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ORIGINAL ARTICLE

Lung function score including a parameter of small airway disease as a highly predictive indicator of survival after allogeneic hematopoietic cell transplantation

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SUMMARY

Some studies on the predictive value of determining pulmonary function prior to allogeneic hematopoietic cell transplantation (allo-HCT) have shown a significant association between pulmonary function test (PFT) parameters and pulmonary complications, and mortality. However, the percentage of patients showing abnormalities in pretransplant PFT parameters is low. We comprehensively evaluated the effect of pretransplant PFT parameters, including a marker of small airway disease (ratio of the airflow rate of 50% vital capacity to the airflow rate of 25% vital capacity ($\dot{V}50/\dot{V}25$), on outcomes in 206 evaluable patients who underwent allo-HCT at our institute. Notable among the significant parameters in a univariable analysis, $\dot{V}50/\dot{V}25$ was the most powerful indicator of survival following allo-HCT (delta-Akaike information criterion [ΔAIC] = 12.47, $\Delta\chi^2 = 14.47$; $P = 0.0001$). Additionally, a pretransplant lung function score (pLFS) established by applying three parameters with superior predictive values including $\dot{V}50/\dot{V}25$ represented a better discriminating variable for the prediction of survival. Our data demonstrate that a pLFS incorporating a parameter of small airway disease, rather than the parameters of central airway obstruction, may be useful for predicting patient survival following allo-HCT.

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Key words

allogeneic hematopoietic cell transplantation, lung function score, prognostic value for survival, small airway disease, $\dot{V}50/\dot{V}25$

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Introduction

Some investigators have demonstrated that lung function evaluated prior to allogeneic hematopoietic cell transplantation (allo-HCT) is useful to identify patients at risk for pulmonary complications or death (1–4). However, the proportion of patients eligible for allo-HCT who show significant abnormalities in the pulmonary function test (PFT) – specifically, percent predicted forced expiratory volume in 1 s (%FEV1.0) and percent predicted vital capacity (%VC) – before allo-HCT is low. Additionally, most abnormalities shown in patients using lung function test parameters before allo-HCT are limited to the subclinical level. Furthermore, how the abnormalities in PFT lead to mortality and what factors predominantly contribute to the

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abnormalities in PFT parameters that are present before allo-HCT have not been well investigated.

A ratio of the airflow rate of 50% vital capacity to the airflow rate of 25% vital capacity ($\dot{V}50/\dot{V}25$) is a sensitive marker for small airway obstruction (5). Abnormal $\dot{V}50/\dot{V}25$ ratios have often been observed, even in patients with %FEV1.0 and/or %VC within normal limits. To our knowledge, no adequate studies have been conducted regarding how much impact small airway alterations that are present before allo-HCT have on a patient's outcome after allo-HCT. We comprehensively evaluated the impact of various PFT parameters measured before allo-HCT on the survival of patients. We also explored the use of a scoring system consisting pretransplant PFT indicators for clinical use to predict patient outcomes.

Patients and methods

Study eligibility and data collection

We retrospectively reviewed the charts of consecutive patients receiving allo-HCT at our institute between June 2004 and March 2014. Patients with available PFT data acquired before allo-HCT were eligible. The study was approved by the Institutional Review Board of Osaka City University (Japan). The context of this study was officially disclosed to the public by a notice at Osaka City University Hospital and on the website of the Department of Hematology at the Graduate School of Medicine of Osaka City University, according to the ethical guidelines for epidemiological research compiled by the Ministry of Education, Culture, Sports, Science & Technology, and the Ministry of Health, Labour and Welfare in Japan.

Pulmonary function test

In this study, patients in whom PFT was performed to ascertain their eligibility for allo-HCT within 45 days before the start of conditioning for allo-HCT were included in the analysis. Lung function tests were performed in our institute using a CHESTAC-33W or CHESTAC-88 spirometer (CHEST M.I., Inc, Tokyo, Japan). PFT parameters – including total lung capacity (TLC), %VC, FEV1.0/forced vital capacity (FVC), % FEV1.0, $\dot{V}25$, $\dot{V}50/\dot{V}25$ ratio, maximal midexpiratory flow, residual volume (RV)/TLC, percent predicted RV (%RV), percent predicted diffusing capacity of the lung for carbon monoxide (%DLco), and %DLco/alveolar volume (%DLco/VA) – were also evaluated. TLC was measured using the helium dilution method. DLco was corrected for hemoglobin using the Cortes method and adjusted for hemoglobin using the Dinakara method, to calculate the pretransplant lung function score (pLFS), which was established at the Fred Hutchinson Cancer Research Center (FHCRC; Seattle, WA, USA) (6).

Definitions

Disease status was stratified into three groups (low, intermediate, and high risk) based on modified criteria described in a previous report (7). Low-risk diseases consisted of chronic myelogenous leukemia (CML) in the chronic phase; myelodysplastic syndrome (MDS) in refractory anemia or refractory cytopenia with multilineage dysplasia and aplastic anemia, chronic myelomonocytic leukemia, primary myelofibrosis, and chronic active Epstein–Barr virus infection. Intermediate-risk diseases included CML in the accelerated phase or in the chronic phase following the blastic phase, acute leukemia or lymphoma in complete remission, MDS in refractory anemia with excess blasts, and chronic lymphocytic leukemia. High-risk diseases included CML in the blastic phase, acute leukemia or lymphoma in relapse, and acute myeloid leukemia with MDS-related cytogenetic changes. HLA matching was defined by serological typing for HLA-A, HLA-B, and HLA-DR antigens.

Pulmonary complications were categorized as infectious, noninfectious pulmonary, and pulmonary complications without a specific diagnosis determined. Infectious or noninfectious fatal pulmonary complications were also assessed. This study excluded pulmonary edema, neoplastic infiltration including suspicious cases, and asymptomatic patchy basal atelectasis from pulmonary complications (8).

Anti-infectious prophylaxis

In our institute, a prophylactic antibiotic is routinely given from the start of conditioning until neutrophil engraftment, or until the treatment switches to other antibiotics. Before June 2010, polymyxin B 3×10^6 units/day was used. We switched from polymyxin B to levofloxacin 500 mg/day for bacterial infection prophylaxis in patients with neutropenic status following transplantation. Fluconazole 200 mg/day was also used from the start of conditioning until at least day 100 for fungal infection prophylaxis. Acyclovir 600 mg/day was administered to help prevent human simplex herpes virus and varicella zoster virus infections

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until neutrophil engraftment; subsequently, acyclovir 200 mg/day was administered at least 1 year after the transplantation or until the cessation of immunosuppressant agents. Trimethoprim–sulfamethoxazole was administered for prophylaxis against *Pneumocystis jirovecii*.

Statistical analysis

For this study, the delta-Akaike's information criterion (ΔAIC) value was evaluated and the $\Delta\chi^2$ likelihood ratio test was performed to compare the improvement in goodness of fit between the two models, one of which was nested within the other. We used the ΔAIC evaluation of superiority for the predictive value of overall survival (OS) (9). ΔAIC was applied to evaluate whether the models with multiple PFT parameters combined with the basic model outperformed other models including any one of the three single PFT parameters to predict survival. In a Cox regression model (10), a ΔAIC absolute value of greater than 2 indicates a meaningful difference in goodness of fit between the methods, while a ΔAIC absolute value of 2 or lower indicates no meaningful difference. The base model included variables, disease status (high risk versus low-intermediate), and multiple transplantations (second or later versus first). A Cox regression model was applied for univariable and multivariable models.

A simple linear regression analysis was applied to evaluate how the pretransplant PFT parameters were associated with age, gender, smoking index, disease status (high versus low-intermediate risk), performance status and intervals between diagnosis and transplantation, history of busulfan or irradiation treatment, and the number of transplantations (second or later versus first).

A Fine–Gray model (11) was used to evaluate the impact of V̇50/V̇25 and pLFS on the incidence of fatal pulmonary complications. Any deaths resulting from events other than pulmonary complications were treated as competing events for fatal pulmonary complications.

Overall survival was estimated using the Kaplan–Meier method and statistically compared using the log-rank test. For survival estimates, patients were censored at the time of their most recent follow-up or at the next transplantation.

Statistical analyses were two-sided, with a *P*-value of 0.05 considered as being statistically significant. All statistical analyses were performed using EZR version 1.24 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (12), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), and IBM SPSS STATISTICS version 20 (IBM, New York, NY, USA).

Results

Patient and transplantation characteristics

In our institution, 335 patients underwent allo-HCT between June 2004 and March 2014. PFT data which were performed within 45 days before transplantation conditioning and after the last conventional chemotherapy was completed were available in a total of 206 patients (median age 46 years, range 16–68 years; 103 males and 103 females) (Table 1). The median follow-up duration for survivors was 607 days. A total of 105 (51%) of the 206 evaluable patients had a history of smoking, and the median smoking index was 20 (range, 0–2000). Of all patients in the study population, 54 (26%) had high-risk disease. This study included 39 patients (19%) who had undergone multiple transplantations.

Relationship between PFT parameters and OS probability

The univariable Cox proportional hazard model showed that TLC, %FEV1.0, V̇50/V̇25, %RV, RV/TLC, and %DLco/VA were significantly associated with survival (all $P < 0.05$) (Table 2). In the ΔAIC evaluation, we applied these significant parameters as variables in the base model, with the exception of %RV, as the %RV results in the analysis did not make physiological sense. Notably, the ΔAIC evaluation revealed that V̇50/V̇25 was the most powerful indicator of survival following allo-HCT among the significant parameters (ΔAIC = 12.47, $\Delta\chi^2 = 14.47$; $P = 0.0001$) (Table 3). The top three most powerful indicators of survival were V̇50/V̇25, %DLco/VA, and TLC. A multivariable analysis confirmed that all three indicators retained their statistical significance with and without variable adjustments, including disease status (high versus low-intermediate risk) and number of transplantations (first versus second or later transplantation; Table 4).

Relationship between pLFS and OS, and the incidence of fatal pulmonary complications after allo-HCT

Of the total number of patients, 58% had an abnormal V̇50/V̇25 ratio (3.0 or greater) before allo-HCT, whereas only 10% and 5.4%, respectively, showed an abnormal %FEV1.0 (<80%) and FEV1.0/FVC ratio (<70%). Next, we established a scoring system for pLFS by applying three significant independent parameters (TLC, V̇50/

Table 1. Patient characteristics

	n
Total number of patients	206
Median age in years (range)	46 (16–68)
Sex, M/F	103/103
History of smoking (yes/no)	105/101
Disease type	
Acute myeloid leukemia	87
Acute lymphoblastic leukemia	33
Myelodysplastic syndrome	33
Non-Hodgkin's lymphoma	22
Adult T-cell leukemia/lymphoma	13
Chronic myeloid leukemia	8
Aplastic anemia	5
Others	5
Disease risk	
Low	38
Intermediate	114
High	54
Donor	
Related	84
Unrelated	122
Donor HLA status*	
Matched	118
Mismatched	88
Stem cell source	
Bone marrow	82
Peripheral blood	77
Cord blood	47
1st/2nd or < transplantation	167/39
Conditioning regimens	
Cyclophosphamide + TBI 12 Gy	19
Cytarabine + Cyclophosphamide + TBI 12 Gy	31
Busulfan + cyclophosphamide	32
Fludarabine/Busulfan-based	67
Fludarabine/Melphalan-based	42
Others	15
GVHD prophylaxis	
Calcinurin alone	8
Calcinurin + methotrexate	121
Calcinurin + mycophenolate mofetil	73
Other	4

GVHD, graft-versus-host disease; Mismatched donor: *HLA disparity is defined by A, B, DR antigen; TBI, total body irradiation.

Table 2. Univariable model for the analysis of PFT parameters affecting survival post-allo-HCT

Variables	HR	95% CI	*P* value
TLC	0.791 (per 10%)	0.651–0.961	0.018*
%VC	0.877 (per 10%)	0.740–1.040	0.131
%FEV1.0	0.798 (per 10%)	0.671–0.949	0.011*
FEV1.0/FVC	0.760 (per 10%)	0.564–1.023	0.070
$\dot{V}25$	0.79 (per 1 l/s)	0.58–1.07	0.121
$\dot{V}50/\dot{V}25$	1.495 (per 1)	1.224–1.826	0.000*
MMF	0.814 (per 1 l/s)	0.652–1.018	0.071
%RV	0.903 (per 10%)	0.819–0.994	0.038*
RV/TLC	1.051 (per 1%)	1.014–1.090	0.006*
%DLco	0.926 (per 10%)	0.804–1.067	0.289
%DLco/VA	0.699 (per 10%)	0.595–0.821	0.000*

*$P < 0.05$, HCT, hematopoietic cell transplantation; PFT, pulmonary function test; HR, hazard ratio; CI, confidence interval; MMF, maximal midexpiratory flow.

$\dot{V}25$, and %DLco/VA) that showed superiority in predicting survival. Importantly, these three parameters have distinct physiological implications. We assigned a separate score (TLC: equal to or lower than 100% = 1, greater than 100% = 0; $\dot{V}50/\dot{V}25$: greater than 3.3 = 1, equal to or lower than 3.3 = 0; %DLco/VA equal to or lower than 80% = 1, greater than 80% = 0) and stratified all patients into the four groups by total score. We also stratified the patients using a LFS, which was established in FHCRC (13) (%FEV and %DLco: greater than 80% = 1, 70–80% = 2, 60–70% = 3, lower than 60% = 4). According to the report, these scores were classified into four categories. Our scoring system consisting TLC, $\dot{V}50/\dot{V}25$, and %DLco/VA represents a better and more significant discriminating variable for the prediction of survival following allo-HCT (Fig. 1), whereas in the FHCRC LFS, only one (0.5%) and eight (4.1%) patients were stratified into categories 4 and 3, respectively.

The pLFS was significantly correlated with age and smoking index ($\beta = 0.26$ and 0.22; $P < 0.0001$ and 0.002, respectively) but not gender, disease status, performance status, interval between diagnosis and transplantation, or history of busulfan treatment or irradiation therapy. Not surprisingly, the pLFS was higher in patients who were scheduled to undergo a second or later transplantation than in those undergoing their first transplantation (mean of 1.68 vs. 1.32, $\beta = 0.17$; $P = 0.02$).

Table 5 summarizes the details of pulmonary complications. Of the total number of patients, 95 (46%) experienced at least one episode of pulmonary complications, while 77 (37%) experienced at least one episode of infectious pulmonary complications. The most frequent episode among infectious pulmonary complications was bacterial pneumonia. Of 114 total infectious episodes observed, 41 (36%) appeared within 3 months and 54 (47%) within 6 months after allo-HCT. At least one episode of noninfectious pulmonary complications occurred in 22 (11%) of the patients. Twenty of 26 noninfectious

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Table 3. Evaluation of superior PFT parameters and combinations of PFT parameters in the prediction of survival

Model 1	Model 2	ΔAIC	Likelihood ratio	
			$\Delta\chi^2$	*P*-value
Effect of adding each PFT parameter				
Base*	Base* + TLC	5.36	7.36	0.007†
Base*	Base* + %FEV1.0	3.45	5.45	0.02†
Base*	Base* + V̇50/V̇25	12.47	14.47	0.0001†
Base*	Base* + RV/TLC	0.13	2.13	0.14
Base*	Base* + %DLco/VA	9.55	11.55	0.0007†
Base*	Base* + V̇50/V̇25+ %DLco/VA	24.83	28.83	<0.0001†
Base*	Base* + TLC + V̇50/V̇25	18.82	22.82	<0.0001†
Base*	Base* + TLC + %DLco/VA	18.56	22.56	<0.0001†
Base*	Base* + TLC + %DLco/VA + V̇50/V̇25	35.57	41.57	<0.0001†

AIC, Akaike's information criterion; PFT, pulmonary function test; Base* model includes variables followed as: disease status (high risk versus low-intermediate risk) and multiple transplantation (multiple versus first).

†$P < 0.05$.

Table 4. Multivariable model for the analysis of PFT parameters affecting survival post-allo-HCT

Variaables	HR	95%CI	*P* value
Model 1			
V̇50/V̇25	1.683	1.358–2.085	<0.0001*
TLC	0.666 (per 10%)	0.540–0.822	0.0001*
%DLco/VA	0.629 (per 10%)	0.534–0.741	<0.0001*
Model 2			
V̇50/V̇25	1.597	1.297–1.966	<0.0001*
TLC	0.685 (per 10%)	0.553–0.849	0.0005*
%DLco/VA	0.678 (per 10%)	0.567–0.811	<0.0001*

Model 2 was adjusted by variables including disease status (high risk versus low-intermediate risk) and the number of transplantations (2nd or later versus first).

*$P < 0.05$, PFT, pulmonary function test; HR, hazard ratio; CI, confidence interval.

episodes (77%) appeared beyond 6 months following allo-HCT. Fatal pulmonary complications (all of which were infectious pulmonary complications) were seen in 13 (6%) patients. In four patients among them, acute graft-versus-host disease (GVHD) ($n = 2$) or chronic GVHD ($n = 2$) also contributed to the death. Other causes of transplanted related death included chronic GVHD (n = 1), adenoviral infection ($n = 1$), thrombotic microangiopathy ($n = 1$), sinusoidal obstruction syndrome ($n = 1$), and second malignancies ($n = 2$).

Additionally, both the pLFS and FHCRC LFS were closely associated with fatal pulmonary complications (hazard ratio [HR] 2.63, 95% confidence interval [CI] 1.59–4.36, $P = 0.00018$; HR 3.06, 95% CI 1.65–5.67, $P = 0.00039$, respectively).

Discussion

The present study confirmed that pulmonary function prior to allo-HCT is a valuable predictor of patient mortality following allo-HCT, which is consistent with previous reports (1–4). Notably, the small airway disease parameter V̇50/V̇25 is the strongest predictor of survival; it has a much higher predictive value than % FEV1.0 and FEV 1.0/FVC, which mainly reflect central airway obstruction. Moreover, adding the small airway disease parameter to the scoring system increased the ability to predict survival from the pretransplantation PFT.

It has not been well elucidated how even subclinical abnormalities in pretransplant lung function can greatly affect patient mortality following allo-HCT. A few reports have shown a significant relationship between PFT prior to allo-HCT and/or autologous HCT, and infectious or noninfectious pulmonary complications (4,8,13–16). We also found a significant relationship between pLFS and fatal pulmonary complications. However, pulmonary complications following allo-HCT do not always result in subsequent mortality (8), and mortality associated with allo-HCT is commonly derived from combined etiologies in the majority of cases. Therefore, the high predictive value of pretransplant PFT indicators of global death is unlikely to be explained simply by the relationship between pretransplant PFT and pulmonary complications following allo-

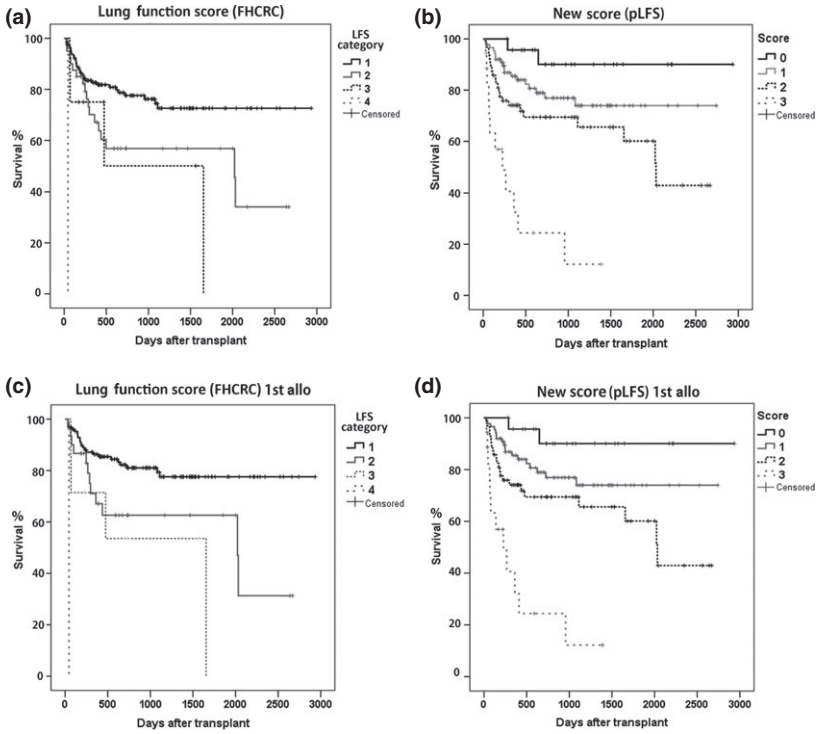

Figure 1 Overall survival curves showing the association with pretransplant lung function scores established (a) in Seattle (13) and (b) based on our results in the entire cohort, as well as (c) in Seattle and (d) based on our results in the first allogeneic transplantation cases. *P*-values for (a–d) were lower than 0.0001.

HCT. Indeed, in a recent prospective observational study, 12 of 73 (16%) pulmonary complication episodes led to mortality (17). In our study, 46% of patients had pulmonary complications; however, death occurred in only 6% of patients.

The HCT comorbidity index (HCT-CI) includes pretransplant PFT data, which are weighted heavily in the index. Interestingly, the predictive ability of HCT-CI decreased after removing the PFT data, suggesting the great predictive potential of pretransplant PFT (18). This may also indicate that pretransplant PFT does not only reflect pulmonary function. Although a decreased value for the PFT parameter can be partially accounted for by age, it is possible that pretransplant PFT is more than just a pulmonary function parameter.

In our study, TLC was found to be a significantly strong indicator of mortality. Importantly, it was reported that low TLC can be linked to respiratory muscle weakness, reflecting the general severity of the physiological condition—a factor that is superior to actual age in terms of predictive ability (19). In patients who underwent allo-HCT, decreased TLC was possibly derived from muscle weakness because of the generally poor condition resulting from extensive chemotherapy administered prior to allo-HCT (4).

Table 5. Prevalence of documented pulmonary episodes

Categories	
Infectious pulmonary complications*	114
Bacteria	60
Fungi	21
Pneumocystis jirovecii	5
Cytomegalovirus	5
Other viruses†	9
Infection NOS	14
Noninfectious pulmonary complications	26
Idiopathic pneumonia syndrome	3
Bronchiolitis obliterans	11
Cryptogenic organizing pneumonia	9
Diffuse alveolar hemorrhage	3
Undetermined specific diagnosis	7
Idiopathic interstitial pneumonitis	3
Localized infiltration	4
ARDS	0
Fatal pulmonary complications	13

*Includes subsequent acute respiratory distress syndrome (ARDS).

†RS viral infection, influenza, BKV, etc.

Furthermore, Ghalie *et al.* (8) reported that the pretransplant values, including FEV1, FVC, TLC, and DLco, were significantly correlated with prior chest

irradiation, thoracotomy, and pulmonary metastases. However, the proportion of patients undergoing allo-HCT who subscribe to these parameters is usually not large. In our study, aging and smoking status were found to be the primary factors compromising the pLFS. Additionally, we surmised that slight pulmonary histological alterations resulting from unapparent pulmonary infection and/or toxicity by anticancer agents during a sequence of conventional chemotherapy before allo-HCT may also affect pulmonary function to some degree. Therefore, although investigated in the current study, as the parameter of small airway disease is sensitive in capturing pulmonary histological alterations, more than one-half of the patients might show an abnormal V̇50/V̇25 ratio prior to allo-HCT.

Pretransplant PFT might be a nonspecific but sensitive indicator of a patient's general physiological condition, toxicity arising from prior treatment and/or a comorbid illness (13). Interestingly, Matute-Bello *et al.* (20) showed a significant association between reduced DLco prior to allo-HCT and the nonpulmonary complication severe hepatic VOD. Therefore, the combination of three independent significant indicators that have distinct physiological or pathological implications may provide our scoring system with accurate predictive power.

The present study has several limitations, including that it was a single-center retrospective study that lacked a large study population. The number of patients with poorer lung function (categories 3 and 4) was small, likely because the low sensitivity of FEV1.0 caused a poor discriminating variable in LFS established in Seattle compared to our pLFS. However, this result was limited to our cohort. Thus, before clinical use, we should prospectively evaluate our model in other external cohorts.

In addition, although V̇50/V̇25 is a sensitive small airway disease parameter, reproducibility problems have been pointed out. For a more precise evaluation of small airway disease, a closing volume or the low-frequency forced oscillation technique (19) may be viable alternatives to V̇50/V̇25. Nevertheless, our data showing the significant association of V̇50/V̇25 might provide further insight into the prediction of a patient's outcome following allo-HCT.

Our data in this study demonstrate a pretransplant scoring system that incorporates an indicator of small airway obstruction rather than central airway obstruction, which may be a useful clinical predictor of patient survival following allo-HCT.

Authorship

Mika N: participated in every aspect of the study. HN and MY: made a concept of the work and designed the study. MY, HK, Mitsu N, YH, TN, YN, AH, HN, and MH: collected the patient data. HN, MY, MH, Mitsu N, YH, TN, YN, and AH: revised the manuscript critically. HK: performed the statistics. HN: helped write the article. All of the authors participated in the discussion and approved the final manuscript.

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Conflict of interest

The authors have no conflict of interest to report.

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