Recovery from Acute Kidney Injury: Determinants and Predictors

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Abstract

Predicting recovery of renal function following acute kidney injury (AKI) is one of the top ten questions in the field of AKI research. Accurate prediction would help physicians distinguish patients with poor renal prognosis in whom further therapy is likely to be futile from those who are likely to have good renal prognosis. Proper stratification of patients with AKI is also critical to design clinical trials to target patients with poor prognosis. Unfortunately, current general clinical severity scores (APACHE, SOFA, etc.) and AKI-specific severity scores (Mehta’s score, Liano’s score, Chertow’s score, etc.) are not the good predictors of renal recovery. Recent progress on the pathophysiology of renal injury and recovery is encouraging. Repopulation of surviving renal tubular epithelial cell with the assistance of certain renal epithelial cell and specific growth factors such as neutrophil gelatinase-associated lipocalin (NGAL), hepatocyte growth factor (HGF), epidermal growth factor, and insulin-like growth factor-I, etc., play a major role in the recovery process. Such findings provide a great opportunity to test and validate these potential biomarkers as candidate markers of renal recovery. This review will describe the current understanding of the renal recovery process, and the role of clinical severity scores and novel biomarkers such as NGAL, HGF, and cystatin C in predicting renal recovery.

The prevalence of renal recovery varies by the definition and the study population (ICU vs. non-ICU). Results from the Beginning and Ending Supportive Therapy (BEST) Kidney Study group, a large multicenter, multinational,
prospective observational study in critically ill patients, showed that 13.8% of surviving patients with AKI requiring renal replacement therapy (RRT) still required it at hospital discharge [1]. A recent, large multicenter clinical trial of intensive versus less intensive renal support for patients with acute kidney injury (AKI) found that only 16% of patients did not require RRT at discharge to home. Moreover, only 25% of the alive participants were dialysis-independent on day 60 and there was no difference between the two treatment strategies in terms of renal recovery [2]. Non-recovery of renal function can have tremendous negative effects on the quality of life and healthcare costs. Therefore, treatments that hasten renal recovery or shorten the duration of AKI are eagerly sought off.

Currently there are no effective treatment strategies to improve renal recovery and one of the most important barriers has been the inability to risk-stratify patients in terms of risk for non-recovery of renal function. During the past few years, several novel urine biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and kidney injury molecule-1 (KIM-1) which represent tubular epithelial cell damage, have been proposed and studied for early diagnosis of AKI in various settings (post-cardiac surgery, post-transplant, contrast administration, and sepsis). Hopefully, the emergence of these novel biomarkers will be useful to predict renal recovery. For example, we have preliminarily shown that plasma NGAL can predict recovery after sepsis-induced AKI with an area under the ROC curve of 0.74 [3].

**Why We Need to Predict Recovery of Renal Function?**

Evidence from the epidemiological study has pointed out that AKI is an important risk factor for ESRD. The ability to predict renal recovery could help identify high-risk patients and possibly lead to the start of specific interventions such as angiotensin-converting enzyme inhibitors. Furthermore, this information will help to determine the duration of follow-up (longer time follow-up in patients who have high risk of chronic kidney disease after AKI). Identifying poor prognosis patients can also help to target the patients who will receive the most benefit from early RRT (fig. 1). We have summarized the benefits of understanding and predicting renal recovery in table 1.

**Physiology of Renal Recovery**

The pathophysiology of AKI appears to involve a complex interplay between tubular injury, renal hemodynamics, and inflammation. After the acute insult to tubular epithelial cells, there are three main types of cells which contribute to
renal repair: surviving renal tubular epithelial cells, renal specific stem cells, and mesenchymal stem cells. Most of the current evidence indicates that surviving renal proximal tubular epithelial cells (RPTCs) play a major role in the repair process and appear to follow a program which shares a number of similarities with the series of events observed during kidney development. RPTCs first appear to undergo dedifferentiation (i.e., loss of apical-basal polarity, lack of tight junctions, accompanied with a decrease in the expression of epithelial cell marker such as N-cadherin, E-cadherin, ZO-1 and an increase in the expression of mesenchymal cell or fibroblast markers such as vimentin, \( \alpha \)-SMA, FSP1), and then proliferation. When the cell population has expanded sufficiently to physically replenish sloughed epithelium, cells undergo a redifferentiation process characterized by a decrease in mesenchymal cell markers and increase in epithelial cell markers to finally restore the physiologic function of RPTCs [4].
A number of growth factors such as the hepatocyte growth factor (HGF), epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), bone morphogenetic protein-7 (BMP-7), and the transforming growth factor-β (TGF-β) help renal repair in the process of dedifferentiation by interaction with the transmembrane receptors of the tubular epithelial cells. The consequence of this interaction leads to the induction of a number of signaling pathways including mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3-K), JAK/STAT and wnt/β-catenin pathway. The important effect of these signaling pathways and appropriate activation or inhibition causes migration of the dedifferentiated tubular epithelial cell to the injury area, cellular proliferation, promoting adhesion of tubular cells to the basement membrane (prevent cellular sloughing), anti-apoptosis, and anti-fibrotic effects in the late phase of recovery [5] (fig. 2).

Ultimately, the renal repair process requires redifferentiation of transformed renal epithelial cell function to restore tubular morphology. Evidence from in vitro studies showed HGF stimulated tubulogenesis by extending spindle-shaped fibroblasts and subsequently these cells regained apicobasolateral polarization and lumen formation by the expression of matrix metalloproteinase (MMP)-13. In addition, during the initial phase of renal injury, there is a loss of tubular epithelial cell polarity and the mislocalization of Na⁺/K⁺-ATPase from the basolateral surface to the apical surface.

Renal hemodynamic derangement also plays an important role in the pathophysiology of AKI. In a constitutive state, the endothelium regulates
migration of inflammatory cells to the areas of injury via upregulating adhesion molecules such as L-selectin and E-selectin, and increasing vascular tone/permeability, and prevention of coagulation. Upon injury, the endothelium loses its ability to regulate these functions and subsequently its influence on renal function [6]. However, currently, we still do not know the specific mechanisms of endothelial repair and recovery.

**Defining Renal Recovery**

Before discussing the clinical predictors of renal recovery, we need to understand the definition of renal recovery. In 2004, the Acute Dialysis Quality Initiative (ADQI) proposed the following definition of renal recovery: ‘complete renal recovery’ was defined as return to pre-morbid renal function, and ‘partial renal recovery’ was defined as a change in RIFLE classification (R, I, or F) but not requiring RRT’. Non-recovery was therefore defined as persistent requirement of RRT, or no change in RIFLE score during hospitalization. Most of the studies evaluating AKI non-recovery have studied only patients receiving RRT. Therefore, AKI non-recovery was only defined as patients who are alive and dialysis-dependent. However, patients who die while still on dialysis should also be considered as AKI non-recovery.

The optimal duration of follow-up for patients with AKI needs to be defined. Some studies assessed the outcome 30, 60 or 90 days after hospital discharge. The consensus from the second ADQI conference suggests using from 60 to 90 days of follow-up for the evaluation of all-cause mortality. Finally, in the case of patients who survive AKI but still have impairment of renal function, which parameter should be assessed to define renal function? Serum creatinine might not be a good marker to use due to the decreasing of muscle mass after the severe illness and other confounding factors. Therefore, the measurement of glomerular filtration rate by radioisotope clearance might be an alternative.

In summary, renal recovery could be defined as complete or partial recovery based on returning of renal function, while non-recovery should include patients who do not survive or who require chronic dialysis. However, we still need further studies to find out the optimal time point to assess the AKI outcome.

**Clinical Predictors of Renal Recovery**

One of the current tools for predicting renal recovery is the clinical severity scores. We can classify severity scores into two types: general illness severity scores and AKI-specific severity scores. Acute Physiology and Chronic
Health Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS), Mortality Probability Model (MPM), Logistic Organ Dysfunction Score (LODS), Multiple Organ Dysfunction Score (MODS), and Sequential Organ Failure Assessment (SOFA) are the examples of current general illness clinical severity scores which are widely used, while AKI-specific scores include the SHARF-II score and scores proposed by Mehta, Liano, Chertow and Paganini. Recently, Uchino et al. [7] tested two general illness severity scores (APACHE II and SOFA), and four AKI-specific severity scores in 1,742 patients as part of the BEST Kidney Study. Unfortunately, none of these scoring systems tested had a high level of discrimination or calibration to predict outcome for AKI patients.

Thus, although not specifically tested, it seems unlikely that any of the current severity scores can provide good prediction for renal recovery. A more complete prediction model should include both mortality and non-mortality renal outcomes such as persistent AKI or dialysis requirement. Although factors such as advanced age, male gender, presence of sepsis/septic shock, oliguria, hypotension, respiratory failure, use of mechanical ventilation, presence of oliguria, septic shock, and high serum bilirubin, low serum creatinine, using vasoactive substances are risk factors for AKI, we do not have a study that is directly designed to identify the factors associated with renal recovery. Moreover, limitations of previous AKI-specific severity scores such as the fact that most of them were single-center designs and involved less than 700 patients makes them less generalizable. Therefore, study designs for the future should be multicentered and include a large cohort of patients.

**Novel Biomarkers for Predicting Renal Recovery**

Based on the physiology of renal recovery, a number of biomarkers have the potential to predict renal recovery.

**Neutrophil Gelatinase-Associated Lipocalin (NGAL)**

NGAL is one of the biomarkers which was extensively studied in the field of AKI. We still do not know the exact origin of urinary NGAL. Does it originate from systemic circulation, or is it locally synthesized by injured tubular epithelial cell, or is it from infiltrating inflammatory cells? In the late phase of AKI, NGAL however plays a role as a growth and differentiation factor for restoring tubular epithelial function with the assistance of siderophore-iron complexes. However, most of the previous studies have tested plasma/urine NGAL as a marker for early diagnosis of AKI, and only a few studies which have tried to test a plasma/urine NGAL as a prognosticate marker of clinical outcome. In the setting of post-cardiac surgery, Wagener et al. [8], Koyner et al. [9] and Bennett et al. [10] have reported that urinary NGAL at the cut-points 190, 150, and 480
ng/ml, respectively, have the sensitivity/specificity of about 81.3/42.9, 100/93.85, and 75/50%, respectively, for predicting in-hospital mortality. In a recent study, Cruz et al. [11] studied critically ill patients and found plasma NGAL at the cut-point of 150 ng/ml which had a sensitivity and specificity 59.6 and 67.5%. However, the number of patients who reached the end-point (mortality) from these studies was relatively small.

**Hepatocyte Growth Factor**

HGF has been demonstrated to have multipotent effects in the kidney including mitogenic, morphogenic, and differentiating effects. In animal models of toxic and ischemic ATN, HGF therapy markedly accelerated renal recovery. However, there is only a small single-center study which demonstrated upregulation of urinary HGF during the acute phase of AKI and a gradual decline with recovering from AKI [12].

**Cystatin C**

Cystatin C is a non-glycosylated 13-kDa basic protein which is a member of the cystatin superfamily of cysteine protease inhibitors, regularly produced by all nucleated cells, freely filtered at the glomerulus, 100% reabsorbed at proximal tubule via megalin-mediated endocytosis, and catabolized. Therefore, it is not normally found in urine. Ketamura et al. [13] found that overexpression of cystatin C can increase the MHC class II expression and T-cell response via suppression of cathepsin activity. In the serum, cystatin C is moderately useful for predicting the RRT requirement (AUC = 0.76) but it was minimally useful for predicting death (AUC = 0.62) [14]. In urine, Herget-Rosenthal et al. [15] showed cystatin C, α-microglobulin, retinal-binding protein, and N-acetyl-β-d-glucosaminidase are the good biomarkers for predicting the RRT requirement which had AUC = 0.92, 0.86, and 0.80, respectively. Moreover, N-acetyl-β-d-glucosaminidase was also a good marker for predicting composite outcome of death or for predicting the RRT requirement (AUC = 0.71). Unfortunately, the accuracy of these biomarkers to predict recovery in patients with established AKI was not tested.

**Conclusions**

Understanding renal recovery is one of the essential parts in improving the outcome of AKI. Unfortunately, the existing clinical risk prediction for renal recovery is limited, at best. Recent knowledge of renal recovery with the emergence of novel biomarkers could be one of the new prognostic tools to solve this issue, but further work is needed to establish reliable test characteristics.
References


