



Outcomes of listing for lung and heart–lung transplantation in pulmonary hypertension: comparative experience in France and the UK

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This comparative analysis of patients with PH listed for lung or heart–lung transplantation in France and the UK provides insights into this specific disease historically characterised by high peritransplant morbidity and mortality <https://bit.ly/400U15b>

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Abstract

Background Lung or heart–lung transplantation (LT/HLT) for severe pulmonary hypertension (PH) as the primary disease indication carries a high risk of waiting list mortality and post-transplant complications. France and the UK both have coordinated PH patient services but with different referral pathways for accessing LT services.

Methods We conducted a comparative analysis of adult PH patients listed for LT/HLT in the UK and France.

Results We included 211 PH patients in France (2006–2018) and 170 in the UK (2010–2019). Cumulative incidence of transplant, delisting and waiting list death within 3 years were 81%, 4% and 11% in France versus 58%, 10% and 15% in the UK ($p < 0.001$ for transplant and delisting; $p = 0.1$ for death). Median non-priority waiting time was 45 days in France versus 165 days in the UK ($p < 0.001$). High-priority listing occurred in 54% and 51% of transplanted patients respectively in France and the UK ($p = 0.8$). Factors associated with achieving transplantation related to recipients' height, male sex, clinical severity and priority listing status. 1-year post-transplant survival was 78% in France and 72% in the UK ($p = 0.04$).

Conclusion Access to transplantation for PH patients is better in France than in the UK where more patients were delisted due to clinical deterioration because of longer waiting time. High rates of priority listing occurred in both countries. Survival for those achieving transplantation was slightly better in France. Ensuring optimal outcomes after transplant listing for PH patients is challenging and may involve early listing of higher risk patients, increasing donor lung utilisation and improving allocation rules for these specific patients.

Introduction

Pulmonary hypertension (PH), including pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease (PVOD) and chronic thromboembolic PH, was the indication for lung transplantation (LT) and heart–lung transplantation (HLT) in 6% of recipients in the UK and 10% in France in 2022 [1, 2]. However, these patients add complexity to the decision-making process around the timing of referral and listing [3, 4].



Many improvements have emerged in PH treatment over the last 15 years, such as the broad adoption of triple therapy for group 1 patients and the availability of balloon angioplasty and riociguat for group 4 patients [5]. Nevertheless, LT or HLT remain the reference treatment for end-stage disease [4, 6]. Ironically, these medical advances may have complicated timely decision to list eligible PH patients, as they can stay in a severe but stable condition for years.

High mortality rate of patients transplanted for PH has been reported, with a high risk of severe primary graft dysfunction in particular [3, 7, 8]. These can potentially be reduced with optimal timing of referral and listing, especially as these patients have very good long-term survival if they survive the early post-operative period.

PAH risk stratification tools have been developed to help clinicians decide when best to refer patients for transplantation. However, the management of patients with end-stage PH remains complex, with the risk of acute life-threatening deterioration [9, 10].

The healthcare systems of the UK and France share similarities such as state funding and almost-universal health coverage [11]. In terms of transplantation, the donor lung allocation process is quite similar. Donor lungs for routinely listed patients are allocated to a specific transplant unit on a rotational basis, where the responsible clinician selects the potential recipient from the waiting list based on a range of factors. There is no individual score for recipients and no routine national allocation of grafts by name [12]. While France and the UK have a similar total population (~67 million inhabitants in both countries in 2021), the number of LTs performed per million population (pmp) is higher in France, with 4.9 procedures pmp compared to 1.5 pmp in the UK in 2021 [13]. Both countries have implemented a system of priority listing, in order to improve access to LT for patients with end-stage and life-threatening disease. In this situation, transplants are first offered to centres where patients are on the urgent transplant list, and then to other centres, on the principle of rotation between centres [14, 15]. In France, clinicians have been able to request national priority listing since 2006, and in the UK, since 2017, this has been available for any patient with PH who is experiencing acute, life-threatening deterioration despite optimal therapy. These requests for priority listing are reviewed by a panel of experts, and a large majority of them are approved.

Our study aims to compare and contrast the outcomes of adult PH patients after being listed for LT or HLT in the UK and in France and to identify the main determinants of patient prognosis.

Methods

This retrospective observational study evaluated adult (aged ≥ 16 years) PH patients (all diagnostic groups except group 2 and group 3 in the international classification for PH [16]) listed for first LT or HLT in the UK and in France. PH diagnosis required a baseline right heart catheterisation confirming pre-capillary PH, defined as mean pulmonary arterial pressure >25 mmHg with mean pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance >2 Wood units according to the definition in effect at the time of the study [17]. Anonymised data are prospectively collected by the UK Transplant Registry held by the NHS Blood and Transplant Results (NHSBT) and by the French Transplant Registry held by the Agence de la Biomedecine. Extraction of data was performed on 28 February 2023. The study period was between 2010 and 2019 in the UK, and 2006–2018 in France, according to the available datasets. Patients registered for a multiorgan transplant (except heart–lung) were not included.

Features of national priority programmes, operating since 2006 in France and 2017 in the UK, are described in the supplementary Methods and figure S1. They can be requested for PH patients suffering from acute life-threatening deterioration despite maximal treatment.

Reveal Lite 2 abridged score was calculated with all variables available for each patient, with at least three variables [18]. Grade 3 primary graft dysfunction (PGD3) could be diagnosed at any time point during the first 72 h post-transplantation.

Statistical analysis

Continuous variables are expressed as median (interquartile range (IQR) 25%–75%). Categorical data are expressed as number (n) and percentage (%). The primary outcome is occurrence of transplantation in listed patients. We used a competing risk regression model, as it allows assessment of the probability of one event (transplant), in the setting of competing events (death without transplant and delisting): transplant and death on the list are indeed two mutually exclusive risks [19]. Actively listed patients were considered as censored patients at the last known follow-up date. As competing risk models can be subjected to dependent censoring, we also used the cause-specific hazard model [20]. As priority listing

for PH patients was only implemented in the UK in 2017, we also compared the outcomes of all French patients to the UK patients who were listed after the implementation of the urgent and super-urgent schemes, *i.e.* from June 2017. Given the differences in patient characteristics and access to transplant, we also performed a sub-analysis of patient outcomes according to the type of organ requested at the time of listing: double-lung *versus* heart–lung. We studied survival on the waiting list and after transplantation with the Kaplan–Meier method and the log-rank test. The date of listing for transplantation and the date of transplantation were respectively used as starting points to determine the post-registration and the post-transplant survivals. Delisting was considered equivalent to death as it was mainly related to severe worsening of clinical status, making transplantation impossible and leading quickly to patient death. Cox proportional hazards regression models were performed to assess the association between access to transplant and risk of death on the list with each baseline variable. To study the national effects of the implementation of the priority schemes in the UK, two eras were defined: January 2010–October 2016, and June 2017–December 2021, with a 6-month gap in between the two eras to minimise a crossover effect. All comparisons were two-sided; a *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using R studio (version 2022.12.0+353).

Results

Patient population at the time of listing

During the study period, 170 UK patients and 211 French patients suffering from PH were listed for LT/HLT. Median follow-up from time of listing was 44 months (7–87). Most patients suffered from group 1 PH, with more PVOD and group 4 patients in France (table 1). French patients were significantly younger, with less severe dyspnoea, better 6-minute walking test distance and better cardiac index. Overall, 43% of patients were at high risk of death according to the Reveal Lite 2 score.

Outcomes after listing

Outcomes of patients after listing are summarised in figures 1 and 2. Cumulative incidence of transplantation was respectively 70–81% in France *versus* 44–58% in the UK after 1 and 3 years on the list (*p*<0.001) (figure 3). Similarly, the cause-specific hazard model showed a hazard ratio (HR) of being transplanted of 2.3 (95% CI: 1.8–2.9) in France compared to the UK (*p*<0.001). Delisting was less frequent in France with the competing risk approach: respectively 3–4% of French patients *versus* 4–10% of UK patients were delisted after 1 and 3 years (*p*=0.004) (figure 3). Using the cause-specific hazard model, HR of being delisted was not different in France compared to the UK (HR 1.0, 95% CI: 0.5–2.1, *p*=0.9).

Risk of death while waiting was not different between countries with both statistical models (figure 3 and HR of death 1.2 in France compared to the UK, 95% CI: 0.6–1.9, *p*=0.8). Since delisting primarily results from a worsening clinical condition that ultimately leads to the patient's death, we examined the HR for the combined outcomes of death and delisting. The HR was 1.1 (95% CI: 0.7–1.7, *p*=0.7) when comparing France to the UK.

Post-listing survival was better in France with respectively 72–63% of French patients and 73–56% of UK patients still alive, either transplanted or waiting on the list, 1 and 3 years after listing (*p*=0.01) (figure 4). High risk score at time of listing was associated with poorer post-listing survival in the overall population (figure 5).

A sub-analysis of patient outcomes according to the type of organ requested is presented in the appendix (supplementary figures S6 to S9). Looking only at patients waiting for a lung transplant, the cumulative incidence of transplantation was significantly higher in France than in the UK, while the cumulative incidence of death and of delisting was lower (supplementary figure S7). Looking only at patients listed for HLT, only the cumulative incidence of transplantation was higher in France, with no statistically significant difference between the two countries in the cumulative incidence of death and of delisting (supplementary figure S9).

Factors associated with the occurrence of death and transplant are summarised in figure 5.

Characteristics of transplanted patients

In both countries, HLT made up approximately one-third of the overall lung transplant activity for PH (table 2). Waiting time was higher in the UK (165 days *versus* 45 days in France for non-priority patients, *p*<0.001), even in priority listing (17 days *versus* 2 days in France, *p*<0.001). Extracorporeal membrane oxygenation (ECMO) was required after transplantation in one-third of patients in both countries. PGD3 occurred in about half of patients. Post-transplant survival was slightly better in France, with respectively 82–72% of UK patients and 85–78% of French patients surviving after the first 3 and 12 months post-transplant (*p*=0.04).

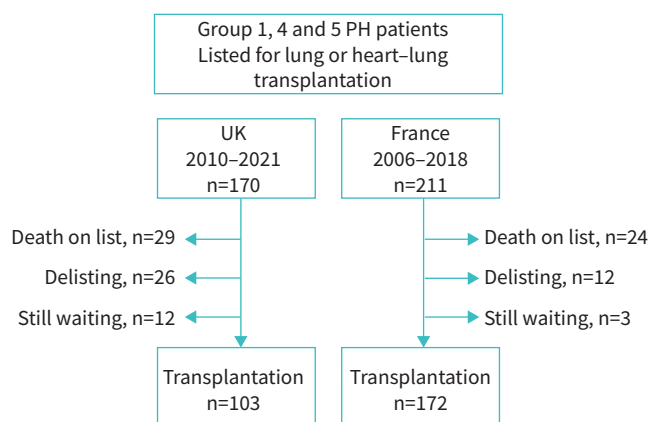
TABLE 1 Demographic and clinical characteristics at the time of listing of pulmonary hypertension patients according to country

	UK	France	Missing data, n (%)	p-value
Patients n	170	211		
Sex, female	125 (74)	139 (66)	0 (0)	0.1 [#]
Age at listing years	43 (32–51)	38 (28–48)	0 (0)	0.003 [#]
Height at listing cm	165 (158–172)	165 (158–172)	0 (0)	0.8 [#]
BMI at listing kg·m⁻²	24 (21–27)	21 (20–24)	0 (0)	<0.001 [#]
PH diagnosis				
CHD	33 (19)	41 (19)	0 (0)	<0.001 [#]
PVOD	7 (4)	31 (15)		
Other PAH	123 (72)	112 (53)		
Group 4	4 (2)	23 (11)		
Group 5	3 (2)	4 (2)		
NYHA functional class				
I, II	13 (8)	34 (17)	19 (5)	0.005 [#]
III	94 (55)	111 (53)		
IV	50 (29)	63 (30)		
6MWD m	300 (174–389)	380 (266–442)	62 (16)	<0.001 [#]
Haemodynamics				
mPAP mmHg	55 (46–66)	58 (49–69)	111 (30)	0.2 [#]
PAWP mmHg	12 (9–22)	9 (6–11)	145 (38)	<0.001 [#]
CI L·min ⁻¹ ·m ⁻²	2.0 (1.7–2.5)	2.7 (2.1–3.3)	142 (37)	<0.001 [#]
Renal function				
Creatinine μmol·L ⁻¹	81 (66–95)	87 (69–104)	75 (20)	0.03 [#]
eGFR mL·min ⁻¹ ·1.73 m ⁻²	80 (61–98)	72 (59–95)	75 (20)	0.2 [#]
Reveal Lite 2 score				
Low risk	7 (6)	26 (16)	100 (26)	<0.001 [#]
Intermediate risk	68 (55)	60 (38)		
High risk	48 (39)	72 (46)		

Continuous variables are expressed as median (IQR) and categorical variables as n (%). BMI: body mass index; PH: pulmonary hypertension; CHD: congenital heart disease; PVOD: pulmonary veno-occlusive disease; PAH: pulmonary arterial hypertension; NYHA: New York Heart Association; 6MWD: 6-min walking distance; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CI: cardiac index; eGFR: estimated glomerular filtration rate. [#]: Fisher's exact test; [#]: Wilcoxon rank sum test.

Role of emergency programmes

During the study period, respectively 53–54% and 34–51% of listed and transplanted patients were prioritised in France and in the UK (from 2017). Priority listing improved the chance of being transplanted (figure 5).

**FIGURE 1** Study flow diagram. PH: pulmonary hypertension.

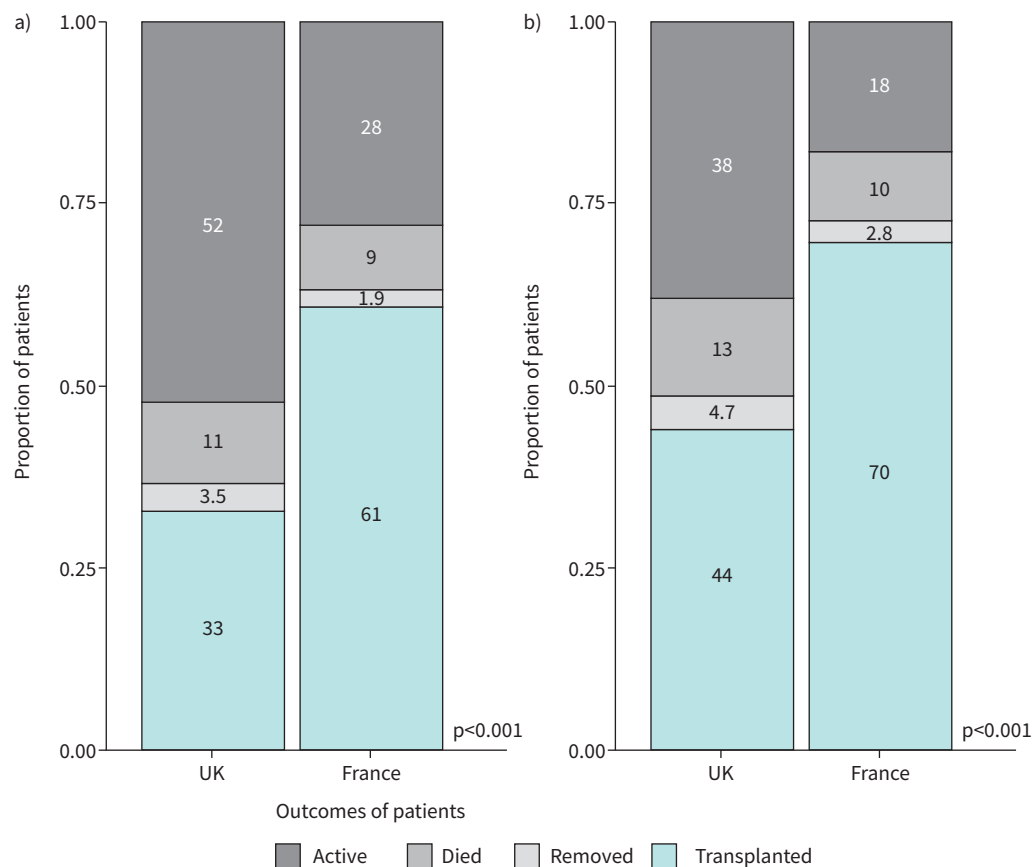


FIGURE 2 Proportion of outcomes at a) 6 and b) 12 months post-registration of pulmonary hypertension patients according to country. Statistical test is Fisher's exact test.

Comparing French patients to UK patients who were listed after the implementation of the priority scheme, occurrence of transplantation was still better in France and rate of delisting lower, regardless of the statistical model (figure 3 and supplementary material).

Comparison of outcomes of UK patients before and after 2017 showed a trend towards improved access to LT with priority listing (supplementary figures S2 and S3).

Discussion

Comparing outcomes of PH patients listed for LT/HLT between France and the UK, we found a significant difference in the access to transplant, even after the implementation in the UK of the high urgency priority programme that has been in place in France since 2006. After a year on the waiting list, cumulative incidence of transplantation was 44% in the UK compared to 70% in France ($p < 0.001$). This differential access to transplant was in line with the average waiting time, which was almost four times longer in the UK, even in case of priority listing. Post-registration survival reflected this difference in access to transplant, with lower survival in the UK.

One of the factors that might explain this disparity is a more severe clinical condition at the time of listing in the UK. Given that UK patients have to wait longer for a transplant, they ultimately have a higher likelihood of delisting due to worsening clinical condition, and a lower transplant rate. In the UK, one might therefore consider putting PH patients on the transplant list earlier. All the more so as the more deteriorated clinical state at the time of listing could explain, at least in part, the lower post-transplant survival rate observed in the UK.

The differences in the organisation of care for PH patients might have an impact on patient outcomes. The French system is highly centralised, as most PH transplant candidates are assessed at the national reference centre. Weekly meetings of PH and transplant specialists might help optimise the timing of listing. >80%

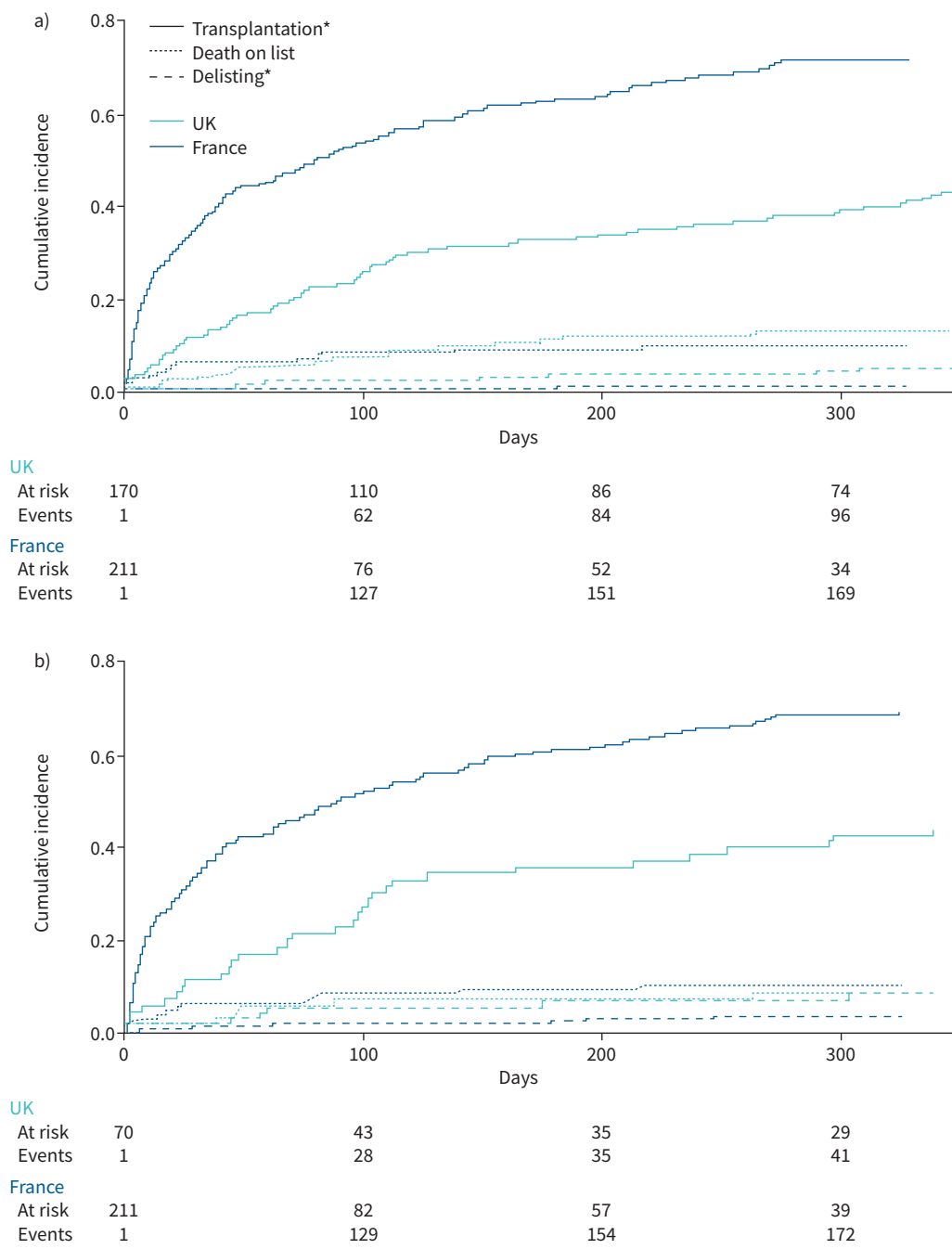


FIGURE 3 Cumulative incidence of transplantation, death and delisting after 1 year of registration in pulmonary hypertension patients, according to country: a) during the entire study period; b) when only considering UK patients that were listed from May 2017 and could therefore benefit from the implementation of the urgent and super-urgent schemes. *: $p < 0.05$ according to Grey's test, between British and French cohort.

of transplants are then performed in a single hospital (Marie Lannelongue Hospital). In the UK, there are five adult LT/HLT centres and seven specialist PH centres, with no regular meeting between PH specialists and transplant specialists. Patients are treated in their nearest specialist centre.

Since timely decision to list PH patients is very challenging, several prognostic scores have been developed to help clinicians. Latest guidelines, mainly based on expert opinion, recommend listing patients for transplantation if they are at high risk of death according to REVEAL 2.0 and/or ERS-ESC score (defined in 2015 with both European Respiratory Society and European Society of Cardiology) despite

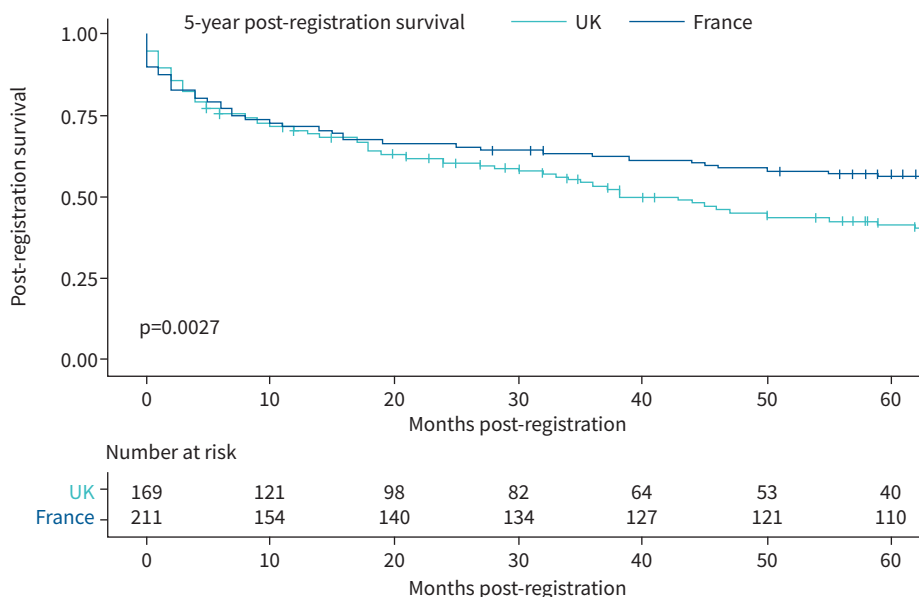


FIGURE 4 5-year post-registration survival of pulmonary hypertension patients according to country. Survival was defined as the time from listing to death or delisting, regardless of whether the patient received a transplant or not. Delisting was considered as equivalent to death as it is mainly related to worsening of the clinical condition, making transplantation impossible and leading to death. Data were censored at the last known follow-up date, either before or after transplant, depending on whether the patient was transplanted or not. Statistical test is a log-rank test.

optimal treatment [6]. Nevertheless, our results confirm the work from VICAIRE *et al.* [21]: patients at high risk of death at the time of listing have a poorer prognosis on the waiting list. Waiting for a patient to be at high risk may be leaving it too late. However, not being at high risk of death according to REVEAL is not a sufficient criterion to reassure patients and doctors. In our cohort, less than half of the patients were at high risk of death at the time of listing. In the end, around half of them were transplanted as part of an

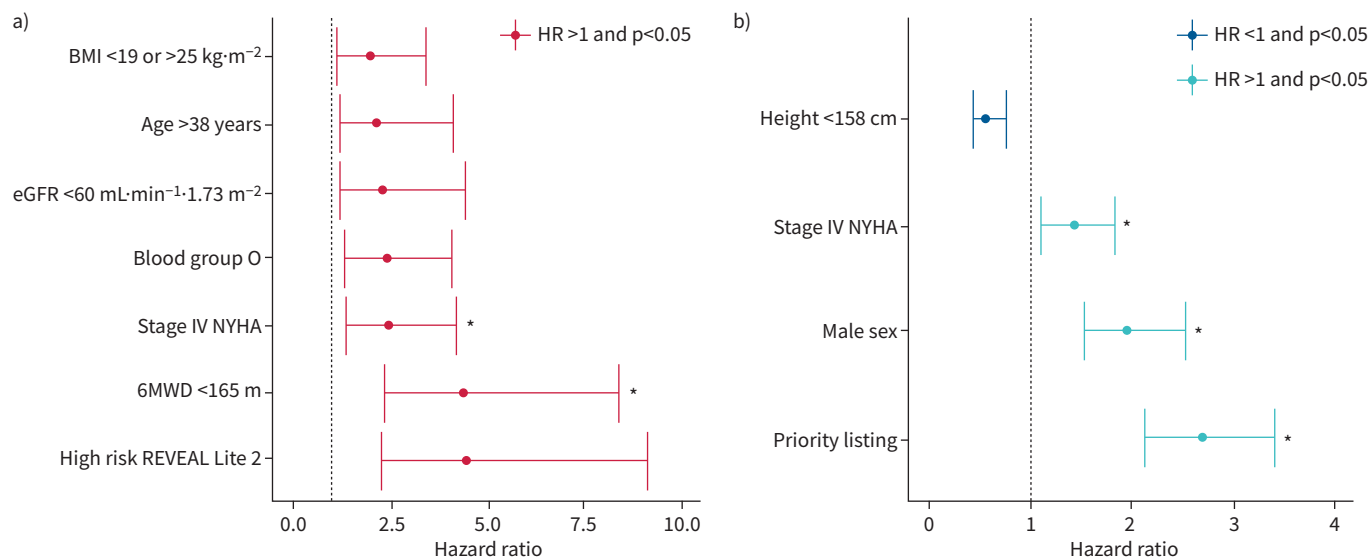


FIGURE 5 Variables associated with the occurrence of a) death and b) transplantation in PH patients. Statistical test is univariate Cox logistic regression performed on the whole cohort. BMI: body mass index; 6MWD: 6-min walking distance, eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; HR: hazard ratio. *: the variable remains statistically significant ($p < 0.05$) in multivariate Cox regression.

TABLE 2 Characteristics of transplanted pulmonary hypertension patients according to the country

	UK	France	Missing data, n (%)	p-value
Patients n	103	172		
Sex, female	72 (70)	111 (65)	0 (0)	0.4 [#]
Age at transplant years	44 (32–51)	38 (28–48)	0 (0)	0.02 [¶]
Regular waiting time days	165 (52–392)	45 (10–184)	0 (0)	<0.001 [¶]
Urgent waiting time days	17 (11–34)	2 (0–7)	0 (0)	<0.001 [¶]
Prioritised patients	20 (51) ⁺	93 (54)	0 (0)	0.8 [#]
ECMO as a bridge to transplant	9 (14)	19 (11)	41 (15)	0.5 [#]
Post-transplant ECMO	32 (32)	59 (35)	6 (2)	0.7 [#]
Type of transplantation			0 (0)	0.8 [#]
Heart–lung	35 (34)	55 (32)		
Double-lung	68 (66)	117 (68)		
Post-transplant haemodialysis/haemofiltration	52 (52)	31 (19)	14 (5)	<0.001 [#]
Grade 3 PGD	27 (53)	62 (57)	116 (42)	0.6 [#]

Continuous variables are expressed as median (IQR) and categorical variables as n (%). ECMO: extracorporeal membrane oxygenation; PGD: pulmonary graft dysfunction. [#]: Fisher's exact test; [¶]: Wilcoxon rank sum test; ⁺: proportion of prioritised transplanted patients from June 2017 in the UK (date of implementation of urgent and super-urgent schemes). Grade 3 PGD was diagnosed at any time point within the first 72 h post-transplantation.

emergency programme, due to acute life-threatening deterioration. This proportion is much higher than that observed in both countries for COPD (<3% of priority listing) and for pulmonary fibrosis and cystic fibrosis (on average 25% of priority listing) [22, 23]. This highlights the challenge of predicting the risk of clinical worsening in PH and anticipating changes in patients' clinical status while they wait for transplant, particularly considering the significant variation in waiting times, which can extend beyond a year in certain cases.

As we could only calculate the abridged version of the REVEAL score, some patients may have potentially been misclassified in their degree of risk. However, the high proportion of intermediate- and low-risk patients in our cohort is significant. This emphasises that clinicians, in some instances, may have listed PH patients for reasons other than classical risk stratification, such as the PVOD phenotype, life-threatening haemoptysis or limited access to transplantation, for example due to significant anti-human leukocyte antigen (HLA) sensitisation. The latest guidelines from the International Society for Heart and Lung Transplantation (ISHLT) stated indeed that “new contemporary multimodal risk stratification tools, which outperform individual predictors of disease progression, combined with other pertinent clinical information, should be used to guide timing of referral and listing for LT” [24]. Several complementary approaches have been proposed for this purpose: the use of cardiac magnetic resonance imaging, innovative biological markers and artificial intelligence techniques [25–28].

Our results highlight the importance of also considering the expected waiting time when listing a patient. This waiting time is highly variable from one country to another, and impacted by individual factors, such as height, blood group, history of sensitisation and sex [15, 29].

Since evolution of PAH can be unpredictable, several countries have implemented a priority allocation programme [14, 15]. In France, after 2 years of operating such a programme, the cumulative incidence of transplantation of PH patients increased from 48% to 76% ($p < 0.0001$), and the cumulative incidence of death or removal from the waiting list because of clinical worsening decreased from 39% to 13% ($p < 0.001$). If half of transplanted PH patients in our cohort benefited from priority listing, these high-urgency programmes cannot be the only answer to improve access to LT. They may have a negative impact on access to transplantation for “non-urgent” patients, especially in the case of graft shortages [30].

Finding the most equitable graft allocation system for PH patients remains an unresolved issue. In the USA, the allocation of transplants depends on an individual score, the lung composite allocation score, that has replaced the lung allocation score (LAS). Despite the revision of the LAS in 2015, PH patients still suffer a higher risk of death while waiting and a lower probability of transplantation [31]. To address this inequality, the Eurotransplant members (Germany, Netherlands, Belgium, Austria) added to the LAS a system of exceptional LAS (eLAS) [32]. Transplant centres can apply for an eLAS if a patient calculated LAS does not accurately reflect the urgency of transplantation. This system is different from the priority

programmes of France and the UK as only a low number of eLAS requests are approved. Between 2011 and 2019, 5183 LTs were performed in these countries with only 420 eLAS (44% of which were for PH) requests, of which only 28% were accepted [32].

Our results about access to transplant for PH patients are not specific to this disease. The annual rate of LT in the UK is one of the lowest in Europe, with 2.5 lung grafts/million inhabitants/year in 2019 compared to 6.0 in France [33]. To increase donation, the “opt-out” law, passed in 2020 in England, stipulates that anyone will be considered as having agreed to donate their own organs when they die, unless they record a decision not to donate [34]. Increasing the utilisation rate of donor lungs could be the biggest challenge. Between 2020 and 2021, only 13% of donor lungs meeting initial suitability criteria and offered for transplantation were finally transplanted, compared to 48% during the same period in France [1, 2]. Before the Covid-19 pandemic, between 2016 to 2019, the UK national lung utilisation rate was 26% compared to 54% in France [2, 35]. Facilitating the access to ECMO is another element to consider, given the high need of pre- and post-transplant ECMO in this population. ECMO is funded in France, as part of the transplant service, unlike in the UK where hospitals have to fund this procedure from within their existing budget. In the event of acute life-threatening deterioration, the choice between delisting and ECMO as a bridge to urgent transplant may be influenced by resource considerations, leading to a more selective use of this technique.

Our study has several limitations. One is that the French cohort is entirely within the time period that priority listing was available, whereas the UK cohort is split over a period before and after the priority scheme was implemented. We limited the impact of this difference by also comparing outcomes of French patients with those of UK patients who were listed from 2017. The fact that the UK data are more recent may have had an impact on the results. The shortage of transplants has indeed worsened in recent years, reducing patients’ access to transplantation. Another limitation is the quality of the data analysed. It limited a granular determination of the aetiology of PH and an exhaustivity in haemodynamic data, as the information was derived from the transplant registry data.

However, despite these limitations, our results highlight a significant disparity in access to LT between the UK and France for PH patients but also illustrate the complexity of managing this disease. Half of the patients in both countries were prioritised for transplantation, even though less than half of them were considered to be at high risk of death at the time of listing. Achieving equity for PH patients is a major challenge, as these patients still suffer from the lowest likelihood of transplant and the highest risk of death in many countries [31].

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