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Acute Kidney Injury as a Risk Factor for Transplant Graft Failure

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Abstract

Acute kidney injury (AKI) has long-term biological effects on many organ systems and high mortality. Incomplete recovery of renal function from AKI is frequently observed, particularly when AKI is superimposed on chronic kidney disease (CKD), and this situation may further facilitate the progression of CKD. Patients with severe AKI in the intensive care unit typically have several failed extrarenal organ systems, including haemodynamic instability and respiratory failure. Consistent with these observations, AKI is associated with increased rates of graft failure and mortality after non-renal transplantation. For example, AKI is a common complication of liver transplantation and is associated with reduced patient and graft survival. AKI after lung transplantation also affects the clinical outcomes. The toxicity of calcineurin inhibitors, intraoperative hypoxemia, hypoperfusion due to diuretics overuse, and the use of antibiotics may be predisposing factors that leads to AKI after lung transplantation. While delayed graft function (DGF) caused by ischemic-reperfusion injury during the early phase of kidney transplantation affects graft function, pretransplantation AKI affecting donor kidneys may not have an adverse effect on long-term outcomes. Several biomarkers, such as gelatinase-associated lipocalin, have been evaluated for predicting DGF and long-term graft function; however, additional studies are required to establish the optimal use of these biomarkers. Recent studies also indicate that AKI during in the maintenance phase of kidney transplantation, frequently associated with sepsis and/or urinary tract infection, is a significant risk factor for graft failure. In this review, we focus on the impact of AKI on non-renal and renal transplant graft survival.

Keywords: Acute kidney injury; Transplant graft survival; Sepsis; Inflammation; Delayed graft function

Introduction

Acute renal failure (ARF), now termed acute kidney injury (AKI), was previously considered a reversible disease without long-term consequences. However, several lines of evidence suggest that AKI has long-term biological effects. For example, the incomplete recovery of renal functions from AKI may be common, depending on the clinical situations. Ali and colleagues found that only 35% achieved full renal recovery in a group of patients with acute-on-chronic renal failure [1]. They also found that the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE) criteria were useful for predicting full renal recovery, dialysis requirement, length of hospitalisation, and in-hospital mortality. Ishani and colleagues found that elderly individuals with AKI, particularly those previously diagnosed with chronic kidney disease (CKD), were at a significantly increased risk for end-stage renal disease (ESRD) [2]. These findings suggest that episodes of AKI may be a risk factor for the progression of renal disease. Lafrance and Miller found that AKI is associated with an increased risk of long-term mortality. They also found that long-term mortality risk was highest for the most severe cases of AKI [3].

In patients hospitalised with a primary diagnosis of AKI in the Department of Veterans Affairs Healthcare System, Chawla and colleagues similarly observed that the patients with AKI who required dialysis and then recovered were at particularly high risk for progression to CKD [4]. The mechanistic link between the occurrence of AKI and the progression to CKD is currently unclear. They authors proposed that the following measures may be important for reducing the risk of progression to advanced CKD: (1) regular follow up to detect reversible causes of renal ischaemia, (2) rigorous control of blood pressure, and (3) avoidance of nephrotoxic medications [4].

Importantly, recent studies suggest that AKI may be associated with graft failure after non-renal and renal transplantation. In this review, we focus on the impact of AKI on transplant graft survival.

Effects of AKI on Graft Survival in Non-Renal Transplantation

ARF is associated with extrarenal organ system failure in the majority of patients in the intensive care unit (ICU). Mehta and colleagues collected clinical data from critically ill patients from five academic medical centres in the United States [5]. They found that over half of patients with ARF in the ICU required dialysis and showed significant haemodynamic instability. Notably, these patients usually had three or four failed organ systems. Among these complications, respiratory failure was common among ARF patients at all sites. By contrast, other comorbid conditions, such as cardiovascular diseases, liver diseases and immunosuppression varied widely by site [5].

Accordingly, it is not surprising that AKI is associated with increased rates of graft failure and mortality after non-renal transplantation. For example, Parikh and colleagues found that AKI was an independent predictor of overall mortality after nonmyeloablative haematopoietic cell transplantation [6]. Barri and colleagues found that AKI following liver transplantation was associated with reduced patient and graft survival [7]. O'Riordan and colleagues also found that AKI Injury and AKI Failure, as defined by the RIFLE criteria, were common complications of orthotopic liver transplants with distinct risk factors, and AKI Failure had serious

clinical consequences [8]. Notably, Leithead and colleagues reported a progressive increase in AKI after liver transplantation, most likely because of the increasing use of high risk liver grafts [9]. Rocha and colleagues found that AKI occurred frequently after lung transplantation and affected important clinical outcomes, particularly when dialysis was required [10]. They found that the incidence of AKI was as high as 56%, and the incidence of AKI requiring dialysis was associated with an increased hazard of dying.

In addition to the toxicity of calcineurin inhibitors, several factors may be involved in the occurrence of AKI and CKD after organ transplantation. For lung transplantation, patients with respiratory failure may experience renal ischaemia [11]. Indeed, patients who developed AKI after lung transplantation were more likely to experience an episode of intraoperative hypoxemia [12]. Xue and colleagues confirmed that severe AKI increased the long-term mortality risk after lung transplantation. They also found that several variables, such as pre-transplantation mechanical ventilation and hypertension were associated with AKI after lung transplantation [13]. Furthermore, capillary leakiness after lung transplantation may lead to the overuse of diuretics, which may also facilitate renal hypoperfusion [10]. In addition to the toxicity of calcineurin inhibitors, intraoperative hypoxemia, and hypoperfusion due to diuretics overuse, the use of antibiotics may also increase the risk of AKI after organ transplantation [10].

Currently, the precise mechanism by which AKI affects graft function after non-renal transplantation remains unknown. However, one possible factor may be inflammation [14]. Consistent with this view, anti-inflammation treatment with leukocyte depletion during cardiopulmonary bypass surgery reduces renal and pulmonary dysfunction [15]. Although the lungs are very sensitive to cardiopulmonary bypass-induced systemic inflammatory response [16], the accumulated neutrophils in renal tissues may also play an important role in the development of AKI [17]. However, other anti-inflammation strategies, such as glucocorticoid administration and miniature extracorporeal circuits were found to have no positive effects on the incidence of AKI [18]. Likely, a large multicentre randomised controlled trial may be required to define the role of inflammation in the occurrence AKI after cardiac surgeries.

Effects of AKI on Graft Survival in Renal Transplantation

Kidney transplantation recipients have various risk factors for AKI, such as the immunosuppressive state, the use of calcineurin inhibitors, CKD with a single kidney, ischaemia-reperfusion injury and surgical complications, including urinary diversion [19]. Prolonged cold ischaemia time is highly associated with delayed graft function (DGF), defined as the need for dialysis within the first week after transplantation. Ojo and colleagues found a 23% increase in the risk of DGF for every 6 hr of cold ischemia [20]. In addition, the occurrence of DGF is associated with lower graft survival [20,21]. The incidence of DGF may be higher in expanded-criteria donation or donation after cardiac death than in standard-criteria donation [22-24]. Several studies has reported that machine perfusion reduces the incidence of DFG [25,26]. Gill and colleagues also found that pulsatile perfusion reduced the risk of DGF irrespective of donor type and cold ischaemia time [27]. By contrast, recent studies suggest that most of the pretransplantation AKI affecting donor kidneys may not have an adverse effect on long-term outcomes [28,29]. Farney and colleagues proposed that kidneys with AKI transplanted into selected patients can have excellent medium-term outcomes [30].

Surprisingly, however, the incidence of AKI during the maintenance phase of kidney transplantation and its impact on graft survival have remained speculative. To clarify these issues, we and others, recently examined the incidence of AKI during the maintenance phase of kidney transplantation to determine the impact of AKI on graft survival. We analysed a total of 289 living-donor transplantation recipients from a single institute in Japan, and the patients were carefully followed up primarily at the out-patient clinic for a mean duration of approximately four years [31]. The overall incidence of AKI defined by the RIFLE criteria three months or later after kidney transplantation was as high as 20.4%. We found that the AKI group as a whole (n=59) had a significantly lower graft survival rate than the non-AKI group. The AKI Risk subgroup (n=30) had significantly lower graft survival rates than the non-AKI group, and AKI Injury/Failure subgroup (n=29) had worse graft survival rates. In a univariate Cox regression model, the incidence of the AKI Risk had a hazard ratio of 2.28 for graft failure. The incidence of the AKI Injury/Failure had a higher hazard ratio of 3.95.

The median time to graft failure after the onset of AKI was 10 months. However, the individual time courses of graft survival after AKI were quite variable, suggesting the involvement of multiple factors in AKI-induced graft failure. We found that AKI was a risk factor for graft survival independent of the incidence of acute rejection. The most common aetiology of AKI was bacterial infection disease (n=27), such as urinary tract infection (n=13) and infectious colitis (n=8). This finding is consistent with a previous report that urinary tract infection is the most common cause of infection-related hospitalisation during post kidney transplantation year 1 [32]. Most likely, the immunocompromised state and urinary diversion may be responsible for the high incident rates of AKI caused by urinary tract infection. It is known that Pneumocystis jirovecii pneumonia is associated with worse outcomes of kidney transplant recipients [33]. Because of the relatively limited number of AKI patients, however, we could not determine whether the types of infection affected the outcomes.

Our study has several limitations, such as a relatively small number of recipients and a study design based on retrospective data obtained from a single centre. However, a strong point of our study is the careful follow up of recipients, enabling us to detect detailed causes of AKI. Furthermore, the recruitment of only living-donor transplantation enabled us to analyse the impact of AKI on graft survival in the absence of initial severe ischaemia-reperfusion injury.

Consistent with our findings, Mehrotra and colleagues also found that AKI was independently associated with increased loss of graft function six months or later after kidney transplantation [34]. They collected 27,232 Medicare-insured transplant recipients, consisting of both living-donor (24%) and deceased-donor (76%) transplantation. The occurrence of AKI was determined using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes from in-hospital Medicare claims files. Between six months and three years after kidney transplantation, 11.3% recipients were hospitalised with AKI. They observed a hazard ratio of 2.74 for graft failure in AKI without a requirement for dialysis. A higher hazard ratio of 7.35 was found for AKI with a requirement for dialysis. Sepsis (13.5%), myocardial infarction (14.0%), congestive heart failure (13.9%), cerebrovascular accident (0.9%) and peripheral arterial disease (2.3%) were concomitant diagnoses of AKI hospitalisation.

One limitation of this study is the use of the ICD-9-CM codes. These codes may be sensitive for the detection of dialysis-requiring AKI. However, they may not be optimal for the detection of AKI that does not require dialysis [35]. Therefore, the study by Mehrotra and colleagues may underestimate the occurrence of less severe AKI. Furthermore, the precise causes of AKI were not identified. Nevertheless, the findings of Mehrotra and colleagues [34] based on a large number of patients clearly confirmed the conclusion by Nakamura and colleagues that AKI during the maintenance phase of kidney transplantation is associated with graft failure [31]. These studies by Nakamura et al. [31] and Mehrotra et al. [34] are summarised in (Table).

	The study by Nakamura et al. [26]	**The study by Mehrotra et al. [28]**
Patient number	289	27,232
Institute	Single	Multiple
Donor type	Living only	Living (24%) and deceased (76%)
Observation period	4 years	3 years
AKI identification method	RIFLE criteria	ICD-9-CM codes
AKI occurrence rate (%)	20.4	11.3
Hazard ratio for graft failure		
[a]Mild AKI	2.28	2.74
[b]Severe AKI	3.95	7.35
[a]AKI Risk in the study by Nakamura et al., and AKI without dialysis in the study by Mehrota et al. [28]		
[b]AKI Injury/Failure in the study by Nakamura et al., and AKI with dialysis in the study by Mehrota et al. [28]		

Table: Summary of the AKI studies during the maintenance phase of kidney transplantation.

Importantly, both of these studies suggest that sepsis is an important factor in the pathogenesis of AKI during the maintenance phase of kidney transplantation. Indeed, the incidence of AKI is very high in severe sepsis and shock, resulting in high mortality [36]. Cytokines released during sepsis may cause haemodynamic instability through endothelial dysfunction [37,38]. In a mouse model of sepsis, Xu and colleagues recently found that glomerular endothelium damage by the cytokine tumour necrosis factor (TNF)-α plays a key role in the pathogenesis of sepsis-induced AKI [39]. Although anti-TNF therapies seem to be successful in animals, the effectiveness of these strategies have not been established in humans [40]. Furthermore, statin-based anti-inflammation therapy, which was once hypothesised as effective for infection/sepsis [41,42], has failed to improve the primary outcomes of sepsis-induced acute respiratory distress syndrome and the associated renal failure [43]. Additional studies are warranted to clarify the detailed pathophysiology of sepsis-induced AKI and develop more effective therapies.

DGF

As previously discussed, DGF because of ischaemia-reperfusion injury is associated with graft failure. However, serum creatinine is an unreliable indicator during the early phase after kidney transplantation, in which rapid fluctuations in graft function usually occur [19]. To overcome this problem, several biomarkers have been tested.

For example, neutrophil gelatinase-associated lipocalin (NGAL) has been identified as one of the most significantly upregulated genes in the kidney after ischaemia [44,45]. Using protocol biopsy samples obtained at one hour of reperfusion after the release of vascular clamps, Mishra and colleagues demonstrated that the NGAL staining intensity in the kidney cortex tubules was correlated with the cold ischemic time, peak post-operative serum creatinine, and dialysis requirement [46]. Bataille and colleagues found that the plasma NGAL level 12 hour after transplantation accurately predicted DGF [47]. Hollmen and colleagues found that urine NGAL was also associated with the occurrence of DGF, but the performance was less than that of the plasma NGAL [48]. By contrast, Hall and colleagues found that peritransplant urinary NGAL and interleukin (IL)-18 accurately predicted both DFG and 1-year allograft outcomes [49,50]. On the other hand, Heyne and colleagues reported that urinary NGAL was particularly sensitive to AKI induced by acute rejection during the maintenance phase of kidney transplantation [51]. Other biomarkers may be also useful for the prediction of DGF. For example, Pianta and colleagues found that both urinary clusterin and IL-18 are useful for detecting DGF [52]. Zaza and colleague found that karyopherin-mediated nuclear transport is involved in the onset and development of DGF [53]. The combination of functional and damage biomarkers may facilitate the early detection of DGF, the estimation of causes of AKI, and the more precise prediction of later graft function. Obviously, additional studies are required to establish the optimal combination of biomarkers for these goals [54]. It is also possible that biomarkers in the preservation solution of machine perfused kidneys may predict DGF. However, Hoogland and colleagues found that the diagnostic accuracy of the perfusate biomarkers to predict viability of donation after cardiac death kidneys varied from poor to fair [55].

Summary

Multiple factors, such as the toxicity of calcineurin inhibitors and the renal hypoxic injury may be responsible for the occurrence of AKI

in organ transplantation. Sepsis and/or urinary tract infection may play an important role in AKI during the maintenance phase of kidney transplantation. Several biomarkers have been tested to predict DGF and longterm kidney allograft function. However, further studies are required to improve graft survival after AKI.

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