



HAL
open science

Operating room extubation: A predictive factor for 1-year survival after double-lung transplantation

Julien Fessler, Marc Fischler, Edouard Sage, Jonathan Ouattara, Antoine Roux, François J.F. Parquin, Charles Cerf, Alexandre Vallee, Morgan Le Guen

► To cite this version:

Julien Fessler, Marc Fischler, Edouard Sage, Jonathan Ouattara, Antoine Roux, et al.. Operating room extubation: A predictive factor for 1-year survival after double-lung transplantation. The Journal of Heart and Lung Transplantation, 2021, 40 (5), pp.334-342. 10.1016/j.healun.2021.01.1965 . hal-03230882

HAL Id: hal-03230882

<https://hal.science/hal-03230882>

Submitted on 9 May 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **OPERATING ROOM EXTUBATION: A PREDICTIVE FACTOR FOR** 2 **ONE-YEAR SURVIVAL AFTER DOUBLE-LUNG TRANSPLANTATION**

3 Julien Fessler, MD,^a Marc Fischler, MD,^a Edouard Sage, MD, PhD,^b Jonathan Ouattara, MD,^c

4 Antoine Roux, MD, PhD,^d François Parquin, MD,^b Charles Cerf, MD,^c

5 Alexandre Vallee, MD, PhD,^f Morgan Le Guen, MD, PhD^a

6
7 ^a Department of Anesthesiology, Hôpital Foch, 92150 Suresnes, France and Université Versailles-Saint-
8 Quentin-en-Yvelines, 78000 Versailles, France

9 ^b Department of Thoracic Surgery, Hôpital Foch, 92150 Suresnes, France and Université Versailles-Saint-
10 Quentin-en-Yvelines, 78000 Versailles, France

11 ^c Department of Anesthesiology, Groupe Hospitalier Paris Saint Joseph, 75674 Paris, France

12 ^d Department of Pneumology, Hôpital Foch, 92150 Suresnes, France and Université Versailles-Saint-
13 Quentin-en-Yvelines, 78000 Versailles, France

14 ^e Department of Intensive Care Medicine, Hôpital Foch, 92150 Suresnes, France

15 ^f Department of Clinical Research and Innovation, Hôpital Foch, 92150, Suresnes, France

16
17 Corresponding Author: Marc Fischler, MD, Department of Anesthesiology, Hospital Foch, 40 rue Worth,
18 Suresnes, France. Email: m.fischler@hopital-foch.com; Phone: +33 1 46 25 24 42 (Business telephone) -
19 +33 6 09 68 78 54 (Mobile); Fax: +33 1 46 25 20 88

20 Reprint requests: Marc Fischler, MD, Department of Anesthesiology, Hospital Foch, 40 rue Worth,
21 Suresnes, France. Email: m.fischler@hopital-foch.org

22 Grant support: This study was supported by Hospital Foch, 40 rue Worth, Suresnes, France. The sponsor
23 played no role in the design or conduct of the study; collection, management, analysis, or interpretation of
24 the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for
25 publication.

1 **OPERATING ROOM EXTUBATION: A PREDICTIVE FACTOR FOR ONE-YEAR**
2 **SURVIVAL AFTER DOUBLE-LUNG TRANSPLANTATION**

3 Fessler, Fischler, Sage, et al.

4

5 **Abstract**

6 **BACKGROUND:** Operating room (OR) extubation has been reported after lung transplantation (LT) in
7 small cohorts. This study aimed to evaluate the prognosis of OR-extubated patients. The secondary
8 objectives were to evaluate the safety of this approach and to identify its predictive factors.

9 **METHODS:** This retrospective single-center cohort study included patients undergoing double lung
10 transplantation (DLT) from January 2012 to June 2019. Patients undergoing multiorgan transplantation,
11 repeat transplantation, or cardiopulmonary bypass during the study period were excluded. OR-extubated
12 patients were compared with intensive care unit (ICU)-extubated patients.

13 **RESULTS:** Among the 450 patients included in the analysis, 161 (35.8%) were extubated in the OR, and
14 four were reintubated within 24 hours. Predictive factors for OR extubation were chronic obstructive
15 pulmonary disease (COPD)/emphysema ($p=0.002$) and cystic fibrosis ($p=0.005$), recipient body mass index
16 ($p=0.048$), and the PaO₂/FiO₂ ratio 10 minutes after second graft implantation ($p<0.001$). OR-extubated
17 patients had a lower prevalence of grade 3 primary graft dysfunction at day 3 ($p<0.001$). Eight (5.0%)
18 patients died within the first year of OR extubation, and 49 (13.5%) patients died after ICU extubation (log-
19 rank test; $p=0.005$). After adjustment for OR extubation predictive factors, the multivariate Cox regression
20 model showed that OR extubation was associated with greater one-year survival (adjusted hazard ratio =
21 0.40 [0.16-0.91], $p=0.028$).

22 **CONCLUSIONS:** OR extubation was associated with a favorable prognosis after DLT, but the
23 association should not be interpreted as causality. This fast-track protocol was made possible by a team
24 committed to developing a comprehensive strategy to enhance recovery.

1 **OPERATING ROOM EXTUBATION: A PREDICTIVE FACTOR FOR ONE-YEAR**
2 **SURVIVAL AFTER DOUBLE-LUNG TRANSPLANTATION**

3 Fessler, Fischler, Sage, et al.

4
5 **Introduction**

6 Mechanical ventilation is a cornerstone of intraoperative and postoperative lung transplantation (LT)
7 practices. Many concepts applied in LT originate from experience in anesthesia during cardiac surgery.
8 Historically, patients were maintained under prolonged sedation and mechanical ventilation until the
9 morning after surgery or even longer. Progressively, the evolution of surgical and anesthetic methods
10 allowed increasingly early extubation. Similarly, the Enhanced Recovery After Surgery (ERAS) Society
11 suggested extubation in the intensive care unit (ICU) within 6 hours after cardiac surgery.¹ This approach
12 reduced the hospital length of stay, morbidity rate, and economic cost.² Immediate extubation, i.e.,
13 extubation in the operating room (OR), was then proposed by some teams after cardiac surgery.^{3,4}
14 Some centers have applied this concept to LT,⁵⁻⁸ but this practice has remained anecdotal since then.
15 However, our team has routinely adopted an OR extubation strategy according to the following
16 fundamental practices: the use of short-acting drugs combined with effective analgesia, such as thoracic
17 epidural analgesia; the avoidance of excessive fluid support; the maintenance of normothermia; and the
18 application of systematic postoperative noninvasive ventilation.⁹ Our group published an OR extubation
19 strategy based on data from two separate cohorts considering specific populations: cystic fibrosis
20 patients¹⁰ and emphysema or chronic obstructive pulmonary disease (COPD) patients.¹¹
21 The main objective of the present study was to predict the prognosis of patients extubated immediately by
22 comparing it with the prognosis of patients extubated in the ICU. The secondary objectives were to
23 evaluate the safety of this approach and to identify predictive factors associated with successful OR
24 extubation.

25

1 **Methods**

2 The Institutional Review Board of the French Society for Anesthesia and Intensive Care approved the
3 analysis of this prospectively maintained institutional anesthesia lung transplant database (CERAR N°IRB
4 00010254 – 2019; June 29, 2019). Informed consent was obtained from all patients. The Foch Lung
5 Transplant Group attests strict compliance with the International Society for Heart and Lung
6 Transplantation ethics statement.

7

8 **Study participants**

9 All consecutive patients undergoing double-lung transplantation (DLT) at Foch Hospital (Suresnes,
10 France) from January 2012 to June 2019 were included in the study. Patients undergoing multiorgan
11 transplantation or cardiopulmonary bypass were excluded from the analysis, as were cases of
12 retransplantation of patients initially transplanted during the study period. The remaining patients were
13 divided into two groups: the OR extubation group and the ICU extubation group (**Figure 1**).

14

15 **Transplant protocol**

16 DLT was performed as two successive sequential single-LT procedures.¹² The surgical approach used
17 two anterolateral thoracotomy incisions. Standardized anesthetic management has been previously
18 described¹³ and is detailed in **Supplementary File 4** (<http://anesthesie-foch.org/protocoles-anesthesie/>).
19 Briefly, thoracic epidural analgesia and total intravenous anesthesia with propofol and remifentanyl,
20 systematic inhaled nitric oxide (iNO), and intraoperative femoral arterio-venous extracorporeal
21 membrane oxygenation (ECMO) were applied either in cases of severe hemodynamic or respiratory
22 failure refractory to medical treatment or as planned a priori (by the preoperative clinical staff).
23 OR extubation was preceded by hemodynamic and respiratory support de-escalation via a three-step
24 weaning trial (**Supplementary Figure 1**). First, in patients under ECMO, a 10-minute weaning trial was
25 performed by reducing the ECMO blood flow progressively to 1-1.5 L.min⁻¹ under clinical and

1 echocardiographic monitoring ("ECMO weaning test"). A positive test was defined as a stable left
2 ventricular outflow and a PaO₂/FiO₂ ratio > 200. In the case of a positive weaning test, surgeons removed
3 the ECMO cannulas.

4 Second, when the surgical procedure was performed without ECMO, the PaO₂/FiO₂ ratio was calculated
5 at the end of surgery, and the following steps were performed:

6 - if the PaO₂/FiO₂ ratio was lower than 100 at the end of the procedure, ECMO was established before
7 transferring the patient to the ICU;

8 - if the PaO₂/FiO₂ ratio was greater than 100, an "iNO weaning test" was performed. iNO was interrupted
9 and reintroduced in cases of a substantial decrease in the PaO₂/FiO₂ ratio (more than 10% diminution) or
10 hemodynamic state worsening (a norepinephrine dose increase greater than 10%, fluid support greater
11 than 250 mL, or a mean pulmonary artery pressure increase with right ventricle dilation on
12 transesophageal echocardiography). In these cases, patients were transferred to the ICU under mechanical
13 ventilation and iNO.

14 Third, for patients whose iNO weaning test was successful, a new PaO₂/FiO₂ ratio was calculated after
15 terminating iNO therapy. OR extubation and a "non-invasive ventilation attempt" were performed if the
16 PaO₂/FiO₂ ratio was greater than 300 and no hemodynamic failure and normothermia were detected.

17 The weaning trial was performed via a double-lumen tube, similar to elective thoracic surgery after the
18 interruption of IV anesthetic agents. The "non-invasive ventilation attempt" consisted of a 20-minute
19 period of non-invasive ventilation in an awake and calm patient using a face-mask and specific ventilator
20 with inspiratory and expiratory airway pressures of 8 and 4 cmH₂O, respectively, with an FiO₂ = 100%,
21 and adapted to patient comfort. If the attempt was successful, patients were then transferred to the ICU
22 with a high-concentration oxygen face mask. Otherwise, the patients were anesthetized and reintubated
23 with a single-lumen tube using a tube exchanger (Cook[®] Airway Exchange Catheter – Extra-Firm with
24 Soft Tip, Cook Medical Incorporated, Bloomington, IN, USA) before transfer to the ICU under
25 mechanical ventilation.

26

1 **Data handling**

2 Data related to the donor and recipient and the intraoperative period were extracted for statistical analysis
3 after anonymization by using the FileMaker Pro database (FileMaker Company, Santa Clara, CA, USA).
4 This database was prospectively completed in real time during each procedure. Details regarding the data
5 collection used for the analysis are provided in **Supplemental File 2**.

6

7 **Primary and secondary outcomes**

8 The main outcome was one-year mortality. The secondary outcomes were the prevalence of early
9 reintubation after surgery, incidence of grade 3 primary graft dysfunction (PGD3) at 1, 2, and 3 days after
10 the operation, ICU-related complications and length of stay. Finally, we looked for predictive factors of
11 OR extubation.

12

13 **Statistical analysis**

14 Continuous variables are presented as median [interquartile range] and were compared using the
15 independent t-test or Mann-Whitney test. Categorical variables are presented as number (%) and were
16 compared using the chi-square test or Fisher's exact test.

17 Multivariable logistic regression was performed to assess the predictive determinants of OR extubation.
18 Factors associated with OR extubation in the univariable analyses (at a significance level of $p < 0.20$) were
19 selected for inclusion in the multivariable analysis. These factors corresponded to donor and recipient
20 characteristics and intraoperative data up to implantation of the second graft; later items were not
21 considered in this analysis, as they were part of the extubation decision.

22 The patient survival rate (time to death at one year) was estimated using the Kaplan-Meier estimator and
23 compared by the log-rank test. A Cox regression model was performed to determine the association
24 between OR extubation and the mortality rate at one year. Predictive determinants of OR extubation were
25 selected as confounding factors for the Cox regression model.

- 1 For all analyses, $p < 0.05$ was considered statistically significant. Statistical analyses were performed using
- 2 SAS software (version 9.4; SAS Institute, Cary, NC).
- 3

1 **Results**

2
3 A total of 475 patients underwent DLT at our institution during the study period. After excluding patients
4 who did not meet the study criteria, 450 patients were included in the analysis; among them, 161 (35.8%)
5 were extubated in the OR (**Figure 1**). All organs were obtained from brain-dead donors, regardless of the
6 etiology, except 22 organs that were donated after circulatory death.

7 8 **Safety of OR extubation**

9 Four patients (2.5%) were reintubated within 24 hours: two in the OR (one case of undiagnosed residual
10 neuromuscular blockade and one case of major agitation due to intense pain despite epidural analgesia in a
11 patient with a past medical history of polytoxicomania) and two in the first hours after admission in the
12 ICU (protocol violation because the PaO₂/FiO₂ ratio was < 300 mmHg after extubation). These patients
13 were maintained in the OR extubation group (intention to treat analysis).

14 Furthermore, eight OR-extubated patients were reintubated during the first postoperative week but after
15 the first 24 postoperative hours; three of them were reintubated because of primary graft dysfunction. Five
16 additional patients were reintubated after one week because of septic complications and bronchial
17 anastomotic leakage.

18 Some cases of protocol violation were observed. Specifically, 9 patients were extubated when their
19 PaO₂/FiO₂ ratio was < 200, and 48 patients were extubated when their PaO₂/FiO₂ ratio was 200-299.
20 Among the OR-extubated patients with a PaO₂/FiO₂ ratio < 200, 2 were reintubated (both within 24
21 hours); one died on day 9, and the other died thereafter. Among the OR-extubated patients with a
22 PaO₂/FiO₂ ratio of 200-299, 2 were reintubated within 24 hours, and 6 were reintubated thereafter. In this
23 last subgroup, only one patient died in the 10th month; he was reintubated on day 6.

1 **Preoperative and intraoperative variables**

2 Recipient and donor characteristics are illustrated in **Table 1**.

3 Intraoperative variables are illustrated in **Table 2**. Compared with ICU-extubated patients, OR-extubated
4 patients experienced less bleeding and required fewer transfusions during surgery ($p<0.001$), had greater
5 hemodynamic stability (less epinephrine support) ($p<0.001$) and required less ECMO support ($p<0.001$), and
6 had a lower blood lactate level and a greater PaO₂/FiO₂ ratio after second graft implantation ($p<0.001$).
7 Nineteen percent of the patients who required intraoperative ECMO were extubated in the OR.

8

9 **Predictive factors of OR extubation**

10 Details of the multivariable analysis are provided in **Supplemental File 3**. Primary pulmonary disease
11 (especially COPD and cystic fibrosis, $p=0.002$ and $p=0.005$, respectively), recipient body mass index
12 ($p=0.048$), and the PaO₂/FiO₂ ratio 10 minutes after second graft implantation ($p<0.001$) were predictive
13 factors for successful OR extubation (**Figure 4**). Receiver operating characteristic (ROC) curve analysis
14 revealed that the model had a sensitivity of 82.2%, a specificity of 70.3%, and an accuracy of 74.2% in
15 predicting OR extubation (area under the curve: 0.83; $r^2=0.39$) (**Figure 5**).

16

17 **Postoperative outcomes**

18 Postoperative outcomes were generally better in the OR extubation group than in the ICU-extubation
19 group (**Table 3**). In particular, compared ~~to~~ with ICU-extubated patients, OR-extubated patients had a
20 significantly lower prevalence of PGD3 at 1, 2, and 3 days after the operation ($p<0.001$ for each time
21 point).

22 Two (1.2%) patients and 17 (5.9%) patients died within the first 30 days after the operation in the OR
23 extubation group and in the ICU extubation group ($p=0.019$), respectively. Eight (5.0%) patients died within
24 the first year in the OR extubation group, and 39 (13.5%) patients died within the first year in the ICU-
25 extubation group; the one-year survival rate was significantly greater in the OR extubation group than in the

1 ICU extubation group (log-rank; $p=0.005$). After adjustment for predictive factors, OR extubation was still
2 associated with better one-year survival in the Cox regression model than ICU extubation (adjusted hazard
3 ratio = 0.40 [0.16-0.91], $p=0.028$) (Figure 2). The rate of mortality at one year was similar in both groups
4 when patients who died within the first 30 days were excluded from the analysis (log-rank test; $p=0.081$)
5 (**Figure 3**). Five-year survival was also better in the OR extubation group than in the ICU extubation
6 group ($p=0.008$) (**Supplemental File 5**).
7

1 **Discussion**

2
3 This retrospective single-center study showed that OR extubation i) was possible for nearly one-third of
4 patients undergoing DLT; ii) was safe; and iii) was a clinical marker of a good prognosis, as the outcomes
5 were better in these patients than in patients extubated in the ICU. Of prime importance was that our
6 protocol did not include the preselection of potential patients for OR extubation and considered that all
7 patients were candidates for OR extubation and that the decision was made at the end of the procedure
8 according to all measured parameters. This was confirmed by the fact that 1 in 5 patients who received
9 intraoperative ECMO were extubated at the end of the procedure. Finally, this possibility can be predicted
10 within a few minutes after implantation of the second graft.

11
12 Interest in fast-track surgery has increased in cardiothoracic anesthesia practice. Cardiac surgery is the
13 discipline in which reducing the time to extubation has been most studied. Historically, this time has
14 decreased from routine extubation the morning after the operation to early extubation under the concomitant
15 pressure of changes in anesthesiology methods (application of short-acting drugs, optimal analgesia, and
16 restoring normothermia),¹⁴ changes in surgical techniques (faster and less invasive techniques),¹⁵ and pressure
17 on ICU staff (to reduce ventilation-related complications and economic constraints). In contrast to fears
18 regarding outcomes, the rate of postoperative complications did not increase;¹⁶ however, the ERAS program,
19 a patient-centered multidisciplinary strategy was required to reduce it.¹ Hemmerling went further as he
20 considered that a successful medical-surgical team should implement an immediate extubation strategy, as it
21 is more difficult and more dangerous to perform extubation later, particularly because of the need to maintain
22 sedation, which can have hemodynamic consequences.³

23
24 Regarding LT, the earliest studies involved relatively small cohorts with different indications, types of
25 transplantation (single-LT and/or DLT, possibly combined with heart transplantation)⁵⁻⁸ and extubation times

1 (a few hours after the procedure⁵ or in the OR at the end of the procedure⁶⁻⁸). These studies proved that it was
2 possible to extubate patients after LT with a low rate of reintubation. However, little information was
3 provided regarding predictive factors of success or long-term follow-up. Our team showed that OR
4 extubation was possible in nearly half of cystic fibrosis¹⁰ and COPD/emphysema patients,¹¹ with few cases
5 of reintubation. Interestingly, in both types of patients, OR extubation was associated with a simpler
6 postoperative course with a low rate of reintubation, a lower prevalence of PGD3 and a shorter ICU length
7 of stay than ICU extubation. In contrast, Felten et al. did not observe a difference in one-year mortality
8 between OR-extubated and ICU-extubated patients in a cystic fibrosis cohort¹⁰, while Assenzo et al. found
9 better one-year survival among OR-extubated patients than ICU-extubated patients in a
10 COPD/emphysema cohort.¹¹ Similarly, among the whole cohort, we observed better one-year survival in
11 the OR extubation group than in the ICU-extubation group. Upon deeper analysis, we found that this long-
12 term mortality difference disappeared when one-year survival was adjusted for 30-day survival.
13 Consequently, OR extubation may be considered a strong surrogate supporting uneventful early follow-
14 up, leading to a low rate of PGD, a low rate of ICU-related complications, and a decreased rate of
15 mortality. Finally, this favorable outcome may also stem from the effect of a fast-track program in which
16 all stakeholders are extensively involved to enhance recovery after surgery and reduce postoperative
17 complications. However, since this was not a randomized control trial, causality is impossible to
18 determine regarding the time of extubation.

19
20 The present study included our whole population of consecutive DLT patients regardless of their primary
21 pulmonary pathology, except patients with primary pulmonary hypertension who were not treated at our
22 center. This wide variety of patients confirmed the feasibility of OR extubation, although at a lower rate
23 than that previously published^{10, 11} and with a minimal reintubation risk (2.8%). This rate could have been
24 even lower if the protocol had been more scrupulously followed. Westerlind et al. initially pointed out the
25 increase in the safety of extubation with the use of continuous positive airway pressure via a face mask.⁵⁻⁸

1 Currently, high-flow nasal cannula oxygen therapy is a sustainable alternative to reintubation in acute
2 hypoxemic respiratory failure after LT.¹⁷

3 Our cohort analysis allowed us to identify predictive factors of OR extubation. First, primary lung diseases
4 such as cystic fibrosis and COPD/emphysema are known to have a better early postoperative course than
5 other pulmonary diseases.¹⁸ Second, a donor body mass index above 25 kg/m² is an independent factor
6 associated with PGD.¹⁹ Third, Pottecher et al. reported that the PaO₂/FiO₂ ratio measured just after graft
7 reperfusion and some other variables that are difficult to measure (extravascular lung water and level of
8 human soluble receptor for advanced glycation end products) are predictors of PGD.²⁰ Similarly, a trend
9 of increased risk of PGD₃ on day 3 was observed when the PaO₂/FiO₂ ratio was <200 at the end of the
10 procedure,²¹ and a low PaO₂/FiO₂ ratio measured upon arrival to the ICU or a few hours later was
11 associated with a similar risk.²²

12 All these elements could lead to a more aggressive approach for nonextubated patients before discharge
13 from the OR. In the absence of specific drug therapy that may reduce the severity of PGD, early prone
14 positioning²³ or prophylactic ECMO²⁴ is suggested. However, it must be noted that among patients with
15 early PGD (6 hours after transplantation), complete resolution of dysfunction within 72 hours and
16 attenuation without complete resolution within 72 hours were observed in 7% and 39% of the cases,
17 respectively.²⁵

18 Finally, a limitation of the generalization of OR extubation could be the fact that our policy increases OR
19 occupation by approximately one hour, sometimes during regular working hours. This is possible in our
20 institution because the whole anesthesia team is fully dedicated to transplant patients.

21

22 Limitations of the study

23 First, our study was subject to all inherent limitations of any retrospective single-center analysis. However,
24 all the data were prospectively collected from an institutional database with strict definitions. It would be
25 interesting to randomize patients likely requiring extubation in the OR into two groups: an OR extubation

1 group and an ICU extubation group, but it seems unethical to us to continue ventilation (and sedation) if it is
2 not necessary. Second, our study focused exclusively on patients extubated in the OR and not on those
3 extubated in the first 6, 12 or 24 hours post-operatively. Third, our cohort included a high proportion of
4 patients with cystic fibrosis (52.0%) or COPD/emphysema (25.1%), a low proportion of patients with
5 interstitial lung disease (14.0%) and an absence of patients with primary pulmonary hypertension. In
6 addition, patients who underwent DLT under cardiopulmonary bypass were excluded because this
7 technique carries a risk of specific complications and has become marginalized during the last decade after
8 the development of ECMO. Fourth, we could not obtain data on all potential variables, such as
9 preoperative frailty assessment results, to compare groups and better understand the differences in
10 prognoses. Finally, in this study, we present unique practices, especially thoracic epidural analgesia
11 combined with total intravenous anesthesia, and a three-step weaning trial at the end of surgery (ECMO
12 systematic withdrawal, iNO withdrawal, extubation trial).¹³

13

14 **Conclusion**

15 In conclusion, OR extubation after DLT is an option for COPD/emphysema patients (51.3% of extubated
16 patients were in this group) and cystic fibrosis patients (36.3%) but probably should not be pursued in patients
17 with interstitial lung disease (14.3%). The survival of patients who underwent OR extubation was higher at all
18 time points. Moreover, OR-extubated patients suffered fewer postoperative complications, including PGD3,
19 than ICU-extubated patients. OR extubation could be considered as a clinical marker of a good prognosis;
20 however, the association between OR extubation and improved outcomes should not be interpreted as
21 causality. These results, made possible by the commitment of all the stakeholders of the project, pave the way
22 for adaptation of the ERAS program for LT. A logical subsequent step is to investigate whether OR-extubated
23 patients could benefit from the prompt removal of catheters and tubes (e.g., Swan-Ganz catheter, central
24 venous line, urinary catheter), which are sources of infectious complications, limit early mobilization and
25 early rehabilitation with physiotherapists, and increase costs.

1 **Conflicts of interest and funding sources**

2 The authors have no conflicts of interest pertinent to the paper to disclose.

3 Funding was provided by Hôpital Foch, 92150 Suresnes, France. Hôpital Foch played no role in the data
4 collection, analysis or interpretation and will have no right to approve or disapprove publication of the
5 finished manuscript.

1 **References**

- 2 1. Engelman DT, Ben Ali W, Williams JB, *et al.* Guidelines for perioperative care in cardiac surgery:
3 Enhanced recovery after surgery society recommendations. *JAMA Surgery* 2019;154:755-66.
- 4 2. Rajakaruna C, Rogers CA, Angelini GD, *et al.* Risk factors for and economic implications of prolonged
5 ventilation after cardiac surgery. *J Thorac Cardiovasc Surg* 2005;130:1270-7.
- 6 3. Hemmerling TM. Immediate extubation after cardiac surgery should be part of routine anesthesia
7 practice for selected patients. *Ann Card Anaesth* 2018;21:114-15.
- 8 4. Nagre AS, Jambures NP. Comparison of immediate extubation versus ultrafast tracking strategy in the
9 management of off-pump coronary artery bypass surgery. *Ann Card Anaesth* 2018;21:129-33.
- 10 5. Westerlind A, Nilsson F, Ricksten SE. The use of continuous positive airway pressure by face mask and
11 thoracic epidural analgesia after lung transplantation. Gothenburg Lung Transplant Group. *J*
12 *Cardiothorac Vasc Anesth* 1999;13:249-52.
- 13 6. Hansen LN, Ravn JB, Yndgaard S. Early extubation after single-lung transplantation: analysis of the
14 first 106 cases. *J Cardiothorac Vasc Anesth* 2003;17:36-9.
- 15 7. Rocca GD, Coccia C, Costa GM, *et al.* Is very early extubation after lung transplantation feasible? *J*
16 *Cardiothorac Vasc Anesth* 2003;17:29-35.
- 17 8. Augoustides JG, Watcha SM, Pochettino A, *et al.* Early tracheal extubation in adults undergoing single-
18 lung transplantation for chronic obstructive pulmonary disease: pilot evaluation of perioperative
19 outcome. *Interact Cardiovasc Thorac Surg* 2008;7:755-8.
- 20 9. Myles PS. Early extubation after lung transplantation. *J Cardiothorac Vasc Anesth* 1999;13:247-8.
- 21 10. Felten ML, Moyer JD, Dreyfus JF, *et al.* Immediate postoperative extubation in bilateral lung
22 transplantation: predictive factors and outcomes. *Br J Anaesth* 2016;116:847-54.
- 23 11. Assenzo V, Assenzo C, Filippo R, *et al.* The feasibility of extubation in the operating room after
24 bilateral lung transplantation in adult emphysema patients: an observational retrospective study.
25 *Eur J Cardiothorac Surg* 2018;54:1128-33.

- 1 12. Pasque MK, Cooper JD, Kaiser LR, *et al.* Improved technique for bilateral lung transplantation:
2 rationale and initial clinical experience. *Ann Thorac Surg* 1990;49:785-91.
- 3 13. Fessler J, Godement M, Pirracchio R, *et al.* Inhaled nitric oxide dependency at the end of double-lung
4 transplantation: a boosted propensity score cohort analysis. *Transpl Int* 2019;32:244-56.
- 5 14. Myles PS, Daly DJ, Djaiani G, *et al.* A systematic review of the safety and effectiveness of fast-track
6 cardiac anesthesia. *Anesthesiology* 2003;99:982-7.
- 7 15. Zubair MH, Smith JM. Updates in minimally invasive cardiac surgery for general surgeons. *Surg Clin*
8 *North Am* 2017;97:889-98.
- 9 16. Wong WT, Lai VK, Chee YE, *et al.* Fast-track cardiac care for adult cardiac surgical patients.
10 *Cochrane Database Syst Rev* 2016;9:CD003587.
- 11 17. Roca O, de Acilu MG, Caralt B, *et al.* Humidified high flow nasal cannula supportive therapy
12 improves outcomes in lung transplant recipients readmitted to the intensive care unit because of
13 acute respiratory failure. *Transplantation* 2015;99:1092-8.
- 14 18. Hayes D, Jr., Cherikh WS, Chambers DC, *et al.* The International Thoracic Organ Transplant Registry
15 of the International Society for Heart and Lung Transplantation: Twenty-second pediatric lung
16 and heart-lung transplantation report—2019; Focus theme: Donor and recipient size
17 match. *The Journal of Heart and Lung Transplantation* 2019;38:1015-27.
- 18 19. Kuntz CL, Hadjiliadis D, Ahya VN, *et al.* Risk factors for early primary graft dysfunction after lung
19 transplantation: a registry study. *Clin Transplant* 2009;23:819-30.
- 20 20. Pottecher J, Roche AC, Degot T, *et al.* Increased Extravascular Lung Water and Plasma Biomarkers of
21 Acute Lung Injury Precede Oxygenation Impairment in Primary Graft Dysfunction After Lung
22 Transplantation. *Transplantation* 2017;101:112-21.
- 23 21. Fessler J, Thes J, Pirracchio R, *et al.* Prognostic value of the PaO₂ /FiO₂ ratio determined at the end-
24 surgery stage of a double-lung transplantation. *Clin Transplant* 2019;33:e13484.

- 1 22. Prekker ME, Herrington CS, Hertz MI, *et al.* Early Trends in PaO₂/fraction of inspired oxygen ratio
2 predict outcome in lung transplant recipients with severe primary graft dysfunction. *Chest*
3 2007;132:991-7.
- 4 23. Riera J, Maldonado C, Mazo C, *et al.* Prone positioning as a bridge to recovery from refractory
5 hypoxaemia following lung transplantation. *Interact Cardiovasc Thorac Surg* 2017;25:292-96.
- 6 24. Hoetzenecker K, Schwarz S, Muckenhuber M, *et al.* Intraoperative extracorporeal membrane
7 oxygenation and the possibility of postoperative prolongation improve survival in bilateral lung
8 transplantation. *J Thorac Cardiovasc Surg* 2018;155:2193-206 e3.
- 9 25. Shah RJ, Diamond JM, Cantu E, *et al.* Latent class analysis identifies distinct phenotypes of primary
10 graft dysfunction after lung transplantation. *Chest* 2013;144:616-22.

11

1 **Figures**

2

3 Figure 1. Flow chart

4 * Some patients presented several criteria for exclusion from the analysis

5

6 Figure 2. One-year survival in the OR extubation and ICU extubation groups

7 Red line: OR-extubated patients

8 Blue line: ICU-extubated patients

9 Solid lines: Kaplan-Meier analysis

10 Dashed lines: 95% confidence interval

11

12 Figure 3. One-year survival in the OR extubation and ICU extubation groups in the sub-cohort of patients

13 who survived at least 30 days

14

15 Figure 4. Predictive factors for successful OR extubation

16 COPD: chronic obstructive pulmonary disease

17 ECMO: extracorporeal membrane oxygenation

18 ICU: intensive care unit

19

20 Figure 5. ROC curve

21

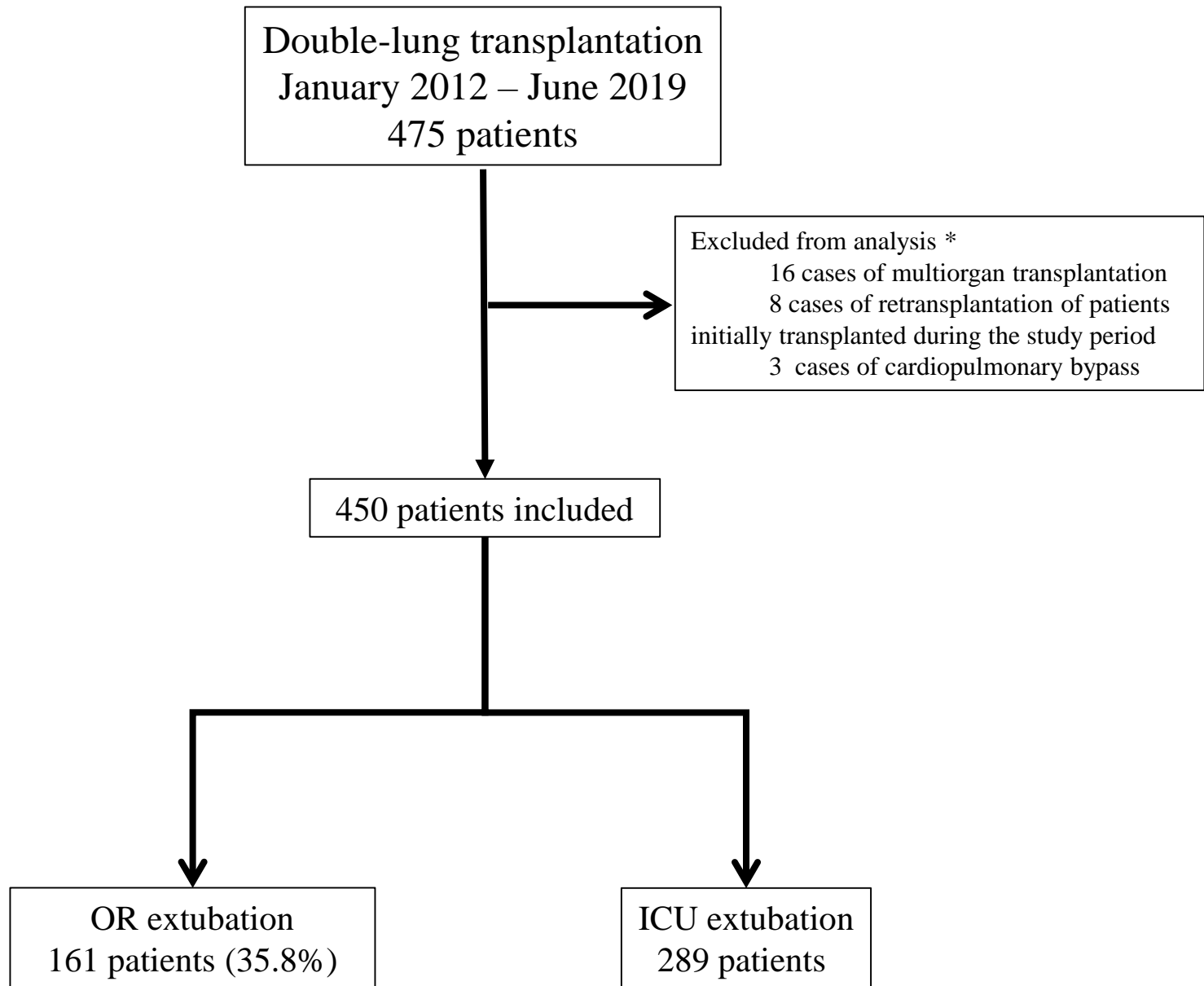
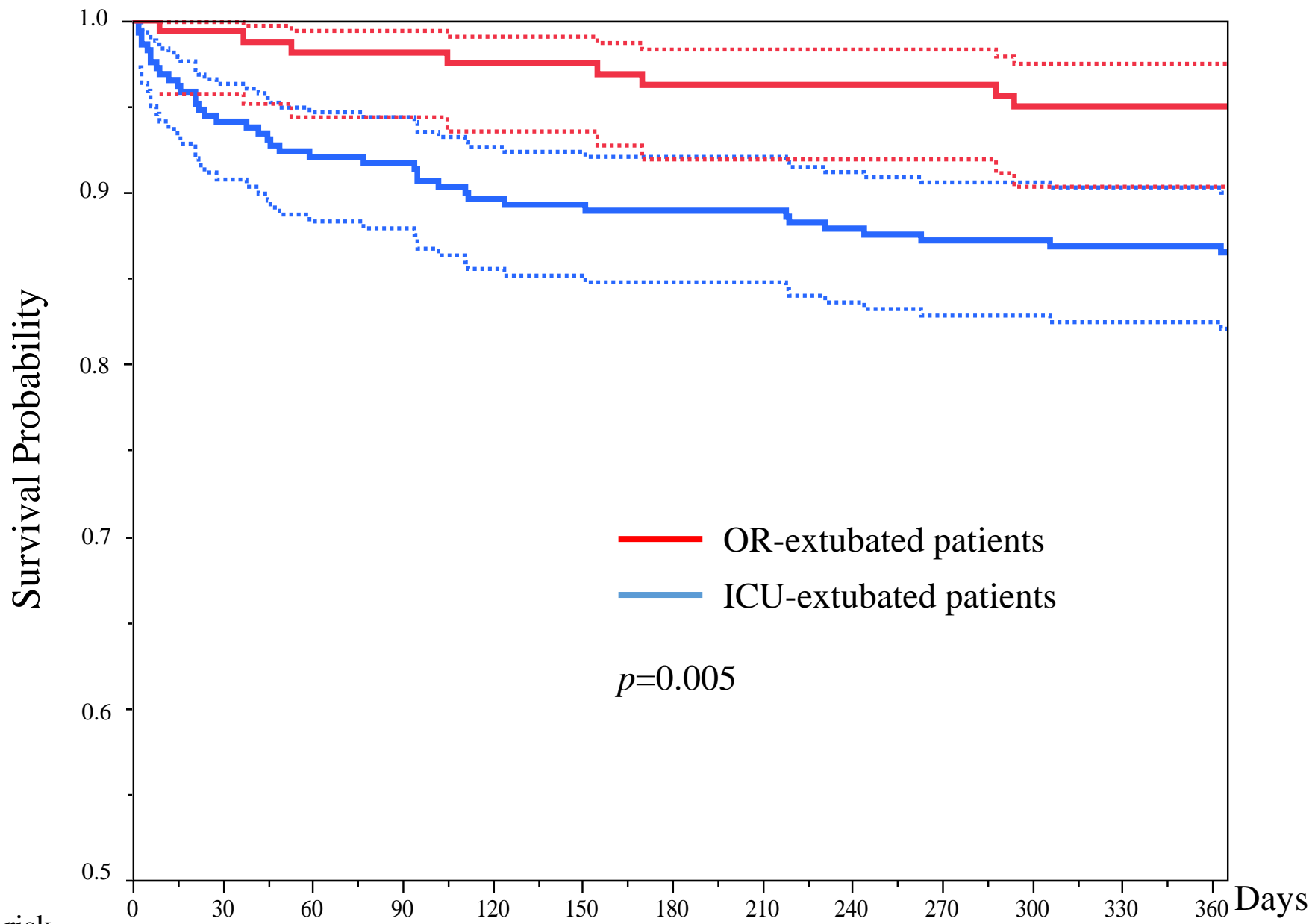
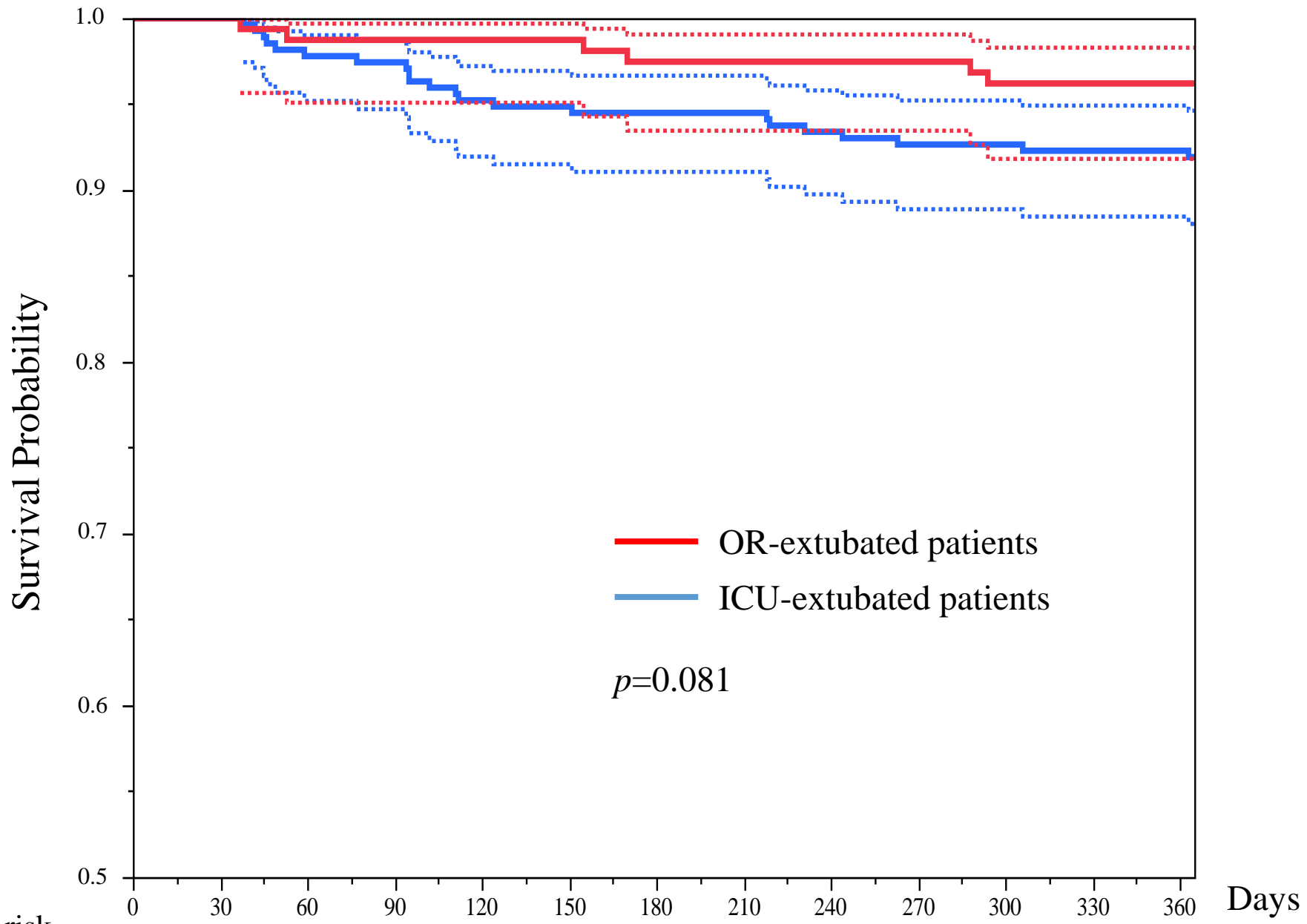


Figure 1



Numbers at risk

OR-extubated patients	161	160	158	158	157	157	156	155	155	155	153	153	153
ICU-extubated patients	289	273	267	266	260	259	258	258	255	253	253	252	250



Numbers at risk

OR-extubated patients	160	158	158	157	157	156	155	155	155	153	153	153
ICU-extubated patients	273	267	266	260	259	258	258	255	253	253	252	250

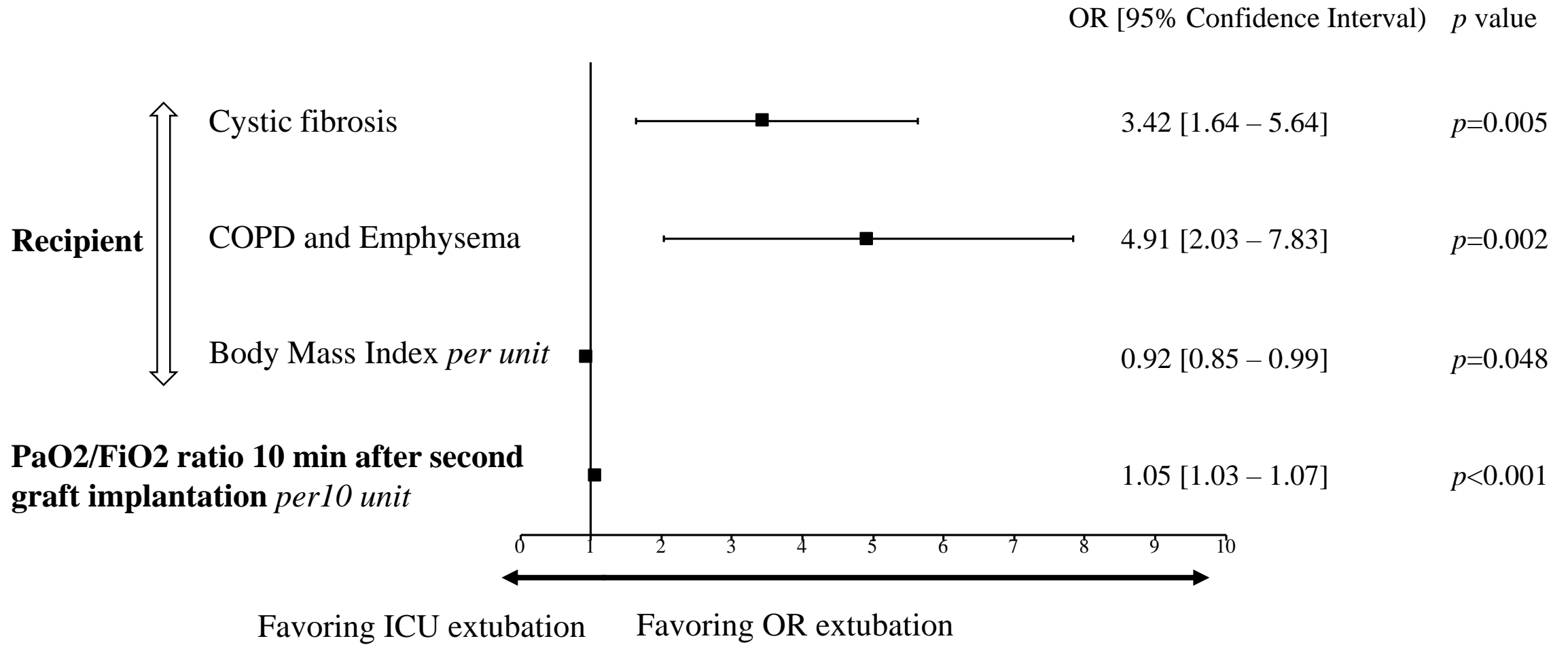


Figure 4

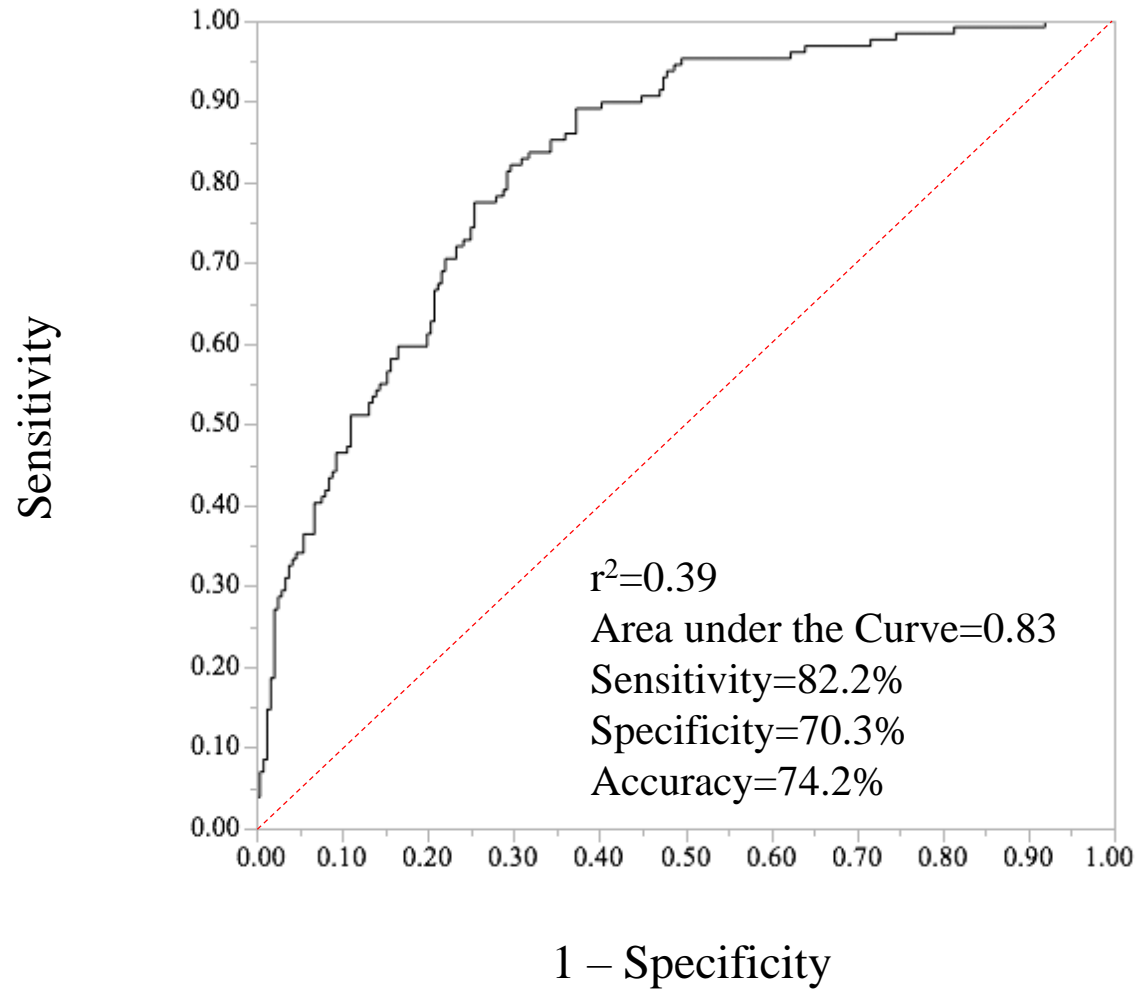


Figure 5

Table 1. Donor characteristics and preoperative patient characteristics

	OR extubation n = 161	ICU extubation n = 289	P
Donor characteristics			
Age, years	49 [27]	40 [26]	0.277
Male sex	89 (55.3)	168 (58.1)	0.558
Weight, kg	74 [17]	74 [20]	0.557
Size, cm	171 [13]	170 [14]	0.765
Body mass index, kg.m ⁻²	25 [6]	25 [6]	0.588
Smoking history, pack-years	0 [8]	0 [18]	0.004
PaO ₂ /FiO ₂ ratio	368 [136]	359 [118]	0.080
Estimated TLC, L	6.2 [2.0]	6.5 [1.9]	0.582
Recipient characteristics			
Age, years	42 [28]	40 [26]	0.277
Male sex	80 (49.7)	142 (49.1)	0.910
Sex mismatch	59 (36.6)	114 (39.4)	0.753
Weight, kg	53 [15]	55 [20]	0.009
Size, cm	166 [12]	166 [12]	0.697
Body mass index, kg.m ⁻²	19 [5]	20 [6]	0.003
TLC, L	6.5 [2.4]	5.5 [2.4]	<0.001
TLC, mismatch*	1.1 [0.5]	0.9 [0.5]	<0.001
Past history			
Primary pulmonary disease			<0.001
Cystic fibrosis	85 (52.8)	149 (51.6)	
COPD/emphysema	58 (36)	55 (19)	
Pulmonary fibrosis	9 (5.6)	54 (18.7)	
Other pathologies	9 (5.6)	31 (10.7)	
Redo transplantation	0	9 (3.1)	0.024
Pulmonary hypertension**	56 (34.8)	124 (42.9)	0.092
Diabetes	41 (25.5)	91 (31.5)	0.176
Previous thoracic surgical procedure	29 (18.0)	72 (24.9)	0.093
Patent foramen ovale	15 (9.5)	26 (9.1)	0.888

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

	OR extubation	ICU extubation	P
	n = 161	n = 289	
Preoperative status			
Time on waiting list, days	21 [39]	17 [40]	0.737
Lung Allocation Score	36 [5]	38 [8]	0.001
High Emergency Lung Transplantation	8 (5)	34 (11.8)	0.018
Hemoglobin, g/dL	12.0 [2.2]	11.9 [2.8]	0.217
ECMO (bridge to transplantation)	3 (1.9)	23 (8.0)	0.006
Preoperative mechanical ventilation	1 (0.6)	16 (5.5)	0.009

Values are number (%) and median [interquartile range]

ICU = intensive care unit; OR = operating room; TLC = total lung capacity; ECMO = extracorporeal membrane oxygenation; COPD = chronic obstructive pulmonary disease

TLC mismatch * = total lung capacity of the donor/total lung capacity of the recipient

Pulmonary hypertension** = mean pulmonary artery pressure > 25 mmHg

Table 2. Intraoperative data

	OR extubation	ICU extubation	P
	n = 161	n = 289	
Technical aspects			
Preoperative plasmapheresis	60 (37.3)	115 (39.8)	0.598
Ex vivo lung perfusion	34 (21.1)	56 (19.4)	0.658
Graft lung reduction	27 (7.8)	71 (24.6)	0.242
Ischemic time, first graft, min	273 [120]	289 [132]	0.173
Ischemic time, second graft, min	393 [158]	422 [151]	0.061
Fluid support, bleeding and transfusion			
Intraoperative fluid support, L	2.7 [1.5]	3 [1.5]	0.039
Estimated blood loss, L	1.0 [0.9]	1.2 [1.3]	<0.001
Packed red blood cells, units	4.0 [2.5]	5.0 [5.0]	<0.001
Fresh-frozen plasma, units	4.0 [4.0]	6.0 [4.0]	<0.001
Packed platelets, units	0 [0]	0 [1]	<0.001
Other variables			
Blood lactate level, mmol/L			
Initial level	0.7 [0.4]	0.9 [0.5]	0.119
At 1 st lung clamping	0.9 [0.6]	1.1 [0.9]	0.262
At 2 nd lung clamping	1.3 [0.9]	2.0 [1.5]	0.235
At 1 st graft implantation	1.3 [1.0]	1.8 [1.6]	0.523
10 min after second graft implantation	2.0 [1.2]	2.9 [2.1]	<0.001
At end-surgery	1.8 [1.3]	2.7 [2.3]	<0.001
PaO ₂ /FiO ₂ ratio 10 min after second graft implantation	311 [209]	174 [192]	<0.001
Major hemodynamic event*	4 (2.5)	28 (9.7)	0.004
Epinephrine during surgery	8 (5.0)	46 (16.0)	<0.001
ECMO during surgery	41 (25.5)	174 (60.2)	<0.001
End-of-surgery status			
PaO ₂ /FiO ₂ ratio	333 [167]	179 [150]	<0.001
PGD3	10 (6.2)	95 (32.9)	<0.001
iNO dependence	1 (0.6)	59 (20.4)	<0.001
Epinephrine requirement	8 (5.0)	28 (9.7)	<0.001
Norepinephrine, µg/kg/min	0 [0]	0 [0.05]	0.018

Table 2. Intraoperative data (continued)

Values are number (%) and median [interquartile range]

ICU = intensive care unit; OR = operating room; PGD3 = grade 3 pulmonary graft dysfunction; ECMO = extracorporeal membrane oxygenation; iNO: inhaled nitric oxide

* A major hemodynamic event corresponds to a cardiac arrest, an episode of myocardial ischemia sometimes due to a coronary air embolism, an episode of right or left ventricular failure, or a hemorrhagic shock.

Table 3. Postoperative complications and outcomes

	OR extubation n = 161	ICU extubation n = 289	P
Lung complications			
PGD			
PDG3 at T24	3 (1.9)	156 (54.0)	<0.001
PGD3 at T48	6 (3.7)	149 (51.6)	<0.001
PGD3 at T72	3 (1.9)	73 (25.3)	<0.001
Time to reintubation, days	3 [7]	2 [7]	0.905
Tracheotomy	8 (5.0)	78 (27.0)	<0.001
LOS under postoperative mechanical ventilation, days	0 [0]	4 [12]	<0.001
Secondary ECMO	2 (1.2)	19 (6.6)	0.010
Time to secondary ECMO, days	7 [12]	3 [17]	0.879
Postoperative ECMO	0 (0)	106 (36.7)	<0.001
Surgical complications			
Reoperation for bleeding	10 (6.2)	76 (26.3)	<0.001
Lower limb complication	8 (5.0)	23 (8.0)	0.230
Vascular complications	16 (9.9)	66 (22.8)	<0.001
Other complications			
Vasopressor support	56 (34.8)	215 (74.4)	<0.001
Atrial fibrillation	31 (19.2)	73 (25.3)	0.148
Thromboembolic complication	17 (10.6)	71 (24.6)	<0.001
Septic shock	16 (9.9)	72 (24.9)	<0.001
Cerebrovascular accident	2 (1.2)	10 (3.5)	0.162
Renal replacement therapy	2 (1.2)	28 (9.7)	<0.001
Bleeding and transfusion			
Postoperative packed red blood cells, units	0 [0]	0 [5]	<0.001
Postoperative fresh-frozen plasma, units	0 [0]	0 [2]	<0.001
Lengths of stay			
Hospital LOS, days	26 [13]	32 [24]	<0.001
ICU LOS, days	4 [3]	8 [11]	<0.001

Table 3. Postoperative complications and outcomes (continued)

	OR extubation	ICU extubation	P
	n = 161	n = 289	
Mortality			
In-hospital mortality	3 (1.9)	28 (9.7)	0.002
30-day mortality	2 (1.2)	17 (5.9)	0.019
90-day mortality	4 (2.5)	24 (8.3)	0.014
One-year mortality	8 (5.0)	39 (13.5)	0.005

Values are number (%) and median [interquartile range]

ICU = intensive care unit; OR = operating room; PGD = pulmonary graft dysfunction; PGD3 = grade 3 pulmonary graft dysfunction; LOS = length of stay; ECMO = extracorporeal membrane oxygenation

OPERATING ROOM EXTUBATION, A PREDICTIVE FACTOR OF ONE-YEAR SURVIVAL AFTER DOUBLE-LUNG TRANSPLANTATION

QUESTIONS:

- 1) Evaluate prognosis of patients extubated in OR after double-lung transplantation (DLT) compared with those extubated in ICU;
- 2) Identify factors related to successful OR extubation;
- 3) Evaluate its safety.

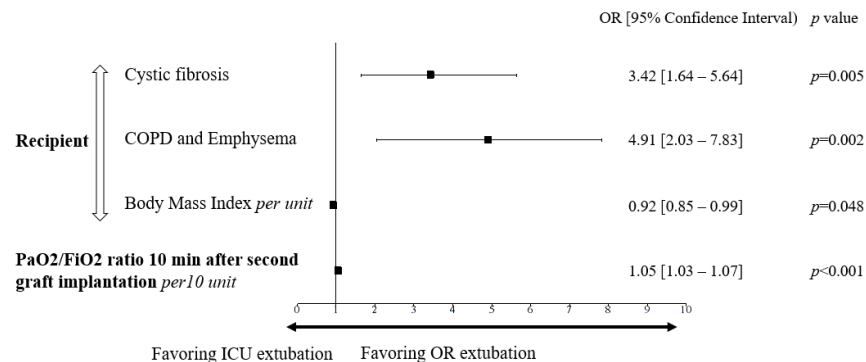
INTRAOPERATIVE MANAGEMENT: Combination of short-acting anesthetic drugs, thoracic epidural analgesia, and inhaled nitric oxide (iNO), ECMO for refractory hemodynamic or respiratory failure, and three-step weaning trial (ECMO, iNO, extubation)

FINDINGS

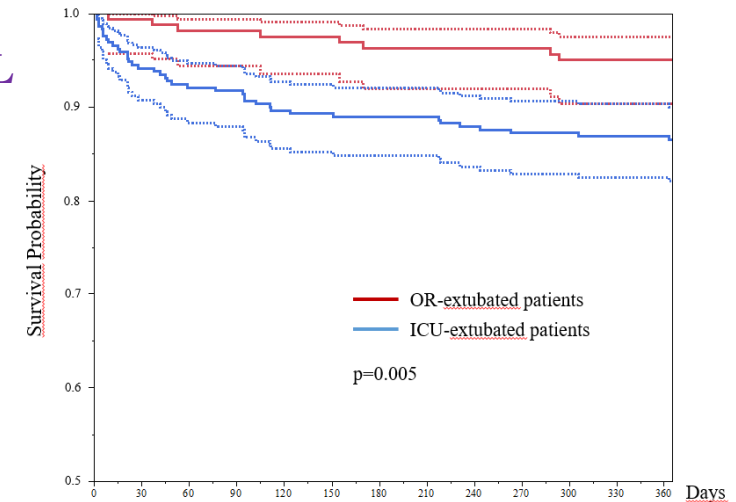
FEASIBILITY: Of 450 patients, 35.8% were extubated in the OR

SAFETY: Four OR-extubated patients were reintubated within 24 hours.

PREDICTORS



ONE-YEAR SURVIVAL



CONCLUSION: OR extubation is associated with a favorable prognosis after DLT, but the association should not be interpreted as causality. This fast-track protocol was made possible by the commitment of a team to developing a global strategy to enhance recovery after lung transplantation.