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Association between transient acute kidney injury and morbidity and mortality after lung transplantation: A retrospective cohort study ☆

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ABSTRACT

Purpose: Acute kidney injury (AKI) is a common occurrence after lung transplantation (LTx). Whether transient AKI or early recovery is associated with improved outcome is uncertain. Our aim was to describe the incidence, factors, and outcomes associated with transient AKI after LTx.

Materials and Methods: We performed a retrospective cohort study of all adult recipients of LTx at the University of Alberta between 1990 and 2011. Our primary outcome transient AKI was defined as return of serum creatinine below Kidney Disease–Improving Global Outcome AKI stage I within 7 days after LTx. Secondary outcomes included occurrence of postoperative complications, mortality, and long-term kidney function.

Results: Of 445 LTx patients enrolled, AKI occurred in 306 (68.8%) within the first week after LTx. Of these, transient AKI (or early recovery) occurred in 157 (51.3%). Transient AKI was associated with fewer complications including tracheostomy (17.2% vs 38.3%; $P < .001$), reintubation (16.4% vs 41.9%; $P < .001$), decreased duration of mechanical ventilation (median [interquartile range], 69 [41-142] vs 189 [63-403] hours; $P < .001$), and lower rates of chronic kidney disease at 3 months (28.5% vs 51.1%, $P < .001$) and 1 year (49.6% vs 66.7%, $P = .01$) compared with persistent AKI. Factors independently associated with persistent AKI were higher body mass index (per unit; odds ratio [OR], 0.91; 95% confidence interval, 0.85-0.98; $P = .01$), cyclosporine use (OR, 0.29; 0.12-0.67; $P = .01$), longer duration of mechanical ventilation (per hour [log transformed]; OR, 0.42; 0.21-0.81; $P = .01$), and AKI stages II to III (OR, 0.16; 0.08-0.29; $P < .001$). Persistent AKI was associated with higher adjusted hazard of death (hazard ratio, 1.77 [1.08-2.93]; $P = .02$) when compared with transient AKI (1.44 [0.93-2.19], $P = .09$) and no AKI (reference category), respectively.

Conclusions: Transient AKI after LTx is associated with fewer complications and improved survival. Among survivors, persistent AKI portends an increased risk for long-term chronic kidney disease.

1. Introduction

Acute kidney injury (AKI) occurs in approximately 50% to 70% of patients after lung transplantation (LTx) [1,2] and portends an increased risk for short- and long-term morbidity and mortality [3].

Although the long-term impact of AKI on survival has been well characterized [4], there is limited information on the modifying impact of transient AKI on renal outcomes. Most studies focused on renal recovery after AKI have used independence from renal replacement therapy (RRT) to define recovery [5]. However, this definition is limited by omitting those patients with milder forms of AKI not receiving RRT. Recovery from less severe AKI has been associated with improved long-term survival among patients undergoing cardiac surgery [6–8]. To date, few studies have

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CI, confidence intervals; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; CyA, cyclosporine; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FEV1/FVC, ratio forced expiratory volume 1 second and forced vital capacity; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; KDIGO, Kidney Disease–Improving Global Outcome; LAS, lung allocation score; LTx, lung transplantation; OR, odds ratio; RRT, renal replacement therapy; sCr, serum creatinine criteria; Tac, tacrolimus.

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described the impact of renal recovery after AKI following LTx [9,10], and no study has specifically evaluated the effect of transient AKI.

We therefore hypothesized that transient AKI would be associated with improved short- and long-term outcomes in patients undergoing LTx compared with those not recovering function. Accordingly, our objectives were to (1) describe the incidence of transient AKI in a large cohort receiving LTx, (2) describe factors associated with transient AKI, and (3) describe the association of transient AKI on the occurrence of postoperative complications, mortality, kidney function, and resource use.

2. Methods

The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies [11]. The local health research ethics board at the University of Alberta approved this study prior to commencement. The requirement for individual informed consent was waived.

2.1. Study design, setting, and population

We performed a retrospective population-based cohort study of all adult patients receiving LTx at the University of Alberta between 1990 and 2011. The LTx program at the University of Alberta, the second largest in Canada [12] with an average of 30 to 35 lung transplants per year in the last decade, is the referral base for LTx in the provinces of Alberta and Saskatchewan (population ~5.2 million).

Inclusion criteria were as follows: (1) age ≥ 18 years and (2) received any of single, double, or combined heart-lung transplantation.

Exclusion criteria were as follows: (1) death within 24 hours of LTx; (2) preoperative advanced chronic kidney disease (CKD) stage 4 or 5, defined by the Kidney Disease–Improving Global Outcome (KDIGO) CKD classification [13]; (3) documented preoperative AKI or receipt of RRT within 1 month prior to LTx; and (4) data unavailable on vital status.

2.2. Surgical technique

Cardiopulmonary bypass (CPB) was used in most cases (76%), with increasing frequency in the more recent LTx recipients. Standardized postoperative care was used in all patients, with hemodynamic monitoring performed in a specialized cardiovascular surgical intensive care unit.

2.3. Immunosuppression protocol

All patients received induction therapy consisting of corticosteroids (intravenous methylprednisolone 0.5 g administered intraoperatively before reperfusion of the allograft followed by tapering postoperatively), antilymphocyte therapy (antithymocyte globulin [ATGAM, Pfizer, United States] 10 mg kg^{-1} d^{-1} for 5-10 days in 308 patients, rabbit antithymocyte globulin [Thymoglobulin, Sanofi, Canada] 1.5 mg kg^{-1} d^{-1} for 5-10 days in 11 patients, or dacluzimab 1 mg/kg on days 1 and 4 in 83 patients), and azathioprine 100 mg/d or mycophenalate mofetil 3 g/d. In 2000, mycophenalate mofetil replaced azathioprine in the baseline regimen for all patients. Calcineurin inhibitors were introduced on days 2 to 5 using either tacrolimus (Tac; target trough 10-15 ng/mL) or cyclosporine (CyA; target trough 250-350 ng/mL) prior to the introduction of Tac. Although CyA was the predominant calcineurin inhibitor used until 2006, Tac was the most commonly prescribed thereafter. The standard perioperative antimicrobial regimen consisted of prophylactic cefazolin (3 doses) or vancomycin (2 doses), if there was a penicillin allergy; sulfamethoxazole 400 mg/trimethoprim 80 mg daily; and fluconazole daily and gancyclovir, if either recipient or donor cytomegalovirus serology was positive. This regimen was individualized according to perioperative tissue cultures.

2.4. Operational definitions

Lung allocation score (*LAS*) was calculated for all patients according to the method described by Egan et al [14]. *Acute kidney injury* was defined and severity was staged according to the serum creatinine criteria (sCr) of the KDIGO classification scheme [15]. We defined the presence of AKI by an absolute increase in sCr ≥ 26.5 μmol/L or 1.5-fold relative change from baseline sCr in the first 7 postoperative days. Severity of AKI was classified as follows: stage I, an increase in sCr ≥ 26.5 μmol/L or 1.5 to 1.9 times baseline; stage II, an increase in sCr 2.0 to 2.9 times baseline; and stage III, an increase in sCr 3.0 times baseline, or an increase to sCr ≥ 354 μmol/L or initiation of RRT. Data on urine output were unavailable, and the urine output criteria of the KDIGO classification were omitted. *Baseline sCr* was defined as the lowest value available prior to day of surgery and estimated glomerular filtration rate (eGFR) was calculated according to the CKD Epidemiology Collaboration formula [16]. *Chronic kidney disease* was defined by an eGFR <60 mL/min per 1.73 m^2 and further classified according to the KDIGO guidelines [13]. *Transient AKI* was defined as sCr values returning to the no-AKI range within the first 7 days after LTx in those not receiving RRT [17]. Patients who received RRT at any time during the first 7 days after LTx or those with incomplete recovery (reduction of sCr but still classified as AKI, irrespective of stage) during the 7 days after LTx were classified as "persistent AKI." The causes of death were categorized according to the groups reported in the International Society for Heart and Lung Transplantation registry: bronchiolitis, acute rejection, malignancy, infection, graft failure technical, and other [18].

2.5. Outcomes

Primary outcome was incidence of transient AKI. Secondary outcomes included the following: (1) mortality in intensive care unit (ICU), hospital, and at 1 year; (2) duration of mechanical ventilation, reintubation rate, and tracheostomy rate; (3) kidney function at 3 months and 1 year; and (4) duration of posttransplant stay in the ICU and hospital and rates of ICU readmission.

2.6. Data collection

Data were obtained from 2 sources: the University of Alberta LTx Program database and medical record review. All patients receiving either LTx or combined heart and LTx have been prospectively entered into this database since 1997, and prior to this, data were retrospectively entered. The LTx database routinely captures demographic (eg, age, sex, and weight), preoperative (eg, pulmonary diagnosis, pulmonary function, and comorbid disease), intraoperative (eg, procedure type, donor, and recipient-specific data), and postoperative data (eg, acute physiology, organ function, adverse events, immunosuppression regimen, survival, and graft function) on standardized case report forms. Patient medical records were reviewed to capture supplementary information not routinely captured by the LTx database (eg, details of RRT, kidney recovery, and long-term kidney function).

2.7. Statistical analysis

Descriptive statistics were calculated for the entire cohort and expressed as mean (SD) or median (25th, 75th percentiles [interquartile range, or IQR]) for parametric and nonparametric continuous variables, respectively, and number (%) for categorical variables. We compared variables between individuals with transient and persistent AKI by using Student *t* test and Mann-Whitney test, or χ^2 and Fisher exact test, where appropriate. For multiple comparisons with 3 groups