Phenotyping of Acute Kidney Injury: Beyond Serum Creatinine

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Summary: Acute kidney injury (AKI) is a common complication in hospitalized patients and is associated with adverse short- and long-term outcomes. AKI is diagnosed by serum creatinine (SCr)-based consensus definitions that capture an abrupt decrease in glomerular filtration rate associated with AKI. However, SCr-based AKI definitions lack sensitivity and specificity for diagnosing structural kidney injury. Moreover, AKI is a heterogeneous condition consisting of distinct phenotypes based on its etiology, prognosis, and molecular pathways, and that may potentially require different therapies. SCr-based AKI definitions provide no information on these AKI phenotypes. This review highlights traditional and novel tools that overcome the limitations of SCr-based AKI definitions to improve AKI phenotyping.

Keywords: AKI, biomarkers, creatinine, cystatin C, NGAL, IL-18, KIM-1, L-FABP, IL-6, furosemide, urine microscopy, urinary casts

Acute kidney injury (AKI) complicates one in five hospital admissions and is associated with adverse short- and long-term outcomes and increased health care expenditure.[1–4] The current gold standard for AKI diagnosis is through consensus definitions such as AKI Network or Kidney Disease: Improving Global Outcomes (KDIGO).[5,6] By using an increase in serum creatinine (SCr) concentration and/or a decrease in urine output, these AKI definitions attempt to capture an abrupt decrease in glomerular filtration rate (GFR) that often is associated with AKI. This standardization has facilitated research, clinical care, and health care management by allowing uniform comparisons across studies, cohorts, and hospitals. However, there is an unmet need to enhance the SCr-based definition to improve phenotyping of AKI for clinical and research purposes. This review covers the limitations of SCr-based AKI definitions and evaluates tools for AKI phenotyping beyond SCr.

LIMITATIONS OF SCR-BASED AKI DEFINITION

SCr-based AKI definition is limited in two ways: lack of accuracy for a diagnosis of structural kidney injury, and in patients with a structural kidney injury it provides no information on AKI etiology, prognosis, molecular pathways, or responses to treatment.[7] For example, a 0.3 mg/dL or 50% increase in serum creatinine concentration, which is the current definition of SCr-based AKI in the KDIGO classification, reflects vastly different phenotypes. This increase in SCr concentration in a patient in the intensive care unit (ICU) with sepsis, hypotension, and granular casts on urine sediment examination indicates structural kidney injury, reflects poor prognosis, and requires aggressive management. In contrast, this increase in SCr concentration in a patient with decompensated congestive heart failure started on diuretic therapy, in a patient with diabetic kidney disease started on renin-angiotensin aldosterone system (RAAS) inhibitors, or in a patient with long-standing hypertension started on intensive blood pressure control, likely reflects a hemodynamic increase in SCr concentration without structural kidney injury, and is not associated with a poor prognosis.[8,9] Similarly, this increase in SCr concentration in a person with advanced chronic kidney disease (CKD) with stable health merely

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may reflect laboratory or biological variation in the creatinine concentration, and does not indicate structural kidney injury.[10]

SCr-Based AKI and Structural Kidney Injury

A conceptual model of the limitations of SCr-based AKI definitions is presented in Figure 1.[11] The goal of SCr-based AKI definitions is to correctly identify all possible cases of structural kidney injury (Fig. 1, box D), while also simultaneously excluding all cases without a structural kidney injury (Fig. 1, box A). However, an increase in SCr concentration denotes a reduced GFR, does not directly capture tubulointerstitial injury, and lacks accuracy for a diagnosis of structural kidney injury.

Kidney Injury Without Increase in SCr Concentration

Kidney injury can occur in the absence of an increase in SCr concentration, which represents an emerging condition called subclinical AKI (Fig. 1, box B).[11–13] Subclinical AKI occurs when the effects of tubular injury and reduced GFR in some nephrons are compensated for by other noninjured and functioning nephrons via a phenomenon called renal reserve. Subclinical AKI is thought to be an early step in the spectrum of kidney injury and is associated with poor outcomes.[13] Animal studies have shown the development of renal fibrosis and abnormal gene expression profiles in kidneys after an episode of kidney injury despite a return of the SCr concentration to normal values.[11,14,15] An analysis of a biopsy series found that 21% of cases of biopsy-proven acute tubular injury (ATI) did not meet the KDIGO SCr-based AKI definition.[16]

Moreover, SCr concentration increases to its peak level at 48 to 72 hours after kidney injury. This delay is undesirable in clinical care because patients experience significant exposure to nephrotoxic agents because clinical AKI has not yet been recognized. The delay also is undesirable in research because potential therapies for AKI may need to be administered early after kidney injury before irreversible damage occurs. Finally, a structural kidney injury also may be missed because the SCr concentration fails to increase from the dilutional effects of fluid administration and decreased SCr production caused by low muscle mass and sepsis.

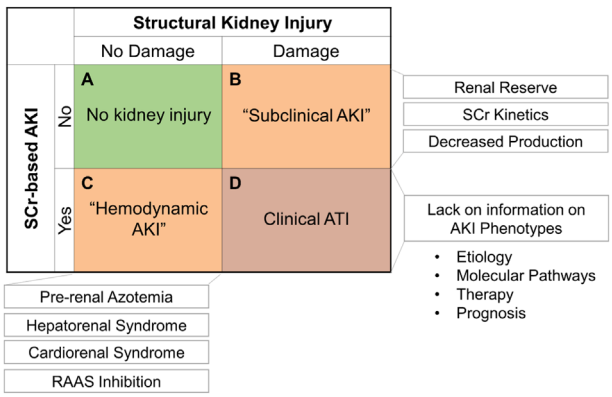

Figure 1. Limitations of SCr-based AKI definition. The SCr-based AKI definition may fail to identify individuals with structural kidney injury (subclinical AKI), or incorrectly identify individuals without structural kidney injury (hemodynamic AKI). Even in individuals with a structural kidney injury identified correctly by the SCr-based AKI definition, it provides no information on AKI etiology, molecular pathways, therapy, or prognosis.

Increase in SCr Concentration Without Kidney Injury

Increases in SCr concentration may not always represent kidney injury (Fig. 1, box C). For example, hemodynamic reduction in renal blood flow and glomerular filtration in cardiorenal and hepatorenal syndromes causes an increase in SCr concentration in the absence of discernible structural kidney injury.[7,10,17] RAAS inhibitors also can lead to increases in SCr concentration owing to a reduced glomerular filtration rate, despite the potential absence of kidney injury. In fact, SCr concentration may be misleading in the setting of RAAS inhibitors because improved patient outcomes are noted with these drugs despite SCr-based AKI.[18] The SCr concentration may increase as a result of medications such as trimethoprim, which inhibit tubular secretion of SCr without a reduction in GFR.

Phenotypes of SCr-Based AKI

Arguably the biggest limitation of the current SCr-based AKI definitions is their failure to provide detailed phenotypes of AKI in patients with a structural kidney injury (Fig. 1, box D). Recognizing this limitation of the SCr-based AKI definition, researchers have turned their attention to discover, test, and validate novel biomarkers to improve AKI phenotyping. Because AKI is a highly heterogenous condition, no single biomarker has overcome all of the limitations of SCr in all settings successfully. However, some novel biomarkers and repurposed, traditional, non–SCr-based biomarkers have shown reliable evidence in specific areas overcoming the deficits of SCr.

TRADITIONAL AND NOVEL BIOMARKERS FOR AKI PHENOTYPING

The Food and Drug Administration defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention."[19] In the past 5 years, more than 700 publications evaluated biomarkers in AKI in