

# Early and Late Results of Lung Transplantation in Advanced Emphysema

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## Abstract

**Introduction and objectives:** Emphysema is the most frequent indication for lung transplant (LT). The purpose of this study was to assess demographic and functional characteristics of patients with emphysema and analyze survival.

**Methods:** Analytic observational study conducted in 84 patients with emphysema who received a LT between June 1994 and March 2012. Survival was analyzed with the Kaplan-Meier method.

**Results:** 84 LTs were performed in 84 patients with chronic obstructive pulmonary disease (COPD) due to advanced emphysema. All the patients were smokers; 11 patients (13%) showed alpha 1-antitrypsin deficiency (A1AD); 70 out of 84 transplants (83%) were single-lung transplants (SLT) and 14 (17%) were double-lung transplants (DLT); 69 (82%) were elective transplants and 15 (18%) were emergency/urgency transplants. Mean age:  $54.95 \pm 6.10$  years, 54 male (64%). Forced expiratory volume in first second (FEV1):  $0.60 \pm 0.28$  l ( $20 \pm 9\%$ ); forced vital capacity (FVC):  $1.78 \pm 0.62$  l ( $46 \pm 16\%$ ); mean pulmonary arterial pressure (MPAP):  $21.08 \pm 5.79$  mmHg; partial pressure of arterial oxygen (PaO<sub>2</sub>):  $67.54 \pm 12.27$  mmHg; partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>):  $46.40 \pm 8.04$  mmHg; six minute walk test (6MWT) distance:  $225.59 \pm 113.67$  m; hospital mortality (HM): 16% (13/84); overall survival at 1, 3, 5, 7 and 10 years: 67%, 53%, 40%, 27% and 13%; conditional survival at 3, 5, 7 and 10 years: 79%, 59%, 41% and 20%.  
**Conclusions:** LT is a therapeutic option for advanced emphysema. This study shows the characteristics and survival of COPD patients who underwent lung transplantation at the Hospital Universitario Fundación Favaloro (HUFF).

**Key words:** Lung transplantation, emphysema, COPD

## Introduction

COPD is characterized by the presence of chronic and partially reversible airflow obstruction, secondary to an anomalous inflammatory reaction mainly to tobacco smoke, even though only one fourth of smokers develop COPD<sup>1</sup>.

Homozygous A1AD is associated with early emphysema in smokers<sup>2</sup> and represents approximately 2% of cases of emphysema.

Referral of patients with COPD for LT shall be considered if there is evidence of progressive impairment, despite an optimum treatment with bronchodilators, oxygen and respiratory rehabili-

tation. It is complicated to determine the suitable moment to make the referral, since patients with COPD may have a relatively good prognosis for survival<sup>3</sup> in spite of the fact that they are very symptomatic and limited.

Recent data suggest a survival improvement in patients with COPD who underwent LT, in comparison with other diagnoses<sup>4</sup>.

As indicated in the international guides for the selection of LT candidates, the transplant shall be performed when post-transplant life expectancy is higher than life expectancy without the procedure<sup>5,6</sup>.

Median survival after LT in patients with COPD is approximately 5 years<sup>7</sup>.

According to the 2010 regulation of the Unique Central National Institute Coordinator of Ablation and Transplant (INCUCAI), there are different clinical situations for lung transplantation (single or double-lung) and heart-lung transplantation.

- **Emergency:** Patients at the critical care unit (coronary care unit [CCU] or intensive care unit [ICU]), that meet one of the following criteria:
  - Intubated patients receiving mechanical respiratory assistance
  - ECMO (extracorporeal membrane oxygenation)
  - Diagnosis of pulmonary fibrosis, cystic fibrosis or bronchiectases plus
    - NIV (noninvasive ventilation)
  - Diagnosis of primary pulmonary vascular disease plus
    - Functional class (FC) IV according to the New York Heart Association (NYHA) functional classification, in need of inotropes and/or vasodilators plus:
    - Pericardial effusion or
    - Serious impairment of the RVSF (right ventricular systolic function) by echocardiogram or RA (right atrium) mean pressure  $\geq 20$  mm
- **Emergency A:** Patients at the critical care unit (CCU/ICU/intermediate care unit), that meet one of the following criteria:
  - FC IV cystic fibrosis or pulmonary fibrosis plus:
    - Systolic pulmonary artery pressure  $\geq 70$  mmHg or
    - Hypercapnia  $\geq 70$  mmHg
  - COPD with NIV
  - FC IV primary pulmonary vascular disease with maximum vasodilator therapy including prostanoids
- **Emergency B:** Outpatient recipients that meet the following criteria:
  - NIV
  - Intravenous, subcutaneous or inhalatory vasodilator therapy with prostanoids

Patients who underwent LT showed an improved pulmonary function<sup>8,9</sup> and a better quality of life<sup>10,11</sup>.

Despite improvements in the preservation of the pulmonary graft<sup>12</sup> and postoperative care, the incidence of complications and morbidity and mortality of this type of transplant is still considerable<sup>13,14</sup>.

According to the data of the international registry of the International Society for Heart and Lung Transplantation (ISHLT) published in 2011<sup>15</sup>, emphysema is the most frequent indication for SLT or DLT.

The analysis of this series is based on the ISHLT 2006 consensus that was in force when this study was developed.

New ISHLT criteria that have been recently published update referral and transplant criteria for patients with advanced pulmonary disease<sup>16</sup>.

The objectives of this study intend to know the demographic and functional characteristics and survival of patients with COPD due to advanced emphysema who received a LT at the HUFF.

## Patients and Methods

An analytic and observational study was performed with retrospective data collection from patients diagnosed with advanced emphysema who received a LT in the HUFF between June 1994 (when the LT program began) and March 2012.

Follow-up of the recipients included in this study was performed until their death or until the end of the study on March 31, 2012.

The diagnostic criteria for emphysema are based on the medical record, computed tomography and respiratory function tests.

Variables were collected from 84 patients who were consecutively transplanted. Pretransplant demographic and clinical characteristics, immediate postoperative evolution and long-term survival were retrospectively analyzed. This information was obtained from the database of the HUFF LT team and medical records.

All the patients signed an informed consent before admission for LT or treatment of transplant complications. The informed consent included the surgical treatment they would undergo, its complications and data management, since it was a university hospital.

The analyzed variables were: age, gender, FEV<sub>1</sub>; FVC; MPAP; PaO<sub>2</sub>; PaCO<sub>2</sub>, 6MWT total distance, HM, overall survival and conditional survival.

## Demographic Variables

**Gender:** Either male or female.

**Age:** The age of the patient when the LT was performed, expressed in years.

**Functional Variables:** At the time of the study for inclusion in the lung transplantation waiting list (LTWL).

**FVC:** Expressed as an absolute value in liters (l), and also as a percentage of the corresponding aforementioned theoretical values according to age, gender, height and race.

**FEV<sub>1</sub>:** Expressed as an absolute value in liters (l), and also as a percentage of the corresponding aforementioned theoretical values according to age, gender, height and race.

**PaO<sub>2</sub>:** Partial pressure of O<sub>2</sub> in baseline arterial blood at ambient air, measured before the LT, expressed in mmHg.

**PaCO<sub>2</sub>:** Partial pressure of CO<sub>2</sub> in baseline arterial blood at ambient air, measured before the LT, expressed in mmHg.

**6MWT:** The total distance was calculated, expressed in m.

### Main Hemodynamic Variable

**MPAP:** Mean pulmonary arterial pressure measured by right cardiac catheterization and expressed in mmHg.

### Survival

**Hospital Mortality:** The mortality that was recorded within the first 30 days after the LT, expressed as an absolute number and a percentage of the total amount of transplant patients.

**Overall Survival:** The possibility to survive beyond certain amount of time (expressed in years). It was calculated taking into account the time from the LT until the death of the patient or end of study.

**Conditional Survival:** The possibility to survive beyond certain amount of time (expressed in years), excluding the first year after the transplant. It was calculated taking into account the time from the LT until the death of the patient or end of study, only in the case of patients whose survival times were greater than one year.

### Statistical Analysis

The patients of the study were subjected to a descriptive analysis. The results of continuous variables are expressed by means of average and standard deviation (SD), whereas categorical variables are expressed by means of percentage, absolute and relative frequencies.

The survival experience of transplant patients was determined by calculating the curves with the Kaplan-Meier method, and the comparison between groups (defined by the clinical status of

the patients and the type of pulmonary transplant that was performed) was made by the Log-Rank Test. Hospital mortality was particularly analyzed (within the first month after surgery).

An associated probability ( $p \leq 0.05$ ) was considered as statistically significant.

The survival analysis, including the charts, was made with SAS software, version 9.2.

## Results

During the study period, 84 consecutive de novo LTs were performed in 84 patients due to emphysema.

11 of the 84 de novo LTs (13%) had A1AD.

70 SLTs (83%) and 14 DLTs (17%) were performed; 69 (82%) were elective transplants and 15 (18%) were emergency/urgency transplants. Mean age was  $54.95 \pm 6.10$  years; 54 patients (64%) were male. Functional and hemodynamic characteristics at the time of the evaluation for inclusion in the waiting list were as follows: FEV<sub>1</sub>:  $0.60 \pm 0.28$  l ( $20 \pm 9\%$  of the aforementioned value); FVC:  $1.78 \pm 0.62$  l ( $46 \pm 16\%$  of the aforementioned value); MPAP:  $21.08 \pm 5.79$  mmHg; PaO<sub>2</sub>:  $67.54 \pm 12.27$  mmHg; PaCO<sub>2</sub>:  $46.40 \pm 8.04$  mmHg; 6MWT distance:  $225.59 \pm 113.67$  m (Tables 1, 2, 3 and 4).

At the end of this study, 35% of patients (29) were alive and the remaining 66% (55) had died. The available follow-up was 248.7 patient-years.

**TABLE 1.** Respiratory Functional Exploration

	Average	SD
FVC (l)	1.78	0.62
FVC (%)	46	16
FEV <sub>1</sub> (l)	0.60	0.28
FEV <sub>1</sub> (%)	20	9
FEV <sub>1</sub> /FVC	34.69	9.33

FVC: Forced vital capacity; l: liters; FEV<sub>1</sub>: Forced expiratory volume in first second

**TABLE 2.** Pulmonary Pressure

	Average	SD
MPAP (mmHg)	21.08	5.79

MPAP: Mean pulmonary arterial pressure; SD: Standard deviation

**TABLE 3.** Baseline Blood Gas at Ambient Air

	Average	SD
PaO <sub>2</sub> (mmHg)	67.54	12.27
PaCO <sub>2</sub> (mmHg)	46.40	8.04

PaO<sub>2</sub>: Partial pressure of oxygen in arterial blood; PaCO<sub>2</sub>: Partial pressure of carbon dioxide in arterial blood; SD: Standard deviation

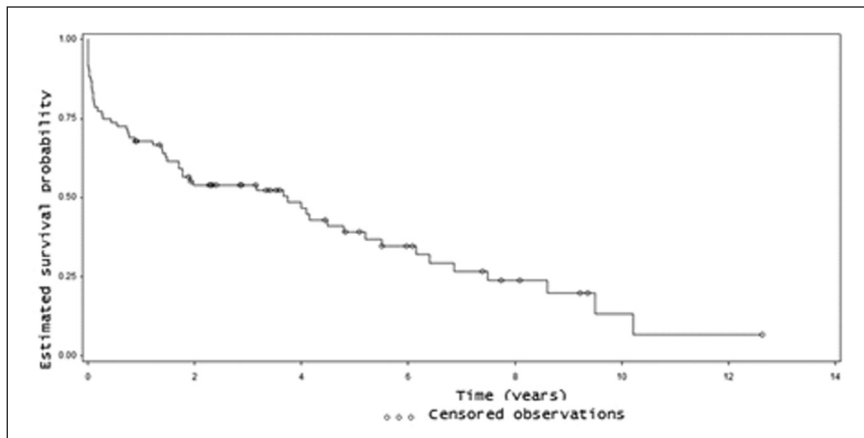
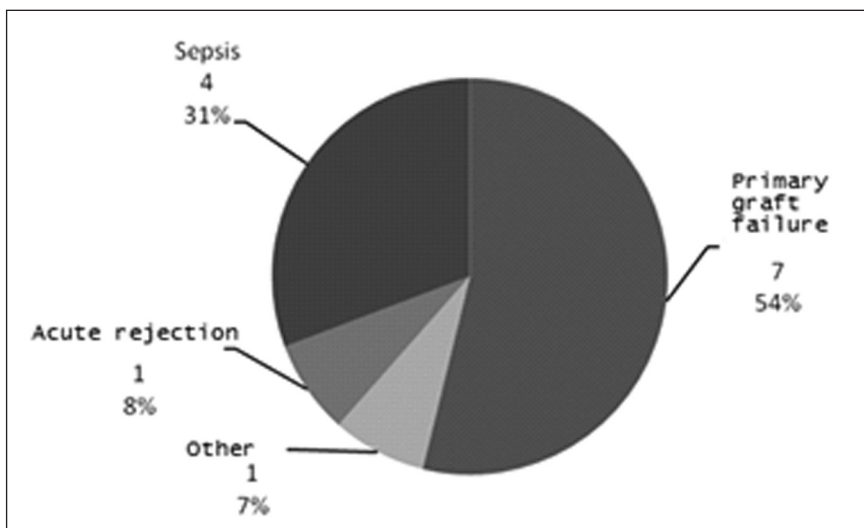
**TABLE 4.** Prueba de marcha de los 6 minutos

	Average	DE
Distance (m)	225.59	113.67

SD: Standard deviation

Hospital mortality (30 days) was 13/84 (16%). Estimated overall survival after 1, 3, 5, 7 and 10 years was 67%, 53%, 40%, 27% and 13%, respectively (Figure 1). The main cause of hospital mortality was primary graft failure (54%) (Figure 2). Excluding the first year post-transplantation (conditional survival), the survival after 3, 5, 7 and 10 years was 79%, 59%, 41% and 20% (Figure 3). At follow-up, sepsis was the most frequent cause of mortality (48%) (Figure 4).

No differences were found in the overall survival of the patients regarding their clinical status, elective versus emergency/urgency. Estimated survival after one year was 66% for the first group and 71% for the second group ( $p=0.295$ , Log-Rank Test) (Figure 5). No differences were found in the overall survival of the patients regarding the type of transplant, single-lung versus double-lung ( $p=0.560$ , Log-Rank Test) (Figure 6).

**Figure 1.** Overall Survival of the Series**Figure 2.** Causes of Hospital Mortality

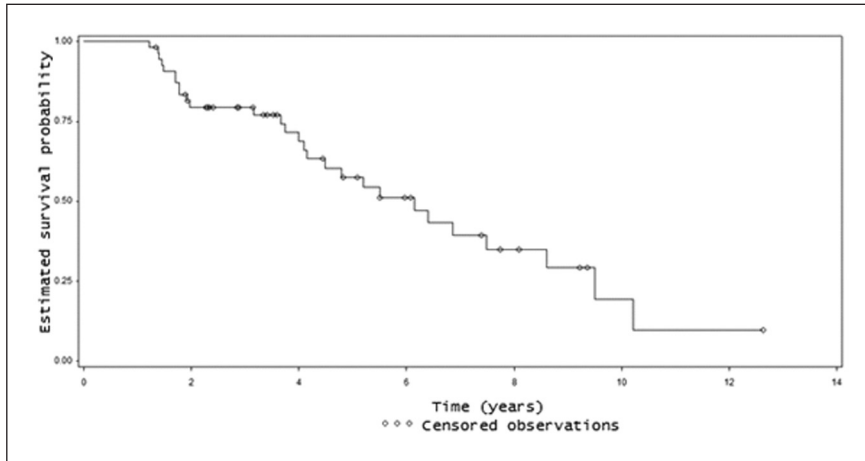


Figure 3. Conditional Survival after the First Year

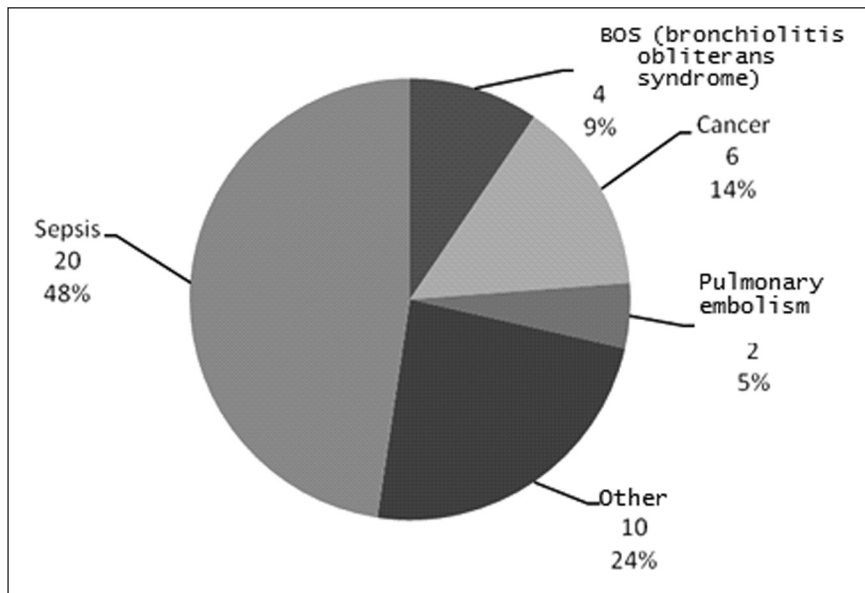


Figure 4. Causes of Late Mortality

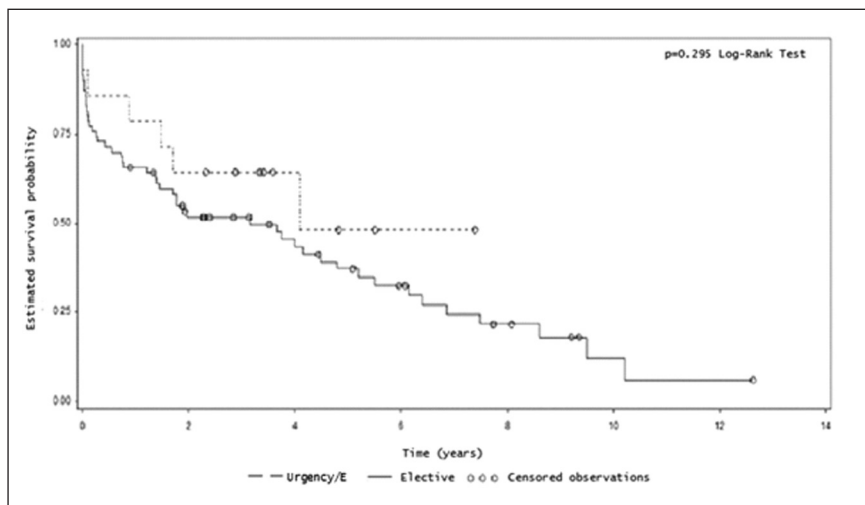


Figure 5. Overall Survival according to Clinical Status

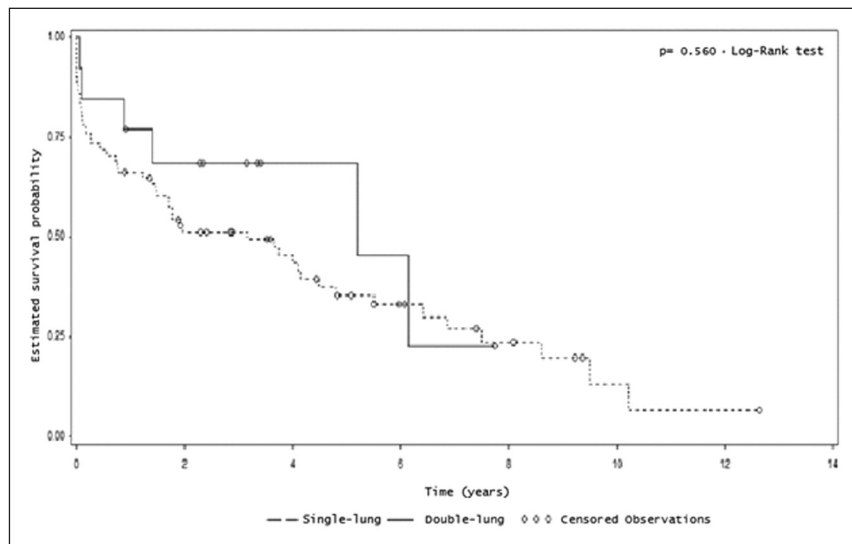


Figure 6. Overall Survival according to Type of Transplantation

These results may be a consequence of the fact that the DLT population was not as large as the SLT population.

## Discussion

COPD is the most frequent indication for LT, both on the international and national levels. The 2011 ISHLT registry established that 36% of transplant patients were transplanted due to advanced pulmonary emphysema. The percentage increases to 43% if we include patients with emphysema secondary to A1AD<sup>15</sup>.

On an institutional level, COPD is also the most frequent indication for LT. In our global series, approximately 40% of patients who have undergone LT had COPD. Significant male predominance was confirmed within LT recipients due to COPD (64%). However, when reviewing the North American series, these data are surprisingly reversed, as with Cassivi et al<sup>17</sup>, where almost two thirds of the 306 patients (60.5%) were females. These differences could be explained by the different smoking habits between males and females in the countries under study.

The mean age of the patients of our series, 54.95 years, is similar to that of the Cassivi et al work, 55 years<sup>17</sup>, and to other international groups<sup>18</sup>.

In our series, the percentage of patients affected by A1AD was 14%. According to the consulted literature, it is a very variable percentage: 6% ob-

tained at the ISHLT<sup>15</sup> international registry, 28% at the Cassivi et al<sup>17</sup> work, 27.4% published by Delgado et al<sup>19</sup> and 32.9% at the Burton et al<sup>20</sup> work.

Regarding the breathing functional condition of the patients, the results of the spirometry performed before the LT show highly developed conditions, with mean FEV<sub>1</sub> values of 0.60 l (20% of the reference value) similar to those reported by other authors<sup>17,18,21,22</sup>. The exercise tolerance of patients the moment they were included in the LTWL also decreased considerably, with an average of 225.59 m at the 6MWT; these results are similar to other studies<sup>17,21,22</sup>. Such a considerable involvement of the breathing reserve and exercise capacity is one of the main indications for this kind of patients to be included in a LT program.

Regarding the kind of procedure, we should emphasize the predominance of SLTs, which represent 83% of LTs performed in our group during the period under study.

These data are within a range that very much differs from that offered by the 2011 ISHLT international registry<sup>15</sup>, where DLTs predominate (approximately 70%) in COPD patients.

However, if we analyze the related literature individually, we can observe certain disparity in the data. The results revealed by Cassivi et al<sup>17</sup> or Lahzami et al<sup>23</sup> are similar to the results reported by the ISHLT in 2011, with a double-lung procedure rate of 67% and 65%, respectively. However, in other international groups, such as Staven et al or Gunes et al<sup>18</sup>, there are fewer double-lung procedu-



res in COPD patients: 43% and 38%, respectively.

On the local level, initial data derive from a collaborative group that was created for the purpose of implementing a LT joint program. Between June 1993 and February 1996, 6 right lung SLTs and 1 sequential DLT were performed in 7 patients with chronic respiratory insufficiency due to pulmonary emphysema associated with a smoking habit<sup>24</sup>. Some years later, a longer-term publication revealed the following related data: between October 1990 and March 2003, 79 LTs were performed: 25 heart-lung transplants (31.6%), 36 SLTs (45.5%) and 18 DLTs (22.7%). The SLTs began in June 1994, and the DLTs in 1996. Indications for SLT (n = 36) were emphysema (n = 23) and pulmonary fibrosis (n = 13). Indications for DLT (n = 18) were secondary bronchiectases (n = 8), cystic fibrosis (n = 8), pulmonary emphysema (n = 1) and bronchiolitis obliterans caused by graft-versus-host disease after a bone marrow transplant (n = 1). Excluding heart-lung transplants, there was a total of 54 LTs, including SLTs and DLTs, 44.4% of which (n = 24) were due to emphysema. 96% of the emphysema cases were SLTs (n = 23) and 4% were DLTs (n = 1)<sup>25</sup>. In both national studies, there was a predominance of SLTs.

Patients with emphysema may receive a SLT or a DLT, since the differences observed in the post-surgery exercise capacity and quality of life are irrelevant<sup>15</sup>.

Indication for SLT in patients with emphysema was controversial in the mid 80s, since it was considered highly probable that as a result of the transplant, perfusion would be preferably distributed in the grafted lung (due to its lower vascular resistance), and most of the ventilation would reach the native lung (as a consequence of greater compliance), possibly generating a serious ventilation-perfusion mismatch. Also, the native emphysematous lung could hyperinflate even more, displace the mediastinum and compress the transplanted lung. Although it has been observed in the practice that the native lung keeps hyperinflating after the transplant, various groups have revealed excellent functional results in emphysematous patients with SLT<sup>24</sup>.

The ISHLT reported in 2002 that patients with bilateral transplants had better survival rates. However, with the SLT, a greater number of patients in the waiting list<sup>26</sup> can be transplanted.

The LT procedure in COPD patients has a high

rate of morbidity and mortality after surgery<sup>27</sup>. In our surgery, HM was established at 16%. These data differ greatly from the data revealed by Günes et al<sup>18</sup>, where in a cohort study of 173 transplanted patients with COPD, there was 95% survival after 30 days, implying a HM of only 5%.

However, it is complicated to make a comparison between most of the authors who analyze this parameter, since there's no uniformity in the time period under analysis or in the subsequent publication of this information.

Cassivi et al<sup>17</sup> reveal similar data, with a really low HM of 6.2%, in one of the longest series that were published in this regard, even though they do not define the exact time period.

The patients of our series had 40% probability of five-year overall survival. These results are slightly lower than the data published in the 2011 ISHLT report, where the five-year survival rate for COPD patients was established around 50%<sup>15</sup>.

Most published series establish a five-year survival rate of approximately 60%<sup>17, 20, 26, 30</sup>.

When analyzing conditional survival after the first year, as revealed in the annual ISHLT report<sup>26</sup>, we got a five-year survival rate of 59%, similar to that published in previous ISHLT reports<sup>15, 28, 29, 31</sup> which was established around 60%. LT profitability in patients diagnosed with COPD, in terms of survival, is still a controversial issue, as shown in the recent publication of various articles and reviews in this regard<sup>32-35</sup>, due to the fact that there are different studies in favor<sup>36-39</sup> and against<sup>6</sup> LT with this indication.

Our results reveal that patients who received a SLT did not show a greater death risk than DLT recipients.

The survival of LT patients reported in recent years shows better results due to the optimization of immunosuppressive therapy and control of infectious complications. Also, in recent years we observed an increase in the number of patients with urgency/emergency transplants. Despite the fact that there is a greater risk within this population, this trend did not modify hospital or overall mortality in a significant way.

## Conclusion

LT in COPD patients is a therapeutic option for subjects with advanced emphysema who meet the criteria for lung transplantation. Also, the results

of the five-year overall survival analysis carried out in our institution were lower than the results of the reports published by the ISHLT, but can be considered similar if we take into account the five-year conditional survival.

**Conflicts of Interest:** AB received funding from Gador SA, Novartis and Roche to attend transplant congresses; as a medical advisor to Thoratec, in mechanical circulatory support, he has informed the media about donation and organ transplantation, with the institutional interest of the Hospital Universitario Fundación Favaloro. JC received funding from GlaxoSmithKline and Bayer to attend congresses; he is main investigator of clinical trials on pulmonary hypertension funded by Actelion and Bayer.

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