Acute kidney injury after lung transplantation: a narrative review

Lei Jing[1,2,3,4,5,6], Wenhui Chen[2,3,4,5,6], Lijuan Guo[2,3,4,5,6], Li Zhao[2,3,4,5,6], Chaoyang Liang[2,3,4,5,6], Jingyu Chen[2,3,4,5,6], Chen Wang[1,2,3,4,5,6]

[1]Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Department of Lung Transplantation, Centre of Lung Transplantation, Centre of Respiratory Diseases, China-Japan Friendship Hospital, Beijing, China; [3]National Center for Respiratory Medicine, Beijing, China; [4]Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China; [5]National Clinical Research Center for Respiratory Diseases, Beijing, China; [6]WHO Collaborating Centre for Tobacco Cessation and Respiratory Diseases Prevention, Beijing, China

Contributions: (I) Conception and design: J Chen, C Wang, L Jing; (II) Administrative support: None; (III) Provision of study materials and patients: L Jing, W Chen; (IV) Collection and assembly of data: L Jing, L Guo, L Zhao, C Liang; (V) Data analysis and interpretation: L Guo, L Zhao, C Liang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jingyu Chen, MD. Director of the Department of Lung Transplantation, Professor of Thoracic Surgery, China-Japan Friendship Hospital, No. 2 Yinghua East Road, Chaoyang District, Beijing 100029, China. Email: chenjy@wuxiph.com; Chen Wang, MD, PhD. President of Chinese Academy of Medical Sciences and Peking Union Medical College, Director of the Centre for Lung Transplantation, Professor of Clinical Medicine, China-Japan Friendship Hospital, No. 2 Yinghua East Road, Chaoyang District, Beijing 100029, China. Email: wangchen66366@163.com.

Abstract: Acute kidney injury (AKI) is a commonly recognized complication after lung transplantation (LT) and is related to increased mortality and morbidity. With the improvement of survival after LT and the increasing number of lung transplant recipients, the detrimental impact of current management on renal function has become increasingly apparent. Multifarious risk factors in the perioperative setting contribute to the development of AKI, including the preoperative status and complications of the recipient, complex perioperative problems especially hemodynamic fluctuation, and exposure to nephrotoxic agents, mainly calcineurin inhibitors (CNIs) and antimicrobial drugs. Identification and minimization of the effects of these risk factors can relieve AKI severity and incidence in high-risk patients. Close monitoring of urine output and serum creatinine (sCr) levels and of specific biomarkers may promote early recognition of AKI and rapid nephrology intervention to improve outcomes. This review summarizes advances in the epidemiology, diagnostic criteria, biological markers of AKI, and further recommends appropriate treatment strategies for the long-term management of AKI related manifestations in lung transplant recipients. Future work will need to focus on developing more accurate measures of renal function and identifying patients before the occurrence of early renal damage. Combining renal protection strategies with the use of new biomarkers to develop early kidney risk identification and protection protocols is a promising idea that requires further investigation.

Keywords: Acute kidney injury (AKI); lung transplantation (LT); incidence; risk factors; impact and management

Introduction

Acute kidney injury (AKI), which commonly occurs following lung transplantation (LT), is a syndrome involving a rapidly dropping glomerular filtration rate (GFR) in response to acute stressors and leads to increased morbidity and mortality (1). Despite prominent improvements in medical management and lung surgery, the mortality and epidemiology of AKI after LT remain unclear. This review summarizes advances in the epidemiology, diagnostic criteria, biological markers and prevention and treatment strategies of AKI with the objective of providing a better understanding of the mechanisms that promote AKI for the optimization of monitoring and management methods to minimize this important source of morbidity and mortality.

Table 1 Staging of acute kidney injury (AKI) based on different criteria

Different criteria	Stage 1 (RIFLE risk)[†]	Stage 2 (RIFLE injury)[†]	Stage 3 (RIFLE failure)[†]	RIFLE loss[†]	RIFLE end stage[†]
RIFLE (2004) (within 7 d)	(I) sCr increase ×1.5 (II) eGFR loss >25% (III) UO <0.5 mL/kg/h for over 6 h	(I) sCr increase ×2.0 (II) eGFR loss >50% (III) UO <0.5 mL/kg/h for over 12 h	(I) sCr increase ×3.0 (II) sCr ≥4.0 mg/dL (≥354 µmol/L) (III) eGFR loss >75% (IV) Anuria for over 12 h (V) UO < 0.3 mL/kg/h for over 24 h	Persistent acute renal failure for over 4 weeks	ESRD for over 3 months
AKIN (2007) (within 48 h)	(I) sCr increase ≥0.3 mg/dL (≥26.5 µmol/L) (II) sCr increase ×1.5 (III) UO <0.5 mL/kg/h for over 6 h	(I) sCr increase ×2.0 (II) UO <0.5 mL/kg/h for over 12 h	(I) sCr increase ×3.0 (II) sCr ≥4.0 mg/dL (≥354 µmol/L) (III) Initiation of RRT (IV) Anuria for over 12 h (V) UO <0.3 mL/kg/h for over 24 h		
KDIGO (2012)	(I) sCr increase ≥0.3 mg/dL (26.5 µmol/L) within 48 h (II) sCr increase ×1.5 within 7 d (III) UO <0.5 mL/kg/h for over 6 h	(I) sCr increase ×2.0 (II) UO <0.5 mL/kg/h for over 12 h	(I) sCr increase ×3.0 (II) sCr ≥4.0 mg/dL (≥354 µmol/L) (III) Initiation of RRT (IV) Anuria for over 12 h (V) UO <0.3 mL/kg/h for over 24 h		

[†], need only 1 criterion for diagnosis. sCr, serum creatinine; UO, urine output; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; ESRD, end-stage renal disease.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7644).

Methods

This study was identified via an electronic search of PubMed database (updated to August 2020) by two authors (LJ and WC). The languages were limited to English. The search terms used were "acute kidney injury" or "renal injury" or "renal failure" or "renal dysfunction" or "kidney disease", combined with "lung transplantation". The "similar articles" function was used to broaden the search.

Reference list for selected articles were searched to get additional relevant records.

Diagnostic criteria and staging of AKI

Since 2004, the diagnostic criteria for AKI have successively evolved into the following three standards: the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria (2), the Acute Kidney Injury Network (AKIN)

criteria (3), and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (4). Among them, the RIFLE criteria do not consider the influence of age, sex and other factors on the serum creatinine (sCr) level (2), and the diagnosis time of AKI within the AKIN criteria is limited to 48 h, resulting in missed diagnoses of patients with slow changes in sCr (3). In 2012, the KDIGO criteria were issued, and these criteria not only extend the diagnosis time but also have a certain predictive value in determining the prognosis of AKI patients; therefore, these criteria have become the most widely used AKI diagnostic standard (4,5). Based on the KDIGO criteria, AKI is defined by an increase in sCr of at least 0.3 mg/dl or a 50% increase over baseline within 48 hours with or without reduced urine output (<0.5 mL/kg per hour) (6). The specific staging of AKI is shown in *Table 1*.

Incidence and mortality of AKI

Recently, AKI has been reported to be observed in 33–69% of LT patients, with 17–37% of LT patients having stage 2-3 AKI and 5–13% needing renal replacement therapy

(RRT) (7-11). The mortality rate of AKI is 16–50% and is strongly related to AKI stage, etiology and patient comorbidities (12,13).

Risk factors for AKI

Preoperative factors

Respiratory failure
Recent studies have highlighted the complexity of organ-organ interactions between the kidney and the lung. The common characteristics of lung injury and the compensatory mechanisms of injury are acidosis and blood gas disorders (14). Additionally, it has been reported that low oxygen and/or high carbohydrate levels can have an impact on renal blood flow and water and salt excretion, which contribute to renal dysfunction (15).

Right-sided heart failure
The proportion of lung transplant candidates with cor pulmonale is very high. Right ventricular congestive states and dysfunction may result in reverse effects of compensatory neurohormonal mechanisms, for example the renin-angiotensin-aldosterone system, high venous pressure and edema, and changes in kidney perfusion and oxygenation, leading to escalating doses of diuretics and renal injury (14,16). In addition, recent findings illustrate that venous hyperemia can increase intracapsular pressure through renal compartment syndrome formation, thereby reducing renal perfusion pressure and oxygen supply (17). Central venous pressure (CVP), one of the most important hemodynamic determinants of renal function deterioration, is related to increased mortality as a surrogate indicator of right ventricular injury (18).

Advanced age

A decline in kidney function is closely associated with aging, and elderly patients are more prone to AKI (19,20). As the success rate of LT has improved, an increasing number of elderly patients have become LT recipients. Due to intraoperative bleeding, the use of nephrotoxic agents, and perioperative hemodynamic instability, elderly patients have a high risk of rapid renal loss after LT (11,21).

Hypertension and diabetes mellitus

Both hypertension and diabetes mellitus are connected with a high risk of chronic kidney disease (CKD) (22-24). LT patients with pretransplant hypertension (20,25) and diabetes mellitus (8,20,26,27) have been shown to be at high risk of AKI after LT. Careful surveillance and control of blood pressure and blood glucose after transplantation are essential to prevent postoperative AKI.

Higher baseline creatinine

A study in an early entirely adult cohort indicated that a change in baseline renal function can predict the prognosis of renal outcomes after LT (21). Studies have demonstrated that recipients with a high baseline creatinine level or preexisting renal impairment have the greatest risk of rapid renal function loss and that these factors are independently associated with posttransplant AKI (7,8,11,21,26-28). Because a higher baseline creatinine level reflects potentially less "renal reserve", such patients cannot tolerate hemodynamic variation and other renal toxicity damage during or after transplantation and may predictably be at higher risk for AKI.

Preoperative mechanical ventilation (MV)

Generally, MV and intubation are requested in end-stage lung disease patients to improve gas exchange and oxygenation. However, studies have indicated that MV induces hemodynamic and neurohormonal alterations and is associated with renal water retention (14). Biological trauma resulting from injurious ventilation tactics can contribute to the migration of pro-inflammatory factors to the lung, which are then transferred to the systemic circulation, causing terminal organ dysfunction, such as AKI (14). A 3-fold increased risk of AKI has been reported in patients with acute respiratory distress syndrome (ARDS) after MV treatment (29). This indicates that ARDS and MV are both independently related to the prognosis of AKI (16,27,30), and 35–60% of patients who develop multiorgan failure after MV need RRT (31).

Extracorporeal membrane oxygenation (ECMO)

Pretransplant ECMO is demonstrated to be a clear risk factor for AKI after LT (16,26,27). The incidence of AKI in patients with ECMO has been reported to be over 70%, and approximately 50% of the patients received RRT (32). The major mechanisms may contribute to renal hypoperfusion, prolonged hypoxemia (ischemia) before ECMO and reperfusion injury after ECMO initiation,

Table 2 Risk factors contributing to acute kidney injury (AKI) after lung transplantation

Preoperative factors	Intraoperative factors	Postoperative factors
Advanced age	Bilateral lung transplantation	Volume depletion
Smoking history	Blood loss	Diuretic use
Higher baseline creatinine	Hemodynamic instability	Calcineurin inhibitors
Higher BMI	Blood transfusion	Sepsis
MV	High dose of catecholamine	Prolonged MV
ECMO	Diuretic use	Prolonged ECMO
Right-sided heart failure	Hypoxia (SpO$_2$ <90%)	Rhabdomyolysis
Diabetes mellitus	Ischemic time (>6 h)	Hemolytic uremic syndrome
Hypertension	HES volume	Acute interstitial nephritis
Pulmonary hypertension Primary disease	Aprotinin use	Thrombotic microangiopathy Rapid IVIG infusion
CF		Other nephrotoxic agents
Higher lung allocation score		
Retransplantation		
Nephrotoxic agents[§]		

§, Nephrotoxic agents include vancomycin, trimethoprim-sulfamethoxazole, aminoglycosides, polymyxin B, amphotericin, ganciclovir/valganciclovir, nonsteroidal anti-inflammatory drugs (NSAIDs), and radiocontrast dye. BMI, body mass index; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; CF, cystic fibrosis; HES, hydroxyethyl starch; IVIG, intravenous immunoglobulin.

microvascular dysfunction and endothelial damage caused by the artificial membrane contact with blood, hemodynamic fluctuations and cannula position dislocation leading to venous obstruction/arterial insufficiency (14,33). A meta-analysis conducted by Thongprayoon *et al.* showed that AKI requiring RRT while on ECMO is related to 3.7-fold increased risk of hospital mortality (34). In patients undergoing ECMO, close monitoring of kidney function is necessary because fluid overload and AKI easily develop in these patients.

Cystic fibrosis (CF)

CF has been demonstrated to be an independent factor for AKI after LT, and patients with CF tend to have preexisting renal disease prior to LT (20,35-37). The causes of renal insufficiency in patients with CF vary but include abnormal calcium metabolism, nephrotoxic drug exposure, and diabetes (38). As part of Pseudomonas aeruginosa management strategies, nephrotoxic antibiotics, such as aminoglycosides, are very commonly used in CF patients (35). In addition, approximately 80–90% of CF patients exhibit pancreatic exocrine dysfunction, and 30–50% of CF patients develop diabetes after LT (38). More than 90% of patients with CF present medullary renal calcification at autopsy, accompanied by a significantly increased incidence of urolithiasis, which may indicate primary abnormal cities in renal calcium metabolism (35,39).

Other risk factors for AKI include a smoking history (21,27,40), high body mass index (BMI) (26), high lung allocation score (16,27,41), pulmonary hypertension (PH) (16,27), retransplantation (16,27) and nephrotoxic agent exposure (7,16,35). Recipients with these risk factors before transplantation have a high risk of kidney injury after transplantation. Thus, to better protect renal function, aggressive risk factors should be modified or treated before LT whenever possible (*Table 2*).

Intraoperative factors

Type of transplant

Bilateral lung transplantation (BLT) has been reported to be another independent risk factor for AKI, with a posttransplant AKI incidence of 39–62%, which may be

due to a longer operating time, increased use of ECMO, higher bleeding risk, and increased blood transfusion rate (7,9,10,25-27,42-44). Studies have also suggested that lung surgery can induce renal epithelial apoptosis by releasing inflammatory mediators and renal hypoperfusion by generating fluid retention, further causing AKI (11).

Blood loss and hemodynamic instability

The kidney is very sensitive and has poor tolerance for hypotension and hypoxia (45). Excessive blood loss during surgery causes systemic hemodynamic instability, leading to decreased effective blood flow and renal hypoxia and even inducing necrosis of renal tubular epithelial cells. On the other hand, low renal perfusion may cause endothelial release of angiotensin and other vasoconstriction factors, which brings about a further reduction in renal blood flow and aggravation of renal ischemia (45). Numerous studies have indicated that hemodynamic instability and intraoperative blood loss are risk factors that cannot be overlooked in AKI after LT (25,42-44,46).

Blood product transfusion

Intraoperative blood transfusion has been identified as an independent risk factor for AKI (25,42,43,47), although the volume and proportions of these blood products related to AKI risk have not been determined. The reasons may be that blood transfusion is an indicator of low blood volume due to hemorrhage and renal ischemic injury and that transfusions may lead to kidney injury through over resuscitation and tissue edema accompanied by a systemic inflammatory response (45,47).

High dose of catecholamines

Vasopressor therapy remains the mainstay for maintaining blood pressure stability and tissue perfusion during LT. However, any therapy that increases the GFR increases renal oxygen consumption, potentially promoting a lack of oxygen in kidney tissue (48). Nguyen *et al.* indicated that intraoperative utilization of catecholamines elevated the risk of AKI after LT by 3-fold, even when the mean blood pressure was maintained at >65 mmHg (46). In refractory septic shock, administration of 0.5–1.0 μg/kg/min (high dose) norepinephrine was related to increased mortality, ranging from 60–100% (49,50).

Other risk factors for intraoperative AKI include hypoxia (<90%) (43), high hydroxyethyl starch (HES) volume (43), ischemic time (>6 h) (11,27), and aprotinin in use (10) (*Table 2*).

Postoperative factors

Volume depletion and diuretic use

Pulmonary edema, either mild or severe, is very common after LT due to ischemia reperfusion injury, and management of these patients usually involves strategies to limit fluid intake and escalation of the doses of diuretics. Intravascular volume depletion and hypotension can cause renal vasoconstriction, aggravating renal hypoperfusion and hypoxia and even causing endothelial injury and tubular necrosis (51). Moreover, the relative capacity depletion of the patients makes them more susceptible to AKI under the condition of nephrotoxic agents, intravenous contrast dye, or calcineurin inhibitors (CNIs) (16,35,51).

Sepsis

Complications from infection account for 19.5% of deaths within 3 to 5 years after LT (52). Sepsis is common in transplant recipients and is a major condition related to AKI occurrence in the intensive care unit (ICU) (approximately 50% of patients) (16,35,51,53,54). The mechanisms include ultrafiltration of circulating microbial toxins that cause stress and injury to tubular cells and secretion of inflammatory cytokines and the microcirculatory flow reduction (51).

Prolonged MV and/or ECMO

AKI commonly occurs in patients with long-term MV and/or ECMO after LT. Studies have shown that either postoperative MV >3 days (42,44) or a duration of ECMO support >2 days (42,55) is an independent factor for AKI development in lung transplant patients. Studies have also demonstrated that treatment with RRT during ECMO support was linked to a high mortality rate both in adult (34,56,57) and pediatric patients (58). In patients who developed AKI, longer invasive MV or ECMO time after surgery has been shown to have a negative correlation with survival (8,11,55).

CNIs

CNIs, such as cyclosporin A (CsA) and tacrolimus, remain the best treatment option for immunosuppression after LT.

However, significant acute or chronic nephrotoxicity, such as renal thrombotic microangiopathy (TMA) (16,59,60), hemolytic uremic syndrome (HUS) (16,59), and acute/chronic interstitial nephritis (AIN/CIN), is caused by CNIs (16,59). CsA can increase levels of the vasoconstrictor endothelin and can reduce the generation of vasodilatory nitric oxide by endothelial cells, thus leading to a decrease in the GFR and renal blood flow (61,62). A high blood level of tacrolimus has a significant effect on AKI, especially combined with prophylactic antimicrobial drugs in the early postoperative course (16,35,63).

Other nephrotoxic drugs

To achieve adequate glomerular hyperfiltration, the renal vascular bed gains a significant portion of resting cardiac output (20–25%), which exposes the interstitium, renal vasculature system and nephrons to a large amount of blood-derived toxins (51). LT patients are frequently exposed to multiple nephrotoxic drugs in the early postoperative period, such as aminoglycosides, amphotericin, vancomycin, trimethoprim-sulfamethoxazole, ganciclovir/valganciclovir, and nonsteroidal anti-inflammatory drugs (NSAIDs), which have been demonstrated to increase the risk of AKI (16,35,64-66).

Other postoperative risk factors for AKI, such as contrast dye exposure (16,35), HUS (35,64), AIN (35,64), TMA (16,59,60), rhabdomyolysis (35) and rapid intravenous immunoglobulin infusion (35), have also been reported (*Table 2*).

Impact of AKI

LT patients with AKI have a higher risk of CKD and hypertension, including end-stage renal failure (67). According to a 2019 report from the International Society for Heart and Lung Transplantation (ISHLT), the prevalence of severe kidney dysfunction (sCr >221 mmol/L) and chronic dialysis was 4.8% and 3.4% at 1 year post-transplantation (68). At 10 years after transplantation, the cumulative incidence of severe kidney insufficiency was 24.6%, with 6.3% of patients having chronic dialysis and 3.6% of patients receiving a kidney transplantation (68). Both AKI and CKD significantly affect patient survival after LT.

Biomarkers of AKI

sCr and urine output

At present, AKI is defined and staged according to urine output or sCr levels. However, sCr has low sensitivity because the level of sCr may not be enhanced until 24–72 h after AKI onset (69). Conversely, the specificity of urine output is low because this functional indicator can decline under the influence of several factors. In addition, the underlying functional and nutritional status of many LT recipients leads to muscle atrophy, and diagnosis of kidney injury using sCr or urine output can contribute to insufficient or prolonged identification of AKI events (16). Interpretation of the sCr level in children is also particularly difficult, with great variation according to age and sex and the method of measurement. Owing to the disadvantages of urine output and sCr levels in timely and reliable identification of AKI, there are increasing expectations for the development of novel biological markers that can be identified in the early stage of AKI, when interventions might be more successful. When individual risk stratification for AKI is possible, we can avert any unnecessary renal stress and even begin to perform preventive treatment (70).

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL, a protein that was first observed in neutrophil granules (71), can be synthesized innumerous human tissues and kidney epithelium. NGAL serves as a structural biomarker to predict AKI progression, is released by damaged tubular epithelial cells and increases rapidly in serum and urine (72-74). NGAL has been measured under a variety of conditions, such as cardiac surgery, sepsis, contrast dye exposure, and post-kidney transplantation, and the specificity and sensitivity of NGAL has been reported to range from 70–80%, while the diagnostic accuracy ranges from 0.53–0.96 based on the receiver operating characteristic (ROC) curve analysis (70,75-78). In particular, NGAL can also be released from neutrophils during inflammation (79). Consequently, inflammation is considered to be a confounding factor for NGAL as a biomarker of AKI in patients with sepsis in the ICU (80-82).

Urine tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor binding protein 7 (IGFBP7)

TIMP2 and IGFBP7, which are both cell cycle arrest regulators, can reflect cell stress in the early stage of tubular cell injury (83,84). TIMP2*IGFBP7 is considered a promising biomarker and has been found to facilitate prediction of AKI caused by a wide variety of insults (70,85-88).

Table 3 The most promising novel biomarkers for early identification of AKI

Biomarker	Type	Function prediction	Settings studied	Source	Measured from
NGAL	Structural biomarker	Tubular reabsorption function	Cardiac surgery, kidney transplantation, contrast nephropathy, sepsis, ER, ICU	Loop of Henle, leukocytes, and collecting ducts	Urine and serum
KIM-1	Structural biomarker	Tubular reabsorption function	Cardiac surgery, ICU	Proximal tubular cells	Urine
IL-18	Structural biomarker	Tubular reabsorption function	Cardiac surgery, ICU, transplantation	Tubular epithelial cells, monocytes, macrophages	Urine
Cystatin C	Functional biomarker	Glomerular filtration function	Cardiac surgery, ICU	Nucleated cells	Serum
TIMP2 and IGFBP7	Stress biomarker	Tubular injury	Sepsis, shock, major surgery, trauma	Tubular epithelial cells	Urine
suPAP	Stress biomarker	Tubular injury	Cardiac surgery, ICU	Endothelial cells, podocytes, monocytes, lymphocytes	Serum

ER, emergency room; NGAL, neutrophil gelatinase-associated lipocalin; ICU, intensive care unit; IL-18, interleukin-18; suPAP, soluble urokinase plasminogen activator receptor; TIMP2, tissue inhibitor of metalloproteinases 2; KIM-1, kidney injury molecule-1; IGFBP7, insulin-like growth factor-binding protein 7.

A value of (TIMP2)*(IGFBP7) of more than 0.3 indicates a population at high risk for AKI, suggesting that preventive measures should be taken against AKI, including reducing renal toxins and improving hemodynamics (86).

Kidney injury molecule-1 (KIM-1)

KIM-1, a type I cell membrane glycoprotein, was originally identified through a representative differential analysis after renal ischemia-reperfusion injury (89). Studies have shown that KIM-1 may be a sensitive biomarker of AKI in patients with non-cardiac or cardiac surgery (90-93), and KIM-1 has been confirmed to be a useful indicator to distinguish acute tubular necrosis from other forms of AKI (70,94).

Interleukin-18 (IL-18)

IL-18 is secreted by the intercalated cells of the collecting tubules of the kidney, the late distal convoluted tubule and the connecting tubule (95). The IL-18 level, which can change 1–2 d before the sCr level, has been shown to be a biomarker of AKI in the early stage (96,97) and may be a predictor of death (70,98).

Cystatin C (Cys-C)

Cys-C is a nuclear protein expressed in all nucleated cells. Cys-C can be freely filtered by the glomerulus and then reabsorbed and disintegrated in the proximal tubular cells (99). Serum Cys-C, which is considered a functional biomarker of AKI (70,100,101), reflects glomerular filtration function and is a more accurate biomarker of renal function than the sCr level (102,103). However, serum Cys-C seems to be affected by thyroid function, malignancy, inflammation, and high doses of corticosteroids (104,105).

Soluble urokinase plasminogen activator receptor (suPAR)

suPAR is a signaling glycoprotein normally expressed at very low levels on endothelial cells, podocytes, monocytes and lymphocytes (106,107). A recent study has reported that high levels of serum suPAR were related to AKI in patients undergoing coronary angiography, patients suffering from critical illness, and patients treated with cardiac surgery (108). The findings suggest that suPAR might serve as a novel biomarker, can be increased prior to AKI occurrence, and may be utilized to predict AKI (69). Moreover, suPAR may be pathogenic, and targeting suPAR might be a potential therapeutic strategy (69). suPAR is thought to have the potential to provide information for preprocedural risk-stratified and clinical decision-making care (69). *Table 3* summarizes the most promising novel
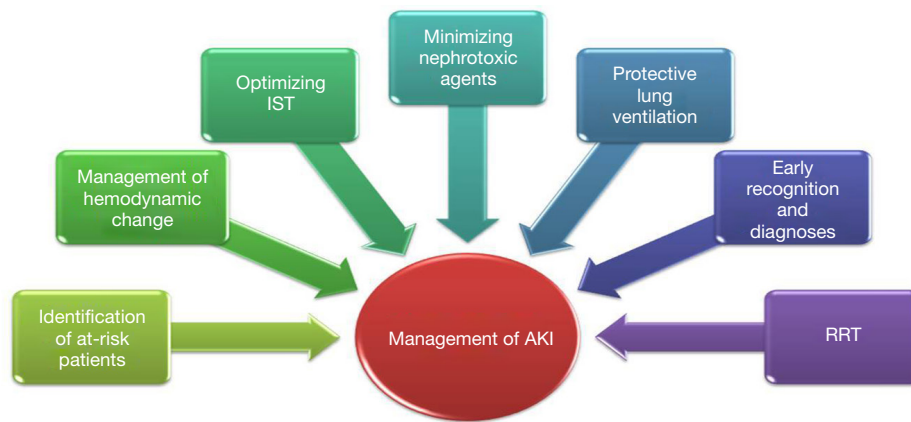
Figure 1 Approaches to prevent and manage AKI after lung transplantation. IST, immunosuppressive therapy; RRT, renal replacement therapy; AKI, acute kidney injury.

indicators for diagnosing AKI in the early stage.

Prevention and management of AKI

The final purpose of identifying biomarkers and risk factors is to ameliorate the prognosis. Early recognition of AKI and therapeutic methods to confine AKI occurrence and development are vital to decrease morbidity and mortality. Considering the high incidence of AKI after LT, it is essential to consider all available therapeutic schedules to support renal function (*Figure 1*).

Identification of at-risk patients

Identifying at-risk patients according to pretransplant risk factors and surgical procedures is essential. There are many types of AKI-associated factors. Generally, those at the highest risk are CF or PH patients; those with advanced age, a smoking history, heart failure, systemic hypertension, or diabetes mellitus in the ICU at transplant time; those undergoing retransplantation; those with preexisting renal impairment; and those with MV or ECMO (16). Thus, screening patients who have such risk factors using a precise estimate of kidney function and continuing to monitor these patients until the risk has subsided is crucial. Lung transplant candidates and recipients with evidence of kidney injury and those at increased risk should be referred early for nephrology consultation because early involvement and coordination of care with nephrology can facilitate prompt diagnosis and preventive management to mitigate AKI (109). Smoking cessation and control of blood pressure and blood sugar levels may also be

beneficial for reducing AKI occurrence and development.

Volume management and maintenance of hemodynamic stability

Perioperatively, optimal fluid management prevents volume depletion and maintains adequate renal perfusion. Careful monitoring of the urine output level and fluid balance can help reduce the mortality of AKI patients (110). For patients with hemodynamic instability, it is necessary to use a Swan-Ganz catheter and optimize the volume status and hemodynamic parameters to closely monitor hemodynamics. Diuretic use, vasopressor therapy and extracorporeal ultrafiltration should be adjusted based on fluid responsiveness and assessment of tolerance, and ventilator settings and lung recruitment maneuvers should be considered. Due to the potential for kidney toxicity, use of HES to perform fluid resuscitation is not recommended in most transplant patients (111).

Optimization of immunosuppressive therapy (IST)

The CNIs CsA and tacrolimus are the most effective drugs to prevent rejection reactions, but they are related to renal toxicity. A whole-blood CNI concentration beyond the treatment range is also associated with early-onset AKI (36,112). Certain factors influence the pharmacokinetics of CNIs: altered liver metabolism and gut absorption, drug interactions (azoles, rifamycin), anemia, and hypoalbuminemia, causing great fluctuations in blood drug concentrations (16). Close monitoring of the CNI trough

concentration is necessary and crucial for lung transplant recipients. For now, there seem to be no agents that can quickly replace the widespread use of CNIs. A CNI minimization strategy (113,114) or conversion to a new immunosuppressive agent, such as belatacept (115,116), requires further investigation.

Limiting exposure to nephrotoxic agents

Most posttransplant patients are likely to be exposed to different types of renal toxins due to infectious complications. Antimicrobials, such as vancomycin, aminoglycosides, trimethoprim-sulfamethoxazole, amphotericin, and ganciclovir/valganciclovir, can lead to renal injury (16). Furthermore, reducing the dosage of antibiotics in a timely manner according to culture results and clinical conditions is crucial. When these nephrotoxic drugs are imperative, they ought to be utilized in conjunction with suitable monitoring of trough levels if possible. Notably, NSAIDs should be avoided. Other potential nephrotoxic agents, such as radiocontrast agents, should be used only when essential, and if possible, a minimal amount of dye should be administered.

Protective lung ventilation

MV can have an impact on the cardiopulmonary system and systemic hemodynamics, further stimulating the neurohormonal system (14). Lung injury and AKI have a bidirectional interaction through a few cellular and pathophysiologic mechanisms (14). Studies have demonstrated that lung-protective ventilation mitigates volutrauma and barotrauma and reduces AKI risk by limiting the breath-induced hemodynamic effects and cytokines that burden the kidney (117). Therefore, during MV, a lung protection strategy should be adopted to maintain renal function.

Early recognition and diagnosis of AKI

The essentials of AKI management are recognition of the underlying etiology and supportive care. Both of these priorities could be ameliorated by recognizing AKI earlier and by closely monitoring renal function (110). sCr and urine output are the basis of AKI diagnosis, staging, and prognosis prediction. For transplant patients, close monitoring of sCr and urinary output levels is vital, particularly in high-risk AKI patients, which can result in earlier and better fluid management. As sCr can be affected

by the nutritional status of patients, using AKI biomarkers that are independent of this condition for preoperative risk assessment and stratification may help clinicians take timely preventive measures (70).

Appropriate utilization of renal replacement therapy

Currently, there are no effective drugs to treat AKI, despite a significant need and historical trials (118). RRT should be considered in patients with volume overload, especially refractory hypoxemia, if conservative treatment fails. For patients on ECMO, RRT can be performed using either a built-in blood filter or by integrating a standard RRT machine into the ECMO loop (16), although many centers prefer venous access for RRT rather than an ECMO loop to reduce thrombosis in the latter (119). In addition, unlike the native kidney, RRT requires close monitoring to avert intradialytic hypotension, hypophosphatemia and hypokalemia (16,119). Oral supplementation or addition of phosphorus/potassium to RRT solutions is necessary to avoid severe electrolyte disturbance.

Next steps

Identification of patients before the occurrence of early renal damage is essential. Several biomarkers have shown promising results in the identification of early renal damage, but the clinical applicability of these biomarkers needs further study. Renal protection strategies including pharmacotherapy, fluid replacement and nutritional support are another area of ongoing research. Combining renal protection strategies with the use of new biomarkers to develop early kidney risk identification and protection protocols is a promising idea that requires further research.

Conclusions

AKI after LT is common and can contribute to increased mortality and morbidity. Due to a variety of perioperative risk factors, AKI usually occurs early after transplantation. Importantly, in patients with high risk, appropriate management of perioperative hemodynamic changes, minimization of the use of nephrotoxic agents, and optimization of IST after LT can significantly reduce AKI severity and occurrence during the perioperative period. Appropriate monitoring for AKI, including the use of biomarkers, is necessary because early alerts and rapid nephrology intervention will impact outcomes. RRT

should be considered when conservative treatment fails, and maintaining hemodynamic stability and electrolyte balance during RRT is crucial. Cross-disciplinary coordination for the care of patients with severe AKI after LT is recommended.

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Footnote

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