Consequences of ICU readmission after lung transplantation: beyond the early postoperative period: SUPPLEMENTARY MATERIAL

Study design

Retrospective and single-centre study. We included all LT patients who were readmitted to the ICU beyond 30 days of the initial ICU discharge after the immediate postoperative period of lung transplantation, over a 6-year period (from January 1, 2011, to December 31, 2016). All patients were admitted to Vall d'Hebron University Hospital (HUVH), Barcelona (Spain), a large referral academic institution managing more than 1000 hospitalization beds and 80 critical care beds (e.g., general, trauma, burn, surgical), and serving a population of nearly 0,3 million. This study followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies [14].

Immunosuppression protocol

In the early postoperative period, LT patients received triple therapy with one calcineurin inhibitor (tacrolimus), one antiproliferative agent (mycophenolate), and corticosteroids. Patients received no induction therapy. In the case of renal failure, the calcineurin inhibitor (tacrolimus) was replaced by basiliximab, an interleukin-2 receptor antagonist. Subsequently, conventional immunosuppression maintenance therapy was based on triple-drug therapy for all patients: tacrolimus, mycophenolate, and corticosteroids. In the absence of chronic allograft dysfunction (CLAD), the dose of all immunosuppressive agents could be reduced. In the case of patients with renal failure or bronchiolitis obliterans syndrome, mammalian target of rapamycin (mTOR) inhibitors were introduced to reduce the dose of calcineurin inhibitor or even replace it.

Source of patients and data collection

The HUVH Institutional Ethics Committee approved this study, and informed consent was waived due to its retrospective nature. All patients who underwent LT at HUVH were identified by retrospective analysis for electronic chart review. Immunosuppressive therapy and infectious disease antimicrobial prophylaxis were managed according to the standard protocol in all patients during the first ICU admission after LT. Postoperative management was performed by a dedicated multidisciplinary and experienced group of professionals, including critical care physicians, pneumologists, and nurses, implementing protocol-driven care. Following hospital discharge after LT, all patients were regularly followed once or twice per week for the first four weeks as outpatients and weekly for up to 3 months. Then, the follow-up was conducted as considered necessary by physicians on-charge. All ICU readmissions beyond the 30-day of the initial post-transplantation ICU discharge, between January 1, 2011, and July 31, 2016, were registered. All LT recipients initially readmitted to other hospitals in the same geographic area were early transferred to HUVH for management within 24 hours of admission. All patients were followed-up for up to one year after ICU readmission. Patients who underwent lung retransplantation, prior or simultaneous organ transplantation, and patients with do-not-resuscitate or do-not-intubate orders were excluded. Demographic and clinical data were collected from the patients´ medical charts and electronic records. Clinical data were recorded, including age, gender, indication for LT, the first second of forced expiration volume (FEV_1) post-LT, the reason for ICU admission, acute severity scores (the Sequential Organ Failure Assessment [SOFA] [15] and Acute Physiology And Chronic Health Evaluation [APACHE] II [16] scores), chronic complications, predisposing conditions prior to ICU admission and supportive therapy during ICU admission. The hospital and ICU length of stay before and

after the index hospitalization for LT were also assessed. For patients with multiple readmissions to the ICU, individual readmissions were analyzed independently. Given the strict postoperative management and supervision of LT recipients, there were no missing data or losses during the follow-up.

Statistical Analyses

We report the distribution of characteristics. To compare characteristics, we used the Chi-square or Fisher´s exact test for categorical variables. We compared continuous variables using the Student's t-test or Mann–Whitney test, as appropriate. Multivariable analysis in the form of logistic regression (backward stepwise) was conducted to evaluate associations between risk factors at ICU readmission and 1-year mortality. All variables showing statistically significant differences between survivors and nonsurvivors were included in the Cox regression model.

Finally, an analysis was conducted to establish the increases in the risk of death associated with each independent variable. For that purpose, the variables regarding patients´ evolution during ICU stay that were different between 1-year survivors and nonsurvivors were added one at a time to the model. We also obtained predicted probabilities of 1-year mortality according to the presence or absence of these variables while holding other variables included in the model at its mean. Statistical analyses were performed using STATA 14 software (Stata Corp. Stata Statistical Software: Release 14. Statistical Software. College Station, TX: StataCorp LP). A two-sided p-value of 0.05 or less was considered statistically significant.

TABLE S1. Microbiological aetiology in patients admitted for respiratory tract infection or septic shock

Type of isolation		N=57
No isolation		20 (35.1%)
Positive culture		37 (64.9%)
	Multidrug-resistant	12 (32.4%)
	GPC	5 (13.5%)
	GNB	22 (59.5%)
	Viral	5 (13.5%)
	Fungical	5 (13.5%)

GPC: Gram positive cocci, GNB: Gram negative bacilli.

TABLE S2. Characteristics of lung transplant complications prior to ICU readmission

Complications of lung transplant prior to ICU readmission (single admissions)	All (N=81)	Nonsurvivors (N= 47)	Survivors (N= 34)	p-value
Lung infection	63 (77.8%)	42 (89.4%)	21 (66.8%)	0.003
Acute rejection	36 (44.4%)	19 (40.4%)	17 (50%)	0.392
Type of acute rejection				0.647
Humoral	3 (8.3%)	2 (10%)	1 (5.9%)	
Cellular	33 (91.7%)	18 (90%)	16 (94.1%)	
Severity of cellular rejection:				0.481
A1	5 (14.2%)	2 (11.8%)	3 (18.6%)	
A2	14 (42.4%)	9 (52.9%)	5 (31.3%)	
A3	11 (33.3%)	4 (23.5%)	7 (43.8%)	
A4	3 (9.1%)	2 (11.8%)	1 (6.3%)	
PGD	15 (18.5%)	10 (21.3%)	5 (14.5%)	0.452
Severity of PGD				0.281
I	1 (6.7%)	1 (10%)	0	
II	1 (6.7%)	0	1 (20%)	
III	13 (86.6%)	9 (90%)	4 (80%)	
CLAD	19 (23.5%)	15 (31.9%)	4 (11.8%)	0.035
Type of CLAD				0.750
RAS	13 (68.4%)	10 (66.7%)	3 (75%)	
BOS	6 (31.6%)	5 (33.3%)	1 (25%)	
CMV	17 (21%)	12 (25.5%)	5 (14.7%)	0.238

PGD: Primary graft dysfunction; CLAD: Chronic lung allograft dysfunction; RAS Restrictive allograft syndrome; BOS: Bronchiolitis obliterans syndrome; CMV: cytomegalovirus

TABLE S3. Characteristics of 1-year nonsurvivors and survivors during ICU stay

Variables			Nonsurvivors (n = 60)	Survivors (n = 37)	p-value
At ICU readmission					
	APACHE II[†]		17 (1)	14 (1)	0.003
	SOFA[*]		4 (0)	5 (1)	0.052
	Baseline respiratory variables				
		PaO_2/F_IO_2 ratio[∞]	209 (15)	235 (19)	0.266
		Respiratory rate (bpm)	29 (1)	27 (1)	0.098
	Chest X ray				
		Bilateral infiltrates	28 (46.7%)	12 (32.4%)	0.167
		Number of quadrants affected	2(0-4)	1 (0-3)	0.045
	Lactate (nmol/L)		1.7 (0.2)	2 (0.47)	0.449
Respiratory supportive therapy at ICU readmission					0.149
	Conventional oxygen therapy		4 (6.7%)	7 (18.9%)	
	HFNC		31 (51.7%)	19 (51.4%)	
	NIV		7 (11.7%)	1 (2.7%)	
	IMV		18 (30%)	10 (27%)	
Evolution during their course in the ICU					
	Sepsis		21 (35%)	10 (27%)	0.504
	Need of vasopressors		24 (40%)	7 (18.9%)	0.043
	Renal failure		33 (55%)	16 (43.2%)	0.300
	Renal replacement therapy		13 (21.7%)	2(5.4%)	0.042
	Need for IMV		52 (86.7%)	14 (37.8%)	<0.001
	Days of IMV		15 (4-29)	9 (1-18)	0.228
Length of stay					
	ICU		13 (3-25)	6 (3-12)	0.074
	Hospital		19 (7-35)	26 (18-43)	0.048

* Plus–minus values are means ±SD. Other quantitative values are expressed as median and interquartile range 25-75% (median (IQR)).

ICU denotes intensive care unit, SOFA sequential organ failure assessment score, APACHE II Acute Physiology and Chronic Health Evaluation II score, HFNC high-flow nasal cannula, NIV noninvasive mechanical ventilation, IMV invasive mechanical ventilation.

* SOFA scores range from 0 to 24, with higher scores indicating more severe organ failure.

† The Acute physiology and Chronic Health Evaluation score ranges from 0-71, with higher scores indication more severe acute condition.

∞ *PaO2/FiO2 ratio* is the ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2) expressed as a fraction, which is a commonly used indicator of lung function in critically ill patients.

TABLE S4. Multivariate analysis of risk factors at ICU readmission for 1-year mortality

Variables (step 2)	Odds ratio	95% CI	p-value
LRTI	3.49	0.86 - 14.16	0.081
Number of quadrants affected in chest X-ray	1.52	1.05 - 2.21	0.027
FEV_1 *	0.96	0.93 - 0.99	0.028
APACHE II †	1.17	1.04 - 1.32	0.009

Variables entered in step 1: LTRI, CLAD, FEV_1, number of quadrants affected in chest X-ray and APACHE II score.

LTRI denotes lower respiratory tract infection, CLAD chronic lung allograft dysfunction FEV_1 forced expiratory volume in one second, APACHE II Acute Physiology and Chronic Health Evaluation II score.

* FEV_1 is the volume of air that can forcibly be blown out in first 1 second, after full inspiration, depend mainly on sex and age. Values of between 80% and 120% of the average value are considered normal.

† The Acute physiology and Chronic Health Evaluation score ranges from 0-71, with higher scores indication more severe acute condition.

Table S5. Addition of different variables, once at a time, to the model presented.

Variables added to the model	Odds ratio	95% CI	p-value
Mechanical ventilation	35.67	7.73 - 164.53	< 0.001
Need for vasopressors	1.12	0.29 - 4.37	0.869
Renal replacement therapy	1.49	0.22 - 10.10	0.680

TABLE S6. Differences in predicted probabilities of 1-year mortality according to each variable.

Variable		Predicted probability of one-year mortality	95% CI
Mechanical ventilation			
	Yes	84%	72-96%
	No	16%	-02-34%
Need for vasopressors			
	Yes	65%	40-90%
	No	62%	47-78%
Renal replacement therapy			
	Yes	62%	48-76%
	No	71%	35-107%

Differences in predicted probabilities of 1-year mortality after ICU admission according to the need for mechanical ventilation, renal replacement therapy and vasopressors while holding other variables included in the model at its mean.