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ACUTE KIDNEY INJURY

Defining prerenal azotemia in clinical practice and research

Chirag R. Parikh and Steven G. Coca

Prerenal azotemia is a common occurrence in hospitalized patients and is generally easier to define in clinical practice than in clinical research. Monitoring the duration of acute kidney injury and biomarkers of kidney function might help distinguish prerenal azotemia from acute tubular necrosis in both clinical practice and research settings.

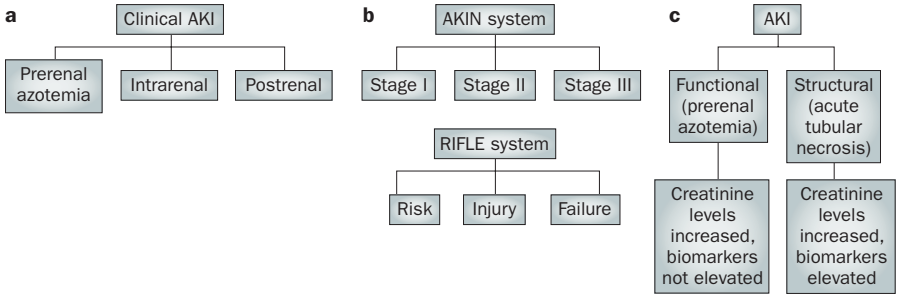
Few data exist on the incidence of prerenal azotemia in patients with acute kidney injury (AKI) and the effect of reversible increases in serum creatinine levels on patient outcomes. Uchino *et al.*[1] have now described the epidemiology of patients with prerenal azotemia by using AKI <3 days duration as a surrogate in a large observational study of >20,000 critically ill patients.[1] The researchers found that 32% of patients who had AKI according to the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria had prerenal azotemia with complete recovery of kidney function, but that the same group of patients had a greater than twofold increase in the risk of hospital mortality compared with patients who did not have AKI. By contrast, patients with sustained AKI (>3 days), who probably represented patients with structural kidney injury, such as those with acute tubular necrosis (ATN), had a sixfold increase in risk of mortality compared with patients without AKI.[1]

The concept of prerenal azotemia is ingrained in the clinical practice of nephrology. AKI, which is defined by sudden increases in serum creatinine levels, can be classified into three categories: AKI caused by prerenal azotemia, AKI induced by intrarenal causes and AKI induced by postrenal obstruction.[2] This classification is based on pathophysiological processes and provides information for further diagnostic testing, disease management and prognosis. Conceptually, prerenal azotemia and postrenal etiologies should spare damage to the kidney tissue, but intrarenal causes of AKI, such as ATN, are caused by inflammatory, ischemic or toxic injury to kidney parenchyma.[2,3] Differentiating ATN from prerenal azotemia in clinical practice is achieved by diagnostic tests, including fractional excretion of sodium (FENa), urine microscopy, volume challenge, and ultrasonography of the kidney to detect hydronephrosis.[3] Prerenal azotemia is a condition in which findings of urine microscopy are typically bland (without urinary casts) and FENa is <1%, indicating that the structure and function of kidney proximal tubular cells are intact. Prerenal azotemia responds to intravenous volume administration or hemodynamic manipulation, leading to complete reversal of the condition within 24–48 h in most cases. Abnormal results from urine microscopy and lack of improvement in levels of serum creatinine after volume challenge suggest tubular cell injury, as occurs in ATN.[2,3]

The classification of AKI according to its three etiologies cannot be as easily applied in the research setting. Information on FENa, the presence or absence of granular casts in urine, and ultrasonography findings are not routinely available in research databases; therefore, distinguishing prerenal azotemia from ATN can be a challenge. This discordance in AKI classification is evident within popular AKI classification systems used in epidemiological AKI research—the Acute Kidney Injury Network (AKIN) criteria and RIFLE criteria—as these criteria do not categorize severity of AKI into prerenal, intrarenal and postrenal causes.[4,5] Both AKI and RIFLE use only the peak increase in serum creatinine level as a measure of AKI severity and prognosis (although the AKIN criteria states that the diagnostic criteria should be applied "following adequate resuscitation"). Undoubtedly, each of the stages within the AKIN and RIFLE criteria will encompass cases of prerenal azotemia together with ATN, which likely reduces the accuracy of these staging systems and demonstrates a limitation in our current epidemiological classification systems of AKI.

Is the separation of prerenal azotemia from ATN necessary in clinical research? Some researchers suggest that such a separation is flawed, unnecessary and practically unfeasible.[6] Moreover, prerenal azotemia and ATN are part of a continuum of AKI, as prolonged prerenal azotemia can progress to ATN. We have seen such examples while treating patients with AKI; however, epidemiological and biological data suggest that these categories should be separated. Evidence from epidemiological studies of AKI over the past year shows substantially different relationships for the subgroups of patients with transient AKI (prerenal azotemia) and sustained AKI (ATN) with mortality. As noted above, the study by Uchino *et al.*[1] used the RIFLE criteria and duration of AKI to demonstrate an adjusted odds ratio of in-hospital mortality of twofold versus sixfold for prerenal azotemia and ATN, respectively. In two other epidemiological studies in which the episode of AKI was classified by duration of AKI, patients who had AKI for <3 days had a lower risk of long-term mortality than those who had AKI for >3 days.[7,8] Coca *et al.*[8] assessed long-term mortality in 35,000 veterans who had diabetes and had undergone noncardiac surgery. AKI was classified by AKIN criteria and duration (<3 days, 3–6 days and ≥7 days). Within each AKIN stage, duration of AKI offered additional prognostic information on the risk of long-term mortality.[8] In another study of 5,000 patients undergoing cardiac surgery, duration of AKI was strongly associated with risk of mortality at 5 years.[7] Patients with <3 days of AKI had a 66% increase in the risk of long-term mortality compared with patients without AKI.[7] By contrast, patients with 3–6 days of AKI had nearly a twofold increase in the risk of mortality and patients with ≥7 days of AKI had a greater than threefold increase in risk of mortality compared with patients without AKI.[7]

Can the clinical research classification of AKI be improved to distinguish prerenal azotemia from ATN? No definition of prerenal azotemia can be easily used in



Advantages			
▪ Conceptual and pathophysiological ▪ Popular among clinicians	▪ Standardizes research findings ▪ Popular in research setting	▪ Conceptual and objective ▪ Links structure and function ▪ Helpful in clinical practice ▪ Can also be applied in research studies in a standardized manner	
Disadvantages			
▪ Difficult to define in research settings	▪ Does not align with clinical practice ▪ Does not separate prerenal azotemia from acute tubular necrosis	▪ Validation studies of biomarkers still ongoing	

Figure 1 | Classification systems for AKI. **a** | Clinical and **b** | research classification systems help to identify the different grades of AKI. **c** | A new paradigm for the classification of AKI in both clinical research and practice could help to distinguish functional AKI (that is, prerenal azotemia) from structural AKI (that is, acute tubular necrosis). Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; RIFLE, Risk, Injury, Failure, Loss and End-stage kidney disease.

AKI research; however, a few approaches exist that could help identify patients with prerenal azotemia. Duration of AKI might be one approach to identify reversible AKI, as patients with transient azotemia might largely represent cases of prerenal azotemia. In the short term, the AKIN and RIFLE systems can be modified to add information on duration of AKI to improve the assessment of disease severity.[4,5] Within each stage, classification of patients into short-term and long-term AKI would be helpful. Alternatively, the classification of AKIN or RIFLE could be applied after a patient has sustained AKI for >48 h. This modification would enable assessment of patients with 'prerenal azotemia' separately from those with ATN.

Of note, it is unlikely that the kidneys or AKI had a causal role in the association of risk of mortality with prerenal azotemia reported in all three of the aforementioned studies,[1,7,8] since the kidney injury in these cases was reversible and no cellular damage to the kidneys would have occurred. In these scenarios, kidney ischemia was probably a surrogate of total body ischemia or ischemia in other vital organs, such as the heart or brain, thereby confounding the relationship between prerenal azotemia and mortality. These studies therefore combine the etiologies of prerenal azotemia and ATN and probably diminish the effect of true kidney injury on patients' outcomes. Furthermore, AKI that involves true structural kidney injury could still be of short duration if the surrounding noninjured parenchyma regains function while the injured tubules are healing. By contrast, prolonged cases of prerenal azotemia could exist with minimal kidney injury (for example, in cardiorenal syndrome). The added dimension of time to AKI classification systems is therefore helpful, but not the ultimate solution to standardize these classifications for both clinical research and practice.

Novel biomarkers to identify subgroups of patients with and without kidney injury could be a useful addition to criteria for AKI classification. Several biomarkers, such as urinary IL-18, NGAL and KIM-1, are specific to the kidney and are only released when necrosis or apoptosis of the proximal tubular cells occurs. Prior publications have demonstrated that these biomarkers are markedly elevated in patients with ATN compared with in patients with prerenal azotemia.[9,10] If the biomarkers used are specific to kidney tubules, then situations in which serum creatinine levels are increased but levels of biomarkers are not elevated might represent prerenal azotemia or functional AKI. AKI episodes in which levels of both biomarkers and serum creatinine are increased would indicate cases of ATN or structural AKI (Figure 1). The addition of novel urinary biomarkers to AKI classifications might therefore represent a novel paradigm that could align and improve the clinical practice and clinical research of AKI. Future research should investigate the usefulness of these modified criteria to distinguish prerenal azotemia from ATN.

*Department of Internal Medicine, Section of Nephrology, Yale University and Veterans Affairs Medical Center, 950 Campbell Avenue, Mail code 151B, West Haven, CT 06516, USA (**C. R. Parikh, S. G. Coca**).*

Correspondence to: C. R. Parikh
chirag.parikh@yale.edu

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Competing interests
The authors declare no competing interests.

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