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Estimating Baseline Serum Creatinine for Assessing Acute Kidney Injury: Not a One Size Fits All Approach

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Acute kidney injury (AKI) frequently occurs in hospitalized patients and represents a considerable burden in terms of health outcomes and hospital costs.[1] AKI has been independently associated with an increased risk of mortality, chronic kidney disease (CKD) and end-stage kidney disease, especially when renal recovery is partial or absent at discharge.[1]

AKI diagnosis is based on the magnitude of changes in serum creatinine (SCr) from a baseline preadmission SCr value[2] or a rolling 48-hour window, thereby reducing the need for preadmission value. There is no current standardized definition for estimating baseline SCr. The mean outpatient SCr within a year of hospitalization is considered the most accurate reflection of baseline kidney function,[3,4] and the most recent outpatient SCr from a maximum of 365 days and a minimum of seven days preadmission is also acceptable.[4] In most studies, up to 50% of patients do not have previous measured SCr values.[5–7] Measures to estimate baseline SCr can either underestimate or overestimate AKI incidence, which affect outcomes associated with presumed AKI (Table 1).[7] In this setting, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest using a SCr computed from the Modification of Diet in Renal Disease (MDRD) formula, assuming an estimated glomerular filtration rate (eGFR) of 75 ml/min/1.73 m^2,[2] whereas the European Renal Best Practice guideline recommend the use of first SCr at admission. The former assumes that there is a relatively low rate of CKD, while the latter assumes that AKI does not occur before hospitalization (Table 1).

In this issue of *Kidney International Reports*, Dr. Cooper and colleagues performed a comparison of commonly used surrogate and imputed baseline creatinine values against a "reference" creatinine, defined as the lowest creatinine within 7-28 days after hospital discharge, in 247 young South-East Asian patients with malaria.[8] Among them, 71 (29%) developed AKI according to KDIGO SCr criteria, most having stage 1 or 2 AKI. None had previous SCr measurements available. The equations assessed included back-calculation using CKD Epidemiology Collaboration (CKD-EPI) equation, back-calculation using MDRD equation with and without a Chinese ethnicity correction coefficient, eGFR from age and sex-standardised reference tables, and the lowest SCr during admission. Back-calculated distributions were performed using eGFRs of 75 and 100 ml/min/1.73 m^2.

In this study, back-calculation with MDRD assuming an eGFR of 75 ml/min/1.73 m^2 as recommended would have underestimated AKI incidence by more than 50%.[8] This could have impeded measures to prevent AKI and adjust treatments as the condition would not have been recognized. In addition, with the exception of MDRD GFR of 100 ml/min/1.73 m^2, all estimated SCr methods were significantly different from the reference SCr using Bland-Altman plots. Back-calculation with MDRD GFR of 100ml/min/1.73 m^2, GFR from age and sex-standardised reference tables, and the lowest measured creatinine during admission most accurately predicted AKI although they still misclassified AKI stages and had low levels of agreement with true AKI diagnoses. In clinical research, this may translate into effective treatments being discarded due to lack of efficacy based on inadequate assessment of baseline kidney function.

These results of this study need to be contextualized in its clinical setting.[8] This Southeast Asian population suffering from mild to

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Table 1. Suggested approach to define and estimate baseline serum creatinine

When baseline creatinine is known:
- Use prehospitalization reference creatinine whenever available (mean SCr 7-365 days before hospitalization or most recent outpatient SCr from a maximum of 365 days and a minimum of 7 days pre-admission)

When baseline creatinine is unknown:
- Aim to accurately reflect baseline SCr depending on the population and outcome
- Clarify how surrogate estimate of baseline SCr is applied
- Discuss potential biases related to the definition of surrogate SCr values
- In populations with a high percentage of patients with missing baseline SCr, use more specific definitions of AKI such as AKI stages 2 and 3, or need for dialysis

Type of population	Outcome	Potential bias on surrogate estimates of baseline serum creatinine
Young population	AKI diagnosis, staging and renal recovery	Suggest using back-calculation with estimated MDRD GFR of 100 mL/min/1.73 m^2, since 75 mL/min/1.73 m^2 will underestimate AKI incidence; other acceptable measures include GFR from age and sex-standardised reference tables, or lowest inpatient SCr
Community-acquired AKI	AKI diagnosis	Use of first SCr will underdiagnose AKI
Expected high incidence of CKD	AKI diagnosis and staging	MDRD or CKD-EPI GFR of 75 mL/min/1.73 m^2 will misclassify patients with stable CKD as AKI and overestimate AKI incidence (even worse with GFR of 100 mL/min/1.73 m^2)
	Renal recovery	MDRD and CKD-EPI GFR of 75 mL/min/1.73 m^2 will underestimate renal recovery after hospital discharge compared to other methods such as first SCr
Prolonged hospital stay or significant fluid overload	AKI diagnosis and staging Renal recovery	Avoid lowest inpatient SCr as this will overestimate AKI diagnosis and misclassify AKI stages Use of lowest inpatient SCr may falsely increase rate of renal recovery

AKI: acute kidney injury; CKD: chronic kidney disease, CKD-EPI: CKD Epidemiology Collaboration; GFR: glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; SCr, serum creatinine.

moderate community-acquired AKI was young. Consequently, it is expected that an eGFR close to 100 ml/min/1.73 m^2 would perform better than other estimating methods, such as an eGFR of 75 ml/min/1.73 m^2. In the literature, patients without baseline SCr are reported to be younger and healthier than those having medical follow-up.[9] Most patients included in this study required hospitalization for less than three days. The use of a creatinine measured 7–28 days after discharge as a reference measure is probably accurate for this young population considering its short length of stay.[4] In comparison, minimal SCr within two weeks after admission markedly overestimated AKI incidence in older critically ill populations.[9] In practice, the use of minimal inpatient SCr or follow-up SCr to diagnose AKI is problematic, as the diagnosis can only be made retrospectively, leading to delays in successful clinical management.

Despite the importance of this issue, a limited number of studies have evaluated the performance of various surrogate methods for missing baseline SCr for AKI diagnosis and outcomes.[5,7,S1-S9] In most populations, as opposed to findings by Cooper and colleagues, both MDRD[5,S1-3,S6,S7] and CKD-EPI equations tend to overestimate AKI incidence due to the inclusion of older populations with more comorbidities.[9,S2,S8] The magnitude of the overestimation increases with higher prevalence of CKD. AKI overdiagnosis may lead to unnecessary investigations and treatments, with potential side effects and increased cost. In opposition, the use of first SCr can lower sensitivity for AKI diagnosis,[9,S3,S7] leading to missed AKI diagnosis, lack of preventive and therapeutic measures, and eventually disease progression.

Factors other than age, sex and race which are included in estimating equations may influence SCr levels and AKI diagnosis, namely nutritional state, muscle mass, fluid balance, and comorbidities.[9,S10-12] The presence of long-term diabetes or hypertension will increase the likelihood of CKD. A few studies have attempted to include comorbidities in equations to predict baseline SCr, with limited improvement in agreement for AKI diagnosis.[9,S4] Creatinine can also be falsely lowered during and shortly after hospitalization, due to loss of muscle mass and low creatinine generation, especially after critical illnesss.[S12,S13] This effect seems to be more important as the length of stay increases. In these conditions, the use of the lowest creatinine during admission should be discouraged (Table 1).

As shown by Cooper and colleagues, estimating equations also affect AKI staging.[8] Other studies have demonstrated that misclassification associated with MDRD SCr and CKD-EPI SCr increases with a higher prevalence of CKD,[S2,S3] while the first SCr will misclassify AKI occurring at hospital admission.[9] Since all patients requiring dialysis should be categorized as AKI stage 3, AKI staging will be improved with a higher proportion of patients requiring dialysis, regardless of the surrogate method used. Finally, although renal recovery was not assessed in this study, others have shown that the use of surrogate methods can greatly affect the rate of renal recovery.[9]

In conclusion, prehospitalization SCr values should be used whenever available to minimize bias as AKI incidence and

outcomes can be significantly affected with the use of various surrogate methods (Table 1). Indeed, AKI incidence has been shown to fluctuate by at least 15% with various surrogate SCr values.[9] Of note, the effect of various surrogate baseline SCr on long-term kidney outcomes after AKI is considered equally important although it has not been well characterized. In the study by Cooper and colleagues, back-calculation with MDRD assuming an eGFR of 75 mL/min/1.73 m^2 as suggested by the KDIGO underestimated AKI incidence by more than 50% leading to missed opportunities for investigation and treatment. When baseline SCr is missing, studies should explain the rationale behind the choice of surrogate baseline SCr values used to diagnose AKI and potential biases related to this decision. Additional studies are therefore needed to improve the estimation of surrogate baseline SCr and understand the effect of using surrogate methods and imputation methods on AKI diagnosis and outcomes, in diverse hospitalized and outpatient settings. Ultimately, limiting heterogeneity in the definition of baseline SCr while aiming to accurately reflect baseline SCr will help standardize AKI definition and facilitate clinical research.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References

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