HHS Public Access

Author manuscript

Transplant Cell Ther. Author manuscript; available in PMC 2024 March 01.

Published in final edited form as:

Transplant Cell Ther. 2023 March ; 29(3): 204.e1–204.e7. doi:10.1016/j.jtct.2022.12.001.

Risk factors for bronchiolitis obliterans syndrome after initial detection of pulmonary impairment after hematopoietic cell transplantation

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Abstract

Introduction: Pulmonary chronic graft-vs-host-disease (cGVHD), or bronchiolitis obliterans syndrome (BOS), is a highly morbid complication of hematopoietic cell transplant. The clinical significance of a single instance of pulmonary decline not meeting BOS criteria is unclear.

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Contributors

Ajay Sheshadri and Amin Alousi conceived the study. All authors participated in data collection. Shikun Wang and Liang Li performed all statistical analyses. Mansour Alkhunaizi, Amin Alousi, and Ajay Sheshadri wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the MD Anderson Institutional Review Board approved (PA17-0732).

Consent for publication

No patient identifiers are included in this document

Competing interests

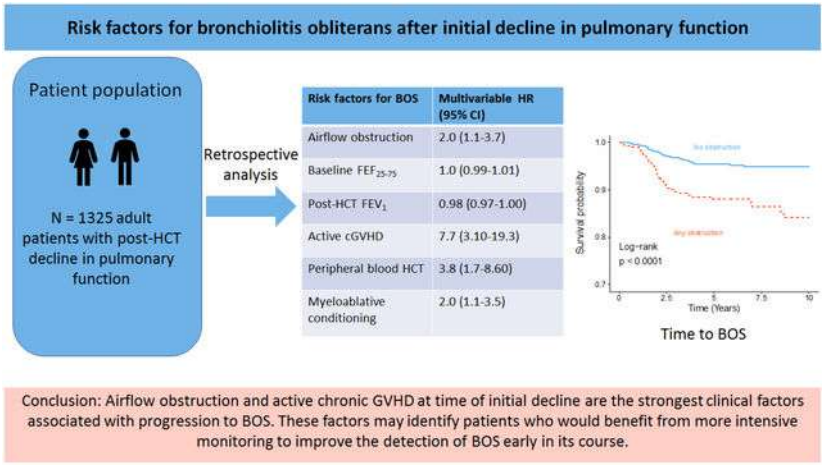
No relevant conflicts of interest.

Methods: We conducted a retrospective analysis on a cohort of patients who had an initial post-HCT decline in the absolute value of FEV_1 of ≥ 10% or mid-expiratory flow rates of ≥ 25% but not meeting criteria for BOS (preBOS). We examined the impact of clinical variables in patients with preBOS on the risk for subsequent BOS.

Results: 1325/3170 (42%) patients developed preBOS, of whom 72 (5%) later developed BOS. Eighty-four patients developed BOS without detection of preBOS by routine screening. Among patients with preBOS, and after adjusting for other significant variables, airflow obstruction (HR 2.0, 95% confidence interval [CI] 1.1–3.7, p=0.02), percent-predicted FEV_1 upon decline (HR 0.98, 95% CI 0.97–1.0 p=0.02), active cGVHD (HR 7.7, 95% CI 3.1–19.3, p<0.001), peripheral blood stem cell source (HR 3.8, 95% CI 1.7–8.6, p=0.001), and myeloablative conditioning (HR 2.0, 95% CI 1.1–3.5, p=0.02) were associated with subsequent BOS. The absence of airflow obstruction and cGVHD had a negative predictive value of 100% at six months for subsequent BOS, but the positive predictive value of both factors was low (cGVHD: 3%, any obstruction: 4%, combined: 6%).

Conclusions: Several clinical factors at the time of preBOS, particularly active cGVHD and airflow obstruction, increase the risk for subsequent BOS. These factors merit consideration to be included in screening practices to improve the detection of BOS, with the caveat that the predictive utility of these factors is limited by the overall low incidence of BOS among patients with preBOS.

Graphical Abstract



Keywords

hematopoietic cell transplantation; bronchiolitis obliterans syndrome; graft-versus-host disease; pulmonary function testing

Introduction

Graft-versus-host-disease (GVHD) is a major complication of allogeneic hematopoietic cell transplant (HCT). Despite GVHD being associated with decreased rates of post-HCT relapse[1], severe chronic GVHD (cGVHD) syndromes such as bronchiolitis obliterans

syndrome (BOS), the primary form of lung cGVHD, have devastating 10-year mortality rates of up to 80%[2]. BOS can be challenging to treat if not detected early in its course[3,4], and HCT recipients who present with severe pulmonary impairment have high mortality[5].

National Institutes of Health (NIH) guidelines recommend that pulmonary function testing be performed periodically to screen for BOS[6,7]. Unfortunately, testing is performed most frequently in the first year after transplantation, but the median time to BOS diagnosis is often reported to be in the second year after transplantation[8]. Furthermore, NIH criteria for the diagnosis of BOS are stringent[9], which is more useful for retrospective identification of BOS than for identifying cases of BOS in clinical practice. Matching the usual practice in lung transplantation, the term BOS 0p, defined as a decline of 10% or greater in forced expiratory volumes in 1 second (FEV_1) or 25% or greater in forced mid-expiratory flow rates ($FEF_{25–75}$) on two consecutive pulmonary function tests (PFTs), has been used to identify early impairment that could herald the subsequent development of BOS. However, BOS 0p has a positive predictive value (PPV) of only about 30% after HCT due to the low incidence of post-HCT BOS. Furthermore, requiring a confirmatory PFT after impairment may allow for early BOS to progress and result in irreversible impairment, minimizing the utility of early identification of impairment in the first place. That being said, eliminating the need for a second confirmatory PFT would further decrease the PPV of BOS 0p, resulting in a high false-positive rate.

To date, there are no data to suggest how often patients who have a single instance of pulmonary impairment subsequently develop post-HCT BOS. Furthermore, clinical factors that may associate with BOS among patients with a single decline are unknown. These factors, if identified, may help to mitigate the expected loss in PPV when removing the requirement for confirmatory PFTs to identify BOS 0p. We conducted a retrospective analysis of consecutive first HCT recipients to determine whether pulmonary and non-pulmonary clinical factors at the time of first impairment could accurately identify who subsequently developed BOS.

Methods

Patient selection

We collected clinical data from our institutional HCT database on all patients at least 18 years of age who underwent their first allogeneic HCT for primary hematological malignancies at The University of Texas MD Anderson Cancer Center between February 1999 and March 2018. We specified first HCT in order to ensure we had all relevant data before and after HCT. The protocol was approved by our institutional review board (PA17–0732) with a waiver of informed consent.

Definitions

We focused our analyses on patients who developed new pulmonary impairment after HCT, defined as an absolute decline of ≥ 10% in FEV_1 or ≥ 25% in $FEF_{25–75}$ on a single PFT, relative to pre-HCT values (hereafter referred to as preBOS). PreBOS differs from the prior BOS 0p definition in that we do not require two consecutive tests indicating pulmonary

impairment. Importantly, we excluded patients who had NIH guideline-defined BOS[6] (Table 1), since they met the outcome of interest before developing preBOS. Active cGVHD was defined by the need for immunosuppressive therapy to control clinically evident cGVHD. We used either one of the following three definitions to identify obstruction at time of impairment: 1) FEV_1/forced vital capacity (FVC) < 0.7, 2) FEV_1/FVC < 5^{th} percentile of predicted values, or 3) $FEF_{25–75}$< 5^{th} percentile of predicted values. A patient was considered to have "any obstruction" if they met any of the three criteria for airflow obstruction. Restriction at time of impairment was defined as total lung capacity (TLC) < 5^{th} percentile of predicted values. We used reference equations from the National Health and Nutritional Examination Survey (NHANES) and adjusted accordingly for age, sex, height, and self-identified race per usual practice during the study period[10].

Statistical analysis

Categorical variables were summarized by frequencies and percentages, and continuous variables were summarized using medians and IQR ranges. For time-to-event outcomes, we first applied univariate Cox proportional hazard regression models to study the association between each risk factor and the outcome. The hazard ratios (HRs) were reported along with their 95% confidence intervals (CI) and p-values. Variables with $p < 0.1$ in univariate analyses were included in a multivariate Cox proportional hazard regression model. Only a single definition for airflow obstruction, whether at baseline, or upon initial decline, was allowed into an individual model to avoid collinearity. Proportional hazards assumption was assessed by standard model diagnosis procedures, including the covariate by time interaction and Schoenfeld residuals. The distribution of time-to-event outcome was estimated and plotted with the Kaplan-Meier method and compared between subgroups with the log-rank test. The prediction accuracy of the multivariate model was evaluated by time-dependent receiver-operating-characteristic (ROC) analysis using bootstrap cross-validation. All statistical analyses were performed using R version 3.6.1. All statistical tests were two-sided with a significance level of 5%.

Results

Between February 1999 and March 2018, 3170 adult patients underwent HCT at our institution for primary hematological malignancies. Of those, 1409 patients developed new post-HCT pulmonary impairment, of whom 84 patients developed BOS as the first manifestation of pulmonary impairment and were excluded from preBOS analyses (Figure 1). The remaining 1325 patients were included in all analyses. Of the 1325 patients with preBOS, 622 patients had a decline in $FEV_1 \geq 10\%$ (47%), 145 patients had a decline in $FEF_{25–75} \geq 25\%$ (11%), and 556 patients had a decline in both FEV_1 and $FEF_{25–75}$ that met the predefined threshold (42%). 42% of the final cohort were female and 75% of all patients identified as white. 19% of patients had a baseline FEV_1 <80% predicted prior to HCT. Active cGVHD at time of preBOS was identified in 53% of patients. Four hundred nineteen patients (32%) met either one of the three pre-defined criteria for obstruction at time of preBOS. Only 72 patients (5%) progressed to BOS after preBOS. Table 2 describes the characteristics of the final study cohort (n = 1325) in more detail.

The median time to BOS for the excluded patients who developed BOS without preBOS (n = 84) was 15.6 months (95% CI 1.4–107 months), while the 72 patients (5%) who progressed to BOS after preBOS, did so at a median of 24 months following HCT (95% CI 2.5–103 months). The median percent-predicted FEV_1 at time of BOS was 48% (range 20% to 102%) and 52% (range 23% to 100%), respectively. In a Kaplan-Meier analysis, we found no difference in mortality between the two groups when using time of BOS as the initial time point (p=0.21, Figure 2). BOS developed at a median of 278 days after detecting preBOS, with a median percent predicted FEV_1 of 67% (range 22% to 104%), and a median percent predicted $FEF_{25–75}$ of 53% (range 9% to 116%) at the time of preBOS.

In univariate analyses, airflow obstruction at time of preBOS –regardless of how obstruction was defined– (HR 1.9–4.7, p<0.001), active cGVHD (HR 10.0, 95% CI 4.0–24.7, p<0.001), peripheral blood stem cell source (HR 4.7, 95% CI 2.2–10.3, p<0.001), myeloablative conditioning (HR 1.9, 95% CI 1.1–3.3, p=0.03), baseline percent-predicted $FEF_{25–75}$ (HR 0.99 per 1% increase, 95% CI 0.98–1.00, p=0.02), percent-predicted FEV_1 at decline (HR 0.97 per 1% increase, 95% CI 0.96–0.98, p<0.001), FEV_1/FVC at time of decline (HR 0.94 per 1% increase, 95% CI 0.92–0.95, p<0.001), and percent-predicted $FEF_{25–75}$ at decline (HR 0.97 per 1% increase, 95% CI 0.96–0.98, p<0.001) were associated with BOS (Table 3). In other words, there was a decreased risk of BOS with each increase of 1% in percent-predicted values of $FEF_{25–75}$ at baseline or at time of decline and FEV_1 at time of decline and each 1% increase in the uncorrected FEV_1/FVC ratio. All definitions of obstruction performed similarly in predicting future BOS (Figure 3). In multivariate analyses, any airflow obstruction (HR 2.0, 95% CI 1.1–3.7, p=0.02), active cGVHD (HR 7.7, 95% CI 3.1–19.3, p<0.001), peripheral blood stem cell source (HR 3.8, 95% CI 1.7–8.6, p = 0.001), myeloablative conditioning (HR 2.0, 95% CI 1.1–3.5, p=0.02), and percent-predicted FEV_1 at time of decline (HR 0.98 per 1% increase, 95% CI 0.97–1.00, p=0.02) were associated with BOS after also adjusting for antithymocyte globulin (ATG) preparation and baseline $FEF_{25–75}$. Compared to univariate models only examining airflow obstruction, the multivariate model had an improved area under the receiver-operating-characteristic curve (AUC) (0.79 for multivariate vs. 0.64 for univariate). (Table 4, Figure 4).

The diagnostic performance of how obstructive impairment and cGVHD are associated with subsequent BOS is outlined in Table 5 and Figure 4, which shows the performance of the univariable and multivariable models using the “any obstruction” definition. Active cGVHD at time of decline had the highest sensitivity for BOS (96%) but low specificity (48%). Other clinical variables had lower sensitivity, including any obstruction (67%), $FEF_{25–75}$ <5th percentile (58%), FEV_1/FVC < 5th percentile (50%), and FEV_1/FVC < 0.7 (46%). Among measured variables, FEV_1/FVC < 0.7 had the highest specificity for BOS (86%). Together, the presence of active cGVHD and obstruction by any definition had good specificity for BOS (73%), while the absence of both effectively ruled out BOS with sensitivity and negative predictive value of 100%.

Discussion

Here, we show that among patients who develop preBOS, or a single instance of pulmonary decline, cGVHD, airflow obstruction, FEV_1 at decline, peripheral blood transplant, and

myeloablative conditioning are associated with subsequent BOS. Our results show that while certain factors can detect patients at relatively high risk for subsequent BOS after the detection of preBOS, many cases of BOS are still missed before the development of BOS. Incorporating a more sophisticated screening approach using the risk variables we identified may improve the efficiency of more intensive screening practices to allow for better detection of this highly morbid disease.

Though BOS 0p is a reliable screening tool for BOS in post-lung transplant patients with high sensitivity and negative and positive predictive values[11], the lower prevalence of BOS after HCT renders this adaptation of BOS 0p far more prone to false-positive results. However, pulmonary screening for BOS becomes less intensive after the first year of transplantation[12], while paradoxically, the median time of BOS diagnosis has typically been reported to be in the second year after transplantation[8]. We found that the median time to BOS diagnosis was 16 months after HCT, similar to others[13,14], and those who developed preBOS before BOS had a longer time to BOS diagnosis. While this may potentially suggest a slower progression of impairment in those who were identified to have preBOS, we have insufficient longitudinal data to comment on trajectories. Our study highlights this gap by showing that even with guideline-driven real-world screening practices at a major HCT center, more than half the patients who developed BOS between 1999–2018 were not detected when they were at the preBOS stage. One can assume that patients, had they been monitored more intensively, must have developed preBOS before BOS based upon the natural history of pulmonary decline, which does not occur instantaneously[5]. Screening PFTs, under standard practices, are performed routinely during the first year post-HCT at 3- to 6-month intervals and yearly thereafter[15], and accordingly, we have shown that the frequency of pulmonary testing drops significantly after the first year[12].

Most patients who develop preBOS will not develop BOS. While more frequent screening with clinic-based PFTs can improve the detection of BOS, this approach is limited by resources and cost[12,16]. Identifying clinical variables that patients at higher risk for BOS may help improve the efficiency of pulmonary screening if patients with these risk factors are monitored more closely than in usual practice. Our study identified several clinical variables that are associated with a high risk for BOS among patients who develop preBOS. Active cGVHD was the strongest risk factor for subsequent BOS, suggesting that patients with active cGVHD are a prime target population for intensive home spirometry (HS) monitoring. At a minimum, these patients would benefit substantially from more intensive clinic-based monitoring. Additionally, and similar to earlier observations, airflow obstruction was also associated with a higher risk for BOS[17]. This is useful because patients who develop new airflow obstruction require particularly close follow-up, whether with routine clinic-based or home spirometry. Furthermore, patients with lower FEV_1 at the time of preBOS had a higher risk for BOS, as may be expected. Our work adds to the body of literature suggesting that airflow obstruction may be more valuable than measuring changes in FEV_1 alone. For example, Jamani et al identified that a lower day 80 $FEF_{25–75}$ was associated an increased BOS risk, and the addition of FEV_1 to mid-expiratory flow measurements had little additional value[18]. Our study measured variables at the time of preBOS, and not at a fixed timepoint, and further included only patients with evidence of pulmonary impairment, and this may explain our finding that the presence of airflow

obstruction and the magnitude of fall in FEV_1 independently increase the risk for subsequent BOS in adjusted models. Other baseline risk factors, such as myeloablative conditioning and peripheral blood stem cell, were independently associated with BOS after adjustment for other factors, and add to our general findings that risk factors for BOS generally apply to patients at the time of preBOS as well. However, caution is necessary when incorporating these risk factors into a screening algorithm without increasing the frequency of screening because requiring one or more of these factors to increase the frequency of pulmonary monitoring will likely worsen the existing shortfall in detecting patients who develop BOS.

However, the absence of one or more BOS risk factors at the time of preBOS does not obviate the subsequent risk for BOS. We found that preBOS in general had low sensitivity for BOS (46%) before considering other clinical factors, and this sensitivity would further decline when necessitating the presence of one or more BOS risk factors, interfering with the primary objective of screening. On the other hand, if an HCT recipient presents with one or more BOS risk factors at the time of preBOS (e.g. active cGVHD with new-onset airflow obstruction), such a patient should be monitored very closely for further progression of pulmonary impairment with retesting after a short time interval. Another possible application of our work would be to implement clinical and spirometric risk factors in a more intensive screening program, such as with HS or frequent clinic-based testing. Including BOS risk factors into screening algorithms may improve the efficiency of such a program, where the volume of observed data in a larger program could otherwise be overwhelming. The effective use of HS can allow for earlier interventions and treatment[19–21]. Recent studies of HS in HCT recipients have shown acceptable adherence, agreement with clinic PFT data, reproducibility over time, and utility to identify early BOS[22,23], but this has not yet been widely implemented in HCT centers. In the scenario of HS, “false positive” results revealing pulmonary decline are likely to be common, as we have previously shown[22], and therefore the identification of other key clinical variables may increase the signal-to-noise ratio. Because HS incorporates data at frequent intervals, adding clinical risk predictors such as airflow obstruction thresholds, particularly in high-risk populations such as those with cGVHD, may improve the specificity of detection without impacting sensitivity because of the frequency of measurements. For example, should a patient with active BOS be missed upon initial screening, a subsequent measurement shortly thereafter would detect the continued decline. In this way, our findings may readily apply to teams that wish to implement HS in a way that can enable smaller teams to monitor a large population of patients. The clinical variables that we found to associate with a higher risk for BOS should be studied in patients undergoing HS. Other biomarkers, such as multiple breath washout (MBR)[24], serum markers such as matrix metalloproteinase-3[25], and imaging modalities such as parametric response mapping (PRM)[26] could also improve the detection of preBOS patients who are at risk for future BOS, but these should be studied prospectively, and additional tests may add further costs and resource utilization.

Our study has notable strengths. This was a large comprehensive analysis of consecutive first allogeneic HCT recipients who have all undergone a systematic evaluation process. All PFT parameters were obtained at baseline and post-HCT. Additionally, all cases of BOS were confirmed by expert adjudication. There were also some weaknesses. First, this was a retrospective study and therefore subject to unmeasured bias, missing data, and other

shortfalls associated with chart review. Second, we were unable to confirm symptoms, measure patient-reported outcomes, or determine why some screening PFTs were not performed. Third, some patients were lost to follow-up, potentially underestimating the true incidence of BOS. Fourth, the inclusion of patients over a 20-year span subjected our data to bias related to variation in treatment and changes in practice. Fifth, the large variability in real-world PFT screening practices in other centers might affect the reproducibility of our results. Sixth, our pulmonary function data were not granular enough to measure the effect of FEV_1 trajectories following preBOS on subsequent BOS. Seventh, patients' respiratory viral infection (RVI) status is missing due to lack of PCR testing during a large portion of the study period; the role of RVIs in the development of BOS is currently under investigation (NCT04099082) and is likely to be a major factor relating to BOS risk[27]. Eighth, we did not have data on the reason for pulmonary impairment in the majority of preBOS cases since preBOS did not necessarily trigger further clinical evaluation.

We conclude that a single instance of impairment when combined with several clinical variables, particularly active cGVHD, can help identify patients at higher risk for BOS after the development of initial pulmonary impairment. Future studies should focus on implementing risk factors into home spirometry or intensive clinic-based screening workflows to improve the detection of BOS and allow for the prompt initiation of treatment to reduce the substantial morbidity and mortality associated with this disease.

Funding

This work was supported by the NIH/NIAID (K23 AI117024; to A.S.) and the National Cancer Institute (Cancer Center Support Grant, P30 CA016672) at the National Institutes of Health.

Availability of data

De-identified data will be made available upon reasonable request. Please address requests to asheshadri@mdanderson.org

Abbreviations:

ATG	antithymocyte globulin
AUC	area under the receiver-operating-characteristic curve
BOS	bronchiolitis obliterans syndrome
cGVHD	chronic graft-versus-host-disease
CI	confidence interval
$FEF_{25–75}$	forced mid-expiratory flow rate
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GVHD	graft-versus-host-disease

HCT	hematopoietic cell transplant
HR	hazard ratio
HS	home spirometry
MBW	multiple breath washout
NHANES	National Health and Nutritional Examination Survey
NIH	National Institutes of Health
PFT	pulmonary function test
PPV	positive predictive value
PRM	parametric response mapping
ROC	receiver-operating-characteristic
RVI	respiratory viral infection
TLC	total lung capacity

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Highlights

- 42% of allogeneic HCT recipients developed new pulmonary impairment after HCT
- Active cGVHD and airflow obstruction increase risk for BOS after initial impairment
- The absence of both cGVHD and airflow obstruction essentially rules out future BOS
- High-risk HCT recipients may benefit from more intensive pulmonary monitoring

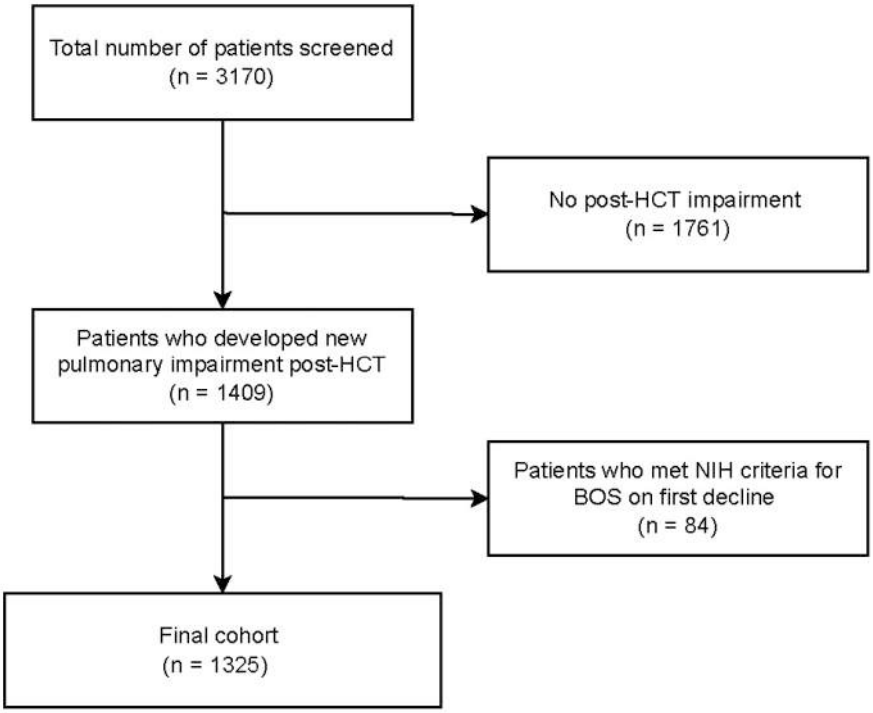

Figure 1. Study cohort enrollment diagram

The flow diagram shows the final study cohort after excluding patients who did not develop post-HCT impairment and patients who developed BOS on first evidence of decline.

Abbreviations: HCT, hematopoietic cell transplant; NIH, National Institute of Health; BOS, bronchiolitis obliterans syndrome.

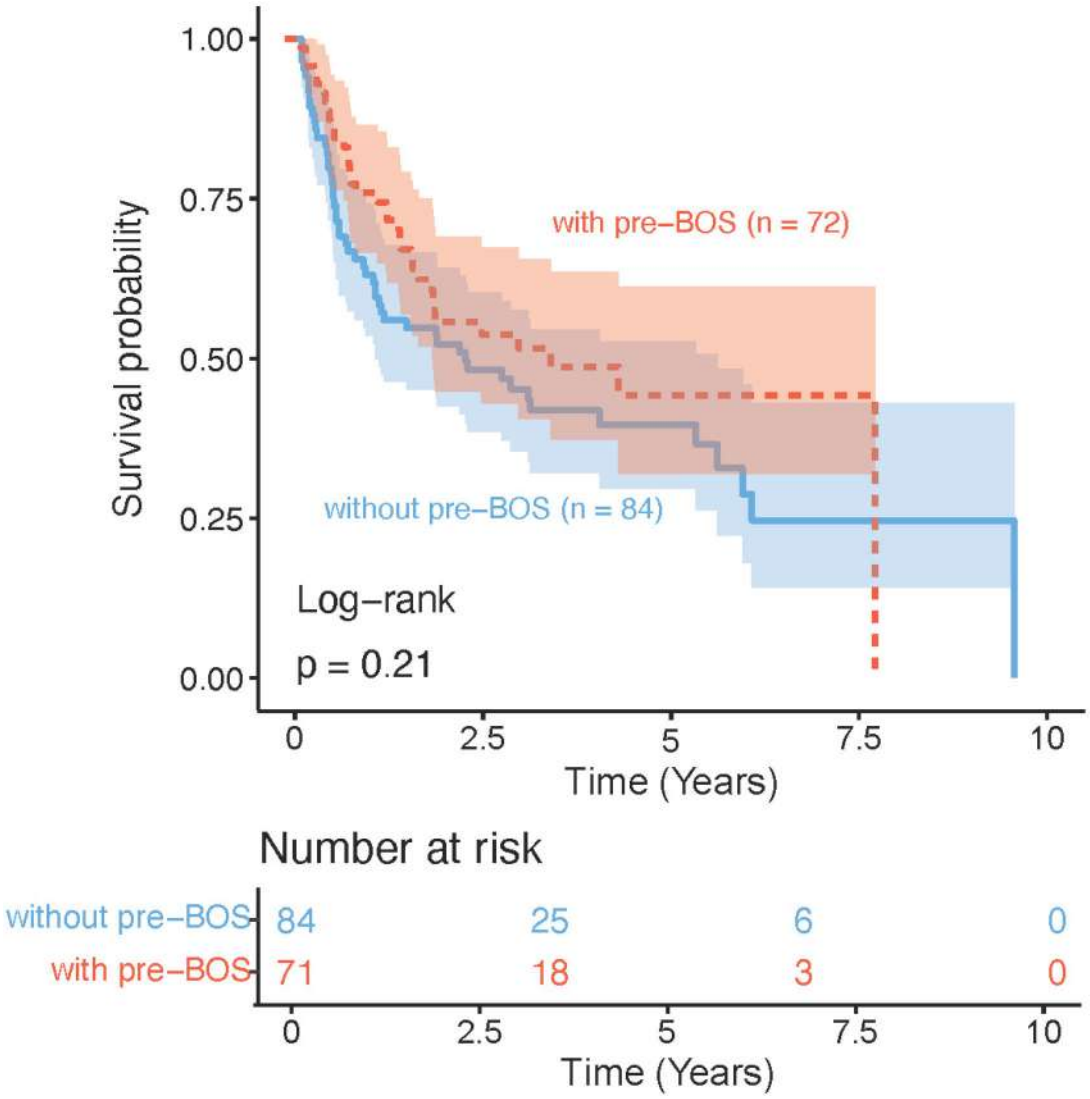

Figure 2. BOS mortality among patients with or without detectable preBOS

The Kaplan-Meier survival curve shows the mortality of patients who developed BOS which was preceded with (red) or without (blue) preBOS.

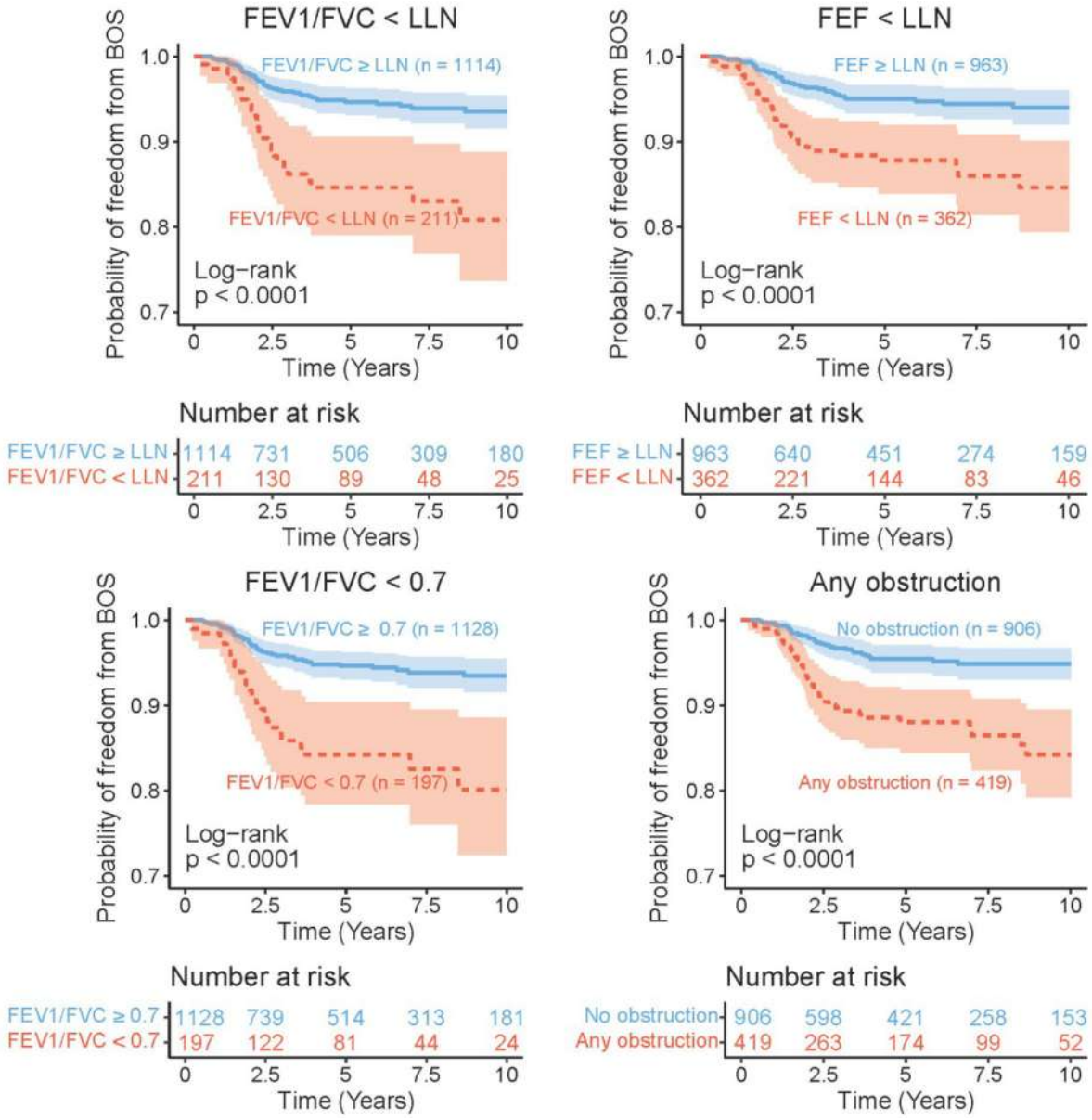

Figure 3. Airflow obstruction increases the risk for BOS after preBOS

The Kaplan-Meir survival curves show the probability of progressing to BOS for patients with and without airflow obstruction. Airflow obstruction was defined as FEV_1/FVC < LLN (panel A), $FEF_{25–75}$ < LLN (panel B), FEV_1/FVC < 0.7 (panel C), or any of the three previously mentioned definitions (panel D). The blue line represents patients who did not meet criteria for obstruction. The red line represents patients who met criteria for obstruction. The presence of any airflow obstruction was associated with higher risk of BOS (P < 0.0001).

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25–75}$, mid-expiratory flow rates; LLN, lower limit of normal.

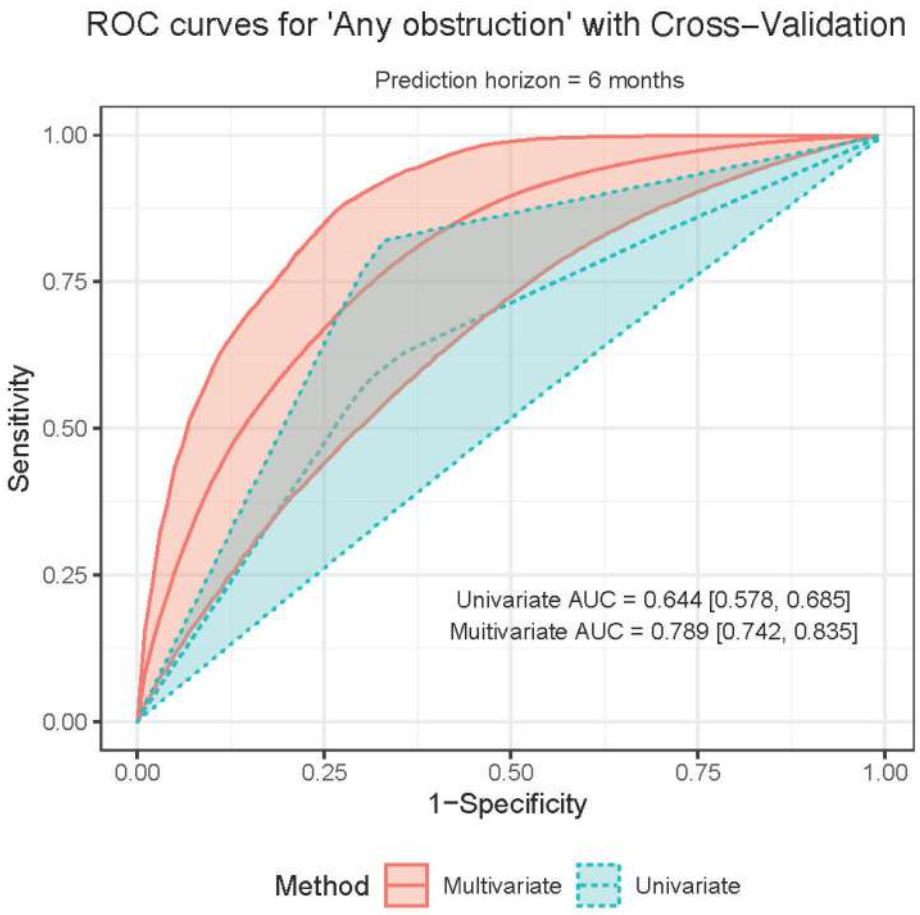

Figure 4. Univariate and multivariate model performance for factors associated with subsequent BOS after initial decline

The AUC plots show estimates of sensitivity and specificity and the associated boundaries of the 95% confidence intervals univariable (red) and multivariable (green) models using “any obstruction” as the definition for airflow obstruction. The AUC corresponds to the predictive performance of obstruction at time of decline for subsequent BOS using univariate (red) and multivariate (green) analyses. The ROC and the ROC 95% confidence intervals (shaded area) were calculated using the bootstrap cross-validation method with 100 bootstrap replicates.

Abbreviations: AUC, area under the ROC curve; ROC, receiver-operating-characteristic.

Table 1.

NIH Diagnostic Criteria for BOS *

1)	FEV_1/FVC less than 0.7 or below the fifth percentile of predicted values
2)	FEV_1 less than 75% of predicted values, with a greater than 10% decline over a period shorter than 2 years
3)	Absence of infection in the respiratory tract documented in investigations directed by clinical symptoms
4)	Evidence of air trapping, small airway thickening, or bronchiectasis on computed tomography images, residual volume/total lung capacity (RV/TLC) ratios elevated outside the 90% confidence interval for predicted values, RV >120% of predicted values, or evidence of GVHD in a non-lung organ

* All four criteria must be present to make a diagnosis of BOS

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; GVHD, graft-versus-host-disease.

Table 2

Characteristics of the study cohort (n = 1325)

Characteristic	N (%)
Female sex	562 (42%)
Race	
White	988 (75%)
Black	66 (5%)
Hispanic	198 (15%)
Other	73 (5%)
Year of HCT	
Earlier than 2001	51 (4%)
2001–2005	201 (15%)
2006–2010	411 (31%)
2011–2015	527 (40%)
2016–2018	135 (10%)
Underlying malignancy	
Acute leukemias	821 (62%)
Chronic leukemias	197 (15%)
Lymphomas	278 (21%)
Multiple myeloma	29 (2%)
Age at transplant (years), median (range)	52 (18–76)
≤40	345 (26%)
41–50	268 (20%)
51–60	414 (32%)
>60	298 (22%)
Cell source	
Peripheral blood	873 (66%)
Cord blood	81 (6%)
Bone marrow	371 (28%)
Donor type	
Mismatch related	89 (7%)
Matched related	2 (0%)
Matched unrelated	507 (38%)
Matched haploidentical	727 (55%)
Preparative regimen	
ATG containing	512 (39%)
Non-ATG containing	813 (61%)
Conditioning regimen	
Myeloablative	925 (70%)
Non-myeloablative	400 (30%)

Characteristic	N (%)
Criteria met for decline	
Decline in $FEV_1 \geq 10\%$	622 (47%)
Decline in $FEF_{25–75} \geq 25\%$	145 (11%)
Both	556 (42%)
Baseline PFT abnormalities	
FEV_1 <80%	254 (19%)
FEF25–75 <70%	241 (18%)
FEV_1/FVC <70%	70 (5%)
cGVHD status at time of preBOS	
Positive	696 (53%)
Negative	625 (47%)
Unknown	4 (0%)
Development of BOS	72 (5%)
Impairment at time of preBOS	
Obstruction	419 (32%)
Restriction	522 (39%)
Combined	183 (14%)
Non-specific	567 (43%)

Abbreviations: HCT, hematopoietic cell transplant; ATG, antithymocyte globulin; FEV1, forced expiratory volume in 1 second; $FEF_{25–75}$, forced mid-expiratory flow rate; FVC, forced vital capacity; PFT, pulmonary function test; cGVHD, chronic graft-versus-host-disease; BOS, bronchiolitis obliterans syndrome.

Table 3.

Univariate regression analysis for the time to BOS

Variable	Univariate HR	95% CI	*p* value
$FEV_1/FVC < 0.7$	3.21	1.98–5.22	<0.001
$FEV_1/FVC < 5^{th}$ percentile	3.12	1.93–5.05	<0.001
$FEF_{25–75} < 5^{th}$ percentile	2.69	1.69–4.27	<0.001
Any obstruction	2.96	1.86–4.72	<0.001
Age at decline	1.00	0.98–1.02	0.9
Active cGVHD	9.96	4.01–24.7	<0.001
Peripheral blood HCT	4.72	2.16–10.3	<0.001
Myeloablative conditioning	1.85	1.05–3.28	0.03
ATG containing prep	0.61	0.36–1.03	0.06
Baseline FEV_1	0.99	0.97–1.00	0.1
Baseline FVC	0.99	0.97–1.01	0.2
Baseline FEV_1/FVC	0.97	0.93–1.00	0.06
Baseline $FEF_{25–75}$	0.99	0.98–1.00	0.02
Baseline TLC	1.00	1.00–1.01	0.1
Baseline RV/TLC	1.00	1.00–1.01	0.1
Baseline DLCO	1.00	0.99–1.00	0.2
Post-HCT FEV_1	0.97	0.96–0.98	<0.001
Post-HCT FVC	0.98	0.97–1.00	0.02
Post-HCT FEV/FVC	0.94	0.92–0.95	<0.001
Post-HCT $FEF_{25–75}$	0.97	0.96–0.98	<0.001
Post-HCT TLC	1.00	1.00–1.01	0.4
Post-HCT RV/TLC	1.00	1.00–1.01	0.4
Post-HCT DLCO	1.00	0.99–1.00	0.7

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25–75}$, forced mid-expiratory flow rate; cGVHD, chronic graft-versus-host-disease; BOS, bronchiolitis obliterans syndrome; HCT, hematopoietic cell transplant; ATG, antithymocyte globulin; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity for carbon monoxide.

Table 4.

Multivariate regression analysis for the time to BOS

	Criteria for obstruction*							
	$FEV_1/FVC < 0.7$		**$FEV_1/FVC <$ 5th percentile**		**$FEF_{25–75} <$ 5th percentile**		**Any obstruction**	
Variable†	**Multivariate HR (95% CI)**	***P* value**	**Multivariate HR (95% CI)**	***P* value**	**Multivariate HR (95% CI)**	***P* value**	**Multivariate HR (95% CI)**	***P* value**
Airflow obstruction	2.4 (1.3–4.2)	0.003	2.2 (1.2–3.9)	0.007	1.4 (0.8–2.7)	0.2	2.0 (1.1–3.7)	0.02
Baseline $FEF_{25–75}$	1.0 (0.99–1.01)	0.5	1.0 (0.99–1.01)	0.7	1.0 (0.90–1.01)	0.8	1.0 (0.99–1.01)	0.7
Post-HCT FEV_1	0.98 (0.96–0.99)	0.002	0.98 (0.96–0.99)	0.003	0.98 (0.96–0.99)	0.008	0.98 (0.97–1.00)	0.02
Active cGVHD	7.9 (3.2–19.9)	<0.001	7.9 (3.2–19.9)	<0.001	7.9 (3.2–19.7)	<0.001	7.7 (3.1–19.3)	<0.001
Peripheral blood HCT	3.7 (1.6–8.2)	0.002	3.6 (1.6–8.2)	0.002	3.8 (1.7–8.5)	0.001	3.8 (1.7–8.6)	0.001
Myeloablative conditioning	2.0 (1.1–3.5)	0.02	1.9 (1.1–3.4)	0.02	2.0 (1.1–3.5)	0.02	2.0 (1.1–3.5)	0.02
ATG containing prep	1.2 (0.7–2.0)	0.5	1.1 (0.7–1.9)	0.6	1.0 (0.6–1.8)	0.9	1.0 (0.6–1.8)	0.9

*Spirometric parameters used to define airflow obstruction. Each column shows an individual model using a distinct spirometric definition for airflow obstruction.

†Each selected variable was included in all four models.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25–75}$, forced mid-expiratory flow rate; cGVHD, chronic graft-versus-host-disease; HCT, hematopoietic cell transplant; ATG, antithymocyte globulin.

Table 5.

Factors associated with BOS at 6 months after onset of preBOS

Variable	Sensitivity	Specificity	PPV	NPV
$FEV_1/FVC < 0.7$	46%	86%	6%	99%
$FEV_1/FVC < 5^{th}$ percentile	50%	85%	6%	99%
$FEF_{25–75} < 5^{th}$ percentile	58%	73%	4%	99%
Any obstruction	67%	69%	4%	99%
Active cGVHD	96%	48%	3%	99%
Active cGVHD **and** any obstruction	63%	73%	6%	99%
Active cGVHD **or** any obstruction	100%	35%	3%	100%

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25–75}$, forced mid-expiratory flow rate; cGVHD, chronic graft-versus-host-disease.