Acute Kidney Injury: Gateway to Chronic Kidney Disease

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Abstract
This review examines the evidence linking acute kidney injury (AKI) with the risk of subsequently developing chronic kidney disease (CKD). The discussion focuses on subjects that recover from an episode of AKI, most of whom do not receive follow-up nephrology care. Many recent studies have shown a strong association between AKI and the risk of developing CKD. Preclinical models provide evidence for a causal link between AKI and CKD while also proposing some of the potential mechanisms for this progression. Large observational studies have begun to quantify the risk for CKD following AKI recovery and identify risk factors for the development of CKD. In summary, there is an association between AKI with incomplete recovery or lack of recovery and CKD. Multiple studies now suggest that even AKI with apparent full recovery confers an independent risk for later development of CKD. Severity of AKI, baseline CKD, and multiple episodes of AKI remain consistent risk factors for CKD after AKI. The proposed risk prediction models that have been developed require further refinement and validation. The identification of patients with AKI recovery who are at high risk for later CKD development remains an important clinical and research goal.

Introduction
Acute kidney injury (AKI) occurs in up to 20% of patients admitted to hospital and results in significant morbidity and mortality [1]. The upfront poor outcomes include in-hospital mortality rates exceeding 50% in critically ill patients requiring renal replacement therapy [1]. Amongst the survivors of an episode of AKI, there is an increasing understanding of long-term consequences that may include an increased mortality risk, the development of chronic kidney disease (CKD), and the progression from CKD to end-stage renal disease (ESRD) [2, 3].

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Incomplete recovery from a severe episode of AKI is a well-recognized pathway to persistent and progressive CKD. Interestingly, more recent studies have demonstrated that even apparent complete recovery from AKI is associated with a subsequent risk for CKD development [3]. This has emerged as an important area for investigation because the majority of these patients will not receive follow-up care with a nephrologist, and there remains significant room for improvement in the care of this population [3].

In this review, we explore the current literature describing the relationship between AKI and the subsequent risk of developing CKD, focusing on the development of de novo CKD following apparent full recovery from AKI. In addition, we will discuss potential opportunities to identify the predictors of progression to CKD after AKI.

Evidence Linking AKI and CKD

Observational Studies

The clearest connection linking AKI to CKD is the scenario whereby severe AKI requiring renal replacement therapy is associated with the lack of renal recovery to dialysis independence and thus results directly in ESRD. The United States Renal Data System discloses that 2–3% of incident ESRD patients in the US have acute tubular necrosis (ATN) as the primary etiology for renal failure, and this percentage rises when considering other separately coded forms of AKI [3]. Partial but incomplete recovery from AKI, resulting in residual CKD, is another well-recognized pattern of CKD development following AKI, with some studies reporting that over half of AKI survivors without preexisting CKD fail to recover to baseline renal function [4]. In these clinical scenarios, the injury likely leads to a critical loss of nephron mass that exceeds the regenerative capability of the kidney to fully recover.

Pediatric studies shed further light on the link between AKI and later development of CKD. In a meta-analysis of studies examining patients with the hemolytic-uremic syndrome, Garg et al. [5] found that 25% of survivors suffered long-term renal complications (CKD, hypertension, or proteinuria). Mammen et al. [6], in one of the largest prospective pediatric AKI studies to date, followed a cohort of pediatric intensive care unit patients with AKI (any stage) and found that only 1 of 126 patients had CKD (estimated glomerular filtration rate, eGFR, <60 ml/min/1.73 m²) at the first follow-up after discharge. However, during the follow-up period of 1–3 years, 10.3% of the cohort developed CKD and 46.8% of patients were considered at risk for CKD based on the development of hypertension, microalbuminuria, or mildly decreased eGFR (60–90 ml/min/1.73 m²).

Dose-Response Observations

A fundamental question regarding AKI and the subsequent risk for CKD is whether AKI causes CKD, or whether this simply represents an associative relationship. Although not definitive, the observation of a biologic gradient – in this case a higher risk for developing CKD with increasing AKI severity – lends support to the former.

A recent study found that, among 20,263 patients without preexisting CKD undergoing cardiac surgery, the risk for incident CKD rose progressively with each increasing category of postoperative creatinine rise. The magnitude of the risk peaked 3 months postoperatively, but the trend remained significant even 5 years later [7]. Thakar et al. [8] used a Veteran’s dataset of over 3,600 diabetic patients to examine the effect of repeated episodes of AKI on the risk of developing CKD stage 4. Patients with any episode of AKI were significantly more likely to develop CKD stage 4 than patients without AKI (hazard ratio, HR, 3.56, 95% confidence interval, CI, 2.76–4.61). In patients with repeated episodes of AKI, each additional AKI event resulted in a doubling of the CKD risk (HR 2.02, 95% CI 1.78–2.30). Another study in the VA population developed clinical prediction models to estimate the risk of CKD stage 4 following AKI, and risk again correlated with AKI severity: each additional episode of AKI increased the risk for developing CKD stage 4 from 1 to 5 years after hospitalization, and an inpatient dialysis requirement increased this likelihood 500 times [9].

Estimating the Risk of CKD following AKI

Several important limitations to the current literature are worth noting: significant heterogeneity in patient populations; lack of uniform AKI definitions and classification, and variable duration of follow-up. Establishing risk estimates for CKD after AKI is further complicated by the inherent delay between AKI recovery and CKD development, which allows for potential interval confounding risk factors for CKD [10]. Despite these limitations, an increased long-term risk for CKD...
development after AKI has been consistently demonstrated in several large studies (table 1), and the development of risk prediction models is an important focus of research.

Wald et al. [11] examined outcomes among 3,769 adult patients with dialysis-requiring AKI who recovered to dialysis independence for at least 30 days following hospitalization. Compared to matched controls, after a median 3-year follow-up interval, the AKI group had a >3 times higher risk of developing ESRD (adjusted HR 3.23, 95% CI 2.70–3.86). Bucaloiu et al. [12] retrospectively evaluated 1,997 patients without preexisting CKD who developed any stage of AKI and recovered to within 90% of baseline eGFR. During a median follow-up period of 3.3 years, AKI patients were significantly more likely to develop de novo CKD stage 3 when compared to propensity-matched controls (adjusted HR 1.91, 95% CI 1.75–2.09). In another study, Jones et al. [13] examined outcomes of 719 patients without preexisting CKD who developed AKI during hospitalization and recovered to within 10% of baseline creatinine. Over a median follow-up period of 2.5 years, 108 (15%) patients developed CKD stage 3, compared to only 3% of control patients (HR 5.93, 95% CI 4.49–7.84).

Unfortunately, retrospective observational studies focus on laboratory data and are unable to clarify the clinical context of these changes, such as creatinine elevations due to medications or prerenal states. These studies can also be confounded by nonsystematic data collection that may be biased by testing indication. Conversely, prospective clinical trials offer the opportunity to study patients with a confirmed clinical syndrome of AKI that are followed in a uniform manner, but, unfortunately, to date such studies have focused on short-term outcomes such as dialysis dependence at hospital discharge [2, 3]. Large, prospective, controlled studies are needed to further delineate long-term risks following AKI.

**Predicting CKD after AKI Recovery**

Despite the increased recognition of AKI as a risk factor for CKD, there remains a paucity of data on predicting which patients will be at highest risk. Such information represents a critical gap in the current knowledge for several reasons. Firstly, no established medical therapies are proven to improve short-term prognosis in severe AKI, and therefore focus should turn to secondary prevention measures aimed at improving outcomes among AKI sur-

| Table 1. Recent studies describing the incidence of CKD after functional recovery from an episode of AKI |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| First author, year | Patient population | AKI definition and severity | Renal recovery definition | Follow-up, years | Incidence of CKD | Comments |
| Wald [11], 2009 | 3,769 hospitalized adults | AKI requiring dialysis | Dialysis independent for 30 days after discharge | Median 3.0 | ESRD incidence of 2.63/100 person years vs. 0.91 in controls | No data for eGFR at time of renal recovery |
| Bucaloiu [12], 2012 | 1,997 hospitalized adults | Any AKIN stage | eGFR within 90% of baseline | Median 3.3 | 28.1/1,000 person years vs. 13.1 in controls | Only 4 patients required RRT |
| Jones [13], 2012 | 719 hospitalized adults | Any AKIN stage | sCr within 10% of baseline | Median 2.5 | 15% developed CKD 3 vs. 3% of controls | Mortality did not differ between groups |
| Mammen [6], 2012 | 126 hospitalized children | Any AKIN stage | eGFR ≥60 ml/min/1.73 m² | Median 1.1 | 10.3% developed CKD 3 | No comparison group |

AKIN = AKI Network; sCr = serum creatinine.

| Table 2. Risk factors for CKD development after AKI recovery |
|------------------|------------------|
| Variable | Definition |
| AKI severity | Repetitive episodes of AKI Degree of serum creatinine rise RRT vs. no RRT |
| Demographic | Increasing age |
| Etiology of AKI | Mixed (multiple causes) vs. pure ATN |
| Biomarkers | Markers of renal recovery vs. ongoing inflammation Decreased serum albumin |

RRT = Renal replacement therapy.
vivors. Secondly, practically speaking, not all AKI patients will suffer complications and there are not enough nephrology health care resources to follow all AKI patients; the identification of patients at greatest risk for downstream complications is necessary for efficient allocation of resources. Thirdly, high-risk patients may be candidates for evolving interventions to mitigate the risk for CKD, and clinical trials of novel therapeutics will be more efficient and possibly more successful if they can target the high-risk population.

Some clinical risk factors for long-term AKI consequences have now been established (table 2), and recent investigations suggest an evolving role for biomarkers in identifying high-risk patients. Recent studies have also attempted to develop clinical prediction models. With evolving research, it is likely that future risk prediction will incorporate both clinical and biochemical risk factor evaluation [2, 3].

**Clinical Risk Factors**

As outlined above, the severity of AKI appears to correlate with the future CKD risk. A recent meta-analysis found that the odds of developing CKD rose with mild, moderate, and severe AKI when compared to no AKI (adjusted HR 2.0, 3.3 and 28.2, respectively) [14]. Although this analysis was not limited to patients who recovered renal function after AKI, patients with severe AKI are clearly at high risk for future complications. Additional factors are required to further risk stratify patients with mild or moderate AKI.

Among demographic variables, older age is a risk factor for both short- and long-term complications following AKI. In a study of 4,730 patients aged 67 years and older who developed AKI during hospitalization, the incidence of CKD within 2 years of discharge was over 70% [15]. Other studies in populations with a broader age range have also found that increasing age is a significant predictor of de novo CKD development after AKI recovery [2].

The etiology of AKI may be another important determinant of long-term renal sequelae. Amdur et al. [16] used the VA database to compare patients with AKI to those given a specific diagnosis of ATN, and found that the ATN group was significantly more likely to develop CKD stage 4 (20.0 vs. 13.2%, p < 0.01). In another study, Schiff and Fischer [17] examined 425 patients with ATN and classified them as either pure (single cause, such as ischemia) or mixed (multiple causes). Over 7 years of follow-up, the mixed ATN cohort had a significantly higher incidence of CKD (38 vs. 5%). At present, the vast majority of studies in AKI patients do not attempt to differentiate between underlying causes, and additional studies are needed to confirm and further elucidate these findings.

**Role of Biomarkers**

Biomarkers continue to emerge as important diagnostic tools for earlier detection of AKI compared to the traditional standard of serum creatinine. Yet the role of biomarkers in clinical decision making remains ill-defined, with a lack of studies demonstrating benefits in clinical outcomes [2]. Nearly all AKI biomarker studies have focused on short-term outcomes and additional studies are needed to determine which biomarkers (if any) may be helpful in the identification of patients with AKI that are at risk for progressing to CKD. However, recent studies suggest some promise in that regard.

In a substudy of the VA/NIH Acute Renal Failure Trial Network study, Srisawat et al. [18] evaluated the ability of several different biomarkers to predict renal recovery, which was defined as dialysis independence 60 days following dialysis initiation. Individually, biomarkers tested were not strongly predictive. However, when combined with a clinical model, the use of a biomarker panel was able to predict renal recovery with an area under the receiver-operating characteristic curve as high as 0.94. Additional biomarker studies focusing on the outcome of renal recovery are currently underway, and the potential role of biomarkers is expected to evolve in the next few years.

**Predictive Models**

A recent study using the VA database sought to develop predictive models for the progression to CKD following AKI. Three different equations were developed, with model variables including age, albumin, diabetes mellitus, and severity of AKI [9]. When applied to a test population, the models performed well with ‘c’ statistic values of 0.81–0.82. Further validation of this equation in more heterogeneous populations is required. However, it is worth noting that other studies have identified similar variables as predictors for CKD after AKI.

**Recent Developments and Future Directions**

Recent in vitro studies have replicated the risk for CKD development following AKI in animal models and shed some light on potential underlying mechanisms. These include loss of renal vascular support for tubular...
regeneration, persistent interstitial inflammation and pathophysiologic changes such as salt-sensitive hypertension [3]. Excitingly, recent studies in animal models targeting some of these mechanisms have demonstrated the ability to attenuate the risk for renal damage after AKI [3, 19]. These studies require additional confirmation, and to date there have not been any such interventional studies in humans. However, these studies provide the groundwork for potential future clinical trials.

Conclusion

AKI remains a common occurrence among hospitalized patients and is associated with a significant increase in mortality. Survivors face an increased risk for long-term complications including both mortality and renal sequelae. AKI, even with apparent recovery, has now been established as an important risk factor for the subsequent development of de novo CKD. An important research target remains the identification of high-risk patients, so that proper follow-up and secondary prevention measures may be implemented or studied. AKI severity appears to be a strong predictor of the future CKD risk, and biomarkers may evolve to further assist in risk stratification. Finally, recent studies have begun to explore some of the underlying mechanisms for CKD development after AKI, raising the possibility for therapeutic interventions to mitigate the CKD risk in the future. Despite much progress and increased recognition in this area, there remains great opportunity to improve the outcome in this patient population.

Disclosure Statement

The authors have no relevant conflicts of interest to declare.