Acute kidney injury following adult lung transplantation

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Abstract

Background: Acute kidney injury (AKI) is a common and serious complication following lung transplantation (LTx), and it is associated with high mortality and morbidity. This study assessed the incidence of AKI after LTx and analyzed the associated perioperative factors and clinical outcomes.

Methods: This retrospective study included all adult LTx recipients at the China-Japan Friendship Hospital in Beijing between March 2017 and December 2019. The outcomes were AKI incidence, risk factors, mortality, and kidney recovery. Multivariate analysis was performed to identify independent risk factors. Survival analysis was presented using the Kaplan–Meier curves.

Results: AKI occurred in 137 of the 191 patients (71.7%), with transient AKI in 43 (22.5%) and persistent AKI in 94 (49.2%). AKI stage 1 occurred in 27/191 (14.1%), stage 2 in 46/191 (24.1%), and stage 3 in 64/191 (33.5%) of the AKI patients. Renal replacement therapy (RRT) was administered to 35/191 (18.3%) of the patients. Male sex, older age, mechanical ventilation (MV), severe hypotension, septic shock, multiple organ dysfunction (MODS), prolonged extracorporeal membrane oxygenation (ECMO), reintubation, and nephrotoxic agents were associated with AKI ($P < 0.050$). Persistent AKI was independently associated with pre-operative pulmonary hypertension, severe hypotension, post-operative MODS, and nephrotoxic agents. Severe hypotension, septic shock, MODS, reintubation, prolonged MV, and ECMO during or after LTx were related to severe AKI (stage 3) ($P < 0.050$). Patients with persistent and severe AKI had a significantly longer duration of MV, longer duration in the intensive care unit (ICU), worse downstream kidney function, and reduced survival ($P < 0.050$).

Conclusions: AKI is common after LTx, but the pathogenic mechanism of AKI is complicated, and prerenal causes are important. Persistent and severe AKI were associated with poor short- and long-term kidney function and reduced survival in LTx patients.

Keywords: Acute kidney injury; Adult lung transplantation; Incidence; Outcomes; Risk factors

Introduction

Acute kidney injury (AKI) is a common cause of perioperative morbidity and mortality following lung transplantation (LTx). Depending on the definition used, the incidence ranges between 39% and 69%, with an associated mortality rate of 16% to 50%. Overall, 5% to 13% of patients require renal replacement therapy (RRT) after AKI.[1-8] To our knowledge, few studies have explored renal recovery from AKI after LTx.[2,8,9] Only one study distinguished transient AKI from persistent AKI and evaluated the impact of transient AKI in LTx patients,[10] and no studies have specifically evaluated the impact of persistent AKI on the clinical outcomes in LTx patients.

Revealing the risk factors of AKI and their impacts on the clinical outcomes in LTx recipients can help to recognize patients with poor prognoses and suggest appropriate prevention strategies. Thus, a retrospective study was performed to describe the incidence and perioperative factors affecting different types and severities of AKI in a single center and to evaluate their impacts on the clinical outcomes of patients after LTx.

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Methods

Ethical approval

This study was approved by the Ethics Committee of the China-Japan Friendship Hospital (2019–164-K113), Beijing, China, and written informed consent was obtained from all the patients.

Study design

We conducted a retrospective cohort study of all adult LTx patients from March 2017 to December 2019 at the China-Japan Friendship Hospital in Beijing, China. The included patients were adults (aged 18–65 years) who underwent LTx (any single or double LTx). The exclusion criteria were: (1) death within 24 hours after LTx; (2) chronic kidney disease (CKD) or diagnosis of AKI before LTx; and (3) lack of available data regarding the vital status.

Anesthetic and surgical management

Anesthetic and surgical technique protocols followed the standard of care at the China-Japan Friendship Hospital in Beijing, China. Single lung transplantation (SLT) generally involved a post erolateral or anterolateral thoracotomy, resection of the recipient's native lung, and implantation of the donor's lung. Double lung transplantation (DLT) was performed with the bilateral sequential LTx method via bilateral anterolateral thoracotomies. Propofol, remifentanil, and atracurium are used for anesthesia. Intraoperative monitoring was performed using an invasive arterial line, a central venous catheter, and Swan–Ganz catheterization. Extracorporeal membrane oxygenation (ECMO) was used selectively in patients with severe pulmonary hypertension (mean pulmonary artery pressure ≥45 mmHg) and/or right ventricular failure, as well as in patients who became unstable during transplantation procedure. RRT was initiated in the following scenarios: urine output <200 mL/12 h, blood urea nitrogen (BUN) >100 mg/dL, or pulmonary edema resistant to diuretic therapy.[11,12]

Immunosuppression and antibiotic protocol

Corticosteroid induction therapy was applied in all patients intraoperatively. About 0.50 g of methylprednisolone was administered intravenously before reperfusion of the first allograft (SLT), and 0.25 g was administered before reperfusion of the other allograft (DLT). Post-operative immunosuppression was accomplished with triple therapy with tacrolimus (target trough concentration 10–15 ng/mL), mycophenolate mofetil (0.50 g/day), and methylprednisolone (0.5 mg/kg followed by tapering). Some patients received induction therapy with basiliximab (20 mg on days 0 and 4). Since there is no clear guidance regarding the use of induction in lung transplant, basiliximab was used for patients who are ≤60 years of age and have no clear infection before LTx at our center.

The perioperative prophylactic antimicrobial regimen included cephalosporin (conventional dose, for 3 weeks) if there was a penicillin allergy, caspofungin (50 mg/day, for 3 weeks), vancomycin (1000 mg/day, for 3 days), and ganciclovir ($5\ mg{\cdot}kg^{-1}{\cdot}d^{-1}$, for 1 month, then switched to valganciclovir 450 mg/day for 5 months) for antifungal and coccal and antiviral prophylaxes. The antimicrobial regimen was adjusted based on perioperative cultures.

Renal function evaluation

AKI was defined and staged using the serum creatinine (sCr) criteria of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[13] The urine criteria were not used because urine data collected retrospectively may be inaccurate. AKI was defined as an increase in sCr ≥26.5 μmol/L or 1.5 times baseline sCr within the first 7 days after LTx. The 7-day evaluation window was selected as most patients with AKI have sCr levels below the AKI range 7 days after surgery,[8,14,15] and this window allowed comparisons with previous studies in this field.[3,8,10] Severity was classified as follows: stage 1, increase in sCr by ≥26.5 μmol/L within 48 hours or increase in sCr to ≥1.5-fold baseline; stage 2, increase in sCr to ≥2.0-fold baseline; and stage 3, increase in sCr to 3.0-fold baseline, sCr ≥353.6 μmol/L or the initiation of RRT. The last sCr value obtained before LTx was used as the baseline. The CKD Epidemiology Collaboration formula was used to calculate the estimated glomerular filtration rate (eGFR).[16] CKD was defined as a persistent eGFR $<60\ mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$.[17] Transient AKI was defined as a return of sCr values below the AKI range within 7 days after LTx. Persistent AKI was defined as incomplete recovery (sCr still above AKI range) or receiving RRT in the first 7 days following LTx.

Data collection

Pre-operative data included age, gender, smoking status, body mass index (BMI), primary disease, comorbidities, basal renal function, use of nephrotoxic agents within 1 month before surgery, and the need for pre-operative mechanical ventilation (MV) or ECMO. Operative variables (LTx type, duration of surgery, blood transfusion volume, and hemodynamic support by ECMO) were recorded. Post-operative variables included blood gas analysis, septic shock, multiple organ dysfunction (MODS), reintubation, reoperation, duration of invasive MV and ECMO, immunosuppression regimen, and use of nephrotoxic agents. Intraoperative or post-operative severe hypotension (mean arterial pressure <65 mmHg) and vasoactive therapy were also recorded.

Statistical analysis

Absolute numbers with ratios were used for qualitative variables and compared using a χ^2 test. When the sample size was <5, Fisher test was used. The medians with interquartile ranges (IQRs) were used for quantitative data variables, and the Mann–Whitney *U* or Kruskal–Wallis test was used as appropriate. The odds ratios (OR) with 95% confidence intervals (CI) were calculated by multivariate logistic regression to determine the independent variables of persistent AKI.

Multivariable Cox proportional hazard regression analysis was used to determine the independent associations between AKI type or stage and 1-year mortality. The 1-year survival analysis was presented using the Kaplan–Meier curves and compared with a log-rank test. $P < 0.050$ was used to indicate statistical significance. SPSS version 23 (IBM Corp, Armonk, NY, USA) was used for statistical analyses.

Results

Of the 206 LTx patients, 191 were included [Figure 1]. The median age (IQR) was 59 years (51–62), and 83% were male. The most frequent primary diseases were interstitial lung disease (ILD; 73% [$n = 140$]), chronic obstructive pulmonary disease (COPD; 12% [$n = 23$]), and cystic fibrosis/bronchiectasis (9% [n = 17]). Eighty-nine (46.6%) patients received double LTx, and 102 (53.4%) patients received single LTx.

Incidence of AKI

The incidence of AKI was 71.7% ($n = 137$) in the first 7 days after LTx. Of these patients, transient AKI occurred in 22.5% ($n = 43$), and persistent AKI occurred in 49.2% ($n = 94$). Of the patients with AKI, stage 1 occurred in 14.1% ($n = 27$), stage 2 in 24.1% ($n = 46$), and stage 3 in 33.5% ($n = 64$) [Figure 1]. RRT was received by 18.3% ($n = 35$) of the patients with AKI.

Risk factors of AKI

Perioperative characteristics were stratified by AKI type, as shown in Tables 1 and 2. AKI was associated with male sex, older age, pre-operative use of MV, intraoperative or post-operative severe hypotension, post-operative lactate >3 mmol/L, septic shock, MODS, reintubation, prolonged MV or ECMO, higher trough level of tacrolimus, and the use of other nephrotoxic agents ($P < 0.050$).

In the univariate Cox proportional hazard regression analysis, persistent AKI was related to the pre-operative use of ECMO, intraoperative or post-operative severe hypotension, norepinephrine >0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ or using epinephrine, post-operative lactate >3 mmol/L, septic shock, MODS, reintubation, prolonged MV or ECMO, higher trough level of tacrolimus, and the use of other nephrotoxic agents ($P < 0.050$) [Table 3].

In the multivariate analysis, persistent AKI was independently related to pre-operative pulmonary hypertension (OR, 2.43; 95% CI, 1.04–5.66; $P = 0.040$), intraoperative or post-operative severe hypotension (OR, 2.43; 95% CI, 1.67–16.46; $P = 0.004$), post-operative MODS (OR, 34.37; 95% CI, 3.43–344.8; $P = 0.003$), higher trough level of tacrolimus (OR, 1.11; 95% CI, 1.01–1.21; $P = 0.024$), and use of other nephrotoxic drugs (OR, 3.03; 95% CI, 1.29–7.08; $P = 0.011$) [Table 3].

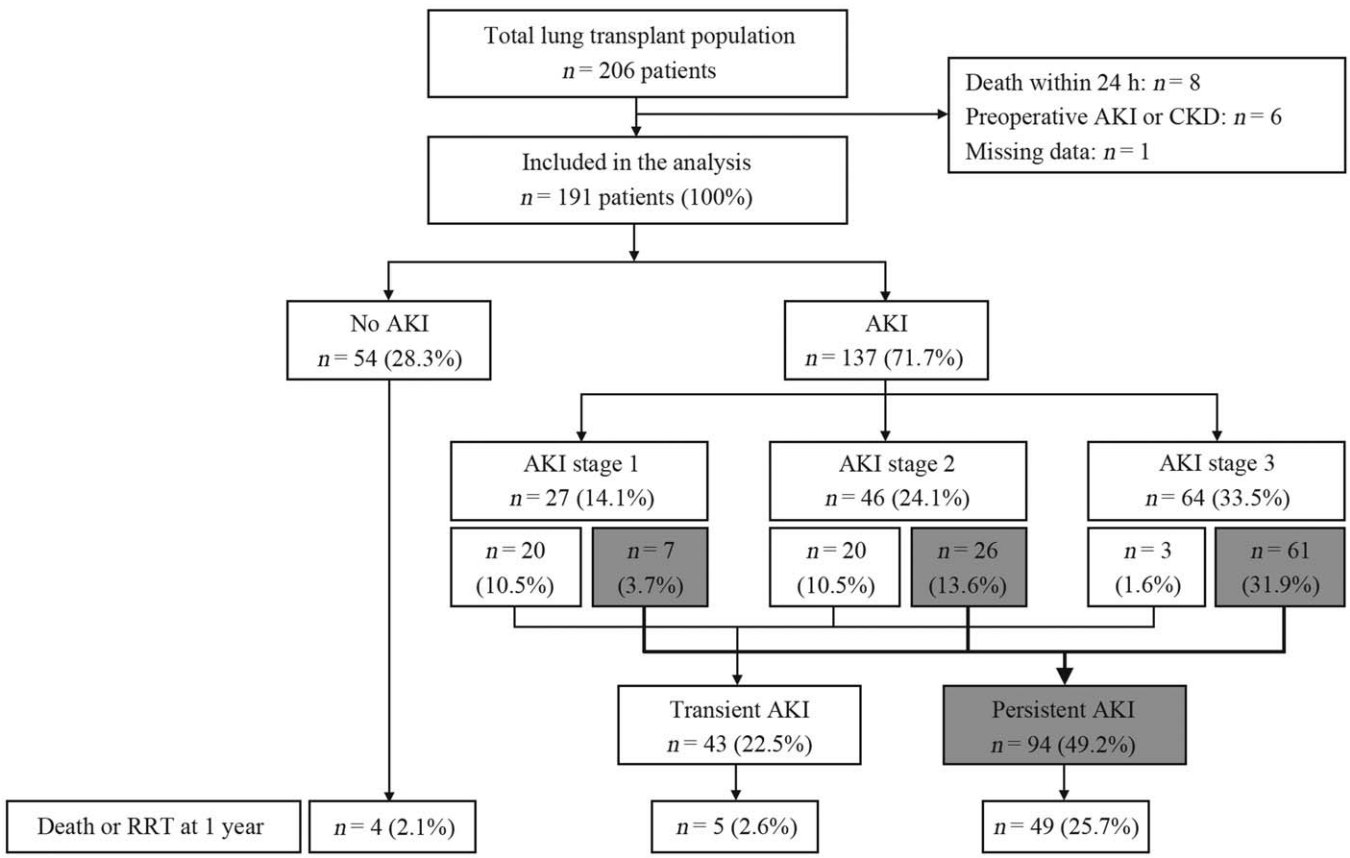

Figure 1: Study flow diagram. AKI: Acute kidney injury; CKD: Chronic kidney disease; RRT: Renal replacement therapy.

Table 1: Pre-operative characteristics of patients undergoing lung transplantation by the status of AKI.

Variables	No AKI ($n = 54$; 28.3%)	AKI ($n = 137$; 71.7%)	*P* value	Transient AKI ($n = 43$; 22.5%)	Persistent AKI ($n = 94$; 49.2%)	*P* value
Male sex, *n* (%)	39 (72.2)	120 (87.6)	0.010	36 (83.7)	84 (89.4)	0.353
Age (years), median (IQR)	56 (49–62)	60 (54–62)	0.025	61 (57–63)	59 (49–62)	0.226
BMI <18.5 kg/m^2, *n* (%)	18 (33.3)	29 (21.2)	0.079	8 (18.6)	21 (22.3)	0.619
BMI >23.9 kg/m^2, *n* (%)	14 (25.9)	41 (29.9)	0.582	17 (39.5)	24 (25.5)	0.097
Smoking history, *n* (%)	35 (64.8)	97 (70.8)	0.420	31 (72.1)	66 (70.2)	0.822
Primary diseases, *n* (%)						
COPD/emphysema	7 (13.0)	16 (11.7)	0.806	4 (9.3)	12 (12.8)	0.558
ILD	38 (70.4)	102 (74.5)	0.566	32 (74.4)	70 (74.5)	0.995
CF/bronchiectasis	6 (11.1)	11 (8.0)	0.501	4 (9.3)	7 (7.5)	0.711
Other diagnosis	3 (5.6)	8 (5.8)	0.940	3 (7.0)	5 (5.3)	0.701
Comorbidities, *n* (%)						
Hypertension	10 (18.5)	36 (26.3)	0.259	13 (30.2)	23 (24.5)	0.477
Diabetes mellitus	18 (33.3)	38 (27.7)	0.444	14 (32.6)	24 (25.5)	0.394
Dyslipidemia	8 (14.8)	26 (19.0)	0.498	6 (14.0)	20 (21.3)	0.310
Pulmonary hypertension, *n* (%)	34 (63.0)	90 (65.7)	0.722	23 (53.5)	67 (71.3)	0.042
sCr (μmol/L), median (IQR)	50.85 (43.0–65.9)	56.00 (46.0–66.0)	0.334	56.60 (48.5–65.5)	53.50 (45.0–67.0)	0.383
eGFR <90 (mL·min^{-1}·1.73 m^{-2}), *n* (%)	5 (9.3)	7 (5.1)	0.287	2 (4.7)	5 (5.3)	0.869
MV before surgery, *n* (%)	0	10 (7.3)	0.041	1 (2.3)	9 (9.6)	0.130
ECMO before surgery, *n* (%)	1 (1.9)	10 (7.3)	0.146	0	10 (10.6)	0.026
Nephrotoxic agents, *n* (%)*	6 (11.1)	20 (14.6)	0.527	6 (14.0)	14 (14.9)	0.885

*Pre-operative administration of any of the following agents were included: aminoglycosides, vancomycin, polymyxin B, amphotericin, trimethoprim-sulfamethoxazole, ganciclovir/valganciclovir, NSAIDs, and radiocontrast dye. AKI: Acute kidney injury; BMI: Body mass index; CF: Cystic fibrosis; COPD: Chronic obstructive pulmonary disease; ECMO: Extracorporeal membrane oxygenation; eGFR: Estimated glomerular filtration rate; ILD: Interstitial lung disease; IQR: Interquartile range; MV: Mechanical ventilation; NSAIDs: Non-steroidal anti-inflammatory drugs; sCr: Serum creatinine.

Table 2: Intraoperative and postoperative variables of patients undergoing lung transplantation according to AKI status.

Variables	No AKI ($n = 54$; 28.3%)	AKI ($n = 137$; 71.7%)	*P* value	Transient AKI ($n = 43$; 22.5%)	Persistent AKI ($n = 94$; 49.2%)	*P* value
Bilateral LTx, *n* (%)	26 (48.1)	63 (46.0)	0.787	15 (34.9)	48 (51.1)	0.078
Duration of surgery (min), median (IQR)	270 (210–330)	275 (210–340)	0.785	240 (210–345)	293 (210–340)	0.713
Blood transfusion >1000 mL during surgery, *n* (%)	7 (13.0)	19 (13.9)	0.869	3 (7.0)	16 (17.0)	0.114
Intraoperative ECMO, *n* (%)	36 (66.7)	101 (73.7)	0.329	31 (72.1)	70 (74.5)	0.769
Intraoperative or post-operative severe hypotension, *n* (%)	4 (7.4)	37 (27.0)	0.003	2 (4.7)	35 (37.2)	<0.01
Norepinephrine >0.5 mg·kg^{-1}·min^{-1} or epinephrine during or after surgery, *n* (%)	7 (13.0)	24 (17.5)	0.442	3 (7.0)	21 (22.3)	0.028
Induction therapy (basiliximab), *n* (%)	24 (44.4)	60 (43.8)	0.935	14 (32.6)	46 (48.9)	0.073
*Lactate >3 mmol/L, *n* (%)	28 (51.9)	94 (68.6)	0.030	24 (55.8)	70 (74.5)	0.029
*pH < 7.20 on ICU admission, *n* (%)	2 (3.7)	10 (7.3)	0.356	1 (2.3)	9 (9.6)	0.130
*Septic shock, *n* (%)	2 (3.7)	26 (19.0)	0.007	0	26 (27.7)	<0.01
*MODS, *n* (%)	1 (1.9)	36 (26.3)	<0.01	0	36 (38.3)	<0.01
*Reintubation, *n* (%)	1 (1.9)	15 (10.9)	0.041	0	15 (16.0)	0.006
*MV ≥ 3 days, *n* (%)	13 (24.1)	56 (40.9)	0.029	8 (18.6)	48 (51.1)	<0.01
*Duration of ECMO support ≥ 2 days, *n* (%)	13 (24.1)	55 (40.1)	0.037	11 (25.6)	44 (46.8)	0.019
*PGD 3 any time 0–72 h	24 (44.4)	60 (43.8)	0.935	15 (34.9)	45 (47.9)	0.111
*Rethoracotomy for hemostasis or abdominal surgery, *n* (%)	5 (9.3)	7 (5.1)	0.287	1 (2.3)	6 (6.4)	0.317
*Trough level of tacrolimus (μmol/L), median (IQR)	5 (3.30–8.80)	8 (5.60–11.00)	0.003	6 (4.95–8.90)	9 (5.70–12.40)	0.027
*Other nephrotoxic agents, *n* (%)†	13 (24.1)	54 (39.4)	0.045	7 (16.3)	47 (50.0)	<0.01

AKI: Acute kidney injury; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; IQR: Interquartile range; LTx: Lung transplantation; MODS: Multiple organ dysfunction; MV: Mechanical ventilation; PGD: Primary graft dysfunction. *After surgery. †Administration of any of the following agents within 1 week after the operation was included: aminoglycosides, polymyxin B, and trimethoprim-sulfamethoxazole.

Table 3: Risk factors for persistent AKI after lung transplantation.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Pulmonary hypertension before surgery	1.74	0.95–3.18	0.071	2.43	1.04–5.66	0.040
ECMO before surgery	11.43	1.43–91.15	0.021	1.90	0.17–21.88	0.606
Intraoperative or post-operative severe hypotension	9.00	3.56–22.71	<0.01	5.25	1.67–16.46	0.004
Norepinephrine >0.5 μg/kg/min or epinephrine during or after surgery	2.25	1.02–4.97	0.045	0.77	0.24–2.49	0.664
*Lactate >3 mmol/L	2.29	1.25–4.21	0.007	1.33	0.61–2.92	0.476
*Septic shock	18.16	4.17–79.11	<0.01	0.81	0.09–7.62	0.855
*MODS	60.63	8.09–454.26	<0.01	34.37	3.43–344.80	0.003
*Reintubation	18.23	2.36–141.03	0.005	2.99	0.24–36.73	0.391
*MV ≥3 days	3.78	2.01–7.09	<0.01	0.84	0.28–2.52	0.754
*Duration of ECMO support ≥2 days	2.68	1.45–4.95	0.002	2.01	0.71–5.74	0.190
*Trough level of tacrolimus (μmol/L)	1.16	1.07–1.24	<0.01	1.11	1.01–1.21	0.024
*Other nephrotoxic agents†	3.85	2.04–7.28	<0.01	3.03	1.29–7.08	0.011

AKI: Acute kidney injury; CI: Confidence intervals; ECMO: Extracorporeal membrane oxygenation; LTx: Lung transplantation; MODS: Multiple organ dysfunction; MV: Mechanical ventilation; OR: Odds ratio. *After surgery. †Administration of any of the following agents within 1 week after the operation was included: aminoglycosides, polymyxin B, and trimethoprim-sulfamethoxazole.

Table 4: Perioperative data of patients who developed post-operative AKI stratified according to the degree of severity (stages 1–3).

Variables	AKI stage 1 (*n* = 27)	AKI stage 2 (*n* = 46)	AKI stage 3 (*n* = 64)	*P* value
Male sex, *n* (%)	25 (92.6)	40 (87.0)	55 (86.0)	0.671
Age (years), median (IQR)	61 (56–64)	60 (58–62)	58 (49–62)	0.225
MV before surgery, *n* (%)	0	5 (10.9)	5 (7.8)	0.221
Intraoperative or post-operative severe hypotension, *n* (%)	0	8 (17.4)	29 (45.3)	<0.01
*Lactate > 3 mmol/L, *n* (%)	18 (66.7)	30 (65.2)	46 (71.9)	0.737
*Septic shock, *n* (%)	0	3 (6.5)	23 (35.9)	<0.01
*MODS, *n* (%)	0	6 (13.0)	30 (46.9)	<0.01
*Reintubation, *n* (%)	0	3 (6.5)	12 (18.8)	0.016
*MV ≥ 3 days, *n* (%)	6 (22.2)	12 (26.1)	38 (59.4)	<0.01
*Duration of ECMO support ≥ 2 days, *n* (%)	6 (22.2)	16 (34.8)	32 (50.0)	0.034
*Trough level of tacrolimus (μmol/L), median (IQR)	6 (5.0–8.7)	7 (5.0–10.3)	9 (6.4–12.2)	0.024
*Other nephrotoxic agents, *n* (%)†	2 (7.4)	19 (41.3)	33 (51.6)	<0.01

AKI: Acute kidney injury; ECMO: Extracorporeal membrane oxygenation; IQR: Interquartile range; MODS: Multiple organ dysfunction; MV; Mechanical ventilation. *After surgery. †Administration of any of the following agents within 1 week after the operation was included: aminoglycosides, polymyxin B, and trimethoprim-sulfamethoxazole.

The different stages of AKI were analyzed in Table 4, and the results indicated that more severe AKI was associated with intraoperative or post-operative severe hypotension, post-operative septic shock, MODS, reintubation, prolonged MV and ECMO, higher trough level of tacrolimus, and the use of other nephrotoxic agents ($P < 0.050$).

Clinical outcomes

Our study showed that patients with AKI had longer durations of post-operative MV [median (IQR), in days] [2 (1–4) *vs.* 2 (1–2) days, $P = 0.022$] and longer durations in the intensive care unit (ICU) [4 (3–7) *vs.* 3 (2–4) days, $P = 0.002$] than patients without AKI. Persistent AKI was associated with longer durations of MV and longer ICU stays (3 [1–8] *vs.* 1 [1–2], $P < 0.001$; 5 [3–9] *vs.* 3 [2–4], $P < 0.001$) than patients with transient AKI. Moreover, persistent AKI patients were more likely to have severe kidney injury (stage 3 AKI, 64.9% *vs.* 7.0%, $P < 0.001$) [Table 5] than transient AKI patients.

Impact of different types and severities of AKI on kidney function

In our study, patients with persistent AKI had statistically lower 1-year eGFR than those with transient AKI after LTx [Table 5 and Figure 2A]. Patients' eGFRs at 1 year after LTx had an obvious decreasing trend with worsening AKI severity [Figure 2B].

Impact of different types and severities of AKI on survival

The 30-day survival rate after LTx was 87.4% (167/191): the survival rate in patients without AKI was 98.1% (53/54), while that in patients with AKI was 83.2% (114/137). The 1-year survival rate after LTx was 71.2% (136/191): the survival rate in patients without AKI was 92.6% (50/54), while that in patients with AKI was 62.8% (86/137). The 30-day and 1-year survival rates in transient patients were 100% (43/43) and 88.4% (38/43), while they were 75.5% (71/94) and 51.1% (48/94) in persistent AKI

Table 5: Outcomes of patients after LTx stratified by AKI and recovery status.

Variables	No AKI ($n = 54$)	AKI ($n = 137$)	*P* value	Transient AKI ($n = 43$)	Persistent AKI ($n = 94$)	*P* value
Duration of MV (days), median (IQR)	2 (1–2)	2 (1–4)	0.022	1 (1–2)	3 (1–8)	<0.01
ICU stays (days), median (IQR)	3 (2–4)	4 (3–7)	0.002	3 (2–4)	5 (3–9)	<0.01
eGFR at 1 year ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), median (IQR)	90 (79–100)	65 (43–90)	<0.01	76 (54–93)	59 (39–85)	0.047
30-day mortality rate, *n* (%)	1 (1.9)	23 (16.8)	0.005	0	23 (24.5)	<0.01
1-year mortality rate, *n* (%)	4 (7.4)	51 (37.2)	<0.01	5 (11.6)	46 (48.9)	<0.01

AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate; ICU: Intensive care unit; IQR: Interquartile range; LTx: Lung transplantation; MV: Mechanical ventilation.

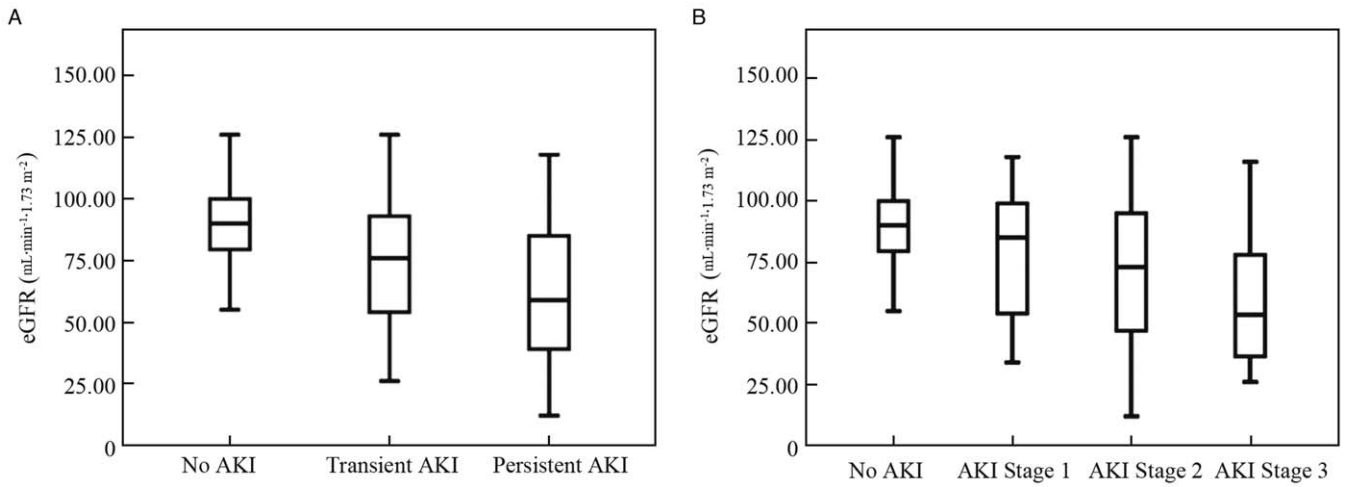

Figure 2: One-year kidney function by AKI type (A) and stage (B). $P < 0.050$ for all groups compared with no AKI except for AKI stage 1 *vs.* no AKI. AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate.

patients, respectively. Both short- and long-term survival rates were statistically lower in persistent AKI patients than in patients with transient AKI or without AKI. No apparent differences were observed in the 30-day or 1-year survival rate between transient AKI patients and patients without AKI [Table 5 and Figure 3A]. In the multivariable Cox proportional hazard regression analysis, patients with persistent AKI showed higher mortality [hazard ratio (HR), 95% CI: [14.65, 3.50–61.28; $P < 0.001$; Table 6].

When stratified by AKI severity, a gradual decrease in 1-year survival rate after LTx with worsening AKI severity was also observed. For patients with no AKI, AKI stage 1, AKI stage 2, and AKI stage 3, the 1-year survival rate was 93%, 85%, 72%, and 47%, respectively [Figure 3B]. Multivariable analysis showed that both AKI stages 2 and 3 were independently related to higher mortality during the 1-year follow-up [Table 6].

Discussion

AKI is common among patients after LTx and is related to a poor prognosis; AKI can significantly affect the outcome of LTx patients.[9] Despite substantial improvements in surgical techniques, LTx remains a procedure with a high risk of bleeding and large changes in circulation capacity during surgery. Hemodynamic instability and nephrotoxic drugs are considered the important risk factors for AKI after LTx.[8] This study retrospectively investigated the incidence, risk factors, and clinical outcomes of AKI after LTx in a single center.

In our study, AKI occurred in 71.7% of the LTx recipients, and RRT was needed in 18.3% of these patients. Our data were consistent with those previous studies, some of which reported even higher rates of AKI (33%–69%) and the need for RRT (5%–13%).[1-4,8] The wide differences in the incidence between studies may be attributed to various AKI definitions used and the period during which AKI was assessed. Compared with previous studies, we used the latest consensus definition of AKI and assessed AKI in the first 7 post-operative days based on published data suggesting that sCr levels return to normal within the first week after surgery among most AKI patients.[8,14,15] This window was selected to allow comparisons with previous studies.[3,8,10]

With regard to perioperative risk factors, our data showed that elderly patients were more likely to develop AKI, which may be attributed to the drop in renal function due to aging and the reduced resistance of elderly patients.[18] The data also showed that AKI was more common in men, which may be related to our relatively small population. Interestingly, the International Society for Heart and Lung

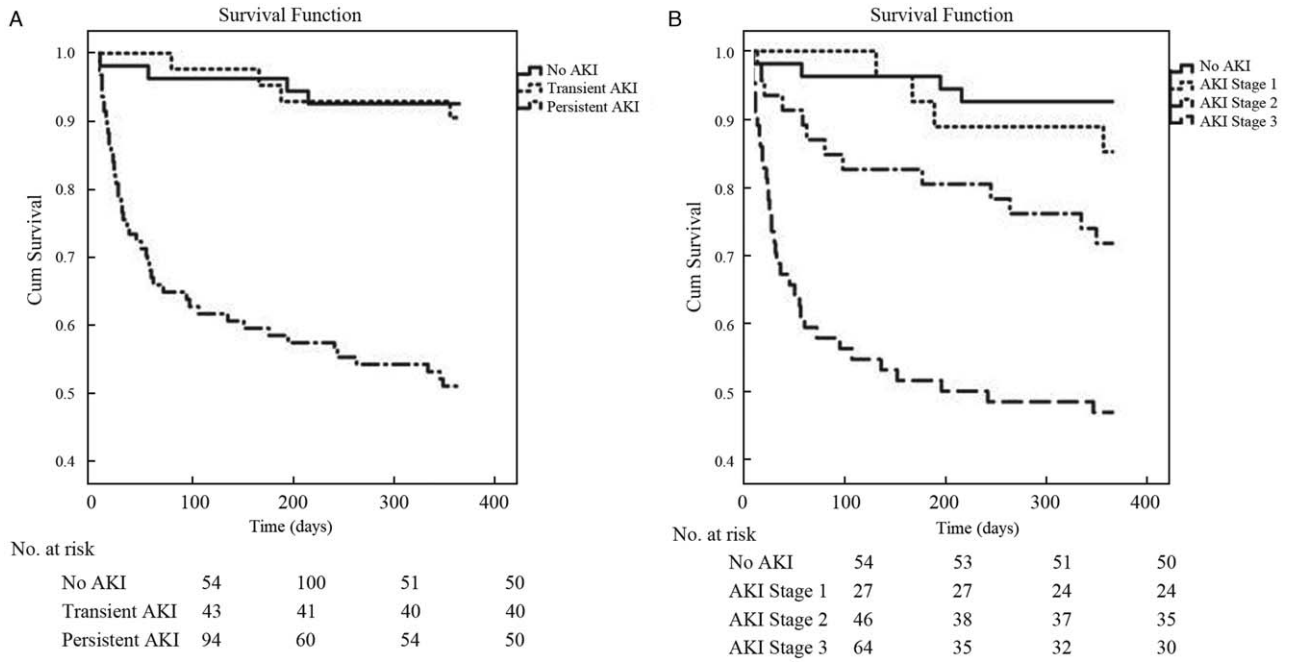

Figure 3: One-year survival rate of patients stratified by AKI type (A) and stage (B). $P < 0.050$ for all groups compared with each other except for transient AKI *vs.* no AKI and AKI stage 1 *vs.* no AKI. AKI: Acute kidney injury.

Table 6: Multivariable Cox proportional hazard regression analysis of the association between AKI type or stage of AKI and 1-year mortality.

	Unadjusted			Adjusted for age and sex		
Items	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
AKI type						
No AKI	Reference			Reference		
Transient AKI	2.46	0.45–13.45	0.298	2.45	0.45–13.46	0.302
Persistent AKI	14.69	3.54–60.91	<0.01	14.65	3.50–61.28	<0.01
Stage of AKI						
AKI stage 1	3.93	0.72–21.46	0.114	3.76	0.68–20.67	0.128
AKI stage 2	6.32	1.38–28.85	0.017	6.16	1.34–28.29	0.019
AKI stage 3	17.29	4.12–72.58	<0.01	16.73	3.97–70.54	<0.01

AKI: Acute kidney injury; CI: Confidence intervals; HR: Hazard ratio.

Transplantation (ISHLT) registry found that males receiving LTx are associated with worse clinical outcomes than females.[19] The pre-operative use of MV or the use of MV for >3 days after LTx was related to the onset of AKI, which may be attributed to the severity of the respiratory failure and reduced kidney blood flow associated with intrathoracic positive pressure.[8,20] Hemodynamics have been shown to have a major impact on AKI development, and we confirmed these previous observations.[1,9] Patients with AKI have poorly controlled hemodynamics during or after surgery, with intraoperative or post-operative severe hypotension and the need for more vasoactive amines and prolonged ECMO support.[8,9]

Similar to Balci *et al*,[21] our study indicated that AKI was related to infection after LTx. Septic shock was more common in AKI patients than in patients without AKI, which can be attributed to hemodynamic instability, the systemic response involving the release of inflammatory cytokines, and/or antimicrobial drug toxicity.[21,22] We also found that post-operative AKI was associated with increased risks of reintubation and MODS. Nephrotoxic agents are known to contribute to AKI.[23,24] We found that high blood levels of tacrolimus or the administration of other nephrotoxic agents in the early phase following LTx, such as aminoglycosides, polymyxin, and trimethoprim-sulfamethoxazole, were associated with the onset of AKI.

The independent predictors of persistent AKI were also investigated. Our data showed that persistent AKI was independently associated with pre-operative pulmonary hypertension, intraoperative or post-operative severe hypotension, post-operative MODS, a higher trough level

of tacrolimus, and the use of other nephrotoxic agents. Moreover, intraoperative or post-operative severe hypotension, septic shock, MODS, reintubation, prolonged MV or ECMO, a higher trough level of tacrolimus, and the use of other nephrotoxic agents in the early phase of LTx were related to severe AKI occurrence (AKI stage 3).

Several studies have shown negative effects of AKI on clinical outcomes and long-term kidney function.[3,8,9,21] In our series, patients with AKI had longer durations of post-operative MV, longer stays in the ICU, and worse kidney function at 1 year compared with those without kidney injury. Patients with persistent AKI had a longer duration of MV, longer ICU stays, more severe kidney injury, and a more obvious decline in kidney function at 1 year following LTx than patients with transient AKI. One-year kidney function following LTx showed obvious gradual decreases with worsening AKI severity.

Our data also confirmed that post-operative AKI had an adverse impact on survival after LTx (30-day survival rate of AKI patients and patients without AKI, 83.2% *vs.* 98.1%, $P = 0.005$; 1-year survival rate, 62.8% *vs.* 92.6%, $P < 0.001$). When compared with transient AKI patients, persistent AKI patients had significantly lower 30-day and 1-year survival rates (75.5% *vs.* 100% and 51.1% *vs.* 88.4%, respectively). The 30-day and 1-year survival rates were similar in transient AKI patients and in patients without AKI in our population. Similar to Fidalgo *et al*,[10] our study showed that persistent AKI patients had a worse long-term survival rate than patients with transient AKI or without AKI. When stratified by AKI severity, we also observed a gradual decrease in 1-year survival rate after LTx with worsening AKI severity, suggesting that both AKI stages 2 and 3 are independently related to higher mortality after LTx, consistent with previous reports.[3,8,9]

Our study has several limitations. First, this is a retrospective and single-center study, and the results may therefore be limited by the features of our study population. Second, the small sample size, the sex imbalance, and the relatively older median age of the study population are also visible limitations that prevent the extrapolation of our results to other populations. Finally, we did not integrate urine output into the KDIGO classification of AKI in our analysis because not all patients had available post-operative urine output data. Fluid overload has been recognized as an independent risk factor for worse kidney recovery and clinical outcomes in AKI patients.[25] The effect of fluid homeostasis on kidney function and survival following LTx needs further study.

Conclusions

AKI is becoming increasingly common after LTx. The pathogenesis of AKI is complicated, and prerenal factors have a vital impact on the development of AKI. The optimization of hemodynamic management, proper vasoactive therapy, and rational use of nephrotoxic agents are useful preventive strategies. Persistent and severe AKI had negative impacts on patients who underwent LTx and were related to longer duration of MV, longer ICU stays, worse downstream kidney function, and reduced survival.

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Conflicts of interest

None.

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