ACUTE KIDNEY INJURY AFTER LUNG TRANSPLANTATION: PERIOPERATIVE RISK FACTORS AND OUTCOME

Enora Atchade (enora.atchade@aphp.fr)
Hôpital Bichat Claude Bernard https://orcid.org/0000-0003-2726-106X

Samira Barour
APHP, CHU Bichat-Claude Bernard, Département d'Anesthésie Réanimation, 46 rue Henri Huchard, 75018 Paris

Alexy Tran-Dinh
APHP, CHU Bichat-Claude Bernard

Sylvain Jean-Baptiste
APHP, CHU Bichat-Claude Bernard

Sébastien Tanaka
APHP, CHU Bichat-Claude Bernard

Parvine Tashk
APHP, CHU Bichat-Claude Bernard

Aurélie Snauwaert
APHP, CHU Bichat-Claude Benard

Brice Lortat-Jacob
APHP, CHU Bichat Claude Bernard

Gisele Mourin
APHP, CHU Bichat-Claude Bernard

Pierre Mordant
APHP, CHU Bichat Claude Bernard

Yves Castier
APHP, CHU Bichat-Claude Bernard

Hervé Mal
APHP, CHU Bichat-Claude Bernard

Christian de Tymowski
APHP, CHU Bichat-Claude Bernard

Philippe Montravers
APHP, CHU Bichat Claude Bernard

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Abstract

BACKGROUND Acute kidney injury (AKI) is associated with increased short-term and long-term mortality and morbidity after lung transplantation (LT). The primary objective of this study was to analyze the perioperative factors associated with AKI according to KDIGO criteria during hospitalization in an intensive care unit (ICU) after LT. METHODS This was a single-center observational, prospective study. AKI was defined according to KDIGO criteria. Results are expressed as median, interquartile range, absolute numbers and percentages. Statistical analyses were performed using Chi-square test, Fisher's exact test and Mann-Witney U test ($p<0.05$ was considered to be significant). Multivariate analysis was performed to identify independent risk factors. RESULTS Between January 2016 and April 2018, 94 patients (pts) underwent LT (70% bilateral LT). AKI occurred during ICU stay in 46 pts (49%). KDIGO 1 AKI was observed in 16 pts (17%), KDIGO 2 in 14 pts (15%), and KDIGO 3 in 16 pts (17%) including 12 pts (75%) who required renal replacement therapy (RRT). AKI occurred before the fifth day after surgery for 38 patients (82% of the AKI patients). On multivariate analysis, independent factors associated with AKI were bilateral LT and mechanical ventilation (MV) > 3 days (OR 4.26 95%CI [1.49; 13.63] p=0.010 and OR 5.56 [1.25; 11.47] p=0.018, respectively). AKI and the need for RRT were significantly associated with ICU mortality, 28-day mortality and one-year mortality. CONCLUSION AKI is common during ICU stay after LT, especially after bilateral LT and is associated with prolonged MV, and increased short-term and long-term mortality.

Background

Acute kidney injury (AKI) is a common complication after lung transplantation (LT), observed in 39 to 69% of LT recipients (1–4) and leading to renal replacement therapy (RRT) in 5 to 13% of cases (4,5). Despite improved surgical techniques, LT remains a procedure associated with a high bleeding risk, with major intraoperative changes of cardiac output and blood volume. The postoperative period also plays a major role in the pathophysiology of AKI, marked by hemodynamic instability and the use of nephrotoxic agents. Interestingly, only a few published studies have described AKI in the post-transplantation period and did not specifically focus on the perioperative period. All of these studies present major limitations, including their retrospective nature, based on small numbers of patients, using widely different definitions of AKI, making it difficult to compare their results. Since 2012, KDIGO criteria can be used to standardize AKI definitions and characterize the severity of renal impairment (6,7). To our knowledge, only one published study has used the KDIGO classification to characterize AKI after LT (4).

The primary objective of this study was to prospectively analyze the preoperative, intraoperative and postoperative factors associated with AKI defined by KDIGO criteria during the ICU stay after LT. Secondary objectives were to assess the incidence of AKI during hospitalization in ICU after LT, determine the characteristics of LT recipients according to KDIGO stage and time of onset, and determine the outcome of patients according to the presence of postoperative AKI, the stage of AKI, and the time of onset.

Methods

Study population

This single-center observational, prospective study included all consecutive patients who underwent LT at Bichat Claude Bernard Hospital, Paris from January 2016 to April 2018. The study period included all of the ICU stay after LT. According to French law, the patient's absence of refusal was obtained before inclusion in the study. The study was approved by the Paris-North-Hospitals Institutional Review board (Paris Diderot University, APHP, IRB No. 0006477).

Perioperative management

Perioperative care, according to our standard protocol, was as follows (8,9). Epidural analgesia was initiated before induction of anesthesia. Propofol, remifentanil and atracurium were used for anesthesia. Intraoperative monitoring was performed using an invasive arterial line, a central venous catheter, Swan-Ganz catheterization, and transesophageal echocardiography. Extracorporeal Membrane Oxygenation (ECMO) for hemodynamic support was planned from the onset of surgery, in the event of severe pulmonary hypertension (mean pulmonary blood pressure > 25 mmHg or systolic pulmonary blood pressure > 35 mmHg) or pre-existing right cardiac dysfunction. ECMO was also implemented when the patient did not tolerate single-lung ventilation, in the presence of right ventricular failure when clamping the pulmonary artery, or in the presence of pulmonary arterial hypertension. Fluid administration was adapted to the patient's hemodynamic status. Hydroxyethyl starches are not used in our institution. A restrictive red-cell transfusion strategy was adopted (hemoglobin concentration <7 g/dL intraoperatively or postoperatively). A cell-saver system (Fresenius, Bad Homburg vor der Höhe, Germany) was used and tranexamic acid was administered in the absence of contraindication. Perioperative antibacterial prophylaxis consisted of second-generation cephalosporin continued for 48 hours, secondarily modified in the case of donor or recipient pneumonia, or preoperative colonization of the recipient. Emergency RRT was initiated in the presence of threatening hyperkalemia or severe metabolic acidosis (pH<7.15) according to current French guidelines (10). RRT was also initiated during the first 24 hours following onset of stage 3 AKI, which appeared unlikely to resolve spontaneously. Intermittent hemodialysis and continuous hemofiltration were both used depending on the patient's hemodynamic stability. Biomarker assays to monitor acute kidney injury (NGAL, IL-18, KIM-1…) are not commonly performed in our current practice. Immunosuppressive therapy was standardized for all patients and based on a combination of methylprednisolone, tacrolimus and mycophenolate mofetil. Antiviral prophylaxis was administered (ganciclovir in the case of donor and/or recipient positive CMV serology, otherwise acyclovir).

Data collection

Demographic characteristics, underlying diseases and clinical data were prospectively recorded at the time of ICU admission. The development of AKI in ICU, according to KDIGO criteria, and the need for RRT were assessed. A diagnosis of AKI before Day-5 after LT was called “early AKI”, while cases identified ≥ Day-5 were called “late AKI”. Preoperative serum creatinine, severity scores (SAPS II and SOFA scores on admission) were also assessed. Hemodynamic support by ECMO, vasoactive support, fluid administration, and intraoperative transfusion were recorded. During the ICU stay, postoperative complications including multiple organ dysfunction syndrome, prolonged ECMO support, primary graft dysfunction (PGD), acute rejection, pneumonia, septic shock, prone position ventilation, need for neuromuscular blocking agent (NBA) administration, reintubations, and reoperations, were recorded. Outcome criteria (tracheostomy, duration of MV and duration of ICU stay) were assessed. ICU, 28-day and one-year mortality rates were assessed. Creatinine clearance one year after LT was also recorded.

Statistical analysis

Qualitative data are expressed as absolute numbers and proportions and were compared by a Chi-square test or Fisher’s exact test, as appropriate. Quantitative data are expressed as median and interquartile range and were compared by Mann-Whitney or Kruskal-Wallis tests, as appropriate. The level of statistical significance was set at 5% and odds ratios (OR) with 95% confidence intervals (95%CI) were reported. Variables significantly associated with AKI in univariate analysis were introduced in a binary logistic regression model. The one-year survival rate was analyzed by Kaplan-Meier analysis and compared by a log rank test. SPSS software was used for statistical analysis (IBM Armonk, New York, USA).

Results

Characteristics of AKI observed in the study population

During the study period, 94 patients underwent LT in our institution. Median operating time was 7 [6-8] hours (7 [6-9] hours for bilateral LT and 6 [4-7] hours for single LT). Median SOFA score on ICU admission was 7 [5-8].

Overall, 46 (49%) patients developed AKI during their ICU stay. Clinical characteristics in patients with and without AKI are presented in Table 1. According to the KDIGO criteria, stage 1 AKI was observed in 16 (17%) patients, stage 2 AKI was observed in 14 (15%) patients and stage 3 AKI was observed in 16 (17%) patients. Among the 66 patients with bilateral LT, 39 (59%) developed AKI (KDIGO 1 in 12 (18%) patients, KDIGO 2 in 11 (17%) patients, KDIGO 3 in 16 (24%) patients). Clinical characteristics according to KDIGO stage are described in Table 2.

Description of patients depending on early/late onset of AKI

AKI occurred during the early postoperative period (<Day-5 after LT) for 38 patients (82% of AKI patients), and later for 8 patients (17% of AKI patients). Patient characteristics according to the early or late onset of AKI are described in Table 3.

Characteristics of patients with KDIGO 3 AKI

Twelve (13%) patients required RRT (continuous hemofiltration for 6 patients, intermittent hemodialysis for one patient, and both techniques for 5 patients). RRT was initiated a median of 7 [3-14] days after LT for a median duration of 8 [2-14] days. Characteristics of patients with KDIGO 3 AKI are described in Table 4.

Perioperative risk factors for AKI

Analysis of risk factors associated with the onset of AKI are presented in Table 1. On multivariate analysis, bilateral LT and prolonged MV were independently associated with AKI.

Outcome of patients with and without AKI

The outcome of LT recipients according to the presence or absence of AKI is reported in Table 5. AKI was observed in all patients who died before Day-28. Stage 3 AKI was reported in most (86%) of these deceased patients. One-year survival according to KDIGO stage is represented in Figure 1 A. One-year survival according to early or late onset of AKI is represented in Figure 1B. After one year, median creatinine clearance of survivors was 59 [48-86] mL/min, similar in patients with and without AKI (54 [34-75] mL/min and 55 [43-71] mL/min, respectively, p=0.75). Only 13 of the surviving patients (13% of the population) had a creatinine clearance > 90 mL/min one year after LT.

Discussion

While AKI is a common complication after LT (1,3,4), this study is, to the best of our knowledge, the first prospective study using KDIGO criteria to characterize renal impairment in the postoperative period after LT. In our cohort, AKI occurred during hospitalization in ICU in 49% of the LT recipients, with the need for RRT in 26% of these cases. In the vast majority of cases, AKI occurred early, before the fifth day after surgery. On multivariate analysis, independent factors associated with AKI were bilateral LT and prolonged MV. AKI and need for RRT were significantly associated with ICU mortality, 28-day mortality and one-year mortality.

The incidence of AKI after LT, reported in retrospective studies, ranges from 39 to 68.8% (3,4,11). This marked variation of incidence can be explained by the various definitions for AKI used in these studies. Most recent studies, using standardized classifications such as AKIN, RIFLE or KDIGO, have reported an AKI incidence ranging from 50% to 68.8% (2,4,12). Interestingly, data on AKI in the early postoperative period have not been presented in ISHLT registry (13). Overall, the results of our cohort are situated in the medium/low range of AKI incidence compared with previous results.

In our cohort, bilateral LT was an independent risk factor associated with AKI in ICU. Previous studies have reported similar results (1,3,5), with an incidence of AKI ranging between 39 to 62% after bilateral LT. A longer operating time alone cannot explain the association between bilateral LT and AKI. Some authors have suggested that lung surgery, by releasing inflammatory mediators, could generate apoptosis of renal epithelium causing AKI (5). Moreover, surgical pulmonary aggression could generate fluid retention and might lead to renal hypoperfusion (5). Perioperative hemodynamic instability, administration of nephrotoxic agents, calcineurin inhibitors and high doses of diuretics exacerbate this phenomenon (5). In our study, bilateral LT was associated with increased use of ECMO during surgery, an increased blood transfusion rate (especially massive transfusion > 5 PRC), as reported in the study by Jacques *et al*. (3). In the light of these results, the association between AKI and bilateral LT could be at least partially attributed to the higher bleeding risk of this surgery.

Interestingly, preoperative impaired creatinine clearance before LT was not significantly associated with AKI after LT, which appears to confirm the major impact of perioperative aggression on the development of AKI. However, the low rate of recipients with pre-existing impaired creatinine clearance in our cohort limits the reliability of this result. Preoperative impaired creatinine clearance also did not appear to have any impact on early or late onset of AKI.

In our study, MV > 3 days was independently associated with AKI. The link between prolonged MV and AKI seems to be related to the severity of respiratory failure. Previous studies have reported that prolonged MV is a risk factor for AKI (1,12,14), which could be due to decreased renal blood flow related to intrathoracic positive pressure. We can also hypothesize that prolonged MV is a marker of severity rather than a risk factor for AKI.

In our study, AKI was associated with increased short-term and long-term mortality rates. Previous studies have also reported the major impact of AKI on mortality in LT recipients. Similar findings have been reported in ICU patients with AKI, in fields other than LT (1,5,14–16). Fidalgo *et al.* observed a higher mortality rate associated with more severe degrees of AKI (4). In addition, the need for RRT appears to have a major impact on survival rates (2,4,5). In the large study by George *et al*., the need for RRT was an independent risk factor associated with one-year mortality (5). In our study, stage 3 AKI was associated with markedly decreased early survival, while stage 2 AKI appeared to be associated with later mortality. No clear explanation can be proposed for this observation.

We observed a significant association between acute antibody-mediated rejection and late onset of AKI. We can hypothesize that this association is a consequence of administration of nephrotoxic multivalent

immunoglobulins.

Our study presents several limitations. Interpretation of the results is limited by the single-center design, and by the characteristics of our study population. Pulmonary fibrosis and COPD are the most common indications for LT in our center, while cystic fibrosis (CF) represents 15.6% of all LT indications worldwide (13). The small number of CF patients and the high median age of the study population is also an obvious limitation to extrapolation of our results. However, as mentioned above, our results are situated in the low range of AKI incidence despite the advanced age of our cohort, a risk factor for renal dysfunction. An additional limitation is related to the fact that the effects of nephrotoxic agents (radiocontrast agents, tacrolimus…) were not recorded in our cohort. Tacrolimus renal toxicity via intrarenal hemodynamic alterations is well established. (17, 18). Our immunosuppression protocol consisted of systematic administration of tacrolimus, although a possible association between tacrolimus overdosage and AKI cannot be determined.

CONCLUSION

Our prospective data based on well-admitted criteria confirm the high rate of AKI following LT. Both short-term and long-term consequences are marked by poor outcome. Survivors generally presented impaired renal function, as no patient had normal creatinine clearance at one year. Unfortunately, the risks factors for AKI identified in our population cannot be easily treated. These observations should encourage physicians in charge of these difficult cases to adopt preventive strategies right from the preoperative phase of LT. Optimization of fluid volume and cardiac output, and careful use of nephrotoxic drugs including immunosuppressive therapy are obvious strategies. The role of biomarkers, anti-inflammatory and preventive approaches has yet to be determined in this high-risk population.

Abbreviations

AKI: Acute Kidney Injury

BMI: Body Mass Index

COPD: Chronic obstructive pulmonary disease

ECMO: Extra-Corporeal Membrane Oxygenation

HBP: High Blood Pressure

ICU: Intensive care unit

ISHLT: International Society for Heart and Lung Transplantation

KDIGO: Kidney Disease: Improving Global Outcome

LT: Lung transplantation

MV: Mechanical ventilation

NBA: Neuromuscular Blocking Agent

OR: Odds ratio

PGD: Primary Graft dysfunction

PRC: Packed Red Cells

RRT: Renal Replacement Therapy

SOFA: Sequential organ failure assessment

Declaration Section

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FUNDING

None

AVAILABILITY OF DATA AND MATERIALS

Datas are available on request to the corresponding author

AUTHORS CONTRIBUTION

EA participated to the study design, acquisition of data, analysis and interpretation of data, performed the statistical analysis and drafted the manuscript. SB participated to the acquisition, analysis and interpretation of data. ATD, SJB, ST, PT, AS, BLJ, GM, PM, YC and HM have made substantial contributions to the interpretation of dtata. CDT and PM were involved in the study design, statistical analysis, interpretation of data and drafted the manuscript. All authors have read and approved the final manuscript.

ETHICS AND CONSENT TO PARTICIPATE

The study was approved by the Paris North Hospitals Institutional Review Board (Paris VII University, AP-HP, IRB No 0006477). According to French law, after information, verbal non opposition of patients to participate was collected.

CONSENT FOR PUBLICATION

Not applicable

COMPETING INTERESTS

No relevant disclosure related to publication of this manuscript

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Tables

TABLE 1: AKI and perioperative risk factors

(BMI Body mass index; LT: lung transplantation; COPD: chronic obstructive pulmonary disease; HBP: High blood pressure; ECMO: Extra-Corporeal Membrane Oxygenation; PRC:

Packed Red Cell; MV: mechanical ventilation; PGD: Primary graft dysfunction; NBA: neuromuscular blocking agent)

			Univariate analysis			Multivariate analysis		
	AKI n= 46	No AKI n= 48	OR	95% CI	P value	OR	95%CI	P value
Preoperative variables								
Age, years, median [IQR]	55.5 [50-59]	54.5[47-67]	-	-	0.47	1.00	0.98-1.07	0.32
BMI, median [IQR]	24 [19;27]	22 [19;27]	-	-	0.21			-
Male gender, n (%)	28 (61)	32 (66)	0.78	0.34-1.81	0.67			-
Diagnosis leading to LT								
§ Pulmonary fibrosis, n (%)	19 (41)	21 (44)	0.91	0.40-2.05	0.84			-
§ COPD, n (%)	18 (39)	11 (23)	2.16	0.88-5.30	0.12			-
HBP, n (%)	14 (30)	11 (23)	1.47	0.59-3.70	0.49			-
Pulmonary hypertension, n (%)	24 (52)	22 (46)	1.49	0.65-3.42	0.40			-
Diabetes mellitus, n (%)	3 (6)	6 (12)	0.49	0.12-2.08	0.32			-
Dyslipidemia, n (%)	11 (24)	6 (12)	2.20	0.74-6.55	0.19			-
BMI < 17.5 $kg \cdot m^{-2}$, n (%)	3 (7)	7 (15)	0.41	0.099-1.69	0.32			-
BMI > 29.9 $kg \cdot m^{-2}$, n (%)	7 (15)	5 (10)	1.54	0.43-5.26	0.55			-
Creatinine clearance, ml/min, median [IQR]	90 [80;90]	90 [64;87]	-	-	0.85			-
Preoperative creatinine clearance > 90 mL/min, n (%)	28 (61)	30 (63)	0.93	0.41-2.15	1			-
High-emergency LT, n (%)	9 (19)	9 (19)	1.05	0.38-2.95	1			-
ECMO before surgery, n (%)	4 (9)	2 (4)	2.19	0.38-12.58	0.43			-
Intraoperative variables								
Bilateral LT, n (%)	39 (85)	27 (56)	4.26	1.49-13.63	0.003	6.72	1.44-13.79	0.010
Operating time, min, median [IQR]	420 [368;510]	420 [315;475]	-	-				-
ECMO support, n (%)	37 (80)	34 (71)	1.69	0.65-4.41	0.34			-
Cardiac arrest during surgery, n (%)	4 (9)	0 (0)	-	-	0.053			
Catecholamine administration, n (%)	43 (93)	45 (94)	0.96	0.18-5.00	0.1			-
Norepinephrine > 42 µg/min or epinephrine, n (%)	18 (39)	15 (31)	1.41	0.56-3.62	0.52			-
Fluid administration > 30 ml/kg, n (%)	43 (93)	43 (89)	2	0.35-11.50	0.68			-

Blood cell transfusion, n (%)	34 (74)	32 (67)	1.42	0.58-3.45	0.50			
Transfusion > 5 PRC, n (%)	11 (24)	4 (8)	3.46	1.01-11.80	0.050	1.27	0.55-9.33	0.26
Fresh frozen plasma transfusion, n (%)	27 (59)	25 (52)	1.31	0.58-2.96	0.54			-
Platelet transfusion, n (%)	13 (28)	9 (19)	1.71	0.65-4.50	0.33			-
Postoperative variables (ICU stay)								
SOFA score on ICU admission, median [IQR]	7 [6-10]	6 [4-7]	-	-	0.001			-
Lactate > 3 mmol/L on ICU admission, n (%)	23 (50)	10 (21)	3.74	1.42-10.53	0.0047			-
Norepinephrine > 42 µg/min on ICU admission, n (%)	12 (26)	7 (15)	2.05	0.66-6.88	0.20			
pH < 7.20 on ICU admission, n (%)	8 (17)	13 (28)	0.57	0.18-1.69	0.32			-
Multiple organ dysfunction during ICU stay, n (%)	22 (48)	5 (10)	7.52	2.52-22.44	0.001			-
Catecholamine administration > 3 days, n (%)	15 (33)	8 (17)	2.42	0.91-6.43	0.094	0.13	0.23-2.75	0.71
Duration of catecholamine administration, days, median [IQR]	2 [1-4]	1 [1-3]	-	-	0.020			-
Postoperative ECMO support, n (%)	14 (30)	12 (25)	1.31	0.53-3.25	0.65			-
Duration of ECMO support > 2 days, n (%)	6 (13)	3 (6)	2.25	0.53-9.59	0.31			
Duration of ECMO support, median [IQR]	0 [0-1]	0 (0)	-	-	0.22			-
Atrial fibrillation, n (%)	14 (30)	19 (39)	0.62	0.26-1.47	0.39			-
Cardiac arrest during ICU stay, n (%)	10 (22)	1 (2)	12.78	1.56-104.49	0.004			-
NBA administration, n (%)	16 (35)	6(12)	3.73	1.31-10.66	0.015			
Prone position, n (%)	6 (13)	2 (4)	3.45	0.66-18.06	0.15			-
Duration of MV, median [IQR]	4 [1-18]	2 [1-3]	-	-	0.008			-
MV > 3 days, n	23 (50)	10 (21)	3.97	1.6-9.86	0.003	5.56	1.25-11.47	0.018

(%)						
Reintubation; n (%)	7 (15)	5 (10)	1.54	0.38-6.68	0.55	-
PGD, n (%)	33 (72)	32 (67)	1.27	0.48-3.37	0.66	-
Stage 3 PGD, n (%)	19 (41)	14 (29)	1.71	0.73-4.02	0.28	-
Septic shock during ICU stay, n (%)	15 (33)	4 (8)	5.08	1.54-16.81	0.009	
Pneumonia > 2 episodes, n (%)	6 (13)	3 (6)	2.20	0.52-9.38	0.32	-
Repeat chest surgery, n (%)	8 (17)	6 (12)	1.47	0.47-4.64	0.57	-
Abdominal surgery during ICU stay, n (%)	10 (22)	2 (4)	6.39	1.32-31.01	0.013	
Acute antibody-mediated rejection, n (%)	9 (19)	14 (29)	0.59	0.23-1.54	0.34	-
Acute cellular rejection, n (%)	7 (15)	3 (6)	2.69	0.65-11.13	0.19	-

TABLE 2: Patient characteristics according to KDIGO stage

(LT: lung transplantation; ECMO: Extracorporeal membrane oxygenation; PRC: packed red cell; MV: mechanical ventilation)

	KDIGO 1 n= 16	KDIGO 2 n= 14	KDIGO 3 n= 16	P value
Creatinine clearance before LT < 90 ml/min, n (%)	9 (56)	6(43)	13 (81)	0.09
Bilateral LT, n (%)	12 (75)	11 (78)	16 (100)	0.11
Support by ECMO, n (%)	12 (75)	12 (86)	13 (81)	-
Intraoperative catecholamine administration, n (%)	15 (94)	12 (86)	15 (94)	-
Intraoperative norepinephrine < 42 µg/min or epinephrine, n (%)	6 (38)	6 (43)	6 (38)	0.94
Intraoperative red blood cell transfusion, n (%)	9(56)	10 (71)	15 (94)	0.05
Transfusion > 5 PRC, n (%)	2 (13)	4 (29)	5(31)	-
Intraoperative fresh frozen plasma transfusion, n (%)	7 (44)	7 (50)	13 (81)	0.07
Intraoperative platelet transfusion, n (%)	2 (13)	5 (36)	6 (38)	-
Intraoperative fluid administration > 30 ml/kg, n (%)	15(94)	12 (86)	16 (100)	0.55
Duration of MV > 3 days, n (%)	5 (31)	6 (43)	13 (81)	0.013

TABLE 3: Patient characteristics according to early or late onset of AKI

(LT: lung transplantation; COPD: chronic obstructive pulmonary disease; HBP: High blood pressure; ECMO: Extra-Corporeal Membrane Oxygenation; BMI Body mass index; PRC: Packed Red Cell; MV: mechanical ventilation; PGD: Primary graft dysfunction; NBA: neuromuscular blocking agent)

			Univariate analysis			Multivariate analysis		
	Early AKI n=38	Late AKI n=8	OR	95%CI	P value	OR	95%CI	P value
Preoperative variables								
Age, years, median	56 [50-59]	55 [47-56]	-	-	0.50		-	
Male gender, n (%)	23 (61)	5 (63)	1.09	0.23-5.24	1		-	
Diagnosis leading to LT								
§ Pulmonary fibrosis, n (%)	14 (37)	3 (38)	0.83	0.17-3.96	1		-	
§ COPD, n (%)	14 (37)	4 (50)	1.71	0.37-7.95	0.69		-	
HBP, n (%)	12 (32)	2 (25)	0.72	0.13-4.12	1		-	
Pulmonary hypertension, n (%)	10 (26)	4 (50)	1.07	0.21-5.47	1		-	
Diabetes mellitus, n (%)	3 (8)	0 (0)	-	-	1		-	
Dyslipidemia, n (%)	10 (26)	1 (13)	0.40	0.04-3.67	0.66		-	
BMI > 29.9 $kg{\cdot}m^{-2}$, n (%)	6 (16)	1 (13)	0.76	0.079-7.37	1		-	
Preoperative creatinine clearance > 90 ml/min, n (%)	24 (63)	4 (50)	0.58	0.13-2.71	0.69			
High emergency LT, n (%)	8 (21)	1 (13)	0.54	0.06-5.01	1		-	
ECMO before surgery, n (%)	3 (8)	1 (13)	1.67	0.15-18.45	0.55		-	
Intraoperative variables								
Bilateral LT, n (%)	32 (84)	7 (88)	0.77	0.014-8.15	1	1.58	0.06-3.00	0.21
Hemodynamic support by ECMO, n (%)	31 (82)	6 (75)	0.68	0.11-4.09	0.65		-	
Cardiac arrest during surgery, n (%)	2 (5)	2 (25)	6	0.70-51.1	0.13			
Intraoperative catecholamine	36 (95)	7 (88)	0.40	0.031-4.90	0.44		-	

administration, n (%)						
Norepinephrine > 42 µg/min or epinephrine administration, n (%)	16 (42)	2 (25)	2.15	0.33-24.46	0.45	-
Fluid administration > 30 mL/kg	35 (92)	8 (100)	-	-	1	-
Red blood cell transfusion, n (%)	29 (76)	5 (63)	0.52	0.10-2.60	0.41	-
Transfusion > 5 PRC, n (%)	8 (21)	3 (38)	2.25	0.44-11.48	0.37	-
Fresh frozen plasma transfusion, n (%)	23 (61)	4 (50)	0.65	0.14-3.02	0.70	-
Platelet transfusion, n (%)	10 (26)	3 (38)	1.68	0.34-8.35	0.67	-
Postoperative variables (ICU stay)						
Lactate on ICU admission >3 mmol/L, n (%)	17 (45)	6 (75)	0.28	0.024-1.81	0.24	-
Norepinephrine > 42 µg/min on admission in ICU, n (%)	10 (26)	2 (25)	1.07	0.15-12.53	1	-
pH < 7.20 on admission in ICU, n (%)	7 (22)	1 (14)	1.57	0.15-81.24	1	-
Postoperative support by ECMO, n (%)	10 (26)	4 (50)	2.8	0.59-13.36	0.22	-
Multiple organ dysfunction during ICU stay, n (%)	16 (47)	6 (75)	4.13	0.74-23.15	0.13	-
Catecholamine administration > 3 days, n (%)	12 (32)	3 (38)	1.30	0.27-6.35	1	-
Duration of catecholamine administration, median [IQR]	2 [1-4]	2 [2-16]				-
Postoperative ECMO support, n (%)	15 (39)	5 (63)	0.40	0.054-2.41	0.26	-
Duration of ECMO support > 2 days,	4 (10)	2 (25)	2.83	0.42-19.07	0.28	-

n (%)								
Duration of ECMO support, median [IQR]	0 [0-1]	1 [1-2]	-	-	0.17			
Atrial fibrillation during ICU hospitalization, n (%)	11 (29)	3 (38)	1.47	0.30-7.25	0.68		-	
Cardiac arrest during hospitalization in ICU, n (%)	8 (21)	2 (25)	1.25	0.21-7.41	1		-	
NBA administration, n (%)	11 (29)	5 (63)	4.09	0.83-20.14	0.11	1.61	0.47-35.21	0.20
Prone positioning, n (%)	3 (8)	3 (38)	7	1.10-44.72	0.056		-	
Duration of MV, median [IQR]	3 [1-10]	20 [14-31]	-	-	0.088		-	
MV > 3 days, n (%)	18 (47)	6 (75)	3.53	0.63-19.83	0.24		-	
Reintubation; n (%)	6 (16)	1 (13)	1.31	0.12-68.86	1		-	
PGD, n (%)	26 (68)	7 (88)	0.32	0.0064-2.94	0.41		-	
Stage 3 PGD, n (%)	14 (37)	5 (63)	2.86	0.59-13.81	0.25		-	
Septic shock during ICU stay, n (%)	10 (26)	5 (63)	4.67	0.94-23.19	0.09		-	
Pneumonia > 2 episodes, n (%)	4 (10)	2 (25)	2.83	0.42-19.07	0.28		-	
Repeat chest surgery, n (%)	6 (16)	2 (25)	1.78	0.29-11.00	0.61		-	
Abdominal surgery during hospitalization in ICU, n (%)	8 (21)	2 (25)	1.25	0.21-7.41	1		-	
Acute antibody-mediated rejection, n (%)	3 (8)	6 (75)	35	4.80-255.47	<0.0001	9.87	4.58-713.88	0.002
Acute cellular rejection, n (%)	4 (10)	3 (38)	5.10	0.87-29.85	0.089			

TABLE 5: Outcome of LT recipients according to AKI or RRT

	AKI n= 46	No AKI n= 48	P value	RRT n=12	No RRT n= 82	P value
ICU mortality rate, n (%)	10 (22)	1 (2)	0.03	7 (58)	4 (5)	< 0.001
28-day mortality rate, n (%)	7 (15)	0 (0)	0.005	6 (50)	1 (1)	< 0.001
One-year mortality rate, n (%)	16 (35)	6 (13)	0.015	7 (58)	15 (18)	0.006
Hospitalization in ICU > 45 days, n (%)	9 (19)	2 (4)	0.02	-	-	-
ICU readmission during the first-year post-LT, n (%)	17 (37)	16 (33)	0.83	2 (17)	31 (38)	0.20
Creatinine clearance < 90 ml/min at 1 year, n (%)	23 (77)	36 (86)	0.36	5 (100)	54 (80)	0.58
Creatinine clearance < 60 ml/min at 1 year, n (%)	17 (56)	25 (59)	0.81	4 (80)	38 (57)	0.39
Duration of MV, days, median [IQR]	4 [1-18]	2 [1-3]	0.008	13 [6-25]	2 [1-4]	< 0.001
Length of ICU stay, days, median [IQR]	16 [10-38]	13 [9-20]	0.11	21 [9-38]	14 [9-23]	0.37

AKI: acute Kidney injury; RRT: renal replacement therapy; ICU: Intensive Care Unit; MV: Mechanical Ventilation;

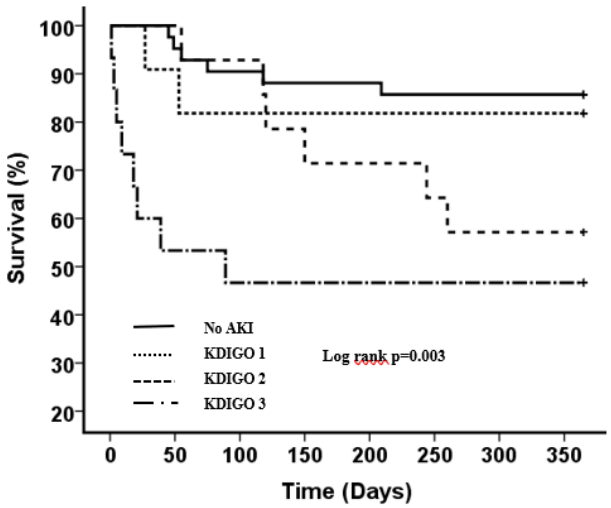
TABLE 4: Patient characteristics according to the presence of KDIGO 3 AKI

			Univariate analysis			Multivariate analysis		
	No KDIGO 3 n=78	KDIGO 3 n=16	OR	95%CI	P value	OR	95%CI	P value
Preoperative variables								
Age, years, median [IQR]	56 [49-62]	52 [46-56]	-	-	0.18			
BMI, median [IQR]	23 [19-27]	26 [18-28]	-	-	0.37			
Male gender, n (%)	52 (67)	8 (50)	1.98	0.58-6.85	0.26			
Diagnosis leading to LT								
§ Pulmonary fibrosis, n (%)	38 (49)	2 (13)	0.15	0.032-0.71	0.011			
§ COPD, n (%)	21(27)	8 (50)	2.71	0.90-8.16	0.081			
HBP, n (%)	19 (24)	6 (38)	1.86	0.60-5.80	0.35			
Pulmonary hypertension, n (%)	38 (49)	8 (50)	1.14	0.38-3.47	1			
Diabetes mellitus, n (%)	9 (12)	0 (0)	-	-	0.35			
Dyslipidemia, n (%)	14 (18)	3 (19)	1.055	0.27-4.20	1			
BMI < 17.5 $kg \cdot m^{-2}$, n (%)	14 (18)	2 (13)	1.25	0.24-6.52	0.68			
BMI > 29.9 $kg \cdot m^{-2}$, n (%)	9 (12)	3 (19)	1.77	0.42-7.43	0.42			
Creatinine clearance, ml/min, median [IQR]	90 [81-90]	90 [90-105]	-	-	0.14			
Preoperative creatinine clearance > 90 mL/min, n (%)	45 (58)	13 (81)	3.18	0.04-12.06	0.095			
High-emergency LT, n (%)	16 (21)	2 (13)	0.55	0.11-2.69	0.73			
ECMO before surgery, n (%)	5 (6)	1 (6)	0.97	0.11-8.94	1			
Intraoperative variables								
Bilateral LT, n (%)	50 (64)	16 (100)	-	-	0.0023	3.59	0.931-68.35	0.058
Duration of surgery, min, median [IQR]	420 [360-480]	420 [370-510]						
ECMO support, n (%)	58 (74)	13 (81)	1.49	0.39-5.79	0.75			
Cardiac arrest during surgery, n (%)	2 (3)	2 (13)	5.43	0.71-41.80	0.13			
Intraoperative catecholamine administration, n (%)	73 (94)	15 (94)	1.03	0.11-9.44	1			
Norepinephrine > 42 µg/min or epinephrine, n (%)	27 (35)	6 (38)	1.13	0.30-3.89	1			
Fluid administration > 30 ml/kg, n (%)	70 (90)	16 (100)	-	-	0.59			
Blood cell transfusion, n (%)	51 (65)	15 (94)	7.94	1.00-63.39	0.033			
Transfusion > 5 PRC, n (%)	10 (13)	5 (31)	3.09	0.89-10.77	0.125			
Fresh frozen plasma transfusion, n (%)	39 (50)	13 (81)	4.33	1.14-16.41	0.028			
Platelet transfusion, n (%)	16 (21)	6 (38)	2.33	0.74-7.36	0.19			
Postoperative variables (ICU stay)								

SOFA score on admission, median [IQR]	6 [4-7]	9 [8-11]						
Lactate on ICU admission > 3 mmol/L, n (%)	23 (29)	10 (63)	3.92	1.14-14.79	0.020			
Norepinephrine > 42 µg/min on admission in ICU, n (%)	13 (17)	6 (38)	2.96	0.75-11.03	0.084			
pH < 7.20 on ICU admission, n (%)	18 (23)	3 (19)	1.30	0.31-7.87	1			
Multiple organ dysfunction during ICU stay, n (%)	13 (17)	14 (88)	33.92	6.87-167.58	<0.0001			
Catecholamine administration > 3 days, n (%)	14 (18)	9 (56)	5.88	1.87-18.46	0.003			
Duration of catecholamine administration, days, median [IQR]	1 [1-3]	4[2-9]	-	-	0.003			
Postoperative ECMO support, n (%)	18 (23)	8 (50)	3.33	1.096-10.14	0.062			
Duration of ECMO support > 2 days, n (%)	5 (6)	4 (25)	4.87	1.14-20.74	0.043			
Duration of ECMO support, median [IQR]	0 [0-0]	1 [0-3]	-	-	0.010			
Atrial fibrillation during ICU hospitalization, n (%)	28 (37)	5 (31)	0.78	0.25-2.47	0.78			
Cardiac arrest during hospitalization in ICU, n (%)	2 (3)	9 (11)	48.21	8.66-268.41	<0.0001			
NBA administration, n (%)	11 (14)	11 (69)	13.40	3.90-46.05	< 0.0001			
Prone position, n (%)	5 (6)	3 (19)	3.37	0.72-15.85	0.13			
Duration of MV, median [IQR]	2 [1-4]	12 [5-20]	-	-	0.0002			
MV > 3 days, n (%)	21 (27)	12 (75)	10.86	2.79-42.32	< 0.001	11.94	2.87-45.58	0.001
Re-intubation, n (%)	7 (9)	5 (31)	4.51	0.95-20.20	0.029			
PGD, n (%)	23 (29)	10 (63)	3.92	1.14-14.79	0.020			
Stage 3 PGD, n (%)	23 (29)	10 (63)	3.99	1.30-12.25	0.020			
Septic shock during ICU stay, n (%)	8 (10)	11 (14)	18.70	5.17-67.67	< 0.0001			
Pneumonia > 2 episodes, n (%)	8 (10)	1 (6)	0.58	0.067-4.95	1			
Repeat chest surgery, n (%)	8 (10)	6 (38)	5.25	1.51-18.30	0.013			
Abdominal surgery during hospitalization in ICU, n (%)	6 (8)	6 (38)	7.20	1.94-26.70	0.005			
Acute antibody-mediated rejection, n (%)	18 (23)	5 (31)	1.51	0.47-4.94	0.53			
Acute cellular rejection, n (%)	6 (8)	4 (25)	4	0.98-16.30	0.063			

Figures

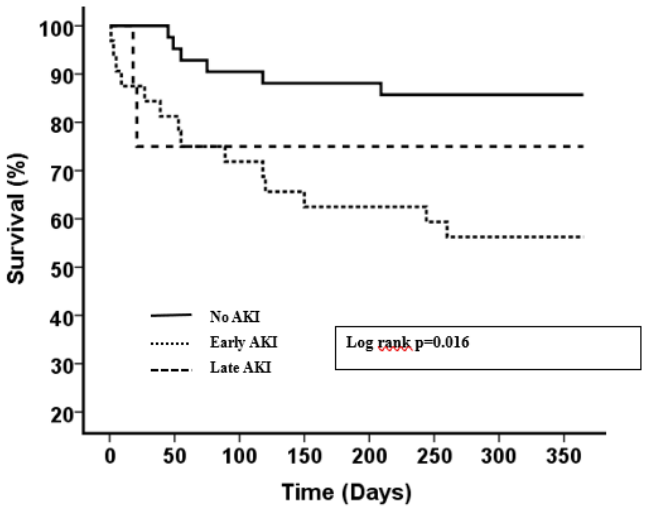
FIGURE 1A: Long-term survival in LT patients according to KDIGO stage



Number at risk

No AKI	42	40	38	37	37	36	36	18
KDIGO 1	11	10	9	9	9	9	9	5
KDIGO 2	14	14	13	11	10	9	8	4
KDIGO 3	15	8	7	7	7	7	7	4

FIGURE 1B: Long-term survival in LT patients according to early or late onset of AKI.



Number at risk

No AKI	42	40	38	37	37	36	36	18
Early AKI	32	26	23	21	20	19	18	9
Late Aki	8	6	6	6	6	6	6	3

Figure 1

A: Long-term survival in LT patients according to KDIGO stage. B: Long-term survival in LT patients according to early or late onset of AKI.