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Cigarette Smoking and Outcomes After Allogeneic Hematopoietic Stem Cell Transplant

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Abstract

Abnormal lung function is a known risk factor for poor outcomes in the allogeneic hematopoietic stem cell transplant (HSCT) population, although the specific causes of these abnormalities have not been well explored. There is limited data on the effect of cigarette smoking on transplant outcomes. We conducted a retrospective observational cohort study of 845 consecutive patients aged ≥ 18 years who underwent allogeneic HSCT at the Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center. Smoking exposure was defined by quit time, smoking status (never, former, and current) and $\log_2$-transformed pack-years. The main outcomes were time to respiratory failure within 100 days of transplant, relapse, and non-relapse mortality. In multivariable analyses, a two-fold increase in pack-years smoked was associated with an increased risk of early respiratory failure (HR 1.33, 95% CI 1.09 to 1.64, p = 0.006). This association was observed independent of pre-transplant lung function. A two-fold increase in pack-years smoked was associated with an increased risk of relapse, but this finding was not statistically significant (HR 1.16, 95% CI 0.92 to 1.46, p = 0.21). An association was not observed between cigarette smoking and non-relapse mortality. Cigarette smoking is associated with an increased risk of respiratory failure and relapse within 100 days of allogeneic HSCT. The association with respiratory failure is mediated in part by abnormal lung function prior to transplant and likely through other mechanisms as well. Given the adverse effects associated with cigarette smoking prior to transplant, future studies should focus on obtaining accurate smoking histories, tracking prospective changes in smoking status, and assessing the benefits of tobacco cessation on outcomes in this population.

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Keywords

smoking; hematopoietic cell transplant; outcomes; respiratory failure; relapse; mortality

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) has become standard therapy to treat a variety of malignant and other hematologic diseases, with over 20,000 allogeneic transplants performed annually worldwide (1). Despite its widespread use, transplant-related mortality and morbidity remain high. The 100-day mortality rate for allogeneic transplants ranges from 10 to 40% (2). In addition, 15 to 40% of all allogeneic HSCT recipients require intensive care admission after transplant (2, 3). Pulmonary complications account for most of the life-threatening conditions that develop post-transplant, and, traditionally, are classified as early or late depending on whether they occur before or after day 100.

Prior studies have suggested that abnormal pre-transplant pulmonary function tests (PFTs) increase the risk of complications, including early respiratory failure and mortality (4–7). Causes for abnormal pre-transplant lung function, however, have not been well explored. Cigarette smoking is known to be a primary cause of abnormal PFTs (8, 9), and previous studies have reported that 14% to 62% of transplant candidates have a former or current history of smoking (10–13). Cigarette smoking, therefore, may account for some of the abnormal PFTs observed before transplant, but there are limited data on the direct effects of cigarette smoking on early pulmonary complications, relapse, and mortality post-transplant. Marks et al. reported that “high dose” smoking, defined by ≥ 10 pack-year history and smoking ≥ 1 pack per day, was associated with an increased risk of treatment-related mortality and disease relapse (12). Some studies have reported an increased risk of early pulmonary complications among smokers, while others have not demonstrated such associations (11, 13). In general, these studies have been limited by small numbers of patients or have focused on only certain transplant populations. Furthermore, despite growing evidence that cigarette smoking impairs immune function, exacerbates cancer treatment-related toxicities, and increases risk of recurrence and secondary malignancies, few clinical oncology studies collect information on smoking history unless the malignancy is primarily smoking-related (14–17). Given these limitations, we conducted a retrospective observational cohort study to assess the relationship between pre-transplant cigarette smoking and early respiratory failure, relapse, and post-transplant non-relapse mortality among adult allogeneic HSCT recipients.

METHODS

Patient Selection

All adult patients (age ≥ 18 years) who received an allogeneic HSCT at Fred Hutchinson Cancer Research Center between June 20, 2005 and June 30, 2009 were eligible for the study (n = 846). On June 20, 2005, routine tracking of smoking history began during pre-transplant pulmonary function testing.

Cigarette Smoking

Cigarette smoking was the primary exposure. Smoking history was obtained via self-report during pre-transplant pulmonary function testing and categorized as never, former, or current. For this study, we defined a former smoker as an individual who quit smoking for at least 1 year prior to the interview. Patients who were currently smoking or had quit for less than 1 year prior to the interview were considered current smokers. Smoking dose was

defined in pack-years (number of cigarettes smoked per day/20 multiplied by years smoked), and $\log_2$-transformed to achieve a normal distribution.

Outcomes Assessment

The primary outcomes were respiratory failure within 100 days, disease relapse, and non-relapse mortality. Early respiratory failure was defined as mechanical ventilation for a non-elective reason within 100 days after transplant. Since the majority of our patients are discharged from our center after 100 days, this time period provides the most complete and accurate respiratory failure data (7). For patients who had multiple episodes of respiratory failure within 100 days, only the time to the first respiratory failure episode was analyzed. Non-relapse mortality was defined as mortality without evidence of disease relapse.

Covariates

Data were collected on patient demographics, including age, gender, and race. Disease risk was defined as low, intermediate, or high risk for mortality as described by Parimon and colleagues (18). Low-risk diseases include chronic myelogenous leukemia (CML) in chronic phase, refractory anemia, and aplastic anemia. Intermediate-risk diseases include chronic myelogenous leukemia in accelerated phase or chronic phase after blast phase, acute leukemia or lymphoma in remission, refractory anemia with excess blasts, and chronic lymphocytic leukemia. High-risk diseases include chronic myelogenous leukemia in blast phase, acute leukemia or lymphoma in relapse, myeloma, solid tumor, and non-hematologic diseases.

Stem cell sources were classified as bone marrow, peripheral blood stem cell (PBSC), cord blood, or a combination of bone marrow and PBSC. Donor match status was determined according to donor-recipient human leukocyte antigen (HLA) compatibility. Conditioning regimens were categorized as myeloablative or non-myeloablative. Myeloablative regimens were further grouped according to the dose of total-body irradiation used: none, ≤ 12 Gy, or > 12 Gy. Cytomegalovirus (CMV) serologic status was assessed in both recipient and donor. Acute graft-versus-host disease (GVHD) was graded I–IV, and categorized as “no” (grades 0–II) or “yes” (grades III–V) based on stages of organ involvement using standard criteria (19, 20). Chronic GVDH was defined by the National Institutes of Health (NIH) 2005 criteria (21).

Pulmonary function testing was obtained routinely prior to transplant and again approximately 80–120 days post-transplant. All pulmonary function tests were performed at the Fred Hutchinson Cancer Research Center according to American Thoracic Society guidelines (22). All pulmonary function values, except the ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC), were expressed as a percentage of predicted values according to published equations (23, 24), unless otherwise specified. Diffusing capacity for carbon monoxide (DL_{CO}) measurements were corrected for hemoglobin levels obtained at the closest time to the DL_{CO} measurement (25).

Statistical Methods

All statistical analyses were performed using STATA 11.0 (StataCorp, College Station, TX). Baseline variables were compared between smoking groups using Pearson χ^2 testing or t-tests for continuous variables. Time-to-event analyses were conducted using Cox proportional hazards regression models to estimate the hazard ratios (HRs) for associations between pre-transplant smoking and transplant outcomes. Huber-White standard errors were used to relax traditional proportional hazards assumptions. In secondary analyses, we used linear regression to examine the association between smoking dose and day 80–120 pulmonary function. The multivariable model included smoking status as a categorical

variable and $\log_2$-transformed pack-years. We decided *a priori* to also include age, gender, and conditioning regimen as potential confounders. Additional covariates, including patient race, disease risk, CMV status, stem cell source, donor HLA match, and acute and chronic GVHD modeled as time-varying covariates, were evaluated independently in the models and included in the final adjusted models based on likelihood ratio testing. Measures of pulmonary function were then added to the multivariable model. Only FEV_1 and DL_{CO} were included in these models because of the high correlation between FEV_1, FVC, total lung capacity (TLC), and the lack of correlation between DL_{CO} and the other pulmonary function parameters (7). Two-sided p-values less than 0.05 were considered statistically significant.

Data for each patient were censored at the time of the event of interest, death, or date of last contact, whichever came first, with the exception of analyses involving early respiratory failure, where patients were censored at 100 days if they did not have the outcome or die. In analyses involving non-relapse mortality and relapse, these outcomes were considered competing events and censored accordingly. Data for 1 patient was censored at 83 days at the time of a second transplant.

RESULTS

From July 20, 2005 to June 30, 2009, 846 patients underwent allogeneic HSCT. One patient was excluded for missing smoking data. Clinical characteristics are summarized in Table 1. There were 230 former smokers (27%) and 85 current smokers (10%). The overall median number of pack-years smoked was 10 (IQR 4–25). The median number of days before transplant that a smoking history was obtained was 24 days (IQR 20–35 days). The median age was 58 years (IQR 51–63 years) in former smokers and 46 years (IQR 32–57 years) in current smokers compared to 50 years (IQR 38–59 years) in never smokers. This is slightly older than in previous studies and reflects the trend of increasing numbers of allogeneic transplants among individuals older than 50 years of age (10–13, 26). Former smokers were more likely to receive a non-myeloablative conditioning regimen, consistent with older age in this group. Although the majority of transplant patients at our institution undergo bronchoscopy for evaluation of acute radiographic abnormalities, specific pulmonary infections are difficult to identify in this cohort because the majority of patients are already on broad-spectrum antibiotic and antifungal therapy prior to bronchoscopy. Nevertheless, there was no significant difference in the rate of bronchoscopies performed in never smokers vs. former or current smokers. There were no significant differences with regard to patient gender, ethnicity, underlying disease severity, donor HLA match, CMV status, and stem cell source between the groups.

PFTs, including spirometry and DL_{CO}, were obtained on 96% of patients prior to transplant. Over 75% of patients in all 3 smoking groups had normal FEV_1, FVC, and TLC percent predicted values (Table 2). Both former and current smokers had slightly lower FEV_1 and FEV_1/FVC compared to never smokers. A greater proportion of current smokers had DL_{CO} values that were < 80%.

Smoking and Early Respiratory Failure

Early respiratory failure occurred in 32 (6%) never smokers, 14 (6%) former smokers, and 2 (2%) current smokers. The median number of days after transplant to respiratory failure was 17.5 days (IQR 11–29.5 days). Forty-four of the 48 patients (92%) died after receiving mechanical ventilation. The main reasons for respiratory failure included acute respiratory distress syndrome (ARDS)/acute lung injury (ALI) (n = 15, 31%), aspiration/mucositis (n = 11, 23%), diffuse alveolar hemorrhage (n = 8, 17%), and idiopathic pneumonia syndrome (n = 7, 14%), as defined by previous criteria (27–29). In multivariable analyses adjusting for age, sex, conditioning regimen, smoking status, and acute GVHD, smoking dose, defined in

pack-years, was associated with a higher risk of early respiratory failure. For each doubling of pack-years, the hazard ratio for early respiratory failure increased 33% (95% CI 1.09 to 1.64, p = 0.006) (Figure 1).

Figure 2 shows the projected cumulative incidence curves, using our model for early respiratory failure, with all HSCT predictors being equal except smoking dose. In this projection, we combined former and current smokers into one group and compared a never-smoking patient to a smoker with a 20 pack-year history and another smoker with a 40 pack-year history.

To better understand how abnormal pulmonary function may have accounted for the association between pre-transplant smoking and early respiratory failure, we then included pre-transplant pulmonary function in the multivariable model. As expected, the addition of variables for pulmonary function attenuated our hazards ratio for early respiratory failure, but an association between the two-fold increase in pack-years and risk of early respiratory failure remained (HR 1.25, 95% CI 1.02 to 1.55, p = 0.03) (Figure 1).

Smoking and Relapse

One hundred and sixty-two of the patients relapsed, including 105 (20%) never smokers, 42 (18%) former smokers, and 15 (18%) current smokers, with a median number of days after transplant to relapse of 103 (IQR 71 – 239 days). Over three quarters of those who relapsed (78%) died. In multivariable analyses adjusting for age, gender, conditioning regimen, smoking status, disease risk, donor HLA type, and acute and chronic GVHD (as time-varying covariates), a two-fold increase in pack-years was associated with a higher risk of relapse, but this finding was not statistically significant (HR 1.16, 95% CI 0.92 to 1.46, p = 0.21) (Figure 1).

Smoking and Non-Relapse Mortality

There were 386 (46%) deaths from all causes in this cohort. Of these, 127 had relapsed, leaving 259 (31%) individuals (156 [37%] never smokers, 79 [42%] former smokers, 24 [34%] current smokers) with non-relapse mortality. The median number of days after transplant to non-relapse mortality was 163 days (IQR 62 – 298 days). In multivariable analyses adjusting for age, gender, conditioning regimen, smoking status, donor HLA type, PAM score, stem cell source, and acute and chronic GVHD, smoking dose was not associated with a higher risk of non-relapse mortality (HR 0.97, 95% CI 0.85 to 1.10, p = 0.64) (Figure 1).

Smoking and Day 100 Pulmonary Function

We performed secondary analyses of the relationship between smoking dose and pulmonary function obtained routinely 80–120 days post-transplant. After adjustment for patient age, gender, conditioning regimen, and smoking status, smoking dose was not significantly associated with changes in FEV_1, FVC, TLC, or DL_{CO} from baseline (data not shown).

Stratification By Donor Type

Because prior studies have cited differential transplant outcomes with HLA-identical sibling transplants versus unrelated matched transplants, we analyzed the association between cigarette smoking and transplant outcomes separately for these subgroups. After adjustment, there was still an increased risk of early respiratory failure with a two-fold increase in pack-years in both groups. Patients who received a HLA-identical related transplant had an 83% increased risk of early respiratory failure (95% CI 1.18 to 2.84, p = 0.007) compared to a 46% increased risk among patients receiving an unrelated matched transplant (95% CI 1.02 to 2.09, p = 0.04) (Table 3). Smoking dose was associated with an increased risk of relapse

in patients receiving an unrelated matched transplant (HR 1.44, 95% CI 1.04 to 2.01, p = 0.03). There was a weak association between pack-years and relapse in related matched donor transplants that was not significant (HR 1.21, 95% CI 0.92 to 1.60, p = 0.17). Smoking dose was again not associated with non-relapse mortality when stratified by donor type (Table 3).

DISCUSSION

The major finding of our study is that lifetime smoking dose is associated with an increased risk of respiratory failure within 100 days of transplant. This relationship appears to be only partially mediated by pre-transplant lung function, suggesting that other biologic mechanisms may be involved. We did not observe significant effects of smoking on overall relapse or non-relapse mortality, although the direction of the association between smoking dose and relapse warrants further investigation.

Few studies have examined whether cigarette smoking is a risk factor for poor transplant outcomes, and those have had conflicting results. Ho et al. found that smoking history, measured by smoking status (never, current, quit >1 year) was not associated with increased risk for early severe pulmonary complications, defined as diffuse alveolar hemorrhage, need for mechanical ventilation, or death from respiratory failure within the first 60 days post-transplant (11). In contrast, a study done by Savani and colleagues reported that a history of smoking was associated with a 5-fold increase in risk of transplant-related mortality from pulmonary causes (13). The latter, however, had a smaller cohort (n = 146), included patients diagnosed with idiopathic pneumonia syndrome, and followed patients for a median of 3.6 years (13). The largest study by Marks et al., with 2,818 patients who received allogeneic transplants for CML in first chronic phase, found that the risk of treatment-related mortality was 57% higher among ≥ 10 pack-year smokers compared to never smokers (12). In addition, such a smoking history was associated with increased risk of disease relapse, a finding consistent with a prior study by Chang et al. (10, 12). These findings, however, were observed only in recipients of HLA-identical sibling donor transplants (12).

We also found an increased risk of relapse associated with smoking, although mainly among patients receiving an unrelated matched HSCT. These results should be considered preliminary, although in light of studies demonstrating that smoking increases the risk of hematologic malignancies, this may be biologically plausible (30, 31). The greater than two-fold increase in relapse risk among recipients of unrelated matched donors in our study may be partly attributable to our cohort having a higher underlying disease risk; we included a variety of underlying diseases that warranted allogeneic transplant as opposed to the cohorts in the Chang and Marks studies, which focused on CML in stable phase. Unlike the study by Marks et al., we did not find an association between smoking and non-relapse mortality, despite observing that 92% of patients who were placed on mechanical ventilation in the first 100 days after transplant ultimately died. It is possible that some patients with respiratory failure chose to forego mechanical ventilation prior to death. Alternatively, it is possible that smoking is not a risk factor for other common causes of non-relapse mortality such as acute or chronic GVHD and non-pulmonary organ toxicity or failure. There are several possible mechanisms for the association between smoking dose and early respiratory failure. Pre-transplant PFTs have been shown to be important predictors of early post-transplant pulmonary complications and mortality (5–7). These parameters likely represent markers of previous lung injury and worse health status prior to transplant. In addition, cigarette smoking has immunomodulatory effects that have been linked to increased susceptibility to infection. The alveolar macrophages found in the lungs of smokers, for example, have a reduced ability to phagocytose bacteria and are known to secrete lower levels of inflammatory cytokines necessary for upregulation of host defenses (32, 33).

Cigarette smoke may also have independent effects on mucociliary clearance and alterations in surfactant proteins (34–38).

The strengths of our study include a large cohort, availability of detailed smoking history, and availability of PFTs near transplant. There are, however, important limitations to consider when interpreting our results. First, social desirability, especially prior to upcoming transplant, may have led to under-reporting of smoking. Although we do not have reason to believe this bias is differential among those who experienced respiratory failure or died, the effect would tend to bias our hazard ratios toward the null. Second, we could not assess whether smoking was continued or resumed during the post-transplant period, which may have affected our outcomes. Third, although there are no firm exclusion criteria with regard to PFTs, smoking status, or pulmonary disease for transplant eligibility at our center, patients with severe pulmonary and other co-morbidities may never have made it to transplant; thus, there could be selection bias. Despite these limitations, the findings that: 1) the vast majority of patients undergoing transplant have normal lung function, including former and current smokers (Table 2), and 2) an association remains between smoking dose and early respiratory failure independent of lung function, lends credence to our conclusion that cigarette smoking, even in patients without serious co-morbidities or compromised lung function, has independent deleterious effects after transplant.

In summary, our study found a significant association between cigarette smoking and respiratory failure within 100 days of transplant. This finding appears to be only partially mediated by abnormal lung function prior to transplant. While we found no significant association between smoking and relapse or non-relapse mortality after allogeneic HSCT, a trend was apparent, and future prospective studies with longer-term outcomes and ongoing monitoring of smoking status are warranted to explore this issue. We are not suggesting that HSCT should be withheld or delayed in patients with a smoking history in need of transplant; however, since cigarette smoking, identifies individuals at increased risk of early morbidity post-transplant, they should be counseled accordingly. Given the prevalence of smoking among HSCT cohorts, further studies should focus on tobacco cessation efforts in this patient population. In addition, they should evaluate the potential impact of length of quit time among former smokers and recent quitters on allogeneic transplant outcomes, as this could identify a window of opportunity for aggressive tobacco cessation interventions. This study also emphasizes the need for routine inclusion of smoking status and more detailed smoking history both prior to and after transplant in future HSCT studies.

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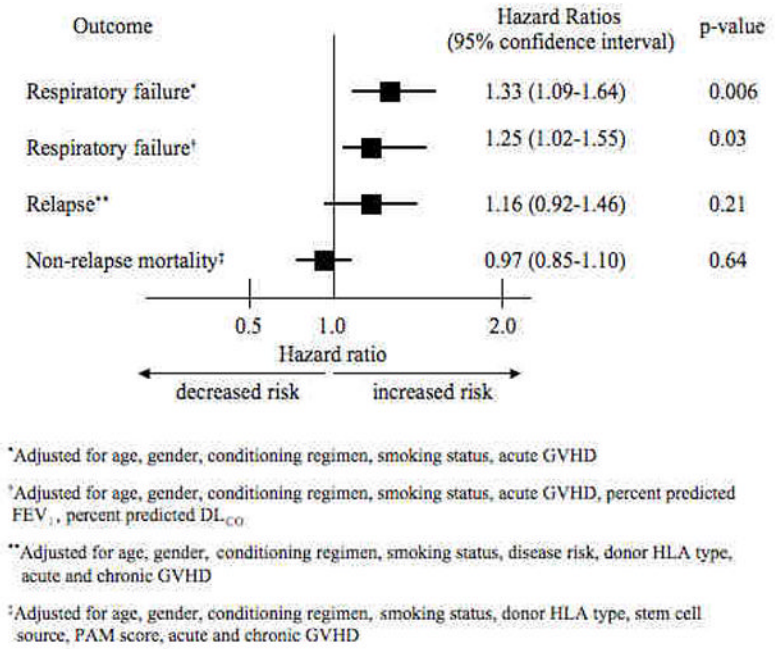

Figure 1.
Multivariable adjusted hazards ratios for the association between cigarette smoking and early respiratory failure, relapse, non-relapse mortality.

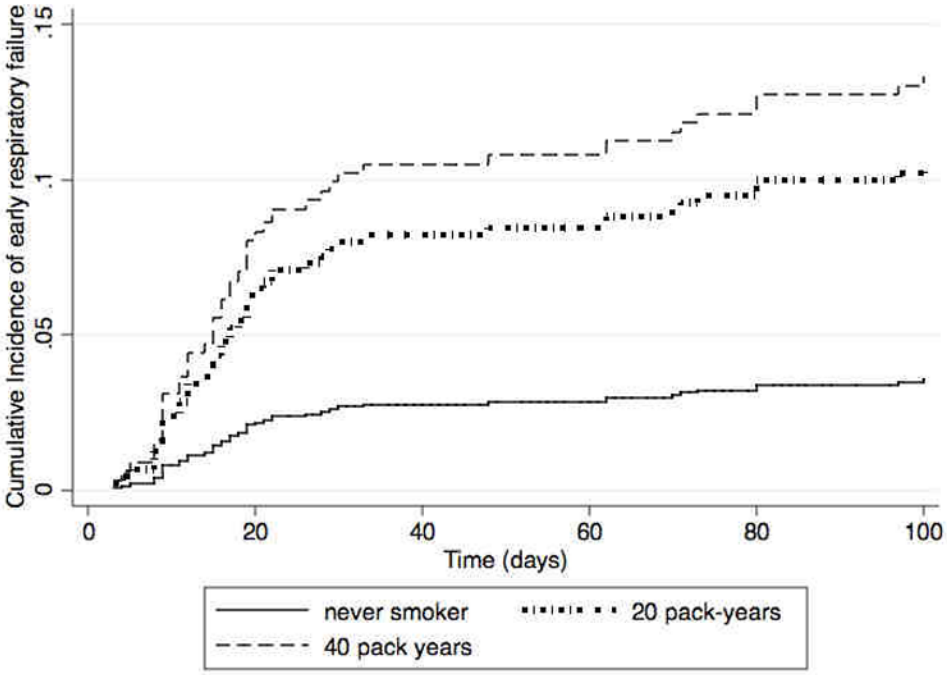

Figure 2.
Projected cumulative incidence curves for early respiratory failure associated with never smoking versus 20 pack-year smoking history versus 40 pack-year smoking history.

Table 1

Patient characteristics

Characteristic	Never Smokers (N=530) (%)	Former Smokers (N=230) (%)	Current Smokers (N=85) (%)	p-value
Age (years)				<0.0005
median (IQR)	50 (38–59)	58 (51–63)	46 (32–57)	
Male	302 (57)	138 (60)	47 (55)	0.67
Caucasian race	456 (89)	205 (92)	77 (93)	0.81
Pack-years				
median (IQR)	-	10 (4–20)	15 (6–30)	0.05
Donor HLA status				0.68
related/matched	191 (36)	86 (37)	30 (35)	
related/mismatched	27 (5)	13 (6)	8 (9)	
unrelated/matched	204 (39)	80 (35)	27 (32)	
unrelated/mismatched	107 (20)	51 (22)	20 (24)	
Disease risk				0.35
Low	41 (8)	11 (5)	7 (8)	
Intermediate	299 (56)	146 (63)	48 (57)	
High	190 (36)	73 (32)	30 (35)	
Conditioning regimen				0.001
Non-myeloablative	204 (38)	123 (53)	25 (29)	
Myeloablative				
Non-TBI	170 (32)	55 (24)	37 (44)	
TBI ≤ 12 Gy	132 (25)	47 (20)	19 (22)	
TBI > 12 Gy	20 (4)	5 (2)	3 (3)	
Stem cell source				0.75
Bone marrow	75 (14)	30 (13)	14 (16)	
PBSC	420 (79)	190 (83)	67 (79)	
BM, PBSC	3 (1)	0	0	
Cord	32 (6)	10 (4)	4 (5)	
CMV (recipient/donor)				0.27
neg/neg	149 (30)	67 (30)	27 (33)	
neg/pos	57 (12)	19 (9)	4 (5)	
pos/neg	140 (28)	77 (35)	27 (33)	
pos/pos	151 (30)	56 (26)	23 (29)	
Acute GVHD	73 (14)	27 (12)	11 (13)	0.74
Chronic GVHD	218 (52)	93 (54)	22 (32)	0.005
Bronchoscopy performed	99 (19)	52 (23)	17 (20)	0.46

Table 2

Distribution of pre-transplant pulmonary function tests

PFT parameter	Never Smokers (N=530) (%)	Former Smokers (N=230) (%)	Current Smokers (N=85) (%)	p-value
Percent predicted FEV_1				0.04
≥ 80%	434 (82)	180 (78)	66 (78)	
70–79%	52 (10)	27 (12)	9 (11)	
60–69%	16 (3)	10 (4)	3 (4)	
< 60%	9 (2)	7 (3)	4 (5)	
Percent predicted FVC				0.57
≥ 80%	456 (86)	202 (88)	74 (87)	
70–79%	39 (7)	17 (7)	7 (8)	
60–69%	9 (2)	4 (2)	0	
< 60%	7 (1)	1 (0.5)	1 (1)	
FEV_1/FVC				
median (IQR)	0.77 (0.73–0.82)	0.75 (0.70–0.79)	0.73 (0.68–0.79)	<0.0005
Percent predicted TLC				0.21
≥ 80%	477 (90)	213 (93)	77 (91)	
70–79%	20 (4)	8 (3)	4 (5)	
60–69%	5 (1)	0	0	
< 60%	7 (1)	1 (0.5)	0	
Percent predicted DL_{CO}				0.0009
≥ 80%	216 (41)	95 (41)	23 (27)	
70–79%	169 (32)	67 (29)	24 (28)	
60–69%	92 (17)	38 (16)	21 (25)	
< 60%	37 (7)	25 (11)	14 (16)	

Table 3

Multivariable adjusted hazards ratios for the association between smoking and early respiratory failure, relapse, or non-relapse mortality, stratified by donor HLA type

Outcome	N (%)	HR	95% CI	p-value
Related matched donor	307 (36%)			
Early respiratory failure*		1.83	1.18 to 2.84	0.007
Relapse**		1.21	0.92 to 1.60	0.17
Non-relapse mortality‡		0.99	0.77 to 1.29	0.97
Unrelated matched donor	311 (37%)			
Early respiratory failure*		1.46	1.02 to 2.09	0.04
Relapse**		1.44	1.04 to 2.01	0.03
Non-relapse mortality‡		0.91	0.74 to 1.12	0.38

*Adjusted for age, gender, smoking status, conditioning regimen, acute GVHD

**Adjusted for age, gender, smoking status, conditioning regimen, disease risk, acute and chronic GVHD

‡Adjusted for age, gender, smoking status, conditioning regimen, stem cell source, PAM score, acute and chronic GVHD