Current Situation and Prognostic Evolution of Combined Heart-lung Transplantation in a European Union Country

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ABSTRACT

Background: This study aims to evaluate the entire experience in heart-lung transplantation (HLTx) in a country of the European Union with 47 million inhabitants according to the etiologies that motivated the procedure.

Methods: A retrospective study on 1,751 consecutive transplants (HLTx: 78) was performed from 1990 to 2020 in two centers. Overall survival, adjusted for clinical profile and etiological subgroups, was compared. 7 subgroups were considered: 1) Cardiomyopathy with pulmonary hypertension (CM + PH). 2) Eisenmenger syndrome. 3) Congenital heart disease (CHD). 4) Idiopathic pulmonary arterial hypertension (IPAH). 5) Cystic fibrosis. 6) Chronic obstructive pulmonary disease (COPD)/Emphysema. 7) Diffuse interstitial lung disease (ILD).

Results: Early mortality was 44% and that of the rest of the follow-up was 31%. There were differences between HTLx and HTx in survival, also comparing groups with a similar clinical profile with propensity score (p= 0.04). Median survival was low in CM + PH (18 days), ILD (29 days) and CHD (114 days), intermediate in Eisenmenger syndrome (600 days), and longer in IPAH, COPD/Emphysema and cystic fibrosis.

Conclusion: HLTx has a high mortality. The etiological analysis is of the utmost interest to make the most of the organs and improve survival.

KEYWORDS: Heart-lung transplantation; Heart transplantation; Survival; Etiology

INTRODUCTION

Heart-lung transplantation (HLTx) is a treatment reserved for selected patients who have concomitant severe lung and heart disease [1-4]. This treatment arises when the usual therapeutic options, whether medical and/or surgical, have already been exhausted or are not applicable [2]. In Europe, HLTx has been performed since 1988, with a frequency close to 1-2 procedures per year per performing center [5].

In Spain, currently, there are only 2 centers that perform this technique in adults [1]. HLTx presents notable differences with other

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Table 1: Characteristics of the population according to the study groups.

	HLTx (n= 78)	HTx (n= 1673)	P-value	SMD
Recipients				
Age (years)a	38.2 (12.2)	51.1 (11.7)	<0.001	1.10
Female (n, %)	32 (41.0)	312 (18.6)	<0.001	0.25
Predicted heart mass[(a)]	148.4 (30.2)	165.7 (26.1)	<0.001	0.65
Bilirubin > 2 mg/dL (n, %)	18 (23.1)	301 (18.0)	0.25	0.05
Glomerular filtration (mL/min/1.73 m^2) [(a)]	88.8 (20.4)	74.2 (26.0)	0.001	0.46
Diabetes (n, %)	3 (3.8)	207 (12.4)	0.02	0.11
Previous infection (n, %)	5 (6.4)	141 (8.4)	0.53	0.03
Mechanic ventilation (n, %)	3 (3.8)	212 (12.7)	0.02	0.12
Positive CMV (n, %)	57 (73.1)	1315 (78.6)	0.25	0.06
Previous sternotomy (n, %)	10 (12.8)	410 (24.5)	0.02	0.12
Donors				
Age (years) [(a)]	32.5 (11.6)	34.2 (13.2)	0.22	0.13
Female (n, %)	36 (46.2)	540 (32.3)	0.01	0.13
Predicted heart mass[(a)]	156.6 (31.4)	171.3 (25.5)	<0.001	0.47
Positive CMV (n, %)	53 (67.9)	1125 (67.2)	0.90	0.01
Donors/Recipients Interactions				
Female donor/male recipient (n, %)	14 (17.9)	396 (23.7)	0.24	0.06
Donor (+)/recipient (-) CMV (n, %)	14 (17.9)	215 (12.8)	0.20	0.07
Cardiac mass ratio[(a)]	1.06 (0.12)	1.04 (0.14)	0.26	0.13
Surgical Procedure				
Urgent transplant (n, %)	18 (23.0)	531 (31.7)	0.11	0.08
Ischemia time (minutes) [(a)]	245.5 (83.8)	178.7 (65.2)	<0.001	0.80
Evolutionary Data				
First year mortality (n, %)	40 (51.3)	394 (24.6)	<0.001	

[(a)]Median (Interquartile range)
Abbreviations: CMV: cytomegalovirus; HLTx: heart-lung transplantation; HTx: heart transplantation; SMD: standardized mean difference

transplants, especially related to its high mortality, which forces us to re-evaluate its usefulness according to clinical and ethical criteria [6, 7]. Thus, HLTx is much less common than the isolated heart (HTx) or lung (LTx) transplantation, not only due to the lower availability of suitable donors and the lower number of indications, but also due to the results; in the short and long term results are worse due to the high complexity of the intervention, especially in some subgroups [7]. Thus, it consumes 3 organs that could be used for 3 different patients and its survival results are worse than those of HTx and LTx, perhaps concerning the low number of cases performed and

Table 2: Univariate analysis for mortality in the first year after transplantation.

Variables	HR	CI 95%	P-value
Heart-lung transplantation	2.69	1.94-3.73	<0.001
Recipient age (years)	1.00	1.00-1.01	0.52
Female recipient	1.25	1.00-1.57	0.05
Recipient predicted heart mass	1.00	0.99-1.00	0.01
Bilirubin > 2 mg/dL	1.52	1.20-1.92	<0.001
Glomerular filtration (mL/min/1.73 m^2)	1.00	0.99-1.00	0.09
Diabetes	1.02	0.76-1.36	0.89
Previous infection	1.51	1.21-2.04	0.007
Mechanic ventilation	1.73	1.35-2.21	<0.001
Positive CMV	0.95	0.72-1.24	0.68
Previous sternotomy	1.69	1.38-2.07	<0.001
Donor age (years)	1.01	1.00-1.02	0.01
Female donor	1.19	0.98-1.44	0.09
Donor predicted heart mass	1.00	0.99-1.00	0.03
Donor Positive CMV	0.92	0.74-1.15	0.46
Female donor / male recipient	1.17	0.95-1.45	0.15
Donor (+)/recipient (-) CMV	1.03	0.74-1.42	0.87
Donor/recipient cardiac mass ratio	1.23	0.62-2.45	0.55
Urgent transplant	1.50	1.23-1.82	<0.001
Ischemia time (minutes)	1.00	1.00-1.00	0.002

Abbreviations: CMV: cytomegalovirus

the complexity of the intervention [7].

The hypothesis when proposing this work was that there is probably a relationship between the etiologies that motivate a HLTx and survival in the short, medium, and long term, in such a way that the identification of risk subgroups would be crucial to improve the results and optimize the use of resources in terms of organ use.

This study aims to analyze the total experience accumulated in HLTx in a European country of 47 million inhabitants, the clinical characteristics of the HLTx performed, compare these transplants with the HTx adjusted by clinical profile, analyze the mortality results of the various HLTx indications and compare these results with other recent published HLTx registries.

MATERIALS AND METHODS

Retrospective observational non-intervention study on HLTx and HTx performed in Spain consecutively from January 1990 to December 2020. All cases performed in the only 2 centers that continue to perform HLTx in this coun-

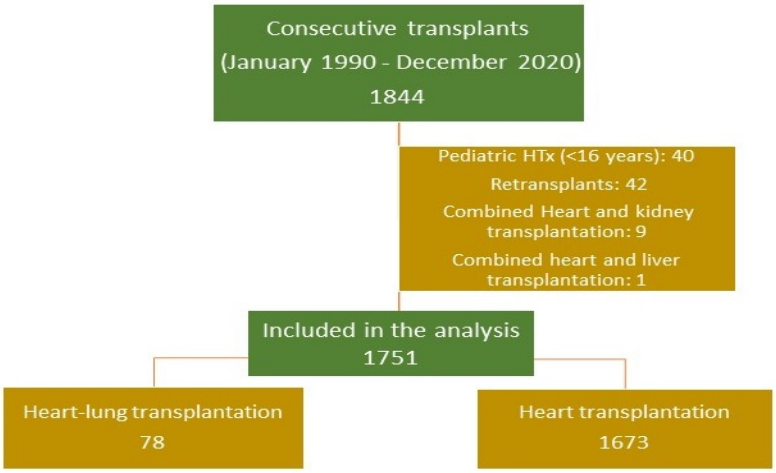

Figure 1: Study flow chart.

try at present were included. Both are centers with maximum transplant activity since the beginning of transplantation in Spain (1980s). The number of patients recruited was 1,844.

Pediatric transplants (<16 years), retransplants, and combined transplants with kidney or liver were excluded. The total number of cases analyzed was 1,751 (HTx 1,673 and HLTx 78). Fig 1 shows the flow chart of the study.

The variables analyzed have been extracted from the database of the Spanish Heart Transplant Registry [8]. This is an official registry validated by the Ministry of Health, Consumption and Social Welfare to which all the centers with transplantation activity in Spain provide data. This registry complies with all ethical regulations and current legislation. Both types of transplantation were compared (HLTx vs HTx). However, given that the clinical profile of both types of patients is very different, a clinical adjustment was made to homogenize it, choosing from all the heart transplanted patients those with similar clinical characteristics to obtain the real difference in the comparison between the two groups. Subsequently, the various etiologies of HLTx were compared looking for subgroups with higher mortality.

For the subgroup analysis, 7 etiological groups were considered: 1) Ischemic or non-ischemic cardiomyopathy with pulmonary hypertension (CM+PH). 2) Eisenmenger syndrome due to atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus, or multiple congenital anomalies. 3) Congenital heart disease (CHD) not defined as Eisenmenger syndrome (transposition of the great vessels with pulmonary hypertension without shunts, corrected ASD or VSD with subsequent development of pulmonary hypertension, corrected transposition of the great vessels with VSD, pulmonary atresia with VSD). 4) Idiopathic pulmonary arterial hypertension (IPAH) 5) Cystic fibrosis. 6) Chronic obstructive pulmonary disease (COPD)/Emphysema. 7) Diffuse interstitial lung disease (sarcoidosis, rheumatic disease, pulmonary fibrosis).

The renal function of the patients was assessed using the glomerular filtration rate estimated with the EPI-CKD equation [9]. The donor and recipient body sizes were estimated using the theoretical cardiac mass for the weight and height of the patients, whose relationship has shown higher prognostic discrimination than the weight or the body mass index [10].

Ethical Considerations

The study was approved by the Ethics Committee for Biomedical Research of one of the participating centers. In addition, the ethical principles for medical research on human subjects defined by the Declaration of Helsinki of 1975 were followed.

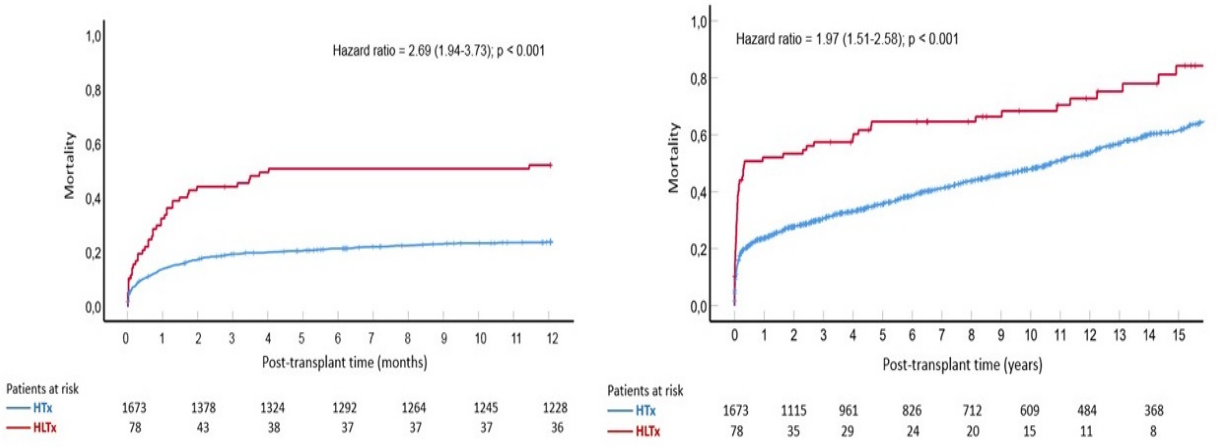

Figure 2: Survival curves (Kaplan-Meier) for heart-lung transplantation vs. heart transplantation in the original population. Hazard ratio calculated using Cox regression. left: Cumulative mortality to the 1st year. right: Cumulative mortality during follow-up.

Statistical Analysis

Continuous variables are expressed as median (interquartile range) since they showed a non-normal distribution (Kolmogorov-Smirnov test). Categorical variables are reported as frequency. The comparison between groups was made using the Mann-Whitney test for continuous variables and using Fisher's exact test or Chi-square test for categorical variables.

To complete missing data, multiple imputations were performed using the fully conditional specification method (Monte Carlo iterative algorithm with Markov chains). The association of HLTx with mortality was computed separately in 10 imputed databases and the aggregate result was obtained by applying Rubin's rules. For propensity score matching after multiple imputations, the scores of the 10 imputations were averaged for each case and this average was used for the final match.

The main outcome variable was all-cause mortality in the first year after transplantation. The secondary endpoint was total mor

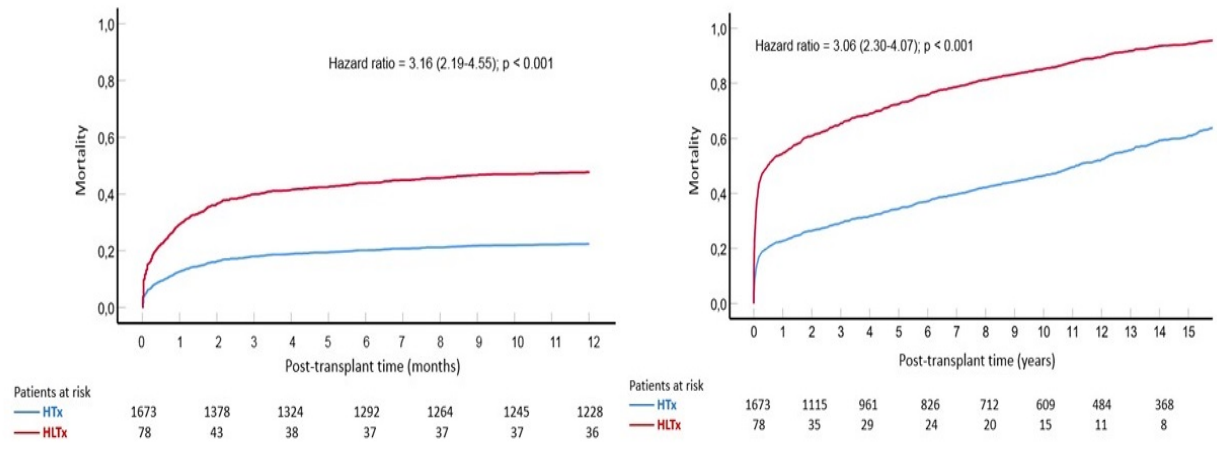

Figure 3: Survival function (Cox regression) for heart-lung transplantation and isolated heart transplantation in the global population. left: Cumulative mortality to the 1st year. right: Cumulative mortality during follow-up.

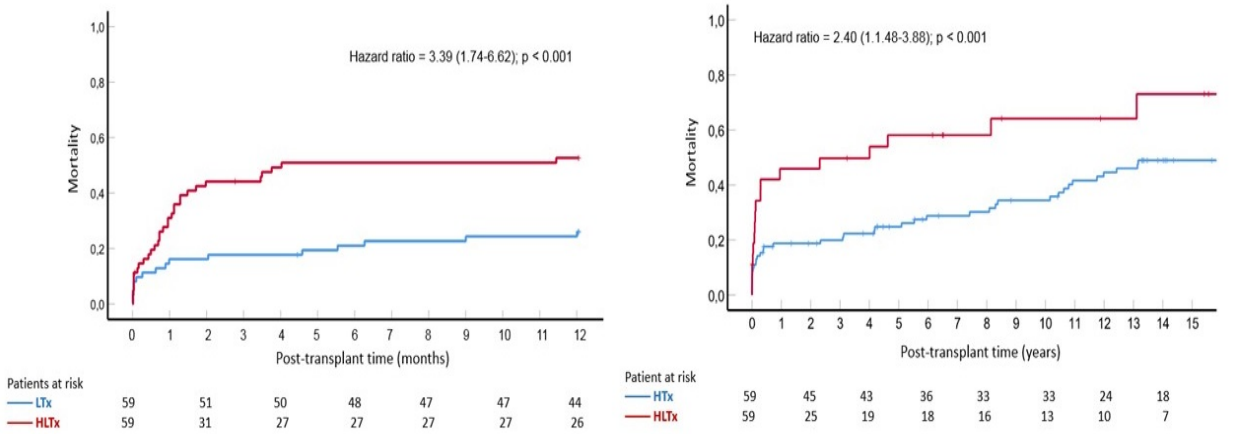

Figure 4: Cumulative mortality curves (Kaplan Meier) for heart-lung transplantation vs. heart transplantation for propensity score-matched populations. Hazard ratio calculated using Cox regression. left: Cumulative mortality to the 1st year. right: Cumulative mortality during follow-up.

tality. Time to death was analyzed using Kaplan-Meier (univariate analysis). A proportional hazards Cox regression model was used to determine the association of the variables with mortality. Due to the differences between the groups of isolated HLTx and HTx, three types of adjustment were performed: first, a multivariate-adjusted model was performed, with an introduction as predictors of variables that showed significant differences for mortality with p< 0.10 in univariate analysis. Second, two samples from each matched group were obtained using the propensity score obtained by logistic regression. In this regression, the variables that appear in Table 1 were introduced. The matching was performed using a 1: 1 protocol without replacement, with a maximum distance of 0.2 standard deviations from the propensity score with the nearest neighbor matching method. The result of the matching was verified using the standardized difference between the means of the quantitative and categorical variables. Third, the propensity score was used to calculate a weight of the inverse probability of belonging to the HLTx group, where the probability of HLTx= 1/Propensity score and the probability of isolated HTx= 1/(1 - Score of propensity). A robust estimator was used by truncation of the inverse probability to a maximum of 100. Mortality tables were used for mortality by periods.

All tests were two-tailed (statistical significance for a p-value< 0.05). The statistical programs used were IBM SPSS Statistics Version 27® and Stata® Statistics/Data analysis version 16.1.

RESULTS

Population Characteristics

The baseline characteristics are shown in Table 1. There were a large number of differences between the patients with a HLTx vs HTx. Thus, HLTx recipients tend to be younger, have a more balanced relationship between the sexes, heart with a lower total ventricular mass, greater glomerular filtration, a lower proportion of diabetes, previous sternotomy, and mechanical ventilation at the time of transplantation. Likewise, HLTx patients receive smaller, female donor hearts. On the other hand, in HLTx the ischemia time is greater with mortality in the first year that is significantly higher than that of HTx and that exceeds 50%.

Univariate, Multivariate, and Similar Clinical Profile Analysis

Many variables associated with mortality were found. HLTx multiplied by 2.69 the probability of death during the first year concerning the HTx. Adjusted analysis increased the HLTx hazard ratio for mortality to 3.16. In the adjustment for inverse probability, the

Table 3: Multivariate analysis for mortality in the first year post-transplantation.

Variables	HR	CI 95%	P-value
Heart-lung transplantation	3.16	2.19-4.55	<0.001
Female recipient	0.78	0.54-1.15	0.21
Recipient predicted heart mass	1.00	0.99-1.00	0.21
Bilirubin > 2 mg/dL	1.28	1.00-1.63	0.05
Glomerular filtration (mL/min/1.73 m^2)	0.99	0.99-1.00	0.003
Previous infection	1.23	0.88-1.72	0.22
Mechanic ventilation	1.37	1.01-1.85	0.04
Previous sternotomy	1.68	1.37-2.07	<0.001
Donor age (years)	1.01	1.00-1.02	0.03
Female donor	0.99	0.78-1.26	0.93
Donor predicted heart mass	1.00	0.99-1.00	0.44
Urgent transplant	1.30	1.01-1.67	0.04
Ischemia time (minutes)	1.00	1.00-1.00	0.68
Variables (adjusted by "inverse probability weighting").			
Heart-lung transplantation	2.26	2.00-2.56	<0.001
Inverse probability weighting	1.01	1.01-1.01	<0.001

association remained significant (HR: 2.26). These data are expressed in Tables 2 and 3. The graphic representation of the differences between the unadjusted and adjusted survival curves at one year and during the rest of the follow-up can be seen in Fig 2 and 3.

Due to the great differences between the clinical profile of the patients for whom a HLTx is indicated versus those for whom a HTx is performed, a propensity score matching was performed to obtain two homogeneous groups where the real differences in mortality could be observed. The characteristics of the matched population can be assessed in Table 4. Fig 4 shows how the increase in mortality of HLTx compared to HTx reaches a significant HR close to 3.5. This significance was maintained throughout the rest of the follow-up.

Analysis of Etiological Subgroups of Cardiopulmonary Transplantation

The most frequent cardiological indication that motivated HLTx was Eisenmenger syndrome. Other causes were CHD not included in this syndrome and dilated cardiomyopathies (ischemic or non-ischemic) associated with pulmonary hypertension. The pneumological etiology that most frequently motivated HLTx was IPAH followed by diffuse interstitial lung disease (ILD), cystic fibrosis, and COPD/Emphysema.

Early mortality (first 30 days after transplantation) was above 25% in almost all groups, but in some, such as ILD and CM + PH, it was practically 75%. Once this period has passed, mortality is reduced. However, during follow-up, the percentage of deaths exceeds, in some groups, 25% of the patients who reach this period.

Table 4: Characteristics of the matched population by propensity score.

	HLTx (n= 59)	HTx (n= 59)	P-value	SMD
Recipients				
Age (years)a	38.0 [32.0-47.0]	39.0 [29.0-49.0]	0.77	0.06
Female (n, %)	22 (37.2)	21 (35.6)	0.84	0.03
Predicted heart mass[(a)]	148.8 [120.7-177.4]	153.3 [128.1-172.2]	0.93	0.01
Bilirubin > 2 mg/dL (n, %)	13 (22.0)	12 (20.3)	0.82	0.04
Glomerular filtration (mL/min/1.73 m^2) [(a)]	88.4 [75.2-105.2]	86.8 [70.5-102.7]	0.77	0.08
Diabetes (n, %)	3 (5.1)	3 (5.1)	1.00	0.00
Previous infection (n, %)	4 (6.7)	6 (10.2)	0.51	0.12
Mechanic ventilation (n, %)	3 (5.1)	3 (5.1)	1.00	0.00
Positive CMV (n, %)	46 (78.0)	41 (69.5)	0.30	0.19
Previous sternotomy (n, %)	9 (15.2)	13 (22.0)	0.34	0.18
Donors				
Age (years) [(a)]	33.0 [22.0-39.0]	26.0 [19.0-36.5]	0.32	0.19
Female (n, %)	31 (52.5)	34 (57.6)	0.58	0.10
Predicted heart mass[(a)]	157.1 [134.9-178.5]	159.0 [140.1-181.4]	0.72	0.06
Positive CMV (n, %)	38 (64.4)	38 (64.4)	1.00	0.00
Donors/Recipients Interactions				
Female donor/male recipient (n, %)	13 (22.9)	15 (18.0)	0.66	0.08
Donor (+)/recipient (-) CMV (n, %)	6 (10.2)	10 (16.9)	0.28	0.20
Cardiac mass ratioa	1.07 [0.97-1.15]	1.05 [0.98-1.13]	0.75	0.03
Surgical Procedure				
Urgent transplant (n, %)	13 (22.0)	14 (23.7)	0.83	0.04
Ischemia time (minutes) [(a)]	235.0 [180.0-260.5]	230.0 [200.0-250.0]	0.95	0.11

[(a)]Median (Interquartile range)
Abbreviations: CMV: cytomegalovirus; HLTx: heart-lung transplantation; HTx: heart transplantation; SMD: standardized mean difference

There were large differences in median survival between the groups. Thus, survival was especially low in CM + PH, CHD and ILD; intermediate in Eisenmenger syndrome; and longer in IPAH, COPD / Emphysema, and cystic fibrosis. These results can be detailed in Table 5 and Fig 5.

DISCUSSION

Combined heart and lung transplantation was first performed successfully in 1981 at Stanford Hospital [11]. Since then, thousands of patients around the world have undergone this procedure, which continues to be a viable treatment option for terminally ill patients with concurrent cardiac and pulmonary pathologies [12-14]. However, given the unique nature of HLTx, several considerations must

Table 5: Mortality analysis.

Exposed Cases (n= 78)	Basal pathology	Mortality 30 days (n, %)	Mortality 30 days-1st year (n, %)	1st year mortality-end of follow-up (n, %)	Median survival AND IQR (days)
11	CM + PH	8 (73)	0 (0)	1 (9)	18 (5.2882)
17	Eisenmenger	7 (41)	1 (6)	6 (35)	600 (15.1965)
9	CHD	3 (33)	1 (11)	2 (22)	114 (9.2377)
21	IPAH	5 (24)	3 (14)	5 (24)	1654 (56.3983)
4	Cystic fibrosis	1 (25)	1 (25)	1 (25)	2448 (27.5104)
4	CPOD/Emphysema	1 (25)	0 (0)	1 (25)	1918 (395.5688)
12	ILD	9 (75)	1 (8)	1 (8)	29 (1.89)

Abbreviations: COPD: chronic obstructive pulmonary disease; CM + PH: cardiomyopathy + pulmonary hypertension; ILD: diffuse interstitial lung disease; IPAH: idiopathic pulmonary arterial hypertension

be taken into account, including organ allocation policies, recipient selection, perioperative and postoperative management, monitoring of graft function, and clinical outcomes. On the one hand, 3 organs are being used for a patient with which the life of three recipients could be prolonged; on the other hand, the published data of this transplant show shorter survival rates than those of HTx or LTx alone [7]. For this reason, the indication is very limited and the experience in this country is concentrated in two Spanish centers that serve as a reference for the entire national territory [1]. In this study, it has been tried to analyze the experience in HLTx of an entire country during 30 years of activity. It has been found that the average annual HLTx is 2.6, far from the more than 300 HTx and the 375 LTx. Also, survival is lower, especially when matching the characteristics of the receptors with HTx. Basically, 7 etiological groups are transplanted and the results are diverse. Thus, the longest survivals would be obtained when the main pathology is pneumological with a median survival of 5.5 years, except for ILD. Instead, when the main reason is cardiological, the median survival is lower, with 1, 6 years in Eisenmenger syndrome. These results currently require consideration of the appropriateness of the indication in certain higher-risk subgroups or with other current alternatives.

This series of 1,751 patients (1,673 HTx and 78 HLTx) is large, taking into account the small number of HLTx procedures performed per year in the world. Thus, the number of HLTx, which peaked in 1989, gradually decreased and finally reached its lowest level in 2015 with 38 patients in total reported as undergoing HLTx, according to the database of the International Society for Transplantation of Heart and Lung (ISHLT). Additionally, in 2009-2016, 63% of heart-lung transplant centers reported an average of 1 procedure per year [15]. This is probably due to a lower threshold to opt for HTx or HLTx due to its higher availability. However, HLTx remains an effective treatment for end-stage cardiopulmonary failure.

In this series, the baseline characteristics of the population subjected to HLTx coincide with those described in the previous literature [5, 7, 14]. However, the clinical profile of the recipient has evolved over the years. Thus, initially the patients were younger and without previous thoracic surgeries, while at present, they are older and present a history of the previous sternotomy in 12.8%. Logically, the ischemia time is longer in HLTx, given the

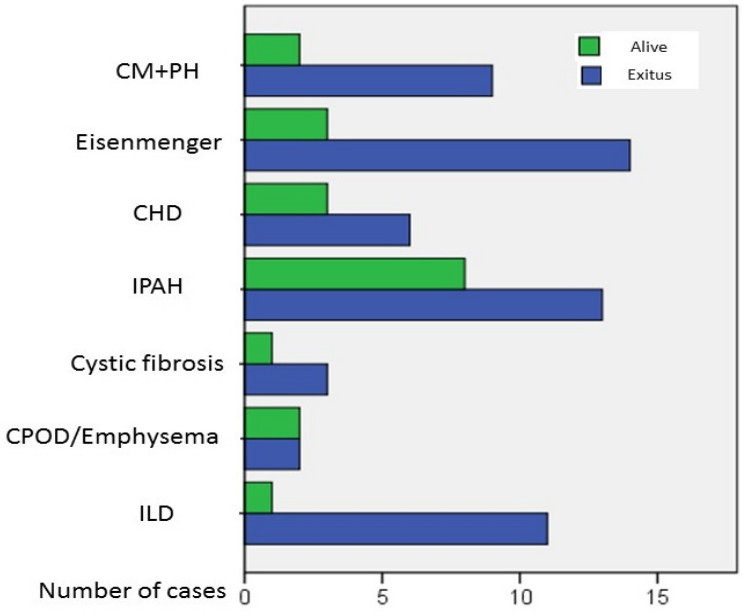

Figure 5: Total number of cases by etiology. Comparison between living patients and death. Abbreviations: CM + PH: cardiomyopathy + pulmonary hypertension; COPD: chronic obstructive pulmonary disease; ILD: diffuse interstitial lung disease; IPAH: idiopathic pulmonary arterial hypertension.

greater complexity of the intervention, which involves 3 organs. We found wide differences between the baseline characteristics of the patients with a HLTx vs HTx; This is why a propensity score matching was carried out, to obtain two homogeneous groups and to be able to observe the real differences in mortality. Thus, HLTx multiplied by 3.16 the probability of death during the first year in the adjusted analysis, and this hazard ratio (HR) increased to close to 3.5 when propensity score matching was performed. To date, it was known that the mortality of HLTx is higher than that of isolated HTx or LTx [16]; However, it is a fact that both populations are basally different, the results being difficult to interpret. This is the first analysis that compares two homogeneous groups, in which the only significant difference was the performance of HLTx vs HTx.

Regarding the indications that motivate transplantation, according to the registry of the International Society for Heart and Lung Transplantation (ISHLT), the most common indications are congenital heart disease with Eisenmenger syndrome (35%), IPAH (27%), and cystic fibrosis (13%) [12]. Thus, in this study, the most frequent cardiac indication for HLTx was Eisenmenger syndrome, followed by other CHD not included in this syndrome. Although patients with CHD usually undergo palliative surgery during childhood, and most surgical procedures result in symptomatic improvement, on many occasions these patients may ultimately require HLTx; for this reason, these patients represent the most frequent indication for HLTx [17]. Dilated ischemic or non-ischemic cardiomyopathies associated with pulmonary hypertension follow in frequency as an indication. However, in these cases, there are currently other therapeutic options other than HLTx, such as the implantation of a left ventricular assist device as a candidate bridge to reverse pulmonary hypertension [18, 19], or in the case of very severe dysfunction of the right ventricle, implant a biventricular assist device or a Total Artificial Heart [20, 21]. Regarding the pulmonological etiology, originally the most common indication for HLTx was terminal lung disease with simultaneous right ventricular dysfunction. In this study, the pulmonological etiology that most frequently motivated HLTx was IPAH, followed by ILD, cystic fibrosis, and COPD/Emphysema. These pathologies are and have been common reasons for HLTx [6, 22]. Specifically, IPAH is the second most common in-

dication of HLTx [14]. However, in the 1990s, double lung transplantation was shown to have better results [23, 24], with a high rate of recovery of right ventricular function in the short term [25]. It has been shown that in these patients, double lung transplantation has better survival [23], especially with the current availability of mechanical circulatory support that allows assistance to the patient if necessary in the postoperative period of double lung transplantation due to right ventricular failure [26, 27].

Regarding the survival of HLTx, the median survival has increased in recent decades to 6.5 years; much of this mortality occurs shortly after transplantation [5,28], with a median survival, conditional on surviving the first year after transplantation, of more than 12 years [12]. The improvement in results is probably due to a reduction in perioperative mortality as a result of more refined surgical techniques, better organ preservation solutions, and greater experience in the management of immunosuppression. However, it is a procedure that continues to present very high mortality [26]. In our study, early mortality was above 25% in almost all groups, reaching early mortality of 75% in some etiological groups. In fact, according to the ISHLT reports, given the high mortality rate in the first year after transplantation, perhaps a more valid measure is the conditional mean survival, which is defined as the mean survival for all patients who survive up to one year. Median conditional survival for patients who undergo HLTx is 10 years, although this varies according to the etiology that motivates the combined transplant.

In the detailed analysis of survival as a function of the etiology that motivates HLTx, the results of this study coincide with the previous literature in some aspects. Thus, survival was especially low in cardiomyopathy with pulmonary hypertension, CHD, and ILD, intermediate in Eisenmenger syndrome, and longer in IPAH, COPD/Emphysema, and cystic fibrosis. These data coincide with other series [7, 17], which find that the diagnosis that leads to transplantation seems to be a very important determinant of survival. Other studies had coincided in the fact that patients with CHD syndrome with or without Eisenmenger have longer conditional survival (11.3 and 13.3 years, respectively) compared to those whose indication was IPAH (10.1 years) [17]. However, there are very few studies in the previous literature that analyze the results of HLTx according to the etiology that produces it, so there are no data from large series of patients that allow us to compare our results.

The main limitation of the study, which must be taken into account when interpreting the data, is the low activity of this type of transplant with a low sample size collected over a very long period. This means that the indication may have been modified and the transplant teams periodically renewed without being able to have a consolidated experience. The merging of data from two centers could also be a limitation, but these are two centers with high annual transplant activity for many years with similar protocols in all aspects. On the other hand, this study is the only one carried out that collects all the activity of a country in this complex procedure in the last 30 years and tries to define the current situation and make some recommendations to optimize the organs and the results. In addition, few studies analyze, in a wide series over so many years of follow-up, the results of the HLTx according to the ethology that indicates it.

In conclusion, it can be said that HLTx activity accounts for less than 1% of total HTx per year1. The probability of dying is increased by 3.5 times for similar clinical profiles. The results of the risk subgroups should be analyzed, discarding those with very low survival rates and taking into account that, at present, since ventricular assist programs have been developed, some indications for a HLTx should be questioned. Thus, in cases of pulmonary hypertension of pulmonary cause with severe right failure, it is preferable to perform a double lung transplant and restore the function of the right ventricle using a short-term mechanical device [29]; or, in cases of fixed pulmonary hypertension of left cause, implant a long-term left ventricular assist device and wait for pulmonary pressures to normalize

before performing an isolated HTx [18]. It is also possible to consider the possibility of performing a LTx with the simultaneous repair of CHD [30], although in practice this possibility is rarely planteable due to surgical inconveniences and very long surgery times.

Heart-lung transplantation is a low-activity procedure with high mortality. The etiological analysis of the causes that indicate it is of maximum interest to make the most of the organs and improve survival.

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