90–0.94)    |
| Systemic cancer                       | 1.26 (1.15–1.37) | 1.06 (1.04–1.09)    |
| Coronary heart disease                | 1.12 (0.97–1.28) | 1.01 (0.96–1.05)    |
| Chronic heart failure                 | 0.99 (0.87–1.13) | 0.91 (0.87–0.96)    |
| Ischemic stroke                       | 0.92 (0.71–1.19) | 1.11 (1.03–1.19)    |
| During index hospitalization           |                  |                     |
| Coronary revascularization            | 1.43 (1.24–1.63) | 0.84 (0.80–0.88)    |
| Sepsis                                | 0.88 (0.80–0.97) | 0.67 (0.65–0.70)    |
| Heart failure                         | 0.91 (0.78–1.05) | 0.50 (0.46–0.53)    |
| Admitted to intensive care unit       | 2.33 (2.15–2.52) | 1.26 (1.23–1.29)    |
| Predicted Mortality Score category    |                  |                     |
| < 0.1%                                | REF              | REF                 |
| 0.1 to < 0.5%                         | 1.08 (0.87–1.35) | 0.94 (0.90–0.97)    |
| 0.5 to < 2%                           | 1.04 (0.85–1.28) | 0.89 (0.85–0.92)    |
| 2 to < 5%                             | 0.83 (0.68–1.03) | 0.84 (0.80–0.87)    |
| 5 to < 10%                            | 0.61 (0.49–0.76) | 0.74 (0.70–0.77)    |
| 10 to < 15%                           | 0.44 (0.34–0.57) | 0.70 (0.65–0.74)    |
| 15 to < 30%                           | 0.39 (0.30–0.50) | 0.70 (0.66–0.75)    |
| ≥ 30%                                 | 0.23 (0.16–0.33) | 0.54 (0.48–0.61)    |
| Unknown                               | 0.81 (0.64–1.04) | 0.80 (0.76–0.84)    |
| Prior documented proteinuria          | 0.94 (0.84–1.04) | 0.87 (0.84–0.90)    |
| Outpatient baseline eGFR              |                  |                     |
| ≥ 60 ml/min per 1.73 m²               | 1.32 (0.81)      | 1.00 (0.39)         |
| 45–59 ml/min per 1.73 m²              | 1.03 (0.94–1.14) | 1.38 (1.34–1.42)    |
| 30–44 ml/min per 1.73 m²              | 1.03 (0.92–1.14) | 1.52 (1.47–1.57)    |
| <30 ml/min per 1.73 m²                | 0.87 (0.76–0.99) | 1.57 (1.49–1.67)    |

eGFR, estimated glomerular filtration rate; REF, reference.

*Multivariable logistic regression was used to identify predictors of a first inpatient Scr <90% of baseline and are expressed as odds ratios (95% confidence intervals). Boldface data represent statistically significant associations.*
within an integrated health care delivery system, which allowed for analysis of patient-level factors stratified by AKI status, an important determinant of admission SCR. Kaiser Permanente Northern California is highly representative of the local and statewide population, so results are likely more generalizable than those from specialized populations (e.g., the predominantly male Veterans Affairs population). A potential limitation is that we focused on individuals with an available outpatient SCR, so no inferences can be made about how to estimate baseline SCR without outpatient data. In those circumstances, given the importance of baseline SCR for AKI classification and given the variation between first inpatient and outpatient baseline SCR that we have shown, clinicians should use all available resources to identify an outpatient baseline SCR.

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DISCLOSURE
All the authors declared no competing interests.

ACKNOWLEDGMENTS
The authors would like to thank members of the ASSESS-AKI Consortium for helpful discussions. This work was supported by research grants from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): R01 DK101507, U01 DK082223.

Contributions: Research idea and study design: KDL, CYH, JY, TCT, ASG; data acquisition and statistical analysis: JY, TCT, ASG; data interpretation: KDL, CYH, JT, TCT, SZ, JDO, ASG; manuscript preparation: KDL and ASG. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KDL and ASG take responsibility that this study has been reported honestly, accurately, and transparently and that no important aspects of the study have been omitted.

SUPPLEMENTARY MATERIAL

Figure S1. Flow diagram of all Kaiser Permanente Northern California adult hospitalizations. A total of 214,802 hospitalizations were identified for this analysis, as described.

Table S1. Baseline characteristics of the overall cohort and by acute kidney injury status.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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Received 21 March 2017; revised 31 July 2017; accepted 21 August 2017; published online 29 August 2017

Kidney Int Rep (2018) 3, 211–215; https://doi.org/10.1016/j.ekir.2017.08.011

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