Recovery from Acute Kidney Injury: The Role of Biomarkers

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Introduction

Substantive progress in the diagnosis of acute kidney injury (AKI) and in identifying its prognosis has followed the development of consensus definitions of AKI and AKI severity, culminating in the current Kidney Disease: Improving Global Outcomes (KDIGO) definitions [1]. However, there has been little systematic effort in defining recovery or in identifying biomarkers predictive of recovery in subjects experiencing AKI. Distinct phases of ischemia-reperfusion AKI have been postulated, but recent evidence suggests AKI is simply a continuum of injury with low levels of damage biomarkers in the prerenal phase, which increase with increasing severity of injury [2].

Examination of consensus definitions highlights that recovery can be defined as a reduction in severity stage. However, in AKI requiring dialysis, recovery has usually been defined simply as becoming dialysis independent [3]. Early reports evaluating hospital or intensive care unit (ICU) discharge of patients who had received intermittent hemodialysis suggested that approximately 30% remained dialysis dependent; later studies, usually fol-
lowing continuous dialysis therapies, suggested only approximately 5% became permanently dialysis dependent and identified chronic kidney disease (CKD) prior to AKI as a major risk factor for permanence [3]. A protocolized approach for defining recovery from dialysis dependence was used in the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ATN) trial; patients with a 6-hour creatinine clearance >20 ml/min were trialed off dialysis, while patients with a creatinine clearance <12 ml/min continued dialysis [4].

Failure to recover to a glomerular filtration rate >60/ml/min/1.73 m² is defined as either acute kidney disease if the duration of impairment is less than 3 months or CKD if longer [5]. Finally, persistence of renal impairment was utilized as a secondary outcome in the investigation of novel biomarker performance, as part of a composite major adverse kidney events (MAKE30, i.e. assessed 30 days following AKI diagnosis), a composite of death, dialysis, or persistence of renal dysfunction (defined by serum creatinine ≥200% of reference) at hospital discharge truncated at 30 days [6]. Thus, as graphically highlighted recently by Goldstein et al. [5], a definition of renal recovery must include the time frame of interest. While there is no formal consensus, the most relevant definition of recovery clearly depends on the stage of AKI.

Biomarkers and Recovery from AKI

Can Biomarkers Track Recovery?

Urinary and plasma biomarkers are well established in diagnosing actual or incipient AKI. An increasing number of studies have used urinary and plasma biomarkers to predict short- or long-term outcomes, including death and need for dialysis [7]. At the very least, recovery can be predicted by a low concentration or a concentration reduction in any damage biomarker that predicts mortality or dialysis need. Perhaps more exciting than a decline in markers of renal injury is the prospect of a biomarker that predicts recovery at a time when measurable changes in urine output (or glomerular filtration rate) are absent; thus, a marker correlating positively with renal ‘wellness’ would significantly guide management.

Predicting recovery from AKI in the ICU is essential. However, the ICU patient cohort is very heterogeneous in cause and duration of AKI, baseline function, and prevalent comorbidities [8]. It is easier to monitor the progress of AKI and evaluate biomarker performance when renal injury is reasonably well timed. The best clinical models with good timing are AKI following cardiopulmonary bypass surgery and renal transplantation, although both groups remain heterogeneous in adults with multiple comorbidities in the former and the often difficult differential diagnosis of nephrotoxic injury or rejection in the latter.

Recovery from AKI after Renal Transplantation

After renal transplantation, some degree of ischemic renal injury is inevitable. Delayed graft function (DGF) is defined as the need for dialysis within the 1st week after transplantation. During DGF, regimens for immunosuppression and prophylaxis against cytomegalovirus must be modified. Renal biopsy is required to exclude transplant rejection. Consequently, there has long been interest in noninvasive biomarkers of rejection and awareness that the changes in function reflected by serum creatinine (sCr), are very late markers. Currently, urinary messenger RNA profiles have performed best as markers of rejection, although no single marker is diagnostic. For example, a linear combination of mRNAs for six markers, CD3, CD105, TLR4, CD14, complement factor B, and vimentin, distinguished acute rejection from acute tubular injury with an area under the curve (AUC) of 0.92 (95% confidence interval, CI: 0.86–0.98) on receiver-operating characteristic analysis [9]. Recovery after rejection is only tracked by sCr.

The performance of the damage biomarkers interleukin(IL)-18, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule (KIM)-1 in predicting dialysis or recovery in the 1st week after renal transplantation was examined by Hall et al. [10]. DGF occurred in 34 of 91 patients. On postoperative day 1, urinary NGAL and IL-18 predicted recovery with identical AUCs, 0.82 (95% CI: 0.72–0.92). Increases in these biomarkers remained predictive of the need for dialysis on multivariate analysis after adjusting for recipient and donor age, cold ischemia time, urine output, and sCr. They also predicted graft recovery up to 3 months later.

Recovery from AKI after Cardiac Surgery

Many studies have demonstrated that urinary and plasma biomarkers predict AKI and associated poor outcomes, including longer length of hospital stay, longer intensive care unit stay, and higher risk for dialysis or death after cardiac surgery. The TRIBE-AKI consortium demonstrated in 1,219 subjects that 5% developed AKI, defined by dialysis or doubling of sCr, and that subjects with the highest quintiles of urinary IL-18 and plas-
A recent proteomic approach identified novel urinary biomarkers that could predict recovery by comparing 12 critically ill patients with early recovery (within 7 days) with 12 patients with late (after 7 days) or no recovery [15]. Analysis of the urinary proteome from day 1 of developing AKI yielded 8 candidate biomarkers. Protein quantitation by ELISA showed that insulin-like growth factor-binding protein (IGFBP)-7 and NGAL best predicted renal recovery. These observations were validated in an independent verification group of 28 patients with and 12 control patients without AKI. Both markers predicted mortality (IGFBP-7: AUC 0.68; NGAL: AUC 0.81), recovery (IGFBP-7: AUC 0.74; NGAL: AUC 0.70), and severity of AKI (IGFBP-7: AUC 0.77; NGAL: AUC 0.69), and were associated with the duration of AKI. IGFBP-7 was a more accurate predictor of renal outcome than NGAL. These results support the results from the large (n = 728) multicenter validation study of the cell cycle arrest biomarkers IGFBP-7 and tissue inhibitor of metalloproteinase (TIMP)-2 in AKI in critically ill patients (Sapphire study) [6]. IGFBP-7 and TIMP-2, both inducers of G1 cell cycle arrest, indicated moderate-to-severe AKI (KDIGO stage 2–3) within 12 h of sample collection: together with an AUC of 0.80, or 0.76 and 0.79, respectively, used alone. In addition, high values of the TIMP-2-IGFBP-7 biomarker combination doubled the risk of the composite outcome (MAKE30), which included persistence of renal dysfunction; this supports a role for this combination of biomarkers as predictors of recovery.

**Prediction of Recovery by Biomarkers of Renal Wellness**

Of the urinary biomarkers validated for the preclinical diagnosis of nephrotoxin-induced AKI, only trefoil factor 3 (TFF3), a small intestinal peptide secreted by goblet cells, which promotes survival and differentiation of epithelial cells, correlated with renal function after AKI [16]. The others, KIM-1, clusterin, osteopontin, lipocalin 2, albumin, and glutathione S-transferase, all increased during injury and then decreased with recovery (ibid). After administering carbapenem to rats, TFF3 levels decreased and then began to recover by day 4, suggesting a positive relationship of this biomarker with ‘wellness’. However, in preliminary studies in 75 patients after renal transplantation, our observations showed that TFF3 levels are high immediately after transplantation and then decline for up
to 7 days, irrespective of the presence or absence of DGF [Pianta et al., unpubl. data]. This suggests that rodent toxicity studies may not all translate to clinical ischemia-reperfusion injury.

Most of the molecules considered so far as biomarkers have been markers of renal epithelial injury. An alternative strategy for discovering wellness markers might be to look for markers of endothelial injury or dysfunction of markers of endothelial function and recovery. A hypothesis-generating study along these lines was undertaken by Yilmaz et al. [17], who examined whether the improvement in flow-mediated dilatation observed after renal transplantation might be related to changes in biomarkers of endothelial damage. The authors measured flow-mediated dilatation before and 180 days after renal transplantation in 175 subjects and also measured sTWEAK [soluble (circulating) tumor necrosis factor-like weak inducer of apoptosis], a type II transmembrane glycoprotein belonging to the tumor necrosis factor superfamily, and asymmetric dimethyl arginine, a residue of proteolysis of arginine-methylated proteins, a potent inhibitor of NO synthesis, well known to accumulate in CKD. Renal transplantation was followed by an improvement in flow-mediated dilatation. This improvement was paralleled by an increase in sTWEAK and a reduction in asymmetric dimethyl arginine after transplantation (p < 0.001 for all). Clearly, the time frame of this study (180 days) is not relevant to biomarkers needed to predict recovery after an episode of AKI. Nevertheless, the study highlights that there is at least one marker of endothelial wellness and there may be others that could be exploited to predict renal recovery.

**Conclusion**

The appropriate definition of renal recovery depends on AKI stage. Recovery should be identified as soon as possible in patients undergoing dialysis for AKI. Timing cessation of dialysis is important in clinical management, and unnecessary dialysis should be avoided since dialysis itself may be injurious to both the myocardium and kidneys, and dialysis may modify therapeutic drug levels in critically ill patients. From a broader perspective, establishing the prognosis for recovery has enormous implications which impact on clinical decision making, including consideration of withdrawal from active therapy. Increasing evidence suggests that decreasing concentrations of damage biomarkers of AKI herald functional recovery. Biomarkers of renal wellness may also become available in the future. If validated, biomarkers of recovery could become outcomes in clinical trials.

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**References**


