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Intraoperative implications of the recipient disease for double-lung transplantation

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Intraoperative implications of the recipient disease for double-lung transplantation

Introduction

The most recent International Society for Heart and Lung Transplantation Registry reported 1- and 5-year survival rates of 85 and 59%, respectively, for adult lung transplant recipients transplanted since 2010.¹ However, survival varies widely depending on the primary pulmonary disease. The best long-term outcome was reached for patients with cystic fibrosis, whereas the worst long-term outcomes were observed for those with pulmonary fibrosis and primary pulmonary hypertension. Patients with chronic obstructive pulmonary disease (COPD) and emphysema had good early survival, but mortality rapidly increased due to underlying cardiovascular disease and cancer.

Anesthetic management of lung transplantation patients has substantially evolved during the last decade with the integration of extracorporeal membrane oxygenation (ECMO), protective ventilation, and modern bleeding management strategies, as well as due to the evolution of related surgeries, such as cardiac surgery and minimally invasive thoracic surgery.²⁻⁴ In fact, these specialties have reduced postoperative complications by integrating the concepts of "early rehabilitation after surgery" and "fast-tracking protocols".

A unique characteristic of lung transplantation is the wide variety of patterns (suppurative, obstructive or restrictive processes, and pulmonary hypertension). Recent reviews have highlighted the importance of adapting anesthesia to the primary pathology of the recipient.⁵ However, there is a lack of knowledge of the effects of preexisting lung disease on intraoperative management.^{6, 7} Indeed, there have been few clinical studies on intraoperative characteristics as they relate to the initial pathology in recipients other than idiopathic pulmonary arterial hypertension.⁸ During the last ten years, our team has adopted a tailored protocol including the systematic administration of inhaled nitric oxide, the use of ECMO only when necessary, and fast-track elements allowing extubation in the operating room after a strict evaluation.

We carried out this retrospective study to fill the current knowledge gap. We analyzed our data regarding the anesthetic management of patients undergoing double-lung transplantation (DLT), which was primarily performed in patients suffering from cystic fibrosis (CF group), patients with

COPD/emphysema (CE group) and patients with pulmonary fibrosis (PF group).

We hypothesized that the initial pathology in these patients could influence one of the three major aspects of anesthetic management during DLT: blood transfusion, ECMO management, and the possibility of extubation at the end of surgery in the operating room.

Methods

Study population

The analysis of the prospective database of the Anesthesia Department at the Foch Hospital covered all patients who received DLT between January 2012 and December 2019 for CF, CE, or PF. In this cohort, some patients suffered from preoperative secondary pulmonary arterial hypertension; however, there were no patients suffering from primary pulmonary arterial hypertension. We excluded patients who had undergone multiorgan transplantation, retransplantation or transplantation under cardiopulmonary bypass. Relevant information concerning donors, patients, anesthetic management, and surgical procedures was extracted from the database after approval was granted from the Ethics Committee of the Société Française d'Anesthésie et de Réanimation (CERAR IRB 00010254 2019 108). Patients undergoing lung transplantation approved the use of their data for clinical research.

Procedure

The intraoperative management protocol has previously been published⁹ and is detailed in **Supplementary file 1**. Briefly, it consisted of a sequential DLT through two anterolateral thoracotomies. ECMO (femoral veno-arterial cannula using a surgical approach after a single bolus of 50 IU/kg unfractionated heparin and additional cannula inserted into the superficial femoral artery to ensure antegrade leg reperfusion; ECMO circuit (Maquet Cardiopulmonary GmbH, Rastatt, Germany) was planned in some cases at the preoperative assessment (major pulmonary arterial hypertension, right ventricular dysfunction or an anatomical defect) or was used in case of refractory intraoperative hemodynamic or respiratory failure.¹⁰ Total intravenous anesthesia (propofol and remifentanyl) was combined with thoracic epidural analgesia except in rare cases in which this technique was contraindicated. Inhaled nitric oxide was systematically administered at 10 ppm throughout the surgical procedure.⁹ Intraoperative hemodynamic monitoring included continuous systemic arterial pressure monitoring, pulmonary artery catheterization and transesophageal echocardiography. At the end of surgery, a "three-step weaning trial" was performed (**Supplementary Figure**). The first step consisted of ECMO withdrawal; in case of success, the second step was the

cessation of inhaled nitric oxide administration, and in case of success, the last step was an extubation attempt in the operating room before transfer to the intensive care unit.⁹

Data collected and evaluation criteria

Data were obtained from a database created with FileMaker Pro (FileMaker Company, Santa Clara, CA 95054). The file was encrypted and accessible only on the local intranet with a password. All data were fully anonymized before extraction for statistical analysis.

Donor data included age, sex, body mass index, smoking history, bronchial aspirations, chest X-ray, PaO₂/FiO₂ ratio, and ex vivo graft procedure.¹¹ Recipient variables included age, sex, body mass index, weight, comorbidities, previous thoracic surgery, lung disease, preoperative mechanical ventilation, preoperative vasopressor use, preoperative pulmonary arterial hypertension, preoperative plasmapheresis (for high-risk donor-specific antibodies), time on the waiting list, participation in the high-emergency lung transplantation program,¹² lung allocation score,¹³ preoperative use of cardiovascular medication (Anatomical Therapeutic Chemical Classification System code for antithrombotic agents code C) and thrombotic agents (Anatomical Therapeutic Chemical Classification System code B01A), and preoperative biological parameters (hemoglobin level, platelet count, hemostasis assessment).

Intraoperative data included the main surgical features, duration of cold ischemia, ECMO details, blood loss, intraoperative fluid support, and transfusion. The following information was recorded at the end of transplantation: the PaO₂/FiO₂ ratio, the blood lactate level, the hemoglobin level, and extubation in the operating room.

Objective of the study

The main objective of this work was to compare three major outcomes (blood transfusion, ECMO management, extubation in the operating room) among three main patient groups defined by the pathology leading to lung transplantation in our center (CF, CE, or PF).

Statistical analysis

Data are expressed as the n (%) [95% confidence interval] or mean \pm standard deviation [95% confidence interval]. The p value refers to the comparison between the three groups (global analysis using ANOVA or the Kruskal–Wallis test) and the post hoc pairwise comparisons are corrected for p values using "Holm" method (Student's test or the Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables).

The analyses were performed using bilateral tests, and a p value less than 0.05 was considered significant.

All analyses were performed with R software version 3.5.1 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Recruitment

During the study period, 510 DLTs were performed. A total of 429 patients were included in the analysis: 246 (57%) had cystic fibrosis (CF group), 117 (27%) had chronic obstructive pulmonary disease/emphysema (CE group), and 66 (15%) had pulmonary fibrosis (PF group) (**Figure 1**).

Preoperative patient characteristics

Demographic characteristics differed between the groups, with younger patients in the CF group (31.1 ± 9.5 [29.9-32.3] years) than in the CE and PF groups (54.3 ± 6.7 [53.1-55.6] and 52.5 ± 8.9 [50.3-54.7], respectively) ($p < 0.001$). Body weight was lower in the CF group than in the CE group and PF group (51.4 ± 9.8 [50.2-52.7], 66.3 ± 15.5 [64.1-68.6], and 73.0 ± 16.6 [68.9-77.1], respectively) ($p < 0.001$). There were more patients with a history of cardiovascular disease in the CE and PF groups (51.3% [41.9 – 60.6] and 43.9% [31.7 – 56.7]) than in the CF group (19.1% [14.4 – 24.6]) ($p < 0.001$). A history of thoracic surgery was more common in the PF group (31.8% [20.9-44.4]) than in the CF group (16.3%, [11.9-21.5]) ($p = 0.02$) (**Table 1**).

Blood transfusion

The prothrombin time (PT) was lower and the activated partial thromboplastin time (aPTT) was higher in the CF group than in the PF and CE groups ($p < 0.001$ and $p = 0.001$, respectively). The platelet count and fibrinogen level were higher in the CF group (347 ± 135 [330-364] g/L and 3.8 ± 1.3 [3.6-4.0] g/L, respectively) than in the CE group (270 ± 87 [254-286] and 3.1 ± 0.8 [2.9-3.2], respectively) and the PF group (260.1 ± 83.8 [239- 280] and 3.2 ± 0.9 [2.9-3.6], respectively; $p < 0.001$ for both) (**Table 2**).

The preoperative hemoglobin level was lower in the CF group (12.1 ± 2.0 [11.8-12.3] g/dL) than in the CE and PF groups (13.7 ± 1.7 [13.4-14.0] and 13.3 ± 1.7 [12.9-13.7], respectively; $p < 0.001$). The estimated blood loss was not significantly different among the groups ($p = 0.21$), but the number of

units of red blood cells transfused was higher in the CF group (5.8 ± 4.4 [5.3-6.4] units) than in the CE group (4.0 ± 2.9 [3.4-4.5] units) ($p < 0.001$). The number of fresh frozen plasma units transfused was higher in the CF group (5.8 ± 4.4 [5.2-6.3] units) than in the CE group (4.2 ± 3.4 [3.7-4.9] units) ($p = 0.004$) (**Table 2**).

Intraoperative ECMO

PF patients required intraoperative ECMO more frequently (37.8% [26.2 – 50.7%]) than CF patients (19.9% [15.1 – 25.5]) and CE patients (15.3% [9.4 – 23.2]) ($p = 0.002$). Similarly, PF patients continued ECMO postoperatively more frequently (39.4% [27.6 – 52.2]) than CF patients (21.9% [16.9 – 27.6]) and CE patients (12.8% [7.3 – 20.3]) ($p < 0.001$). The time of implantation was different for PF patients compared to CF patients ($p < 0.001$) and CE patients ($p = 0.04$).

No significant difference was found among the groups regarding the causes of ECMO implantation and causes of ECMO weaning failure (**Table 3**).

Extubation at the end of the surgical procedure

At the end of surgery, the PaO₂/FiO₂ ratio was higher in the CE group (297 ± 137 [271 - 322]) than in the CF group (252 ± 124 [237 - 268]) and the PF group (218 ± 128 [186 - 249]) ($p < 0.001$). This was associated with more frequent extubation in the operating room in the CF and CE groups (37.4% [31.3 - 43.8] and 50.4% [41.0 - 59.8], respectively) than in the PF group (13.6% [6.4 - 24.3]) ($p < 0.001$). Two patients were reintubated within 24 hours after the operation in the CE group, and one was reintubated in the CF group (**Table 4**). They had grade 3 pulmonary graft dysfunction at T72.

Postoperative complications are presented in **Supplementary file 2**.

Discussion

The main findings of this single-center database analysis were that i) CF patients required more transfusions than other patients, but their hemoglobin levels were lower; ii) PF patients more often required intraoperative ECMO, which was mostly implanted at the beginning of surgery, and it was more often continued after surgery; and iii) CF and CE patients were more often extubated at the end of surgery in the operating room, with a low risk of reintubation or of postoperative respiratory failure.

Pena et al. recently reviewed surgery- and recipient-related risk factors for intraoperative bleeding during lung transplantations. They identified respiratory pathology (pleural adhesions secondary to a prior surgery or inflammation) and preoperative anemia as recipient-related risk factors.¹⁴

In our series, prior surgery was more common among PF patients; these surgeries were mainly performed to establish the diagnosis. In addition, the CE group received antithrombotic agents more frequently, but this did not increase bleeding because of specific preoperative treatment with vitamin K or administration of cryoprecipitate.

Although estimated blood loss, an imprecise metric, was not different among groups, it was not related to body weight, and it was apparently relatively lower in CF patients. Moreover, the risk of the need for transfusion was increased in CF patients, despite CF patients having a lower preoperative hemoglobin level. Frequent anemia in CF patients may be explained by repeated blood sampling in such low-weight patients, in addition to the chronic inflammatory state and malnutrition specific to CF pathology. Preoperative treatment of anemia, including perhaps the administration of iron carboxymaltose,¹⁵ should be emphasized. The increased risk of the need for significant blood transfusion in CF patients was also due to the nonutilization of intraoperative blood salvage techniques in our protocol, except "washing" in the case of massive uncontrollable hemorrhage that exceeded the capacity for replacement by transfusion. This attitude was supported by a precautionary principle given the importance of avoiding pulmonary infection, even though cell washing and leukocyte depletion filtration probably facilitates a 99% reduction in bacterial contamination.¹⁶

Preoperative hemostasis assessment showed simultaneously lower PTs and a higher partial thromboplastin time ratio, platelet count and fibrinogen level. Such values could be explained in part by liver dysfunction¹⁷ and the chronic inflammatory state of this population (due to chronic bacterial colonization). Hence, these hemostatic disturbances modified the balance between anticoagulant and procoagulant activity.¹⁸

Our practice of using a 1:1 ratio of red blood cells and fresh frozen plasma as proposed in trauma patients to prevent coagulopathy¹⁹ could be improved because it does not sufficiently take into account intraoperative biological examinations, particularly thromboelastography-guided protocols, because coagulation disorders could stem from hepatic insufficiency, hyperfibrinolysis, platelet dysfunction, or antithrombotic agents (despite preoperative correction).²⁰

Finally, there remains an unanswered question regarding the value of aprotinin. It has been reported that the estimated blood loss is similar in transplanted patients receiving aprotinin or a placebo; however, the values in the placebo group varied widely.²¹

If we exclude patients with primary pulmonary arterial hypertension, the indications for ECMO and, more rarely today, for cardiopulmonary bypass are still debated. Few data are available for pulmonary fibrosis, emphysema or cystic fibrosis.

In a recent study, it was reported that a past medical history of cystic fibrosis and chronic obstructive pulmonary disease/emphysema were protective factors against the need for unplanned intraoperative ECMO.¹⁰ Furthermore, as CF patients had less preoperative pulmonary arterial hypertension, they were able to better adapt to an increase in pulmonary arterial resistance due to pulmonary artery clamping. A possible explanation could be that due to their younger age, their right heart is more likely to be able to adapt to increased pulmonary arterial resistance, increasing their cardiac output.²²

PF patients more often had preoperative pulmonary arterial hypertension and major intraoperative hemodynamic disturbances, as reported by Hayanga et al.²³ They more often required an unplanned intraoperative insertion of an ECMO,^{10, 24} with the main indication being hemodynamic disturbance, especially after the induction of anesthesia or after the first pulmonary artery clamping. Some of these problems may also be due to the comparatively small rib cage due to its retraction²⁵ and to the total

lung capacity mismatch between donor and recipient. Our policy is to choose a graft with a total lung capacity close to the recipient's theoretical value and not to the recipient's measured total lung capacity to avoid undersizing and the long-term loss of lung function.²⁶ In addition, we try to avoid lung reduction to correct a volume mismatch between the recipient and the graft; however, it was still performed in 20% of the cases.

Failure of ECMO withdrawal at the end of lung transplantation has been described in up to 24% of cases, and some independent predictors have been identified (donor age, donor PaO₂, and duration of the intervention).²⁷ With the exception of fibrosis patients, in which continued ECMO could be prophylactic in the case of oversized grafts, as described above, ECMO failure occurred only in one-quarter of patients with CF and one-eighth of patients with COPD/emphysema, mainly due to pulmonary edema. Finally, taking into account side effects and cost, systematic ECMO implantation and its continuation in the intensive care unit seem questionable for these patients, especially in COPD/emphysema patients with simpler intraoperative management.

Immediate extubation in the operating room after lung transplantation was described in 2003,^{28, 29} a few years after Westerlind et al. reported their experience of early extubation, with a median length of ventilation of 4.5 hours (range 2.0 to 47.0 hours).³⁰ Despite the call for randomized trials by Myles et al., no study on ultrafast-track or immediate extubation after lung transplantation has been published.³¹ Two cohorts have been reported more recently: one of CF patients by Felten et al. in 2016³² and one of COPD patients by Assenzo et al. in 2018.³³ Both studies reported the feasibility of immediate extubation "in the operating room" in approximately half of the patients, and pulmonary graft dysfunction and one-year mortality were relatively better in COPD patients.

This bold practice of fast-tracking such a complex surgery is feasible and safe, as evidenced by the low early reintubation rate. Immediate extubation was more common in CE and CF patients, as their surgery was simpler, with a lower rate of ECMO requirement. However, it remains to be demonstrated in what way this strategy of extubation in the operating room leads to favorable consequences with regard to the postoperative evolution in the intensive care unit, or even in the longer term.

Strengths and limitations

Standardization of care and prospective intraoperative data collection were strengths of our study. However, it is important to highlight several limitations. First, it was a single-center study and our practice had several unique characteristics, e.g., inhaled nitric oxide was used routinely, CBP was commonly used in our practice, most ECMO was unplanned, and one-third of our patients were extubated before transfer to the ICU. Second, our cohort was distinguished by a high proportion of CF patients (53%) and the complete absence of patients with primary pulmonary arterial hypertension. Third, we chose to exclude patients undergoing some categories of procedures: retransplantation because the damage to the lungs differed from that inflicted by their original disease; multiorgan transplantation (lung-liver or lung-kidney procedures), which have specific inherent problems; and transplantations performed with cardiopulmonary bypass because of the particular hemostasis complications. All these excluded patients represented only 16% of all DLTs performed during the study period in our center. Fourth, the transfusion protocol for fresh frozen plasma was very liberal, and we observed a high ratio of fresh frozen plasma to red blood cell packs. Coagulation disorders have to be improved via the implementation of a protocol target for thromboelastography as a point-of-care device.³⁴ Fifth, the choice of the grafts made by the surgeon could be a source of bias, as observed with regard to donor age, which was older among PF patients than in the other two groups. However, this is a complex issue because the classic repartition into three groups (optimal donor group, donor with extended criteria group, and marginal donor group) is being increasingly discussed³⁵ in the context of the growing practice of ex vivo transplantation, which was initially described by the Toronto group³⁶ and which allows donor lung to be evaluated and possibly improved.

Conclusion

In conclusion, this analysis helps clarify the three main indications for lung transplantation and could support changes in practice. It is important to treat anemia preoperatively, particularly in CF patients; to further develop the management of ECMO, especially in PF patients; and to precisely monitor the hemostatic status of patients to guide blood transfusion; and to enable early rehabilitation after lung transplantation surgery in selected patients. Such differences should be taken into account in specific

clinical studies and intraoperative management protocols.

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Figure legend

Figure 1. Flow chart

* Some patients met more than one of the exclusion criteria

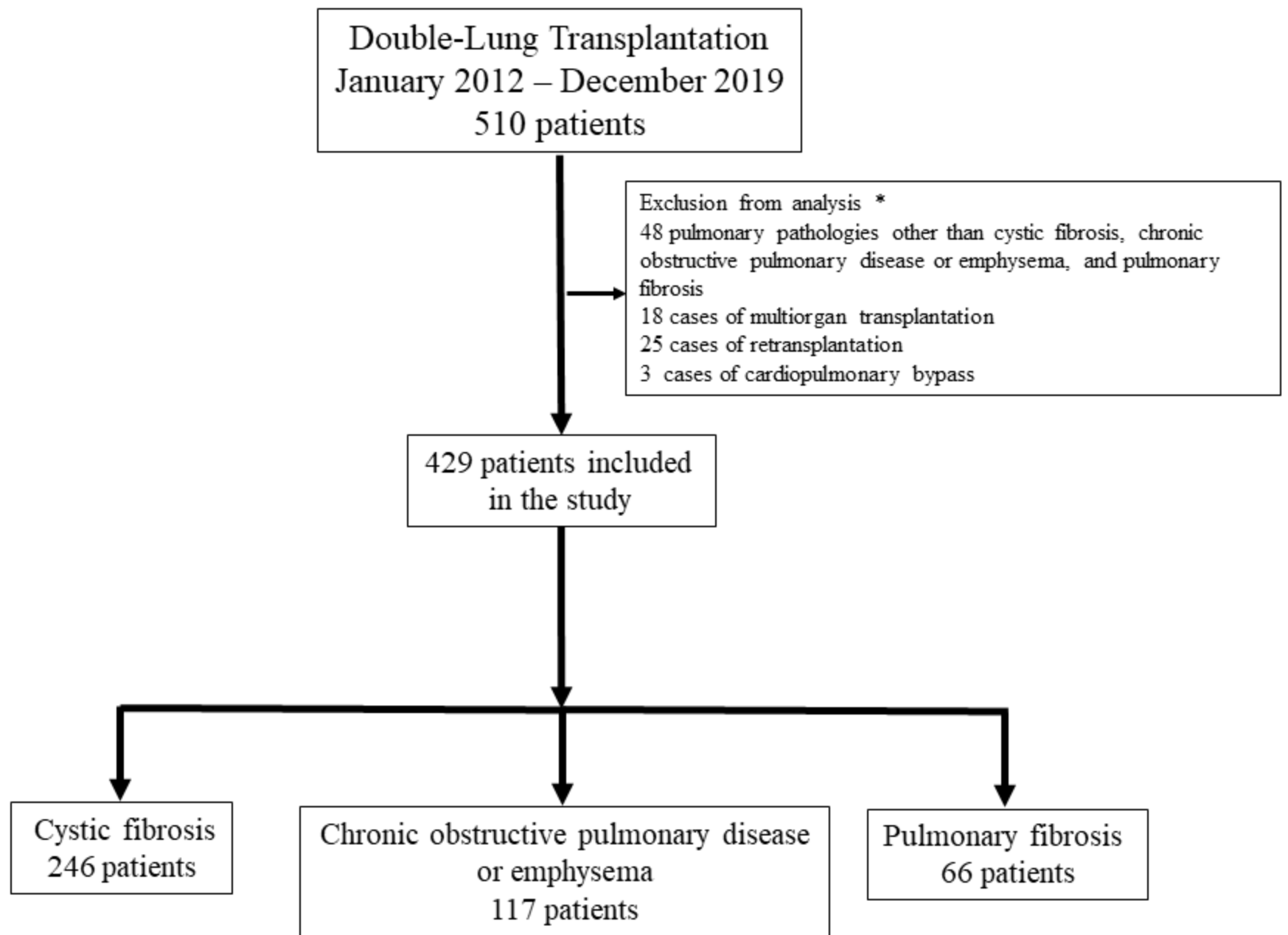


Figure 1

Table 1. Donor characteristics and preoperative patient characteristics

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
Donor characteristics							
Male sex	134 (54.5)	76 (65.0)	41 (62.1)	0.14			
	[48.0-60.8]	[55.6-73.5]	[49.3-73.8]				
Age (years)	46.2 ± 15.3	48.5 ± 15.7	51.4 ± 14.5	0.04	0.37	0.04	0.45
	[44.3 - 48.1]	[45.6 - 51.4]	[47.8 - 54.9]				
Smoking history (pack-years)	{243}	{116}	{65}	0.14			
	6.4 ± 9.9	7.7 ± 11.4	9.8 ± 12.9				
	[5.1-7.6]	[5.6-9.8]	[6.6-13.0]				
Smoking history (pack-years > 10)	{243}	{116}	{65}	0.33			
	58 (23.9)	33 (28.4)	21 (32.3)				
	[18.6 – 29.7]	[20.4 – 37.6]	[21.2 – 45.0]				
PaO2/FiO2 ratio	{245}	{117}	{66}	0.07			
	381 ± 88	357 ± 95	374 ± 89				
	[370-392]	[340-375]	[352-396]				
Body mass index (kg.m ⁻²)	25.2 ± 4.7	25.2 ± 4.4	24.9 ± 3.7	0.89			
	[24.6-25.8]	[24.4-26.0]	[24.0-25.9]				

Table 1. Donor characteristics and preoperative patient characteristics (continued)

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
p Values							
Recipient characteristics							
Demographic data and past medical history							
Male sex	115 (46.7)	57 (48.7)	45 (68.2)	0.01	0.93	0.01	0.03
	[40.4-53.2]	[39.4 – 58.1]	[55.6 – 79.1]				
Age (years)	31.1 ± 9.5	54.3 ± 6.7	52.5 ± 8.9	<0.001	<0.001	<0.001	0.37
	[29.9-32.3]	[53.1-55.6]	[50.3-54.7]				
Weight (kg)	51.4 ± 9.8	66.3 ± 15.5	73.0 ± 16.6	<0.001	<0.001	<0.001	0.001
	[50.2-52.7]	[64.1-68.6]	[68.9-77.1]				
Body mass index (kg/m ²)	18.9 ± 2.7	22.4 ± 4.0	25.0 ± 4.8	<0.001	<0.001	<0.001	<0.001
	[18.5-19.2]	[21.6-23.1]	[23.7-26.1]				
Diabetes	119 (48.4)	5 (4.3)	8 (12.1)	<0.001	<0.001	<0.001	0.44
	[42.0-54.8]	[1.4-9.7]	[5.4-22.5]				
Previous thoracic surgery procedure	40 (16.3)	21 (17.9)	21 (31.8)	0.02	0.92	0.01	0.06
	[11.9-21.5]	[11.5-26.1]	[20.9-44.4]				
Cardio-vascular therapy (ATC code C)	47 (19.1)	60 (51.3)	29 (43.9)	<0.001	<0.001	<0.001	0.53
	[14.4 – 24.6]	[41.9 – 60.6]	[31.7 – 56.7]				

Table 1. Donor characteristics and preoperative patient characteristics (continued)

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
Listing grade							
Lung allocation score	41.8 ± 11.1 [40.4-43.2]	33.9 ± 3.6 [33.3-34.6]	42.3 ± 11.4 [39.5-45.1]	<0.001	<0.001	0.91	<0.001
High-emergency transplantation	29 (11.8) [8.0-16.5]	0.0 (0.0) [0.0-3.1]	8 (12.1) [5.4-22.5]	<0.001	<0.001	0.99	0.01
Time on waiting list (days)	31.0 ± 42.2 [25.7-36.4]	38.7 ± 57.4 [28.2-49.2]	35.7 ± 41.4 [25.5-45.9]	0.33			
Preoperative status							
Pulmonary hypertension*	86 (35.0) [29.0-41.3]	50 (42.7) [33.6-52.2]	34 (51.5) [38.9-64.0]	0.04	0.33	0.04	0.47
Hospitalized in the ICU	39 (15.8) [11.5-21.0]	2 (1.7) [0.2-6.0]	9 (13.6) [6.4-24.3]	0.001	<0.001	0.87	0.04
On mechanical ventilation	10 (4.1) [2.0-7.3]	1 (0.9) [0.0-4.7]	1 (1.5) [0.0-8.1]	0.18			
Immediate preoperative plasmapheresis	91 (37.0) [30.9-43.3]	49 (41.9) [32.8-51.4]	28 (42.4) [30.3-55.2]	0.56			
Ex vivo procedure	51 (20.7) [15.8-26.3]	31 (26.5) [18.8- 35.5]	11 (16.7) [8.6-27.9]	0.26			

Table 1. Donor characteristics and preoperative patient characteristics (continued)

NOTE. Data are expressed as the n (%) [95% confidence interval] or mean \pm standard deviation [95% confidence interval]. In cases in which the data are incomplete, the number of available data points is indicated between { }.

Abbreviations: CF, cystic fibrosis; CE, chronic obstructive pulmonary disease and emphysema; PF, pulmonary fibrosis; PaO₂/FiO₂ ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; ATC code C, Anatomical Therapeutic Chemical Classification System code for cardiovascular system; ICU, intensive care unit.

* Pulmonary hypertension is defined by a mean pulmonary arterial pressure of at least 25 mmHg at rest as assessed by right heart catheterization or echocardiography.

Table 2. Transfusion

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
Preoperative antithrombotic agents (ATC code B01A)	24 (9.8)	24 (20.5)	13 (19.7)	0.01	0.02	0.10	0.99
	[6.3 – 14.2]	[13.6 – 29.0]	[10.9 – 31.3]				
Hemoglobin (g/dL)	{243}	{116}	{64}	<0.001	<0.001	<0.001	0.46
	12.1 ± 2.0	13.7 ± 1.7	13.3 ± 1.7				
	[11.8-12.3]	[13.4-14.0]	[12.9-13.7]				
Preoperative assessment of hemostasis							
Platelet count (G/L)	{244}	{116}	{66}	<0.001	<0.001	<0.001	0.85
	347 ± 135	270 ± 87	260.1 ± 83.8				
	[330-364]	[254-286]	[239- 280]				
Prothrombin time (%)	{244}	{116}	{66}	<0.001	<0.001	0.003	0.01
	83.3 ± 11.2	93.5 ± 10.4	88.4 ± 12.5				
	[81.9-84.7]	[91.6-95.4]	[85.3-91.5]				
International normalized ratio	{223}	{79}	{59}	0.005	0.003	0.42	0.33
	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.2				
	[1.1-1.2]	[1.0-1.1]	[1.1-1.2]				
Activated partial thromboplastin time ratio	{231}	{113}	{64}	0.001	0.001	0.09	0.72
	1.1 ± 0.2	0.97 ± 0.1	0.99 ± 0.2				
	[1.0-1.1]	[0.950- 0.99]	[0.93-1.06]				

Table 2. Transfusion (continued)

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
Fibrinogen (g/L)	{136}	{68}	{31}	<0.001	<0.001	0.04	0.73
	3.8 ± 1.3	3.1 ± 0.8	3.2 ± 0.9				
	[3.6-4.0]	[2.9-3.2]	[2.9-3.6]				
Previous thoracic surgery procedure	40 (16.3)	21 (17.9)	21 (31.8)	0.02	0.92	0.01	0.06
	[11.9-21.5]	[11.5-26.1]	[20.9-44.4]				
Blood loss, fluid support and transfusion							
Estimated blood loss (mL)	{243}	{117}	{66}	0.21			
	1526 ± 1786	1215 ± 1265	1468 ± 1252				
	[1300-1752]	[983-1447]	[1160- 1776]				
Intraoperative fluid support (mL)	2875 ± 1070	2976 ± 1186	3089 ± 1315	0.36			
	[2741-3010]	[2759-3194]	[2766-3413]				
Red blood cell packs (units)	5.8 ± 4.4	4.0 ± 2.9	4.9 ± 3.0	<0.001	<0.001	0.21	0.25
	[5.3-6.4]	[3.4-4.5]	[4.2-5.7]				
Fresh frozen plasma (units)	5.8 ± 4.4	4.2 ± 3.4	5.2 ± 2.9	0.004	0.003	0.55	0.29
	[5.2-6.3]	[3.7-4.9]	[4.5- 5.9]				
Platelets (units)	0.2 ± 0.6	0.2 ± 0.5	0.2 ± 0.5	0.84			
	[0.2-0.3]	[0.1- 0.3]	[0.1-0.4]				

Table 2. Transfusion (continued)

NOTE. Data are expressed as n (%) [95% confidence interval] or mean \pm standard deviation [95% confidence interval]. In cases in which the data are incomplete, the number of available data points is indicated between { }.

Abbreviations: CF, cystic fibrosis; CE, chronic obstructive pulmonary disease and emphysema; PF, pulmonary fibrosis; ATC code B01A, Anatomical Therapeutic Chemical Classification System code for antithrombotic agents

Table 3. ECMO requirement

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
ECMO period of use							
ECMO implanted before surgery	21 (8.5) [5.4 – 12.7]	1 (0.9) [0.0 – 4.7]	3 (4.5) [0.0 – 12.7]	0.03	0.008	0.07	0.98
Strictly intraoperative ECMO	49 (19.9) [15.1 – 25.5]	18 (15.3) [9.4 – 23.2]	25 (37.8) [26.2 – 50.7]	0.01	0.61	0.001	<0.001
ECMO continued postoperatively	54 (21.9) [16.9 – 27.6]	15 (12.8) [7.3 – 20.3]	26 (39.4) [27.6 – 52.2]	<0.001	0.09	0.02	<0.001
Intraoperative ECMO							
Cause of implantation*	{92}	{33}	{50}	0.10			
Hemodynamic failure	38 (41.3) [31.1 – 52.0]	19 (57.6) [39.2 – 74.5]	25 (50.0) [35.5 – 64.4]				
Hypoxemia	23 (25.0) [16.5 – 35.1]	6 (18.2) [7.0 – 35.5]	8 (16.0) [7.2 – 29.1]				
Hypercapnia	9 (9.8) [4.6 – 17.8]	3 (9.1) [1.9 – 24.3]	4 (8.0) [2.2 – 19.2]				
Hemodynamic and respiratory failure	9 (9.8) [4.6 – 17.7]	2 (6.0) [0.7 – 20.2]	1 (2.0) [0.05 – 10.6]				
Prophylactic	13 (14.1) [7.7 – 22.9]	3 (9.1) [1.9 – 24.3]	12 (24.0) [13.1 – 38.2]				

Table 3. ECMO requirement (continued)

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
Time of implantation	[92]	[33]	[49]	0.02	0.39	<0.001	0.04
Induction	15 (13.3) [7.6 – 20.9]	7 (20.6) [8.7 - 37.9]	19 (36.5) [23.6 – 51.0]				
First lung dissection	28 (24.8) [17.1 – 33.8]	9 (26.5) [12.9 – 44.4]	20 (38.5) [25.3 – 53.0]				
First lung implantation	10 (8.8) [4.3 – 15.7]	3 (8.8) [1.9 – 23.7]	0 (0.0) [0.0 – 6.8]				
Second lung dissection	32 (28.3) [20.2 – 37.6]	12 (35.3) [19.7 – 53.5]	8 (15.4) [6.9 – 28.1]				
Second lung implantation	7 (6.2) [2.5 – 12.3]	2 (5.9) [4.0 – 19.7]	2 (3.8) [2.7 – 13.2]				

Table 3. ECMO requirement (continued)

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
Cause of ECMO weaning failure	{54}	{15}	{26}	0.10			
Hypoxemia	33 (61.1) [46.9-74.1]	10 (66.7) [38.4-88.2]	12 (46.1) [26.6-66.6]				
Hemodynamic failure	6 (11.1) [4.2-22.6]	1 (6.7) [1.7-31.9]	0 (0) [0.0-13.2]				
Combined hemodynamic and respiratory abnormality	14 (25.9) [15.0-39.7]	3 (20.0) [4.3-48.1]	9 (34.6) [17.2-55.7]				
Prophylactic	1 (1.8) [0.0- 9.9]	1 (6.7) [0.0-31.9]	5 (19.2) [6.6-39.3]				

NOTE. Data are expressed as the n (%) [95% confidence interval]. In cases in which the data are incomplete, the number of available data points is indicated between { }.

Abbreviations: CF, cystic fibrosis; ECMO, extracorporeal membrane oxygenation

* cause and time of ECMO implantation is based on patients having ECMO implanted during surgery. Patients who underwent ECMO before surgery were excluded.

Table 4. Extubation at the end of the surgical procedure

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
Surgical characteristics							
Ischemic time, first graft (min)	333.6 ± 153.4 [314.3-352.9]	340.4 ± 172.2 [308.9-372.0]	325.7 ± 136.3 [292.2-359.2]	0.82			
Ischemic time, second graft (min)	471 ± 162 [450-491]	447 ± 173 [412-478]	438 ± 130 [406-470]	0.21			
Lung reduction	49 (19.9) [14.9-24.9]	22 (18.8) [11.6-26.0]	16 (24.2) [13.6-34.8]	0.66			
Status at the end of surgery							
Intraoperative major hemodynamic disturbance*	8 (3.2) [1.0-5.5]	9 (7.7) [2.8-12.6]	9 (13.6) [5.1-22.1]	0.005	0.22	0.005	0.23
Norepinephrine (µg/kg/min)	0.3 ± 0.5 [0.2-0.4]	0.3 ± 0.5 [0.2-0.4]	0.2 ± 0.2 [0.2-0.3]	0.40			
Epinephrine	17 (6.9) [4.1-10.8]	6 (5.1) [1.9-10.8]	7 (10.6) [4.4.-20.6]	0.38			
Serum lactate (mmol/L)	{241} 3.2 ± 3.3 [2.7-3.6]	{116} 2.4 ± 1.7 [2.1-2.7]	{63} 3.6 ± 4.4 [2.5-4.7]	0.05			

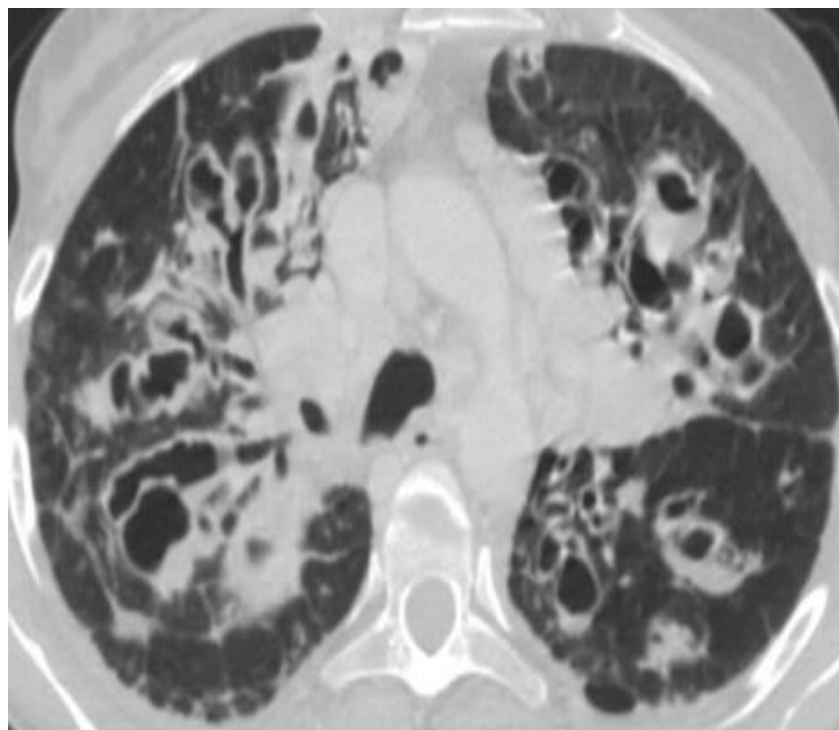
Table 4. Extubation at the end of the surgical procedure (continued)

	CF group n=246	CE group n=117	PF group n=66	Global analysis	CF vs CE	CF vs PF	CE vs PF
	p Values						
PaO ₂ /FiO ₂ ratio	252 ± 124 [237-268]	297 ± 137 [271-322]	218 ± 128 [186-249]	<0.001	0.006	0.13	<0.001
Extubation in the operating room	92 (37.4) [31.3-43.8]	59 (50.4) [41.0-59.8]	9 (13.6) [6.4-24.3]	<0.001	0.04	0.001	<0.001
Reintubation within the first postoperative 24 hours	1 (0.4) [0.0-1.2]	2 (1.7) [0.0-4.1]	0 (0.0) [0.0-0.0]				
Main Complications during ICU stay							
Grade 3 PGD at T24	84 (34.1) [28.2-40.1]	29 (24.8) [16.8-32.7]	32 (48.5) [36.1-60.9]	0.005	0.18	0.07	0.003
Grade 3 PGD at T48	79 (32.1) [26.3-38.0]	28 (23.9) [16.1-31.8]	34 (51.5) [39.1-63.9]	0.002	0.26	0.01	<0.001
Grade 3 PGD at T72	34 (13.8) [9.5-18.2]	9 (7.7) [2.8-12.6]	27 (40.9) [28.7-53.1]	0.0003	0.27	<0.001	<0.001
In-hospital mortality	7 (28) [1.1-5.8]	9 (7.7) [3.6-14.1]	10 (15.1) [7.5-26.1]	0.001	0.16	0.001	0.10

NOTE. Data are expressed as n (%) [95% confidence interval] and mean ± standard deviation [95% confidence interval]. In cases in which the data are incomplete, the number of available data points is indicated between { }. Abbreviations: CF, cystic fibrosis; CE, chronic obstructive pulmonary disease and emphysema; PF, pulmonary fibrosis; ICU, intensive care unit; PGD, pulmonary graft dysfunction. *: acute and massive bleeding or acute hypotension requiring administration of epinephrine

Recipient pathology implications on the characteristics of the intraoperative period of double-lung transplantation

CYSTIC FIBROSIS



- ↑ Blood loss
- ↑ Transfusion
- ↑ Extubation in the OR

COPD/EMPHYSEMA



- ↑ Extubation in the OR

LUNG FIBROSIS



- ↑ Intraop ECMO
- ↑ Postop ECMO