Clinical Determinants of Renal Recovery

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Key Words

Acute kidney injury · Clinical markers · Renal recovery · Renal replacement therapy

Abstract

Acute kidney injury (AKI) is associated with increased mortality, prolonged hospitalization, and renal replacement therapy. Until recently, it was believed that the vast majority of patients recover from AKI without subsequent consequences. It is now recognized that patients with AKI may have very different renal outcomes, including complete recovery, incipient and progressive chronic kidney disease, and end-stage renal disease. Factors that influence these different outcomes have not been thoroughly evaluated and so are not currently understood. The patient's baseline demographic characteristics, subsequent clinical evolution, and factors associated with the treatment of these patients may all influence global and renal outcomes. Recovery from AKI is a potentially modifiable event and should be targeted for therapy. Useful tools are needed to monitor renal recovery and identify the patients at high risk for adverse outcomes.

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Introduction

Many studies have identified the increased mortality risk associated with acute kidney injury (AKI), but very little is still known regarding the factors influencing renal recovery in surviving patients. During the 1970s, acute tubular necrosis requiring dialysis was a reversible process in the vast majority of patient who survived: only 3% of patients remained dialysis dependent after hospital discharge [1]. More recent studies show that as many as 33% of patients fail to be independent of dialysis after AKI [2–4]. This may be due to the changing pathogenesis of multifactorial AKI. Critically ill older patients with more comorbid diseases are now surviving more severe insults, including pharmacologic, hemodynamic, and complex surgical interventions as well as sepsis. Additionally, de novo chronic kidney disease (CKD) and CKD progression is increasingly being recognized following AKI,

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which may contribute to the complexity of comparing renal recovery amongst different trials [5–8]. In this article, we will review patient characteristics, clinical settings, and factors associated with the process of care that may influence the prognosis of CKD after AKI.

Determinants

Demographics

Many patient risk factors have been identified for the development of AKI but their impact on renal recovery has only been evaluated in a small number of studies. The patient's baseline characteristics may influence their renal outcome. Advanced age, independent of comorbid disease, is associated with a lower level of renal recovery, presumably due to the already decreasing renal function reserve observed in this population [9–11]. Ishani et al. [6] evaluated the risk of end-stage renal disease (ESRD) in a Medicare random sample of over 200,000 AKI patients >67 years old; compared to patients without AKI, they found their risk to be significantly increased, especially in patients with previously decreased renal function.

Preexisting CKD is an important factor for the prediction of renal recovery. In a study by Pannu et al. [12], lower baseline glomerular filtration rate (GFR) before AKI (especially <30 ml/min) was associated with more severe ESRD and dialysis requirement after hospital discharge. In an analysis by Hsu et al. [13], hospitalized patients who experienced AKI on CKD (baseline GFR <45 ml/min) had an increased risk of ESRD within 1 month after discharge compared to CKD patients without AKI. A recent meta-analysis by Coca et al. [14] identified AKI as an independent risk factor for CKD, ESRD, and death. In a study comparing continuous and intermittent renal replacement therapies (RRT), baseline GFR was found to be the only predictor of renal recovery [15]. However, not all studies have demonstrated an association between CKD and lower renal recovery after AKI. In a subanalysis of the Acute Renal Failure Trial Network, Srisawat et al. [11] did not find baseline serum creatinine and urine output at termination of dialysis to be predictive of renal recovery, but it must be noted that CKD stages 4 and 5 were excluded from this trial.

Diabetes is a well-defined risk factor for AKI and CKD. In a longitudinal follow-up study in over 4,000 diabetics from a Veterans Affairs Medicare system, Thakar et al. [16] noted that patients hospitalized for AKI had a significantly higher risk of progression to CKD stage 4 than patients without an AKI episode, regardless of baseline

GFR. Other factors found to be predictors of progression included an increased baseline serum creatinine, hypertension, and proteinuria.

The patient's general comorbidity burden is also associated with impaired renal recovery. In a subset of patients from the Acute Renal Failure Trial Network, the Charlson comorbidity index score was independently predictive of poor renal recovery and particularly when combined with patient age [11]. In a retrospective propensity score-matched cohort, Bucaloiu et al. [8] identified increasing age, Charlson comorbidity index score, baseline hypoalbuminemia, congestive heart failure, and hypertension to be associated with a higher risk of CKD following AKI [8]. Although obesity is commonly identified as a risk factor for CKD, it is also associated with an increased risk of postsurgical AKI [17, 18]. In a trial by Druml et al. [19], the mortality risk attributed to AKI seems to be reduced in obese patients, but the relationship between obesity and renal recovery remains to be clarified. Additionally, the impact on renal recovery from other demographic risk factors for AKI, such as male gender and African-American ethnicity, needs to be evaluated in future studies.

Clinical Features

The patient's clinical presentation and course leading to AKI may influence renal recovery. Oliguria is a sensitive and early marker of AKI associated with increased mortality [20, 21]. Limited data are available on its prognostic value for renal recovery. In a post hoc analysis of the Beginning and Ending Supportive Therapy for the Kidney study, urine output at termination of dialysis was predictive of freedom from dialysis at hospital discharge, especially when this was accomplished without diuretics [22, 23]. Whether this is a reflection of the severity of disease or an independent risk factor and the underlying mechanisms remain to be evaluated further.

Procedures and medications may also influence renal prognosis. Adult respiratory distress syndrome, ventilator support, and requirement for antibiotics have been associated with reduced recovery of renal function in critically ill AKI patients requiring dialysis [24]. These factors may represent a general assessment of severity of critical disease rather than independent risk factors for poor renal recovery and need to be further evaluated. On the other hand, nutritional support may offer positive renal effects. In a 2012 Cochrane Database Systematic Review, intravenous essential L-amino acids were associated with

Table 1. List of clinical determinants implicated in renal recovery

Baseline demographics	Clinical features	Process-of-care factors
Increasing age [4, 6, 9–11]	Oliguria [22]	Delay before antibiotics [43]
CKD [12, 13, 15, 16, 22]	Anemia ^a	Fluid overload [23, 44]
Diabetes [16]	Hypotension severity and duration [35–38]	Mechanical ventilation [24]
Hypertension [8, 16]	General severity index scores [11, 39]	Lack of nutritional support [25]
Proteinuria [16]	Timing of AKI [40] ^b	RRT dose [26–28] ^b
Charlson comorbidity index [8, 11]	Underlying cause of AKI [5, 41]	RRT modality [29]
Hypoalbuminemia [8]	Severity of AKI [34]	Late or no nephrology involvement [30]
Congestive heart failure [8]	Duration of AKI [42]	
Obesity ^a		
Male ^a		
African-American ^a		

^a Factors that have been associated with AKI but not studied for renal recovery.

^b No significant difference in renal recovery rate in available studies.

a significantly increased recovery rate for AKI and survival in dialyzed patients compared to hypertonic glucose alone [25]. These studies have not been repeated in recent years with current standards for nutritional support.

Trials comparing RRT dose have failed to demonstrate a significant relationship between RRT dose and survival or renal recovery [26–28]. A recent meta-analysis comparing the effects of different RRT modalities on renal recovery have demonstrated a favorable effect of continuous therapies compared to intermittent therapies on the likelihood of renal recovery. However, this effect was mainly driven by observational studies, and the signal was lost when evaluating only randomized controlled trials. It is noteworthy to mention that in the pooled analysis, patients who received intermittent therapy appeared to be less severely ill, required less vasopressors or mechanical ventilation, and had a lower percentage of CKD. This suggests that there might be a positive effect of continuous modalities on renal outcomes, but has yet to be firmly established in a randomized controlled trial [29]. The influence of RRT on renal recovery will be further discussed extensively in another article of this issue.

Early nephrology consultation for hospital-acquired AKI has been associated with reduced need for RRT, mortality, and length of hospital stay. In a retrospective study by Meier et al. [30], non-critically ill patients with no or late (>5 days) referrals in nephrology for hospital-acquired AKI had lower rates of partial and complete recovery compared to the early nephrology referral groups. This may be explained by the early identification and intervention on modifiable patient risk factors, such as suspension of nephrotoxic medication or prevention of fluid overload [31].

Patterns of Renal Recovery

The time to renal recovery following an AKI insult is often influenced by several factors, including exposure to multiple insults. In a retrospective study by Swaminathan et al. [32], amongst all the different variables tested to define renal recovery, the percent decrease in creatinine 24 h after its peak value was found to be the most strongly associated with survival and magnitude of recovery for all stages for AKI.

Time to improvement should be further evaluated in future studies as a modifiable factor for influencing recovery from other outcomes associated with AKI. The renal prognosis after AKI can be very different from one patient to another. Even complete renal recovery can be followed by incipient or accelerated CKD. Partial and non-recovery are associated with both progression of CKD and ESRD. Risk factors for the development of CKD after AKI recovery are increasing patient age, AKI severity and frequency, and acute tubular necrosis, as opposed to other AKI etiologies [33]. A predictive model including age, diabetes, albumin, and AKI severity has been described to identify patients at risk of CKD after recovery from AKI [34]. Further validation of this model in heterogeneous populations is needed.

Conclusion

Recovery from AKI is a potentially modifiable event and should be targeted for therapy. Some factors associated with lower rates of recovery cannot be modified,

such as advanced age, diabetes, preexisting CKD, and overall comorbidities (table 1). Efforts should be made to identify possible clinical and therapeutic factors on which we may intervene to positively influence renal outcomes, such as prevention of hypotension and anemia, early antibiotic use in sepsis, avoidance of fluid overload, prompt nephrology consultation for AKI, and prevention of subsequent episodes of AKI. Serum creatinine remains an imperfect marker for both the diagnosis of AKI and renal

recovery. An early rapid decrease in creatinine is associated with an increased likelihood of renal recovery and better survival. Evaluations of newer biomarkers are still trying to identify and validate normal pathological levels before being able to eventually predict renal recovery. An integrated approach using many of the clinical factors mentioned should be used to identify these targets of therapy and modify renal and patient outcomes.

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