Pretransplant Lung Function, Respiratory Failure, and Mortality after Stem Cell Transplantation

Tanyalak Parimon, David K. Madtes, David H. Au, Joan G. Clark, and Jason W. Chien

Clinical Research Division, Fred Hutchinson Cancer Research Center; and Health Services Research and Development, VA Puget Sound Health Care System, Department of Veterans Affairs, Seattle, Washington

Rationale: The role of pulmonary function before stem cell transplant as a potential risk factor for the development of early post-transplant respiratory failure and mortality is controversial. **Methods:** We conducted a retrospective analysis of the pretransplant pulmonary function of 2,852 patients who received their transplant between 1990 and 2001. **Measurements:** Pretransplant FEV₁, FVC, total lung capacity (TLC), diffusing capacity of carbon monoxide (DL_{CO}), and the alveolar-arterial oxygen tension difference P(A-a)O₂ were measured and assessed for association with development of early respiratory failure and mortality in Cox proportional hazard logistic models. **Main Results:** In multivariate analyses, progressive decrease of all lung function parameters was associated with a stepwise increase in risk of developing early respiratory failure and mortality when assessed in independent models. On the basis of a significant correlation between FEV₁ and FVC ($r = 0.81$), FEV₁ and TLC ($r = 0.61$), and FVC and TLC ($r = 0.80$), and a lack of correlation between FEV₁ and DL_{CO}, we developed a pretransplant lung function score based on pretransplant FEV₁ and DL_{CO} to determine the extent of pulmonary compromise before transplant. Multivariate analysis indicated that higher pretransplant lung function scores are associated with a significant increased risk for developing early respiratory failure (category II hazard ratio [HR], 1.4; category III HR, 2.2; category IV HR, 3.1; $p < 0.001$) and death (category II HR, 1.2; category III HR, 2.2; category IV HR, 2.7; $p < 0.005$). **Conclusions:** These results suggest that not only does compromised pretransplant lung function contribute to the risk for development of early respiratory failure and mortality but this risk may be estimated before transplant by grading the extent of FEV₁ and DL_{CO} compromise.

Keywords: bone marrow transplantation; mortality; pretransplant pulmonary function tests; respiratory failure

Pulmonary function tests (PFTs) are routinely performed before hematopoietic stem cell transplantation (HCT) as a screen for underlying respiratory abnormalities and to provide baseline lung function measurements. Pretransplant studies serve as comparison studies for post-transplant PFTs that are obtained when HCT-related pulmonary complications are suspected. Although the uses of pretransplant PFTs are well accepted, little is known about their relationship with post-transplant complications, such as early post-transplant respiratory failure and mortality (1).

Studies that have examined the predictive value of pretransplant PFTs for post-transplant complications suggest that poor

lung function before transplant increases the risk for post-transplant pulmonary complications (2–6) and mortality (3, 7, 8). These findings were not, however, confirmed in the largest study conducted by Crawford and Fisher (9), in 1992, which did not find spirometric or lung volume measurements to be associated with mortality. In addition, the majority of these analyses disagreed on which pretransplant lung function parameter was the strongest predictor of post-transplant pulmonary complications and mortality and they were limited by relatively small cohorts consisting of both autologous and allogeneic HCT patients (1, 4–6, 8). Given the conflicting conclusions of previous studies and the significant changes in HCT care over the last decade, we conducted a 12-year retrospective cohort study to assess whether compromised pretransplant pulmonary function is associated with an increased risk for developing early respiratory failure and post-transplant mortality among adult allogeneic HCT patients. Some of the results of these studies have been previously reported in the form of an abstract (10).

METHODS

Patient Selection

All patients who underwent allogeneic HCT at Fred Hutchinson Cancer Research Center between January 1, 1990, and December 31, 2001, were eligible for the study ($n = 3,765$). Patients who were younger than 15 years ($n = 289$) and without a pretransplant PFT ($n = 624$) were excluded.

Clinical Data

The patient's underlying disease state was categorized as low, intermediate, or high risk (11). Low-risk diseases included chronic myeloid leukemia in chronic phase, refractory anemia, aplastic anemia, and Blackfan-Diamond syndrome. Intermediate-risk diseases included chronic myeloid leukemia in accelerated phase or in chronic phase after blast phase, acute leukemia or lymphoma in remission, refractory anemia with excess blasts, chronic lymphocytic leukemia, and paroxysmal nocturnal hemoglobinuria. High-risk diseases included chronic myeloid leukemia in blast phase, juvenile chronic myeloid leukemia, acute leukemia or lymphoma in relapse, refractory anemia with excess blasts in transformation, and myeloma. Solid malignancies and nonhematologic diseases were classified as high risk. Donor match status was determined according to donor-recipient ABO compatibility and HLA-A, HLA-B, and HLA-DR status. Stem cell sources were classified as bone marrow, peripheral blood stem cell, and other, which included cord blood, or a combination of bone marrow and peripheral blood stem cell. Patients in the nonmyeloablative group received 2 Gy of total body irradiation (TBI). Patients in the myeloablative group were subdivided as receiving either a TBI- or non-TBI-based regimens. The TBI regimens were subgrouped according to dose (≤ 12 or > 12 Gy). The non-TBI-based regimens were subgrouped according to use of busulfan (4 mg/kg/day for 4 consecutive days) or targeted busulfan (4 mg/kg/day for 4 consecutive days, target of 600–900 ng/ml). Acute graft-versus-host disease (GVHD) was graded based on stages of organ involvement using standard criteria and categorized as “no” (grades 0–II) or “yes” (grades III–IV), as previously reported (11–13). The diagnosis and staging of chronic GVHD were established by using clinical, histologic, and laboratory criteria published previously (14), and were characterized according to the presence or absence of clinical extensive chronic GVHD. Acute and chronic GVHD were then integrated and categorized as no acute

(Received in original form February 10, 2005; accepted in final form May 10, 2005)

Supported by National Institutes of Health grants 1R01 HL71914-01, 1K23HL69860-01, HL36444, CA18029, CA78902, and CA15704; an American Lung Association of Washington Research grant; and the Amy Strelzer Manasevit Research Award from the National Marrow Donor Program. D.H.A. is supported by a VA Health Services Research and Development Career Development Award.

Correspondence and requests for reprints should be addressed to Jason W. Chien, M.D., Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Suite D5-280, Seattle, WA 98109-1024. E-mail: jchien@fhcrc.org

Am J Respir Crit Care Med Vol 172, pp 384–390, 2005

Originally Published in Press as DOI: 10.1164/rccm.200502-2120C on May 13, 2005

Internet address: www.atsjournals.org

or chronic GVHD, acute GVHD alone, *de novo* chronic GVHD (not preceded by acute GVHD), quiescent-onset chronic GVHD (preceded by acute GVHD that was followed by a period of quiescence), or progressive-onset chronic GVHD (preceded by acute GVHD without period of quiescence).

Lung Function Testing

According to standard transplant protocol at our center, when possible, all patients received a PFT and arterial blood gas before transplant. The PFT and arterial blood gas values obtained closest to the time of transplant were used in the analysis. Among patients who received a bronchodilator challenge during the PFT ($n = 510$), only the prebronchodilator values were selected for study. All PFTs were performed at the Fred Hutchinson Cancer Research Center, according to the American Thoracic Society guidelines (15), using the Gould 1001 (Gould, Inc., Dayton, OH) from January 1990 to June 1991, the Sensormedics 2100 (Sensormedics Co., Yorba Linda, CA) from July 1991 to August 1999, and the Sensormedics V-Max 22 with Autobox 6200 (Sensormedics Co.) from September 1999 to December 2001. Published equations for adults were used to determine predicted values of FEV₁, FVC, total lung capacity (TLC), and diffusing capacity of carbon monoxide (DL_{CO}) (16). All DL_{CO} measurements were corrected for the hemoglobin measurement obtained closest to the time the diffusion capacity was measured (17). All pulmonary function values, except for the FEV₁/FVC ratio, were expressed as a percentage of the predicted values. The FVC, FEV₁, TLC, FEV₁/FVC, and DL_{CO} were categorized as greater than 80%, 70 to 80%, 60 to 70%, and less than 60%. As per protocol, arterial blood gas samples were obtained by percutaneous radial artery puncture while the patients breathed room air, unless the patient's platelet count was less than 50,000 / μ l, the collateral arterial flow was inadequate, or if the patient refused. The alveolar-arterial oxygen tension difference (P(A-a)O₂) was calculated using the alveolar gas equation (18). The P(A-a)O₂ was categorized as less than 20, 20 to 30, and greater than 30 mm Hg.

Early-Onset Respiratory Failure

Patients were defined as having developed early respiratory failure if they required mechanical ventilation for a nonelective reason within 120 days after transplant. Respiratory failure occurring after 120 days was not assessed because patients are routinely discharged from our center after the first 120 days post-transplant. Mortality after mechanical ventilation was defined as death occurring while receiving mechanical ventilation or death occurring within 30 days after extubation.

Statistical Methods

All statistical analyses were performed using STATA 8.0 (StataCorp, College Station, TX), and p values of less than 0.05 were considered statistically significant. PFT values and other covariates were considered as categorical variables in the analyses. Pretransplant pulmonary function variables were compared using Pearson's χ^2 tests. The rates of developing early respiratory failure and mortality according to lung function parameters were estimated using Kaplan-Meier curves and assessed using the log-rank test. Each PFT parameter was analyzed in independent multivariable Cox proportional hazard models that included other variables found to be significant in forward and backward stepwise analyses. Development of acute and chronic GVHD and disease relapse were included as time-dependent covariates. The proportional hazard assumption was tested using Schoenfeld residuals. Correlation (r) between FEV₁, FVC, TLC, and DL_{CO} was assessed by including all of these variables into the respiratory failure and mortality models described above and assessing the correlation between the coefficients of these parameters.

RESULTS

Clinical Characteristics and Baseline Lung Function

The clinical characteristics of 2,852 patients are summarized in Table 1. The median number of days before transplant that PFTs were performed was 25 days (range, 5–344 days). Pretransplant spirometric measurements before HCT were complete for the entire cohort. Of these, 2,823 (98.9%), 2,811 (98.5%), and 1,311

TABLE 1. PATIENT CHARACTERISTICS

Clinical Variables	No. Patients (%)
Age, yr (median, 40.6; range, 15–72.5)	2,852 (100)
< 20	171 (6)
20–40	1,215 (42)
40–60	1,393 (49)
> 60	73 (3)
Sex, M:F	1:1.4
Race	87.4% White
Disease risk at transplant	
Low	845 (30)
Intermediate	775 (27)
High	1,232 (43)
Donor HLA status	
HLA-matched related	1,429 (50)
HLA-mismatched related	297 (10)
Unrelated	1,126 (40)
Stem cell source	
Bone marrow	2,262 (79)
PBSC	568 (20)
Others	22 (1)
Cytomegalovirus serologic status, recipient–donor	
Negative–negative	929 (33)
Negative–positive	405 (14)
Positive–negative	662 (23)
Positive–positive	832 (30)
Conditioning regimens	
Nonmyeloablative	143 (5)
Myeloablative	
1.1. TBI $\leq$ 12 Gy	752 (26)
1.2. TBI > 12 Gy	1,043 (36)
1.3. Non-TBI-based	
Targeted busulfan	535 (19)
Nontargeted busulfan	274 (10)
Others	105 (4)
GVHD category	
No acute or chronic GVHD	136 (5)
Acute GVHD only	1,142 (40)
<i>De novo</i> chronic GVHD	311 (11)
Quiescent chronic GVHD	1,055 (37)
Progressive chronic GVHD	208 (7)
Disease status post-transplant	
Nonrelapsed	2,210 (78)
Relapsed	642 (22)

Definition of abbreviations: F = female; GVHD = graft-versus-host disease; M = male; PBSC = peripheral blood stem cell; TBI = total body irradiation.

(39.6%) patients had TLC, DL_{CO}, and arterial blood gas measurements before transplant, respectively. Over 80% of the patients had a normal FEV₁, FVC, FEV₁/FVC, TLC, and DL_{CO} before transplant (Table 2). Among 1,311 patients who had an arterial blood gas performed, the median P(A-a)O₂ was 5.4 (range, 0–52.9) mm Hg. There were 1,115 (85%), 140 (11%), and 56 (4%) patients who had a P(A-a)O₂ of less than 20, 20 to 30, and greater than 30 mm Hg, respectively.

Pretransplant Lung Function and Early Respiratory Failure

Early respiratory failure developed in 396 of 2,852 patients (14%). The median number of days after transplant to respiratory failure was 21 days (range, 1–120 days). The median numbers of total ventilator days was 5 days (range, 1–110 days). A total of 359 patients (91%) died after receiving mechanical ventilator support. In comparison to patients who did not develop early respiratory failure, patients with respiratory failure were more likely to have impaired lung function. Univariate analysis demonstrated that pretransplant FEV₁, FVC, TLC, DL_{CO}, and P(A-a)O₂ were more likely to be reduced among patients who developed early respiratory failure (Table 3). In inde-

TABLE 2. DISTRIBUTION OF PRETRANSPLANT PULMONARY FUNCTION TEST PARAMETERS

PFT Parameters	> 80%, n (%)	70–80%, n (%)	60–70%, n (%)	< 60%, n (%)	Median (range)
FEV ₁ , %	2,329 (82)	322 (11)	113 (4)	88 (3)	93.2 (26–171)
FVC, %	2,535 (89)	187 (6)	80 (3)	50 (2)	99.9 (23–155)
FEV ₁ /FVC	2,676 (94)	139 (5)	31 (1)	6 (< 1)	94.5 (49–163)
TLC, %	2,581 (91)	172 (6)	50 (2)	20 (1)	98.8 (20–169)
DL _{CO} , %	2,320 (83)	298 (11)	126 (4)	68 (2)	98.2 (10–213)

Definition of abbreviations: DL_{CO} = diffusing capacity of carbon monoxide; PFT = pulmonary function test; TLC = total lung capacity.

pendent multivariable analyses for each lung function parameter, the association of reduced pretransplant lung function and development of early respiratory failure was significant for FVC, TLC, and DL_{CO} less than 80% and for P(A-a)O₂ of more than 30 mm Hg. Pretransplant FEV₁ of less than 70% was significantly associated with presence of early respiratory failure. All of these models included other potential risk factors for developing early respiratory failure, such as age at transplant, disease risk at transplant, donor HLA status, stem cell source, cytomegalovirus serology, conditioning regimens, and the presence of acute GVHD.

Pretransplant Lung Function and Post-Transplant Mortality

Kaplan-Meier analyses indicated that a significant stepwise increase in mortality risk was associated with progressively worse pretransplant lung function, regardless of which pulmonary function parameter was used (Figures 1A–1D). Univariate analysis demonstrated that pretransplant FEV₁, FVC, TLC, DL_{CO}, and P(A-a)O₂ were more likely to be compromised among patients

who died (Table 4). After adjustments that included other risk factors for post-transplant mortality (age at transplant, disease risk at transplant, donor HLA status, cytomegalovirus serology, stem cell sources, conditioning regimens, presence of acute and chronic GVHD, and disease relapse), a significant increase in mortality risk was not observed until the lung function parameters were less than 70%, or the P(A-a)O₂ was greater than 20 mm Hg (Table 4).

The Pretransplant Lung Function Score

Because PFT parameters represent variables that are not likely to be independent predictors of the outcome variables, we assessed for potential significant correlation between the individual PFT parameters. FEV₁ significantly correlated with FVC ($r = 0.81$) and TLC ($r = 0.61$). FVC was also significantly correlated with TLC ($r = 0.80$). There was no significant correlation between DL_{CO} and any of the other PFT parameters (DL_{CO} and FEV₁, $r = 0.35$; DL_{CO} and FVC, $r = 0.42$; DL_{CO} and TLC, $r = 0.38$). Given the significant correlation between FEV₁, FVC, and TLC,

TABLE 3. DISTRIBUTION OF PRETRANSPLANT LUNG FUNCTION PARAMETERS AND THEIR ASSOCIATED RISK FOR DEVELOPMENT OF EARLY RESPIRATORY FAILURE

Lung Function Parameters	Early Respiratory Failure				
	No (%) (n = 2,456)	Yes (%) (n = 396)	p Value	HR (95% CI)*	p Value
FEV ₁ , %					
> 80	2,046 (83)	283 (72)		Referent	—
70–80	269 (11)	53 (13)		1.3 (0.9–1.8)	NS
60–70	75 (3)	38 (10)		2.9 (2.1–4.2)	< 0.001
< 60	66 (3)	22 (5)	< 0.001	2.7 (1.7–4.2)	< 0.001
FVC, %					
> 80	2,221 (90)	314 (79)		Referent	—
70–80	142 (6)	45 (11)		2.1 (1.5–2.9)	< 0.001
60–70	58 (3)	22 (6)		2.7 (1.7–4.2)	< 0.001
< 60	35 (1)	15 (4)	< 0.001	3.4 (2.0–5.9)	< 0.001
TLC, %					
> 80	2,255 (93)	326 (84)		Referent	—
70–80	132 (5)	40 (10)		1.7 (1.2–2.4)	< 0.001
60–70	35 (1)	15 (4)		3.3 (1.9–5.6)	< 0.001
< 60	13 (1)	7 (2)	< 0.001	3.5 (1.6–7.5)	0.001
DL _{CO} , %					
> 80	2,033 (84)	286 (74)		Referent	—
70–80	242 (10)	56 (14)		1.7 (1.3–2.2)	< 0.001
60–70	100 (4)	26 (7)		2.4 (1.6–3.6)	< 0.001
< 60	49 (2)	19 (5)	< 0.001	3.4 (2.1–5.4)	< 0.001
P(A-a)O ₂					
< 20	1,061 (86)	54 (74)		Referent	—
20–30	128 (10)	12 (16)		1.9 (1.0–3.6)	NS
> 30	49 (4)	7 (10)	0.013	2.4 (1.03–5.6)	0.041

Definition of abbreviations: CI = confidence interval; DL_{CO} = diffusing capacity of carbon monoxide; HR = hazard ratio; NS = not significant; P(A-a)O₂ = alveolar–arterial oxygen tension difference; TLC = total lung capacity.

*Each pretransplant lung function parameter was analyzed in independent Cox proportional hazard models that adjusted for age at transplant, disease risk at transplant, donor match, stem cell source, cytomegalovirus serology, conditioning regimens, and the presence of acute graft-versus-host disease.

Figure 1. (A–D) Kaplan-Meier survival curves demonstrating the relationship between survival probability and pretransplant lung function parameters, including lung function reflected by the pretransplant lung function score (LFS). The p values for all figures were less than 0.001. These panels indicate that the pretransplant LFS can distinguish the risk for mortality more clearly than FEV₁, diffusing capacity of carbon monoxide (DL_{CO}), and alveolar–arterial oxygen tension difference (P[A–a]O₂) alone.

TABLE 4. DISTRIBUTION OF PRETRANSPLANT LUNG FUNCTION PARAMETERS AND THEIR ASSOCIATED RISK FOR MORTALITY

Lung Function Parameters	Mortality		p Value	HR (95% CI)*	p Value
	Survived (%; n = 1,233)	Died (%; n = 1,619)			
FEV ₁ , %					
> 80	1,077 (87)	1,252 (77)		Referent	—
70–80	109 (9)	213 (13)		0.9 (0.8–1.1)	NS
60–70	33 (3)	80 (5)		1.7 (1.3–2.1)	< 0.001
< 60	14 (1)	74 (5)	< 0.001	2.2 (1.7–2.8)	< 0.001
FVC, %					
> 80	1,153 (93)	1,382 (85)		Referent	—
70–80	52 (4)	135 (8)		1.1 (0.9–1.4)	NS
60–70	20 (2)	60 (4)		1.7 (1.3–2.2)	< 0.001
< 60	8 (1)	42 (3)	< 0.001	2.1 (1.5–2.9)	< 0.001
TLC, %					
> 80	1,173 (96)	1,408 (88)		Referent	—
70–80	41 (3)	131 (8)		1.1 (0.9–1.3)	NS
60–70	10 (1)	40 (3)		2.4 (1.7–3.3)	< 0.001
< 60	3 (< 0.5)	17 (1)	< 0.001	2.0 (1.2–3.2)	0.005
DL _{CO} , %					
> 80	1,087 (89)	1,232 (77)		Referent	—
70–80	90 (7)	208 (13)		1.1 (0.9–1.3)	NS
60–70	35 (3)	91 (6)		2.1 (1.7–2.7)	< 0.001
< 60	5 (< 0.5)	63 (4)	< 0.001	2.5 (1.9–3.2)	< 0.001
P(A–a)O ₂					
< 20	817 (88)	298 (77)		Referent	—
20–30	88 (10)	52 (13)		1.4 (1.02–1.9)	0.037
> 30	19 (2)	37 (10)	< 0.001	3.2 (2.2–4.6)	< 0.001

For definition of abbreviations, see Table 3.

*Each pretransplant lung function parameter was analyzed in independent Cox proportional hazard models that adjusted for age at transplant, disease risk at transplant, donor match, stem cell source, cytomegalovirus serology, conditioning regimens, presence of acute and chronic graft-versus-host disease, and disease relapse.

TABLE 5. THE PRETRANSPLANT LUNG FUNCTION SCORE CATEGORIES

Pretransplant LFS Category	Description	Pretransplant LFS
I	Normal	2
II	Mildly decreased	3–4
III	Moderately decreased	5–6
IV	Severely decreased	7–8

Definition of abbreviation: LFS = lung function score.

The pretransplant LFS represents the sum of the FEV₁ and DL_{CO} score, where > 80% = 1, 70–80% = 2, 60–70% = 3, and < 60% = 4.

and lack of correlation between the DL_{CO} and these parameters, we investigated whether lung function measured by both the FEV₁ and the DL_{CO} together would result in a stronger association with the outcomes of interest. Using the current categories, we assigned a separate score to the pretransplant FEV₁ and DL_{CO} of 2,811 patients (> 80% = 1, 70–80% = 2, 60–70% = 3, < 60% = 4). These scores were then summed and divided into four categories as the pretransplant lung function score (LFS; Table 5). Comparison of the independent FEV₁, DL_{CO}, and P(A-a)O₂ Kaplan-Meier survival curves with the pretransplant LFS curves indicated the LFS curves were more clearly associated with the survival probability (Figure 1D). Multivariable analysis demonstrated that, in contrast to the independent FEV₁ and DL_{CO} models, each successively higher LFS category was associated with a significant increase in risk for development of both outcomes (Tables 6 and 7). Univariate analysis of the pretransplant LFS stratified by the conditioning regimen (Figure 2) indicates that the survival probability was lowest for patients with a pretransplant LFS in category IV who received a TBI-based regimen (Figures 2C and 2D).

DISCUSSION

The pretransplant PFTs play an important role in the management of HCT patients. These tests are widely used as part of standard assessments to help the clinician identify patients with compromised lung function before transplant. However, the potential post-transplant implications of abnormal pretransplant PFTs remain elusive and controversial, probably because only a few small studies have been conducted to examine this issue. One moderately sized study by Ghalie and colleagues (2) found that a reduced pretransplant FEV₁ is associated with the development of early post-transplant pulmonary complications, defined as a localized or diffuse pulmonary infiltrate, pulmonary hemorrhage, and adult respiratory distress syndrome. Other studies have found an association between pretransplant lung function and early mortality (7, 9). In 1992, Crawford and Fisher (9)

conducted a study at Fred Hutchinson Cancer Research Center on 1,297 patients that found pretransplant spirometric and lung volume measurements were not useful in predicting mortality risk during the first year after transplant. However, this study did find a DL_{CO} of less than 80% and a P(A-a)O₂ difference of more than 20 mm Hg were associated with a small increased risk of mortality. Goldberg and coworkers (7) also found that a decreased pretransplant DL_{CO} (< 52%) was associated with mortality within the first 100 days after HCT in 378 patients (p = 0.02). In addition, they also found a mildly decreased FEV₁ (< 78%; p = 0.0002) was significantly associated with early mortality.

The results of the current study are in general agreement with the findings of previous smaller studies; patients with abnormal lung function before transplant are likely to be at higher risk for developing post-transplant pulmonary complications and mortality. Unique to our data is the finding that all PFT parameters, as well as the P(A-a)O₂ difference, were significantly associated with early respiratory failure and mortality. Our multivariate analyses demonstrated that there was a significant stepwise increase in risk associated with incremental compromise of pretransplant lung function as measured by all of the parameters. This is in contrast to the previous studies that demonstrated associations with select mildly or moderately decreased lung function. Part of the robustness of our results can be attributed to the size of our study cohort, which provided sufficient power to detect these associations with the most severely compromised lung function category for all of the parameters.

An important aspect of our study is the finding that, when the pretransplant FEV₁ and DL_{CO} are considered together as the pretransplant LFS, they appear to represent a more discriminating variable for risk of early respiratory failure and mortality than when they are considered independently. This is likely because the FEV₁ and DL_{CO} represent different sensitive surrogate markers of a patient's physiologic state. FEV₁ is a well recognized measure of lung function that is affected by both obstructive and restrictive pulmonary processes. Although the causes of an obstructive pattern on PFTs are limited to the airway, a restrictive pattern on the PFTs can be secondary to parenchymal and/or nonparenchymal changes, both of which can be affected by many conditions common in our population, such as advanced malignant disease, thoracic radiation and/or chemotherapy, generalized muscle weakness, or spinal cord compression. The DL_{CO} reflects the availability of the pulmonary-capillary surface area and is affected by a number of factors, including alveolar membrane thickness, hemoglobin level, cardiac function, and heterogeneity of regional ventilation and perfusion (19, 20). Reduction of the pretransplant DL_{CO} likely represents an abnormality in one or more of these factors, which can also be caused by advanced malignant disease, thoracic radia-

TABLE 6. THE PRETRANSPLANT LUNG FUNCTION SCORE AND ITS ASSOCIATION WITH EARLY RESPIRATORY FAILURE

Pretransplant Lung Function Score, Respiratory Failure*	Distribution of HCT Recipients (n = 2,811)		HR (95% CI)	p Value
	No Respiratory Failure (n = 2,424; %)	Respiratory Failure (n = 387; %)		
Category I	1,789 (74)	232 (60)	Referent	—
Category II	489 (20)	98 (25)	1.4 (1.3–1.6)	< 0.001
Category III	112 (5)	43 (11)	2.2 (1.8–2.6)	< 0.001
Category IV	34 (1)	14 (4)	3.1 (2.3–4.2)	< 0.001

Definition of abbreviations: CI = confidence interval; HCT = hematopoietic stem cell transplantation; HR = hazard ratio.

*Adjusted for age at transplant, disease risk at transplant, donor HLA status, stem cell sources, cytomegalovirus serology, conditioning regimens, and the presence of acute graft-versus-host disease.

TABLE 7. THE PRETRANSPLANT LUNG FUNCTION SCORE AND ITS ASSOCIATION WITH MORTALITY

Pretransplant Lung Function Score, Mortality*	Distribution of HCT Recipients (n = 2,811)		HR (95% CI)	p Value
	Survived (n = 1,217; %)	Died (n = 1,594; %)		
Category I	977 (80)	1,044 (66)	Referent	—
Category II	202 (17)	385 (24)	1.2 (1.1–1.3)	0.005
Category III	35 (3)	120 (7)	2.2 (1.8–2.7)	< 0.001
Category IV	3 (< 1)	45 (3)	2.7 (2.0–3.7)	< 0.001

For definition of abbreviations, see Table 6.

*Adjusted for age at transplant, disease risk at transplant, donor HLA status, cytomegalovirus serology, stem cell sources, conditioning regimens, presence of acute and chronic graft-versus-host disease, and presence of relapsed underlying malignancies post-transplant.

tion and/or chemotherapy, as well as other processes, such as previous thoracic surgery or severe pulmonary infections. When the pretransplant FEV₁ and DL_{CO} are considered together, they may be a more comprehensive marker than FEV₁, FVC, FEV₁/FVC, TLC, DL_{CO}, or P(A-a)O₂ considered alone for the presence of pretransplant lung injury and compromised health status before transplant.

There are two other important findings in our study that are related to mortality risk. First, we demonstrate that the mortality rate among patients who develop early respiratory failure requiring mechanical ventilation was extremely high. This is in agreement with previous studies that found the mortality rate of bone marrow transplant patients who receive mechanical ventilation ranges from 82 to 96% (summarized by Bach and colleagues [21]). Despite the many significant methodologic differences between these studies, including differences in institutional practice, changes in physician behavior, and differences in patient populations and diagnoses, as well as significant advancements in the development of conditioning regimens, immunosuppressive

agents, and prophylactic antibiotic protocols, the fact remains that the observed survival rate after mechanical ventilation at many transplant centers remains low over the last two decades. Given the strength of the association we identified between the pretransplant LFS and the development of respiratory failure, these data may be useful when counseling a transplant candidate with abnormal pretransplant lung function about the risks and outcome for developing early respiratory failure and mechanical ventilation.

Second, our analysis demonstrates for the first time a potential interaction between the conditioning regimen and pretransplant lung function that appears to affect the mortality risk. No patients who were within the highest LFS category and received a TBI-based regimen survived beyond 2 years after transplant. When reviewing these data, it is important to avoid overinterpretation of the results. As mentioned above, the pretransplant LFS likely provides a global measure of a patient's physiologic status. Any preexisting condition that leads to a significantly decreased pretransplant physiologic state and the requirement of a TBI-

Figure 2. (A–D) Kaplan-Meier survival curves demonstrating the relationship between survival probability and the pretransplant LFS, stratified according to the conditioning regimen. The p values for all figures were less than 0.001, except for A, which was 0.032. These figures demonstrate that patients in LFS category IV who received a total body irradiation (TBI)-based myeloablative regimen had the lowest survival probabilities.

based conditioning regimen would confound the potential relationship between the pretransplant LFS and conditioning regimens. An example of this might be an advanced malignancy that has required intense radiation to the chest region. However, a potential alternate explanation for these results is that patients with a higher pretransplant LFS are less able to tolerate the potential pulmonary effects associated with a TBI-based regimen.

There are several other important considerations when interpreting our results. First, our findings were based only on the presence or absence of abnormal lung function before transplant. We did not attempt to determine the causes of the abnormal pretransplant lung function. Although these data may be interesting, our database was not complete in this regard. This issue may be more effectively addressed in a prospective study. Second, due to the lack of complete records for GVHD prophylaxis, our study did not consider the influence of this variable in the multivariate analysis, which may have influenced the hazard ratios associated with the pretransplant LFS. Finally, although the LFS mortality curve (Figure 1D) suggested this score may be a pretransplant predictor of a patient's risk for these outcomes, the current analysis does not take into account the many other variables that may influence mortality risk, such as other organ dysfunction before transplant. However, these results indicate that future studies will need to validate the use of the pretransplant LFS as a predictor of mortality, in a setting where other potential pretransplant risk factors are also considered in an integrated model.

Our current study confirms that compromised pretransplant lung function is a significant risk factor for the development of early respiratory failure and mortality after allogeneic HCT. This is likely because PFTs provide a sensitive but nonspecific measure of the patient's pretransplant physiologic state and comorbid illnesses, which can significantly impact a patient's mortality risk after HCT (22). Because an individual's risk of mortality is likely determined by many variables in addition to the baseline lung function, future studies should consider the development of an accurate HCT risk assessment score that incorporates several key parameters, including FEV₁ and DL_{CO}, to provide an integrated measure of a patient's pretransplant risk for post-transplant mortality.

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

- Chien JW, Madtes DK, Clark JG. Pulmonary function testing prior to hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2005;35:429–435.
- Ghalie R, Szidon JP, Thompson L, Nawas YN, Dolce A, Kaizer H. Evaluation of pulmonary complications after bone marrow transplantation: the role of pretransplant pulmonary function tests. *Bone Marrow Transplant* 1992;10:359–365.
- Chien JW, Martin PJ, Gooley TA, Flowers ME, Heckbert SR, Nichols WG, Clark JG. Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Respir Crit Care Med* 2003;168:208–214.
- Chien JW, Martin PJ, Flowers ME, Nichols WG, Clark JG. Implication of early airflow decline after myeloablative allogeneic stem cell transplantation. *Bone Marrow Transplant* 2004;33:759–764.
- Horak DA, Schmidt GM, Zaia JA, Niland JC, Ahn C, Forman SJ. Pretransplant pulmonary function predicts cytomegalovirus-associated interstitial pneumonia following bone marrow transplantation. *Chest* 1992;102:1484–1490.
- Ho TV, Weller E, Lee SJ, Alyea EP, Antin JH, Soiffer RJ. Prognostic factors for early severe pulmonary complications after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2001;7:223–229.
- Goldberg SL, Klumpp TR, Magdalski AJ, Mangan KF. Value of the pre-transplant evaluation in predicting toxic day-100 mortality among blood stem cell and bone marrow transplant recipients. *J Clin Oncol* 1998;16:3796–3802.
- Chien JW, Maris MB, Sandmaier BM, Maloney DG, Storb RF, Clark JG. Comparison of lung function after myeloablative and 2 Gy of total body irradiation-based regimens for hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2005;11:288–296.
- Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. *Chest* 1992;101:1257–1264.
- Parimon T, Madtes DK, Au DH, Clark JG, Chien JW. Risk of respiratory failure and mortality among allogeneic stem cell transplantation: role of pretransplant pulmonary function tests [abstract]. *Proc Am Thorac Soc* 2005;2:A418.
- Koc S, Leisenring W, Flowers MED, Anasetti C, Deeg HJ, Nash RA, Sanders JE, Witherspoon RP, Storb R, Appelbaum FR, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood* 2002;100:48–51.
- Sullivan KM. Graft-versus-host disease. In: Thomas E, Blume K, Forman S, editors. *Hematopoietic stem cell transplantation*, 2nd ed. Malden, MA: Blackwell Science; 1999. pp. 518–519.
- Przepiorka D, Smith TL, Folloder J, Khouri I, Ueno NT, Mehra R, Korbiling M, Huh YO, Giral S, Gajewski J, et al. Risk factors for acute graft-versus-host disease after allogeneic blood stem cell transplantation. *Blood* 1999;94:1465–1470.
- Shulman HM, Sullivan KM, Weiden PL, MacDonald GB, Striker GE, Salc GE, Hackman R, Tsoi MS, Storb R, Thomas ED. Chronic graft-versus-host syndrome in man: a long-term clinicopathologic study of 20 Seattle patients. *Am J Med* 1980;69:204–217.
- American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;144:1202–1218.
- Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659–664.
- American Thoracic Society. Single breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique: the official statement of the American Thoracic Society. *Am Rev Respir Dis* 1987;136:1299–1307.
- West JB, Wagner PD. Ventilation, blood flow, and gas exchange. In: Murray JF, Nadel JA, editors. *Textbook of respiratory medicine*, 3rd ed. Philadelphia: W.B. Saunders; 2000. pp. 71.
- Crapo RO, Forster RE. Carbon monoxide diffusing capacity. *Clin Chest Med* 1989;10:187–198.
- Yamaguchi K, Mori M, Kawai A, Takasugi T, Oyamada Y, Koda E. Inhomogeneities of ventilation and the diffusing capacity to perfusion in various chronic lung diseases. *Am J Respir Crit Care Med* 1997;156:86–93.
- Bach PB, Schrag D, Nierman DM, Horak D, White P Jr, Young JW, Groeger JS. Identification of poor prognostic features among patients requiring mechanical ventilation after hematopoietic stem cell transplantation. *Blood* 2001;98:3234–3240.
- Sorror ML, Maris MB, Storer B, Sandmaier BM, Diaconescu R, Flowers C, Maloney DG, Storb R. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. *Blood* 2004;104:961–968.