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Supportive Care

Pre-Hematopoietic Stem Cell Transplantation Lung Computed Tomography as an Alternative to the Pulmonary Function Test during the COVID-19 Pandemic

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A B S T R A C T

The pulmonary function test (PFT) is an important test for risk stratification before allogeneic transplantation (allo-HCT). However, it might be preferable to avoid PFT as much as possible in the recent era of coronavirus disease 2019 (COVID-19), because PFT requires forced expirations and might produce aerosols, increasing the risk of COVID-19 transmission. Therefore, we tried to predict normal PFT results before allo-HCT based on computed tomography (CT) findings. This study included 390 allo-HCT recipients at our center for whom lung CT images and PFT results before allo-HCT were available. Abnormal CT findings were less likely to be observed in the normal PFT group (47.0% versus 67.4%, $P = .015$), with a high negative predictive value of 92.9%. In a multivariate analysis, normal CT was significantly associated with normal PFT (odds ratio, 2.47; 95% confidence interval, 1.22 to 4.97; $P = .012$). A model for predicting normal PFT was constructed based on the results of a multivariate analysis, and the area under the curve of the receiver operating characteristic analysis was 0.656, which gave a sensitivity of 45.5% and a specificity of 86.0%. The relatively high specificity of the model suggested that PFT can be omitted in patients with normal CT findings before allo-HCT.

Pulmonary complications are some of the most critical complications in allogeneic hematopoietic stem cell transplantation (allo-HCT). They can include various disease entities such as pulmonary infectious diseases, bronchiolitis obliterans, and interstitial pneumonia [1-4]. Therefore, it is important to assess pulmonary function before allo-HCT. The hematopoietic cell transplantation comorbidity index is a risk stratification system in allo-HCT that includes the results of a pulmonary function test (PFT) [5]. PFT is a widely used noninvasive test to assess pulmonary functions such as percent vital capacity (%VC), percent forced expiratory volume in 1 second (FEV1%), and percent diffusing capacity of the lung for carbon monoxide (%DLCO) [6]. Most recipients of allo-HCT undergo a PFT before their procedure, and their transplantation plans are sometimes modified according to the results of PFT. However, it might be preferable to avoid PFT as much as possible in the recent era of coronavirus disease 2019 (COVID-19). Because the PFT requires forced expirations, this procedure may produce aerosols, increasing the risk of COVID-19 transmission [7,8]. Thus, it is an important challenge to be able to identify candidates for allo-HCT who have normal pulmonary function without the use of a PFT and thus reduce the number of unnecessary PFTs. In this study, we tried to predict normal pulmonary function before allo-HCT based on computed tomography (CT) findings and other clinical information.

PATIENTS AND METHODS

Patients and Pulmonary Examinations

We reviewed the charts of 390 patients who received allo-HCT at our center between May 2008 and September 2019 and for whom a lung CT scan image and PFT results before allo-HCT were available. Lung CT scan images before allo-HCT were obtained at our center or at the referring medical institutions, and all images were reviewed by 2 radiologists (N.O.-M. and T.A.). CT findings were classified according to the definition in the Fleischner Society's glossary of terms for thoracic imaging [9]. PFT was also performed according to the standardized method [6]. If the results regarding %DLCO were available, the score was corrected by hemoglobin according to the method by Dinakara et al. [10]. This retrospective study was approved by the Institutional Review Board of Jichi Medical University Saitama Medical Center and performed in accordance with the Declaration of Helsinki and its later amendments.

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Treatment

Patients younger than 55 years generally received myeloablative conditioning, whereas older patients (>55 years) received reduced-intensity conditioning. Patients with lymphoid malignancies, central nervous system involvement, or a human leukocyte antigen mismatched donor preferably received a regimen containing total body irradiation (TBI). The decision regarding whether or not patients with highly deteriorated pulmonary function received a non-TBI regimen was made based on the physician's discretion. A calcineurin inhibitor (cyclosporin or tacrolimus) with short-term methotrexate was used for graft-versus-host disease prophylaxis. A targeted concentration of calcineurin inhibitors was modified according to the disease risk, as previously reported [11]. In cases of lymphoid malignancies or severe aplastic anemia, lenograstim was used until neutrophil engraftment.

Statistical Analysis

Patient characteristics were compared between the normal and abnormal CT groups by Fisher exact test for categorical variables and by the Mann-Whitney *U*-test for continuous variables. Normal pulmonary function (NORMAL1) was defined as both FEV1% >70% and %VC >80% according to the Japanese standard reference values [12]. The correlations between CT findings and abnormal pulmonary functions were assessed in terms of sensitivity, specificity, and positive and negative predictive values. Thereafter, a predictive model for NORMAL1 was constructed by logistic regression. Among recipients for whom %DLCO results were available, we also defined normal pulmonary function (NORMAL2) as FEV1% >70%, %VC >80%, and %DLCO >80%. Similarly, a predictive model for NORMAL2 was constructed. Receiver-operating characteristic (ROC) analyses were performed to assess the predictive potential of the constructed logistic regression models in terms of the area under the curve (AUC). A 2-tailed *P* value <.05 was considered statistically significant. All analyses in this study were performed with EZR (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html, Jichi Medical University Saitama Medical Center, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [13].

RESULTS

Patient Characteristics

Patient characteristics are shown in Table 1. Their median age was 48 years (range 15 to 69) and the median follow-up duration was 21.4 months (range 0.4 to 145.4). The patient group with CT abnormalities tended to be older, frequently received a lower dose of TBI, and included more recipients with a history of smoking.

Abnormal CT findings were observed in 192 recipients: ground-glass opacity in 40, emphysema in 31, multiple nodular lesions in 34, a single nodular lesion in 36, and consolidation in 27. With regard to PFT in the whole cohort, the median FEV1% was 83.0% (range, 59.5% to 102.2%), and the median %VC was 107.4% (range, 40% to 155.3%).

Relationships between Normal PFT Results and Pretransplant Clinical Factors

Table 2 shows the relationships between normal PFT results (NORMAL1) and pretransplant clinical factors, including CT

Table 1
Patient Characteristics

Characteristic	Total Cases (N = 390)	Any CT Abnormality (n = 192)	No CT Abnormality (n = 198)	*P* Value
Age, median (range)	48 (15-69)	53 (16-69)	45 (15-68)	<.001
Sex, No. (%)				
Male	234 (60.0)	114 (59.4)	120 (60.6)	.84
Female	156 (40.0)	78 (40.6)	78 (39.4)	
Diagnosis, No. (%)				
AML	164 (42.1)	81 (42.2)	83 (41.9)	.16
ALL	69 (17.7)	34 (17.7)	35 (17.7)	
MDS	57 (14.6)	32 (16.7)	25 (12.6)	
NHL	43 (11.0)	23 (12.0)	20 (10.1)	
MPN	23 (5.9)	8 (4.2)	15 (7.6)	
SAA	15 (3.8)	7 (3.6)	8 (4.0)	
MM	10 (2.6)	1 (0.5)	9 (4.5)	
Other	9 (2.3)	6 (3.1)	3 (1.5)	
Disease risk, No. (%)				
Standard	276 (70.8)	129 (67.2)	147 (74.2)	.15
High	114 (29.2)	63 (32.8)	51 (25.8)	
HCT-CI, median (range)	0 (0-7)	0 (0-7)	0 (0-7)	.0061
Donor type, No. (%)				
Matched sibling	86 (22.1)	32 (16.7)	54 (27.3)	.018
Matched unrelated	168 (43.1)	96 (50.0)	72 (36.4)	
Mismatched sibling	51 (13.1)	28 (14.6)	23 (11.6)	
Mismatched unrelated	58 (14.9)	23 (12.0)	35 (17.7)	
Cord blood	27 (6.9)	13 (6.8)	14 (7.1)	
Conditioning, No. (%)				
MAC	241 (61.8)	107 (55.7)	134 (67.7)	.017
RIC	149 (38.2)	85 (44.3)	64 (32.3)	
TBI dose, median (range)	4 (0-12)	4 (0-12)	12 (0-12)	.0014
Smoking habit, No. (%)	218 (55.9)	120 (62.5)	98 (49.5)	.011
HT, No. (%)	58 (14.9)	29 (15.1)	29 (14.6)	1.0
DLP, No. (%)	20 (5.1)	8 (4.2)	12 (6.1)	.49
DM, No. (%)	25 (6.4)	12 (6.3)	13 (6.6)	1.0

AML indicates acute myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; MPN, myeloproliferative neoplasm; SAA, severe aplastic anemia; MM, multiple myeloma; HCT-CI, hematopoietic cell transplantation comorbidity index; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; HT, hypertension; DLP, dyslipidemia; DM, diabetes mellitus.

Table 2
Relationship between Normal PFT and Clinical Data

Characteristic	Normal PFT (n = 347), No. (%)	Abnormal PFT (n = 43), No. (%)	*P* Value
Any abnormal CT	163 (47.0)	29 (67.4)	.015
GGO	34 (9.8)	6 (14.0)	.42
Emphysema	23 (6.6)	8 (18.6)	.013
Multiple nodules	31 (8.9)	3 (7.0)	1.0
Single nodule	33 (9.5)	3 (7.0)	.78
Consolidation	24 (6.9)	3 (7.0)	1.0
Age >48 yr	171 (49.3)	21 (48.8)	1.0
Male sex	207 (59.7)	27 (62.8)	.74
Smoker	195 (56.2)	23 (53.5)	.75
High-risk disease	94 (27.1)	20 (46.5)	.012

GGO indicates ground-glass opacity.

findings. The NORMAL1 group showed a lower incidence of abnormal CT findings (47.0% versus 67.4%, *P* = .015), especially emphysema (6.6% versus 18.0%, *P* = .013). The frequencies of other CT findings were statistically equivalent between the groups. Additionally, the NORMAL1 group included fewer recipients with high-risk disease (27.1% versus 46.5%, *P* = .012).

Abnormal CT findings could be used to predict abnormal PFT results with a sensitivity of 67.4%, a specificity of 53.0%, a positive predictive value of 15.1%, and a negative predictive value of 92.9%. In the same manner, the presence of emphysema suggested abnormal PFT results with a sensitivity of 18.6%, a specificity of 93.4%, a positive predictive value of 25.8%, and a negative predictive value of 90.3%.

Models for Predicting Normal PFT Results (NORMAL1)

Models for predicting normal PFT results were constructed using either normal CT findings or the absence of emphysema (Table 3). In a multivariate analysis (Table 3), these CT findings were significantly associated with normal PFT results (NORMAL1), with an odds ratio (OR) of normal CT of 2.47 (95% confidence interval [CI], 1.22 to 4.97; *P* = .012) and an OR of absence of emphysema of 4.28 (95% CI, 1.62 to 11.3; *P* = .0036). The ROC analysis suggested that the AUC of the model using normal CT findings was 0.656, which gave a sensitivity of 45.5% and a specificity of 86.0%. On the other hand, in the model that considered the absence of emphysema instead of normal CT findings, the AUC was 0.690, which gave a sensitivity of 73.2% and a specificity of 62.8%.

Models for Predicting Normal PFT Results Considering %DLCO (NORMAL2)

Data on %DLCO were available in 355 patients, and the median %DLCO was 123.7% (52.4% to 343.7%). NORMAL2 was observed in 308 patients and was not significantly related to the absence of abnormal CT findings but related to the absence of emphysema or high-risk disease (Supplementary Table S1). Abnormal CT findings predicted abnormal PFT results with a sensitivity of 57.4%, a specificity of 51.6%, a positive predictive value of 15.3%, and a negative predictive value of 88.8%. On the other hand, the presence of emphysema suggested abnormal PFT results with a sensitivity of 17.0%, a specificity of 93.2%, a positive predictive value of 27.6%, and a negative predictive value of 88.0%.

Table 3
Models for Predicting Normal PFT Results

Characteristic	Univariate *P* Value	OR (95% CI)	*P* Value
Any abnormal CT findings			
No abnormalities before allo-HCT	.015	2.47 (1.22-4.97)	.012
Age ≤48 yr	1.0	0.898 (0.461-1.75)	.75
Female sex	.74	1.39 (0.664-2.90)	.38
Nonsmoker	.75	0.623 (0.297-1.31)	.21
Standard-risk disease	.012	2.35 (1.21-4.55)	.011
ROC	AUC (95% CI)	0.656 (0.577-0.735)	
	Cutoff	0.915	
	Sensitivity	45.5%	
	Specificity	86.0%	
Emphysema			
No emphysema before allo-HCT	.013	4.28 (1.62-11.3)	.0035
Age ≤48 yr	1.0	0.909 (0.464-1.78)	.78
Female sex	.74	1.15 (0.547-2.43)	.71
Nonsmoker	.75	0.594 (0.276-1.28)	.18
Standard-risk disease	.012	2.60 (1.34-5.05)	.0048
ROC	AUC (95% CI)	0.690 (0.601-0.779)	
	Cutoff	0.873	
	Sensitivity	73.2%	
	Specificity	62.8%	

Models for predicting NORMAL2 were also constructed (Supplementary Table S2). In the ROC analysis with normal CT findings, the AUC was 0.652, which gave a sensitivity of 35.4% and a specificity of 87.2%.

DISCUSSION

In this study, normal PFT results were significantly associated with normal CT findings, especially the absence of emphysema. Models for predicting normal PFT results were constructed (NORMAL1 and 2), and models that included normal CT findings showed relatively high specificity. An analysis with %DLCO showed similar results, although the relationship between normal CT findings and normal PFT results was not statistically significant.

The clinical significance of PFT results in allo-HCT has been repeatedly confirmed in previous reports [14,15]. A retrospective study of reduced-intensity conditioning patients revealed that total lung capacity was significantly associated with post-transplant pulmonary complications (OR, 4.2; 95% CI, 2 to 8.5), nonrelapse mortality (OR, 3.8; 95% CI, 1.7 to 8.5), and overall survival (OR, 2.3; 95% CI, 1.2 to 4.1) [14]. Another retrospective study showed that %DLCO and midexpiratory flow 25% were significantly associated with nonrelapse mortality [15]. Therefore, PFT is considered one of the most important tests for risk stratification before allo-HCT [5].

However, it might be necessary to avoid PFT as much as possible in the COVID-19 era. COVID-19 is a viral disease that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Major symptoms of COVID-19 are fever and cough [16], and specimens collected from nasal swabs, sputum, and bronchoalveolar lavage frequently test positive for SARS-CoV-2 RNA [17]. Therefore, the virus seems to be transmitted via direct contact or droplets by coughing and sneezing. Additionally, recent studies have reported that aerosols could transmit SARS-CoV-2 in specific situations [7]. A forced expiration in PFT probably produces droplets and aerosol and might increase the risk of SARS-CoV-2 transmission. Thus, it is important to be able to predict pulmonary dysfunction without use of the PFT and to reduce the number of PFT procedures during the current pandemic.

CT may be a good alternative to PFT. Previous studies have reported that CT can be used to evaluate various pathologic conditions [18-21], and CT might be superior to PFT for diagnosing several diseases. However, the clinical significance of CT has not been clearly demonstrated, and there remains a matter of debate regarding its use for assessment before allo-HCT [22-24]. While Kaste et al. [22] and Kasow et al. [23] reported that there is little benefit in obtaining routine CT scan before allo-HCT, Akahoshi et al. [24] reported that antifungal prophylaxis could be modified based on CT before allo-HCT for recipients who had previously been diagnosed as having invasive fungal infection. In this study, normal CT findings were significantly associated with normal PFT results before allo-HCT, suggesting that normal CT findings might be able to predict a lower incidence of pulmonary complications and better survival outcomes instead of normal PFT. The targeted disease and the definition of abnormal CT findings may have caused a discrepancy regarding the clinical significance of CT before allo-HCT between this study and previous studies. The present study assessed any slight abnormal findings on lung CT such as mild emphysema and micronodular lesions, whereas previous reports mainly considered invasive fungal infection. Therefore, the normal CT findings in previous studies might have included slight abnormalities. The clinical significance of CT before allo-HCT might be more apparent with a more precise definition of abnormal CT findings.

Based on these results, models were constructed to predict the presence of normal PFT results (NORMAL1 and 2) based on lung CT findings before allo-HCT. Although the models that considered normal CT findings showed low sensitivity, they showed relatively high specificity (>80%). Therefore, according to these models, PFT could be omitted in patients with normal CT findings before allo-HCT. In the present study, normal PFT results were confirmed in most standard-risk patients with normal CT findings.

This study has several limitations due to its retrospective nature. First, in some cases, PFT was performed at other hematology hospitals. Although the procedure is mostly standardized in Japan, there might be some slight variation between institutions. Second, the threshold for normal PFT results was based on Japanese standard reference values. Therefore, our findings should be carefully interpreted when the predictive model is applied in other ethnic groups. However, to our knowledge, this is the first report to suggest that CT scan may be used to screen for the necessity of PFT.

In conclusion, normal CT findings and the absence of emphysema were significantly associated with normal PFT results before allo-HCT. The predictive model developed here may be useful for identifying patients who could be expected to have normal PFT results and thus might reduce the number of PFTs required. These results should be confirmed by further cohort or prospective studies.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2020.08.025.

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