

Acute Kidney Injury and Chronic Kidney Disease: A Work in Progress

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Short-term outcomes of acute kidney injury (AKI), such as length of hospital stay and inpatient mortality, are well documented. Recently, the impact of AKI on long-term outcomes—a largely undefined body of knowledge—has come into focus. Evidence associating AKI in the inpatient setting with extended outcomes of mortality and the development of chronic kidney disease (CKD) has materialized. Several studies have linked severity of AKI with increased likelihood of mortality, developing end-ESRD, or chronic kidney disease (1–3). Others have found an association between temporary dialysis support for AKI in CKD patients and progression to ESRD (4).

The detrimental effect of AKI episodes on the development and progression of CKD has been explored in animal models. For instance, Nath *et al.* found that repetitive nephrotoxic insults over time results in chronic renal disease in rats (7). Furthermore, Basile *et al.* found persistent changes at the gene transcription level in the kidneys of rats subjected to ischemic insult, even after serum creatinine levels had recovered to match those of untreated controls (8). These findings support the clinical findings associating AKI episodes with progressive kidney disease.

A review of the recent literature reveals several studies linking AKI to the progression of kidney disease, five of which are presented in Table 1. Of the five presented, the length of studies ranged from 3.3 to 8 years in various settings. With regard to outcomes, three out of five studies used ESRD as the primary outcome, two used progression of CKD as the outcome, and one used incident CKD. In general, all studies demonstrate an increased risk of adverse renal outcomes, irrespective of how AKI was defined. For example, of the studies using ESRD as their primary outcome, the hazard associated with an AKI episode ranged from 1.45 to 11.74 (2–6). Unfortunately, the role of recurrent AKI on development and progression of CKD remains underexplored in the clinical realm. Most recent studies have examined the impact of one episode of acute kidney injury on patient outcomes. In the current issue of *CJASN*, Thakar and colleagues examine the association between solitary and multiple AKI episodes and the risk of chronic kidney disease in a cohort of diabetic patients (9).

Briefly, Thakar *et al.* studied a cohort of 4082 pa-

tients with diabetes who sought ambulatory and inpatient treatment within the Veterans Affairs health-care system between January 1, 1999, and December 31, 2004, and followed them until December 31, 2008. Prospective patients were identified as having diabetes, based on ICD-9 codes, during at least one outpatient clinic encounter. After excluding patients with fewer than three creatinine levels or an eGFR <30 ml/min per 1.73 m² at the time of first creatinine measurement, 3679 patients remained for evaluation. AKI was defined according to the Acute Kidney Injury Network criteria. A total of 1822 patients required at least one hospitalization, 530 of 1822 patients experienced one AKI episode, and 158 of 530 patients experienced two or more AKI episodes. The mean age of patients in the study was 61.7 years, mean baseline creatinine was 1.10 mg/dl, and mean time of observation was 61.2 months. The study's findings reveal a significantly increased hazard of developing stage 4 CKD and mortality in individuals suffering from AKI during hospitalization compared with individuals without AKI. In addition, each additional AKI episode (up to three total) was associated with an independent and cumulative increase in the risk for the development of stage 4 CKD (hazard ratio = 2.02).

There are several aspects of Thakar's work that require special attention. First, the results of the multivariable Cox proportional hazards model suggest that while AKI is a significant risk factor for stage 4 CKD, it also has the same magnitude of risk as proteinuria (defined as an either urinary microalbumin concentration of >30 mg/g creatinine or a protein-creatinine ratio of >0.5 g/g, or a dipstick with >100 mg/dl protein), a well defined risk factor for ESRD in patients with diabetes. This finding suggests that determining a history of AKI in diabetic CKD patients may be on par with proteinuria with regard to assessing risk. Second, the association between AKI and progression of CKD is of similar magnitude irrespective of baseline eGFR, suggesting that an AKI history, even in patients with preserved kidney function, may be a risk marker for adverse renal outcomes.

While Thakar's study demonstrates an association between both solitary and multiple AKI episodes, and an increased risk of reaching stage 4 CKD, it does have limitations. This study does not include infor-

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Table 1. Recent studies linking AKI to long-term outcomes

Authors	Length of Study (Years)	Setting	Definition of AKI	Outcomes	Results, HR
Newsome <i>et al.</i> (5)	4.1 (median)	Acute MI	Increase in serum creatinine (increments of 0.1 mg/dl) from baseline during hospitalization for acute MI	ESRD	0.1 mg/dl increase, HR 1.45 0.2 mg/dl increase, HR 1.97 0.3 to 0.5 mg/dl increase, HR 2.36 0.6 to 3.0 mg/dl, increase HR 3.26 AKI 1, HR 4.15 AKI 2 to 3, HR 11.74
James <i>et al.</i> (2)	3.3 (maximum)	Coronary angiography	AKI stage 1, 2, or 3, according of Acute Kidney Injury Network definitions within 7 days	ESRD	
Hsu <i>et al.</i> (4)	8 (maximum)	Hospitalization	postcoronary angiography ≥50% increase in serum creatinine compared with last outpatient value and receipt of dialysis during hospitalization in patients with baseline eGFR <45 ml/min per 1.73 m ²	ESRD/death (combined)	AKI, HR 1.30
Lo <i>et al.</i> (3)	8 (maximum)	Hospitalization	≥50% increase in serum creatinine compared with last outpatient value and receipt of dialysis during hospitalization in patients with baseline eGFR ≥45 ml/min per 1.73 m ²	Stage 4 or 5 CKD	AKI, HR 28.1
Ishani <i>et al.</i> (6)	5.1 (mean)	Cardiac bypass	Percent change in serum creatinine comparing peak value within 7 days postbypass with baseline value	CKD (i), CKD (p)	1% to 24% increase; HR 1.4 (i), 1.5 (p) 25% to 49% increase; HR 1.9 (i), 1.7 (p) 50% to 99% increase; HR 2.3 (i), 1.7 (p) ≥100% increase; HR 2.3 (i), 2.4 (p)

AKI, acute kidney injury; MI, myocardial infarction; HR, hazard ratio; eGFR, estimated GFR; CKD, chronic kidney disease; (i), incident; (p), progression.

mation on whether patients with an AKI episode required temporary dialysis or on its duration, a likely strong effect modifier. Also not reported is the number of individuals who progressed to ESRD and required chronic renal replacement therapy by the end of the study, an outcome of significant importance to both patients and clinicians. Finally, it is likely that this study overestimates the risk of developing stage 4 CKD but not of mortality. Individuals with CKD have fluctuations in their serum creatinine levels, potentially resulting in temporary eGFR drops. These temporary declines of eGFR likely are not the result of CKD stage progression, as they are not likely representative of the patient's true eGFR. It is possible that a number of individuals with these transient nonsustained dips in kidney function, either from variation around their baseline or from undergoing outpatient AKI episodes, are flagged as having achieved stage 4 CKD, potentially magnifying the risk attributable to AKI. Finally, it remains unknown how AKI episodes are associated with progressive CKD. Could it be that individuals with progressive kidney disease have an increased risk of AKI, in which case the AKI episode is simply a marker of progressive kidney disease? Alternatively, AKI may not be causal of progressive kidney disease or ESRD but may identify individuals who fail their renal "stress test" based on their limited renal reserve. Irrespective of whether AKI is simply a marker or causal of progressive kidney disease, its presence identifies a high-risk population of patients likely to have progressive kidney disease. Using AKI episodes to identify patients at high risk for kidney disease progression is appealing, as it is relatively easy to ascertain and enables therapies be to be targeted at those most likely to benefit.

In summary, AKI, previously thought to be a relatively benign process without significant long-term sequelae, has been recently identified as a long-term risk factor for CKD, ESRD, and mortality. This knowledge leads—as scientific findings always do—to more questions. For example, is it now possible to classify an entire subset of CKD as due to AKI? Given that AKI is a strong marker of individuals who will have future episodes of AKI and ESRD and will die, should patients with a single AKI episode be systematically followed by a nephrologist?

Disclosures

None.

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See related article, "Acute Kidney Injury Episodes and Chronic Kidney Disease Risk in Diabetes Mellitus," on pages 2567–2572.

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