

Published in final edited form as:

J Pediatr Hematol Oncol. 2012 May ; 34(4): 304–309. doi:10.1097/MPH.0b013e3182346ed8.

Lung Function Before and After Pediatric Allogeneic Hematopoietic Stem Cell Transplantation: A Predictive Role for DL_{COa}/VA

Troy C. Quigg, DO*, Young-Jee Kim, MD†, W. Scott Goebel, MD, PhD*, and Paul R. Haut, MD*

*Sections of Pediatric Hematology/Oncology/Hematopoietic Stem Cell Transplantation;

†Pediatric Pulmonology, Department of Pediatrics, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN.

Abstract

Background—Pre-allogeneic hematopoietic stem cell transplantation (aHSCT) and post-aHSCT lung function of 41 eligible patients at Riley Hospital for Children were assessed to identify risk factors for post-aHSCT morbidity and mortality.

Observations—One year post-aHSCT pulmonary function tests were significantly lower compared with baseline. These findings recovered at 2 years post-aHSCT. Refractory disease before aHSCT correlated with lower pulmonary function tests after aHSCT. Graft-versus-host disease was significantly associated with higher post-aHSCT residual volume. Importantly, low pre-aHSCT carbon monoxide diffusing capacity adjusted for hemoglobin and alveolar volume was predictive of death.

Conclusions—Among survivors, lung function improves over time after pediatric aHSCT. Measurement of carbon monoxide diffusing capacity adjusted for hemoglobin and alveolar volume before pediatric aHSCT should be further investigated as a predictor of pulmonary dysfunction and mortality.

Keywords

allogeneic hematopoietic stem cell transplantation; pulmonary function tests; graft-versus-host disease; DL_{COa}/VA ; mortality

Allogeneic hematopoietic stem cell transplantation (aHSCT) provides life-saving therapy for a variety of malignant and nonmalignant pediatric diseases. Despite improvements in supportive care, pulmonary complications account for meaningful morbidity and mortality after aHSCT. The incidence of post-aHSCT pulmonary complications in pediatric patients

Copyright © 2012 by Lippincott Williams & Wilkins

Reprints: W. Scott Goebel, MD, PhD, Pediatric Hematopoietic Stem Cell Transplantation Program, Section of Pediatric Hematology/Oncology Indiana University School of Medicine, Riley Hospital for Children, 705 Riley Hospital Drive, Room 4340, Indianapolis, IN 46202 (sgoebel2@iupui.edu).

W.S.G. is medical director of General Biotechnology, LLC, The Genesis Bank, LLC, and Renovocyte, LLC. The other authors have no conflict of interest.

has been reported to be 25% and was associated with higher mortality (65% with pulmonary complications vs. 44% without).¹ Many studies in adults have demonstrated that abnormal pulmonary function tests (PFTs) may be predictive of post-aHSCT mortality and may identify patients at-risk for noninfectious pulmonary complications post-aHSCT.²⁻⁴ Few studies have focused on pediatric aHSCT recipients, and these studies have reported conflicting results on predictors of post-aHSCT morbidity and mortality.

We retrospectively reviewed pre-aHSCT and post-aHSCT PFTs on 41 patients transplanted at our institution over a 5-year period to assess the prevalence of abnormal lung function and to identify PFT variables that may predict post-aHSCT morbidity and mortality. We examined relationships linking lung function abnormalities with age, disease status, earlier pulmonary-toxic chemotherapies, aHSCT conditioning regimen, graft-versus-host disease (GVHD), cytomegalovirus (CMV) immune status, and post-aHSCT death. Importantly, we describe the utility of adjusting carbon monoxide diffusing capacity (DL_{CO}) for both hemoglobin (DL_{COa}) and alveolar volume (DL_{COa}/VA), and its ability to predict post-aHSCT mortality in pediatric patients.

MATERIALS AND METHODS

Patient Characteristics

We retrospectively reviewed PFT and clinical data from patients who underwent aHSCT at Riley Hospital for Children between 2001 and 2006. Institutional review board approval was obtained. A total of 41 of 46 patients from 5 to 19 years of age were eligible for analysis. Five patients were excluded because they were missing baseline PFT data or had nonstandard follow-up times. Thirty-one of 41 recipients had 1-year follow-up PFTs. One year post-aHSCT, 1 patient had transferred care, 4 patients had died (2 of 4 with 1 y post-aHSCT PFTs before death), and 7 patients were alive but without PFTs performed post-aHSCT. Seventeen of 41 recipients had 1 and 2 year follow-up PFTs. At 2 years post-aHSCT, 7 additional patients had died and 13 patients did not follow-up for 2 year post-aHSCT PFTs. Demographic and clinical characteristics are shown in Table 1.

Table 1 shows the number of patients who received agents during conditioning that could cause acute or delayed lung injury. Other conditioning agents (not shown) used during conditioning included antithymocyte globulin, etoposide, bis-chloroethylnitrosourea, and melphalan. Details of GVHD prophylaxis are summarized in Table 1. GVHD was documented as “no” or “yes” (biopsy-proven), and was subcategorized as acute, chronic, or having evidence of both.

Pulmonary Function Testing

All PFTs were performed in the Pediatric Pulmonary Function Laboratory at Riley Hospital for Children. All patients had spirometry, lung volume by plethysmography, and DL_{CO} measured. VA was measured using methane gas. DL_{CO} was measured by the single breath-hold maneuver⁵ using Vmax Encore (VIASYS Healthcare, Yorba Linda, CA), and was adjusted for hemoglobin (DL_{COa}) and VA (DL_{COa}/VA). PFT data were reviewed by a single Pediatric Pulmonologist (Y.J.K.) to ensure reliability. Testing, equipment, and interpretation

of PFTs followed the recommendations of the American Thoracic Society and European Respiratory Society.⁵ Lung function variables were expressed as percent-predicted normal values for age, sex, and height-matched controls. Forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), FEV₁/FVC, forced expiratory flow at midexpiration (FEF_{25%-75%}), total lung capacity (TLC), DL_{COa}, and DL_{COa}/VA <80% of predicted values were considered abnormal. Residual volume (RV) >120% was considered abnormal and suggestive of air trapping.

Statistical Methods

Statistical analyses were performed using SPSS 16 (SPSS Inc., Chicago, IL). P values <0.05 were considered significant. Logistic regression with generalized estimating equations was used to model the association of abnormal PFTs at baseline, 1 and 2 years post-aHSCT. Repeat measures models and logistic regression were used to test associations between pre-aHSCT and post-aHSCT PFT variables and various clinical characteristics. Logistic regression models were used to model the association of abnormal baseline PFTs with death.

RESULTS

Patient Characteristics and Pulmonary Function Testing

The clinical characteristics of the 41 aHSCT patients are summarized in Table 1. Seventeen of 41 patients (41.4%) received pulmonary-toxic chemotherapy before aHSCT. No patients had lung irradiation before aHSCT. Baseline PFT data are summarized in Tables 2 and 3. Absolute numbers and percentages of patients with abnormal PFT parameters at baseline are summarized in Table 3. Twenty-nine of the 41 patients (70.7%) studied had 1 or more abnormal PFT parameters at baseline. Nine of 41 patients (21.9%) had preaHSCT obstructive lung patterns evidenced by an abnormally low FEV₁, FEV₁/FVC, FEF_{25%-75%}, or RV. Fourteen patients (34.1%) presented to aHSCT with abnormally low DL_{COa} and DL_{COa}/VA. We found no significant association between individual before pulmonary-toxic chemotherapy and baseline PFTs.

Thirty-one patients (75.6%) had follow-up PFTs at 11.9 ± 2.2 months post-aHSCT; of these, 17 had follow-up PFTs at a mean of 28.5 ± 5.9 months post-aHSCT. From baseline to first reassessment of lung function post-aHSCT, significantly lower FEV₁ (P = 0.007), FVC (P = 0.007), TLC (P = 0.013), but similar FEV₁/FVC values were observed (Table 2). Although lung volumes decreased over the first year post-aHSCT, mean PFT data were largely within the normal range. DL_{COa} significantly decreased between baseline and 1 year post-aHSCT (Tables 2 and 3), but when adjusted for VA, there was no significant decline in DL_{COa}/VA.

The only significant change in PFT parameters between baseline and 2 years post-aHSCT was an increase in RV (P = 0.041; Table 2); no other PFT data demonstrated evidence of obstructive lung disease. Patients who had refractory disease (n = 4) had significantly lower FEV₁, FVC, and TLC 1 year post-aHSCT, compared with patients with complete remission or nonmalignant disease.

Effect of Clinical Characteristics and Conditioning on Post-aHSCT Lung Function

Using repeated measures models, we studied the effect of pertinent pre-aHSCT and peri-aHSCT clinical data on 1 year post-aHSCT lung function (Table 4). Age (younger than or equal to 8 or older than 8 y) at transplant, preaHSCT CMV serology, human leukocyte antigen match, hematopoietic stem cell source (bone marrow, cord blood, or peripheral blood), and related versus unrelated donor status did not statistically impact post-aHSCT PFTs.

There was no statistically significant effect of total body irradiation (TBI) conditioning on 1 year posttransplant PFTs (Table 4). Ten patients received busulfan/cyclophosphamide (BU/CY) conditioning and had significantly lower DL_{COa}/VA at 1 year posttransplant PFTs, compared with patients who received other conditioning ($P = 0.019$; Table 4). Four BU/CY patients developed infectious pulmonary complications posttransplant and 1 went on to develop pulmonary fibrosis (+12 mo).

GVHD and Post-aHSCT Pulmonary Function

GVHD occurred in 53.7% of patients ($n = 22$). Thirteen patients (31.7%) had acute GVHD (aGVHD), 4 (9.8%) developed chronic GVHD (cGVHD), and 5 (12.2%) had both aGVHD and cGVHD. Eighteen of 22 patients with GVHD had measurement of PFTs at 1 year post-aHSCT and 11 had PFTs at 2 years post-aHSCT. There were no statistically significant changes in PFT parameters related to GVHD at 1 and 2 years post-aHSCT, except for RV. The average RV in patients with GVHD at 1 year post-aHSCT was $91.5 \pm 29.7\%$, compared with preaHSCT RV of $86.6 \pm 44.7\%$ ($P = 0.014$; Table 4), which suggests more air trapping and possible obstruction. At 2 years post-aHSCT, the mean RV increased to $105 \pm 17.9\%$, but this increase was not statistically significant. The average RV for patients without GVHD ($n = 11$, $91.7 \pm 33.8\%$) was similar to the RV for patients with GVHD at 1 year post-aHSCT. The RV for patients without GVHD decreased at 2 years post-aHSCT ($n = 6$, $73.8 \pm 13.8\%$), although this was not statistically significant.

Of patients who had both aGVHD and cGVHD ($n = 5$), the RV at 1 year post-aHSCT was $119 \pm 17\%$, compared with $65 \pm 35.6\%$ at baseline ($P = 0.009$). The RV at 2 years post-aHSCT ($120 \pm 13\%$) remained elevated similar to 1 year post-aHSCT, but was significantly increased compared with baseline ($P = 0.009$). This pattern suggests development of post-aHSCT air trapping and may suggest that development of pulmonary obstruction related to GVHD may be persistent and gradual over time.

Baseline Lung Function as a Predictor of Mortality

Overall post-aHSCT mortality was 26.9% ($n = 11$) at 2 years. Time to post-aHSCT death was 546.3 ± 374.5 days. Of the 4 patients (9.7%) who died within 1 year post-aHSCT, 2 died of disease progression, 1 died of disease progression and fungemia, and 1 succumbed to bacterial sepsis and aGVHD of the liver and skin. All 4 patients had abnormal DL_{COa}/VA before aHSCT, but otherwise normal PFTs. After 1 year post-aHSCT, 1 patient died of unknown cause (lost to follow-up) and 6 patients died of disease progression. Of these 7 patients, only 2 had abnormal PFTs aside from abnormal DL_{COa}/VA . In our cohort of pediatric aHSCT recipients, only an abnormal pre-aHSCT DL_{COa}/VA (univariate analysis)

was found to be a statistically significant predictor of post-aHSCT mortality ($P = 0.038$). No other abnormalities in baseline PFT parameters, including DL_{COa} uncorrected for VA, were predictive of post-aHSCT mortality.

DISCUSSION

The most important observation of this study is that a low pre-aHSCT DL_{COa}/VA , but no other PFT abnormalities, was found to be highly predictive of mortality by 2 years. Among childhood aHSCT survivors, a significant decline in lung function was seen 1 year after transplantation, but recovered to a large degree by 2 years after transplantation. Although lung function significantly improved between 1 and 2 years post-aHSCT in our patient cohort (Table 2), post-aHSCT PFTs remained below baseline values, but not significantly. Overall, our data and the more recent literature support the finding that lung function declines post-aHSCT, but tends to recover over time.⁶⁻⁹ Unlike other studies, which reported the experience of both autologous and allogeneic SCT recipients, we report only allogeneic SCT recipients over a 5-year period, as this group represents the vast majority of SCT-related morbidity and mortality. Two important limitations of our study are the relatively small sample size and retrospective nature of the study, which also made it difficult to correlate respiratory symptoms with pre/post-aHSCT PFTs. Although the literature on pediatric aHSCT recipients and lung function is growing, many of the referenced articles reflect patient sample sizes similar to our study.

Although abnormal PFTs tend to recover after pediatric aHSCT, a few centers have found residual pulmonary dysfunction in survivors at 2 to 10 years post-aHSCT.^{6,10-12} At 1 year, our patients exhibited lower FEV_1 , FVC, and TLC, whereas FEV_1/FVC , $FEF_{25\%-75\%}$, RV, and DL_{COa}/VA remained unchanged. Unlike earlier studies, which showed a greater decline in FVC than FEV_1 ,^{10,12} our cohort demonstrated a proportional decline in FEV_1 and FVC supporting post-aHSCT lung obstruction, not restriction.

We did not find significant changes in pediatric PFTs in association with GVHD, similar to other published reports.^{6,9,12} However, we found that patients who had aGVHD that progressed to cGVHD demonstrated a significant increase in 1 and 2 year post-aHSCT RV compared with baseline (Table 4). We confirmed that patients with refractory disease had significantly worse PFTs post-aHSCT compared with patients in complete remission or patients with nonmalignant disease.^{6,11,12} We did not find any significant correlation between age, CMV status, or earlier pulmonary-toxic chemotherapy and pre/post-aHSCT lung function parameters, morbidity, or mortality. In a study of 90 pediatric aHSCT recipients, Lee et al¹³ reported on the respiratory failure and mortality of 5 of 6 patients with suspected or confirmed CMV pneumonia. Although rates of post-aHSCT CMV antigenemia were similar between our 2 cohorts (24.8% vs. 24.4%), the Korean cohort had higher pre-aHSCT CMV seropositivity of 90% compared with 31.7% in our cohort, which often predicts risk of post-aHSCT CMV reactivation and disease.¹³ In the reported deaths, only 1 of 6 cases of CMV pneumonia were confirmed, which suggests other factors may have contributed. Despite 1 confirmed and 1 suspected case of CMV pneumonia in our cohort, no deaths or respiratory failure ensued. Evaluation of pre-aHSCT PFTs in the Korean cohort may provide insight to the high degree of mortality related to CMV pneumonia.

We did not find a significant difference in post-aHSCT PFTs in the 25 patients (61%) who received TBI in our retrospective cohort, similar to earlier reports.^{1,6,7,9-12} However, our data showed a significant decline in DL_{COa}/VA (Table 4) in patients who received BU/CY conditioning 1 year post-aHSCT. BU has been found to contribute to abnormal lung function after pediatric aHSCT.^{6,10,11} One caveat to our finding is the lack of significant decline in DL_{COa} , compared with DL_{COa}/VA , which would suggest that decline in diffusing capacity in our cohort was dependent on loss of lung volume and VA.

In assessing baseline lung function as a predictor for mortality, patients with a pretransplant $DL_{COa}/VA < 80\%$ had significantly decreased overall survival ($P = 0.038$). Perhaps surprisingly, we did not find a significant association of DL_{COa} with death. Pulmonologists debate whether or not DL_{COa} should be corrected for VA. DL_{COa} is affected by VA, which is in turn dependent on chest size. Thus, DL_{COa} in younger children will be lower than that in adults; a direct comparison without correction for VA could give misleading results. Furthermore, patients with restrictive lung disease tend to have underestimated DL_{COa} and overestimated DL_{COa}/VA , making such measures difficult to interpret and predict clinical importance of lung impairments.¹⁴ Some experts recommend comparing DL_{COa}/VA with TLC to optimize clinical interpretation in patients with known restrictive lung disease.¹⁵ It is important to note that without adjustment for VA, it is difficult to determine whether abnormally low DL_{COa} is due to a deficit in gas exchange, low lung volume, or a combination of both.¹⁶ Despite the difficulty in interpreting DL_{COa} and DL_{COa}/VA , our findings support the concept of adjusting DL_{COa} for VA in aHSCT.¹⁴⁻¹⁹

In a large adult cohort, reduced DL_{COa} and alveolararterial oxygen gradient were associated with increased 1 year post-HCST mortality.² Studies in adult⁴ and pediatric⁶ patients have demonstrated reductions in DL_{CO} over time, but these results have not correlated with posttransplant mortality. Parimon et al¹⁹ described the use of a predictive pre-aHSCT “lung function score,” based on pretransplant FEV_1 and DL_{COa} . Although these authors described predominantly an adult cohort, higher pre-aHSCT lung function scores derived from lower FEV_1 and DL_{COa} values correlated with increased risk of post-aHSCT death. Ginsberg et al⁷ reported a similar finding, but did not adjust DL_{CO} for hemoglobin or VA.

Hoffmeister et al¹⁸ demonstrated that 20% of evaluable pediatric aHSCT survivors had low DL_{COa} and DL_{COa}/VA , suggesting underlying pulmonary vascular disease, which may affect long-term lung function. These results stress the importance of using both DL_{COa} and DL_{COa}/VA in pre-aHSCT and post-aHSCT monitoring of lung function, and imply that DL_{COa}/VA may help identify a subgroup of pre-aHSCT patients at risk for pulmonary dysfunction and mortality. Although some pulmonary data has failed to demonstrate a difference in the ability of DL_{COa} or DL_{COa}/VA to predict abnormal gas exchange or desaturations with exertion, 1 study demonstrated that patients with known abnormal gas exchange were more likely to have lower DL_{COa}/VA than DL_{COa} .¹⁷ We argue that given our data and recent findings, DL_{COa} should be corrected for VA due to the intense treatment many aHSCT recipients receive before aHSCT, and its potential to better identify at-risk patients when used with other PFT parameters.

The American Society for Blood and Marrow Transplantation and the European Group for Blood and Marrow Transplantation have published joint guidelines on long-term monitoring of lung function after HSCT.²⁰ However, these guidelines do not reflect the potential importance in correcting DL_{CO} for hemoglobin and VA. Our data suggests that correction for VA may be important in using DL_{CO} as a pre-aHSCT risk factor, and that utilization of “lung function scores” may be misinterpreted without appropriate adjustment of DL_{CO}. A multicenter, prospective study of lung function in pediatric aHSCT patients could improve current clinical practice and patient outcomes, test previously described predictive tools,^{3,7,8,19} and provide resolution to the conflicting literature on interpretation of DL_{CO} with associated correction in hemoglobin and VA.

Acknowledgments

The authors thank Courtney Spiegel, Riley Hospital HSCT Data Management, and Kathy Christoph, Riley Hospital PFT Lab Coordinator, for their participation in data retrieval, and Katie Lane, Indiana University School of Medicine Department of Biostatistics, for performing statistical analyses.

Supported by the Riley Hospital for Children, Section of Pediatric Hematology/Oncology and the Pediatric Hematopoietic Stem Cell Transplantation Program.

REFERENCES

1. Eikenberry M, Bartakova H, Defor T, et al. Natural history of pulmonary complications in children after bone marrow transplantation. *Biol Blood Marrow Transplant*. 2005; 11:56–64. [PubMed: 15625545]
2. Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. *Chest*. 1992; 101:1257–1264. [PubMed: 1582281]
3. Marras TK, Szalai JP, Chan CK, et al. Pulmonary function abnormalities after allogeneic marrow transplantation: a systematic review and assessment of an existing predictive instrument. *Bone Marrow Transplant*. 2002; 30:599–607. [PubMed: 12407435]
4. Marras TK, Chan CK, Lipton JH, et al. Long-term pulmonary function abnormalities and survival after allogeneic marrow transplantation. *Bone Marrow Transplant*. 2004; 33:509–517. [PubMed: 14716347]
5. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005; 26:948–968. [PubMed: 16264058]
6. Kaya Z, Weiner DJ, Yilmaz D, et al. Lung function, pulmonary complications, and mortality after allogeneic blood and marrow transplantation in children. *Biol Blood Marrow Transplant*. 2009; 15:817–826. [PubMed: 19539213]
7. Ginsberg JP, Alpenc R, McDonough J, et al. Pre-transplant lung function is predictive of survival following pediatric bone marrow transplantation. *Pediatr Blood Cancer*. 2010; 54:454–460. [PubMed: 19876892]
8. Walter EC, Orozco-Levi M, Ramirez-Sarmiento A, et al. Lung function and long-term complications after allogeneic hematopoietic cell transplant. *Biol Blood Marrow Transplant*. 2010; 16:53–61. [PubMed: 20053332]
9. Fanfulla F, Locatelli F, Zoia MC, et al. Pulmonary complications and respiratory function changes after bone marrow transplantation in children. *Eur Respir J*. 1997; 10:2301–2306. [PubMed: 9387957]
10. Bruno B, Souillet G, Bertrand Y, et al. Effects of bone marrow transplantation on pulmonary function in 80 children in a single paediatric centre. *Bone Marrow Transplant*. 2004; 34:143–147. [PubMed: 15170172]
11. Inaba H, Yang J, Pan J, et al. Pulmonary dysfunction in survivors of childhood hematologic malignancies after allogeneic hematopoietic stem cell transplantation. *Cancer*. 2010; 116:2020–2030. [PubMed: 20186702]

12. Cerveri I, Fulgoni P, Giorgiani G, et al. Lung function abnormalities after bone marrow transplantation in children: has the trend recently changed? *Chest*. 2001; 120:1900–1906. [PubMed: 11742920]
13. Lee JW, Kang HJ, Park JD, et al. Early pulmonary complications after hematopoietic stem cell transplantation in pediatric patients: association with cytomegalovirus infection. *J Pediatr Hematol Oncol*. 2009; 31:545–551. [PubMed: 19636275]
14. Frans A, Nemery B, Veriter C, et al. Effect of alveolar volume on interpretation of single breath DLCO. *Respir Med*. 1997; 91:263–273. [PubMed: 9176644]
15. Stam H, Splinter TAW, Versprille A. Evaluation of diffusing capacity in patients with a restrictive lung disease. *Chest*. 2000; 117:752–757. [PubMed: 10713002]
16. Johnson DC. Importance of adjusting carbon monoxide diffusing capacity (DL_{CO}) and carbon monoxide transfer coefficient (K_{CO}) for alveolar volume. *Respir Med*. 2000; 94:28–37. [PubMed: 10714476]
17. Kaminsky DA, Whitman T, Callas PW. DL_{CO} versus DL_{CO}/VA as predictors of pulmonary gas exchange. *Respir Med*. 2007; 101:989–994. [PubMed: 17055236]
18. Hoffmeister PA, Madtes DK, Storer BE, Sanders JE. Pulmonary function in long-term survivors of pediatric hematopoietic cell transplantation. *Pediatr Blood Cancer*. 2006; 47:594–606. [PubMed: 16086420]
19. Parimon T, Madtes DK, Au DH, et al. Pretransplant lung function, respiratory failure, and mortality after stem cell transplantation. *Am J Respir Crit Care Med*. 2005; 172:384–390. [PubMed: 15894602]
20. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2006; 12:138–151. [PubMed: 16443512]

TABLE 1

Demographic and Clinical Characteristics of 41 aHSCT Recipients

	N (%)
Male	26 (63.4%)
White	37 (90.2%)
Age (y, mean \pm SD)	12.5 \pm 4.3
Age \geq 8 y	10 (24.4%)
Time from diagnosis to aHSCT (d)	828 \pm 990
Median time to aHSCT (d)	522
Diagnosis	
ALL	17 (41.5%)
AML	12 (29.3%)
Hodgkin lymphoma	1 (2.4%)
Non-Hodgkin lymphoma	3 (7.3%)
Nonmalignant disease*	8 (19.4%)
Pretransplant CMV status	
IgG positive	13 (31.7%)
IgM negative [†]	2 (4.9%)
IgG negative	26 (63.4%)
Earlier pulmonary-toxic chemotherapy	
Bleomycin	1 (2.4%)
Methotrexate	14 (34.1%)
Fludarabine	2 (4.9%)
Disease status [‡]	
CR1	10 (24.4%)
CR2	15 (36.6%)
CR3	4 (9.8%)
Refractory	4 (9.8%)
Nonmalignant disease	8 (19.4%)
Conditioning	
Total body irradiation	25 (61.0%)
Cyclophosphamide	34 (82.9%)
Busulfan	10 (24.4%)
Fludarabine	4 (9.8%)
aHSCT product	
Bone marrow	23 (56.1%)
Umbilical cord blood	14 (34.1%)
PBPC	4 (9.8%)
Donor-recipient HLA match	
6/6	27 (65.8%)
5/6	4 (9.8%)
4/6	10 (24.4%)

	N (%)
Related donor	22 (53.7%)
GVHD prophylaxis	
Cyclosporine + methylprednisolone	7 (17.2%)
Cyclosporine + methotrexate	31 (75.6%)
Cyclosporine + mycophenolate mofetil	1 (2.4%)
Cyclosporine (single agent)	1 (2.4%)
Tacrolimus + methotrexate	1 (2.4%)
GVHD	22 (53.7%)
Acute	13 (31.7%)
Chronic	4 (9.8%)
Both	5 (12.2%)
Hepatic sinusoidal obstruction syndrome	1 (2.4%)
Post-aHSCT deaths (overall mortality)	11 (26.9%)

aHSCT indicates allogeneic hematopoietic stem cell transplantation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CMV, cytomegalovirus; CR, complete remission; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; PBPC, peripheral blood progenitor cells.

* Nonmalignant disease: severe aplastic anemia (n = 5), Kostmann syndrome (n = 1), Fanconi anemia (n = 1), and hemophagocytic lymphohistiocytosis-HLH (n = 1).

† Only CMV IgM obtained pre-aHSCT (n = 2).

‡ CR1: first complete remission, CR2: second complete remission, CR3: third complete remission.

TABLE 2

PFT Values at Pre-aHSCT, 1 Year and 2 Year Post-aHSCT

PFT Parameter	Years From aHSCT*	Mean (%)	SD (\pm %)	From Baseline to 1 y Post-aHSCT (P)	From Baseline to 2 y Post-aHSCT (P)	Change Between 1 and 2 y Post-aHSCT (P)
FEV ₁	2	88.1	18.0	0.007	0.405	0.157
FEV ₁	1	83.3	17.5			
FEV ₁	0	91.7	14.7			
FVC	2	88.5	20.8	0.007	0.443	0.146
FVC	1	83.4	19.7			
FVC	0	91.9	14.1			
FEV ₁ /FVC	2	87.9	7.59	0.393	0.895	0.370
FEV ₁ /FVC	1	88.8	6.52			
FEV ₁ /FVC	0	88.0	6.91			
FEF _{25%-75%}	2	103	26.9	0.761	0.086	0.166
FEF _{25%-75%}	1	97.3	25.6			
FEF _{25%-75%}	0	96.3	29.1			
RV	2	95.6	22.3	0.142	0.041	0.575
RV	1	91.9	30.2			
RV	0	82.4	31.7			
TLC	2	92.4	16.3	0.013	0.523	0.186
TLC	1	88.7	17.6			
TLC	0	94.1	14.3			
DL _{COa}	2	76.9	13.7	0.002	0.212	0.258
DL _{COa}	1	72.0	18.9			
DL _{COa}	0	82.2	14.9			
DL _{COa} /VA	2	85.5	13.9	0.686	0.342	0.074
DL _{COa} /VA	1	81.8	16.0			
DL _{COa} /VA	0	82.9	13.3			

aHSCT indicates allogeneic hematopoietic stem cell transplantation; DL_{COa}, carbon monoxide diffusing capacity adjusted for hemoglobin; FEF_{25%-75%}, forced expiratory flow at midexpiration; FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function test; RV, residual volume; TLC, total lung capacity; VA, alveolar volume.

Statistically significant values are in bold.

* Time 0 = Pre-aHSCT (n = 41), Time 1 = Estimated 1 y post-aHSCT (n = 31), Time 2 = Estimated 2 y post-aHSCT (n = 17).

TABLE 3

Number and Percent of Patients With Abnormal PFTs at Each Time Point

PFT Parameter	Baseline* n (%)	1 y Post-aHSCT† n (%)	2 y Post-aHSCT‡ n (%)	Baseline to 1 y Post-aHSCT P	Baseline to 2 y Post-aHSCT P
FEV ₁	8 (19.5%)	11 (35.5%)	3 (17.6%)	0.013	0.774
FVC	8 (19.5%)	11 (35.5%)	5 (29.4%)	0.009	0.190
FEV ₁ /FVC	3 (7.3%)	3 (9.7%)	2 (11.8%)	0.362	0.256
FEF _{25%-75%}	13 (31.7%)	7 (22.6%)	4 (23.5%)	0.310	0.433
RV	4 (10.5%)	4 (13.3%)	3 (17.6%)	0.682	0.416
TLC	5 (13.2%)	8 (26.7%)	3 (17.6%)	0.075	0.883
DL _{COa}	14 (43.8%)	18 (72.0%)	10 (62.5%)	0.012	0.193
DL _{COa} /VA	14 (43.8%)	11 (44.0%)	5 (31.3%)	0.643	0.444

aHSCT indicates allogeneic hematopoietic stem cell transplantation; DL_{COa}, carbon monoxide diffusing capacity adjusted for hemoglobin; FEF_{25%-75%}, forced expiratory flow at midexpiration; FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function test; RV, residual volume; TLC, total lung capacity; VA, alveolar volume.

* Total patients with baseline PFTs = 41.

† Total patients with 1 y post-aHSCT PFTs = 31.

‡ Total patients with 2 y post-aHSCT PFTs = 17.

TABLE 4

Effect of Age, CMV Status, Conditioning, and GVHD on 1 Year Post-aHSCT PFTs*

PFT Parameter	Age 8 y	Pre-aHSCT CMV Status	TBI	BU/CY	GVHD [†]
FEV ₁	0.939	0.457	0.493	0.863	0.891
FVC	0.392	0.186	0.237	0.699	0.876
FEV ₁ /FVC	0.688	0.094	0.215	0.531	0.509
FEF _{25%-75%}	0.527	0.050	0.340	0.940	0.653
RV	0.846	0.264	0.688	0.486	0.014
TLC	0.309	0.054	0.795	0.620	0.180
DL _{COa}	0.887	0.850	0.601	0.157	0.417
DL _{COa} /VA	0.167	0.743	0.122	0.019	0.434

aHSCT indicates allogeneic hematopoietic stem cell transplantation; CMV, cytomegalovirus; CR, complete remission; DL_{COa}, carbon monoxide diffusing capacity adjusted for hemoglobin; FEF_{25%-75%}, forced expiratory flow at midexpiration; FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; GVHD, graft-versus-host disease; PFT, pulmonary function test; RV, residual volume; TBI, total body irradiation; VA, alveolar volume.

Statistically significant values are in bold.

* No significant effects at 2 y post-aHSCT (data not shown).

[†] Presence of GVHD.