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ung transplantation after allogeneic stem cell transplantation: a pan-European experience.

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Lung Transplantation After Allogeneic Stem Cell Transplantation: A Pan-European Experience.

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Abstract [213 words]

Background: Late-onset non-infectious pulmonary complications (LONIPCs) affect 6% of allogeneic stem cell transplantation (SCT) recipients within 5 years, conferring subsequent 5-year survival of 50%. Lung transplantation (LTx) is rarely performed in this setting due to concomitant extra-pulmonary morbidity, excessive immunosuppression and concerns about recurring malignancy being considered contraindications. This study assesses survival in highly selected patients undergoing LTx for LONIPCs after SCT.

Methods: SCT patients undergoing LTx at 20 European centres between 1996-2014 were included. Clinical data pre- and post LTx were reviewed. Propensity score matched controls were generated from the Eurotransplant and Scandiatransplant registries. Kaplan Meier survival analysis and Cox proportional hazard regression models evaluating predictors of graft loss were performed.

Results: Graft survival at 1, 3 and 5 years was 84, 72 and 67% among the 105 SCT patients proved comparable to controls (p=0.75). Sepsis accounted for 15/37 (41%) deaths, with prior mechanical ventilation (HR 6.9 (95%CI 1.0 – 46.7); $p<0.001$) the leading risk factor. No SCT-specific risk-factors were identified. Recurring malignancy occurred in 4 (4%) patients. LTx ≤2 years post-SCT increased all-cause 1-year mortality (HR 7.5 (95%CI 2.3-23.8; $p=0.001$).

Conclusions: LTx outcomes following SCT were comparable to other end-stage diseases. LTx should be considered feasible in selected candidates. No SCT-specific factors influencing outcome were identified within this carefully selected patient cohort.

Introduction [399 words]

Allogeneic hematopoietic stem cell transplantation (SCT) represents an established treatment option for an increasing number of benign and malignant diseases, with procedure rates exceeding 8000 in the United States and 14,500 in Europe annually (1). Leading indications include acute myeloid leukaemia (AML) and acute lymphocytic leukaemia (ALL), which currently account for 35% and 16% of procedures respectively. Although refinements in SCT protocols have improved early outcomes, late-onset non-infectious pulmonary complications (LONIPCs) continue to limit long-term survival (2). LONIPCs occur in 20% of SCT patients and encompass the entire spectrum of lung disease, ranging from interstitial lung disease, pleuroparenchymal fibroelastosis to pulmonary veno-occlusive disease and classical bronchiolitis obliterans (BO) (3). Although the latter has long been considered ubiquitous for pulmonary graft vs. host disease (pGvHD), recent studies suggest additional interstitial lung involvement in some patients (4, 5). Treatment strategies ranging from oral macrolides to intensified immunosuppression and extracorporeal photopheresis have demonstrated benefit, but outcomes remain unpredictable and response rates disappointing (6-8).

Lung transplantation (LTx) is considered viable treatment in highly selected patients with various end-stage lung diseases. Since 1995, over 47,000 adult LTx procedures worldwide have been reported to the International Society for Heart and Lung Transplantation (ISHLT), with emphysema (38%) being the leading indication (9). Reports of LTx for LONIPCs extend as far back as 1992 (10), but data is extremely limited. Of the 450 LTx (1.1%) performed for obliterative bronchiolitis in the past 20 years, only 65 were attributed to LONIPCs.

Shortages in suitable donor lungs universally limits transplant activity, with many regions adopting weighted scoring systems such as the Lung Allocation Score (LAS) that focus on disease-related early survival probability, calculated from existing United Network for Organ Sharing (UNOS) registry data (11). Inevitably, this discourages LTx in orphan diseases along with conditions of poorer predicted outcome. Given SCT volume and the projected incidence of LONIPCs, LTx rates are much lower than

anticipated. Published experience is limited to case series and small cohorts with mixed outcomes leading to a common perception that LONIPCs candidates are “high-risk” (12-14), with peri-operative sepsis due to excessive prior immunosuppression, complications of previous long-term steroid treatment, existing microbial colonization and the ever-present risk of recurring, primary malignancy being cited as potential pit-falls (14).

The aim of this study is to quantify these risks and evaluate LTx outcomes in carefully selected SCT patients with LONIPCs in a large multi-centre cohort, paying particular attention to peri-operative sepsis and recurring primary malignancy.

Methods [458 words]

All patients undergoing LTx for LONIPCs following allogenic SCT at 20 European centres between 1996-2014 were retrospectively analysed. Clinical data pertaining to patient demographics, SCT treatment protocols, GvHD incidence and subsequent management were collated, along with imaging and native lung histology data prior to LTx. Subsequent LTx follow-up data until 30.06.2016 was standardized using detailed reporting protocols.

Autologous SCT, living-donor lobar LTx following SCT from the same donor and SCT patients with LTx indications other than LONIPCs, such as smoking-related emphysema, were excluded. Life-long LTx centre follow-up with a minimum of twice-yearly review was mandatory.

SCT were considered as being bone marrow transplantations (BMT) or peripheral blood stem cell transplants (PBSC) using accepted definitions (15, 16).

Spirometry adhered to ATS/ERS guidelines and was performed at each attendance in all centres (17, 18). Baseline forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) after LTx were calculated from the mean of the two highest values recorded a minimum of 3 weeks apart from one another. Diagnosis of chronic lung allograft dysfunction (CLAD) required a ≥3-week loss in FEV_1 of ≤80% baseline in the absence of an alternative cause. Sub-classification into obstructive *bronchiolitis obliterans syndrome (BOS)* or *restrictive CLAD (rCLAD)* adhered to currently proposed definitions (19-21).

A matched control cohort of non-SCT LTx recipients was generated from the entire Eurotransplant and Scandiatransplant registries for 1st LTx between 1996-2014 to compare LTx graft survival. Propensity score matching for gender, age at LTx, LTx year, LTx procedure (single or bilateral graft) and patient admission status at LTx was performed using logistic regression with nearest neighbour matching, a 0.2 calliper and a 1:50 matching ratio. Kaplan-Meier survival curves for overall graft as well as CLAD-free survival were constructed and the Log Rank test used to assess significance.

Factors influencing 1-year mortality and early sepsis were assessed with single and multivariate Cox proportional hazard regression to calculate Hazard Ratios (HR) with 95% confidence intervals (95%CI).

The proportional hazards assumption was confirmed, taking $p>0.05$ upon generation of the respective time-dependent covariates. Multivariate Cox Regression analysis used forward stepwise (likelihood ratio) modelling, taking p=0.05 and p=0.10 as entry and removal cut-offs at each iteration.

Risk factors for 5-year recurrence of malignancy and 10-year CLAD development were assessed using competing risk regression, missing values being omitted over a maximum 10 iterations.

Non-parametric tests were used for all variables and reported as median [interquartile range (IQR)] unless otherwise stated. Categorical variables were tested with either Chi^2 test or Fisher's exact test. Continuous variables were analysed using Mann-Whitney U test or Kruskal-Wallis H test. Reported *p*-values 2-tailed, with $p<0.05$ being considered significant. Analysis was performed using IBM SPSS Statistics for Macintosh, Version 24 (IBM Corp. Armonk, USA) and Graphpad Prism 6.0 (Graphpad Software Inc., La Jolla, USA).

Results [1370 words]

In total, 112 patients were identified. Seven were excluded from the analysis, with four considered to have had smoking-related emphysema and three due to autologous rather than allogenic SCT. Of the 105 patients analysed, 66 (63%) were male. Median age at LTx was 31.4 [20.5-43.5] years, with 18/105 (17%) being <18 years. AML was the leading SCT indication, comprising 38/105 (36%) patients. Twelve patients had benign diseases, including thalassemia, severe combined immunodeficiency, Wiscott-Aldrich syndrome and paroxysmal nocturnal haematuria. Demographic data are summarized in Table 1.

All patients exhibited advanced lung disease with median FEV_1 of 18% and FVC 35% predicted. Our previously reported clinical dichotomy in LONIPCs (4) persisted. Interstitial fibrosis was found in 51/105 (49%) explanted lungs, corresponding to lower FVC (31 *vs.* 45% predicted; p=0.005) and TLC (89 *vs.* 110% predicted; p=0.02) despite similar FEV_1 (17 *vs.* 18% predicted; p=0.58) in those patients.

In the absence of specific guidelines for LTx candidate selection for patients post-SCT, 17/20 centres (85%) reported adapting ISHLT consensus for cystic fibrosis (colonization, BMI) in conjunction with 2-year cancer-free interval prior to listing (22). Otherwise no additional criteria were reported. In the 3 remaining centres, formal multidisciplinary collaboration with local haematologists was undertaken, to assure quiescent extra-pulmonary GvHD. All centres reported monitoring serum immunoglobulins prior to transplant, with substitution only being offered to those demonstrating IgG deficiency in the setting of ≥2 infect episodes within 6 months.

During both the peri- and post-LTx phases, considerable variation in standard management across the 20 centres was evident, due in part to variations in local reimbursement policies across the 12 jurisdictions involved. Induction therapy was routinely used in 7/20 centres (35%), accounting for 35/105 SCT patients (33%). All but one centre used the same agent as for non-SCT patients. The remaining centre replaced their standard anti-thymocyte globulin (rATG) with basiliximab due to physician preference. In total 21/105 patients (20%) received basiliximab and 14/105 (13%) rATG.

Neither receipt of induction therapy, nor either of specific agents used appeared to influence the risk of sepsis (HR= 0.83 (0.21-3.29); p=0.79) or early mortality (HR= 0.30 (0.04-2.50); p=0.27).

All centres initiated standard triple immunosuppression post-LTx, combining a calcineurin inhibitor, anti-metabolite and steroids. The commonest protocol was tacrolimus, mycophenolate and prednisolone, which was used in 79/105 patients (75%). In the remaining 26 patients cyclosporine A was used, 7 of whom also received azathioprine instead of mycophenolate as per standard local policy. Prednisolone dosage of ≤10mg/d at 4 weeks post-LTx was targeted at all institutions.

Anti-infective prophylaxis again did not deviate between SCT and non-SCT patients at individual centres but significant variation between institutional protocols existed. Lifelong *Pneumocystis jirovecii* prophylaxis along with fungal prophylaxis in the first 4 weeks was advocated by all centres. Lifelong systemic azole prophylaxis was offered to only 28/105 patients (27%). The remaining centres reported aggressive management of Aspergillus species if detected during surveillance. Reported rates of life-threatening fungal infections among the SCT group was low, with only a single fatality reported. Cytomegalovirus prophylaxis again followed local protocols for all patients, varying between 4 weeks to 12 months depending on the donor and recipient constellation.

Total LTx volume at the participating centres during the observation period was 10693, with current centre volumes ranging from 15 – 120 procedures per year (median 40/year). Median patient follow-up post-LTx was 34 [9-75] months.

Graft Survival

Graft survival at 1, 3 and 5-years post-LTx was 85, 72 and 67% respectively. Thirty-seven patients (35%) died, with sepsis and CLAD being the leading causes of death.

Within Eurotransplant and Scandiatransplant 9,895 first-time LTx were performed between 1996-2014. Using the defined criteria, 4,075 patients were included in the matched control cohort (Table S1). Given the comparatively young age and high rates of bilateral LTx in the SCT cohort, it should be noted that cystic fibrosis (CF) and non-CF bronchiectasis were disproportionately over-represented

(32 *vs.* 18% of registry cohort) and emphysema correspondingly under-represented (29 vs. 41%). Compared to controls, no differences in graft survival at 1, 3 or 5-years were evident (Fig. 1).

Sixteen patients (15%) died within 12 months, of whom 14 did not survive to hospital discharge. Sepsis accounted for 10 of these deaths. In the univariate Cox Regression analysis, the only SCT-specific risk factors to achieve significance were prior calcineurin inhibitor treatment within 6 months of LTx and a time interval of less than 24 months between the final SCT and LTX (Table 2). Only the latter however retained significance in the subsequent multivariate analysis (HR= 7.5 [95%CI: 2.3-23.8]; p=0.001), along with FEV_1/FVC≥0.7 (HR=5.0 [95%CI: 1.4-17.9]; p=0.012) and requiring inpatient care immediately prior to LTx (HR=3.4 [95%CI: 1.2-10.0]; p=0.03).

Sepsis

In total 15/37 deaths (41%) during the observation period were attributable to sepsis. Three deaths occurred in patients with advanced CLAD exhibiting the BOS phenotype. Eight of the 12 remaining deaths occurred peri-operatively, with median survival of 42 [IQR 24-67] days. Other than a single case of fatal cytomegalovirus infection within 90 days, no details regarding the fatal pathogens in the remaining cases were available. Only 2 had reported colonization prior to LTx, being *Pseudomonas aeruginosa* (PsA) and methicillin- sensitive *Staphylococcus aureus* (MSSA) respectively.

Univariate Cox Regression identified ALL as the sole SCT risk factor for early sepsis (HR=4.6 [95%CI: 1.3-18.7]; p=0.02), alongside deteriorating native lung and kidney function and increasing dependency on medical support immediately prior to transplant (Table S2). In the multivariate analysis, only the latter retained significance with intensive care unit (ICU) admission prior to LTx (HR=5.2 [95%CI: 1.2-23.4]; p=0.03), mechanical ventilation (HR=6.9 [95%CI: 1.0-46.7]; p<0.001) and dual-bridging (HR=7.8 [6.2-98.3]; p=0.001) being relevant.

Malignancy

Malignancy accounted for 8/37 deaths (22%), with all occurring among the 93 patients with malignant SCT indications. Only half however were due to recurrence of the original malignancy. AML accounted for 2 cases in whom recurrence occurred within 12 months of LTx, with death ensuing within 12 months of diagnosis. Both patients had received LTx within 2 years of SCT, well below the median 72 [IQR 47-135] month interval in the other 34 AML patients.

Single recurrences of ALL and Non-Hodgkin Lymphoma (NHL) were recorded, with both presenting much later at 3 and 5 years post-LTx respectively. Competing risks regression analysis for recurrence within 5 years of LTx suggested both myeloablative induction therapy at SCT and LTx within 2 years of SCT as being contributory.

The 4 remaining fatal malignancies were colorectal cancer, melanoma and two cases of PTLD unrelated to the primary malignancy. Taking all eight malignancies together, the only significant risk factor on multivariate Cox Regression was LTx within 24 months of SCT (HR: 6.4 [95%CI: 1.3-46.0]; *p*=0.03).

Extra-Pulmonary Chronic GvHD

Chronic GvHD involving other organs was reported in 74/105 patients (70%), with skin involvement exhibiting the highest prevalence (49%) and gastrointestinal disease the lowest (30%, Table 1). Within the cohort, neither involvement of specific organs (*p*=0.88) nor cumulative site involvement (*p*=0.95) impacted on LTx survival. Notably, inpatient LTx had lower rates of extra-pulmonary GvHD (27 *vs.* 55%; *p*=0.007), particularly skin involvement (25 *vs.* 45%; *p*=0.03). No differences in incidence regarding ICU or bridging requirements were observed.

Chronic Lung Allograft Dysfunction and Re-Transplantation

CLAD developed in 29/79 patients (37%) surviving beyond the first year, developing at median 29 [IQR 15-56] months post-LTx. Both CLAD phenotypes were evident, with 21/29 (72%) developing BOS and the remaining 8/29 (28%) rCLAD. No clear relationship between CLAD onset or phenotype, and

previous LONIPC phenotype were evident. rCLAD occurred earlier (median 13 *vs.* 47 months; *p*=0.002) and resulted in earlier graft loss (median 30 *vs.* 71 months post-LTx; *p*=0.01). Limitations of the registry data used for the matched control cohort unfortunately prevented accurate comparisons for CLAD-free and with-CLAD survival. Broad comparisons with ISHLT data for CLAD-free survival, dependent upon surviving ≥14 days post-LTx, appear favourable (median 5.6 *vs.* 11.9 years) but interpretation is limited.

Competing risks regression analysis for 10-year CLAD risk identified only need for ICU (*p*=0.02) and mechanical ventilation (*p*=0.01), with no evidence of any immunological associations between CLAD phenotype and previous GvHD characteristics.

Five redo-LTx were performed. Two were attempted for primary graft dysfunction (PGD), with both patients dying within 1 week. CLAD accounted for the remaining procedures, of which two had rCLAD. One rCLAD patient died peri-operatively due to bleeding. The remaining two redo LTx patients remained alive at study completion, 12 and 20 months post-operatively.

Discussion [922 words]

This pan-European experience of LTx as treatment for carefully selected candidates with life-limiting LONIPCs following allogenic stem cell transplant, represents the largest known cohort of such patients. The most significant finding was that survival at 1, 3 and 5 years in this cohort was similar to matched controls with other end-stage lung diseases.

Given the current reported SCT volumes and reported incidence and outcomes of LONIPCs, approximately 350 patients die annually in Europe alone. Demonstrating the feasibility of LTx and generating awareness is important for both pulmonologists and haematologists alike. While unlikely that all would be suitable LTx candidates, the disparity to current LTx rates is hard to ignore.

These findings provide encouraging guidance to LTx physicians, assisting in difficult decision-making regarding candidacy of such patients. Discouragement of orphan diseases is an inherent limitation of organ allocation systems. With the intent of optimizing graft utility, their reliance on 1-year outcome data tends to discriminate when a critical-mass of data does not exist. Furthermore, the body of evidence available appears to suggest that such carefully selected patients can be managed in a very similar fashion to other LTx recipients, without affecting outcomes.

Being a retrospective analysis involving numerous centres of varying LTx experience, it is inevitable given the condition's reputation that cautious decision-making resulted in candidate selection bias at listing. Young recipient age, high outpatient LTx rates and lack of comorbidities among hospitalized patients are all suggestive. Ideally, consideration of rejected candidate referrals and wait-list deaths would add value to the analysis, but obtaining data from all centres proved unfeasible. While minimizing inter-observer variability, use of standardized data collection enforced a "lowest common denominator" approach to maximize completeness, generating more qualitative data. For certain aspects, such as treatment exposure or extent of disease, greater reliance on quantitative data may have proved more insightful.

Due caution is encouraged in interpreting the Cox Proportional Hazard models given the infrequent events within a small cohort. The spread in the 95% confidence intervals reflect this, casting a degree

of uncertainty that can only be resolved with increasing case volume. As such, the results reflect current experience to assist physicians facing difficult decision-making when assessing or managing such patients.

Nonetheless, the findings provide an important insight into the factors impacting upon early survival, and dispel some of the common concerns about sepsis risk and recurring malignancy. The relevance of 1-year all-cause mortality is rooted in allocation policies. Apart from LTx within 2 years of SCT, all the identifiable risk-factors in the uni- and multivariate analysis reflected the general clinical condition and as highlighted in the ISHLT Registry, are by no means exclusive to LONIPCs (9). Interestingly, the recent recognition of LONIPC phenotypes appears relevant, as those with restrictive spirometry (FEV_1/FVC ≥70%: HR 5.0 [95%CI: 1.4-17.9]; *p*=0.012) exhibited poorer early survival on multivariate analysis. It is however unclear if this reflects patient condition or the duration of prior immunosuppression which, as stated previously (4), was significantly longer among patients with restrictive lung function (54 [30-108] vs. 114 [70-152] months; p=0.002).

Early fatal sepsis accounted for 8/17 deaths (47%), which appears to exceed (192/781 deaths; 25%) ISHLT Registry reports (9). Except for ALL, no other SCT-specific factors were identified. Caution due to the small numbers involved is again advised, but 4/16 LTx recipients with a history of ALL died of early sepsis, accounting for half of such deaths. No clear explanation was evident, but it is noteworthy that sepsis-related death is problematic among ALL patients following SCT (23) with immunoglobulin deficiencies being implicated (24). Importantly however, concerns related to prior immunosuppression or microbial airway colonization could not be substantiated. The consensus view among the authors was that colonization should not represent an absolute contraindication, rather remain an individual-case consideration. It should be noted however, that none of the cohort were colonized with more contentious pathogens such as *Mycobacterium abcessus*, *Scedosporium* or *Burkholderia* species.

Recurrence rates of primary malignancy were low at 4%. Given the small numbers involved and proportionately large number of early deaths of alternative cause, concealed confounders are likely.

To compensate for this a competing risks regression was used, identifying LTx within 2 years of last SCT as the only risk factor. While AML data appears to support this, the interaction between factors remains unclear and should be considered in context. Current candidate selection guidelines recommend a malignancy-free interval of 2 years for all LTx(22) and given all-cause mortality data presented here (Fig. 2), no clear evidence to the contrary can be provided.

Extra-pulmonary chronic GvHD causes considerable comorbidity and its lack of influence on outcomes suggests inadequacy of data. Concerns regarding inadequate nutrition or oral immunosuppression in gastrointestinal GvHD, should be considered analogous with those in cystic fibrosis where attainment of stable body mass with or without enteral feeding represents a basic LTx requirement (22).

Given their similarities, both in terms of end-organ damage and unpredictable responses to broadly similar treatment strategies, the development of *host vs. graft* CLAD in patients with existing graft vs. host disease is somewhat unique. Unfortunately, no associations regarding incidence, timing or phenotypic recurrence were found. Furthermore, there was nothing in the observed CLAD demographics to suggest substantial deviation from reported patterns in other disease groups.

In conclusion, LTx is a feasible treatment option for refractory LONIPCs in thoroughly evaluated, carefully selected candidates, with comparable survival rates to other indications. Accurate characterization of LONIPCs and timely referral appear important in minimizing risk. Candidate evaluation, selection and peri-operative care should adhere to similar local protocols and values afforded to other end-stage lung diseases.

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Patient Demographics		
N	105	
Male, N (%)	66	(63)
Age at LTx, years	31.4	[20.5 – 43.5]
- Patients <18years, N (%)	18	(17)
Never-smoker, N (%)	88	(84)
FEV_1 %Predicted	18	[15-21]
FVC %Predicted	35	[25-48]
TLC %Predicted	103	[74-119]
Restrictive GvHD Phenotype, N (%)	51	(49)
Airway Colonization, N (%)	39	(37)
- Pseudomonas aeruginosa, N (%)	20	(19)
- Aspergillus fumigatus, N (%)	8	(8)
eGFR (CKD-EPI), ml/min/1.73m^2	93.1	[84.5-119.3]
Stem Cell Transplantation		
Indication		
AML, N (%)	38	(36)
ALL, N (%)	16	(15)
CML, N (%)	18	(17)
CLL, N (%)	2	(2)
Non-Hodgkin Lymphoma, N (%)	6	(6)
Hodgkin Lymphoma, N (%)	6	(6)
Myelodysplastic Syndrome, N (%)	7	(7)
Non-malignant disease, N (%)	12	(11)
Type		
Bone Marrow, N (%)	51	(49)
Peripheral Blood, N (%)	54	(51)
Age at first SCT, years	22.7	[14.4 – 36.3]
>1 SCT attempts, N (%)	*6*	*(6)*
Timing SCT after diagnosis, months	11.2	[4.5 – 21.0]
Conditioning Treatment		
Reduced-intensity, N (%)	16	(18)
Myeloablative, N (%)	87	(83)
- Busulphan, N (%)	*32*	*(35)*
- Cyclophosphamide, N (%)	*47*	*(52)*
- Fludarabine, N (%)	*20*	*(22)*
- Melphalan, N (%)	*17*	*(19)*
Total Body Irradiation[#], N (%)	46	(53)
Graft-versus-Host Disease		
Involvement of any extra-pulmonary site, N (%)	74	(70)
Skin, N (%)	52	(49)
Gastrointestinal, N (%)	31	(30)
Ocular, N (%)	33	(31)
Mucosal, N (%)	43	(41)
No. of extra-pulmonary sites	2	[0-3]
Treatment		
Ciclosporine, N (%)	75	(71)
Steroid, N (%)	68	(65)
Mycophenolate, N (%)	31	(30)
Methotrexate, N (%)	18	(17)
No. GvHD treatments at LTx	2	[2-3]
Lung Transplantation		
Bilateral LTx, N (%)	89	(85)
Timing LTx after SCT, months	69	[36-122]
- LTx <2 years post-SCT, N (%)	*15*	*(14)*

Induction, N (%)	35	(33)
Inpatient, N (%)	38	(36)
Intensive Care, N (%)	23	(22)
- Mechanical Ventilation only, N (%)	*14*	*(13)*
- ECMO only, N (%)	*5*	*(5)*
- Combined Mechanical Ventilation & ECMO, N (%)	*4*	*(4)*
Inpatient Stay post-LTx, days	37	[23-71]
Patient Follow-Up post LTx, months	34	[9-75]

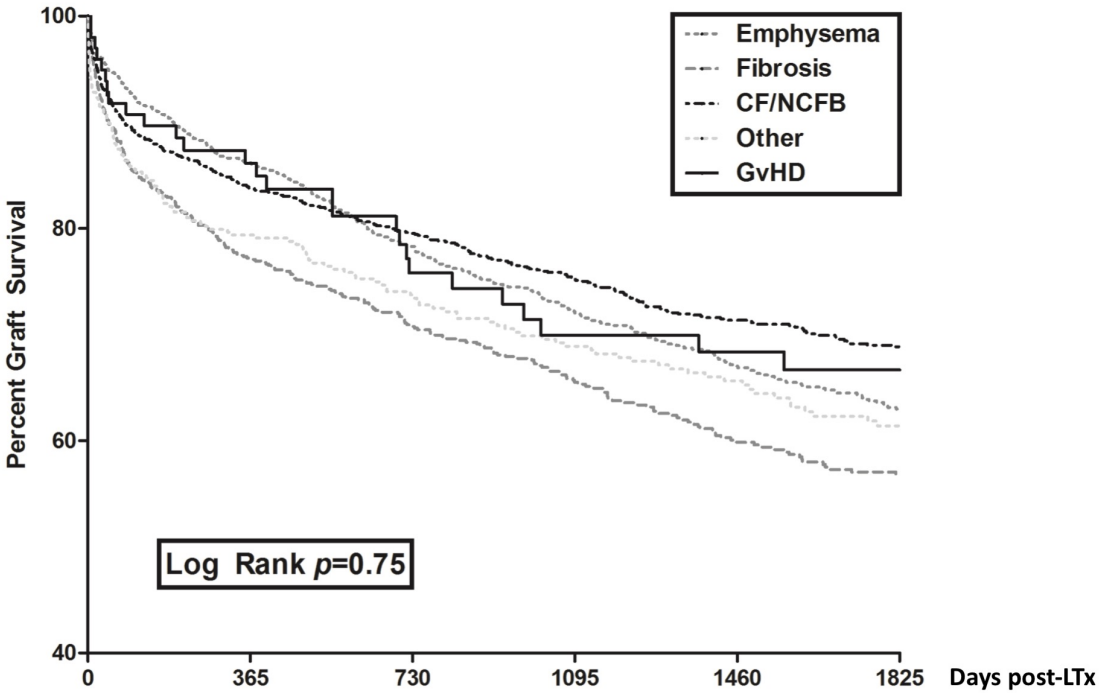
Table 1: Summary of stem cell transplant (SCT) patient demographics, including treatment up to and including lung transplantation (LTx). Values are median [interquartile range] unless otherwise stated. Key: ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; ECMO: extracorporeal membrane oxygenation; eGFR: estimated Glomerular Filtration Rate, calculated using the CKD-EPI (2012) Formula(25); FEV_1: Forced expiratory volume in 1s; FVC: Forced vital capacity; rATG: Anti-thymocyte Globulin and TLC: Total lung capacity *Data available for 91pts. #Data available for 86pts.

All Cause 1yr Mortality	N	Proportional Hazard	Univariate Analysis			Multivariate Analysis		
			HR	(95% CI)	*p*	HR	(95% CI)	*p*
Demographics								
Male	66	0.71	2.59	(0.90-7.42)	0.08			
Never-Smoker	89	0.92	0.45	(0.13-1.54)	0.20			
Age per 10y increase	105	0.18	1.08	(0.74-1.55)	0.70			
FEV_1 per 10% pred loss	105	0.43	1.12	(0.64-1.89)	0.43			
FVC per 10% pred loss	105	0.44	5.14	(1.21-21.88)	0.03			
FEV_1/FVC ≥0.7	92	0.32	1.45	(0.27-7.90)	0.67	5.04	(1.42-17.90)	0.012
TLC ≤90% predicted	16	0.55	0.40	(0.14-1.15)	0.09			
Isolated BO on CT	54	0.95	0.79	(0.28-2.24)	0.65			
Colonized	39	0.67	1.18	(0.29-4.78)	0.81			
- *PsA*	20	0.27	2.43	(0.23-15.43)	0.46			
- *Aspergillus*	8	0.61	0.86	(0.09-8.65)	0.89			
eGFR <90ml/min	65	0.53	1.45	(0.54-3.96)	0.46			
Primary Diagnosis								
AML	38	0.59	1.09	(0.91-1.33)	0.41			
ALL	16	0.49	1.95	(0.54-6.98)	0.29			
CML	18	0.57	0.93	(0.77-1.13)	0.73			
CLL	2	0.86	1.69	(0.42-6.77)	0.30			
NHL	6	0.50	1.04	(0.69-1.45)	0.97			
HL	6	0.47	1.01	(0.11-9.48)	1.00			
MDS	7	1.00	0.83	(0.76-0.91)	0.59			
Benign	12	0.99	0.82	(0.74-0.90)	0.21			
Stem Cell Transplant								
BMT	51	0.32	0.38	(0.13-1.09)	0.07			
Multiple SCT	6	0.62	0.95	(0.12-7.91)	0.96			
SCT-LTx 2yrs	15	0.44	3.32	(1.19-9.23)	0.02	7.46	(2.33-23.84)	0.001
Myeloablation	87	0.69	1.46	(0.19-11.11)	0.71			
- *Busulphan*	32	0.58	1.07	(0.27-4.26)	0.93			
- *Cyclophosphamide*	47	0.40	1.40	(0.35-5.61)	0.63			
Total Body Irradiation	46	0.92	1.75	(0.60-5.14)	0.31			
Extra-Pulmonary GvHD								
GvHD Skin	52	0.29	1.56	(0.55-4.44)	0.41			
GvHD GI	31	0.60	1.35	(0.42-4.38)	0.62			
GvHD Eye	33	0.12	3.46	(0.83-14.51)	0.09			
GvHD Mucosa	43	0.50	2.23	(0.70-7.04)	0.18			
Calcineurin Inhibitor <6mts	75	0.33	2.95	(0.99-8.82)	0.05			
Mycophenolate <6mts	31	0.90	0.68	(0.23-2.02)	0.48			
Systemic Steroids <6mts	68	0.57	0.86	(0.15-3.07)	0.62			
Peri-LTx Treatment								
DLTx	89	0.69	0.54	(0.33-0.89)	0.02			
Induction	35	0.36	0.30	(0.04-2.50)	0.27			
Inpatient at LTx	38	0.45	4.46	(1.23-16.15)	0.02	3.40	(1.16-10.01)	0.03
ICU	23	0.36	0.78	(0.12-5.27)	0.80			
MV	14	0.23	8.47	(2.36-37.19)	<0.001			
ECMO	5	0.48	5.08	(0.50-31.81)	0.17			
Dual Bridging	4	0.44	10.80	(1.60-42.75)	0.02			

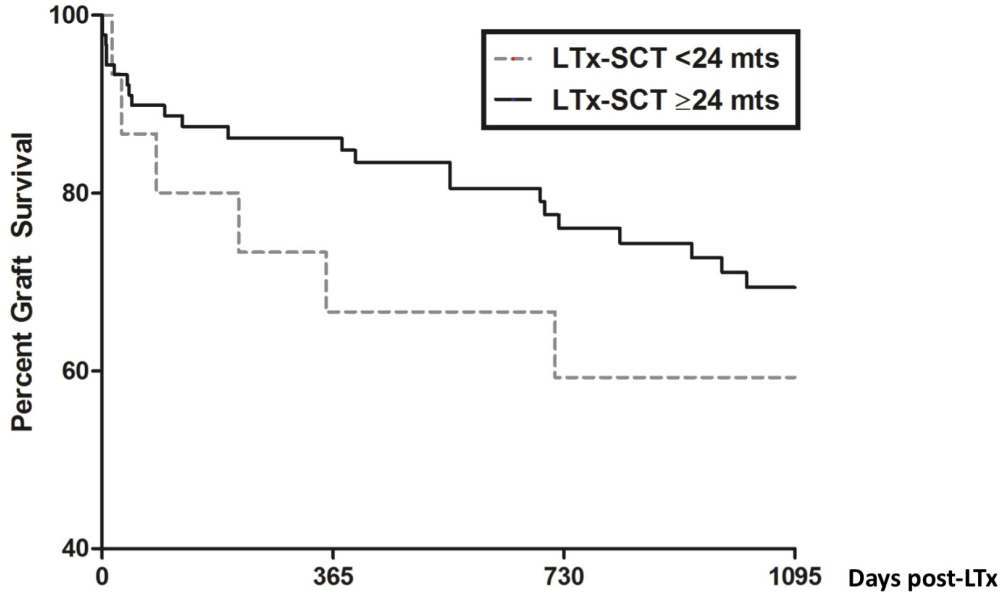
Table 2: Uni- and multivariate Cox regression analysis assessing risk factors for all-cause mortality ≤12 months after lung transplantation (LTx). Hazard ratio (HR) with 95% confidence intervals (95%CI). Key: FEV_1 – forced expiratory volume in 1s, FVC – forced vital capacity, TLC – total lung capacity, BO – bronchiolitis obliterans, CT – computerized tomography, PsA – Pseudomonas aeruginosa, GFR – estimated glomerular filtration rate (calculated using CKD-EPI), AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; CLL: chronic lymphocytic leukemia; NHL – non-Hodgkin lymphoma, HL – Hodgkin lymphoma, MDS – myelodysplastic syndrome, BMT – bone marrow transplantation, SCT – stem cell transplantation, TBI – total body irradiation, GvHD – graft vs. host disease, ICU – intensive care unit, MV – mechanical ventilation and ECMO – extracorporeal membranous oxygenation.

Fig.1 Kaplan Meier Curve showing graft survival following 1st LTx among SCT patients as well as matched controls from the other main disease groups. Comparing SCT vs. non-SCT patients, no differences in survival were observed at 1, 3 and 5 years post-LTx. Key: SCT: allogeneic stem cell transplant; CF: cystic fibrosis; NCFB: non-cystic fibrosis bronchiectasis.

Fig.2 Kaplan Meier Curve showing graft survival following 1st LTx among SCT patients, dependent upon the time interval between procedures. Early survival was worse in those proceeding to LTx within 2 years of SCT, but beyond the first year no differences remained. Key: LTx: lung transplantation; SCT: allogeneic stem cell transplant; yrs: years.



Number Of Patients At Risk						
Emphysema	1183	982	796	629	504	412
Fibrosis	911	662	518	411	301	236
CF/NCFB	1303	1053	895	728	604	490
Other	678	497	425	359	312	243
GvHD	105	73	57	48	43	36



Number Of Patients At Risk				
SCT-LTx <24mts	15	10	8	8
SCT-LTX ≥24mts	90	63	49	40

% Graft Survival			
SCT-LTx <24mts	67%	60%	60%
SCT-LTX ≥24mts	89%	81%	77%
Log Rank	**0.038**	**0.111**	**0.258**

	SCT		Controls		Emphysema		Fibrosis		CF/NCFB		Other	
Patients												
Pre-matching, N (%)	105		9,895		4014	(41)	2368	(24)	1815	(18)	1698	(17)
Post-matching, N (%)	105		4,075		1183	(29)	911	(22)	1303	(32)	678	(17)
Male, N (%)	66	(63)	2381	(58)	726	(61)	626	(68)	695	(53)	334	(49)
Age LTx, years	31	21-43	43	27-54	55	49-59	50	41-58	26	21-33	34	23-46
DLTx, N (%)	89	(85)	3268	(80)	789	(67)	604	(66)	1272	(98)	603	(89)
Status at LTx												
Elective, N (%)	67	(64)	2919	(72)	1055	(89)	620	(68)	807	(62)	437	(64)
Urgent, N (%)	15	(14)	127	(3)	35	(3)	33	(4)	44	(3)	15	(2)
High-Urgent, N (%)	23	(22)	1029	(25)	93	(8)	258	(28)	452	(35)	226	(34)

Supp. Table 1: Summary of the control cohort. Demographic data relates to matched controls only. Values are median [interquartile range] unless otherwise stated. Key: LTx: lung transplantation; DLTx: bilateral lung transplantation; SCT: allogeneic stem cell transplant; CF: cystic fibrosis; NCFB: non-cystic fibrosis bronchiectasis.

Early Sepsis Risk	N	Proportional Hazard	Univariate Analysis			Multivariate Analysis		
			HR	(95% CI)	*p*	HR	(95% CI)	*p*
Demographics								
Male	66	0.73	1.08	(0.96-1.21)	0.21			
Never-Smoker	89	0.20	1.13	(0.89-1.45)	0.18			
Age per 10y increase	105	0.11	1.14	(0.83-1.57)	0.41			
FEV_1 per 10% pred loss	105	0.68	1.36	(1.02-3.31)	0.03			
FVC per 10% pred loss	105	0.38	3.61	(1.32-13.91)	0.01			
FEV_1/FVC ≥0.7	92	0.83	2.52	(1.71-4.63)	0.05	4.26	(1.01-17.97)	0.04
TLC ≤90% predicted	16	0.91	0.67	(0.14-3.14)	0.61			
Isolated BO on CT	54	0.55	0.58	(0.16-2.06)	0.40			
Colonized	39	0.25	1.82	(0.29-14.59)	0.57			
- PsA	*20*	*0.46*	*1.38*	*(0.09-22.03)*	*0.82*			
- Aspergillus	*8*	*0.99*	*1.13*	*(0.84-1.42)*	*0.98*			
eGFR <90ml/min	65	0.57	3.77	(1.03-14.55)	0.04			
Primary Diagnosis								
AML	38	0.89	0.93	(0.83-1.04)	0.32			
ALL	16	0.65	4.61	(1.34-18.74)	0.02			
CML	18	0.19	1.23	(0.24-6.36)	0.68			
CLL	2	0.98	1.83	(0.46-7.31)	0.18			
NHL	6	0.54	1.37	(0.18-10.79)	0.19			
HL	6	0.99	0.90	(0.84-1.04)	0.59			
MDS	7	1.00	0.93	(0.81-1.12)	0.54			
Benign	12	0.99	0.89	(0.73-1.02)	0.42			
Stem Cell Transplant								
BMT	51	0.31	0.55	(0.16-1.95)	0.35			
Multiple SCT	6	1.00	1.10	(0.84-1.21)	0.59			
SCT-LTx 2yrs	15	0.32	2.12	(0.55-8.19)	0.28			
Myeloablation	87	0.71	2.82	(0.35-22.55)	0.33			
- Busulphan	*32*	*0.46*	*1.06*	*(0.15-7.54)*	*0.95*			
- Cyclophosphamide	*47*	*0.97*	*1.85*	*(0.31-11.09)*	*0.48*			
Total Body Irradiation	46	0.23	2.97	(0.62-14.43)	0.17			
Extra-Pulmonary GvHD								
GvHD Skin	52	0.99	1.02	(0.27-3.86)	0.98			
GvHD GI	31	0.90	0.76	(0.19-3.01)	0.70			
GvHD Eye	33	0.64	3.35	(0.43-26.17)	0.43			
GvHD Mucosa	43	0.51	1.20	(0.30-4.77)	0.79			
Calcineurin Inhibitor <6mts	75	0.57	3.26	(0.78-13.67)	0.11			
Mycophenolate <6mts	31	0.35	0.94	(0.23-3.95)	0.94			
Systemic Steroids <6mts	68	0.63	1.27	(0.26-6.29)	0.77			
Peri-LTx Treatment								
DLTx	89	0.87	0.54	(0.12-2.44)	0.35			
Induction	35	0.30	0.83	(0.21-3.29)	0.79			
Inpatient at LTx	38	0.19	4.93	(1.24-19.07)	0.012			
ICU	23	0.92	4.37	(1.27-15.12)	0.02	5.19	(1.15-23.43)	0.03
MV	14	0.44	6.41	(1.85-22.23)	0.003	6.92	(1.03-46.71)	<0.001
ECMO	5	0.68	5.39	(1.14-25.54)	0.05			
Dual Bridging	4	0.55	13.01	(5.67-56.19)	0.007	7.79	(6.17-98.31)	0.001

Supp Table 2: Uni- and multivariate Cox regression analysis assessing risk factors for early sepsis (≤12 months) after lung transplantation (LTx). Hazard ratio (HR) with 95% confidence intervals (95%CI). Key: FEV_1 – forced expiratory volume in 1s, FVC – forced vital capacity, TLC – total lung capacity, BO – bronchiolitis obliterans, CT – computerized tomography, PsA – Pseudomonas aeruginosa, GFR – estimated glomerular filtration rate (calculated using CKD-EPI), AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; CLL: chronic lymphocytic leukemia; NHL – non-Hodgkin lymphoma, HL – Hodgkin lymphoma, MDS – myelodysplastic syndrome, BMT – bone marrow transplantation, SCT – stem cell transplantation, TBI – total body irradiation, GvHD – graft vs. host disease, ICU – intensive care unit, MV – mechanical ventilation and ECMO – extracorporeal membranous oxygenation.