



Early View

Original article

Lung transplantation for sarcoidosis: outcome and prognostic factors

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LUNG TRANSPLANTATION FOR SARCOIDOSIS: OUTCOME AND PROGNOSTIC FACTORS

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Take home message

Posttransplant survival in patients with pulmonary sarcoidosis was similar to that in patients
with other indications for lung transplantation. The main factors associated with worse
survival were older age and extensive preoperative lung fibrosis.

Running head: Lung Transplantation in Sarcoidosis

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This article has an online data supplement.

Abstract

Study question: In patients with sarcoidosis, past and ongoing immunosuppressive regimens, recurrent disease in the transplant, and extrapulmonary involvement may affect outcomes of lung transplantation. We asked whether sarcoidosis lung phenotypes can be differentiated and, if so, how they relate to outcomes in patients with pulmonary sarcoidosis treated by lung transplantation.

Patients and methods: We retrospectively reviewed data from 112 patients who met international diagnostic criteria for sarcoidosis and underwent lung or heart-lung transplantation between 2006 and 2019 at 16 European centres.

Results: Patient survival was the main outcome measure. At transplantation, median age was 52 [46-59] years; 71 (64%) were male. Lung phenotypes were individualised as follows (i) extended fibrosis only; (ii) airflow obstruction; (iii) severe pulmonary hypertension (sPH) and airflow obstruction; (iv) sPH, airflow obstruction, and fibrosis, (v) sPH and fibrosis, (vi) airflow obstruction and fibrosis, (vii) sPH and (viii) none of these criteria, in 17%, 16%, 17%, 14%, 11%, 9%, 5% and 11% of patients, respectively. Posttransplant survival rates after 1, 3, and 5 years were 86%, 76%, and 69%, respectively. During follow-up (median, 46 [16-89] months), 31% of patients developed chronic lung allograft dysfunction. Age and extended lung fibrosis were associated with increased mortality. Pulmonary fibrosis predominating peripherally was associated with short-term complications.

Answer to the study question: Posttransplant survival in patients with pulmonary sarcoidosis was similar to that in patients with other indications for lung transplantation. The main factors associated with worse survival were older age and extensive preoperative lung fibrosis.

INTRODUCTION

Irreversible respiratory failure is a valid indication for lung transplantation (LTx) in selected patients with sarcoidosis(1). However, gaps in knowledge persist about lung transplantation in pulmonary sarcoidosis. While pre-transplantation lung abnormalities are usually typical in patients with pulmonary arterial hypertension, idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD), advanced pulmonary sarcoidosis appears more complex. Although many patients present with predominant pulmonary hypertension (PH), others may exhibit pulmonary fibrosis(2) which usually differs from the IPF pattern(3) and is often associated with airflow obstruction or a mixed ventilatory defect. Overlap between these profiles may occur. Moreover, severe bronchiectasis and granuloma recurrence in the grafted lung are common specific characteristics of sarcoidosis(4). Finally, organs other than the lungs may be involved by sarcoidosis, and most patients have a long history of treatment with glucocorticoids and other immunosuppressants.

Three large studies demonstrated that PH and pulmonary fibrosis involving more than 20% of the lungs by computed tomography (CT) were each independently associated with mortality(5-7). However, no quantitative models predicting short-term mortality in sarcoidosis are available, and pulmonary function tests (PFTs) may fail to reflect the clinical behaviour of the disease. In addition, overall posttransplant outcomes in sarcoidosis are unclear. Factors possibly associated with worse outcomes might include a higher prevalence of primary graft dysfunction(8) and more difficult surgical pleural dissection resulting in a higher risk of postoperative haemothorax(9). Although sarcoidosis itself has been claimed to independently predict mortality after LTx, some reports suggest similar long-term outcomes to those seen in other conditions(10-12). In a large cohort, median survival rates after LTx were similar in patients with and without sarcoidosis(1). Another report found no increase in

the occurrence of chronic lung allograft dysfunction (CLAD)(13). However, whether double LTx is preferable to single LTx is controversial and may depend on the underlying lung condition(1,14).

By conducting this retrospective international study, our primary objective was to determine whether pre-transplantation pulmonary sarcoidosis phenotypes could be differentiated based on the analysis of PFTs, haemodynamic parameters, and thoracic CT. Secondary objectives were to investigate LTx outcomes and to identify prognostic factors among pre-transplantation parameters including lung phenotypes.

METHODS

We conducted a retrospective study, which complied with the Declaration of Helsinki. French law requires neither ethics committee approval nor informed consent for studies of retrospective data; however, all data were anonymised and compiled as required by the *Commission Nationale de l'Informatique et des Libertés* (the French data protection authority). Anonymised data from other participating countries were obtained and reported as approved by local ethical and data protection authorities.

Only patients meeting previously reported diagnostic criteria for sarcoidosis were included.

Study design

We retrospectively reviewed the medical files of consecutive patients with sarcoidosis who underwent cadaveric heart-lung transplantation (HLT_x) or LT_x from 2006 to 2019 at 16 European centres. Only patients with available PFT, thoracic CT, and right-heart catheterisation data were included. We chose 2006 as the starting year for study inclusion

because during that year in France extracorporeal life support became widely used and the high-emergency lung-transplant allocation programme was started.

Collection of baseline data

The baseline data collected for the study and definition of PH are detailed in the online data supplement.

Pre-transplantation thoracic CT images of the chest were evaluated using the scoring method detailed in the online supplement.

Patient management

Details on patient management are available in the online data supplement.

Outcome measure

Patient survival was the outcome measure. Information on vital status was collected by each centre and was available for all patients. Survival analyses were performed in the overall population and in clinical subgroups defined by the extent of fibrosis ($>$ or \leq median value).

Statistical analysis

Baseline demographics were described as median with the 1st-3rd quartiles for continuous variables and as percentages for categorical variables. Baseline features were compared among groups using ANOVA, Fisher's exact test, or Kruskal-Wallis ANOVA depending on distribution and sample size. Survival was evaluated using the Kaplan-Meier method. Patients who underwent re-transplantation were censored at the re-transplantation date. Cox proportional hazards models were built for univariate and multivariate analyses of patient survival after verifying that the proportionality assumption was met. Independent predictors of patient survival were identified by building multivariate models using the

variables associated with p values ≤ 0.05 by univariate analysis and variables that showed statistically significant differences between subgroups in the descriptive analysis. Since the number of HLTx and single-lung transplant (single-LTx) recipients was very small, lung transplantation procedure was dropped from the analysis. In addition, due to missing values, ischemic time variables were also excluded from the analysis. For the univariate and multivariate analyses of continuous variables, estimations of the risk over time were described by their hazard ratios (HRs) with their 95% confidence intervals (95% CIs). Two-tailed p values < 0.05 were considered significant. No patients were lost to follow-up. All statistical analyses and graphics were performed using R v3.6.0 with the 'ggplot2', 'survival', 'cmprsk', and 'kmi' packages.

RESULTS

Patients

Between January 2006 and January 2019, 166 patients with pulmonary sarcoidosis underwent single-LTx, double-LTx, or HLTx at the 16 participating centres. We excluded the 54 patients for whom the following tests were missing: thoracic CT, $n=27$; right heart catheterisation, $n=26$; and/or PFT, $n=8$ (**Figure 1**). The remaining 112 patients met diagnostic criteria for pulmonary sarcoidosis and were included in the study. Among them, 3 underwent HLTx, 8 single-LTx and 101 double-LTx (Table 1).

Numbers of inclusions by centre were as follows: Hanover (Germany), $n=28$ (25%); Plessis Robinson (France), $n=18$ (16%); Copenhagen (Denmark), $n=10$ (9%); Oslo (Norway), $n=10$ (9%); Suresnes (France), $n=9$ (7%); Paris (France), $n=7$ (6%); Strasbourg (France), $n=7$ (6%); Brussels (Belgium), $n=4$ (4%); Gothenburg (Sweden), $n=3$ (3%); Leuven (Belgium),

n=3 (3%); Lyon (France), n=3 (3%); Madrid (Spain), n=3 (3%); Marseille (France), n=3 (3%); Bordeaux (France), n=2 (2%); Milan (Italy), n=1 (1%); Toulouse (France), n=1 (1%).

Supplemental Figure 3 reports the main differences between included and excluded patients.

Haemodynamics, lung function and thoracic CT characteristics

In our cohort, 110 (98%) patients had PH at the time of transplantation, including 53 (48%) with sPH. Although fibrosis and PH were present in most patients, we were able to individualise eight lung phenotypes (defining the pulmonary status at the time of transplantation), according to whether values were over or under thresholds. “Fibrosis” was thus defined as a thoracic CT fibrosis extent >7 , (the median value; see supplementary materials) and occurred in the ‘extended fibrosis only’ phenotype and in phenotypes combining fibrosis with other abnormalities. The ‘airflow obstruction phenotype’ was defined by a forced expired volume in 1 s /forced vital capacity <0.7 and the ‘sPH’ phenotype as mean pulmonary artery pressure ≥ 35 mm Hg or as mean pulmonary artery pressure ≥ 25 mm Hg with a cardiac index ≤ 2.0 L/min/m². The eight lung phenotypes were as follows: (i) extended fibrosis only; (ii) airflow obstruction; (iii) sPH and airflow obstruction; (iv) sPH, airflow obstruction, and fibrosis; (v) sPH and fibrosis; (vi) airflow obstruction and fibrosis; (vii) sPH and (viii) none of these criteria. These phenotypes occurred in 17%, 16%, 17%, 14%, 11%, 9%, 5% and 11% of the patients, respectively (**Figure 2**).

Survival analysis

Median follow-up was 43 [IQR, 15-68] months after LTx. At last follow-up, 76 patients were alive, 36 had died, and none were lost to follow-up. The 1-, 3-, and 5-year survival estimates were 86%, 76%, and 69%, respectively, with a median survival of 9.7 years

(Figure 3). In addition, survival rates at 1 year according to clinical phenotypes were significantly worse in the fibrosis phenotype (68%) compared to the other phenotypes, in which 1-year survival rates were above 83%. Moreover, although not significantly so, in-hospital mortality was higher in the fibrosis phenotype (**Table 1**).

Table 3 reports associations of selected variables with survival by univariate analysis. Age > median; preoperative extrathoracic sarcoidosis, more extensive preoperative fibrosis, the fibrosis phenotype, and the fibrosis plus obstructive phenotype were significantly associated with worse survival by univariate analysis. In the multivariate model, age > median, the fibrosis phenotype, and the fibrosis plus obstructive phenotypes were the only variables significantly associated with worse survival (**Table 4**).

Of note, overall survival rates between included and excluded patients were similar (Logrank, $p=0.30$).

Causes of death

During follow-up, 35 patients died. The main causes of death were CLAD (n=14) and infection (n=9). The other causes of death were bleeding (n=2), sudden death (n=2), multiple-organ failure (n=2), cancer (n=1), primary graft dysfunction (n=1) and other (n=3). The cause of death remained unknown in 1 patient. Of note, 3 patients underwent re-transplantation.

Post-transplant sarcoidosis complications

Among the 110 and the 88 patients with available information, 24 (22%) developed grade 3 primary graft dysfunction at 72 h and 16 (18%) developed haemothorax (**Table 1**). Patients with the extended fibrosis only and the sPH plus fibrosis phenotypes were at higher risk for primary graft dysfunction ($p=0.01$). A significantly higher rate of haemothorax was

found in patients with the isolated fibrosis phenotype (**Table 1**), which was associated with more honeycombing and fewer central masses (**Table 2**).

After transplantation, recurrence of pulmonary sarcoidosis defined by the presence of granulomas on transbronchial biopsies occurred in 11 (14%) patients, usually within 24 months (mean, 15; range, 2.3-67). Mean corticosteroid dosage at recurrence was 11 mg (range, 5-15 mg). In the 9 patients whose date of recurrence was known, sarcoidosis relapses occurred significantly less often after 2012 (2 of 72 patients) than in the early period (9 of 39 patients) ($p=0.02$).

DISCUSSION

Sarcoidosis is a systemic disorder of unknown cause that usually involves the lungs(15-17). A minority of patients progress to end-stage fibrocystic lung disease which represents the main cause of premature death (16). LTx can be performed for advanced irreversible disease refractory to medical therapy (18). Uncertainties persist regarding the presentation of end-stage sarcoidosis, post-LTx survival, and graft outcomes. Complicating factors are the recurring nature of the disease (19), presence in many patients of extrapulmonary involvement, occurrence of chronic lung infections (20), and paucity of published data(10,21,22). Here, we report a large international multicentre study of patients with end-stage pulmonary sarcoidosis. We classified patients into 8 lung phenotypes at the time of transplantation. The phenotypes were differentiated based on findings from right heart catheterisation, thoracic CT, and PFTs. The main distinguishing features were fibrosis extent, presence of sPH, and airflow obstruction. Survival after LTx or HLTx was 69% after 5 years, which is in line with other indications of LTx/HLTx. The main predictors of poorer survival

were age > median and more extensive pre-operative lung fibrosis on CT. Of note, pretransplant haemodynamic parameters were not significantly associated with posttransplant survival.

Our study enabled us to accurately classify all the patients into phenotypes. Although most patients had fibrosis and sPH, eight distinct lung phenotypes emerged. Among them, extended fibrosis only was associated with a higher rate of early post-transplant complications including primary graft dysfunction and haemothorax, as well as with higher early mortality.

Unexpectedly, older age at the time of transplantation was also associated with a worse outcome.

The largest published cohort includes 695 patients with LTx representing 3.3% of LTx recipients enrolled in a US registry(1). Only limited information is available on pretransplant lung phenotypes. Median survival rates were similar to those in the LTX recipients without sarcoidosis(1). Interestingly, our study shows a favourable posttransplant outcome in patients with sarcoidosis, with a median survival of 9.7 years. In patients in a European scleroderma registry(23) who underwent LTx for interstitial lung disease and PH and were of comparable age, survival rates were similar, with 1-, 3-, and 5-year survival estimates of 79%, 75% and 71% respectively. In IPF, median survival barely exceeded 5 years(24) and multiple complicating factors, including older age and tobacco exposure, were common(25).

A striking finding from our study is that more extensive pre-operative pulmonary fibrosis was associated with poorer survival. In addition, extensive fibrosis as an isolated lung phenotype ~~or combined with sPH~~ was predominantly associated with early mortality. Furthermore, this phenotype was associated with significantly higher rates of primary graft dysfunction and ~~a trend towards higher rates~~ haemothorax, two events that can affect early survival and possibly long-term survival. End-stage fibrotic sarcoidosis may raise challenges during pleural dissection, thereby increasing the risk of post-operative haemothorax(9).

Phenotypes including extensive fibrosis had more peripheral fibrosis with more honeycombing and fewer central masses. Haemothorax occurred in 16 (18%) patients, in keeping with an earlier study (25%(9)). Haemothorax may result in fewer ventilator-free days and longer ICU and hospital stays after LTx. Explanting lungs can be extremely challenging due to pleural adhesions with substantial intraoperative bleeding(26). Pleural adhesions at the upper thoracic cavity in end-stage sarcoidosis may be largely driven by inflammatory/fibrotic remodelling consecutive to granulomatous involvement of the visceral pleura. Fibrovascular pleural adhesions were shown to be vascularised by systemic arteries originating from the intercostal arteries (bronchial arteries for the visceral pleura(27,28). The haemorrhagic complications seen in our patients may be related to such regional remodelling. A 2014 meta-analysis involving 10,042 LTx recipients, including 98 with sarcoidosis, showed that sarcoidosis was an independent risk factor for primary graft dysfunction(8). Fifty per cent of sarcoidosis patients experienced primary graft dysfunction. In our study, primary graft dysfunction occurred in 22% of the patients. Difficult dissection is associated with a longer ischaemic time, which has been shown to be related to the risk of primary graft dysfunction(29). In addition, sPH is a risk factor for primary graft dysfunction(30).

Of note, and perhaps due to the limited available data, chronic pulmonary aspergillosis was not associated with outcomes.

Sarcoidosis affects the pulmonary arterial and venous vasculature and may lead to PH by multiple mechanisms(2), including interactions between the pulmonary vasculature and the parenchymal, mediastinal, and cardiovascular compartments. Pulmonary arterial pressure elevation may be due to granulomatous pulmonary vessel involvement or may occur as an indirect consequence of advanced parenchymal destruction or compressive mediastinal infiltration(2). In our cohort, 110 (98%) patients had PH, including 48% with sPH. Patients with sPH were more likely to have airflow obstruction or a mixed PFT defect, and a

significant correlation linked PFT results to DLCO and pulmonary arterial pressure. They more frequently had a history of smoking and emphysema. In addition, sPH patients had more central masses (data not shown). However, haemodynamic parameters were not associated with impaired post-transplant survival. This result contrasts with IPF waiting-list patients, among whom up to 85% have PH(31), which increases the risk of primary graft dysfunction and early postoperative mortality(32).

Posttransplant recurrence in lung allografts, originating from the recipient(33), affects up to 35% of patient(34). Most recurrences are detected by post-transplant monitoring bronchoscopies(35,36). In our study, recurrence of sarcoidosis in the allograft occurred in 11 (14%) patients, among whom 5 developed CLAD. A case has been reported of sarcoid recurrence after single-LTx, necessitating repeat transplantation, which was followed again by sarcoid recurrence(37). This report supports bilateral LTx, which provides a greater functional reserve in case of disease recurrence compared to single-LTx, and also prevents additional infections due to persistent bronchiectasis. The decreased occurrence of sarcoidosis relapses from 2013 onwards suggests a role for mTOR inhibitors, which became more widely used to prevent rejection at about this date and which might inhibit granuloma formation via mTOR inhibitor properties(38,39). In addition, the possibility that the switch from cyclosporin to tacrolimus in the early 2010s might be implicated in the decreased incidence of relapses has been suggested but remains at present merely a hypothesis that requires further evaluation. ~~However, this hypothesis needs further investigation before any recommendation can be made.~~

Two patients experienced sudden death, suggesting, among other hypotheses, potential sub-clinical myocardial sarcoid involvement. This hypothesis supports the need for both a rigorous work-up to exclude myocardial involvement during the listing evaluation and for

routine serial monitoring for involvement of the heart and other organs by sarcoidosis after LTx.

The general applicability of our findings deserves discussion. Only 112 of 166 screened patients were included, with selection bias towards greater disease severity requiring a more extensive work-up. However, the survival analyses in the screened vs. the included patients were not significantly different (data not shown). Furthermore, our study involved 16 European transplantation centres. Conceivably, the overall transplantation activity or the number of sarcoidosis patients included by each centre may have affected the results. However, all centres performed more than 20 surgical LTx a year. In addition, in our statistical model, we tested the number of included patients and found no effect on outcome (data not shown). Furthermore, although our main results suggest a potential role for peripheral fibrosis on early outcomes, we were not able to include pleural thickening in the CT categorisation, because no standardised CT criteria for pleural thickening in pulmonary sarcoidosis exist, except in the case of coexistent chronic pulmonary aspergillosis. In addition, although deconditioning at the time of transplantation is a crucial consideration, our study design did not allow us to include this parameter in our analysis. Last, there might be a bias towards double-lung transplantation, which was performed in 98% of the 103 patients treated with LTx. The higher prevalence of PH in transplant candidates with sarcoidosis, the risk of infection related to the high frequency of clinically significant bronchiectasis of the remaining lung in the event of single-LTx, and the greater parenchymal reserve offered by double-LTx in case of disease recurrence may explain this preference for double-LTx. In patients with idiopathic fibrosis, although the proportion of patients receiving double-LTx has increased over time, it was only 61% in the ISHLT database through June 2018(40). ~~in the charts used for the study, prescriptions of anti-rejection molecules were not recorded. Therefore, the possibility that the switch from cyclosporin to tacrolimus in the early 2010s might be~~

~~implicated in the decreased incidence of relapses is merely a hypothesis that requires evaluation.~~

In conclusion, our study adds valuable evidence that LTx for end-stage pulmonary sarcoidosis is associated with favourable outcomes. Pretransplant lung phenotyping allowed us to identify eight distinct clinical profiles. Among them, extensive fibrosis was associated with the poorest survival, the most likely mechanism being difficult pleural dissection with a higher risk of haemothorax and primary graft dysfunction. Patients with extensive fibrosis should therefore be referred to high-volume centres.

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CAPTIONS

Figure 1. Flow chart of the retrospective review of patients who underwent lung or heart-lung transplantation for sarcoidosis between 2006 and 2019 at 16 European centres.

PFT, pulmonary function tests; RHC, right heart catheterisation; CT, computed tomography

Figure 2: Distribution of lung phenotypes according to the presence of severe pulmonary hypertension, obstructive ventilatory defect, and fibrosis extent by high-resolution computed tomography. Lung phenotypes were defined according to the presence of measurement values over thresholds defining predominant patterns. Clinical phenotypes were (i) extended fibrosis only, if fibrosis extent on thoracic HRCT > 7 , i.e., the median value; (ii) airflow obstruction when there was an obstructive ventilatory defect defined by forced expired volume in 1 s /forced vital capacity < 0.7 ; (iii) airflow obstruction combined with severe pulmonary hypertension (sPH) defined as follows: mean pulmonary artery pressure ≥ 35 mm Hg or as mean pulmonary artery pressure ≥ 25 mm Hg plus cardiac index ≤ 2.0 L/min/m²; (iv) sPH, airflow obstruction, and fibrosis; (v) sPH and fibrosis; (vi) airflow obstruction and fibrosis; (vii) sPH; and (viii) none of these criteria. These phenotypes were found in 17%, 16%, 17%, 14%, 11%, 9%, 5% and 11% of our patients, respectively. To improve readability, the dimensions are not strictly proportional.

Figure 3: Kaplan-Meier survival estimates from the date of transplantation in the overall population of 112 patients. Survival rates were 86%, 76%, and 69% at 1, 3, and 5 years, respectively.

Tables

Table 1: Main features of the overall population according to lung phenotypes[#]

	Overall n = 112	Fibrosis n = 19	Airflow obstruction n = 18	sPH* Airflow obstruction, n = 19	sPH* Airflow obstruction Fibrosis n = 16	sPH* Fibrosis n = 12	Airflow obstruction Fibrosis n = 10	sPH* n = 6	None n = 12	P* value
Male, n (%)	71 (64)	11 (58)	11 (61)	12 (63)	14 (87)	7 (58)	6 (60)	4 (67)	6 (50)	0.62
Recipient age, med [IQR]	52 [46 - 59]	53 [48 - 60]	53 [49 - 59]	49 [45 - 54]	56 [52 - 60]	51 [47 - 57]	52 [42 - 61]	47 [41 - 57]	51 [45 - 54]	0.42
Body mass index, kg/m ² med [IQR]	23 [20 - 26]	24 [20 - 28]	25 [20 - 27]	23 [19 - 25]	21 [20 - 22]	24 [20 - 26]	21 [19 - 26]	23 [21 - 25]	20 [17 - 25]	0.65
Caucasian, n (%)	92 (82)	15 (79)	16 (89)	15 (79)	15 (94)	10 (83)	8 (80)	3 (50)	10 (83)	0.49
Smoker, med [IQR]	6 [0 - 19]	4 [0 - 20]	10 [0 - 15]	7 [0 - 19]	10 [10 - 35]	5 [0 - 30]	7 [2 - 10]	0 [0 - 5]	10 [0 - 20]	0.54
Extrathoracic sarcoidosis, 0/1/2/3, n (%)	90 (80)/20 (18) / 1 (1)/1 (1)	15 (79)/3 (16)/0/1 (5)	16 (89)/2 (11)/0/0	17 (89)/2 (11)/0/0	14 (87) / 2 (13) / 0/0	8 (67)/4 (33)/0/0	5 (50)/4 (40)/0/1 (10)	6 (100) / 0/0/0	9 (75)/3 (25)/0/0	0.24
History of pulmonary aspergillosis, n (%), n / 94	18 (19)	2 (13)	2 (13)	4 (25)	2 (13)	4 (44)	1 (11)	0	3 (27)	0.46
Blood group, O/A/B/AB, %	39 / 44 / 16 / 1	42 / 58 / 0 / 0	22 / 50 / 28 / 0	63 / 21 / 16 / 0	56 / 31 / 13 / 0	33 / 50 / 17 / 0	30 / 40 / 30 / 0	17 / 50 / 17 / 16	25 / 59 / 16 / 0	0.11
Lung transplantation delay, d, med [IQR]	92 [27 - 299]	86 [18 - 279]	84 [39 - 396]	113 [27 - 261]	73 [20 - 330]	103 [4 - 463]	90 [69 - 194]	67 [29 - 182]	151 [56 - 419]	0.98
Lung transplantation procedure DLT/HLT/SLT, n (%)	101 (90) / 3 (3) / 8 (6)	17 (89) / 0 / 2 (11)	16 (90) / 0 / 2 (10)	18 (95) / 0 / 1 (5)	14 (88) / 1 (6) / 1 (6)	11 (92) / 0 / 1 (8)	8 (80) / 1 (10) / 1 (10)	6 (100) / 0 / 0	11 (92) / 1 (8) / 0	0.90
High-emergency transplant programme, n (%)	17 (15)	3 (16)	2 (11)	5 (26)	2 (12)	3 (25)	0	1 (17)	1 (8)	0.64
Cardiopulmonary bypass, n (%), n / 108	54 (50)	8 (44)	9 (56)	10 (52)	7 (44)	5 (42)	7 (70)	2 (34)	6 (50)	0.90
Right ischaemic time, min, med [IQR], n / 59	300 [240 - 372]	378 [270 - 420]	300 [240 - 309]	348 [240 - 360]	240 [183 - 247]	360 [280 - 372]	327 [255 - 360]	280 [220 - 354]	210 [180 - 279]	0.11
Left ischaemic time, min, med [IQR], n / 44	360 [300 - 395]	377 [300 - 514]	390 [360 - 585]	277 [221 - 300]	450 [420 - 480]	330 [282 - 372]	345 [318 - 360]	318 [229 - 355]	402 [330 - 405]	0.07
Induction, n (%), n / 83	28 (34)	7 (47)	1 (8)	4 (27)	4 (33)	4 (50)	3 (37)	3 (100)	2 (20)	0.08
Dialysis during intensive care unit stay n (%), n / 100	14 (14)	3 (16)	1 (7)	3 (17)	2 (15)	2 (18)	2 (22)	1 (25)	0	0.73
Primary graft dysfunction score Grade 3 at 72 hours, n (%), n / 110	24 (22)	6 (33)	4 (22)	4 (21)	0	7 (58)	1 (10)	0	2 (17)	0.01
Ventilation time during intensive care unit stay, med [IQR], n / 108	2 [1 - 19]	6 [1 - 26]	1 [0 - 3]	4 [1 - 22]	1 [0 - 4]	21 [1 - 28]	3 [2 - 11]	1 [1 - 13]	1 [1 - 6]	0.16
Haemothorax, n (%), n / 88	16 (18)	6 (35)	1 (7)	1 (7)	0	2 (17)	2 (22)	1 (20)	3 (25)	0.01
Pulmonary sarcoidosis recurrence, n (%), n / 81	11 (14)	1 (7)	2 (15)	2 (21)	0	0	4 (44)	0	0	0.09
Chronic lung allograft dysfunction at last follow-up, n (%), n / 106	33 (31)	3 (18)	6 (33)	6 (32)	6 (37)	3 (30)	4 (44)	1 (20)	4 (33)	0.90
In-hospital mortality, n(%)	18 (16)	7 (37)	2 (11)	2 (11)	3 (19)	2 (17)	1 (10)	1 (20)	0	0.25
Retransplantation, n (%)	4 (3)	0	1 (4)	1 (5)	1 (6)	1 (8)	0	0	0	0.78

Lung phenotypes were defined according to the presence of measurement values over thresholds defining predominant patterns. Lung phenotypes were (i) extended fibrosis only, if fibrosis extent on thoracic HRCT >7 (the median value); (ii) airflow obstruction if there was an obstructive ventilatory defect defined by forced expiratory volume in 1 s /forced vital capacity <0.7; (iii) airflow obstruction combined with severe pulmonary hypertension (sPH) defined as mean pulmonary artery pressure ≥ 35 mm Hg or as mean pulmonary artery pressure ≥ 25 mm Hg plus cardiac index ≤ 2.0 L/min/m²; (iv) sPH, airflow obstruction, and fibrosis; (v) sPH and fibrosis; (vi) airflow obstruction and fibrosis; (vii) sPH; and (viii) none of these criteria. These phenotypes were found in 17%, 16%, 17%, 14%, 11%, 9%, 5% and 11% of our patients, respectively (See Figure 2).

* sPH, severe pulmonary hypertension defined as mean pulmonary artery pressure ≥ 35 mm Hg or as mean pulmonary artery pressure ≥ 25 mm Hg plus cardiac index ≤ 2.0 L/min/m²

** Comparison between clinical phenotype subgroups

Table 2: Haemodynamics, lung function test results, and thoracic CT findings[#]

	Overall n = 112	Fibrosis n = 19	Airflow obstruction n = 18	sPH* Airflow obstruction, n = 19	sPH* Airflow obstruction Fibrosis n = 16	sPH* Fibrosis n = 12	Airflow obstruction Fibrosis n = 10	sPH* n = 6	None n = 12	P**
World Health Organisation functional class III/IV, n (%) n / 104	54 (52) / 47 (45)	12 (67) / 4 (22)	9 (50) / 4 (36)	5 (28) / 6 (40)	9 (60) / 6 (40)	5 (45) / 6 (55)	5 (62) / 3 (38)	2 (40) / 3 (60)	7 (63) / 4 (36)	0.34
6-minute walk test, m, n / 97	300 [228 – 370]	300 [228 – 375]	285 [260 – 381]	270 [177 – 360]	266 [228 – 330]	307 [230 – 360]	321 [235 – 374]	197 [152 – 295]	323 [200 – 350]	0.79
Lung function tests										
Forced vital capacity (% predicted)	40 [33 – 47]	36 [30– 40]	39 [36 – 41]	42 [36 – 47]	47 [41 – 57]	47 [30 – 68]	34 [32 – 36]	63 [57 – 87]	32 [24 – 40]	<0.01
Forced expired volume in 1 s (% predicted)	31 [23 – 42]	34 [30 – 49]	23 [20 – 26]	24 [18 – 30]	33 [28 – 41]	52 [31 – 66]	23 [19 – 38]	61 [58 – 73]	33 [24 – 38]	<0.01
Forced expired volume in 1 s /Forced vital capacity	65 [45 – 80]	81 [74 – 93]	49 [40 – 65]	40 [32 – 57]	59 [43 – 62]	80 [75 – 83]	58 [45 – 65]	82 [79 – 90]	87 [81 – 91]	<0.01
Total lung capacity (% predicted)	60 [49 – 88]	43 [36 – 50]	95 [80 – 110]	89 [73 – 99]	79 [57 – 79]	59 [53 – 61]	91 [74 – 100]	59 [53 – 78]	45 [34 – 68]	<0.01
Diffusing capacity for carbon monoxide (% predicted)	30 [23 – 40]	29 [25 – 32]	43 [32 – 50]	34 [30 – 46]	25 [16 – 30]	19 [14 – 29]	30 [23 – 49]	26 [18 – 33]	28 [22 – 28]	<0.01
PaO ₂ , mm Hg	61 [52 – 68]	57 [44 – 60]	70 [65 – 82]	60 [55 – 68]	57 [50 – 61]	57 [51 – 71]	56 [52 – 62]	54 [45 – 66]	70 [66 – 72]	<0.01
PaCO ₂ , mm Hg	44 [37 – 49]	48 [44 – 52]	44 [41 – 49]	45 [38 – 53]	41 [25 – 44]	36 [30 – 42]	46 [37 – 51]	38 [33 – 44]	43 [38 – 49]	0.07
Right heart catheterisation										
Right atrial pressure, mm Hg	6 [4 – 9]	3 [1 – 7]	5 [4 – 8]	8 [5 – 15]	5 [5 – 11]	7 [6 – 8]	3 [0 – 5]	13 [8 – 17]	5 [2 – 5]	<0.01
Mean pulmonary artery pressure, mm Hg	25 [19 – 33]	24 [19 – 29]	29 [26 – 32]	44 [40 – 51]	45 [41 – 46]	46 [41 – 54]	26 [19 – 29]	44 [43 – 45]	20 [19 – 26]	<0.01
Pulmonary capillary wedge pressure, mm Hg	9 [7 – 11]	6 [3 – 9]	9 [7 – 11]	9 [7 – 15]	9 [8 – 11]	10 [8 – 15]	10 [6 – 10]	10 [6 – 13]	9 [8 – 10]	0.11
Cardiac index, litres/minute/m ²	3.0 [2.5 – 3.4]	3.3 [2.6 – 3.6]	3.2 [2.7 – 3.7]	2.9 [2.3 – 3.2]	2.6 [1.8 – 3.0]	2.9 [2.3 – 3.2]	3.2 [2.8 – 3.5]	2.8 [2.3 – 3.3]	3.2 [2.8 – 4.2]	0.12
Pulmonary vascular resistance, WU	4.0 [3.2 – 4.3]	2.8 [2.1 – 3.9]	4.0 [3.2 – 4.4]	6.7 [5.2 – 8.7]	7.8 [6.8 – 9.8]	7.1 [4.5 – 8.5]	2.9 [1.9 – 4.3]	6.4 [4.1 – 10.0]	3.1 [2.2 – 5.0]	<0.01
Thoracic computed tomography										
Pulmonary artery diameter /Aorta diameter, med [IQR]	1.1 [1.0-1.3]	1.1 [1.0-1.1]	1.3 [1.1-1.5]	1.2 [1.0-1.5]	1.2 [1.1-1.2]	1.2 [0.9-1.3]	1.2 [1.1-1.2]	1.2 [1.2-1.3]	1.1 [0.8-1.1]	0.11
Extent of fibrosis, med [IQR]	7 [3-11]	10 [9-14]	3 [3-4]	4 [3-5]	11 [9-13]	12 [10-16]	9 [7-12]	3 [1-5]	4 [1-5]	<0.01
Reticulation	3 [1-5]	6 [4-8]	1 [0-2]	1 [0-2]	4 [3-5]	4 [3-6]	3 [2-3]	0 [0-3]	1 [0-3]	<0.01
Honeycombing	0 [0-2]	2 [0-4]	0 [0-0]	0 [0-0]	1 [0-2]	2 [0-3]	1 [0-1]	0 [0-0]	0 [0-0]	<0.01
Bronchiectasis	3 [0-5]	3 [2-6]	2 [0-3]	2 [1-3]	5 [3-5]	5 [4-6]	5 [4-8]	1 [1-3]	1 [0-3]	<0.01
Extent of ground-glass opacities, med [IQR]	1 [0-3]	2 [0-4]	0 [0-2]	1 [0-3]	1 [1-4]	2 [0-4]	0 [0-3]	3 [1-4]	2 [0-4]	0.11
Extent of emphysema, med [IQR]	4 [0-6]	2 [0-6]	5 [3-8]	5 [3-8]	5 [1-8]	2 [1-4]	6 [0-7]	3 [1-4]	2 [0-4]	0.20
Extent of central masses, med [IQR]	1 [0-2]	0 [0-1]	1 [0-3]	1 [0-4]	1 [1-2]	0 [0-1]	0 [0-0]	0 [0-4]	0 [0-2]	0.09
Cavity containing solid material, n(%), n / 55	8 (14)	0	0	3 (37)	1 (12)	1 (12)	1 (12)	1 (17)	1 (20)	0.44

[#] See supplementary materials where the scoring system is detailed

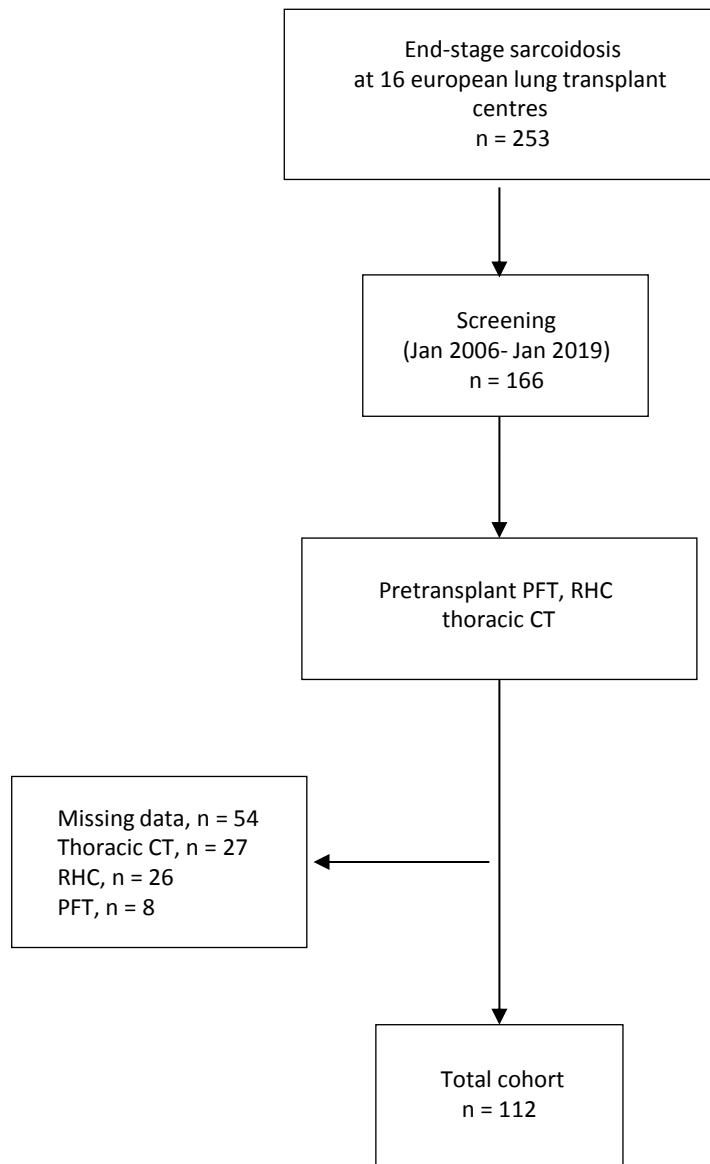
*sPH, severe pulmonary hypertension defined as mean pulmonary artery pressure ≥ 35 mm Hg or as mean pulmonary artery pressure ≥ 25 mm Hg plus cardiac index ≤ 2.0 L/min/m²

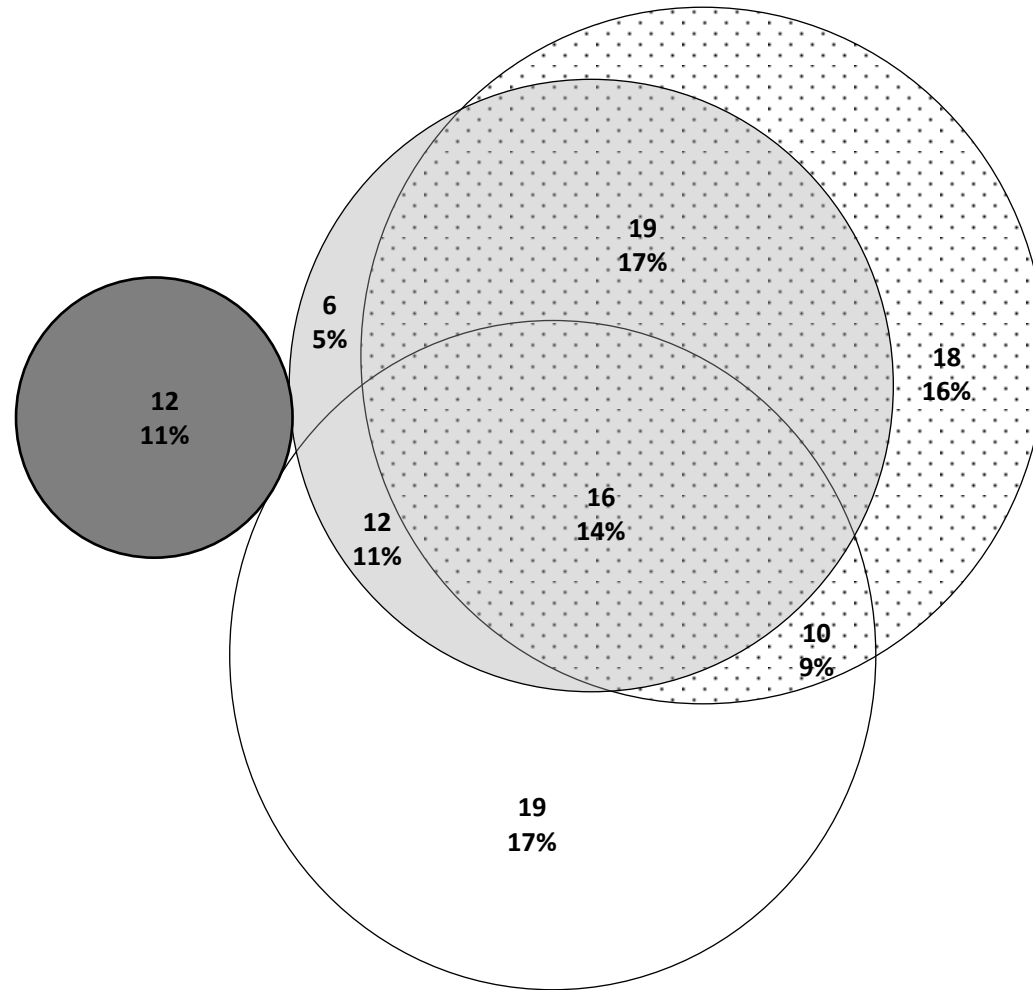
** comparison between clinical phenotype subgroups





Table 3: Univariate and multivariate analyses of factors associated with survival

	Reference	Modality	Univariate			Reference	Modality	Multivariate		
			HR	95%CI	P value			HR	95%CI	P value
Age at lung transplant > 50 y	No	Yes	2.21	1.06 – 4.60	0.03			2.38	1.13 – 5.00	0.02
Gender	Male	Female	0.74	0.31 – 1.52	0.42					
Caucasian	No	Yes	0.69	0.31 – 1.52	0.35					
Body mass index		Continuous	1.06	0.98 – 1.14	0.18					
Smoker	No	Yes	0.69	0.34 – 1.39	0.29					
CMV D positive/R negative	No	Yes	1.97	0.92 – 4.23	0.08					
Blood group A	No	Yes	1.60	0.83 – 3.09	0.16					
Blood group O	No	Yes	0.66	0.33 – 1.33	0.25					
Extrathoracic sarcoidosis	No	Yes	2.16	1.08 – 4.37	0.04			1.66	0.75 – 3.67	0.21
WHO functional class III-IV	No	Yes	0.97	0.20 – 1.57	0.45					
Six-minute walking distance (n = 97)		Continuous	1.00	1.00 – 1.00	0.94					
Forced vital capacity		Continuous	0.96	0.94 – 1.19	0.11					
Forced expiratory volume in one second		Continuous	0.65	0.45 – 1.06	0.10					
Forced expiratory volume in one second / Forced vital capacity <0.7	No	Yes	1.00	0.98 – 1.02	0.96					
Total lung capacity		Continuous	1.00	0.98 – 1.01	0.86					
Diffusing capacity for carbon monoxide		Continuous	1.00	0.96 – 1.04	0.89					
PaO2		Continuous	0.98	0.95 – 1.01	0.19					
PaCO2		Continuous	1.03	1.00 – 1.06	0.08					
Right atrial pressure		Continuous	1.02	0.95 – 1.09	0.59					
Pulmonary wedge pressure		Continuous	0.95	0.87 – 1.05	0.32					
Mean pulmonary arterial pressure		Continuous	0.98	0.94 – 1.03	0.16					
Cardiac index		Continuous	1.32	0.93 – 1.89	0.12					
Pulmonary artery diameter /Aorta diameter		Continuous	0.82	0.29 – 2.38	0.97					
Extent of ground-glass opacities		Continuous	1.01	0.88 – 1.16	0.86					
Extent of emphysema,		Continuous	1.03	0.95 – 1.13	0.39					
Extent of central masses		Continuous	1.05	0.89 – 1.24	0.53					
Extent of fibrosis		Continuous	1.03	0.98 – 1.09	0.20					
Cavity containing solid material	No	Yes	0.54	0.12 – 2.35	0.41					
High-emergency transplant programme	No	Yes	0.51	0.16 – 1.68	0.27					
Ischaemic time right, n / 59		Continuous	1.00	1.00 – 1.00	0.47					
Ischaemic time left, n / 44		Continuous	1.00	1.00 – 1.00	0.83					
Induction, n / 83	No	Yes	1.83	0.84 – 3.99	0.13					
Posttransplant thoracotomy for bleeding	No	Yes	1.30	0.58 – 2.90	0.53					
Primary graft dysfunction grade 3 at 72 hours	No	Yes	1.19	0.24 – 2.54	0.66					
Haemothorax	No	Yes	0.79	0.28 – 2.25	0.28					
Lung phenotypes*										
Fibrosis	None	Yes	10.81	1.38 – 84.81	0.05	None	Yes	10.72	1.36 – 84.28	0.01
Fibrosis Airflow obstruction	None	Yes	9.07	1.09 – 75.49	0.05	None	Yes	5.66	0.65 – 49.22	0.12
Airflow obstruction	None	Yes	5.96	0.71 – 49.64	0.10	None	Yes	6.20	0.73 – 52.84	0.10
sPH Fibrosis	None	Yes	2.74	0.25 – 30.34	0.41	None	Yes	2.26	0.20 – 25.10	0.51
sPH Airflow obstruction	None	Yes	3.06	0.36 – 26.29	0.31	None	Yes	4.05	0.46 – 35.71	0.21
sPH Airflow obstruction Fibrosis	None	Yes	3.67	0.41 – 32.97	0.24	None	Yes	3.17	0.35 – 28.97	0.31
sPH	None	Yes	5.47	0.49 – 60.57	0.22	None	Yes	8.90	0.78 – 101.52	0.09

* Lung phenotypes were defined according to the presence of measurement values over thresholds defining predominant patterns. Lung phenotypes were (i) extended fibrosis only, if fibrosis extent on thoracic HRCT >7 (the median value); (ii) airflow obstruction if there was an obstructive ventilatory defect defined by forced expiratory volume in 1 s /forced vital capacity <0.7 ; (iii) airflow obstruction combined with severe pulmonary hypertension (sPH) defined as mean pulmonary artery pressure ≥ 35 mm Hg or as mean pulmonary artery pressure ≥ 25 mm Hg plus cardiac index ≤ 2.0 L/min/m²; (iv) sPH, airflow obstruction, and fibrosis; (v) sPH and fibrosis; (vi) airflow obstruction and fibrosis; (vii) sPH; and (viii) none of these criteria. These phenotypes were found in 17%, 16%, 17%, 14%, 11%, 9%, 5% and 11% of our patients, respectively (See Figure 2).

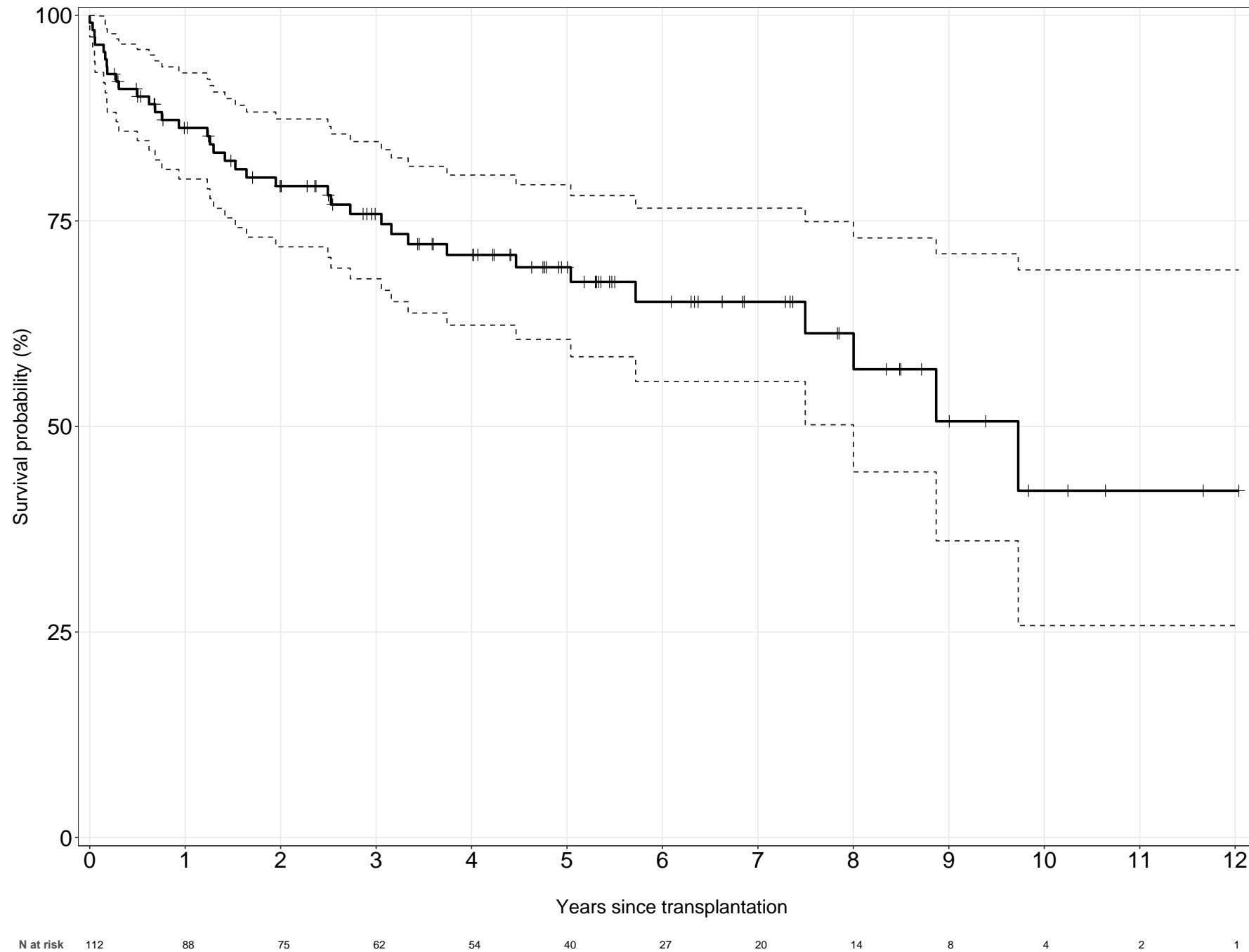




-  Fibrosis
-  Airflow obstruction
-  Severe pulmonary hypertension
-  None

Overall survival

Figure 3



Supplementary appendix

Collection of baseline data

We used standardised forms to record the following information: demographic data; medical history, including age at sarcoidosis onset; physical findings; World Health Organisation functional class; routine blood test results; 6-minute walking distance(1); and most recent PFT results before lung transplantation including forced vital capacity (FVC), forced (2) expiratory volume in 1 s (FEV1), and diffusing capacity for carbon monoxide (DLCO), measured according to established protocols and reported as percent of predicted values.

PH was sought during right heart catheterisation and defined as mean pulmonary artery pressure >20 mm Hg, pulmonary capillary wedge pressure ≤ 15 mm Hg, and pulmonary vascular resistance >3 WU in the absence of other known causes of PH (3). Severe PH (sPH) was defined as follow: mean pulmonary artery pressure ≥ 35 mm Hg or as mean pulmonary artery pressure ≥ 25 mm Hg with a cardiac index ≤ 2.0 L/min/m²(4).

Thoracic CT protocol and review

All patients were scanned in the supine position from the lung apices to the lung bases at full suspended inspiration using standard exposure parameters (90 mA and 120kVp). All images were anonymised and reviewed independently by two thoracic radiologists or one thoracic radiologist and one pulmonologist working independently of each other and using standard window settings for lung parenchyma visualisation.

The readers had no knowledge of pulmonary function data or other clinical indicators of disease severity. The presence and extent of the following patterns, based on the Fleischner Society's glossary of terms for thoracic imaging (5) with some minor modifications were

Patient management

Most of the patients with sPH were transplanted with intraoperative veno-arterial ECMO. ECMO was switched prophylactically from its central location to peripheral cannulation after implantation of the lungs. Patients were cannulated in the groin, and the ECMO device used intraoperatively was connected. A Swan-Ganz catheter and transthoracic echocardiography were used to measure pulmonary artery pressures, assess cardiac function, and monitor the adequacy of fluid management and adrenergic support. ECMO flow was kept at a low level, usually about half the normal cardiac output. ECMO remained in place until the patients were haemodynamically stable and had normal chest X-ray findings, adequate oxygenation (fraction of inspired oxygen <0.5), a low ventilation pattern and, most importantly, a normal fluid balance, i.e., removal of the excessive fluid load (no oedema or ascites).

Primary graft dysfunction (PGD) grade was assessed prospectively, using the International Society for Heart and Lung Transplantation criteria, defined by the Pa_{O_2}/Fi_{O_2} ratio and the presence of infiltrates within the allograft or allografts (7).

Post-transplantation immunosuppression and induction therapy were given according to local guidelines at each centre. All patients received life-long *Pneumocystis jirovecii* pneumonia prophylaxis with cotrimoxazole. Valganciclovir for cytomegalovirus prophylaxis was given according to local guidelines. Monitoring transbronchial biopsies were obtained routinely or as clinically indicated depending on the standard protocol at each centre. Patients with allograft dysfunction were investigated for acute cellular rejection, lymphocytic bronchiolitis/neutrophilic reversible allograft dysfunction, and airway injury caused by infection/colonisation. CLAD was diagnosed based on international criteria when FEV_1 and/or FVC declined to $\leq 80\%$ of the best postoperative value (8) during routine outpatient assessments after a minimum of 3 months post-lung transplantation. Comprehensive PFTs

including spirometry and lung volume measurements, HRCT of the chest, and bronchoscopy with bronchoalveolar lavage and transbronchial biopsy were performed to look for causes of lung allograft dysfunction, including persistent acute rejection, azithromycin-responsive allograft dysfunction, infection, anastomotic stricture, and sarcoidosis recurrence.

Figure 3: Main features of the overall population according to inclusion/exclusion status

	Overall n = 166	Included n = 112	Excluded n = 54	P* value
Male, n (%)	102 (61)	71 (64)	31 (57)	0.57
Recipient age, med [IQR]	51 [44 - 57]	52 [46 - 59]	46 [40 - 53]	<0.01
Body mass index, kg/m ² med [IQR]	22 [20 - 26]	23 [20 - 26]	22 [16 - 34]	0.51
Caucasian, n (%)	141 (85)	92 (82)	49 (91)	0.49
Smoker, med [IQR]	5 [0 - 18]	6 [0 - 19]	1.5 [0 - 16]	0.26
Extrathoracic sarcoidosis, 0/1/2/3, n (%) n/165	137 (83)/26 (15) /1 (1)/1 (1)	90 (80)/20 (18) /1 (1)/1 (1)	47 (89)/6 (11)/0/0	0.71
History of pulmonary aspergillosis, n (%), n / 155	25 (18)	18 (19)	7 (16)	0.87
Blood group, O/A/B/AB, %	40 / 43 / 14 / 3	39 / 44 / 16 / 1	43 / 43 / 11 / 3	0.54
Lung transplantation delay, d, med [IQR]	88 [25 - 283]	92 [27 - 299]	76 [19 - 245]	0.29
Lung transplantation procedure DLT/HLT/SLT, n (%)	139 (84) / 6 (4) / 21 (12)	101 (90) / 3 (3) / 8 (6)	38 (70) / 3 (6) / 13 (24)	0.04
High-emergency transplant programme, n (%)	27 (16)	17 (15)	10 (19)	0.74
Cardiopulmonary bypass, n (%), n / 161	71 (44)	54 (50)	17 (33)	0.07
Right ischaemic time, min, med [IQR], n / 86	288 [238 – 378]	300 [240 – 372]	285 [204 – 390]	0.69
Left ischaemic time, min, med [IQR], n / 65	360 [300 – 401]	360 [300 – 395]	376 [312 – 405]	0.61
Induction, n (%), n / 123	49 (38)	28 (34)	21 (48)	0.18
Dialysis during intensive care unit stay n (%), n / 144	21 (14)	14 (14)	7 (15)	0.99
Primary graft dysfunction score Grade 3 at 72 hours, n (%) , n / 159	33 (21)	24 (22)	9 (19)	0.84
Ventilation time during intensive care unit stay, med [IQR], n / 153	3 [1 - 17]	2 [1 - 19]	3 [1 - 11]	0.95
Haemothorax, n (%), n / 127	26 (20)	16 (18)	10 (26)	0.41
Pulmonary sarcoidosis recurrence, n (%), n / 119	11 (9)	11 (14)	0	0.03
Chronic lung allograft dysfunction at last follow-up, n (%), n / 159	61 (38)	33 (31)	28 (54)	0.01
In-hospital mortality, n(%)	22 (13)	18 (16)	4 (7)	0.35
Retransplantation, n (%)	4 (2)	3 (3)	1 (2)	0.67

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