TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

# High Emergency Lung Transplantation: dramatic decrease of waiting list death rate without relevant higher post-transplant mortality

Antoine Roux,[1,2] Laurence Beaumont-Azuar,[1] Abdul Monem Hamid,[1] Sandra De Miranda,[1] Dominique Grenet,[1] Guillaume Briend,[1,3] Pierre Bonnette,[4] Philippe Puyo,[4] François Parquin,[5] Jerome Devaquet,[6] Gregoire Trebbia,[6] Elise Cuquemelle,[5] Benoit Douvry,[1] Clément Picard,[1] Morgan Le Guen,[7] Alain Chapelier,[4] Marc Stern[1] and Edouard Sage[4] FOCH Lung Transplant Group

1 Pneumology Department, Foch Hospital, Suresnes, France
2 UPRES EA220, Université de Versailles Saint-Quentin-en-Yvelines, Suresnes, France
3 Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Pneumologie et Soins Intensifs, Paris, France
4 Thoracic Surgery Department, Foch Hospital, Suresnes, France
5 Thoracic Intensive Care Unit, Foch Hospital, Suresnes, France
6 Intensive Care Unit, Foch Hospital, Suresnes, France
7 Anesthesiology Department, Foch Hospital, Suresnes, France

**Keywords**
graft allocation, lung transplantation, mortality on waiting list.

**Correspondence**
Dr. Antoine Roux, MD, PhD, Pneumology Department, Lung Transplant Unit, Hopital Foch, 40 rue Worth, 92500 Suresnes, France. Visitor Scholar at UCLA Immunogenetics, Los Angeles, CA, USA.
Tel.: +33 688 0847 54;
Fax: 310-206-3216;
e-mail: a.roux@hopital-foch.org; ARoux@mednet.ucla.edu

See Appendix 1 for FOCH Lung Transplant Group.

**Conflicts of interest**
Dr Antoine Roux served as a consultant for Novartis France. Others authors have disclosed no relevant financial relationships.

Received: 19 December 2014
Revision requested: 22 January 2015
Accepted: 5 May 2015
Published online: 27 May 2015

doi:10.1111/tri.12604

## Summary

Many candidates for lung transplantation (LT) die on the waiting list, raising the question of graft availability and strategy for organ allocation. We report the experience of the new organ allocation program, "High Emergency Lung Transplantation" (HELT), since its implementation in our center in 2007. Retrospective analysis of 201 lung transplant patients, of whom 37 received HELT from 1st July 2007 to 31th May 2012. HELT candidates had a higher impairment grade on respiratory status and higher Lung Allocation Score (LAS). HELT patients had increased incidence of perioperative complications (e.g., perioperative bleeding) and extracorporeal circulatory assistance (75% vs. 36.6%, $P = 0.0005$). No significant difference was observed between HELT and non-HELT patients in mechanical ventilation duration (15.5 days vs. 11 days, $P = 0.27$), intensive care unit length of stay (15 days vs. 10 days, $P = 0.22$) or survival rate at 12 (81% vs. 80%), and 24 months post-LT (72.9% vs. 75.0%). Lastly, mortality on the waiting list was spectacularly reduced from 19% to 2% when compared to the non-HELT 2004–2007 group. Despite a more severe clinical status of patients on the waiting list, HELT provided similar results to conventional LT. These results were associated with a dramatic reduction in the mortality rate of patients on the waiting list.

## Introduction

Lung transplantation (LT) is an established treatment option for patients with a wide variety of end-stage lung diseases. The limitation of this treatment is the shortage of donors and its associated consequence: the significant number of patients who die while on the waiting list [1,2].



 

Measures have been taken worldwide against the imbalance between graft supply and recipient demand. Graft collection has been improved with the development of regionalization and calls for organ donation. At the same time, extension of donor criteria [3] and new *ex vivo* conditioning techniques have permitted a substantial increase in the number of grafts available without radically changing receiver outcome [4]. Improving graft allocation, particularly using the prioritization system, is a complementary way to diminish mortality while on the waiting list. The different prioritization policies for graft allocation currently used are summarized and compared in Table S1. In May 2005, the Organ Procurement and Transplantation Network (OPTN) changed the policy for lung allocation for transplantation in the United States to a system that repartitions based primarily on a Lung Allocation Score (LAS) [5]. First reports of experience with this score in the United States showed a significant decrease in waiting time and mortality while on the list. In addition, no significant difference was shown for in-hospital mortality and 1-year survival since LAS implementation, whereas some observations recorded an increase of primary graft dysfunction and length of stay in intensive care [6–8].

An Australian single center experience reported that LT in critically ill inpatients does give poorer survival compared to outpatients, although this was associated with a definitive survival advantage compared to untransplanted patients [9].

In Europe, different measures have been taken to improve graft repartition, as demonstrated by both Eurotransplant [10,11] and the Spanish prioritization programs [12] (see Table S1).

In France, the High Emergency Lung Transplantation (HELT) allocation system was defined in July 2007 to prioritize graft allocation to patients with short-term severe prognoses. The French National Transplantation Agency (*Agence de la Biomédecine* (ABM)) predefined inclusion criteria, combining severity markers, and etiological conditions (Table 1). Specifically, LT benefit is partly predicted by the underlying disease [13].

In 2012, Boussaud *et al.* conducted the first multicenter study evaluating the HELT program between July 2007 and June 2008. The survival rates in the 32 HELT recipients at 1, 3, 6, 12, and 24 months were significantly lower than those for the 154 patients who underwent regular LT during the same period. The authors also suggested that the new allocation rules could increase waiting list mortality for those not selected for the HELT procedure [14].

As allocation prioritization strategies remain a key issue for the success of transplant programs, and our center's clinical impression differs from these previous studies, we critically analyzed our experiences with the HELT program.

**Table 1.** HELT registration criteria.

| Cystic fibrosis | Pulmonary fibrosis | Pulmonary hypertension |
|---|---|---|
| Invasive MV or ECMO or PaCO2 > 80 mmHg and NIV>18 h/24 for 72 h | Invasive MV or ECMO or SaO2 < 90% despite high concentration O2 therapy and medical maximal treatment | Invasive MV or ECMO or NYHA IV and cardiac index <2L/min and PVR>1200 dyn.s/cm³ Maximal medical treatment for 72 h |

The objective is to select high-risk patients for those 3 indications of LT. Exclusion criteria define (i) patients whose clinical statement is not compatible with surgery (to reduce graft "misuse," that is, hemodynamic failure, multiple organ failure, or uncontrolled sepsis), (ii) or responding to etiological criteria (COPD, emphysema, retransplantation), for whom the benefit-risk balance for accelerating transplant procedure is unclear. Already registered on a waiting list for LT, HELT patients are registered for a period of 8 days, renewable once. All the requests are systematically reviewed and approved by an expert. If more than one candidate is listed simultaneously, the graft is allocated to the first subscriber.

In this regard, we compare both the time and mortality rate on the waiting list between pre- and post-HELT eras, as well as evaluate post-transplantation survival in HELT and non-HELT patients.

## Methods

### Population and data collection

To assess the impact of the HELT program, we conducted a retrospective monocentric cohort study between July 2007 and May 2012 in the Foch Hospital Thoracic Department. This retrospective observational study was approved by the research protocol evaluation committee of the *Institutional Review Board of the French Learned Society For Respiratory Medicine—Société de Pneumologie de Langue Française.*

For historical comparison, we considered the Foch cohort population during two periods: pre-HELT era (January 2004–June 2007) and the HELT era (July 2007–May 2012); we evaluated the impact of the HELT program on both time and death rate while on the waiting list. All data were collected from exhaustive examination of medical reports.

The HELT era population was composed of all patients who had both HELT and non-HELT during this period (July 2007–May 2012). Pretransplantation status, transplantation procedure, perioperative outcome, long-term outcome, and survival were compared between the HELT and non-HELT groups. The *ex vivo* lung perfusion (EVLP) procedure was introduced in April 2011 [15]; therefore, we also considered the HELT era before (HELT era pre-EVLP) and after implementation of the EVLP (HELT era post-EVLP). Interestingly, only non-HELT patients benefited from this procedure.

### Pretransplantation status

Time on the regular or HELT waiting list, preoperative clinical status (including age, sex, initial pulmonary disease, size, weight, BMI, plasmatic creatininemia, PaCO2, PaO2), systolic pulmonary arterial pressures (sPAP measured by cardiac echography), oxygen flow rate, need for and length of mechanical ventilation (MV; invasive or not), vasoactive drug requirement, and LAS were reported. Extra corporeal membrane oxygenation (ECMO) was indicated for oxygenation or decarboxylation.

### Perioperative management and transplant procedure

Donors were matched with recipients for ABO blood group and size and, if possible, for CMV and EBV. Donor's age, smoking status and PaO2/FiO2 ratio (P/F ratio) and waiting place, surgical procedure (unilateral or bilateral transplantation), need for graft volume reduction, pleural adherence, ischemic time, perioperative bleeding, need for ECMO or cardiopulmonary bypass (CPB), and immediate postoperative extubation (according to a standardized algorithm) were reported.

### Early postoperative outcome

For this period, the following data were considered as relevant: primary graft dysfunction (PGD) at 72 h (as previously defined [16]), invasive MV duration, postoperative ECMO, need for surgical revision, bronchial ischemia, infection during the first month, acute cellular, or humoral rejection.

### Clinical management and long-term monitoring

All patients received 500 mg bolus of methylprednisone perioperatively alone, or in conjunction with either Thymoglobulin® (2.5 mg/kg/daily immediately after arrival in the Intensive care unit and discontinued on POD 5) or Basiliximab® (20 mg on day 0 and day 4) unless contraindicated. Additionally, patients received maintenance immunosuppressive therapy associated steroids, anticalcineurin molecules, and purine inhibitors.

Fiberoptic bronchoscopy surveillance was very strict, with protocol transbronchial biopsy at day 7, and at month 1, 2, 3, 4, 6, 9, and 12. Additional fiberoptic bronchoscopy with biopsy was also performed for cause (pulmonary function worsening or other pulmonary complications). We used standard criteria to classify acute rejection [17].

Pulmonary function tests were performed twice a month until month 3, once a month until month 6, every 45 days until month 12, and then every 3 months thereafter. Chronic lung allograft dysfunction (CLAD) was diagnosed according to ISHLT Pulmonary Council guidelines [18]. In addition, a strict surveillance of CMV and EBV was systematically performed using PCR.

### Statistical analysis

Analyses involved use of SAS JMP 8.0 software (SAS, Cary, NC, USA). Continuous variables were expressed as mean±standard deviation or median (interquartile, range 25–75 IQR), and qualitative variables as frequencies. Comparison were performed using nonparametric Mann–Whitney or Wilcoxon tests for quantitative variables and chi-square Pearson or Fisher's exact test, as appropriate, for qualitative variables. Survival was estimated by the Kaplan–Meier method and the Log-rank test was used to compare both groups. The *P*-value was considered statistically significant under 0.05.

## Results

During the HELT era, 201 patients received lung transplantation at our center, Foch Hospital. Among them, 37 were registered on the HELT list, whereas 164 patients received a regular inscription procedure.

### Preoperative status

Overall, the primary diagnosis was mainly cystic fibrosis (CF) (54.2%), chronic obstructive pulmonary disease (COPD)/emphysema (22.4%), infiltrative lung disease (ILD) (15.4%), and other (8%) (Table 2). No COPD or retransplantation were included in the HELT group, according to the *Agence de la Biomédecine* selection criteria (Table 1) and patients with CF represented the vast majority of the HELT group. Age was significantly lower in the HELT group (27.7 [23–35.3] vs. 40.2 [27.7–53], $P < 0.05$), as well as BMI (17.8 [42–57.5] vs. 19.1 [47–65], $P = 0.0083$), and creatinine levels (52 [41.2–63.5] vs. 65 [52.2–75.7], $P = 0.0003$). No difference between the HELT and non-HELT groups was noted concerning pleural surgery history, which is usually cause for surgical difficulties.

Respiratory status was much poorer in the HELT group, regarding PaCO2 (75 mmHg vs. 50 mmHg, $P < 0.0001$), oxygen level request (5.5 l/min vs. 2 l/min, $P < 0.0001$), need for invasive MV ($P < 0.0001$), and waiting place. Resorting to ECMO was necessary for eight patients in the HELT group, whereas it was unnecessary for any patients in the non-HELT group. Hemodynamic status was also significantly poorer in the HELT group, illustrated by the use of catecholamine (<1 mg/h for three patients, with a maximal dose of 2 mg/h for one of the three remaining patients) exclusively in that group (six patients, vs. 0, $P < 0.0001$). Unsurprisingly, the LAS was significantly higher in the

**Table 2.** Preoperative conditions and characteristics of the patients receiving LT.

| Patient characteristics | HELT ($n$ = 37) | Non-HELT ($n$ = 164) | $P$ |
|---|---|---|---|
| Age (years) | 27.7 [23–35.3] | 40.2 [27.7–53] | 0.0002 |
| Male, *n* (%) | 15/37 (40.5) | 84/163 (51.2) | 0.24 |
| Weight (kg) | 48 [42–57.5] | 52.5 [47–65] | 0.0116 |
| Size (m) | 1.66 [1.6–1.73] | 1.65 [1.6–1.72] | 0.95 |
| BMI (kg/m$^2$) | 17.8 [16.2–19.5] | 19.1 [17.3–23.5] | 0.0083 |
| Primary diagnosis | | | |
| COPD emphysema, *n* (%) | 0 | 45 (27.4) | 0.0011 |
| ILD, *n* (%) | 6 (16.2) | 25 (15.2) | |
| Cystic fibrosis, *n* (%) | 30 (81.1) | 78 (47.5) | |
| Other, *n* (%) | 1 (2.7) | 14 (8.5) | |
| Retransplantation, *n* (%) | 0 | 2 (0.12) | |
| Waiting time on regular list (days) | 6 [3.5–15] | 41 [17–117] | <0.0001 |
| Waiting time on the HELT list (days) | 4 [1–5] | – | – |
| Waiting place | | | |
| Residence, *n* (%) | 0 | 144 (87.8) | <0.0001 |
| Hospital, *n* (%) | 4 (10.8) | 20 (12.2) | |
| ICU, *n* (%) | 33 (89.2) | 0 | |
| PaCO2 (mmHg) | 75 [61.5–90.5] | 50 [45–60] | <0.0001 |
| MV | | | |
| None, *n* (%) | 4 (10.8) | 82 (50) | <0.0001 |
| NIV, *n* (%) | 13 (35.1) | 74 (45.4) | |
| Invasive, *n* (%) | 20 (54.1) | 8 (4.9) | |
| MV length (h/day) | 12 [8–22] | 12 [10–24] | 0.23 |
| Preoperative ECMO | 8 (21%) | 0 | <0.0001 |
| O2 flow (l/min) | 5.5 [2.75–8] | 2 [2.3] | <0.0001 |
| PAPs (mmHg) | 38.5 [30–45] | 35.5 [30–45] | 0.96 |
| Vasoactive drugs requirement, *n* (%) | 6 (16.2) | 0 | <0.0001 |
| Creatinine level (μmol/l) | 52 [41.2–63.5] | 65 [52.2–75.7] | 0.0003 |
| LAS | 51.5 [41.4–74.7] | 36.7 [33.3–40.6] | <0.0001 |

*n* (%) or med [25; 75].

COPD, Chronic obstructive pulmonary disease; ILD, Infiltrative lung disease; HELT, High emergency lung transplantation; ICU, Intensive care unit; NIV, Noninvasive ventilation; MV, Mechanical ventilation; ECMO, Extra corporeal membrane oxygenation; PAPS, systolic pulmonary artery pressure; LAS, Lung allocation score.

HELT group (51.5 [41.4–74.7] vs. 36.7 [33.3–40.6], $P < 0.0001$). Finally, waiting time on regular LT list was shorter for HELT patients than for non-HELT patients.

### Surgical procedure and perioperative outcome

Donor age, smoking history and respiratory status (illustrated by P/F ratio), and serology mismatch (CMV or EBV) were roughly similar in both groups (Table 3).

A higher proportion of bilateral lung transplantation was reported in the HELT group (100% of total LT vs. 87% of total LT in the standard group, $P = 0.023$). This is likely due to the fact that at the beginning of the study period, single lung transplantation was more frequent for emphysema and COPD which are noninclusion criteria for HELT.

Resort to circulatory assistance during surgery (ECMO or CPB) was significantly higher in the HELT group (75% vs. 36.6%, $P = 0.0005$), and a lower rate of on-table extubation was observed (13.5% vs. 43.3%, $P < 0.0001$).

No significant difference in pleural adherence during surgery was noticed, nor in the resort to donor lung volume reduction. Nevertheless, we observed a significantly higher rate of perioperative bleeding (38.3 ml/kg vs. 20.5 ml/kg, $P < 0.0001$) in HELT group.

### Early postoperative data

No difference between groups for intensive care stay or total length of stay (10 days vs. 15 days, $P = 0.22$; 28 days vs. 37 days, $P = 0.15$, respectively) was observed (Table 4).

Invasive ventilation duration (including MV with intubation and/or tracheotomy) was significantly longer in the HELT group (9 days vs. 2.5 days, $P = 0.0041$). Additionally, postoperative ECMO use was higher in the HELT group (38.9% vs. 14.6%, $P = 0.0008$). Among the eight patients receiving preoperative ECMO, five were successfully weaned from ECMO at the end of surgery.

**Table 3.** Perioperative conditions.

| | HELT ($n$ = 37) | Non-HELT ($n$ = 164) | $P$ |
|---|---|---|---|
| Donor P/F ratio | 406 [346–450] | 386.50 [312.25–452.75] | 0.2 |
| Donor age | 46 (26–54.5) | 50 (39–57) | 0.16 |
| Donor smoking history | 15 (40.5%) | 62 (37.8%) | 0.8 |
| Bilateral transplantation, *n* (%) | 37 (100) | 143 (87.2) | 0.0214 |
| Graft volume reduction, *n* (%) | 12 (32.4) | 43 (26.2) | 0.44 |
| Pleural adherences, *n* (%) | 16 (43.2) | 62 (37.8) | 0.57 |
| Maximal ischemic time* (min) | 350 [300–395] | 330 [285–390] | 0.16 |
| Preoperative assistance | | | |
| None, *n* (%) | 11 (25) | 103 (63.4) | 0.0005 |
| CPB, *n* (%) | 5 (13.9) | 12 (7.3) | |
| ECMO, *n* (%) | 21 (58.3) | 46 (28) | |
| CPB then ECMO, *n* (%) | 1 (2.8) | 2 (1.2) | |
| Preoperative bleeding (ml/kg) | 38.3 [24.3–55.7] | 20.5 [13.3–33.3] | <0.0001 |
| Extubation in operative room, *n* (%) | 5 (13.5) | 71 (43.3) | 0.0006 |

*n* (%) or med [25; 75].

CPB, Cardiopulmonary bypass; HELT, High Emergency Lung Transplantation; ECMO, Extracorporeal membrane oxygenation; P/F ratio, Ratio of partial arterial pressure of O2 (PaO2); and Fraction of inspired O2 (FiO2).

*Defined as the time from cross-clamping of the aorta in the donor until release of the pulmonary arterial clamp in the lung transplant recipient, excluding *ex vivo* rehabilitation value. Time for the second graft placement is mentioned, if bilateral LT.

**Table 4.** Early postoperative outcome.

| | HELT ($n$ = 37) | Non-HELT ($n$ = 164) | $P$ |
|---|---|---|---|
| Length of stay in ICU (days) | 15.0 [5.0–30.5] | 10.0 [5.0–18.7] | 0.22 |
| Total length of stay (days) | 37.00 [24.00–64.00] | 28.50 [20.25–46.70] | 0.15 |
| Invasive VM duration (days) | 9 [2.25–23] | 2.5 [0–16.7] | 0.0041 |
| Total VM duration (days) | 15.5 [8–28.7] | 11.0 [7–22.7] | 0.27 |
| Postoperative ECMO, *n* (%) | 14 (38.9) | 24 (14.6) | 0.0008 |
| Postoperative ECMO duration (days) | 4 [2.7–7.2] | 5 [3–7.7] | 0.9 |
| PGD Grade 3 at 72 h, *n* (%) | 11 (31.4) | 28 (17) | 0.06 |
| Bacterial sepsis <30 days, *n* (%) | 18 (50) | 106 (65) | 0.12 |
| Bacterial pneumonia <30 days, *n* (%) | 17 (77.3) | 81 (78.6) | 1 |
| CMV infection <30 days, *n* (%) | 2 (40) | 5 (11.9) | 0.15 |
| Acute cellular rejection at 7 days *n* (%) | 11 (29.7) | 50 (30.7) | 1 |
| Acute cellular rejection at M12 (mean, SD) | 1.3 (1.3) | 1.4 (1.6) | 0.98 |
| Humoral alloimmunization* | | | |
| None, *n* (%) | 18 (48.6) | 67 (40.8) | 0.52 |
| Presence of DSA without AMR, *n* (%) | 15 (40.5) | 71 (19.6) | |
| AMR†, *n* (%) | 3 (8.1) | 23 (14) | |
| Surgical revision, *n* (%) | 12 (32.4) | 23 (14.1) | 0.03 |
| Bronchial stenosis, *n* (%) | 4 (11.4) | 18 (11) | 1 |

*n* (%) or Med [25;75].

DSA, Donor-specific Antigen; ECMO, Extra corporeal membrane oxygenation.

*Four patients (1 in HELT group and 3 in non-HELT group) died before having DSA evaluation.

†Defined as association of DSA and allograft dysfunction and/or compatible histologic findings and/or C4d deposition.

Comparison of PGD rates (grade 3 at 72 h) did not reach significance despite a trend for higher frequency in the HELT group (31.4% vs. 17.0%, $P = 0.06$). No difference in renal failure occurrence was observed (19% vs. 20% in non-HELT and HELT group, respectively).

No significant difference was noted for bronchial stenosis (11.4% vs. 11.0%, $P = 1$). Also, no difference was observed in pleural complications such as pneumothorax, pleural effusion, or empyema. Nonetheless, we reported a higher rate of surgical resumption in the HELT group (32.4% vs. 14.1%, $P = 0.03$).

There was no significant difference observed between groups regarding pneumonia incidence, nor bacterial, viral, or mycotic systemic infection (data not shown) for

the first thirty days following surgery and for the total follow-up.

Relative frequencies of donor-specific antibodies (DSA) with or without humoral rejection (as defined previously [19]), acute cellular rejection at d7, and cumulative number of acute rejections at month 12 ($1.3 \pm 1.3$ vs. $1.4 \pm 1.6$, $P = 0.58$) did not differ between the two groups.

### Long-term follow-up and survival

No difference in percentage of theoretical FEV1 was shown between groups at months 3, 6, and 12 following transplantation (respectively, in HELT and non-HELT groups at month 3: 66% [52–77.5] vs. 64.5% [49.7–80], $P = 0.95$; at month 6: 71.5% [54–79.25] vs. 67% [50–85], $P = 0.83$; at month 12: 74% [62–84] vs. 71% [57–86], $P = 0.7$). Also, early CLAD occurrence rate was not significantly different in HELT and non-HELT groups at 12 months and at 24 months (respectively, 11.5% vs. 4.4%, $P = 0.17$ and 16% vs. 7%, $P = 0.16$, Fisher's exact test).

Comparison of survival curves between HELT and non-HELT patients (log-rank test, Fig. 1) and intermediate survival rate (81% vs. 80%, 72.9% vs. 75% at 1 and 2 years, respectively) showed no significant difference after a 2-year follow-up. Patients with CF represent the majority of our study population and more than 80% of the HELT patients. As patients with CF are supposed to have better long-term prognosis, we then analyzed the survival curves in this subpopulation (non-HELT-CF versus HELT-CF patients). Non-HELT-CF had a significantly higher survival rate than HELT-CF patients (90% vs. 76% at 1-year post-LT, Fig. S1).

### Influence of HELT on waiting time and death rate on list

While the rate of lung transplant has raised inexorably, the number of deceased patients on the waiting list has steadily decreased over 8 years (Fig. 2). Since 2007, in the HELT era, the death rate on the waiting list dropped dramatically from 19% to 2%. We observed a sharp, simultaneous reduction between pre-HELT era and the HELT era in total time on waiting list specifically for the HELT group (82 days vs. 6 days, $P < 0.0001$), as well as non-HELT group (82 days vs. 40 days, $P < 0.0001$) (Fig. 3). It is worth noting that case mix of effectively transplanted patients did not significantly change over the two periods: Pre-HELT era (Emphysema-COPD = 15.8%; ILD = 13.8%; CF = 52.4%; Other and retransplantation = 18%) and HELT era ($P = 0.19$, chi-square test). Analysis of the HELT era before (July 2007–April 2011) and after (April 2011–May 2012) the introduction of EVLP shows a decreased amount of time on the waiting list for non-HELT patients after EVLP implementation (Fig. S2).

## Discussion

In this 5-year experience, HELT provided similar survival rates to standard LT despite the more severe clinical status of the candidates on waiting list and a higher rate of perioperative complications. Nevertheless, after that critical period, it appears that both groups of patients present the same short- and long-term prognosis. Moreover, no difference was noted between both overall survival rates after a minimum 2-year follow-up. Such results are associated with a dramatic reduction in waiting time and mortality rate of critical patients on the waiting list without an increase of waiting time for non-HELT patients.

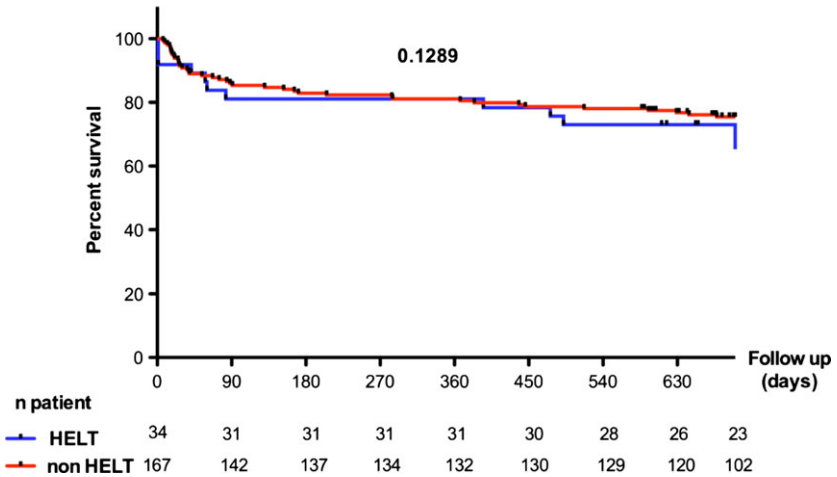


**Figure 1** High Emergency Lung Transplantation (HELT) and non-HELT Kaplan–Meier's survival until 2 year follow-up. HELT and non-HELT lines indicate the number of subject at each time point.

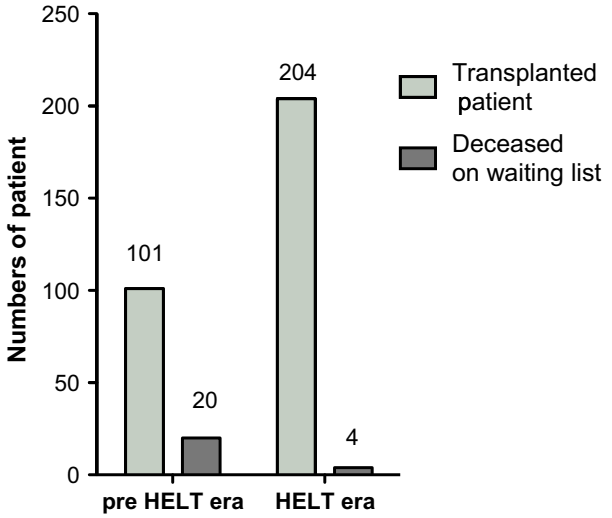


**Figure 2** Total number of transplanted patients and death rate on waiting list in the pre-High Emergency Lung Transplantation (HELT) era and HELT era. Transplanted patients during the pre-HELT and HELT era are 101 and 204, respectively. Deaths on waiting list during each period are 20 and 4, respectively.

### Higher perioperative morbidity

High Emergency Lung Transplantation patients clearly have higher severity of disease before surgery and in the early postoperative period. The success of this HELT program is in part due to comprehensive management, including extensive use of ECMO as a bridge to transplantation and strict respect for absolute contraindication (such as uncontrolled sepsis or multiple organ failure). There was a wide range of LAS in our HELT patients; the notably lower values could be explained by (i) exclusive pulmonary failure without any comorbidities as seen in acute exacerbations in ILD and CF or (ii) the wide use of ECMO which improves LAS parameters and leads to an underestimation of the severity by this score. Interestingly, others have described the latter as a constitutive weakness of LAS and since 2011, it has been proposed that inclusion of ECMO during LAS calculation may be more accurate and helpful in predicting mortality risk [11].

### Similar overall survival

Most LAS prognosis studies only provide comparisons of before and after LAS implementation, whereas in our study we analyzed not only before after HELT implementation but also compared HELT and non-HELT groups in the post-implementation period. As such our results differ from previous HELT evaluation studies.

At the beginning of the implementation program, the principal criticism which has arisen with the HELT program is the poor clinical status of the eligible patients. Thus, Boussaud *et al.* [14] showed that the survival rate was significantly lower in HELT patients, which was due to the critical conditions of the HELT population, as explained by the authors. The higher rate of immediate postoperative complications [14], such as dialysis request (41% vs. 19% in our study), suggests a more severe clinical status than our population.

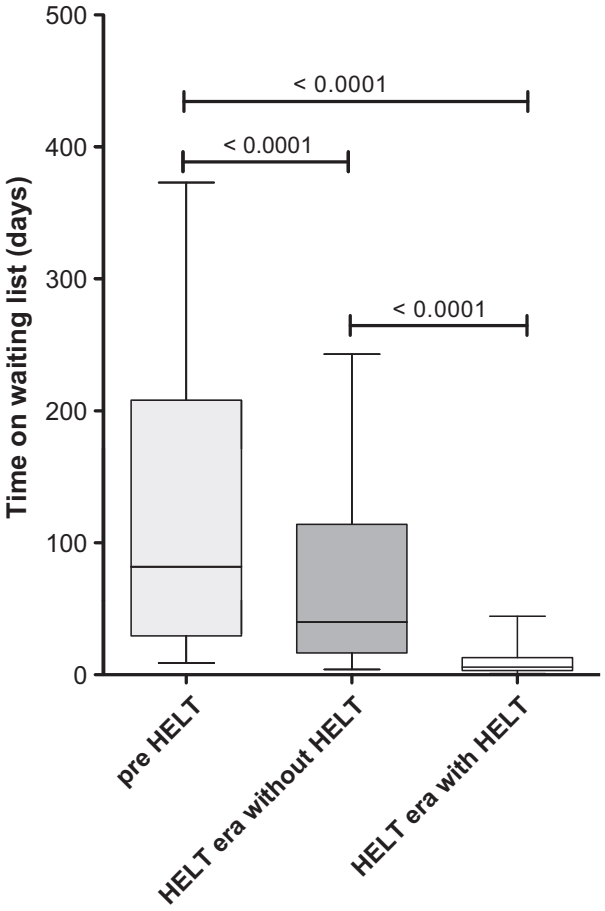


**Figure 3** Time on waiting list between LT inscription and transplantation. Comparison of time on waiting list (median [range]) between pre-High Emergency Lung Transplantation (HELT) era (82 [208–29]) and HELT era, without (40 [114–16.5]) or with HELT procedure (6 [13–3.2]).

According to the last report of the ABM [19] for the 2013 year, a rough comparison to national data (all centers, including Foch) clearly shows that Foch hospital's 1-year survival (80% vs. 62.7% for national HELT and 81% vs. 79.3% for national non-HELT patients) and median time on waiting list (1.3 months for Foch hospital during our study period vs. 3.2 months) at the national level for a similar period (2008–2013) are better than the average of the national data supplied by all LT centers. For the period 2007–2012, ABM shows a significant difference between HELT and non-HELT survival (Log-rank test) regardless of

the underlying disease. Our results may differ from those of ABM due to the fact that the HELT survival rate is higher in the Foch cohort compared to the national data set. Of note, ABM did not provide a detailed analysis stratified by underlying disease in HELT versus non-HELT patient survival, specifically the effect of HELT versus non-HELT among the CF subgroup. Therefore, we cannot compare our non-HELT survival to the national cohort for the CF subpopulation.

Orsini *et al.* [20] reported an analysis of mortality risk factor for HELT patient from seven LT centers on a period similar to ours, highlighting ECMO as a bridge to LT association with worst survival. Their 1-year survival (67.5%) in the HELT group was similar to that of the ABM report and therefore obviously lower than our result (80%). Patients with CF represent 60% of the national HELT population compare to 81.1% in our population. This may partly explain the discrepancy between the previously published results of Orisini *et al.*, the national report, and our results. Neither the ABM report nor Orsini *et al.* provide detailed analyses concerning the CF subgroup; subsequently, we are unable to compare our results to theirs for this important etiological subgroup.

Another large-scale study published in 2010 demonstrated high LAS recipients had significantly worse actuarial survival at 90 days and 1 year compared with those whom had lower LAS. However, when stratified by underlying disease, these findings were only statistically significant for recipients with COPD and pulmonary fibrosis, and no significant difference was shown at 2 and 3 years postoperative [21]. Survival analysis according to LAS stratification showed that postoperative mortality is associated with higher LAS or LASplus (including ECMO resort rating) [11,21]. However, regarding only the CF subpopulation, Russo *et al.* did not find any difference for 1-year mortality between high and low LAS.

### Survival analysis in CF subpopulation

Our population presents distinct characteristics compared to other studies. The proportion of CF in both groups was greater than previously reported in LAS studies [6,10], in accordance with the fact that Foch Hospital is a CF reference center. Regarding survival by primary diagnosis in national data [22], patients with CF have a better prognosis after LT than COPD and IPF patients (88, 48, and 25 months median survival, respectively). This particular case mix probably contributes to improved survival in the two groups, both in non-HELT and most particularly in our HELT group where CF represents more than 80% of the diagnoses. Because of this repartition, the age of patients was significantly lower (27.7 vs. 40.2, $P < 0.05$) in the HELT group, which also contributes to better prognosis. This case mix discrepancy is a common methodological bias found in other publications comparing waiting patients according to their severity [11,21].

In our study, mortality in HELT-CF patients remains quite low (25% at month 12), similar to the top end of the survival range reported by ISHLT [23] and lower than the 35.3% of mortality reported by Orsini *et al.* [20]. The survival difference between HELT and non-HELT in the CF subpopulation may be due to the high survival rate of the non-HELT patients treated in our center (more than 90% at one and 2 years post-LT (Fig. S1)).

Furthermore, the survival comparison between HELT and non-HELT is insufficient to appreciate the individual benefit of this strategy. Without HELT, a patient fulfilling HELT criteria would have a day 30 mortality of 90% without transplantation instead of a post-transplant day 30 mortality of 25% [24]. Finally, one could consider this increased mortality rate in HELT-CF patients as a largely acceptable outcome attributed to the multiple benefits of HELT.

### Time and mortality on waiting list

Anticipation that the HELT graft allocation system would have hypothetically increased the time and mortality rate on the waiting list for non-HELT patients is contradicted by our analysis. First, waiting time in both the non-HELT and HELT group has decreased considerably since HELT implementation in our center, in accordance with national data. The shorter waiting time in the HELT era between the inscriptions on non-HELT and HELT lists reflects an early and appropriate management in patients with severe clinical status, increased use of ECMO and less stringent graft acceptance policy, all contributing to improved outcome in the HELT group.

As graft collection and distribution have been ameliorated, new techniques like EVLP, which were developed during the same period (April 2011–2012), also have led to increased graft availability and total number of lung transplantations. Moreover, our center probably uses wider graft acceptance criteria than most others: the graft refusal rate is lower in the Foch Hospital than the national rate (50.0% vs. 77.5% in 2012, respectively [22]), also leading to decreased waiting time on the list. As the number of transplantations in the Foch Hospital and France remained stable during HELT era pre-EVLP compared to the pre-HELT era, reduction in time on the waiting list cannot be explained by a boom in the number of LT. Since April 2011, according to more efficient graft recruitment and *ex vivo* implementation, the number of LT is growing and may partly explain the reduction in time on the waiting list. Lastly, with a median time of 2 days to transplantation, the

HELT strategy limits the time for global status worsening to occur during the preoperative period.

Amelioration in regular LT waiting time, associated with strict HELT admission criteria, reduces inappropriate registration on the HELT list by physicians and has led to the stability of the HELT rate, which represents annually approximately 20% of total French lung transplants [22].

Decreased waiting time has been associated with a dramatic reduction in mortality rate while on the waiting list, which has dropped from 19% to 2% in our center since HELT implementation, while no death on the waiting list has been registered since 2008. Similar reasons may be involved, more specifically, the development of preoperative intensive care techniques such as ECMO, which potentiates surgical conditions by reducing hypercapnia and improving tissue oxygenation, and can be used as a bridge for lung transplant in more severe recipients. Several evaluation studies have shown a benefit from ECMO in medium-term survival, especially in patients with CF [25,26]. In our population, ECMO is needed as preoperative support for 24% of the HELT group, involving up to 60% during surgery. A previous national evaluation study showed a lower rate of 11.9% of ECMO use in the HELT population, suggesting underutilization of the technique, and a potential for increased graft survival if used more often [26].

In the HELT era, parameters such as progressive change in practice for inscription timing and acceptance of very severe patients with CF (lately referred to our center) are difficult to appreciate; our results do not provide information concerning the bias these factors may introduce in allograft survival analysis. Importantly, the waiting time reduction may offer access to transplantation to some high-severity patients who would have been contraindicated prior to the HELT era. Also delaying inscription on the waiting list for LT of some less severe patients may additionally explain the decreased time on the waiting list in a pro-cyclical fashion. Those practices, which are difficult to quantify, may have resulted in the decreased time on the regular waiting list (before HELT inscription) and on the total waiting time.

We are aware that success of this strategy probably relies on other associated factors: At the individual level, respect of contraindication and pretransplant intensive treatment (such as ECMO) has dramatically improved survival for the most severe patients; at the collective level, the relatively small number of centers in France and expert evaluation avoid transplantation of critically ill patients, thereby keeping the level of HELT around 20% of total LT. In this situation and with this rate, this strategy did not negatively impact graft accessibility for non-HELT patients. Apparently less complex than LAS, based on a regression equation analyses, the HELT allocation program leads to similar decreases in both time on the waiting list and associated mortality, as well as not altering the transplant case mix at the expense of patients with COPD. Both the USA and the Eurotransplant group demonstrated LAS allows for a dramatic decrease in both time on the waiting list and mortality, while postoperative survival was similar to the pre-LAS era [7,8,10]. Alternatively, the change in the case mix of transplanted patients works to the detriment of COPD, possibly driving an unjustifiable increased mortality for these patients with end-stage disease.

## Conclusion

HELT graft allocation, a prioritization system among others, has transformed the prognosis of more severe allograft recipients. Despite worse clinical status and perioperative critical conditions, we have reported herein a similar survival rate as seen in conventional LT. Conditions of success are management of the patient with appropriate supportive care practices and strict respect of eligibility criteria. Association between these allocation rules and the increase of available graft numbers, provided by techniques such as *ex vivo* reconditioning, is key for improving the future management of patients with end-stage lung disease requiring LT.

## Authorship

AR and LBA: contributed to clinical management, data collection, study design, statistical data analysis, and manuscript composition. MS: contributed to clinical management, study design, statistical data analysis, and manuscript composition. AMH, SDeM, DG, GB, PB, PP, FP, JD, GT, EC, BD, CP, MLG, AC and ES: contributed to clinical management, data analysis, and manuscript editing.

## Funding

The authors have declared no funding.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** HELT and non HELT Kaplan–Meier survival curves among CF patients to 2 year follow up.

**Figure S2.** Effect of EVLP on time on waiting list.

**Table S1.** Comparison of different prioritization policies for graft allocation.

## References

1. De Meester J, Smits JM, Persijn GG, Haverich A. Lung transplant waiting list: differential outcome of type of end-stage

lung disease, one year after registration. *J Heart Lung Transplant* 1999; **18**: 563.
2. OPTN annual data report 2012. 2013.
3. Schiavon M, Falcoz PE, Santelmo N, Massard G. Does the use of extended criteria donors influence early and long-term results of lung transplantation? *Interact Cardiovasc Thorac Surg* 2012; **14**: 183.
4. Cypel M, Yeung JC, Liu M, *et al.* Normothermic *ex vivo* lung perfusion in clinical lung transplantation. *N Engl J Med* 2011; **364**: 1431.
5. Egan TM, Murray S, Bustami RT, *et al.* Development of the new lung allocation system in the United States. *Am J Transplant* 2006; **6**: 1212.
6. Gries CJ, Mulligan MS, Edelman JD, Raghu G, Curtis JR, Goss CH. Lung allocation score for lung transplantation: impact on disease severity and survival. *Chest* 2007; **132**: 1954.
7. Kozower BD, Meyers BF, Smith MA, *et al.* The impact of the lung allocation score on short-term transplantation outcomes: a multicenter study. *J Thorac Cardiovasc Surg* 2008; **135**: 166.
8. McCue JD, Mooney J, Quail J, Arrington A, Herrington C, Dahlberg PS. Ninety-day mortality and major complications are not affected by use of lung allocation score. *J Heart Lung Transplant* 2008; **27**: 192.
9. Doi A, Lee G, Snell G, Bloch M, Summerhayes R, Marasco S. Lung transplantation as rescue therapy in patients too sick to be discharged from acute care. *Transpl Proc* 2014; **46**: 256.
10. Gottlieb J, Greer M, Sommerwerck U, *et al.* Introduction of the lung allocation score in Germany. *Am J Transplant* 2014; **14**: 1318.
11. Smits JM, Nossent GD, de Vries E, *et al.* Evaluation of the lung allocation score in highly urgent and urgent lung transplant candidates in Eurotransplant. *J Heart Lung Transplant* 2011; **30**: 22.
12. Roman A, Calvo V, Ussetti P, *et al.* Urgent lung transplantation in Spain. *Transpl Proc* 2005; **37**: 3987.
13. De Meester J, Smits JM, Persijn GG, Haverich A. Listing for lung transplantation: life expectancy and transplant effect, stratified by type of end-stage lung disease, the Eurotransplant experience. *J Heart Lung Transplant* 2001; **20**: 518.
14. Boussaud V, Mal H, Trinquart L, *et al.* One-year experience with high-emergency lung transplantation in France. *Transplantation* 2012; **93**: 1058.
15. Sage E, Mussot S, Trebbia G, *et al.* Lung transplantation from initially rejected donors after *ex vivo* lung reconditioning: the French experience. *Eur J Cardiothorac Surg* 2014; **46**: 794.
16. Lee JC, Christie JD, Keshavjee S. Primary graft dysfunction: definition, risk factors, short- and long-term outcomes. *Semin Respir Crit Care Med* 2010; **31**: 161.
17. Stewart S, Fishbein MC, Snell GI, *et al.* Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant* 2007; **26**: 1229.
18. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant* 2014; **33**: 127.
19. Berry G, Burke M, Andersen C, *et al.* Pathology of pulmonary antibody-mediated rejection: 2012 update from the Pathology Council of the ISHLT. *J Heart Lung Transplant* 2013; **32**: 14.
20. Orsini B, Sage E, Olland A, *et al.* High-emergency waiting list for lung transplantation: early results of a nation-based study. *Eur J Cardiothorac Surg* 2014; **46**: e41–7; discussion e7.
21. Russo MJ, Iribarne A, Hong KN, *et al.* High lung allocation score is associated with increased morbidity and mortality following transplantation. *Chest* 2010; **137**: 651.
22. Rapport annuel Agence de la Biomédecine. http://www.agence-biomedecine.fr/annexes/bilan2013/donnees/organes/04-coeur-poumon/pdf/pcp.pdf. 2014.
23. Yusen RD, Christie JD, Edwards LB, *et al.* The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report–2013; focus theme: age. *J Heart Lung Transplant* 2013; **32**: 965.
24. Gottlieb J, Warnecke G, Hadem J, *et al.* Outcome of critically ill lung transplant candidates on invasive respiratory support. *Intensive Care Med* 2012; **38**: 968.
25. Del Sorbo L, Ranieri VM, Keshavjee S. Extracorporeal membrane oxygenation as "bridge" to lung transplantation: what remains in order to make it standard of care? *Am J Respir Crit Care Med* 2012; **185**: 699.
26. Lafarge M, Mordant P, Thabut G, *et al.* Experience of extracorporeal membrane oxygenation as a bridge to lung transplantation in France. *J Heart Lung Transplant* 2013; **32**: 905.

## Appendix 1: FOCH Lung Transplant Group

Thoracic Surgery Department: P. Bonnette, D. Mitilian, P. Puyo, E. Sage, A. Chapelier.

Pneumology Department: S. De Miranda, B, Douvry, D. Grenet, A. Hamid, C. Picard, A. Roux, M. Stern.

Anesthesiology Department: J. Bresson, V. Dumans-Nizard, JL. Dumoulin, S. Ghiglione, S. Jacqmin, M. Le Guen, L. Ley, N. Liu, J-Y. Marandon, M. Michel-Cherqui, O. Pruszkowski, B. Rives, B. Szekely, B. Vandenbunder, N. Verroust, M.Fischler.

Intensive Care Unit: J. Devaquet, F. Parquin, A-G Si Larbi, G. Trebbia, C. Cerf.