Analysis of Intrahospital Mortality in Patients With Lung Transplant Due to Diffuse Parenchymal Lung Disease

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ABSTRACT

Background. Patients with diffuse parenchymal lung disease (DPLD) have the poorest survival rates both before and after lung transplantation (LT). Early mortality among LT patients as a result of DLPD is estimated at 10% to 20%. The aim of the study was to assess intrahospital mortality after LT procedures for DLPD and to identify factors in the recipient, donor, intra- and postoperative periods that might improve early outcomes.

Methods. A retrospective, observational, cohort, single-hospital study was conducted. Data from 67 patients with LT patients owing to DPLD were recorded between October 2008 to June 2017 in Madrid, Spain.

Results. Out of 67 LT recipients with DPLD, 51 had idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP), 6 nonspecific interstitial pneumonia (NSIP), and 10 other DPLD. Intrahospital mortality took place in 13.4% of patients, with a median survival time of 34 days (interquartile range [IQR], 27.50–66).
In the preoperative period, there were no differences in the recipients' demographic and hemodynamic characteristics, respiratory function, or time spent in the waiting list, except higher doses of systemic steroids in nonsurvivors (prednisone 15 vs 10 mg, $P = .046$). No differences were reported in the donors' characteristics (age, mechanical ventilation hours, PaO_2/FiO_2).
In the intraoperative and postoperative periods, we found differences statistically significant in longer cold ischemia time and development of primary graft dysfunction (PGD) grade 3 in the nonsurvivor group.

Conclusions. The mortality rate in our series was 13.4%, and the main risk factors for intrahospital mortality were longer cold ischemia time and greater incidence of PGD grade 3.

ALL adult patients undergoing Lung Transplantation (LT) have unadjusted global survival rates of 89% at 3 months, 80% at 1 year, 65% at 3 years, 54% at 5 years, and 31% at 10 years. The most frequently reported causes of death within the first 30 days are graft failure and noncytomegalovirus (CMV) infections [1]. Few studies have analyzed intrahospital mortality in patients with diffuse parenchymal lung disease (DPLD) and modifiable risk factors in this population.

The aim of the study was to assess intrahospital mortality after LT procedure in patients with DLPD and evaluate our experience to identify factors that might improve the early outcomes.

METHODS

Study Design

A retrospective, observational, cohort, single-hospital study of 67 patients with LT as a result of DPLD was recorded between October 2008 to June 2017 in Madrid, Spain.

Study Population

The study population included all adult patients with DPLD who underwent single-lung or double-lung transplantation in one hospital between October 2008 and June 2017.

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Table 1. Recipient, Donor, Intraoperative, and Postoperative Characteristics in Patients With Lung Transplant Due to Diffuse Parenchymal Lung Disease

Variable	Intrahospital Mortality (n = 9)	Survivors (n = 58)	*P* value
Recipient on the Waiting List			
Age, years, median (IQR)	63 (55–66)	60 (52–63)	.261
Male sex, n (%)	5 (55.6)	42 (72.4)	.434
FVC (%), mean (SD)	50 ± 15	49 ± 12	.793
TLC (%), median (IQR)	51 (50–59)	53 (46–61)	1.000
DLCO (%), mean (SD)	31 ± 11	28 ± 8	.341
pO_2, mmHg, mean (SD)	62 ± 12	59 ± 10	.543
6MWT, meters, mean (SD)	296 ± 55.67	302.38 ± 16.74	.904
PAP mean, mmHg, median (IQR)	21 (17–24)	22 (19–30)	.277
Steroids treatment, n (%)	6 (66.7)	30 (51.7)	.488
Dose, mg, median (IQR)	15 (10–20)	10 (5–10)	.046
Statins treatment, n (%)	3 (33.3)	15 (25.9)	.638
Awaiting on list, days, median (IQR)	86 (44–488)	144 (61–240)	.861
Donor			
Age, years, mean (SD)	58.00 ± 9.165	49.53 ± 14.438	.094
History of smoking, n (%)	1 (12.5)	28 (50.9)	.121
Mechanic ventilation, hours, median (IQR)	48 (24–72)	24 (24–66)	.714
PaO_2/FiO_2, mean (SD)	419.71 ± 46.295	464.89 ± 67.775	.096
Surgery			
Unilateral, n (%)	5 (55.6)	32 (55.2)	1
Bilateral, n (%)	4 (44.4)	26 (44.8)	
ECC, n (%)	5 (55.6)	21 (36.2)	.294
Ischemic time 1st, minutes, median (IQR)	360 (310–377)	285 (254–330)	.009
Ischemic time 2nd, minutes, median (IQR)	468 (399–641)	433 (379–486)	.299
Postoperative Outcomes			
ICU stay, days, median (IQR)	37 (31–60)	6 (4–14)	<.001
Cardiac output <2.2, n (%)	5 (55.6)	7 (14.9)	.016
Pulmonary hypertension, n (%)	5 (55.6)	12 (24.5)	.106
Mechanic ventilation–days, median (IQR)	31 (21–43)	3 (1–6)	<.001
Tracheostomy, n (%)	8 (88.9)	12 (20.7)	<.001
Acute kidney injury, n (%)	6 (66.7)	9 (16.4)	.004
Grade 3 PGD, n (%)	5 (55.6)	6 (10.3)	.004

Abbreviations: 6MWT, 6-minute walk test; DLCO, diffusing capacity of carbon monoxide; ECC, extracorporeal circulation; FVC, forced vital capacity; ICU, intensive care unit; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; SD, standard deviation; TLC, total lung capacity.

We analyzed specific database medical records, recipients and donor demographics characteristics, preoperative risk factors, respiratory function, hemodynamic variables, and days on waiting list. Donors risk factors, intraoperative variables, postoperative outcomes, and complications were also evaluated.

Patients were stratified according to survivors and nonsurvivors. Intrahospital mortality was defined as any death taking place after the transplantation of patients not being discharged, regardless of the length of admission. One patient with retransplantation was previously excluded from the analysis.

Pulmonary graft dysfunction (PGD) severity was defined and graded according to the International Society for Heart and Lung Transplantation (ISHLT) consensus, using the partial pressure or arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2). Grade 3 PGD was defined as a PaO_2/FiO_2 ratio <200 mmHg [2].

Study Endpoints

The primary outcome was to assess intrahospital mortality of LT patients with DPLD. The secondary outcomes were to identify potentially modifiable risk factors in the recipient, donor, intraoperative, and the postoperative periods; length of ICU (intensive care unit) and hospital stay; complications; and all-cause intrahospital mortality.

Statistical Analysis

Preoperative and postoperative continuous variables were compared using the Student *t* test or Mann-Whitney U test for normally and non-normally distributed variables, respectively. Values were expressed as mean and standard deviation or medians and interquartile range (25th-75th percentile). Categorical variables were compared using the χ^2 or Fisher exact test. Values were expressed as a frequency in the group from which they were derived.

All tests of significance were two-tailed, and *P* values of .05 or less were considered statistically significant.

Statistical analysis was performed using SPSS, version 21.0 for Windows.

RESULTS

Demographics

Among the 67 patients who underwent LT during the study period, 51 had idiopathic pulmonary fibrosis (IPF) or usual interstitial pneumonia (UIP), 6 nonspecific interstitial pneumonia (NSIP), and 10 other DPLD.

Baseline preoperative, intraoperative, and postoperative characteristics of recipient and donors are presented in

Table 1. Mean recipient age was 57 ± 9.7 years. Male sex predominated in both groups who were overweight (body mass index of 26 ± 2.86). Mean donor age was 51 ± 14 years. Among all LT, 37 (55.2%) were single and 20 (29.8%) double.

Primary Outcome

Intrahospital mortality was 13.4% (9/67), with a median survival time after lung transplantation of 34 days (IQR, 27.50–66).

Secondary Outcomes

Unadjusted analysis revealed no significant differences in the preoperative period in recipients' demographic characteristics, respiratory function, hemodynamic, or time spent in the waiting list, nor in the donors' characteristics (age, smoking history, mechanical ventilation hours, PaO_2/FiO_2 ratio), except higher doses of systemic steroids treatment in nonsurvivors (prednisone 15 vs 10 mg, $P = .046$). No significant differences in intrahospital mortality were reported among patients older than 65 (2/9 patients, 22%) and ≤65 years old (7/58 patients, 12%; $P = .4$).

We found differences in longer cold ischemia time in the intraoperative period and development of PGD grade 3, longer ICU stay, mechanical ventilation, tracheostomy, and development of acute kidney injury in the nonsurvivor group in the postoperative period.

All-cause in-hospital mortality included: 1 case of surgical complications; 1 acute graft rejection; 1 fungal infection; 1 bacterial sepsis; 1 intestinal perforation; 1 primary graft dysfunction; and 3 cases of respiratory distress.

DISCUSSION

After chronic obstructive pulmonary disease (COPD), the second most common indication of LT consisted of the broad category of interstitial lung disease or pulmonary fibrosis (30%), mainly consisting of idiopathic interstitial pneumonia (IIP; 24.8%) and non-IIP interstitial lung disease (5.5%) [3]. This group of patients have the poorest survival rates both before and after transplantation, with an early mortality rate after LT estimated at 10% to 20% [4]. The intrahospital mortality rate in our series was 13.4%, similar to international series, with a median survival time after LT of 34 days (IQR, 27.50–66).

The mayor reported that causes of death independent of the underline diagnosis (January 1990 through 2014) within the first 30 days after transplantation were graft failure, noncytomegalovirus infections, and cardiovascular and technical causes. Other risk factors associated with death during first posttransplant year in multivariable analysis included recipient male sex, pretransplant chronic steroids use, older recipient age at transplant, lower cardiac output, lower percentage predicted value of the forced vital capacity, and longer lung allograft ischemia time [1].

Currently, there are a few studies of sufficient quality trying to identify modifiable risk factors in DLPD to improve survival. In our experience, in the preoperative period we did not find any difference in the recipients' demographic and hemodynamic characteristics, respiratory function, or time spent in the waiting list that could help to predict an adverse outcome, except higher doses of systemic steroids in nonsurvivors (prednisone 15 vs 10 mg, $P = .046$), according to Arango et al, who demonstrated in their study of 117 IPF that previous corticosteroid treatment was an independent risk factor for development of early mortality (OR, 5.128; $P = .05$) [4].

We stratified our patients by age (less than and greater than 65 years) and we did not find any significant difference in early survival by procedure type—single vs bilateral lung transplant (SLT vs BLT; $P = .4$)—which is in contrast to Arango et al and Force et al, who showed that SLT was an independent risk factor to early mortality [4] and recommended consideration of BLT for younger patients with IPF to increase 1-year survival [5]. Our findings are in line with the ISHLT registry, which found that BLT recipients had better survival than SLT recipients in the first year after transplantation, and this difference increased during the next 14 years of follow-up but not previously, showing that both groups had 93% to 94% survival at 1 month [3].

According to characteristics of donors, no differences were reported in our series among survivors and nonsurvivors (age, history of smoking, mechanical ventilation hours, PaO_2/FiO_2). In the intraoperative period, we found significant differences regarding longer cold ischemia time in spite of the LT procedure in the nonsurvivor group. This was demonstrated in the 34th ISHLT Registry and also evidenced that longer allograft ischemic times occurred in association with older donors, but younger recipient age and recipients who had allograft ischemic time of >6 hours had a lower Kaplan-Meier unadjusted 30-day survival than the other allograft ischemic time groups [3].

Finally, through the multicenter study conducted by Rello et al, who assess prognostic factors in the early period following lung transplantation in Spain in 2013, we found that grade 3 PDG, defined as a PaO_2/FiO_2 ratio <200 mmHg, according to the ISHLT registry [2] was an independent risk factor for intrahospital mortality in DPLD [6]. Trying to ameliorate this, Raphael et al, in a single-institution cohort study of all indication lung transplantation recipients, demonstrated that perioperative use of satins is independently associated with reduced risk of development of PGD after lung transplant, as a protective effect [7]. In contrast in our cohort of DPLD lung transplantation patients, we didn't find differences in mortality; nevertheless, we did not study this effect in the subgroup of patients who development PGD.

Patients in the nonsurvivor group also presented prolonged ICU stay, mechanic ventilation, tracheostomy, and acute kidney failure with adverse consequences, according to the ISHLT registry and other series [3].

According to our results, the main risk factors for intrahospital mortality were longer cold ischemia time and greater incidence of PGD grade 3, without differences in pretransplant recipients' and donors' characteristics that

could help us to predict which patients would have an increased risk of intrahospital mortality. Nevertheless, these findings are in a DLPD subgroup of patients and can't be extrapolated to the rest of LT patients.

The main limitation of the study was the retrospective design and the number of patients.

Future adequately powered, prospective trials with larger samples sizes are needed to identify risk factors for intrahospital mortality.

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