Review Article

Definition of Acute Kidney Injury

P Sri Ram Naveen

Introduction : Acute kidney injury (AKI) is the abrupt loss of kidney function, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes. The term AKI has largely replaced acute renal failure (ARF), reflecting the recognition that smaller decrements in kidney function that do not result in overt organ failure are of substantial clinical relevance and are associated with increased morbidity and mortality. The term ARF is now reserved for severe AKI, usually implying the need for renal replacement therapy.
The loss of kidney function that defines AKI is most easily detected by measurement of the serum creatinine, which is used to estimate the glomerular filtration rate (GFR). Three problems are associated with the use of serum creatinine to quantitatively define AKI:

1. Serum creatinine does not accurately reflect the GFR in a patient in whom it is not in steady state. In the early stages of AKI, the serum creatinine may be low, even though the actual (not estimated) GFR is markedly reduced, since there may not have been sufficient time for the creatinine to accumulate. When the serum creatinine is rising, estimates of GFR based on creatinine values will overestimate the true GFR, conversely, estimates of GFR will underestimate the true GFR during recovery of kidney function, when the serum creatinine concentration is declining.

2. Creatinine is removed by dialysis. As a result, it is usually not possible to assess kidney function by measuring the serum creatinine once dialysis is initiated. One exception is when the serum creatinine continues to fall on days when hemodialysis is not performed, indicating recovery of renal function.

3. Numerous epidemiologic studies and clinical trials have used different cut-off values for serum creatinine to quantitatively define AKI.[1]

Prior lack of consensus in the quantitative definition of AKI, in particular, has hindered clinical research, since it confounds comparisons between studies. Some definitions employed in clinical studies have been extremely complex, with graded increments in serum creatinine for different baseline serum creatinine values.[1,2]

Several consensus definitions of AKI have been developed in order to provide a uniform definition of AKI. In 2004, the Acute Dialysis Quality Initiative (ADQI) group, which included expert intensivists and nephrologists, proposed consensus and evidence based guidelines for the treatment and prevention of AKI[3]. Recognizing the need for a uniform definition for AKI, the ADQI group proposed a consensus graded definition, called the RIFLE criteria[3]. A modification of the RIFLE criteria was subsequently proposed by the Acute Kidney Injury Network (AKIN, which included the ADQI group), as well as representatives from other nephrology and intensive care societies [4,5,6]. More recently, the Kidney Disease/Improving Global Outcomes (KDIGO) AKI Workgroup proposed a modified definition, harmonizing differences between the RIFLE and AKIN definitions[7].

RIFLE Criteria : The RIFLE criteria consists of three graded levels of kidney dysfunction (Risk, Injury, and Failure), based upon either the magnitude of increase in serum creatinine or urine output, and two outcome measures (Loss and End-stage renal disease [ESRD]). The RIFLE strata are as follows [3]

Risk: 1.5-fold increase in the serum creatinine, or glomerular filtration rate (GFR) decrease by 25 percent, or urine output <0.5 mL/kg per hour for six hours

Injury: Twofold increase in the serum creatinine, or GFR decrease by 50 percent, or urine output <0.5 mL/kg per hour for 12 hours

Failure: Threefold increase in the serum creatinine, or GFR decrease by 75 percent, or urine output of <0.3 mL/kg per hour for 24 hours, or anuria for 12 hours.

Loss: Complete loss of kidney function (eg, need for renal replacement therapy) for more than four weeks

ESRD: Complete loss of kidney function (eg, need for renal replacement therapy) for more than three months.

The change in serum creatinine was specified as occurring over not more than seven days. Subsequent to publication of RIFLE, it was noted that the change in serum creatinine concentrations do not correlate with the percent decrease in GFR that is cited in the RIFLE classification; a 1.5-fold increase in serum creatinine societies [4,5,6], corresponds to a 33 rather than 25 percent decrease in GFR[8]. More recently, the Kidney Disease/Improving Global Outcomes (KDIGO) AKI Workgroup proposed a modified definition, harmonizing differences between the RIFLE and AKIN definitions[7].

However, given the absence of readily available methods for measurement of GFR when serum creatinine is not in steady state, as is the case during acute kidney injury (AKI), changes in GFR are not included in the Acute Kidney Injury Network (AKIN) classification system, Improving Global Outcomes (KDIGO) AKI classification system, except for the classification of children under the age of 18 years.

The RIFLE criteria correlated with prognosis in a number of studies [8.9,10,11,12,13,14,15,16,17,18] As an example, a systematic review of 13 studies demonstrated a stepwise increase in the relative risk of death in patients who met the RIFLE criteria for various stages of AKI[15]. Compared with patients who did not have AKI, patients in the RIFLE stages of "risk," "injury," and "failure" had increased relative mortality risks of 2.4 (CI 1.94-2.97), 4.15 (CI 3.14-5.48), and 6.37 (CI 5.14-7.9). Despite significant heterogeneity among studies, results from most individual reports were qualitatively similar.

The relative risk for mortality by RIFLE stage, based on change in serum creatinine, does not correlate well with the mortality risk by RIFLE stage, calculated basis of urine output criteria. The observed relative risk was greater in studies that used the creatinine criteria alone compared with those that used both the creatinine and urine output criteria to determine RIFLE stage, with a much smaller increment between the "risk" and "injury" stages using urine output than with creatinine. These results suggest that the calibration between the serum creatinine and urine output criteria for staging is poor.

AKIN Criteria : A modification of the RIFLE criteria was developed by the Acute Kidney Injury Network (AKIN), providing both diagnostic criteria and a staging system for acute kidney injury (AKI)[4,5,6].

Diagnostic criteria - The AKIN diagnostic criteria for AKI specify an abrupt (within 48 hours), absolute increase in the serum creatinine concentration of $\geq$ 0.3 mg/dL (26.4 micromol/L) from baseline; a percentage increase in the serum creatinine concentration of $\geq$ 50 percent; or oliguria of <0.5 mL/kg per hour for more than six hours

The latter two of these criteria are identical to the RIFLE "risk" criteria. The addition of an absolute change in serum creatinine of $\geq$ 0.3 mg/dL was based on epidemiologic data that demonstrated an 80 percent increase in mortality risk associated with changes in serum creatinine concentration of as little as 0.3 to 0.5 mg/dL[19]. Including a time constraint of 48 hours is based upon data that showed that poorer outcomes were associated with small changes in the creatinine when the rise in creatinine was observed within 24 to 48 hours [20,21]. However, it should be recognized that this time frame differed from the seven-day time specified in the RIFLE criteria.

Two additional caveats were proposed by the AKIN group:

✧ The diagnostic criteria should be applied only after volume status had been optimized.

✧ Urinary tract obstruction needed to be excluded if oliguria was used as the sole diagnostic criterion.

Staging system - The classification or staging system for AKI is comprised of three stages of increasing severity, which correspond to the Risk (stage 1), Injury (stage 2), and Failure (stage 3) components of the RIFLE criteria, with the addition of the $\geq$ 0.3 mg/dL increase in serum creatinine to the stage 1 criteria. Loss and End-stage renal disease (ESRD) are removed from the staging system and defined as outcomes.

The AKIN modifications to RIFLE have not substantively changed the classification of patients with AKI or improved its ability to predict hospital mortality[22].

KDIGO modifications to RIFLE and AKIN - The Kidney Disease / Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury (AKI) included a revision to the definition of AKI while retaining the AKI Network (AKIN) staging criteria [7]. In the KDIGO definition, the time frame for an absolute increase in serum creatinine of $\geq$ 0.3 mg/dL is retained from the AKIN definition (48 hours), while the time frame for a $\geq$ 50 percent increase in serum creatinine reverted to the seven days originally included in the Acute Dialysis Quality Initiative (ADQI) RIFLE criteria.

According to KDIGO, AKI is defined by any of the following:

1. Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 micromol/L) within 48 hours. or
2. Increase in serum creatinine by ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days; or
3. Urine volume <0.5 mL/kg/h for six hours

The KDIGO criteria only utilize changes in serum creatinine and urine output, not changes in glomerular filtration rate (GFR) for staging, with the exception of children under the age of 18 years, for whom an acute decrease in estimated GFR (eGFR) to <35 mL/min per 1.73 m^2 is included in the criteria for stage 3 AKI. As with the RIFLE and AKIN staging systems, KDIGO suggested that patients be classified according to criteria that result in the highest (ie, most severe) stage of injury. Using the KDIGO criteria, AKI is staged as follows:

Stage 1: Increase in serum creatinine to 1.5 to 1.9 times baseline, or increase in serum creatinine to e"0.3 mg/dL (e"26.5 micromol/L), or reduction in urine output to <0.5 mL/kg per hour for 6 to 12 hours.

Stage 2: Increase in serum creatinine to 2.0 to 2.9 times baseline, or reduction in urine output to <0.5 mL/kg per hour for ≥ 12 hours.

Stage 3: Increase in serum creatinine to 3.0 times baseline, or increase in serum creatinine to ≥ 4.0 mg/dL (≥ 353.6 micromol/L), or reduction in urine output to <0.3 mL/kg per hour for ≥ 24 hours, or anuria for ≥12 hours, or the initiation of renal replacement therapy, or, in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2.

Limitations : Several commentaries have been published raising concerns regarding the use of these criteria to diagnose acute kidney injury (AKI), although all commentaries stress the importance of a consensus approach for research purposes[23,24].

In a commentary on the Kidney Disease/Improving Global Outcomes (KDIGO) AKI guidelines, the European Renal Best Practice (ERBP) working group agreed that AKI be defined on the basis of either a change in creatinine or reduction in urine output. The ERBP group recommended that the first documented serum creatinine be used as the baseline, rather than using historical creatinines (ie, prior to the acute illness) or a calculated value based on a presumed baseline glomerular filtration rate (GFR) of 75 mL/min [23]. The ERBP work group also recommended that urine output be assessed per shift using ideal body weight rather than true weight.

Another important issue is the use of urine output as a sole criterion for AKI. By all criteria discussed above, stages are defined by either change in serum creatinine or urine output. However, the assignment of the corresponding changes in serum creatinine and changes in urine output to the same strata is not based on robust evidence. Studies that have examined the prognostic and diagnostic utility of urine output have yielded variable results. As an example, in one assessment of the RIFLE classification, which compared the serum creatinine and urine output criteria, the serum creatinine criteria were strong predictors of intensive care unit (ICU) mortality, whereas the urine output criteria did not independently predict mortality[13]. Another study, however, has suggested that urine output may be a more sensitive marker for AKI than serum creatinine[26].

The KDOQI and ERBP groups have offered opinions on the use of urine output as a criterion for AKI[23,24]. The ERBP group stressed the importance of using both urine output and the serum creatinine and stated that, although all criteria included the urine output, in practice, it is often omitted from studies[23]. The KDOQI working group noted that brief durations of oliguria do not prognostically correlate with small changes in the serum creatinine and may just reflect insufficient volume resuscitation[24]. Until this issue is resolved, it is reasonable to use the criteria that result in the least favorable strata, as suggested in the Acute Dialysis Quality Initiative (ADQI) group[3] and affirmed by KDIGO.

The determination of a baseline creatinine for individual patients is another issue that has been raised as a potential criticism. It is impossible to calculate the change in serum creatinine in patients who present with AKI, but without a baseline measurement of serum creatinine. The authors of the RIFLE criteria had initially suggested back-calculating an estimated baseline serum creatinine concentration using the four-variable MDRD equation, assuming a baseline GFR of 75 mL/min/1.73 m^2 [3]. However, this approach has been demonstrated to result in significant misclassification [23] and should not be utilized. As noted above, the ERBP group recommended that the first documented serum creatinine be used as the baseline, rather than using historical creatinines (ie, prior to the acute illness) or a calculated value based on a presumed baseline GFR of 75 mL/min[23].

A more global concern raised by the KDOQI work group is that the use of a definition based upon a biomarker, such as serum creatinine, or a variable, such as urine output, may result in a marked increase in the number of nephrology consultations, which would provide uncertain benefit to the patient [24]. As noted by an accompanying editorial to the KDOQI commentary, discretion is required to determine the clinical significance of a diagnosis of AKI [27]

Clinical Utility : The clinical utility of these criteria is uncertain. This issue has been raised by both a multidisciplinary work group convened by KDOQI and the Canadian Society of Nephrology[24,25]. These criteria have greatest utility in epidemiologic studies and in defining consistent inclusion criteria and/or endpoints for clinical studies.

It seems likely that these criteria will eventually be replaced, at least in part, by sensitive and specific biomarkers of renal tubular injury. The use of such biomarkers, analogous to troponin as a marker of myocardial injury, will permit development of a new paradigm for classifying acute kidney injury (AKI) that is not solely dependent upon serum creatinine or other functional markers.

References

1. Mehta RL, Chertow GM. Acute renal failure definitions and classification: time for change? J Am Soc Nephrol 2003; 14:2178.
2. Hou SH, Bushinsky DA, Wish JB, et al. Hospital-acquired renal insufficiency: a prospective study. Am J Med 1983; 74:243.
3. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:R204.
4. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11:R31.
5. Levin A, Warnock DG, Mehta RL, et al. Improving outcomes from acute kidney injury: report of an initiative. Am J Kidney Dis 2007; 50:1.
6. Molitoris BA, Levin A, Warnock DG, et al. Improving outcomes from acute kidney injury. J Am Soc Nephrol 2007; 18:1992.
7. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012; 2:8.
8. Ali T, Khan I, Simpson W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 2007; 18:1292.
9. Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006; 34:1913.
10. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10:R73.
11. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V. Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. Ann Thorac Surg 2006; 81:542.
12. Cruz DN, Bolgan I, Perazella MA, et al. North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury (NEiPHROS-AKI): targeting the problem with the RIFLE Criteria. Clin J Am Soc Nephrol 2007; 2:418.
13. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007; 35:1837.
14. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. Kidney Int 2008; 73:538.
15. Bagshaw SM, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. Nephrol Dial Transplant 2008; 23:1203.
16. Thakar CV, Christianson A, Freyberg R, et al. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. Crit Care Med 2009; 37:2552.
17. Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 2009; 35:1692.

18. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005; 16:3365.

19. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 2004; 15:1597.

20. Levy MM, Macias WL, Vincent JL, et al. Early changes in organ function predict eventual survival in severe sepsis. Crit Care Med 2005; 33:2194.

21. Bagshaw SM, George C, Bellomo R, ANZICS Database Management Committe. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. Nephrol Dial Transplant 2008; 23:1569.

22. Ad-hoc working group of ERBP, Fliser D, Laville M, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. Nephrol Dial Transplant 2012; 27:4263.

23. Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013; 61:649.

24. James M, Bouchard J, Ho J, et al. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013; 61:673.

25. Claure-Del Granado R, Macedo E, Chertow GM, et al. Toward the optimal dose metric in continuous renal replacement therapy. Int J Artif Organs 2012; 35:413.

26. Levey AS, Levin A, Kellum JA. Definition and classification of kidney diseases. Am J Kidney Dis 2013; 61:686.

Financial Support : Declared None
Conflict of Interest : Declared None