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Early View

Original Research Article

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Increased delay to lung transplantation for women candidates:
gender-based disparity matters in the lung transplant trajectory

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Trial registration

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Author Contribution

A. Tissot had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tissot, Lemarchand, Coatanea, Rousseau, Blanc and Karakachoff

Acquisition, analysis, and interpretation of data: Coatanea, Tissot, Lair, Roux, Coiffard, Demant, Renaud-Picard, Le Pavec, Magnan, Mornex, Villeneuve, Falque, Salpin, Boussaud, Knoop, Reynaud-Gaubert, Kessler, Dauriat and Foureau

Drafting of the manuscript: Rousseau, Lemarchand and Tissot.

Critical revision of the manuscript for important intellectual content: Lemarchand, Karakachoff, Blanc.

Statistical analysis: Rousseau and Karakachoff

Study supervision: Lemarchand, Blanc and Tissot

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ACR: acute cellular rejection

BMI: body mass index

BOS: bronchiolitis obliterans syndrome

CF: cystic fibrosis

CI: confidence interval

CLAD: chronic lung allograft dysfunction

CMV: cytomegalovirus

COLT: cohort in lung transplantation

COPD: chronic obstructive pulmonary disease

D: Donor

DLCO: diffusing capacity for carbon monoxide

DSA: donor-specific antibodies

EBV: Epstein-Barr virus

ILD: interstitial lung disease

FEV1: forced expiratory volume in one second;

FVC: forced vital capacity

HBP: high blood pressure

HLA: human leukocyte antigen

HR: hazard ratio

ILD: interstitial lung disease

IPF: idiopathic pulmonary fibrosis

IQR: interquartile range

LT: lung transplantation

PAH: pulmonary arterial hypertension

PFTs: pulmonary function tests

PGD: primary graft dysfunction

pTLC: predicted total lung capacity

R: Recipient

RAS: restrictive allograft syndrome

TLC: total lung capacity

Abstract

Background

Lung transplantation (LT) is a highly dynamic segment of solid organ transplantation in which gender plays a central role. Our objective was to investigate the causes of outcome differences between women and men all along the LT pathway.

Methods

We used data from the COhort in Lung Transplantation (COLT) study (12 participating LT centers). Analyses were performed in three phases: baseline clinical characteristics, peri-transplantation period, and post-transplantation follow-up.

Results

Overall, 1710 participants (802 women and 908 men) were included in this study. Women were less likely than men to undergo transplantation (91.6% vs. 95.6%, $p=0.001$) and waited longer before transplantation (115 vs. 73 days, $p<0.001$). Female gender and pre-transplant class I anti-HLA antibodies were identified as independent factors associated with longer waiting time duration. Female LT recipients commonly received lungs from height- and sex-matched donors, despite higher female waiting-list mortality and a higher proportion of male donors. Importantly, women with oversized lung transplantation (defined by predicted TLC ratio and weight mismatch) did not have worse survival. The overall post-transplant survival of female recipients was significantly higher than that of male recipients (65.6% vs 57.3%, $p<0.001$), although the prevalence of specific major LT outcomes did not differ according to gender.

Conclusion

Women waited longer and were less likely to undergo transplant. Women transplanted with an oversized lung did not have worse survival after transplantation, suggesting that size matching criteria based on pTLC ratio and weight mismatch may be less stringent in this context.

Introduction

The number of lung transplantations performed each year has almost constantly risen since the 1990²⁵, and to date nearly 70,000 adult procedures have been reported worldwide ¹. The field of lung transplantation has made significant advances over the last decades with improvement of donor lung utilization and allocation ²⁻⁵, surgical techniques and intensive care management ⁶. It is the fastest growing segment of organ transplant, but despite those favorable trends, lung transplantation remains fraught with a high mortality risk and morbidity ⁷. Understanding factors associated to the natural history of lung transplantation, from waiting list to short- and long-term survival, is important for predicting and potentially improving outcomes.

Gender as a critical intrinsic and extrinsic factor plays a pivotal role in the field of transplantation ⁸. Recent studies have pointed out gender differences and disparities all along the transplantation path, from the access to the waiting list to post-transplantation outcomes ⁹. Lung transplantation data from the United States of America demonstrated that women had a lower chance of being transplanted than men (83.9% vs. 88.7%) and that women waited longer before transplant ^{10,11}. As for survival after lung transplantation, there seems to be an advantage for female recipients which has not been fully explained ^{12,13}. These studies have mostly been performed using the United Network of Organ Sharing (UNOS) registry and more studies from different countries in other regions of the world are needed to confirm their results. Furthermore, no study has attempted to specifically evaluate the potential differences between men and women both before and after transplantation in the same cohort, and to investigate the potential causes for these differences.

We performed a retrospective study of French participants extracted from the Cohort in lung transplantation (COLT) database, in order to carry out a comparative analysis between women and men at three different periods of the lung transplantation process: waiting list, lung transplantation itself, and post-transplantation periods.

Materials and Methods

Patients

Patients were selected among those enrolled in COLT (NCT00980967)¹⁴. COLT cohort was a prospective study that included French patients between September 2009 and December 2018. The ethics committee (Comité de Protection des Personnes Ouest 1-Tours, 2009-A00036-51) approved the study and all participants provided written informed consent. To obtain a complete donor data set, we selected patients who were also included in the French Biomedical Agency database¹⁵. Consequently, patients on the transplant waiting list of 12 French COLT partner centers were included. Patients with previous history of lung transplantation were excluded. This study complied with the International Society for Heart and Lung Transplantation statement on Transplant Ethics.

Collected data

Patients were enrolled at the time of registration on the waiting list before lung transplantation and then followed up to 10-year post-transplant. Clinical data were collected from a dedicated database approved by the Commission Nationale Informatique et Libertés (CNIL, Authorization number: 911142). Collected data included baseline characteristics such as demographics, medical history, pulmonary function tests (PFTs), transplantation data (surgery, per-and post-operative complications), and follow-up outcomes (rejections, infections, treatment, and PFT results). Gender was self-reported. The 6 minute walking test was performed according to ATS guidelines¹⁶. The following classifications were used to describe the underlying diseases: cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD)/emphysema, pulmonary arterial hypertension (PAH), interstitial lung disease

(ILD) (including idiopathic pulmonary fibrosis (IPF)), and other (including scleroderma, sarcoidosis, lymphangiomyomatosis, and other connective tissue diseases).

Chronic lung allograft dysfunction (CLAD) phenotype was assessed for every patient at 3 and 5-years post-transplantation or at death/retransplantation by an adjudication committee. Classification was initially made according to the proposition of Verleden et al. and updated from the 2019 ISHLT consensus report^{17,18}.

The French lung allocation policy is detailed in Supplemental 1. The choice of a lung donor and the matching with a recipient, including lung volume matching, was the responsibility of the local lung transplantation team with no written common policy. Weight mismatch was calculated as (donor weight – recipient weight). For the donor-to-recipient predicted total lung capacity (pTLC) ratio, we used donor and recipient pTLCs calculated according to the Global Lung Function Initiative references values^{19,20}. To address the non-linear association between pTLC ratio and overall survival, a spline was used to separate transplanted individuals into 3 relevant categories (supplemental figure 3)²¹.

Statistical analysis

Analysis were performed in three phases according to transplantation process. The first set of results analyzed the socio-demographic, medical history, and baseline clinical characteristics. The second one analyzed peri-transplantation period variables, including recipient-donor and mismatch characteristics. The third set of analyses involved the post-transplantation follow-up and graft rejection features.

The characteristics of women and men included in the study were expressed as numbers, medians, and proportions, according to the type of variable. Continuous variables were reported as mean [\pm SD] or median [\pm IQR], as indicated in tables, and comparisons between groups were computed using Student's *t* test in case of variables normally distributed and Wilcoxon's test otherwise. Categorical variables were

reported as counts and percentages, comparisons were computed through Pearson χ^2 test or Fisher test. Censored time-dependent variables, including living status, delay to transplantation, CLAD occurrence, high-emergency transplantation, and related time-to-event curves, were analyzed using the Kaplan-Meier method. Log-rank tests were used to compare curves between genders, weight mismatch, gender-related mismatch, age class, and other relevant groups.

Survival curve adjustment and the influence of predictor variables were investigated using Cox proportional hazards regression models after validation of the proportional hazard assumption. Hazard ratios, 95% confidence intervals, and p-values were computed at univariable, gender-adjusted and multivariable levels. In gender-adjusted analysis, p-values were corrected following the Benjamini-Hochberg method. Variables presenting a p-value < 0.2 in the univariable analysis were selected to perform a multivariable model using a stepwise forward variable selection with Akaike information criterion threshold.

Missing values were reported for each variable if applicable and were not included when performing comparison tests. No imputation was applied to missing data, excepted for medical history variables, considered as “not having the disease”, when missing. A p < 0.05 was considered as statistically significant. All analyses were performed using R, version 4.0.4.

Results

Pre-transplant characteristics

A total number of 1710 patients were included in the present study, in which 802 were women (47%) and 908 were men (53%) (Figure 1). In both genders, the main underlying disease was COPD/emphysema, followed by CF and ILD (Figure 2). At the time of registration on lung transplant waiting list, women were younger (47 vs 54 years; p<0.001) (Table 1) and displayed fewer comorbidities than men, including

ischemic heart disease (2.7 vs 6.8%, $p<0.001$) and cardiovascular risk factors (dyslipidemia, high blood pressure, and smoking history) (Table 1). Mean height and weight were higher in men (67 vs. 53 kg, $p<0.001$ and 173 vs. 160 cm, $p<0.001$). Pre-transplant anti-HLA antibodies were more prevalent in women than in men (46 vs. 26%, $p<0.001$) for both class I and II. Regarding respiratory failure severity, women were less likely to be on long-term oxygen therapy (81 vs 86%; $p=0.03$) and performed a slightly higher predicted distance in the 6-minute walk test (45 vs. 43 % of predicted, $p=0.03$). PFTs according to underlying disease are shown in Supplemental table 1.

Peri-transplantation phase

Lung transplantation was less often performed in women (735/802, 91.7%) than in men (868/908, 95.6%, $p=0.001$). Reasons for removal from waiting list were not significantly different according to gender (Supplemental table 2). Time duration on waiting list before lung transplantation differed markedly in women and men: women waited significantly longer before transplantation, with a median of 115 days (34-295) *versus* 73 days (28-184 for men ($p<0.001$) (Table II and Figure 3A). As for the procedure itself, women had less single lung transplantation (9.4 vs. 15.8%; $p<0.001$) but more volume reduction than men (16.6% vs 7.8%; $p<0.001$) (Table II). We observed on univariable analysis that gender, age, height, underlying disease, positive anti-HLA antibodies pre-transplant, specific listing on the high emergency program, smoking history, CMV positive serology and the 6-minute walk test performance had a significant impact on waiting time duration before transplantation (Supplemental table 3). Independent factors associated with a shorter waiting time duration before transplantation, identified in multivariable analysis, were the followings: male gender, age and listing on the high emergency lung transplantation program. In contrast, the number of pre-transplant class I anti-HLA antibodies was associated with an increased waiting time duration

before transplantation, together with underlying diagnosis of COPD and other underlying diseases (Figure 3C and Supplemental table 4).

Donor clinical characteristics are presented in Supplemental table 5. A minority of recipients underwent gender-mismatched transplants, and women were more frequently transplanted with a male donor than men with a female donor (38 vs. 27.9%; $p < 0.001$, Table II). More women than men had a high donor-to-recipient predicted TLC ratio (pTLC ratio > 1.41 : 10.1 vs. 0.1%, $p < 0.001$). Additionally, more transplantations with lungs from a donor weighing more than 15 kg than the recipient were performed in women than in men (41.2% in women vs. 30.6% in men, $p < 0.001$). Similar findings were also observed using height and body surface area (data not shown). In summary, women waited longer to get a lung transplantation and gender was an independent factor associated with the waiting list duration time. Lung volume mismatch with donor of larger stature than recipient was more frequently observed in women.

Post-transplant outcomes

The median follow-up post-transplantation for the entire cohort was 5.7 [1.9;7.9] /*- years. After lung transplantation, survival was higher in women than in men, with death occurring in 34.4% female recipients and in 42.7% male recipients ($p < 0.001$, Table III). In female recipients, survival at 1 year, 3 years and 5-years post-transplantation was 83%, 73%, and 70%, whereas in male recipients, the figures were 79%, 69%, and 61%, respectively (Figure 4A). Main causes of death in both groups were infection and graft failure, with no significant gender difference (Supplemental table 6). There was no significant gender difference in CLAD prevalence (14.7% female and 15.7% male recipients, $p = 0.9$), and time to CLAD did not differ significantly between both genders (Figure 4B, Table III). Women and men also exhibited similar rates of acute cellular rejection (40.3 vs 39%, $p = 0.3$) and antibody-mediated rejection (19.5 vs. 17.9%, $p = 0.18$). Finally, there was no difference in bacterial, fungal, or viral infection

occurrence, but cancer occurred more frequently after transplantation in men (12.3 vs. 8.7%, $p=0.02$) (Table III).

Univariable analysis identified multiple variables as significantly associated with post-transplantation survival, including gender, age, donor age, and pTLC ratio between donor and recipient (Supplemental table 7). Multivariable analysis identified that variables associated with a lower survival were the followings: male gender, single lung transplantation, heart and lung transplantation, volume reduction, history of ischemic heart disease, COPD, ILD, other underlying diseases, EBV mismatch, donor age and recipient age (Figure 4C, Supplemental table 8).

Regarding gender matching combinations between donors and recipients, survival was not significantly different according to donor gender, in contrast with recipient gender, with a higher survival in female recipients even in case of gender mismatch ($p=0.01$, Figure 5A). For the whole population, weight-negative mismatch (defined as donor weight - recipient weight ≤ -15 kg) had a negative impact on survival, whereas weight-positive mismatch (defined as donor weight - recipient weight ≥ 15 kg) did not impact survival (Figure 5B). Similar results were observed when separating female and male recipients (Supplemental figure 2). Survival rate according to pTLC ratio was similar between the 3 pTLC ratio categories as defined above (Figure 5C). To question a possible role of menopause on survival in female recipients, we analyzed survival according to age and did not find a statistical difference between female recipients ≤ 50 and > 50 years ($p=0.4$) (Figure 5D). Overall, stature mismatch with high pTLC ratio or lower recipient weight as compared to donor did not have consequence on survival. Finally, we performed a survival analysis between female and male recipients according to the underlying disease, showing a significant lower survival for male recipients with COPD. No difference in survival according to gender was observed for other underlying diseases (Supplemental figure 2).

Discussion

Our study identified striking differences between men and women along their lung transplantation trajectory. Time duration on waiting list before transplantation was on average 6 weeks longer for women, and fewer women were transplanted than men. The multivariable analysis identified, among other factors, female gender as an independent factor associated with a longer waiting time duration before transplantation. After transplantation, female recipient survival was significantly higher than that of male recipients, while the prevalence of specific lung transplantation outcomes including PGD, CLAD, ACR, and infection, were not different according to gender.

One strength of our study lies in the multicentric, nationwide nature of the cohort, associating all existing centers in France and from a European setting which presents differences with the north American context, notably in terms of recipient and donor characteristics^{22,23}. The specific reasons for which women waited longer before transplantation are complex to decipher but beyond the already known role of HLA sensitization, we hypothesized that lung volume played an important role for delayed lung transplantation due to the lack of compatible donors. Gender disparities on lung transplant waiting list have already been analyzed in previous studies. The most recent and largest one also showed a longer median waiting list duration time for women²⁴, and another study by Wille et al. showed that women were more likely than men to worsen or die within 3 years of registering on the waiting list in the USA (16 vs 11%, odds ratio = 1.58, $p < 0.001$) and they were indeed less likely than men to be transplanted (83.9% vs 88.7%, odds ratio = 0.63, $p < 0.001$)¹⁰. Sell et al. also observed that short stature was associated with a lower rate of lung transplantation and higher rates of death and respiratory failure while awaiting transplantation, and that female patients were being disproportionately affected by this disparity¹¹. A transplantation with a lung volume mismatch may be more complex, and it has been shown that

transplantation with undersized lung (based on donor-recipient's height ratio) was associated with worse post-transplantation outcomes^{1,21,25-27}. Importantly, oversized transplanted lungs are not deleterious, except for candidates with ILD^{1,20,21}.

We observed that despite the fact that donors were mostly men (56%), taller by 16 cms and heavier by 22 kgs as compared to the average height and weight of female recipients, a majority of recipients were size-matched to their donor and most transplants were performed with gender matching. However, when considering LT with lung volume mismatch, there were more female recipients than male transplanted with a pTLC ratio > 1.41, and in consequence more volume reduction in this group. Importantly, women overall who did receive an oversized lung did not have worse survival after transplantation than those who did not. Historically, size matching in France has relied upon height and sex only. This study may support a more widespread use of pTLC for size matching, which may be more accurate and may decrease the volume reduction number, as volume reduction was associated with reduced overall survival. As a result, it may possibly allow a higher proportion of female recipients to receive male donor transplants in a safe way and thus, addressing some of the gender inequalities on waiting list.

The other major known factor affecting waiting time duration before transplantation is pre-transplant HLA immunization. As pregnancy is an important trigger for immunization, anti-HLA antibodies are mostly found in women. Several studies have highlighted this issue^{28,29}. Our work confirms these data and this result is a strength of our study, as in the study discussed above, in which gender was associated with longer waiting time, this variable was not specifically assessed^{11,24}.

The main limitation of our study, besides the retrospective nature of the analysis, lies in the cohort size which is smaller as compared to UNOS-based studies on this topic. Furthermore, some items presented a high rate of missing data such as volume

reduction or the 6 minutes walking test data, and the unknown reason for waiting list removal, which could not be retrieved.

Finally, increased late survival in female lung transplant recipients has been observed in several studies with different cohorts^{1,15,27}. However, the reason for poorer overall survival in male recipients is equivocal and probably multifactorial. Indeed, men are significantly older than women at the time of lung transplantation and have more cardiovascular comorbidities. This is especially true for patients with COPD, in which even without lung transplantation, differences in survival between men and women are observed to the advantage of the latter³². This difference may also be partly related to factors that could also be gender-related, including resumption of smoking after transplantation, poorer compliance or risk-taking more frequently observed among men than women³³. The fact that in our study gender difference in survival was only significant in COPD recipients, the only behavioral disease of concern here, supports this hypothesis. Another interesting result is that less women were listed for LT than men, which raises the question of unequal access to LT program. However, although women were younger, had less cardiovascular risk factors and were less frequently on long term oxygen, we did not have information available to support the fact that listing criteria differed in the way that marginal men candidates were accepted for listing whereas women candidates were declined. Interestingly, we bring new evidence that CLAD incidence does not seem to be influenced by gender. Finally, Bonner et al. recently analyzed from UNOS data the intersection of race/ethnicity, gender and primary diagnosis on 1-year mortality and adjusted 5-year survival, identifying a clear impact of social factors²².

Conclusion

Women were less likely to be transplanted and waited significantly longer than men to get a lung transplant and this longer duration for women may be related to shorter

stature and the presence of pre-transplant anti-HLA antibodies. This discrepancy was observed despite a higher number of volume reduction, to overcome more frequent oversizing in female recipients.

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Tables

Table I. Demographic and clinical characteristics in women and men listed for lung transplantation.

Variables	Women (n = 802)	Men (n = 908)	p-value ^a
Age, years	47 [32 ; 57]	54 [39 ; 60]	<0.001
Medical history			
Ischemic heart disease	22 (2.7)	62 (6.8)	<0.001
Dyslipidemia	36 (4.5)	64 (7.0)	0.032
High blood pressure	76 (9.5)	117 (12.9)	0.032
Diabetes	113 (14.1)	147 (16.2)	0.25
Heart failure	9 (1.1)	12 (1.3)	0.88
PH group III	89 (11.1)	105 (11.6)	0.82
Kidney failure	0 (0.0)	5 (0.6)	0.1
Osteoporosis	58 (7.2)	45 (5.0)	0.06
Cancer	46 (5.7)	37 (4.1)	0.14
Gastroesophageal reflux disease	82 (10.2)	88 (9.7)	0.77
Smoking history	339 (42.3)	539 (59.4)	<0.001
Missing data (%) ^b	166 (20.7)	142 (15.6)	
Weight, kg	53 (± 12)	67 (± 15)	<0.001
Missing data (%)	124 (15.5)	90 (9.9)	
Height, cm	160 (± 7)	173 (± 7)	<0.001
Missing data (%)	122 (15.2)	90 (9.9)	
BMI, kg/m ²	20.6 (± 4.1)	22.6 (± 4.6)	<0.001
Missing data (%)	126 (15.7)	94 (10.4)	
Pre-transplant anti-HLA antibodies	366 (45.6)	232 (25.6)	<0.001
Pre-transplant anti-HLA class I antibodies			<0.001
None	518 (64.6)	739 (81.4)	
[1-10]	219 (27.3)	162 (17.8)	
[11-20]	33 (4.1)	3 (0.3)	
[21-30]	22 (2.7)	4 (0.4)	
>30	10 (1.2)	0 (0.0)	
Pre-transplant anti-HLA class II antibodies			<0.001
None	571 (71.2)	775 (85.4)	
[1-10]	199 (24.8)	127 (14.0)	
[11-20]	31 (3.9)	5 (0.6)	
[21-30]	1 (0.1)	1 (0.1)	
Bacterial colonization	375 (46.8)	491 (54.1)	0.01
Missing data (%)	24 (3.0)	23 (2.5)	
Fungal colonization	437 (54.5)	545 (60.0)	0.07
Missing data (%)	24 (3.0)	23 (2.5)	
6-minute walk test, % of predicted	45.3 (± 16.4)	43.1 (± 17.0)	0.026
Missing data (%)	289 (36.0)	293 (32.3)	
Non-invasive ventilation	314 (39.2)	340 (37.4)	0.18
Missing data (%)	77 (9.6)	69 (7.6)	

Long-term oxygen	651 (81.2)	779 (85.8)	0.035
Missing data (%)	69 (8.6)	57 (6.3)	

Data are expressed as numbers (%), means (\pm standard deviations), or medians [IQR].
^a Estimated with χ^2 , Student's, or Wilcoxon tests. ^b There were no missing data in variables where there is no corresponding line. PH: pulmonary hypertension, BMI: body mass index, HLA: human leukocyte antigen.

Table II. Per-transplant outcomes in female versus male lung transplant recipients.

Variables	Women (n = 735)	Men (n = 868)	p-value ^a
Waiting time duration before transplantation, days	115 [34 ; 295]	73 [28 ; 184]	<0.001
High emergency	124 (16.9)	117 (13.5)	0.07
Procedure			<0.001
Double lung	579 (78.8)	662 (76.3)	
Single lung	69 (9.4)	137 (15.8)	
Heart and lung	24 (3.3)	22 (2.5)	
Missing data (%) ^b	63 (8.6)	47 (5.4)	
Volume reduction	122 (16.6)	68 (7.8)	<0.001
Missing data (%)	143 (19.5)	139 (16.0)	
Total graft ischemic time, minutes	603 (± 165)	609 (± 168)	0.51
Gender mismatch	279 (38.0)	242 (27.9)	<0.001
Blood type mismatch	42 (5.7)	51 (5.9)	0.94
Missing data (%)	131 (17.8)	149 (17.2)	
Weight mismatch (donor weight – recipient weight, in absolute value)			<0.001
[-15 ; +15] kg difference between donor and recipient	344 (46.8)	437 (50.3)	
Donor weight > +15 kg recipient weight	303 (41.2)	266 (30.6)	
Donor weight < -15 kg recipient weight	31 (4.2)	115 (13.2)	
Missing data (%)	57 (7.8)	50 (5.8)	
pTLC ratio between donor and recipient			<0.001
[0.92 ; 1.41]	523 (71.2)	542 (62.4)	
< 0.92	73 (9.9)	263 (30.3)	
> 1.41	74 (10.1)	1 (0.1)	
Missing data (%)	65 (8.8)	62 (7.1)	
CMV mismatch	140 (19.0)	181 (20.9)	0.55
Missing data (%)	36 (4.9)	36 (4.1)	
EBV mismatch	48 (6.5)	52 (6.0)	0.54
Missing data (%)	40 (5.4)	38 (4.4)	
Number of HLA incompatibilities	6 [5 ; 6]	6 [5 ; 7]	0.35
Missing data (%)	72 (9.8)	77 (8.9)	
Primary graft dysfunction	184 (25.0)	185 (21.3)	0.2
Missing data (%)	130 (17.7)	166 (19.1)	

Data are expressed as counts (%), means (± standard deviation), or medians [IQR].

^a Estimated with χ^2 , Student's, or Wilcoxon tests. ^b There were no missing data in variables where there is no corresponding row. pTLC: predicted total lung capacity, CMV, cytomegalovirus; EBV, Epstein-Barr virus; HLA, human leukocyte antigen.

Table III. Post-transplant outcomes in female versus male transplant recipients.

Variables	Women (n = 735)	Men (n = 868)	p- value^a
Death	253 (34.4)	371 (42.7)	<0.001
Follow-up, years	6.1 [2.3 ; 8.2]	5.3 [1.6 ; 7.8]	0.001
Patients with k acute cellular rejection episode > grade A1 (per year)			0.34
k = 0	409 (55.6)	506 (58.3)	
k in]0 - 1]	268 (36.5)	311 (35.8)	
k > 1	28 (3.8)	28 (3.2)	
Missing data (%) ^b	30 (4.1)	23 (2.6)	
Antibody-mediated rejection	143 (19.5)	155 (17.9)	0.18
Missing data (%)	30 (4.1)	23 (2.6)	
Chronic lung allograft dysfunction			0.88
No chronic lung allograft dysfunction	415 (56.5)	471 (54.3)	
Bronchiolitis obliterans syndrome	87 (11.8)	106 (12.2)	
Restrictive allograft syndrome	13 (1.8)	17 (2.0)	
Mixed	8 (1.1)	13 (1.5)	
Missing data (%)	212 (28.8)	261 (30.1)	
Cancer	64 (8.7)	107 (12.3)	0.023
Missing data (%)	30 (4.1)	23 (2.6)	
Dialysis	68 (9.3)	67 (7.7)	0.12
Missing data (%)	85 (11.6)	79 (9.1)	
Kidney transplantation	10 (1.4)	10 (1.2)	0.26
Missing data (%)	30 (4.1)	23 (2.6)	
Post-transplant anti-HLA Donor specific antibodies	180 (24.5)	172 (19.8)	0.015
Missing data (%)	30 (4.1)	23 (2.6)	
Number of patients with k bacterial infection episode (per year)			0.06
k = 0	158 (21.5)	207 (23.8)	
k in]0 - 1]	448 (61.0)	495 (57.0)	
k in]1 - 2]	55 (7.5)	66 (7.6)	
k > 2	44 (6.0)	77 (8.9)	
Missing data (%)	30 (4.1)	23 (2.6)	
Number of patients with k fungal infection episode (per year)			0.2
k = 0	383 (52.1)	454 (52.3)	
k in]0 - 1]	283 (38.5)	329 (37.9)	
k > 1	39 (5.3)	62 (7.1)	
Missing data (%)	30 (4.1)	23 (2.6)	
Number of patients with k viral infection episode (per year)			0.22
k = 0	374 (50.9)	422 (48.6)	
k in]0 - 1]	297 (40.4)	385 (44.4)	
k in > 1	34 (4.6)	38 (4.4)	
Missing data (%)	30 (4.1)	23 (2.6)	
Re-transplant(s) during follow-up = Yes	27 (3.7)	22 (2.5)	0.24

Data are expressed as counts (%), means (\pm standard deviation), or medians [IQR].
^a Estimated with χ^2 , Student's, or Wilcoxon tests. ^b There were no missing data in variables where there is no corresponding row. HLA: human leukocyte antigen.

Figures

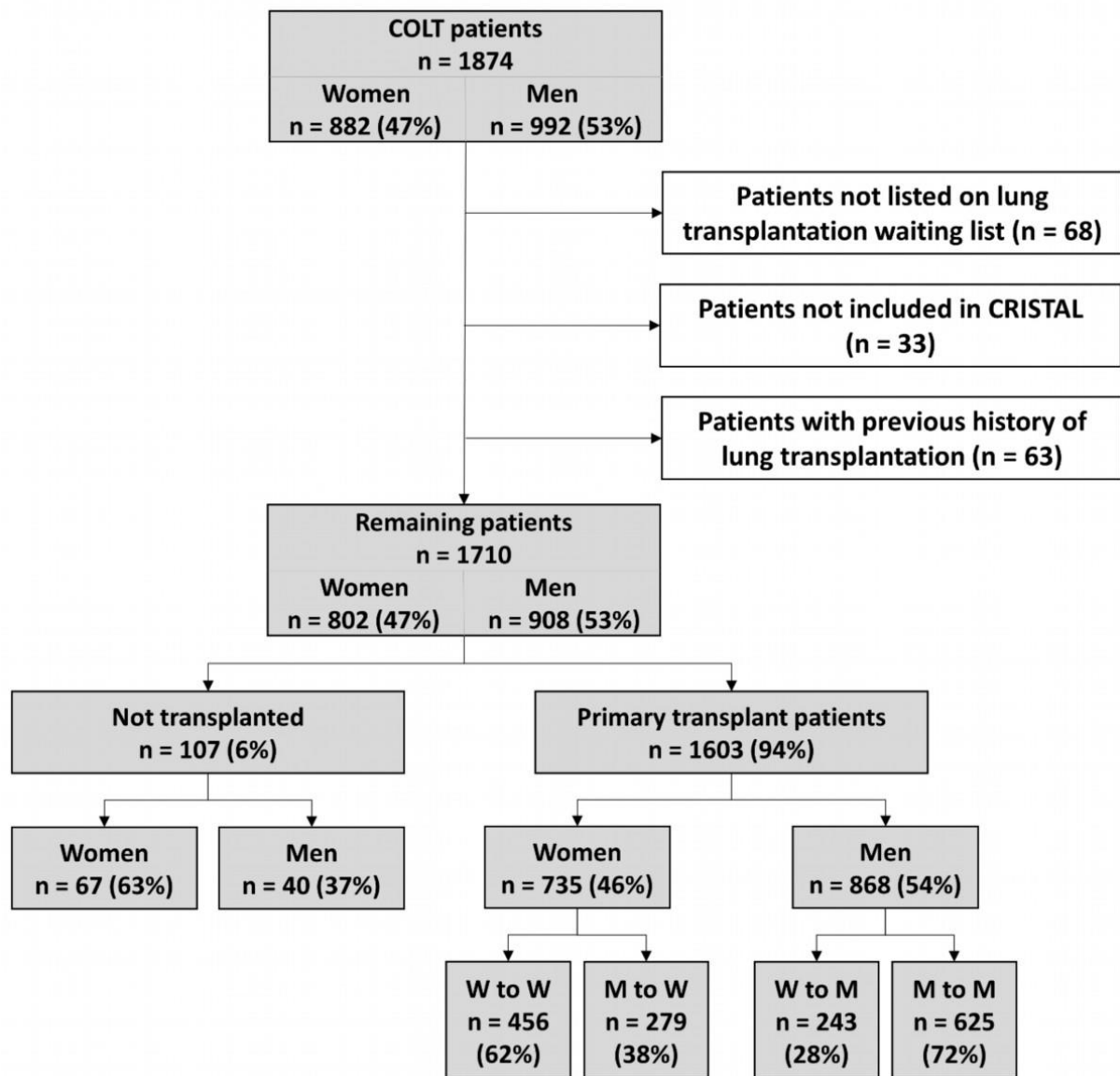


Figure 1. Flowchart. COLT: COhort in Lung Transplantation, CRISTAL: French biomedical agency database, W: women, M: men.

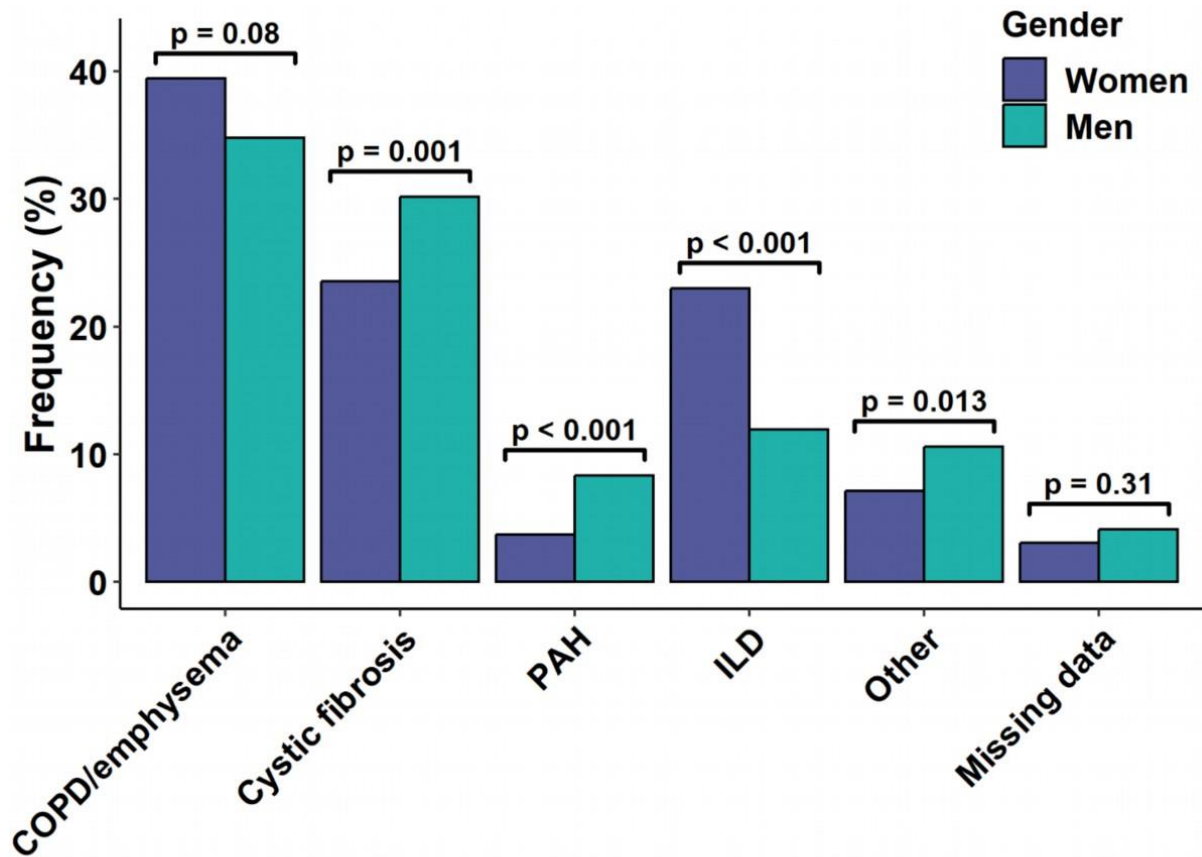


Figure 2. Underlying diagnosis in women and men awaiting lung transplantation, χ^2 tests used. ILD: Interstitial lung disease, PAH: Pulmonary arterial hypertension, COPD: Chronic obstructive pulmonary disease.

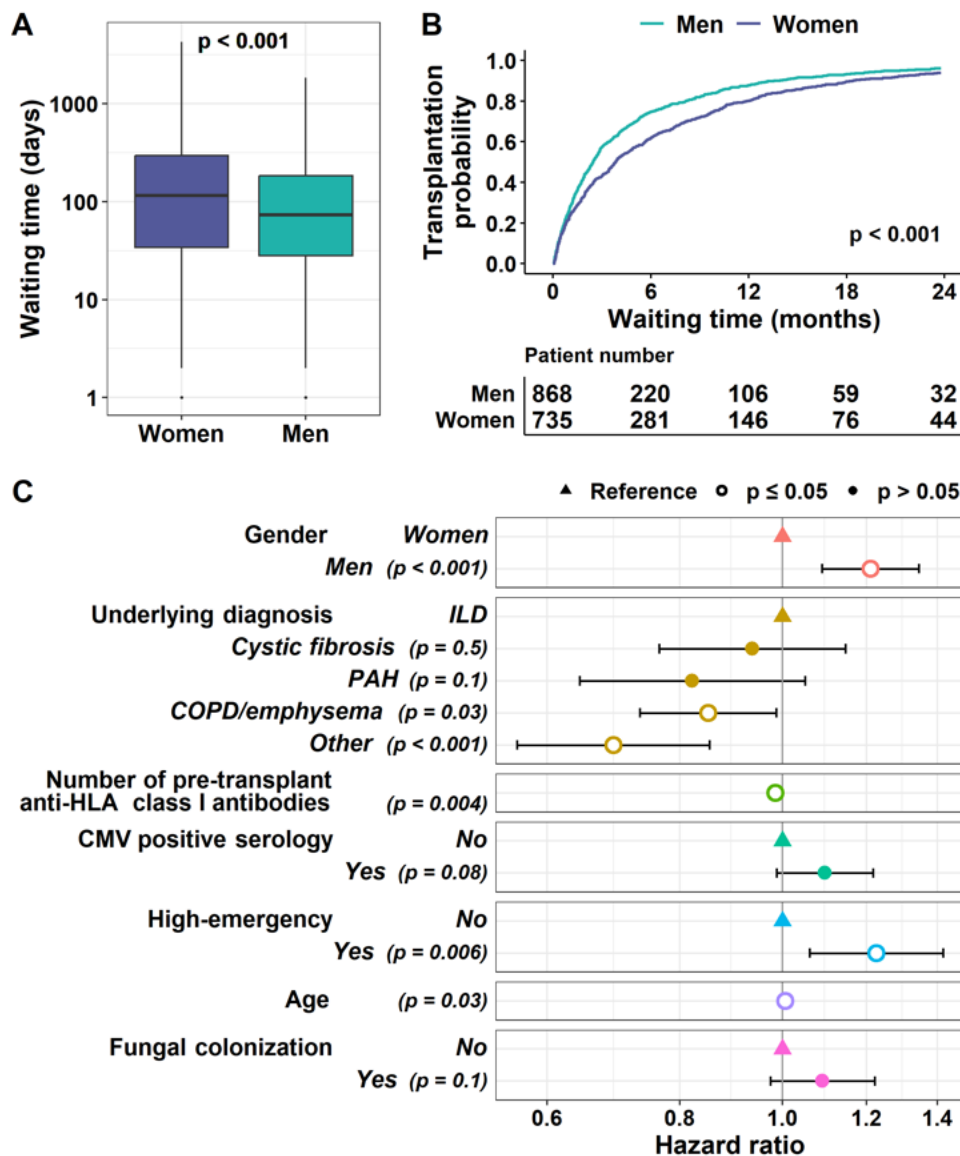


Figure 3. Waiting time duration before lung transplantation according to gender. (A) Boxplot representation of waiting time duration (log10 applied, Wilcoxon test). (B) Kaplan-Meier transplantation curves in men and women over 24 months, log-rank test used. (C) Multivariable Cox proportional hazards model showing factors associated with a shorter ($HR > 1$) or longer ($HR < 1$) waiting time duration before lung transplantation. Variables with a p-value < 0.2 in the univariable analysis were selected, and a forward stepwise selection using Akaike information criterion was used for the final multivariable Cox model. ILD: Interstitial lung disease, PAH: Pulmonary arterial hypertension, COPD: Chronic obstructive pulmonary disease, HLA: human leucocyte antigen, CMV: cytomegalovirus.

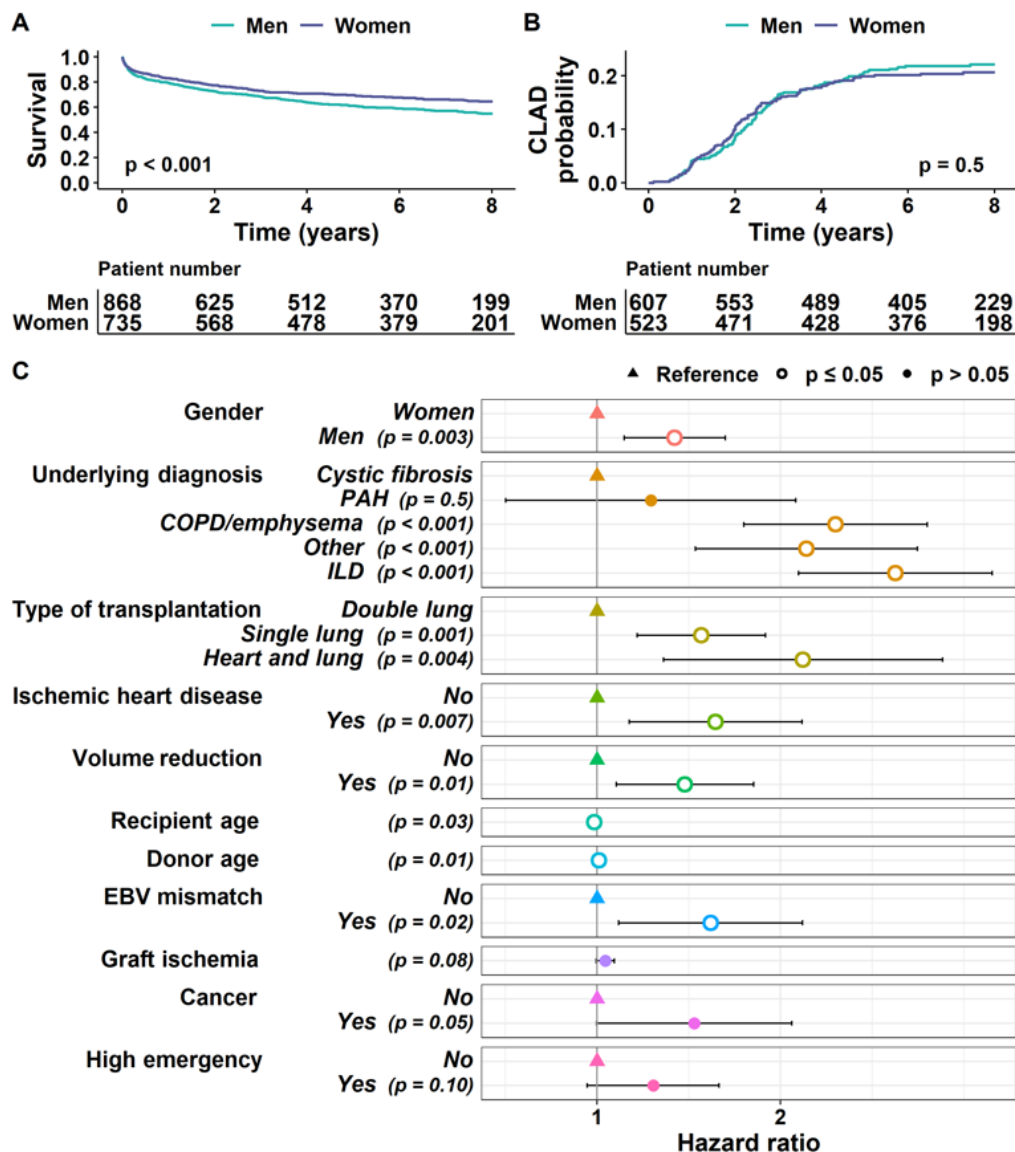


Figure 4. Overall survival and CLAD occurrence following lung transplantation according to recipient gender. (A) Kaplan-Meier survival curves over 8 years between women and men, log-rank test used. (B) Comparison of CLAD occurrence between women and men over 8 years, log-rank test used. (C) Multivariable Cox proportional hazards model showing factors associated with a shorter (HR < 1) or longer (HR > 1) survival. Variables with a p-value < 0.2 in the univariable analysis were selected and a forward stepwise selection using Akaike information criterion was used for the final multivariable Cox model. ILD: Interstitial lung disease, PAH: Pulmonary arterial hypertension, COPD: Chronic obstructive pulmonary disease, EBV: Epstein-Barr virus.

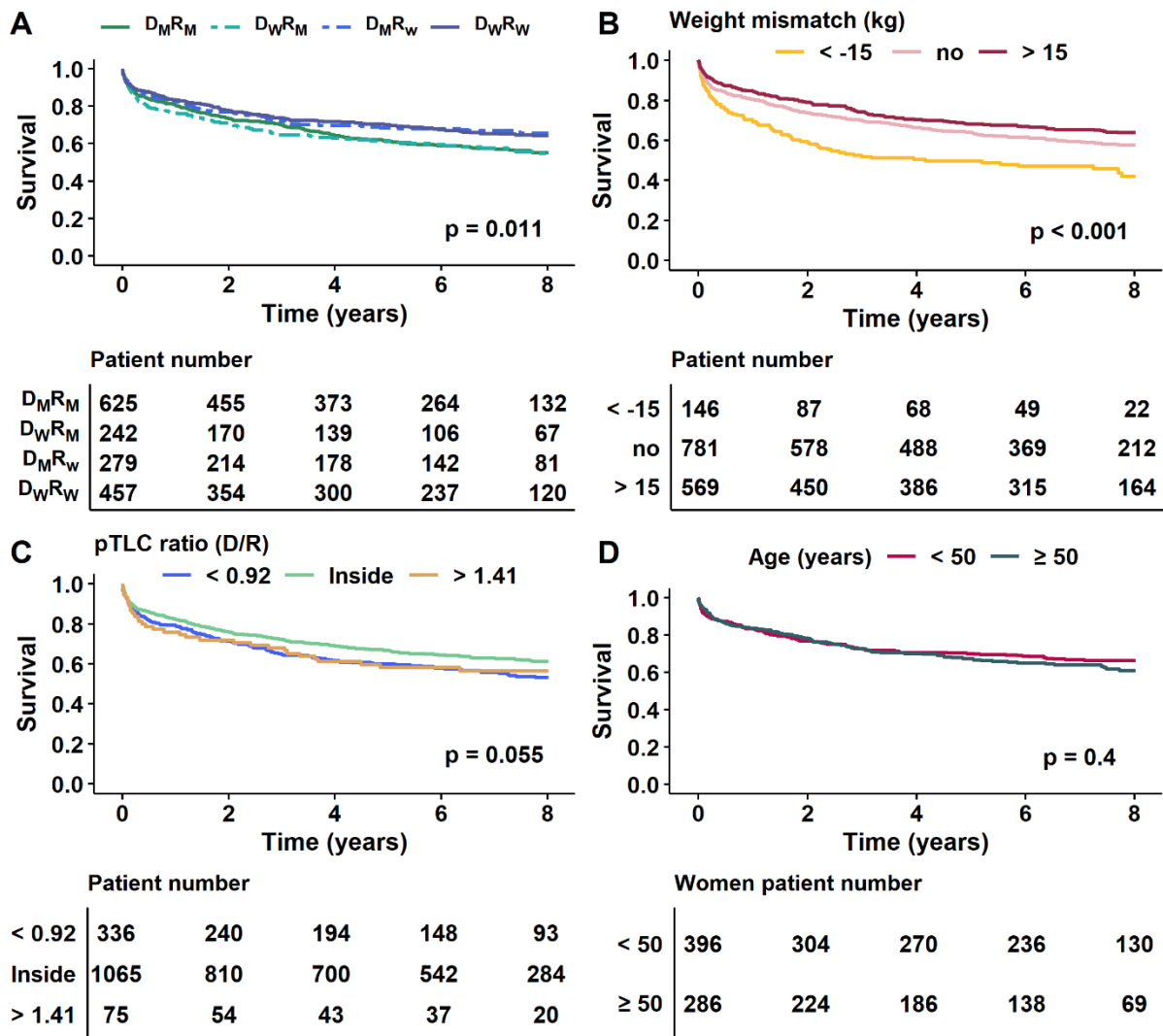


Figure 5. Factors influencing survival after lung transplantation according to recipient gender. (A) $\left(\frac{|donor\ height - recipient\ height|}{recipient\ height} \times 100\right) \chi^2$ Kaplan-Meier survival curves according to donor vs recipient gender combinations over 8 years, log-rank test used. D_M : men donor, D_W : women donor, R_M : men recipient, R_W : women recipient. Kaplan-Meier survival over 8 years, log-rank tests used. (B) Survival according to weight mismatch (donor weight - recipient weight), No: [-15, 15]. (C) Survival according to pTLC ratios between donor and recipient. (D) Survival according to age, in female recipients only.

Supplementary Appendix

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Supplemental 1. French lung allocation policy

Lung transplant candidates whose life is threatened in the very short term are given a priority access at the national level, according to procedures and terms defined by the Agence de la Biomédecine which includes a referral to a college of experts. If several recipients are registered in the lung high-emergency category, the graft is offered to the earliest candidate registered in this category. Priority is granted for 8 days and may be extended to another 8 days.

The next level of allocation is local, in which the donor lung is proposed to the nearest lung transplantation centre from the donor site.

The final level of allocation is a national round where the donor lung is proposed successively to the lung transplantation teams.

Apart from the high-emergency procedure, the choice of the recipient within its waiting list is the responsibility of the lung transplantation team.

Overall, donor proposition is made for a candidate of similar blood group. Special access for a different compatible group can be asked to the agency with expert review (e.g. B candidate for O donor).

Supplemental table 1. Pulmonary function tests at registration on waiting list in female versus male patients with cystic fibrosis, ILD, COPD and pulmonary arterial hypertension.

Variables	Women	Men	p-value ^a
Cystic fibrosis	n = 242	n = 214	
FEV1 as % of predicted	24.0 [19.9 ; 29.0]	22.0 [19.0 ; 27.2]	0.014
Missing data (%)	9 (3.7)	5 (2.3)	
FVC as % of predicted	41.0 [33.0 ; 50.0]	41.0 [33.0 ; 48.1]	0.26
Missing data (%)	14 (5.8)	10 (4.7)	
DLCO as % of predicted	46.0 [37.5 ; 53.4]	46 [38 ; 56]	0.73
Missing data (%)	199 (82.2)	170 (79.4)	
TLC as % of predicted	105 [95 ; 117]	102 [87 ; 114]	0.08
Missing data (%)	112 (46.3)	97 (45.3)	
Interstitial lung disease	n = 96	n = 209	
FEV1 as % of predicted	42.5 [33.8 ; 54.0]	51.0 [38.1 ; 61.0]	0.001
Missing data (%)	12 (12.5)	11 (5.3)	
FVC as % of predicted	40 [33 ; 50]	46 [36 ; 58]	0.002
Missing data (%)	11 (11.5)	14 (6.7)	
DLCO as % of predicted	25.6 [18.4 ; 34.8]	22.0 [17.0 ; 30.0]	0.14
Missing data (%)	70 (72.9)	89 (42.6)	
TLC as % of predicted	47 [41 ; 61]	50 [43 ; 62]	0.32
Missing data (%)	39 (40.6)	51 (24.4)	
COPD/emphysema	n = 279	n = 358	
FEV1 as % of predicted	22.0 [18.0 ; 27.0]	20.5 [17.0 ; 27.0]	0.12
Missing data (%)	12 (4.3)	17 (4.7)	
FVC as % of predicted	56.4 [43.0 ; 70.0]	54.0 [44.0 ; 69.0]	0.59
Missing data (%)	16 (5.7)	26 (7.3)	
DLCO as % of predicted	20.0 [13.4 ; 27.6]	22.0 [16.0 ; 29.9]	0.17
Missing data (%)	161 (57.7)	184 (51.4)	
TLC as % of predicted	139 [126 ; 155]	125 [110 ; 140]	<0.001
Missing data (%)	80 (28.7)	94 (26.3)	
Pulmonary arterial hypertension	n = 67	n = 34	
FEV1 as % of predicted	78 [65 ; 89]	83.0 [62.3 ; 97.2]	0.55
Missing data (%)	14 (20.9)	6 (17.6)	
FVC as % of predicted	94 [76 ; 104]	94 [70 ; 102]	0.6
Missing data (%)	17 (25.4)	8 (23.5)	
DLCO as % of predicted	58.0 [40.2 ; 66.3]	35.0 [27.8 ; 57.6]	0.016
Missing data (%)	35 (52.2)	12 (35.3)	
TLC as % of predicted	94 [84 ; 108]	93 [82 ; 100]	0.47
Missing data (%)	23 (34.3)	9 (26.5)	

Data are expressed as median [interquartile range] and missing data as number (%).

^a Estimated using the Wilcoxon test. FEV1: forced expiratory volume in one second. FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; TLC, total lung capacity; COPD, chronic obstructive pulmonary disease.

Supplemental table 2. Causes of removal from waiting list

	Women (n = 66)	Men (n = 41)	p- value
Cause (%)			0.07
Improvement	5 (7.7)	0 (0.0)	
Contra indication	4 (6.2)	5 (12.2)	
Death	34 (52.3)	28 (68.3)	
Undetermined	23 (33.8)	8 (19.5)	

Supplemental table 3. Univariate Cox regression analysis for waiting time duration before lung transplantation and gender-adjusted analysis.

Variables	Univariate analysis		Gender adjusted analysis (Surv(delay, transplantation) ~ gender + variable) ^a			
	HR (95% CI)	P-value	Gender adjusted HR (95% CI)	Gender adjusted p-value	Variable adjusted HR (95% CI)	Variable adjusted p-value
Male gender	1.28 (1.16-1.42)	<0.001				
Age	1.01 (1.00-1.01)	0.001	1.26 (1.14-1.39)	<0.001 ***	1.00 (1.00-1.01)	0.006 *
Underlying diagnosis						
Interstitial lung disease	Ref.	-	1.25 (1.13-1.38)	<0.001 ***	Ref.	-
Cystic fibrosis	0.76 (0.66-0.88)	<0.001	-	-	0.78 (0.67-0.91)	0.001 *
Pulmonary arterial hypertension	0.77 (0.61-0.97)	0.029	-	-	0.81 (0.64-1.02)	0.075
COPD/emphysema	0.83 (0.72-0.95)	0.008	-	-	0.83 (0.72-0.96)	0.012
Other	0.68 (0.55-0.83)	<0.001	-	-	0.69 (0.57-0.85)	<0.001 *
CMV positive serology	1.12 (1.01-1.24)	0.026	1.28 (1.16-1.42)	<0.001 ***	1.13 (1.02-1.25)	0.016
EBV positive serology	0.99 (0.82-1.21)	0.942	1.29 (1.16-1.43)	<0.001 ***	0.98 (0.81-1.19)	0.838
Bacterial colonization	1.01 (0.91-1.11)	0.903	1.28 (1.16-1.41)	<0.001 ***	0.99 (0.90-1.10)	0.921
Fungal colonization	1.10 (1.00-1.22)	0.058	1.27 (1.15-1.41)	<0.001 ***	1.09 (0.98-1.20)	0.103
6-minute walk test, % of predicted	1.00 (0.99-1.00)	0.005	1.31 (1.16-1.47)	<0.001 ***	1.00 (0.99-1.00)	0.026

Non-invasive ventilation	0.98 (0.88-1.09)	0.692	1.26 (1.13-1.39)	<0.001 ***	0.98 (0.88-1.09)	0.711
Long-term oxygen	1.14 (0.96-1.36)	0.14	1.27 (1.14-1.40)	<0.001 ***	1.14 (0.96-1.35)	0.149
Ischemic heart disease	1.11 (0.88-1.39)	0.391	1.28 (1.16-1.42)	<0.001 ***	1.05 (0.83-1.32)	0.698
High blood pressure	1.10 (0.94-1.29)	0.218	1.28 (1.16-1.41)	<0.001 ***	1.06 (0.91-1.24)	0.448
Pulmonary hypertension group III	0.86 (0.73-1.01)	0.06	1.29 (1.16-1.42)	<0.001 ***	0.86 (0.73-1.00)	0.054
Dyslipidemia	1.10 (0.90-1.36)	0.35	1.28 (1.16-1.42)	<0.001 ***	1.06 (0.86-1.31)	0.58
Diabetes	0.94 (0.82-1.07)	0.349	1.28 (1.16-1.42)	<0.001 ***	0.94 (0.82-1.08)	0.393
Heart failure	0.86 (0.54-1.36)	0.516	1.28 (1.16-1.42)	<0.001 ***	0.84 (0.53-1.34)	0.476
Gastroesophageal reflux	0.98 (0.83-1.15)	0.786	1.28 (1.16-1.42)	<0.001 ***	0.97 (0.82-1.14)	0.713
Kidney failure	1.76 (0.56-5.45)	0.331	1.28 (1.16-1.42)	<0.001 ***	1.57 (0.50-4.88)	0.436
Cancer	1.00 (0.80-1.26)	0.996	1.28 (1.16-1.42)	<0.001 ***	1.00 (0.80-1.26)	0.993
Number of pre-transplant anti-HLA class I antibodies	0.98 (0.97-0.99)	<0.001	1.25 (1.13-1.38)	<0.001 ***	0.99 (0.98-1.00)	0.005 *
Number of pre-transplant anti-HLA class II antibodies	0.98 (0.96-0.99)	0.01	1.26 (1.14-1.40)	<0.001 ***	0.98 (0.96-1.00)	0.072
Height, cm	1.01 (1.01-1.02)	<0.001	1.26 (1.10-1.45)	0.001 **	1.00 (1.00-1.01)	0.505
Recipient's blood type						
A	Ref.	-	1.32 (1.19-1.48)	<0.001 ***	Ref.	-
AB	1.08 (0.81-1.45)	0.586	-	-	1.06 (0.79-1.43)	0.674

B	1.10 (0.92-1.32)	0.308	-	-	1.09 (0.91-1.30)	0.371
O	0.94 (0.84-1.06)	0.296	-	-	0.91 (0.81-1.03)	0.131
Smoking history	0.90 (0.80-1.01)	0.061	1.27 (1.14-1.42)	<0.001 ***	0.87 (0.78-0.97)	0.016
High emergency	1.14 (1.00-1.31)	0.057	1.30 (1.18-1.43)	<0.001 ***	1.18 (1.03-1.36)	0.018

^a Where Surv() is the survival function; delay is the time between the day of registration on the waiting list and transplantation (or the day of data extraction for non-transplanted patients), transplantation is the event of the survival analysis, gender is present in all the adjusted bivariable analysis, and variable corresponds to the other explanatory variables. Results with significant p-values corrected by Benjamini-Hochberg are indicated as follows: * p < 0.05, ** p < 0.01, and *** p < 0.001. HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CMV, Cytomegalovirus; EBV, Epstein-Barr Virus; HLA, human leukocyte antigen.

Supplemental table 4. Multivariable Cox regression analysis for waiting time duration before lung transplantation.

Variables (n = 1,529)	HR (95% CI)	P-value
Male gender	1.21 [1.09-1.34]	<0.001
Underlying diagnosis		
Interstitial lung disease	Ref.	-
Cystic fibrosis	0.94 [0.77-1.15]	0.52
Pulmonary arterial hypertension	0.82 [0.64-1.05]	0.12
COPD/emphysema	0.85 [0.73-0.99]	0.03
Other	0.69 [0.56-0.85]	<0.001
Number of pre-transplant anti-HLA class I antibodies	0.98 [0.97-1.00]	<0.001
CMV positive serology	1.10 [0.99-1.22]	0.08
High-emergency	1.23 [1.06-1.42]	0.01
Recipient age	1.01 [1.00-1.01]	0.03
Fungal colonization	1.09 [0.97-1.22]	0.13

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HLA, human leukocyte antigen; CMV, Cytomegalovirus.

Supplemental table 5. Clinical characteristics of female and male donors

Variables	Women (n = 699)	Men (n = 904)	p-value ^a
Age, years	51.0 [40.0 ; 59.0]	44.5 [30.0 ; 56.0]	<0.001
Missing data (%) ^b	55 (7.9)	56 (6.2)	
Weight, kg	65 (± 13)	75 (± 13)	<0.001
Height, cm	163 (± 7)	176 (± 7)	<0.001
Body mass index, kg/m ²	24.3 (± 4.7)	24.2 (± 3.6)	0.69
Cause of death			<0.001
Vascular	453 (64.8)	390 (43.1)	
Traumatic, public road accident	59 (8.4)	154 (17.0)	
Traumatic, non-road accident	61 (8.7)	184 (20.4)	
Anoxia	98 (14.0)	139 (15.4)	
Meningitis	11 (1.6)	11 (1.2)	
Tumor	8 (1.1)	2 (0.2)	
Intoxication	3 (0.4)	5 (0.6)	
Other	6 (0.9)	18 (2.0)	
Missing data (%)	0 (0.0)	1 (0.1)	
Smoking history	244 (34.9)	377 (41.7)	0.007
Blood type			0.41
A	273 (39.1)	329 (36.4)	
AB	12 (1.7)	20 (2.2)	
B	60 (8.6)	82 (9.1)	
O	298 (42.6)	416 (46.0)	
Missing data (%)	56 (8.0)	57 (6.3)	
CMV positive serology	369 (52.8)	420 (46.5)	0.014
EBV positive serology	678 (97.0)	852 (94.2)	0.027
Missing data (%)	0 (0.0)	1 (0.1)	
Toxoplasmosis positive serology	355 (50.8)	495 (54.8)	0.27
Missing data (%)	98 (14.0)	112 (12.4)	

Data are expressed as numbers (%), means (± standard deviations), or medians [interquartile ranges].
^aEstimated with χ^2 , Student's, or Wilcoxon tests. ^b There are no missing data for variables for which there is no corresponding line. CMV, Cytomegalovirus; EBV, Epstein-Barr Virus.

Supplemental table 6. Cause of death after transplantation

	Women (n = 253)	Men (n = 371)	p- value
Cause of death (%)			0.51
Cancer	15 (5.9)	28 (7.5)	
Cardiovascular	19 (7.5)	23 (6.2)	
Cerebrovascular	4 (1.6)	8 (2.2)	
Digestive	0 (0.0)	1 (0.3)	
Graft failure	91 (36.0)	116 (31.3)	
Hemorrhage	23 (9.1)	23 (6.2)	
Infection	58 (22.9)	95 (25.6)	
MOF	14 (5.5)	29 (7.8)	
Other	13 (5.1)	15 (4.0)	
Traumatic	0 (0.0)	3 (0.8)	
Unknown	16 (6.3)	30 (8.1)	

Supplemental table 7. Univariate Cox regression for overall survival, and gender-adjusted analysis

Variables	Univariate analysis		Gender adjusted analysis (Surv(time, rejection) ~ gender + variable) ^a			
	HR (95% CI)	P-value	Gender adjusted HR (95% CI)	Gender adjusted p-value	Variable adjusted HR (95% CI)	Variable adjusted p-value
Male gender	1.32 (1.12-1.55)	0.001				
Age	1.01 (1.01-1.02)	<0.001	1.26 (1.07-1.48)	0.006 **	1.01 (1.01-1.02)	<0.001 ***
Underlying diagnosis						
Cystic fibrosis	Ref.	-	1.19 (1.01-1.41)	0.035 *	Ref.	-
Pulmonary arterial hypertension	1.32 (0.88-1.98)	0.177	-	-	1.35 (0.90-2.03)	0.147
COPD/emphysema	1.82 (1.46-2.26)	<0.001	-	-	1.80 (1.45-2.24)	<0.001 ***
Other	2.04 (1.50-2.78)	<0.001	-	-	2.08 (1.52-2.83)	<0.001 ***
Interstitial lung disease	2.82 (2.23-3.58)	<0.001	-	-	2.72 (2.14-3.46)	<0.001 ***
CMV positive serology	1.07 (0.91-1.25)	0.431	1.32 (1.12-1.55)	0.001 **	1.08 (0.92-1.26)	0.362
EBV positive serology	0.84 (0.63-1.13)	0.254	1.32 (1.12-1.55)	0.001 **	0.84 (0.63-1.12)	0.235
Bacterial colonization	1.40 (1.20-1.65)	<0.001	1.28 (1.09-1.51)	0.002 **	1.39 (1.18-1.62)	<0.001 **
Fungal colonization	1.11 (0.94-1.30)	0.209	1.30 (1.11-1.53)	0.001 **	1.10 (0.94-1.29)	0.248
6-minute walk test, % of predicted	1.00 (0.99-1.00)	0.096	1.40 (1.15-1.70)	0.001 **	1.00 (0.99-1.00)	0.147
On noninvasive ventilation before transplantation	0.75 (0.63-0.88)	0.001	1.31 (1.11-1.55)	0.001 *	0.74 (0.63-0.88)	0.001 **

Long term oxygen supplementation	1.07 (0.80-1.41)	0.657	1.32 (1.12-1.56)	0.001 **	1.04 (0.78-1.37)	0.808
Ischemic heart disease	1.87 (1.39-2.52)	<0.001	1.29 (1.10-1.52)	0.002 **	1.80 (1.34-2.43)	<0.001 **
High blood pressure	1.12 (0.88-1.42)	0.367	1.31 (1.12-1.54)	0.001 **	1.09 (0.86-1.39)	0.483
Secondary pulmonary arterial hypertension	0.95 (0.73-1.22)	0.669	1.32 (1.12-1.55)	0.001 **	0.94 (0.73-1.21)	0.642
Dyslipidemia	1.51 (1.13-2.02)	0.006	1.30 (1.11-1.53)	0.001 **	1.46 (1.09-1.96)	0.011 *
Diabetes	0.78 (0.62-0.98)	0.033	1.32 (1.13-1.55)	0.001 **	0.77 (0.61-0.97)	0.025
Heart failure	1.15 (0.57-2.30)	0.701	1.32 (1.12-1.54)	0.001 **	1.13 (0.56-2.27)	0.735
Gastroesophageal reflux	0.77 (0.58-1.03)	0.075	1.32 (1.12-1.55)	0.001 **	0.77 (0.58-1.02)	0.073
Kidney failure	0.00 (0.00-Inf)	0.988	1.32 (1.13-1.55)	0.001 **	0.00 (0.00-Inf)	0.988
Osteoporosis	0.96 (0.69-1.34)	0.827	1.32 (1.12-1.54)	0.001 **	0.98 (0.70-1.37)	0.906
Cancer	1.60 (1.17-2.19)	0.003	1.33 (1.13-1.56)	0.001 **	1.63 (1.19-2.23)	0.002 *
Pre-transplant anti-HLA antibodies	0.88 (0.75-1.05)	0.149	1.30 (1.10-1.53)	0.002 **	0.93 (0.78-1.10)	0.413
Height, cm	1.01 (1.00-1.02)	0.085	1.36 (1.10-1.68)	0.005 **	1.00 (0.99-1.01)	0.59
pTLC ratio between donor and recipient						
[0.92 ; 1.41]	Ref.	-	1.30 (1.09-1.55)	0.003 **	Ref.	-
< 0.92	1.25 (1.04-1.51)	0.02	-	-	1.17 (0.96-1.41)	0.116
> 1.41	1.19 (0.83-1.70)	0.346	-	-	1.36 (0.94-1.98)	0.104

Recipient's blood type						
A	Ref.	-	1.31 (1.10-1.55)	0.002 **	Ref.	-
AB	0.93 (0.58-1.49)	0.768	-	-	0.92 (0.58-1.47)	0.729
B	0.91 (0.68-1.21)	0.517	-	-	0.92 (0.69-1.23)	0.578
O	0.96 (0.80-1.15)	0.661	-	-	0.96 (0.80-1.15)	0.636
Smoking history	1.53 (1.26-1.85)	<0.001	1.33 (1.11-1.61)	0.002 **	1.46 (1.20-1.77)	<0.001 **
High emergency	1.47 (1.21-1.80)	<0.001	1.33 (1.13-1.56)	0.001 **	1.49 (1.22-1.82)	<0.001 **
Type of transplantation						
Double lung transplant	Ref.	-	1.28 (1.08-1.51)	0.004 **	Ref.	-
Single lung transplant	1.72 (1.14-2.60)	0.01	-	-	1.76 (1.16-2.65)	0.007 *
Heart and lung transplant	1.87 (1.53-2.29)	<0.001	-	-	1.81 (1.48-2.21)	<0.001 ***
Volume reduction	1.24 (0.98-1.57)	0.068	1.45 (1.21-1.73)	<0.001 **	1.35 (1.07-1.71)	0.013 *
Graft ischemia, hours	1.04 (1.01-1.07)	0.012	1.31 (1.12-1.54)	0.001 **	1.04 (1.01-1.07)	0.016
Gender mismatch	0.97 (0.82-1.15)	0.745	1.32 (1.12-1.55)	0.001 **	1.00 (0.85-1.19)	0.962
Blood type mismatch	0.95 (0.68-1.33)	0.755	1.31 (1.10-1.55)	0.002 **	0.95 (0.68-1.33)	0.757
Weight mismatch (D-R)						
No weight mismatch	Ref.	-	1.23 (1.04-1.45)	0.016 *	Ref.	-
Donor weight < -15 kg recipient weight	1.57 (1.22-2.01)	<0.001	-	-	1.50 (1.17-1.92)	0.002 **

Donor weight > +15 kg recipient weight	0.83 (0.70-0.99)	0.038	-	-	0.84 (0.71-1.01)	0.061
CMV mismatch	1.08 (0.89-1.31)	0.418	1.31 (1.12-1.54)	0.001 **	1.08 (0.89-1.31)	0.432
EBV mismatch	1.26 (0.94-1.70)	0.122	1.32 (1.12-1.55)	0.001 **	1.27 (0.94-1.70)	0.114
Count of HLA incompatibilities	1.00 (0.94-1.06)	0.963	1.30 (1.10-1.54)	0.002 **	1.00 (0.94-1.06)	0.936
Primary graft dysfunction	1.56 (1.29-1.89)	<0.001	1.38 (1.15-1.65)	0.001 **	1.60 (1.32-1.93)	<0.001 ***
Donor age, years	1.01 (1.00-1.01)	0.002	1.32 (1.12-1.56)	0.001 **	1.01 (1.00-1.01)	0.001 **
Weight, kg	1.00 (0.99-1.00)	0.648	1.35 (1.15-1.60)	<0.001 **	1.00 (0.99-1.00)	0.179
Height, cm	1.00 (0.99-1.01)	0.707	1.40 (1.18-1.66)	<0.001 **	0.99 (0.98-1.00)	0.073
Body mass index, kg/m ²	1.00 (0.98-1.02)	0.818	1.32 (1.12-1.55)	0.001 **	1.00 (0.98-1.02)	0.707
Cause of death						
Vascular	Ref.	-	1.32 (1.12-1.55)	0.001 **	Ref.	-
Traumatic, public road accident	0.89 (0.70-1.14)	0.354	-	-	0.88 (0.69-1.13)	0.307
Traumatic, non-road accident	1.07 (0.85-1.33)	0.58	-	-	1.04 (0.83-1.31)	0.717
Anoxia	0.99 (0.79-1.25)	0.951	-	-	0.98 (0.78-1.24)	0.886
Meningitis	1.57 (0.88-2.80)	0.124	-	-	1.58 (0.89-2.82)	0.117
Tumor	0.66 (0.21-2.07)	0.478	-	-	0.62 (0.20-1.95)	0.416
Intoxication	2.07 (0.86-5.01)	0.106	-	-	1.92 (0.79-4.65)	0.149

Other	0.89 (0.46-1.72)	0.728	-	-	0.84 (0.43-1.63)	0.608
Smoking history	1.02 (0.87-1.20)	0.801	1.32 (1.12-1.54)	0.001 **	1.01 (0.86-1.18)	0.936
Blood type						
A	Ref.	-	1.30 (1.10-1.53)	0.002 **	Ref.	-
AB	0.88 (0.48-1.61)	0.671	-	-	0.86 (0.47-1.57)	0.62
B	1.06 (0.80-1.42)	0.667	-	-	1.08 (0.81-1.44)	0.594
O	1.00 (0.84-1.19)	0.989	-	-	1.00 (0.84-1.19)	0.996
Anti-CMV antibodies	1.08 (0.92-1.26)	0.363	1.32 (1.13-1.55)	0.001 **	1.09 (0.93-1.27)	0.293
Anti-EBV antibodies	1.09 (0.74-1.60)	0.662	1.32 (1.12-1.55)	0.001 **	1.11 (0.75-1.63)	0.609
Anti-toxoplasmosis antibodies	1.03 (0.87-1.23)	0.734	1.33 (1.12-1.58)	0.001 **	1.03 (0.87-1.23)	0.724

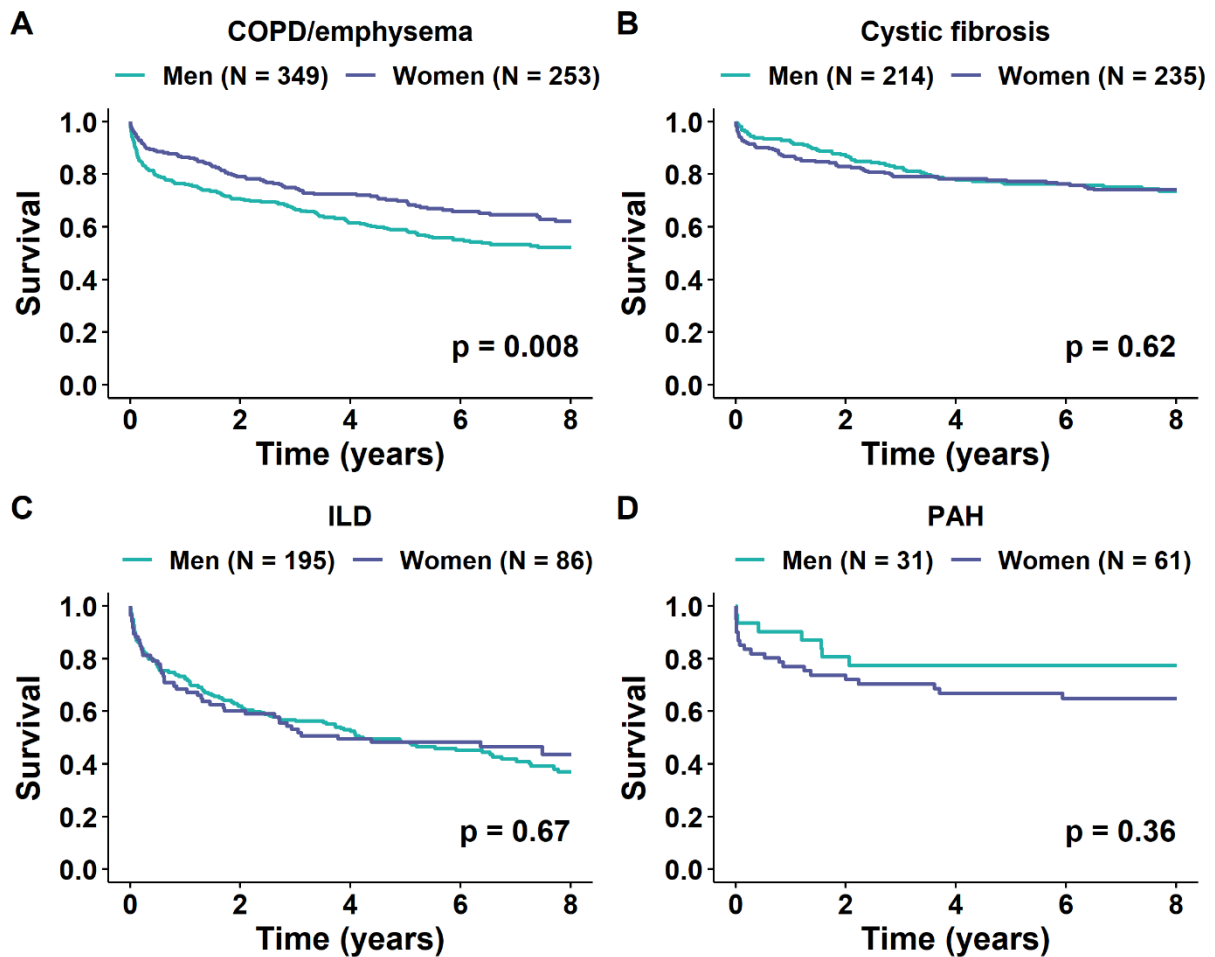
^a Where $Surv(t)$ is the survival function, $time$ is the time between the transplantation day and the rejection or the day of the last follow-up, $rejection$ is the event of the survival analysis, $gender$ is present in all the adjusted bivariable analyses, $variable$ corresponds to the other explanatory variables. Results with significant p-values corrected by Benjamini-Hochberg are indicated as follows: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CMV, Cytomegalovirus; EBV, Epstein-Barr Virus; pTLC, predicted total lung capacity; HLA, human leukocyte antigen; D: Donor, DSA, donor-specific antibodies; R: Recipient.

Supplemental table 8. Multivariable Cox regression for overall survival

Variables (n = 1,256)	HR (95% CI)	P-value
Male gender	1.34 [1.11-1.62]	<0.001
Underlying diagnosis		
Cystic fibrosis	Ref.	-
Pulmonary arterial hypertension	1.23 [0.71-2.12]	0.47
COPD/emphysema	2.46 [1.74-3.48]	<0.001
Other	2.21 [1.45-3.35]	<0.001
Interstitial lung disease	3.09 [2.14-4.45]	<0.001
Type of transplantation		
Double lung transplant	Ref.	-
Single lung transplant	1.48 [1.16-1.89]	<0.001
Heart and lung transplant	2.18 [1.28-3.69]	<0.001
Ischemic heart disease	1.57 [1.13-2.17]	0.01
Volume reduction	1.39 [1.07-1.81]	0.01
Recipient age	0.99 [0.98-1.00]	0.03
Donor age	1.01 [1.00-1.01]	0.01
EBV mismatch	1.54 [1.09-2.17]	0.02
Graft ischemia, hours	1.03 [1.00-1.07]	0.08
Cancer	1.44 [1.00-2.09]	0.05
High emergency	1.24 [0.96-1.59]	0.1

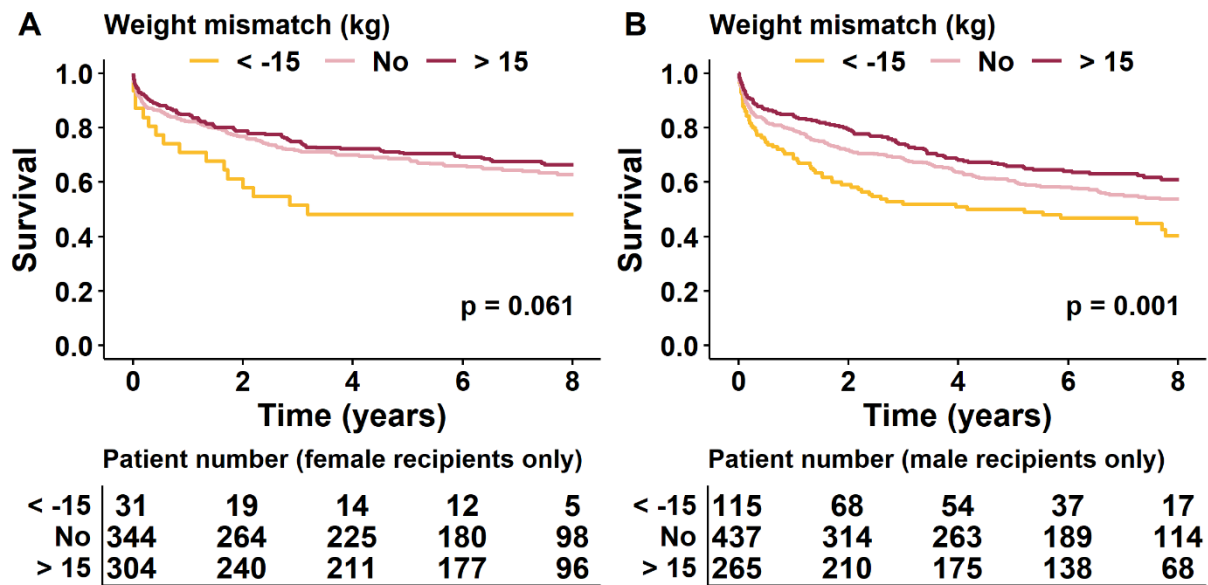
After the pre-selection of variables with a p-value < 0.2 in the univariate analysis, a stepwise forward selection was applied with the Akaike information criterion to create a multivariate model with the recipient's gender. HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EBV, Epstein-Barr Virus.

Supplemental figure 1. Comparison of survival between women and men over 8 years according to underlying diagnosis.



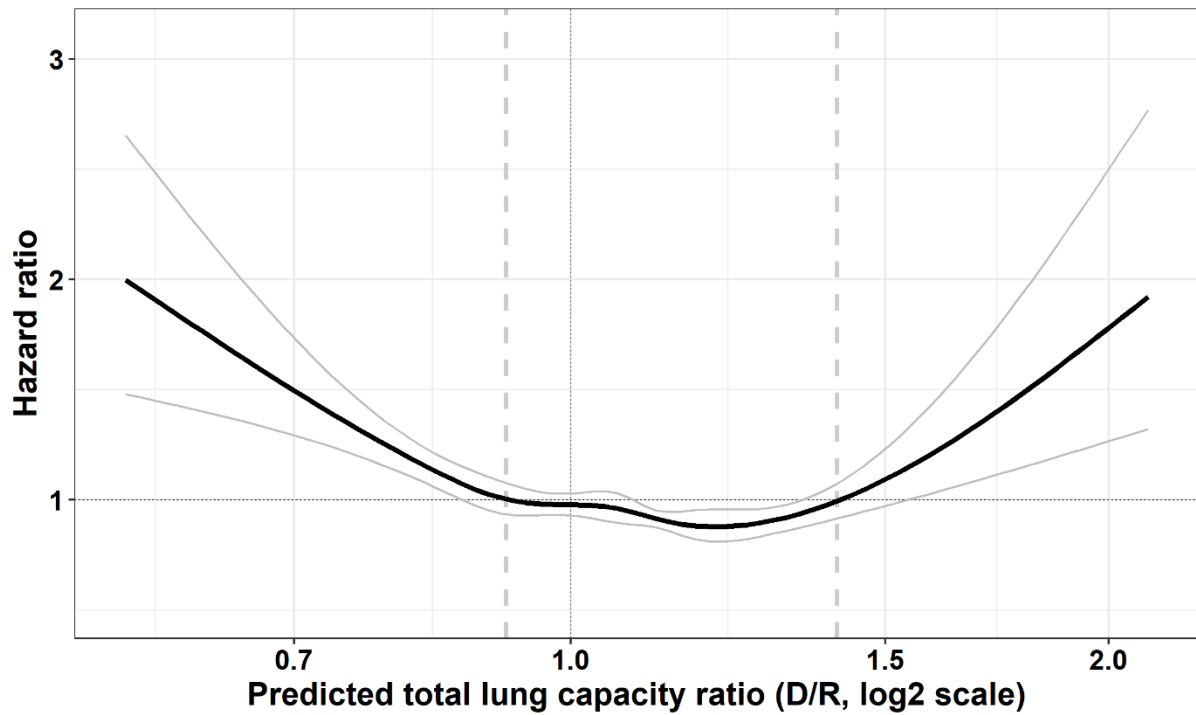
Log-rank tests used. (A) COPD/emphysema. COPD: Chronic obstructive pulmonary disease. (B) Cystic fibrosis. (C) ILD: Interstitial lung disease. (D) PAH: Pulmonary arterial hypertension.

Supplemental figure 2. Comparison of survival according to weight mismatch (donor weight – recipient weight) over 8 years.



Log-rank tests used. No corresponds to no mismatch (with a weight difference between -15 and 15kg). (A) Only female recipients and (B) only male recipients are considered.

Supplemental figure 3. pTLC ratio nonlinear association with declining risk of death.



The impact of pTLC ratio values on recipient survival was computed with a Cox model. pTLC ratios were modeled with a spline to deal with the nonlinear relationship between those variables. The intersection points between pTLC ratio spline with the hazard ratio value 1 served as cutoff points to categorize pTLC ratio values.