Respirology

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Journal:	*Respirology*
Manuscript ID	RES-18-491.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	14-Nov-2018
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Subject Category – Select up to 3 subject categories that best match your manuscript and list them in order of preference.:	Rare Lung Disease, Lung Function
Keywords - Select up to 5 keywords:	Rare lung diseases, Respiratory function tests

Editorial Office Notes:

RES-18-491.R1

ORIGINAL ARTICLE

Received 9 July 2018
Invited to revise 23 August 2018
Revised 14 November 2018
Accepted 3 December 2018
Associate Editor: Helen Whitford
Senior Editor: Yuben Moodley

Publication fee waiver: YES
Volume: 24

Rapid versus gradual lung function decline in bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation is associated with survival outcome

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Summary at a glance

Patients with post-hematopoietic stem cell transplant (HSCT) bronchiolitis obliterans syndrome (BOS) who manifested initial rapid lung function decline within three months after BOS diagnosis had significantly poorer lung function and worse overall survival compared with those with initial gradual decline in lung function after BOS diagnosis.

ABSTRACT

Background and objective Bronchiolitis obliterans syndrome (BOS) after hematopoietic stem cell transplantation (HSCT) presents with lung function decline. The pattern of lung function decline after BOS diagnosis could impact on prognostication of BOS as complication after HSCT. The aim of this study was to assess the impact of lung function decline on overall survival in BOS subjects.

Methods Subjects with BOS were compared to those without BOS, matched for age, gender, primary diagnoses, conditioning regimes and chronic graft versus host disease. Lung function tests at baseline, at BOS diagnosis and every three-monthly after HSCT were evaluated.

Results Of 1461 subjects undergoing allo-HSCT between 1998 and 2015, 95 (6.5%) were diagnosed to have BOS. 159 matched HSCT recipients without BOS were identified. A 25% decline in FEV_1 within the first three months after BOS diagnosis would separate BOS subjects into a sub-group with initial rapid decline and the other sub-group with initial gradual decline in lung function. The rapid decline group showed lower subsequent lung function parameters and significantly worse overall survival compared to the gradual decline group ($p = 0.013$)

Conclusion Post-HSCT BOS subjects with initial rapid lung function decline in three months after BOS diagnosis will have significantly poorer lung function and worse overall survival compared to those with initial gradual decline in lung function after BOS diagnosis. HSCT BOS patients with rapid initial decline in lung function warrant closer monitoring for development of other post-HSCT complications that could affect their survival.(Abstract word count: 243)

Keywords: Bronchiolitis obliterans syndrome, lung function decline, hematopoietic stem cell transplantation

Short title: Lung function decline in BOS after HSCT

INTRODUCTION

Pulmonary complications are major causes of morbidity and mortality in hematopoietic stem cell transplantation (HSCT) recipients. Bronchiolitis obliterans syndrome (BOS) is an important pulmonary complication after allogeneic HSCT. BOS is usually regarded as a manifestation of graft-versus-host disease (GVHD) affecting the lung [1, 2], reported to occur in 2 - 3% of allogeneic HSCT (allo-HSCT) recipients [3-5]. Symptomatic BOS impairs quality of life and increases mortality [2]. Specific therapy effective in improving long-term outcome of BOS in HSCT recipients has not been defined, although immunosuppressive drugs are often used as part of treatment for GVHD. Knowledge on the clinical course of BOS may give insight into prognostication of post-HSCT complications and hence could allow for opportunity to improve survival in post-HSCT BOS subjects.

BOS is typified by new onset of dyspnea or airflow limitation detected on lung function tests, while the presence of mosaic patterns on computed tomographic images indicating air-trapping associated with airflow limitation is a late radiological feature [1, 2, 6]. Established risks for BOS post-HSCT include allo-HSCT, chronic GVHD (cGVHD) and factors related to donors, recipients, treatment and post-HSCT complications [4, 7].

In order to understand the clinical course of post-HSCT BOS, this retrospective study was performed to analyze the clinical characteristics of patients with post-HSCT BOS in addition to GVHD. As a comparator, post-HSCT patients with GVHD but without BOS were analyzed. The aim of this study was to assess the impact of lung function decline on overall survival in BOS subjects.

METHODS

Patients

Consecutive adult patients who underwent allo-HSCT and survived for ≥ 100 days at Queen Mary Hospital, Hong Kong from January 1998 to December 2015 were retrospectively analyzed. Reference values of lung function parameters from local Hong Kong subjects were used [8]. Patients were excluded if they died within three months of HSCT, or had pre-HSCT obstructive lung diseases, including chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma and bronchiectasis. GVHD was diagnosed according to standard criteria [9]. Ethical approval was obtained from the Institutional Review Board (IRB) of the Hong Kong Hospital Authority Hong Kong West Cluster / University of Hong Kong (UW 15-284). As this was a retrospective study, individual consent was waived by the IRB.

Diagnosis of BOS

The modified NIH criteria for diagnosis of BOS were adopted [10]: [1] forced expiratory volume in one second (FEV_1) of < 75% predicted, or decrease of the FEV_1 by 10% in comparison to pre-transplant value, [2] FEV_1/forced vital capacity (FVC) of <70%; [3] absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms; [4] one of the following two features of air trapping, viz., residual volume (RV) or RV/total lung capacity (TLC) >120% of predicted, or evidence of air trapping on high-resolution computed tomography (HRCT). If a patient already had cGVHD diagnosed in other organs, only the first three criteria were necessary to document lung involvement by cGVHD. If BOS was the only clinical manifestation in a patient without a prior established diagnosis of cGVHD, a lung

biopsy was required to establish the diagnosis of cGVHD [10].

Statistical analysis. In comparing allo-HSCT patients with and without BOS, the following parameters were matched: age, donor / recipient gender, primary diagnoses, conditioning regimen and cGVHD. Lung function tests at baseline (pre-HSCT), at diagnosis of BOS and three-monthly thereafter, were evaluated. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Differences between groups were assessed using the chi-square test or Fisher's exact test for categorical variables and Student's t-test or the Mann-Whitney U test for continuous variables. Paired t-tests were performed to compare changes in lung function tests results after allo-HSCT in patients with BOS. Overall survival was defined as the duration from diagnosis of HSCT to death or the last follow up. Kaplan-Meier survival analyses were performed, with differences between groups evaluated by log-rank test. Multivariate analysis was performed with Cox regression. Receiver Operator Characteristics (ROC) analysis was performed to determine the best cutoff values of lung function parameters (with either decline of FEV_1 or FEV_1 % predicted values within the subsequent three months) to discriminate rapid *versus* gradual lung function decline within three months after the diagnosis of BOS. All statistical analyses were performed using PASW Statistics, version 21 (SPSS Inc., Chicago, IL, USA). Two- sided p values of < 0.05 were taken as the level of statistical significance.

RESULTS

Patients

Of 1461 allo-HSCT recipients from January 1998 to December 2015, 95 patients (6.5%) were diagnosed to have BOS (BOS group), 90 after their first allo-HSCT, and 5 after

their second allo-HSCT (Figure 1). As the matching group (non-BOS), 159 patients matched for age, gender, underlying hematological diseases, conditioning regimens and cGVHD, were identified (Figure 1) (Tahle 1).

Comparison between the BOS and non-BOS groups

The BOS and non-BOS groups did not differ in baseline demographic and clinical characteristics including gender, age, diseases leading to HSCT, types of donors and HSCT, duration of follow-up, and frequencies of GVHD (acute and chronic) (Table 1). The BOS groups had significantly fewer disease relapses compared with the non-BOS groups (21/95, 22.1% *versus* 61/195, 38.4%; P=0.007). However, the frequencies of deaths in these two groups were comparable.

BOS group

Acute myeloid leukemia (AML) (35.8%) and chronic myeloid leukemia (CML) (33.7%) were the most common underlying diagnoses. Upon diagnosis of BOS, patients were treated with inhaled corticosteroids and long-acting bronchodilators in addition to their usual systemic immunosuppressants. Lung function test parameters including FEV_1, FVC and $FEF_{25–75\%}$ decreased significantly ($p < 0.001$) with development of BOS.

Survival. Fifty-two patients (52/95, 54.7%) in the BOS group died. Patients without GVHD, as compared to patients with both BOS and cGVHD, had comparable OS (Figure 2a).

Decline of lung function within three months after diagnosis of BOS

Out of the 95 BOS subjects, 87 (91.5%) had regular lung function tests performed for at least every three months for the first year and then yearly or more frequently subsequent to diagnosis of BOS. Based on the proportion of initial FEV_1 decline (%

decline of FEV_1 at three months after diagnosis of BOS compared with pre-BOS FEV_1 level), ROC analysis was performed to test the cutoffs that would give the best discrimination between subjects with rapid *versus* gradual decline in lung function. A 25% decline in FEV_1 within the first three months after BOS diagnosis was found to give 99.3% separation between one group (N = 38) of rapid decline (showing more than 25% decline in FEV_1), and the other group (N = 49) with gradual decline (showing less than 25% decline in FEV_1) (Figure 3a). The same discrimination into a rapid and a gradual decline group could also be achieved with a 50% decline in FEV_1 (% predicted) within the first three months after BOS diagnosis (Figure 3b). After the initial three months of BOS diagnosis, the lung function parameters after the rapid decline would stay consistently and significantly lower than those of the gradual decline group (Figure 4 and Table 2). The characteristics of the rapid decline group and the gradual decline group was compared (Table 3). The rapid decline group showed worse survival outcome compared with the gradual decline group (p = 0.013) (Figure 2b)

DISCUSSION

Complications from allo-HSCT, including BOS and GVHD, are associated with high mortality within the first two years after HSCT [5, 11]. HSCT recipients with BOS, compared with those without BOS, have been reported to exhibit a worse prognosis, with two-year survival rates of about 45%, and a 5-year survivals of 13% [3, 12]. In our study, however, we did not find a significant difference in survivals between the BOS and non-BOS groups. In fact, the BOS group showed an 8-year OS of 57%, which was apparently superior to those reported in other series of BOS. However, the survival curves of the two groups were different. The survival curve of the non-BOS group

showed a rapid decline within the first 6 – 8 years, followed by a gradual plateauing afterwards. On the other hand, the survival curve of the BOS group showed a slower decline within the first 6-8 years, but continued to fall thereafter, showing no obvious plateauing up to 20 years post-HSCT. These differences were related to the cause of mortality. The non-BOS group had a higher chance of recurrence of the original disease, which usually occurred within the first several years post-HSCT; so that relapse-related mortality accounted in part for the more rapid initial drop in survival. Thereafter, as relapses became infrequent and post-HSCT complications abated, the survival curve plateaued. On the other hand, the BOS group had fewer relapses and hence less relapse-related mortality. Because BOS might be considered a special form of GVHD, the fewer relapses observed were consistent with the fact that disease recurrence is inversely proportional to the severity of GVHD. For this reason, the survival curve of the BOS group showed a slower initial decline. However, continued BOS resulted in gradual health deterioration and progressive increase in BOS-related mortality, so that the survival curve showed a continuous fall. These different patterns and causes of mortality led to a resultant comparable survival for the two groups of patients.

The prevalence of BOS among our cohort of allo-HSCT patients was 6.5%. This result was similar to that reported in previous studies [5, 13], which showed that the overall prevalence of BOS to be about 5.5% [5]. As a form of GVHD, BOS often co-exists with GVHD affecting other organs, including the skin and mucosa, gastrointestinal tract and liver. The concomitant presence of different forms of GVHD could affect the survival of patients with BOS [11, 14, 15]. In previous reports, cGVHD was analyzed as a potential risk factor for BOS. In our study, the BOS and non-BOS groups were matched for the occurrence of GVHD, thereby eliminating the confounding effect of GVHD, allowing us to specifically examine the impact of BOS on lung function and survival.

To our knowledge this study is the first one to demonstrate that different patterns of lung function decline after BOS diagnosis would be associated with different long-term lung function and survival outcomes. It has been suggested that impaired pulmonary function within the first six months post-HSCT may reflect temporary functional changes related to peri-transplant events [5, 16]. In a recent report by Cheng et al, where the lung function results after HSCT in at least two cohorts of subjects recruited from different centers for other clinical studies with variable lung function test surveillance protocol, there was observed to be lung function decline in subjects as early as in the six months prior to the diagnosis of BOS[17]. The present study relied on the regular lung function surveillance after HSCT in our local protocol (baseline [before HSCT], three-monthly regular lung function tests for up to two years; if there is any diagnosis of BOS, this would be followed by a three-monthly lung function tests on subsequent clinical follow-up, while for those without BOS development, lung function tests will continued on regular three-monthly intervals after HSCT. Two years after HSCT, if there is no development of BOS, lung function tests will only be performed with new respiratory symptoms.). This study showed that patients with more rapid decline of lung function within first three months after BOS diagnosis had a significantly worse residual lung function and overall survival. HSCT BOS patients with rapid initial decline in lung function within the first three months would warrant closer monitoring in subsequent clinical course for development of further post-HSCT complications that could affect their survival. A recent prospective study that included 22 BOS subjects among 43 patients with non-infectious lung complications after HSCT showed that it was possible to identify BOS subjects early by means of regular lung function screening in patients after HSCT [18]. The early detection or anticipation of lung function decline in BOS subjects may allow for opportunity of early intervention. This will include augmentation of immunosuppression as for GVHD, or the use of newer

targeted agent for treatment of GVHD that may also help to slow the rate of lung function decline.

This study has several limitations. Firstly, this was a retrospective study of medical records, though all consecutive allo-HSCT patients were included. Secondly, onset and presence of respiratory symptoms were not systemically evaluated. BOS subjects who present with respiratory symptoms may reflect more severe lung function impairment than asymptomatic patients detected by deterioration of lung function[19]. Full lung function tests were not performed for all follow , so that the effects of RV/TLC and diffusing capacity [20] could not be evaluated from the present study. The diagnosis of BOS was based on the modified NIH criteria in terms of lung function, without histological confirmation from lung biopsy, although this is not uncommon in post-HSCT BOS. Similar to earlier studies , our results cannot clarify whether acute GVHD was an important risk factor in predicting mortality in BOS post-HSCT .This is mainly because lung function tests could not be performed during the phase of acute GVHD, when patients are generally ill. Concerning the matching between BOS and non-BOS group, the severity of any acute GVHD and the underlying hematological diseases could not be matched and that may underestimate the impact of these factors in the development of BOS and GVHD in this cohort.

In conclusion, the development of BOS in addition to GVHD in allo-HSCT recipients could be associated with two distinct patterns of lung function decline, either with initial rapid deterioration within the first three months after diagnosis of BOS, or with gradual decline. The initial rapid decline group showed significantly poorer subsequent lung function and a worse survival outcome than the gradual decline group.

Acknowledgements

The authors would like to thank Ms. Crosby Lu for database management and Ms. Crystal Kwan for statistical analysis.

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Table 1 Characteristics of HSCT recipients with or without BOS, matched for age, gender, hematological diagnosis, donor, conditioning regimes and cGVHD.

		Non-BOS (N = 159)		BOS (N = 95)		P-values
Gender	Male	93	(58.4%)	51	(53.7%)	0.454
	Female	66	(41.5%)	44	(46.3%)	
Age (years, mean ± SD)		36.1 ± 10.2		36.4 ± 8.7		0.745
Hematological diagnosis	AML	75	(47.2%)	34	(35.8%)	
	ALL	15	(9.4%)	7	(7.4%)	
	CML	46	(28.9%)	32	(33.7%)	
	MDS	3	(1.9%)	8	(8.4%)	
	NHL	12	(7.5%)	4	(4.2%)	
	Myeloma	5	(3.1%)	6	(6.3%)	
	MPD	1	(0.6%)	1	(1.1%)	
	Biphenotypic acute leukemia	0	(0.0%)	1	(1.1%)	
	SAA	2	(1.3%)	1	(1.1%)	
Conditioning regimes	TBI	47	(29.6%)	32	(33.7%)	0.176
	Non TBI	95	(59.7%)	60	(63.2%)	
	ATG	3	(1.9%)	1	(1.1%)	
	Others	14	(8.8%)	2	(2.1%)	
Donor	Allogeneic	135	(84.9%)	75	(78.9%)	0.225
	Matched-unrelated	24	(15.1%)	20	(21.1%)	
Source of stem cells	Allo	152	(95.6%)	87	(91.5%)	0.189
	Mini-allo	7	(4.4%)	8	(8.5%)	
Number of GVHD Px	0	4	(2.5%)	1	(1.1%)	0.778
	1	3	(1.9%)	3	(3.2%)	

	2	143	(89.9%)	85	(89.5%)	
	3	9	(5.7%)	6	(6.3%)	
aGVHD	No	95	(59.7%)	46	(48.4%)	0.079
	Yes	64	(40.3%)	49	(51.6%)	
cGVHD	Present	127	(79.9%)	83	(87.4%)	0.127
	None	32	(20.1%)	12	(12.6%)	
Median duration follow up (months)		101		122		
Disease Relapse	No	98	(61.6%)	74	(77.9%)	0.007*
	Yes	61	(38.4%)	21	(22.1%)	
Death	No	85	(53.5%)	43	(45.3%)	0.206
	Yes	74	(46.5%)	52	(54.7%)	
Causes of death	Pneumonia	22	(29.7%)	29	(55.8%)	
	Severe GVHD	7	(9.5%)	0	(0.0%)	
	Disease relapse	36	(48.6%)	13	(25.0%)	
	Second malignancy#	7	(9.5%)	4	(7.7%)	
	Unrelated Accidents	2	(2.7%)	0		s

HSCT = hematopoietic stem cell transplantation, BOS = bronchiolitis obliterans syndrome, AML = acute myeloid leukemia, ALL = acute lymphoid leukemia, CML = chronic myeloid leukemia, MDS = myelodysplastic syndrome, NHL = non-Hodgkin's lymphoma, MPD = myeloproliferative disease, SAA = severe aplastic anemia; GVHD = graft versus host disease; aGVHD = acute graft versus host disease, cGVHD = chronic graft versus host disease; Px = prophylaxis; #Second malignancy = tumors in the head and neck region; SD = standard deviation; *p < 0.05 statistical significance.

Table 2 Two patterns of lung function decline after diagnosis of BOS

	Rapid decline (N = 38)	Gradual decline (N = 49)	
FEV_1			
Pre-HSCT, L	2.73 ± 0.51	3.05 ± 0.63	0.067
Pre-HSCT, % predicted	97.5 ± 11.6	109.9 ±14.6	0.261
FEV_1, at BOS diagnosis, L	2.38 ± 0.46	2.82 ± 0.49	0.164
FEV_1, 3 months, L	1.43 ± 0.18	2.79 ± 0.14	<0.001*
FEV_1, 6 months, L	1.24 ± 0.13	2.43 ± 0.10	<0.001*
FEV_1, 1 year, L	1.00 ± 0.08	2.23 ± 0.09	<0.001*
FEV_1, 2 years, L	1.01 ± 0.12	1.98 ± 0.13	<0.001*
FVC			
Pre-HSCT, L	3.26 ± 0.71	3.65 ± 0.78	0.064
Pre-HSCT, % predicted	107.2 ± 10.6	101.3 ±12.6	0.561
FVC, at BOS diagnosis, L	2.93 ± 0.42	3.42 ± 0.45	0.315
FVC, 3 months, L	2.20 ± 0.19	3.39 ± 0.15	<0.001*
FVC, 6 months, L	2.32 ± 0.14	3.19 ± 0.13	<0.001*
FVC, 1 year, L	2.22 ± 0.12	3.17 ± 0.12	<0.001*
FVC, 2 years, L	2.13 ± 0.15	2.99 ± 0.16	<0.001*
$FEF_{25-75\%}$			
Pre-HSCT, L	3.07 ± 0.75	3.34 ± 1.08	0.203

Pre-HSCT, % predicted	107.5 ± 11.3	108.3 ±11.6	0.610
At BOS diagnosis	2.42 ± 0.51	3.15 ± 0.56	0.456
3 months, L	1.17 ± 0.27	2.91 ± 0.22	<0.001*
6 months, L	0.81 ± 0.21	2.32 ± 1.11	<0.001*
1 year, L	0.39 ± 0.04	1.88 ± 0.18	<0.001*
2 years, L	0.51 ± 0.15	1.55 ± 0.19	<0.001*

BOS = bronchiolitis obliterans syndrome; FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, $FEF_{25-75\%}$ = forced mid-expiratory flow; L = liter; * $p < 0.05$ statistical significance.

Table 3 Characteristics of BOS subjects with rapid or progressive decline in lung function after diagnosis of BOS.

		Rapid (N = 38)		Gradual (N = 49)		P-values
Gender	Male	14	(36.8%)	31	(63.3%)	0.014*
	Female	24	(63.2%)	18	(36.7%)	
Age (years)		36.4 ± 8.5		36.4 ± 8.8		0.745
Hematological diagnosis	AML	20	(52.6%)	11	(22.4%)	0.087
	ALL	3	(7.9%)	4	(8.2%)	
	CML	11	(28.9%)	17	(34.7%)	
	MDS	3	(7.9%)	4	(8.2%)	
	NHL	1	(2.6%)	4	(8.2%)	
	Myeloma	0	(0.0%)	6	(12.2%)	
	MPD	0	(0.0%)	1	(2.0%)	
	Biphenotypic acute leukemia	0	(0.0%)	1	(2.0%)	
	SAA	0	(0.0%)	1	(2.0%)	
Conditioning regimes	TBI	26	(68.4%)	29	(59.2%)	0.200
	Non TBI	0	(0.0%)	1	(2.0%)	
	ATG	2	(5.3%)	0	(0.0%)	
	Others	10	(26.3%)	19	(38.8%)	
Donor	Allogeneic	27	(71.1%)	43	(87.8%)	0.051
	Matched-unrelated	11	(28.9%)	6	(12.2%)	
Number of GVHD Px	0	1	(2.6%)	0	(0.0%)	0.132
	1	1	(2.6%)	2	(4.1%)	
	2	31	(81.6%)	46	(93.9%)	
	3	5	(13.2%)	1	(2.0%)	
aGVHD	No	24	(63.2%)	36	(73.5%)	0.302

	Yes	14	(36.8%)	13	(26.5%)	
cGVHD	Present	18	(47.4%)	21	(42.9%)	0.675
	None	20	(52.6%)	28	(57.1%)	
Disease Relapse	No	29	(76.3%)	38	(77.6%)	0.892
	Yes	9	(23.7%)	11	(22.4%)	
Maintenance treatment before BOS	Prednisolone	9	(23.7%)	4	(8.1%)	0.352
	Cyclosporin	26	(68.4%)	17	(34.7%)	
	Mycophenolate mofetil	13	(34.2%)	5	(10.2%)	
	Azathioprine	6	(15.8%)	8	(16.3%)	
Added on treatment after BOS	Prednisolone	12	(31.6%)	8	(16.3%)	0.689
	Cyclosporin	1	(2.6%)	1	(2.0%)	
	Mycophenolate mofetil	1	(2.6%)	1	(2.0%)	
	Regular IVIg	4	(10.5%)	2	(4.1%)	
	Inhaled glucocorticosteroids	13	(34.2%)	18	(36.7%)	
Disease duration	From HSCT to BOS, median months (range)	10	(2 – 26)	13	(2 – 22)	0.091
	From HSCT to death, median months (range)	98	(8 – 308)	202	(31 – 298)	0.001*
Death	No	15	(39.5%)	26	(53.1%)	0.208
	Yes	23	(60.5%)	23	(46.9%)	
Cause of death	Pneumonia	14	(60.9%)	15	(65.2%)	0.094
	Disease relapse	5	(21.7%)	8	(34.8%)	

	Second malignancy#	4	(17.4%)	0	(0.0%)	

HSCT = hematopoietic stem cell transplantation, BOS = bronchiolitis obliterans syndrome, AML = acute myeloid leukemia, ALL = acute lymphoid leukemia, CML = chronic myeloid leukemia, MDS = myelodysplastic syndrome, NHL = non-Hodgkin's lymphoma, MPD = myeloproliferative disease, SAA = severe aplastic anemia; GVHD = graft versus host disease; aGVHD = acute graft versus host disease, cGVHD = chronic graft versus host disease; Px = prophylaxis; *$p < 0.05$ statistical significance.

Figure legends

Figure 1 A flow diagram to explain the number of HSCT recipients at different stage of analysis. The thicker two-sided arrow in middle indicates comparison between the BOS group and the matched non-BOS group.

HSCT = hematopoietic stem cell transplantation, BOS = bronchiolitis obliterans syndrome, cGVHD = chronic graft versus host disease.

Figure 2 (a) Survival of HSCT patients with or without BOS matched for GVHD; (b) Subjects with the two different patterns of lung function decline (rapid initial decline vs gradual decline) after diagnosis of BOS showed significantly different overall survival.

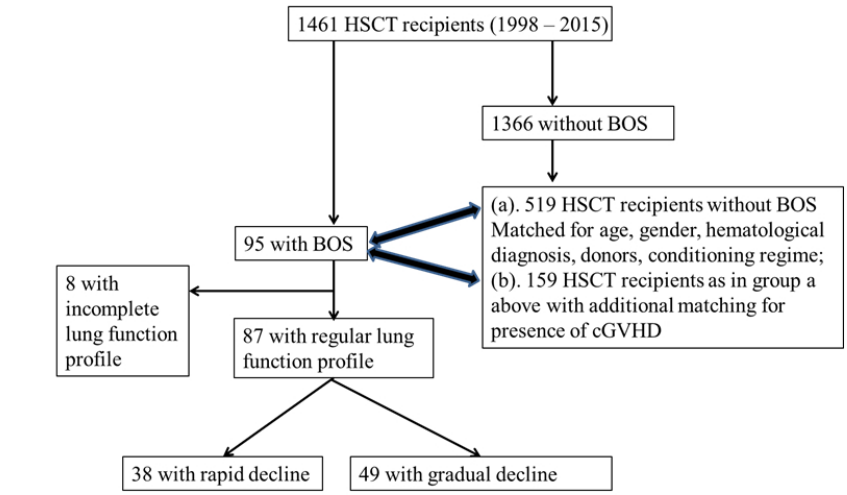
HSCT = hematopoietic stem cell transplantation, BOS = bronchiolitis obliterans syndrome, FEV_1 = forced expiratory volume in one second

Figure 3 Receiver Operator Curve (ROC) analysis showed that using (a) a 25% decline in FEV_1 and (b) a 50% decline in FEV_1 (% predicted), within three months of diagnosis of BOS as the cutoff value would give complete separation of BOS into a rapid decline group and a gradual decline group.

Figure 4 Serial lung function profiles from diagnosis of BOS in (a) FEV_1, (b) FVC and (c) $FEF_{25-75\%}$.

BOS = bronchiolitis obliterans syndrome; FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, $FEF_{25-75\%}$ = forced mid-expiratory flow; L = liter. All the lung function parameters were represented by the mean values ± standard deviation

Figure 1

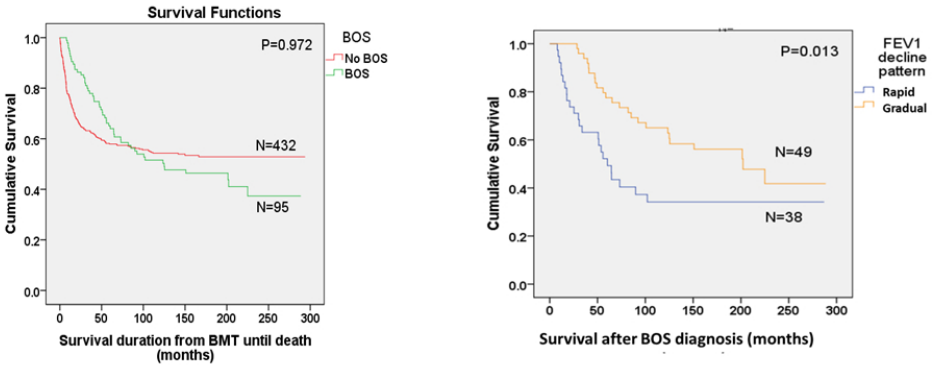


HSCT = hematopoietic stem cell transplantation, BOS = bronchiolitis obliterans syndrome, cGVHD = chronic graft versus host disease.

Figure 1. A flow diagram to explain the number of HSCT recipients at different stage of analysis. The thicker two-sided arrow in middle indicates comparison between the BOS group and the matched non-BOS group.

254x190mm (96 x 96 DPI)

Figure 2 (a) Figure 2 (b)

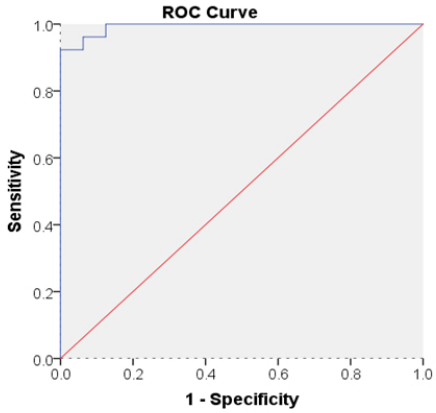


BOS = bronchiolitis obliterans syndrome, FEV_1 = forced expiratory volume in one second, BMT = bone marrow transplantation

(a) Survival of HSCT patients with or without BOS matched for GVHD; (b) Subjects with the two different patterns of lung function decline (rapid initial decline vs gradual decline) after diagnosis of BOS showed significantly different overall survival.

254x190mm (96 x 96 DPI)

Figure 3 (a)

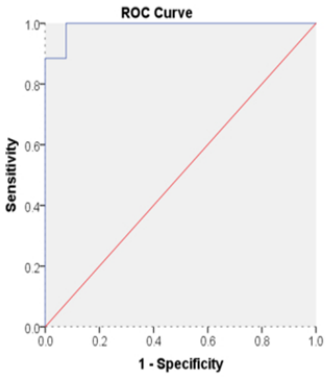


N = 87; Area under curve (AUC) = 99.3%, SE = 0.008, 95% CI = 97.7%-100%, $p < 0.001$

Receiver Operator Curve (ROC) analysis showed that using (a) a 25% decline in FEV1 and (b) a 50% decline in FEV1 (% predicted), within three months of diagnosis of BOS as the cutoff value would give complete separation of BOS into a rapid decline group and a gradual decline group.

254x190mm (96 x 96 DPI)

Figure 3(b)



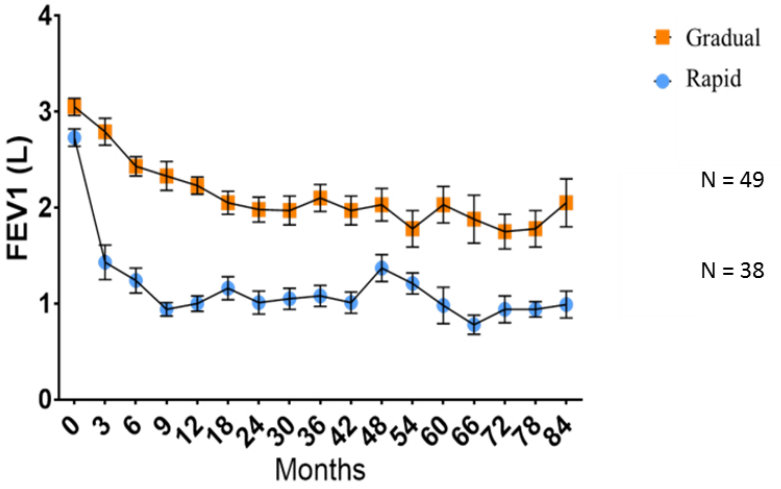
N = 87; Area under curve (AUC) = 99.3%, SE=0.011, 95% CI: 97.0%-100%;

p-value < 0.001

Receiver Operator Curve (ROC) analysis showed that using (a) a 25% decline in FEV1 and (b) a 50% decline in FEV1 (% predicted), within three months of diagnosis of BOS as the cutoff value would give complete separation of BOS into a rapid decline group and a gradual decline group.

254x190mm (96 x 96 DPI)

Figure 4(a)

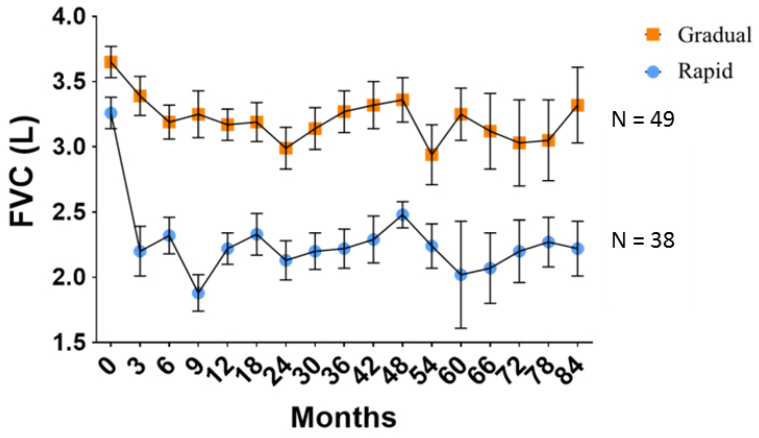


FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, $FEF_{25-75\%}$ = forced mid-expiratory flow; L = liter

Serial lung function profiles from diagnosis of BOS in (a) FEV1, (b) FVC and (c) FEF25-75%.

254x190mm (96 x 96 DPI)

Figure 4(b)

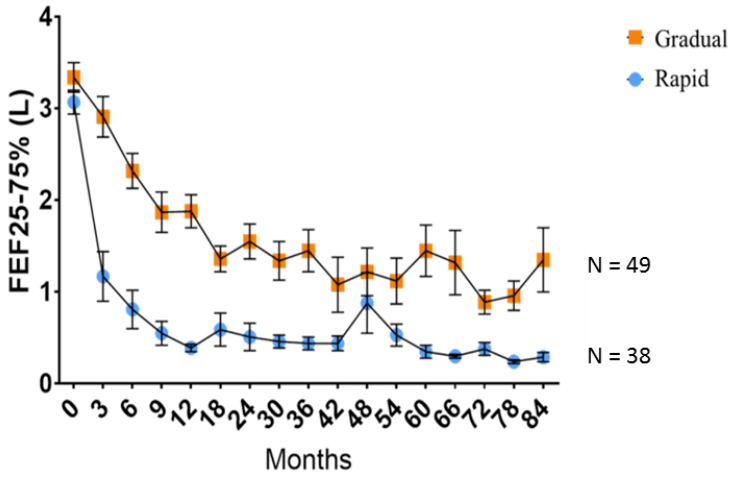


FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, $FEF_{25-75\%}$ = forced mid-expiratory flow; L = liter

Serial lung function profiles from diagnosis of BOS in (a) FEV1, (b) FVC and (c) FEF25-75%.

254x190mm (96 x 96 DPI)

Figure 4(c)



FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, $FEF_{25-75\%}$ = forced mid-expiratory flow; L = liter

Serial lung function profiles from diagnosis of BOS in (a) FEV1, (b) FVC and (c) FEF25-75%.

254x190mm (96 x 96 DPI)