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Recovery of Pulmonary Function after Allogeneic Hematopoietic Cell Transplantation in Children is Associated with Improved Survival

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Abstract

Abnormal pulmonary function is prevalent in survivors of allogeneic hematopoietic cell transplantation (HCT). Post-transplantation recovery of pulmonary function, and its effect on survival, in children are not known. This retrospective cohort study of 308 children followed for 10 years after HCT at a single institution included 2 groups of patients. Group 1 comprised 188 patients with 3 or more pulmonary function test (PFT) results, of which at least 1 was abnormal, and group 2 comprised 120 patients with 3 or more PFTs, all of which were normal. Pulmonary function normalized post-transplantation in 51 patients (27%) in group 1. Obstructive lung disease, restrictive lung disease, mixed lung disease, and normal pattern were seen in 43%, 25%, 5%, and 27% of patients, respectively, at a median of 5 years (range, 0.5 to 11.9 years) post-transplantation. Lung volumes recovered better than spirometric indices. Pulmonary complications were seen in 80 patients (43%) in group 1. Patients who recovered pulmonary function had better overall survival ($P = .006$), which did not differ significantly from that in patients in group 2 with normal lung function post-transplantation ($P = .80$). After adjusting for duration of follow-up, pulmonary complications ($P = .01$), and lower pretransplantation forced vital capacity z -scores ($P = .01$) were

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SUPPLEMENTARY DATA

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associated with poor recovery. T cell depletion ($P < .001$), lower pretransplantation forced expired volume in 1 second z -scores ($P = .006$), and chronic graft-versus-host disease ($P < .001$) increased the risk for pulmonary complications. Nonrecovery of lung function with pulmonary complications ($P = .03$), acute graft-versus-host disease ($P = .004$), and mechanical ventilation ($P < .001$) were risk factors for nonrelapse mortality. Normalization of pulmonary function is possible in long-term survivors of allogeneic HCT. Strategies to decrease the risk of pulmonary complications may improve outcomes.

Keywords

Lung function; Pediatric; Hematopoietic cell transplantation; Recovery; Survival

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment for patients with certain hematologic malignancies and nonmalignant disorders. Impaired pulmonary function and post-transplantation pulmonary complications contribute significantly to the morbidity and mortality associated with this procedure [1,2].

Abnormal pulmonary function is prevalent in survivors of allogeneic HCT. One study of adult HCT survivors found that their single-breath diffusing capacity for carbon monoxide (DLCO) reached a nadir at 5 years but normalized at 10 years post-transplantation [3]. However, normalization of pulmonary function in children, and its effect on survival, are not clear. We hypothesized that poor recovery of lung function increased the risk of late mortality after 1-year post-transplantation.

As the rapidly increasing numbers of HCT survivors age, with potentially decades of life ahead of them, understanding the recovery process may aid the development of strategies to preserve lung function.

METHODS

Study Population

The retrospective initial group consisted of 797 patients aged < 21 years who underwent allogeneic HCT during a 25-year period (January 1990 through December 2014, both inclusive) at St Jude Children's Research Hospital. Patients age < 6 years (273 patients) were excluded because of their inability to perform a PFT. Patients with early post-transplantation mortality who were unable to perform more than 2 PFTs (216 patients) were excluded as well. The majority of these patients (57%) were 0 to 6 months post-transplantation. Therefore, the final cohort consisted of 308 patients.

All patients except those who died were followed until 10 years after transplantation. There was no loss to follow-up. Patients age 6 to 8 years were followed up to age 18 years. The mean duration of follow-up for patients in the final group of 308 patients was 4.1 years, with a median duration of 4.5 years (range, 0.4 to 12 years). This study was approved by the St Jude Institutional Review Board.

Patient-related variables were abstracted from a prospectively collected database. The conditioning regimen was classified as myeloablative or reduced intensity. Patients in the myeloablative group included those who received either total body irradiation (TBI) 5 Gy in a single dose or 8 Gy in fractionated doses or busulfan >8 mg/kg. Patients in the reduced-intensity group received a fludarabine-based regimen.

Haploidentical transplantation was done with T cell–depleted grafts. Ex vivo T cell depletion of the graft was performed using the Miltenyi CliniMACS system (Miltenyi Biotec, Bergisch Gladbach, Germany).

Prophylaxis for graft-versus-host disease (GVHD) was provided with a calcineurin inhibitor and either mycophenolate mofetil or methotrexate. Patients undergoing haploidentical HCT received mycophenolate mofetil for GVHD prophylaxis. The assessment of acute GVHD was based on consensus criteria [4].

All patients received prophylaxis against *Pneumocystis jirovecii* for up to 1 year after transplantation. Patients at risk for cytomegalovirus or Herpes simplex virus reactivation received acyclovir prophylaxis until 1 year after transplantation. Antifungal prophylaxis was provided with micafungin until engraftment, and with voriconazole thereafter.

An infectious pulmonary complication was defined as the isolation or detection of an organism associated with symptoms suggestive of lower respiratory tract involvement or the detection of a new lung infiltrate by chest radiography. Specimens obtained for analysis included nasopharyngeal wash, tracheal aspirate, bronchoalveolar lavage, blood cultures, and lung autopsy.

Noninfectious pulmonary complications included idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage, bronchiolitis obliterans syndrome (BOS), cryptogenic organizing pneumonia (COP), and interstitial lung disease, as defined previously [5–7]. Management of pulmonary complications in all patients was standardized as described previously [8]. Infectious and noninfectious pulmonary complications were grouped together in our study.

PFT

Spirometry, lung volume measurement by body plethysmography, and DLCO were performed at St Jude's PFT laboratory by a certified technician in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [9], using a Platinum Elite DX series body plethysmograph (MedGraphics, St Paul, MN). All patients underwent PFTs pretransplantation, at 3 and 6 months post-transplantation, and yearly thereafter. The pre- and post-HCT PFTs consisted of spirometry, including measurements of the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), FEV₁/FVC ratio, and forced expiratory flow during the mid-portion of vital capacity (FEF_{25-75%}). Lung volume measurements included total lung capacity (TLC). The DLCO was corrected for hemoglobin content. In 308 patients, 1430 PFTs were performed, with a mean of 4, a median of 5, and a range of 3 to 17 PFTs per patient.

Global Lung Initiative (GLI)-2012 indices were used for all spirometry values, with predictive values, lower limits of normal (LLN), and z -scores for FVC, FEV₁, FEV₁/FVC, and FEF_{25-75%} [10]. The GLI-2012 equations are based on a very large reference population of patients age 3 to 95 years and produces age-specific spirometric indices for LLN [10]. Lung volumes were normalized according to prediction equations published by Crapo et al. [11] and Miller et al. [12], and were adjusted for race [13].

Statistical Analysis

Pulmonary function was classified as normal, obstructive, restrictive, or mixed based on an algorithm published by Pellegrino et al. [14] and the ATS/ERS task force for the standardization of lung function testing. Patients with FEV₁/VC and VC values equal to or greater than the LLN were categorized as normal. Patients with obstructive, restrictive, or mixed defects were categorized as abnormal. Group 1 (188 patients) comprised patients with 3 or more PFT results, of which at least 1 was abnormal, and group 2 (120 patients) comprised patients with 3 or more PFT results, all of which were normal (Figure 1).

Descriptive statistics for patients in groups 1 and 2, and for patients in group 1 who did and did not experience recovery of lung function, were reported and compared using either Pearson's chi-square test or Fisher's exact test for categorical variables and the 2-sample t test or Wilcoxon's rank-sum test for quantitative variables based on the normality assumption criteria. Descriptive statistics for the patients in group 2 and for those who recovered in group 1 were also compared using the same approach.

The distributions of the pre-HCT and the most recent post-HCT z -scores were compared using either a 1-sample t test or Wilcoxon's signed-rank test based on the normality assumption. The time periods for the PFTs were specified as 0 to 100 days, 100 to 365 days, and >365 days after HCT. These groups reflect PFTs completed at 3 months, 6 months, and then annually after transplantation. The distributions of the changes in PFTs between any 2 time points were compared using the same approach as above.

Logistic regression analyses for group 1 were done using recovery and pulmonary complications as binary outcomes, to evaluate their association with the covariates outlined below. Logistic regression analysis for pulmonary complications was performed for group 2. The overall survival (OS) probabilities for patients in group 1 who recovered and for group 2 were estimated using the Kaplan–Meier method and compared using the log-rank test. In group 1, the OS of patients who recovered or did not recover normal lung function with or without pulmonary complications were estimated and compared using the same method. OS was defined as the time from HCT until death from any cause, censoring those patients who were still alive at the last follow-up. The Cox proportional hazards model was used to evaluate the associations between OS, recovery, pulmonary complications, and covariates outlined below. The assumption of proportional hazard was confirmed in all survival analyses.

The cumulative incidence of an event was estimated by the Kalbfleisch–Prentice method [15] and compared using Gray's test [16]. In the estimation of cumulative incidence of deaths due to nonrelapse, deaths due to relapse were considered competing events. The Fine

and Gray regression model [17] was used to evaluate the associations between cumulative incidence and all other covariates.

Covariates considered in univariate analysis for pulmonary complications included age at transplantation, diagnosis, disease status, donor type, sex, race, type of product received, T cell depletion, receipt of TBI, conditioning (myeloablative versus reduced intensity), cytomegalovirus donor/recipient serostatus, acute and chronic GVHD, HCT time cohort (1990 to 1999 versus 2000 to 2014), receipt of multiple HCTs, pretransplantation PFT z -scores, and duration of follow-up. Apart from the covariates outlined above, for univariate analysis of recovery, covariates such as pulmonary complications, and ventilator status were considered. Similarly for OS and nonrelapse mortality (NRM), covariates such as recovery, pulmonary complications, and ventilator status were also considered in the analysis. A pretransplantation PFT z -score was considered normal if it was >2 SDs in the left tail of the normal distribution ($-2 < z$), mildly reduced ($-3 < z < -2$), moderately reduced ($-4 < z < -3$), or severely reduced ($z < -4$) [18].

The parameters associated with outcomes in univariate analyses at a nominal level of .10 were included in their respective multivariate analyses based on a stepwise model selection strategy that used logistic regression, Cox proportional hazards, and Fine and Gray regression models. All reported P values are 2-sided and considered significant at $<.05$. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC), and R version 2.13.1 (R Institute for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

Demographic data of patients in group 1 with abnormal PFTs were compared with those of patients in group 2 with normal PFTs (Table 1). The patients in group 2 were younger ($P = .003$) and more likely to have received a marrow product ($P = .004$). The demographic data of patients in group 1 in whom pulmonary function normalized were not significantly different from that of patients with persistently abnormal PFT results (Table 1).

Recovery of Pulmonary Function

Pretransplantation PFTs were abnormal in 74 of the 188 patients (39%) in group 1 (Figure 1). Obstructive, restrictive, and mixed lung disease was seen in 45 patients (24%), 27 patients (14%), and 2 patients (1%), respectively. Patients with abnormal PFTs post-transplantation (group 1) had lower pretransplantation FEV₁ ($P < .001$), FVC ($P < .001$), FEF_{25-75%} ($P < .001$), and TLC z -scores ($P < .001$) compared with patients with all normal PFTs (group 2). Patients who did not recover lung function in group 1 had lower pretransplantation FEV₁ ($P = .01$), FVC ($P < .001$), FEV₁/FVC ($P = .003$), and TLC z -scores ($P = .04$).

FEV₁, FVC, FEV₁/FVC, FEF_{25-75%}, and TLC z -scores in group 1 patients were significantly lower in the most recent post-transplantation PFTs compared with the pretransplantation baseline; however, the corrected DLCO z -score was unchanged (Figure 2). Obstructive, restrictive, and mixed lung disease and normal pattern was seen in 80

patients (43%), 48 patients (25%), 9 patients (5%), and 51 patients (27%), respectively, at a median follow-up of 5 years (range, 0.4 to 11.9 years) post-transplantation.

Pulmonary function normalized in 51 patients (27%) (Table 2). Changes in pulmonary function were compared at 0 to 100 days, 101 to 365 days, and more than 365 days post-transplantation in patients with and without normalization of pulmonary function (Table 3). Patients who recovered had improved FVC, TLC, and corrected DLCO *z*-scores. Patients who did not recover had worse FEV₁, FVC, FEV_{25-75%}, and FEV₁/FVC *z*-scores, but an improved corrected DLCO *z*-score (Table 3).

Univariate logistic regression analysis for patients in group 1 showed that patients with pulmonary complications ($P = .005$; odds ratio [OR], .36; 95% confidence interval [CI], .18 to .73), and those with mildly reduced pretransplantation FVC *z*-score ($P = .02$; OR, .09; 95% CI, .01 to .65) were less likely to experience normalization of pulmonary function.

Multivariate logistic regression analysis showed that after adjusting for duration of follow-up, patients with pulmonary complications ($P = .01$; OR, .39; 95% CI, .19 to .82), and those with mildly reduced pretransplantation FVC *z*-score ($P = .01$; OR, .07; 95% CI, .01 to .57) were less likely to experience normalization of pulmonary function.

Pulmonary Complications

Pulmonary complications were seen in 80 patients (43%) in group 1 and in 37 patients (31%) in 2 ($P = .04$). A univariate logistic regression analysis of pulmonary complications for patients in group 1 is presented in Supplementary Table S2. On multivariate analysis, T cell depletion ($P < .001$; OR, 3.27; 95% CI, 1.69 to 6.33), moderately to severely reduced pretransplantation FEV₁ *z*-score ($P = .006$; OR, 9.97; 95% CI, 1.92 to 51.84), and chronic GVHD ($P < .001$; OR, 3.42; 95% CI, 1.70 to 6.89) were associated with increased risk for pulmonary complications.

Multivariate logistic regression analysis of pulmonary complications for patients in group 2 showed an association between severe acute GVHD and increased risk for pulmonary complications ($P = .02$; OR, 2.86; 95% CI, 1.22 to 6.70).

Fourteen patients in group 1 had noninfectious pulmonary complications, including BOS in 5 patients, diagnosed by high-resolution chest computed tomography and pulmonary function tests; diffuse alveolar hemorrhage in 2 patients, diagnosed by clinical findings and bronchoalveolar lavage; and COP 6 patients and interstitial lung disease in 1 patient, respectively, diagnosed by lung biopsy. Two patients were diagnosed with IPS at 4 months and 7 months before being diagnosed with COP. Noninfectious pulmonary complications were preceded by acute grade III-IV GVHD in 9 patients. (Supplementary Table S1). Sixty-six patients in group 1 had only infectious complications (Supplementary Table S1).

OS and NRM

Patients in group 1 had worse OS compared with those in group 2 ($P < .001$). Patients in group 1 who recovered pulmonary function had better OS ($P = .006$), which was not different from that of patients in group 2 ($P = .80$). Twelve patients (8%) died of pulmonary

complications in group 1. No patients in group 1 who had normalized pulmonary function or patients in group 2 died of pulmonary complications.

The mean and median durations of follow-up for the 188 patients in group 1 were 4.86 and 4.02 years, respectively (range, 0.43 to 11.56 years). The probabilities of OS and NRM for patients who did not recover lung function and had pulmonary complications were 47.6% (95% CI, 32.1% to 61.4%) and 42% (95% CI, 27.5% to 56%), respectively, compared with 86.6% (95% CI, 66.6% to 95%) and 8.1% (95% CI, 1.2% to 24%) for patients who recovered lung function and had no pulmonary complications (Figure 3).

The results of univariate analysis of OS and NRM for patients in group 1 are shown in Supplementary Table S2. On multivariate analysis, mechanical ventilation ($P < .001$; hazard ratio [HR], 7.71; 95% CI, 3.79 to 15.71) and nonrecovery of lung function with pulmonary complications ($P = .02$; HR, 2.18; 95% CI, 1.12 to 4.23) were associated with increased risk for overall mortality.

Mechanical ventilation ($P < .001$; HR, 17.41; 95% CI, 6.89 to 43.97), nonrecovery of lung function with pulmonary complications ($P = .03$; HR, 3.31; 95% CI, 1.12 to 9.78), and severe acute GVHD ($P = .004$; HR, 2.68; 95% CI, 1.37 to 5.27) were associated with increased risk for NRM.

Univariate and multivariate analyses of OS and NRM for patients in group 2 were inconclusive due to insufficient power. Only 10 patients died in this group, 4 due to relapse.

DISCUSSION

Our study of a large cohort of children who underwent allogeneic HCT with long follow-up at a single institution reveals that normalization of pulmonary function is possible in long-term survivors of allogeneic HCT, and that normalization is associated with improved survival. Patients with pulmonary complications were less likely to develop normal pulmonary function.

Lung volumes recovered better than spirometric indices. Significant improvements in TLC and DLCO at more than 1 year post-transplantation were seen in patients whose pulmonary function normalized. A decline in spirometric indices at more than 1 year post-transplantation has been corroborated by other studies [19–22]. Previous studies also have identified older age at the time of HCT [23] and receipt of a peripheral blood stem cell graft [21] as risk factors for PFT decline, which was confirmed in our present study.

Kaya et al. [19], in a smaller cohort of patients, reported declines in spirometric indices and lung volumes at 3 to 6 months post-transplantation. In that study, spirometric indices were improved at 12 to 24 months post-transplantation but remained significantly below pretransplantation values, and lung volumes recovered to baseline during that period. Recovery of spirometric indices and lung volumes to normal values in children at long-term follow-up is a novel finding. Approximately one-quarter of patients with abnormal lung function pretransplantation recovered to normal on post-transplantation follow-up in our study. OS was not significantly different between patients whose lung function normalized

and patients who had no deterioration in lung function post-transplantation. This is a novel finding.

Factors associated with the normalization of lung function have not been previously studied in children or adults. In our study, patients with pulmonary complications were less likely to experience lung function normalization and had a high mortality. Patients without pulmonary complications experienced recovery of lung function and had significantly better survival. T cell depletion was associated with an increased risk of pulmonary complications. This may be related to poor immune reconstitution with an increased risk of respiratory infections [24]. A reduced pretransplantation FEV₁ z-score also was associated with increased risk for pulmonary complications. Horak et al. [25] recognized reduced FEV₁ as a strong risk factor for the development of viral-associated interstitial pneumonia in HCT recipients [25]. Damage to airways as a result of previous therapy, alloreactivity due to GVHD, and recurrent infections may lead to irreversible steroid-unresponsive airway obstruction and bronchiectasis. Hoffmeister et al. [26] reported that patients surviving more than 20 years after HCT and those with chronic GVHD had a substantially higher risk of obstructive lung disease [26]. The association between GVHD and BOS is well recognized [27,28].

Although lung volumes recovered better than spirometric indices, restrictive lung disease was associated with higher mortality. Because we censored patients with early NRM who were unable to perform more than 2 PFTs, the number of patients with restrictive lung disease, particularly IPS, is likely underrepresented, highlighting the importance of restrictive lung disease on OS. Cooke et al. have reported high mortality in patients with IPS [29], and noted that early recognition and therapy with etanercept and corticosteroids may improve outcomes [30]. Associations between acute GVHD, chronic GVHD, and the subsequent development of COP have been reported [31]. Modification of transplantation strategies to reduce chronic GVHD may reduce the risk of pulmonary complications.

In this study, lower pretransplantation FVC z-scores were associated with poor recovery of lung function. Lower FEV₁ or FVC increased the risk of early respiratory failure, as also observed by Kaya et al [19], and acute respiratory failure and mechanical ventilation decreased OS and increased the risk for NRM. A recent prospective multicenter study on the outcome of invasive mechanical ventilation after pediatric allogeneic HCT reported a 52% mortality rate [32], which was clearly improved compared with previous studies [33].

Strengths of our study include a large retrospective cohort of children with a long follow-up. PFTs were standardized using the same instrumental method for the duration of the study. The ATS/ERS standardized algorithm for defining lung function abnormality using the FEV₁/VC ratio was used for the first time in this population.

Previous long-term studies of pulmonary function have used percent predicted values rather than the recent GLI-2012 indices. Using percent predicted equations and fixed thresholds for FEV₁/FVC has been reported to result in the misdiagnosis of more than 20% of patients undergoing PFTs [34]. The ATS and ERS recommend using the 5th percentile to define

LLN (i.e., -1.64 z-score). Unlike percent predicted, z-scores allow for uniform interpretation of test results.

Previous studies also have included autologous transplants and patients at risk for increased transplantation-related mortality, thereby precluding accurate assessment of recovery of pulmonary function. Both NRM and OS were included as outcome measures.

Our study is limited by its retrospective nature. PFTs were compared over broad time spans rather than at specific time points. Children age <6 years were excluded. Causes of pretransplantation abnormal lung function were not determined, and although therapy was standardized for pulmonary complications, individual differences in patient management may have contributed to outcomes. Further studies are needed to validate our findings in an independent, larger retrospective cohort, and to evaluate modified transplantation strategies aimed at reducing the risk of pulmonary complications. Close follow-up of airway obstruction post-transplantation will be important as this population of survivors continues to age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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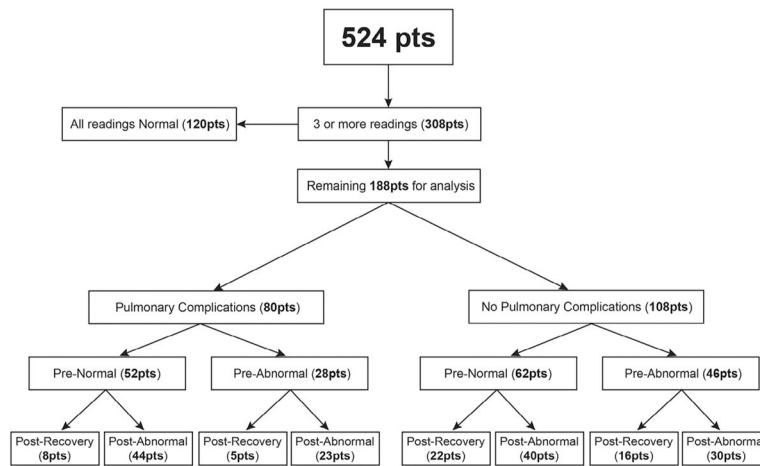


Figure 1.

Study population flow chart for the analysis of recovery of pulmonary function after HCT. The results of PFTs were classified as normal or abnormal based on the algorithm published by Pellegrino et al. [14]. Patients with restrictive, obstructive, and mixed defects were categorized as abnormal; all others were categorized as normal. All patients had a minimum of 3 readings, including pretransplantation PFTs, post-transplantation PFTs, and the most recent PFTs. The series of 188 patients were categorized as with or without pulmonary complications and with normal or abnormal pretransplantation and post-transplantation PFTs. Recovery indicates that normal pulmonary function was restored.

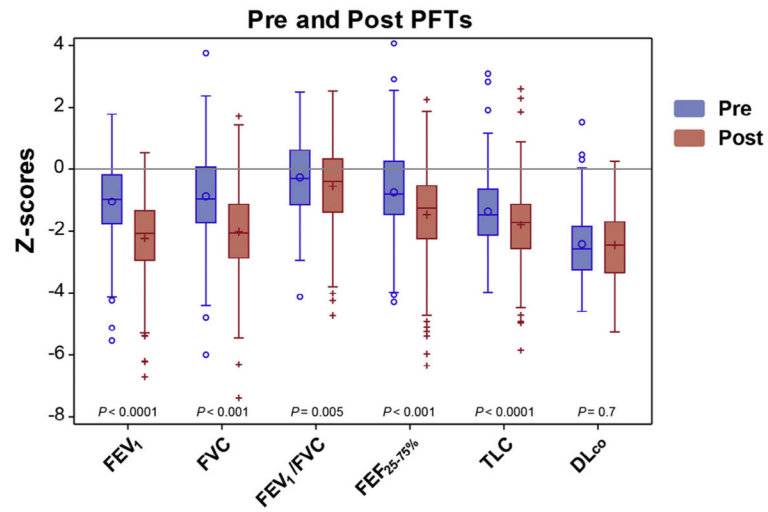


Figure 2. Boxplots for z-scores of patients in group 1 with the pretransplantation and the most recent post-transplantation PFTs.

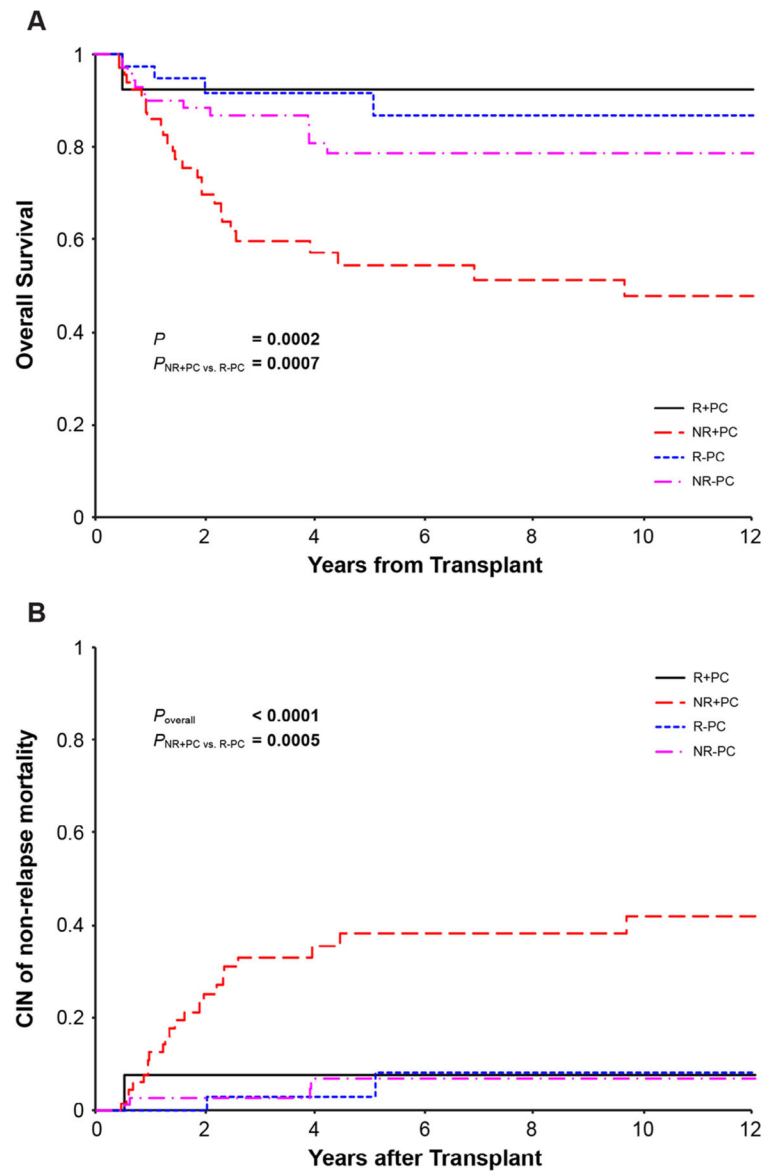


Figure 3.

(A) OS of patients in group 1 who recovered (R) or did not recover (NR) normal lung function with (+) or without (–) pulmonary complications (PCs). (B) Cumulative incidence (CIN) of NRM of patients in group 1 who recovered (R) or did not recover (NR) normal lung function, with (+) or without (–) PCs.

Table 1
 Characteristics of Patients in Group 1 with and without Normalization of Pulmonary Function and Patients in Group 2

Characteristic	Group 1 (n = 188)		Normalization		P Value*	Group 2 (n = 120)	P Value†
	Yes (n = 51)	No (n = 137)	Yes (n = 51)	No (n = 137)			
Age, yr					.16		.003
Mean (SD) age at HCT	13.54 (3.49)	12.90 (3.60)	13.77 (3.44)	12.28 (3.78)			
Median	13.82	13.45	13.91	12.50			
Range	6.60–20.45	6.60–18.83	6.64–20.45	6.21–20.08			
Race, n (%)					.63		.58
White	136 (72)	37 (72)	99 (72)	93 (78)			
African-American	35 (19)	8 (16)	27 (20)	17 (14)			
Other	17 (9)	6 (12)	11 (8)	10 (8)			
Male sex, n (%)	105 (56)	25 (49)	80 (58)	67 (56)	.32		1.00
Underlying disease, n (%)					.74		.30
Hematologic malignancy	152 (81)	39 (76)	113 (83)	93 (77)			
Heme disorders	29 (15)	10 (20)	19 (14)	24 (20)			
Immune disorders	3 (2)	1 (2)	2 (1)	3 (3)			
Solid tumors	4 (2)	1 (2)	3 (2)	0 (0)			
Remission at HCT, n (%)	120 (64)	28 (55)	92 (67)	77 (64)	.13		1.00
Donor match, n (%)					.23		.30
Fully matched	129 (69)	40 (78)	89 (65)	92 (77)			
Haploidentical	44 (23)	9 (18)	35 (25)	20 (17)			
Mismatched	15 (8)	2 (4)	13 (10)	8 (6)			
Multiple transplants, n (%)	39 (21)	6 (12)	33 (24)	6 (5)	.07		.39
Product type, n (%)					.04		.004
HPC-A	55 (29)	11 (21)	44 (32)	17 (14)			
HPC-M	131 (70)	38 (75)	93 (68)	102 (85)			
HPC-C	2 (1)	2 (4)	0 (0)	1 (1)			
Time cohort, n (%)					.29		.90
Before 2000	54 (29)	18 (35)	36 (26)	36 (30)			
On or after 2000	134 (71)	33 (65)	101 (74)	84 (70)			

Characteristic	Group 1 (n = 188)		Normalization		P Value*	Group 2 (n = 120)		P Value [†]
	Yes (n = 51)	No (n = 137)	Yes (n = 51)	No (n = 137)		Yes (n = 51)	No (n = 137)	
T cell depletion, n (%)	66 (35)	15 (29)	51 (37)	35 (29)	.39	35 (29)	35 (29)	.32
Reduced-intensity conditioning, n (%)	50 (27)	11 (22)	39 (29)	36 (30)	.45	36 (30)	36 (30)	.52

HPC-M indicates human progenitor cell, marrow; HPC-A, human progenitor cell, apheresis or peripheral blood stem cell product; HPC-C, human progenitor cell, cord.

Group 1 includes patients with 3 or more PFT results, of which at least 1 was abnormal. Group 2 includes patients with 3 or more PFT results, all of which were normal.

* P value comparing patients in group 1 who did and did not normalize lung function.

† P value comparing patients in group 1 and group 2.

Table 2
Outcomes of Patients in Group 1 with and without Normalization of Pulmonary Function and Patients in Group 2

Characteristic	Group 1 (n = 188)		Normalization		P Value*	Group 2 (n = 120)		P Value†
	Group 1 (n = 188)	No (n = 137)	Yes (n = 51)	No (n = 137)		Group 2 (n = 120)	P Value†	
Acute GVHD, n (%)‡	57 (30)	41 (30)	16 (31)	41 (30)	.86	31 (26)	.44	
Chronic GVHD, n (%)	53 (28)	41 (30)	12 (24)	41 (30)	.47	25 (21)	.18	
PC, n (%)	80 (43)	67 (49)	13 (26)	67 (49)	.005	37 (31)	.04	
Noninfectious PC, n (%)	14 (8)	14 (10)	0 (0)	14 (10)	.01	1 (1)	.007	
Infectious PC, n (%)	66 (35)	53 (39)	13 (26)	53 (39)	.09	36 (30)	.39	
Survival, n (%)					.006		<.001	
Alive	143 (76)	97 (71)	46 (90)	97 (71)		110 (92)		
Died	45 (24)	40 (29)	5 (10)	40 (29)		10 (8)		
Death due to PC, n (%)	12 (6)	12 (9)	0 (0)	12 (9)	.04	0 (0)	.004	

PC indicates pulmonary complications.

* P-value comparing patients in group 1 who did and did not normalize lung function.

† P-value comparing patients in group 1 and group 2.

‡ Severe acute GVHD grade II-IV.

Table 3 z-Scores of Pulmonary Function Variables of Patients in Group 1 with Lung Function Did or Did Not Normalize, by Time Period Post-Transplantation

Characteristic	Statistic	Recovery (n = 51)			No Recovery (n = 137)			P Value
		0-100 d	101-365 d	>365 d	0-100 d	101-365 d	>365 d	
FEV ₁								
NS								
Number		21	26	45	68	71	106	P 0-100 versus 101-365 = .001 ↓
Mean (SD)		-1.46 (1.40)	-1.56 (1.44)	-.91 (.58)	-1.67 (1.31)	-2.33 (1.26)	-2.42 (1.20)	P 101-365 versus >365 = .009 ↓
Median (range)		-.95 (-4.14~-78)	-1.39 (-4.49~-2.35)	-1.01 (-2.11~.53)	-1.53 (-4.68~-1.97)	-2.38 (-6.16~-88)	-2.22 (-6.45~-8)	P 0-100 versus >365 < .001 ↓
FVC								
P 101-365 versus >365 = .005 ↑								
Number		21	26	45	68	71	106	P 0-100 versus >365 = .001 ↓
Mean (SD)		-1.23 (1.59)	-1.41 (1.46)	-.70 (.78)	-1.54 (1.40)	-2.17 (1.42)	-2.17 (1.36)	
Median (range)		-1.43 (-4.08~-1.45)	-1.52 (-3.67~-2.95)	-.84 (-1.75~-1.35)	-1.57 (-5.11~-2.63)	-2.28 (-5.21~-2.09)	-2.19 (-7.28~-1.79)	
FEV ₁ /FVC								
NS								
Number		21	26	45	67	71	106	P 101-365 versus >365 = .008 ↓
Mean (SD)		-.39 (1.24)	-.44 (1.05)	-.36 (.77)	-.37 (1.11)	-.45 (1.32)	-.64 (1.37)	P 0-100 versus >365 = .02 ↓
Median (range)		-.20 (-2.83~-1.53)	-.42 (-2.74~-1.34)	-.34 (-2.15~-1.18)	-.35 (-3.31~-1.59)	-.014 (-4.72~-1.85)	-.55 (-4.24~-2.21)	
FEF _{25-75%}								
NS								
P 0-100 versus 101-365 = .003 ↓								

Characteristic	Statistic	Recovery (n = 51)			No Recovery (n = 137)			P Value	P Value
		0-100 d	101-365 d	>365 d	0-100 d	101-365 d	>365 d		
	Number	21	26	45	68	71	106	<i>P</i> 101-365 vs. >365 = .01 ↓	
	Mean (SD)	-1.03 (1.24)	-.99 (1.20)	-.64 (.76)	-1.07 (1.24)	-1.49 (1.34)	-1.64 (1.47)	<i>P</i> 0-100 versus >365 = . 002 ↓	
	Median (Range)	-1.14 (-3.44-0.53)	-.97 (-4.12-0.78)	-.79 (-2.26-1.02)	-1.16 (-4.29-1.03)	-1.21 (-6.25-0.71)	-1.62 (-5.76-1.59)	NS	
TLC									
	Number	21	26	45	68	71	103		
	Mean (SD)	-1.70 (1.44)	-1.62 (1.08)	-1.10 (.90)	-1.72 (1.20)	-1.98 (1.31)	-1.79 (1.20)		
	Median (Range)	-1.68 (-4.77-1.12)	-1.72 (-4.18-1.12)	-1.21 (-2.69-1.91)	-1.92 (-3.85-1.63)	-2.00 (-4.92-1.88)	-1.89 (-4.38-2.17)	<i>P</i> 101-365 versus >365 = . 002 ↑	
DLCO									
	Number	21	25	45	66	70	102	<i>P</i> 0-100 versus >365 = . 0006 ↑	
	Mean (SD)	-2.72 (1.46)	-2.94 (.78)	-2.05 (.82)	-3.08 (.82)	-3.10 (.87)	-2.57 (.97)		
	Median (Range)	-3.06 (-4.54-1.66)	-3.05 (-4.93--1.47)	-2.12 (-3.74--0.08)	-3.26 (-4.55--1.49)	-3.28 (-4.77--1.07)	-2.58 (-4.49-.46)		

NS indicates not significant.

Time periods include 0 to 100, 101 to 365, and >365 days post-transplantation.