Defining Early Recovery of Acute Kidney Injury

Stephen Duff and Patrick T. Murray

CJASN 15: 1358–1360, 2020. doi: https://doi.org/10.2215/CJN.13381019

Standardized systems for defining and staging AKI predict mortality in a stage-dependent manner. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) criteria unified the preceding RIFLE and AKIN classifications (Figure 1A) (1). However, AKI remains a syndrome with devastating clinical outcomes, no approved specific therapies, and only supportive care.

Need for a Definition of AKI Recovery

The growing recognition of the mechanisms, timing, and extent of AKI recovery as key factors in determining patient outcomes and development of potential AKI therapies has focused attention on the need to standardize the diagnosis/staging of AKI recovery. CKD is now among the recognized potential sequelae of AKI, even in those with normal pre-AKI kidney function. Animal models and epidemiologic studies suggest that apoptosis, maladaptive repair, and fibrosis lead to new or worsening CKD in a significant proportion of patients with AKI (2). Accordingly, the 2012 KDIGO clinical practice guidelines recommended clinical follow-up of surviving patients at 3 months after an episode of AKI to determine if new or worsening CKD has developed and requires ongoing management (Figure 1C) (1). Furthermore, clinical trials of potential new therapies use composite clinical outcomes that expand on the traditional outcome of dialysis-free survival to incorporate measures of new/worsening CKD. However, less attention has been paid to the importance of the rate and extent of AKI recovery during the initial weeks of an AKI episode. Here, we review recent literature proposing approaches to define and stage AKI recovery, and propose novel criteria for the retrospective diagnosis and staging of AKI that was present on admission and recovered within 7 days (Figure 1B).

Epidemiologic Data and Observational Studies of AKI Recovery

AKI recovery has been defined by the Acute Disease Quality Initiative 16 consensus group as the absence of AKI by both serum creatinine and urine output criteria (per KDIGO) within 7 days after AKI onset (Figure 1C) (3,4). Transient AKI is defined by rapid reversal of AKI within 48 hours and is strongly correlated with reduced morbidity and mortality (3–7) compared with persistent AKI, which is defined by reversal of AKI within 2–7 days (Figure 1C). AKI that has not recovered within a week is termed acute kidney disease (AKD; a term first proposed in the original KDIGO AKI guidelines) (Figure 1C) (1). AKD is assigned stages 1–3 on the basis of the occurrence of KDIGO AKI criteria during the 7–90 day period after the initial AKI. Stage 0 subgroups A–C represent patients without stage 1–3 criteria but at increased risk of progression to CKD (lesser decrements of GFR, loss of kidney functional reserve, proteinuria, other markers of kidney damage; Figure 1C). Finally, CKD is defined as kidney disease persisting for 3 months or longer.

A growing evidence base supports the adoption of this conceptual framework and proposed definitions. In 2017, Kellum *et al.* (5) studied 16,968 critically patients with KDIGO AKI stage 2/3 at the University of Pittsburgh and found that approximately 40% of patients with AKI in this cohort progressed to AKD. AKD that has not recovered by hospital discharge was associated with a doubling of 1-year mortality. They also found that recurrent AKI that occurred before discharge was associated with significantly increased 1-year mortality. One-year mortality was 31% for those who had at least one relapse but recovered by hospital discharge, versus 58% in those who relapsed but did not recover in hospital, and in contrast was only 10% in for those who had a sustained recovery within a week. These data demonstrated the importance of early AKI recovery, versus progression to AKD. Similarly, in their recent large retrospective population-based cohort study, James *et al.* (8) studied residents of Alberta, Canada. AKI occurred in 15,777 (1%) and AKD without AKI (kidney dysfunction without an AKI-defining event) occurred in 42,487 (4%) of the population studied. Both AKI and AKD were associated with significantly increased mortality versus those without kidney disease (adjusted hazard ratio, 3.23; 95% confidence interval [95% CI], 3.16 to 3.31, and adjusted hazard ratio, 1.42; 95% CI, 1.39 to 1.45, respectively). They also demonstrated a substantial increase in the risk of both CKD, defined by eGFR loss or proteinuria, and ESKD among both AKI and AKD without AKI cohorts. Also in 2019, Hsu *et al.* (9) presented AKI data from the Assessment, Serial Evaluation, and Subsequent Sequelae in AKI and Chronic Renal Insufficiency Cohort studies. A total of 324 patients had an AKI episode, which was associated with a 9% increase in the urine protein-to-creatinine ratio in multivariable analysis. Proteinuria correlated

School of Medicine, University College Dublin, Dublin, Ireland

Correspondence: Prof. Patrick Murray, University College Dublin School of Medicine, Catherine McAuley Education & Research Centre, Nelson Street, Dublin 7, Ireland. Email: patrick.murray@ucd.ie

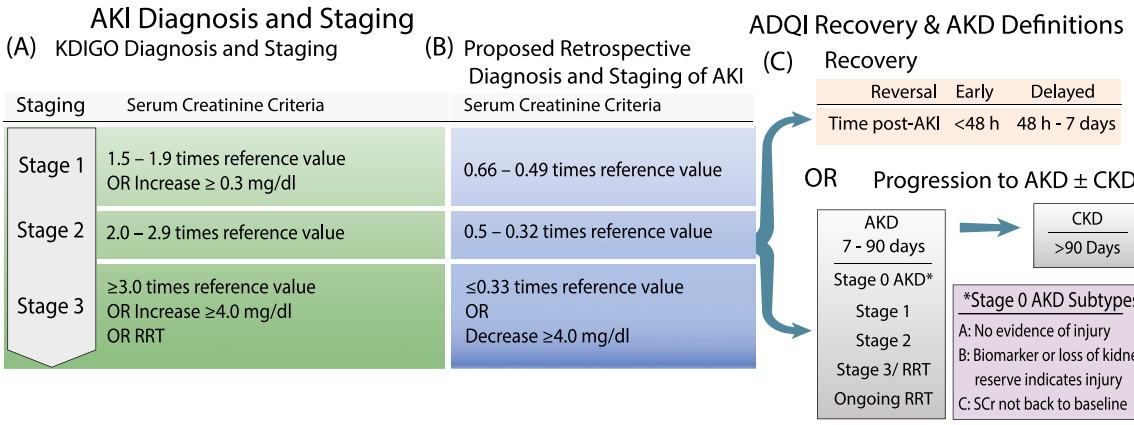

Figure 1. | Conceptual model of proposed retrospective staging of AKI on admission. (A) Kidney Disease: Improving Global Outcomes (KDIGO) AKI serum creatinine definitions. For urine output criteria, see KDIGO guideline. (B) Proposed criteria for retrospective diagnosis and staging of AKI. The minimum serum creatinine (SCr) within 7 days is compared with the reference (first/admission) value. (C) ADQI recovery and acute kidney disease (AKD) definitions. AKI may then reverse within 7 days (AKI recovery) or progress to AKD with or without CKD. Modified from reference 3, with permission.

with the severity of the initial injury, with patients who had AKI stage 3 having a 24% increase in urine protein-to-creatinine ratio (95% CI, 1.09 to 1.40; $P<0.001$). These findings underline the importance of continuum of AKI recovery, the potential development of AKD post-AKI, and its relationship with CKD. More data on the evolution of proteinuria and GFR loss post-AKI are needed to understand the pathobiology of this syndrome and the potential utility of routinely monitoring urinary protein excretion in the early period (<3 months) post-AKI.

In their large AKI cohort study (8), James *et al.* defined 43% of their AKI cases using a "decrease in serum creatinine >50% in 7 days." This illustrates the frequency of recovering AKI at presentation, which could otherwise be missed. This phenomenon was highlighted in the 2012 KDIGO AKI guidelines, which first proposed a decrement in serum creatinine of ≥50% occurring within a week as a retrospective definition of AKI (1). Similarly, in our recent prospective study of a critically ill cohort, we used a threshold of a ≥33% decrease from the intensive care unit admission (reference) serum creatinine during the first 7 days to identify patients with recovering AKI at admission (10). An additional 177 AKI cases (26% of total cohort, added to 38% who developed AKI by standard KDIGO criteria; with an overall AKI incidence of 65%) were identified using this criterion. We chose a 33% decrease in serum creatinine, rather than a 50% decrease, as it represents the inverse of the ≥50% increase within 7 days that prospectively defines KDIGO stage 1 AKI (see proposed retrospective AKI definition and staging system below; Figure 1B).

AKI Recovery: A Proposed Definition

We thus propose the retrospective diagnosis of recovering AKI that was present at admission, on the basis of a decrease from the reference serum creatinine of at least 33% in the following 7 days (Figure 1B). A serum creatinine decrease of ≥0.3 mg/dl (≥26.5 μmol/L) within 48 hours was considered, but not included in stage 1 of the proposed classification, as it may not be sufficiently specific (prior CKD, rapid volume shifts, *etc*). We further categorize recovering AKI into stages 1–3 on the basis of the inverse of the AKI KDIGO serum creatinine criteria (Figure 1B). In clinical practice and epidemiologic studies, this approach would substantially increase the recognition of AKI that reverses within the initial week of hospitalization, whether transient (<48 hours) or persistent (2–7 days) according to the proposed KDIGO AKI recovery criteria, which we also endorse (Figure 1C). Taken together, we think that these emerging data should prompt additional analyses of the epidemiology, pathobiology, and clinical importance of early AKI recovery, and the continuum of AKI, AKD, and CKD as defined and staged using these criteria. This will facilitate AKI research and management that achieves optimal AKI recovery and outcomes.

Disclosures

P.T. Murray reports receiving personal fees from AM-Pharma, personal fees from FAST Biomedical, and personal fees from Sphingotec, outside the submitted work. The remaining author has nothing to disclose.

Funding

S. Duff was supported by the University College Dublin Foundation Newman Fellowship in AKI.

Acknowledgments

The content of this article does not reflect the views or opinions of the American Society of Nephrology (ASN) or *CJASN*. Responsibility for the information and views expressed herein lies entirely with the author(s).

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2: 1–138, 2012
2. Chawla LS, Eggers PW, Star RA, Kimmel PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 371: 58–66, 2014

3. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, Bittleman D, Cruz D, Endre Z, Fitzgerald RL, Forni L, Kane-Gill SL, Hoste E, Koyner J, Liu KD, Macedo E, Mehta R, Murray P, Nadim M, Ostermann M, Palevsky PM, Pannu N, Rosner M, Wald R, Zarbock A, Ronco C, Kellum JA; Acute Disease Quality Initiative Workgroup 16.: Acute kidney disease and renal recovery: Consensus report of the acute disease quality initiative (ADQI) 16 workgroup. *Nat Rev Nephrol* 13: 241–257, 2017
4. Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G: Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol* 26: 2231–2238, 2015
5. Kellum JA, Sileanu FE, Bihorac A, Hoste EA, Chawla LS: Recovery after acute kidney injury. *Am J Respir Crit Care Med* 195: 784–791, 2017
6. Brown JR, Kramer RS, Coca SG, Parikh CR: Duration of acute kidney injury impacts long-term survival after cardiac surgery. *Ann Thorac Surg* 90: 1142–1148, 2010
7. Coca SG, King JT Jr., Rosenthal RA, Perkal MF, Parikh CR: The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. *Kidney Int* 78: 926–933, 2010
8. James MT, Levey AS, Tonelli M, Tan Z, Barry R, Pannu N, Ravani P, Klarenbach SW, Manns BJ, Hemmelgarn BR: Incidence and prognosis of acute kidney diseases and disorders using an integrated approach to laboratory measurements in a universal health care system. *JAMA Network Open* 2: e191795, 2019
9. Hsu CY, Hsu RK, Liu KD, Yang J, Anderson A, Chen J, Chinchilli VM, Feldman HI, Garg AX, Hamm L, Himmelfarb J, Kaufman JS, Kusek JW, Parikh CR, Ricardo AC, Rosas SE, Saab G, Sha D, Siew ED, Sondheimer J, Taliercio JJ, Yang W, Go AS; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators and the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) Study: Impact of AKI on urinary protein excretion: Analysis of two prospective cohorts. *J Am Soc Nephrol* 30: 1271–1281, 2019
10. McMahon BA, Galligan M, Redahan L, Martin T, Meaney E, Cotter EJ, Murphy N, Hannon C, Doran P, Marsh B, Nichol A, Murray PT: Biomarker predictors of adverse acute kidney injury outcomes in critically ill patients: The Dublin acute biomarker group evaluation study. *Am J Nephrol* 50: 19–28, 2019

Published online ahead of print. Publication date available at www.cjasn.org.