

Prognostic Value of Bronchiolitis Obliterans Syndrome Stage 0-p in Single-Lung Transplant Recipients

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Rationale: Early diagnosis of bronchiolitis obliterans syndrome (BOS) is critical in understanding pathogenesis and devising therapeutic trials. Although potential-BOS stage (BOS 0-p), encompassing early changes in FEV₁ and forced expiratory flow, midexpiratory phase (FEF_{25-75%}), has been proposed, there is a paucity of data validating its utility in single-lung transplantation. **Objective:** The aim of this study was to define the predictive ability of BOS 0-p in single-lung transplantation. **Methods:** We retrospectively analyzed spirometric data for 197 single-lung recipients. Sensitivity, specificity, and positive predictive value of BOS 0-p were examined over time using Kaplan-Meier methodology. **Results:** BOS 0-p FEV₁ was associated with higher sensitivity, specificity, and positive predictive value than the FEF_{25-75%} criterion over different time periods investigated. The probability of testing positive for BOS 0-p FEV₁ in patients with BOS (sensitivity) was 71% at 2 years before the onset of BOS. The probability of being free from development of BOS 0-p FEV₁ in patients free of BOS at follow-up (specificity) was 93% within the last year. Of patients who met the BOS 0-p FEV₁ criterion, 81% developed BOS or died within 3 years. The specificity and positive predictive value curves for the BOS 0-p FEV₁ were significantly different between patients with underlying restrictive versus obstructive physiology ($p = 0.05$ and 0.01 , respectively). **Conclusion:** The FEV₁ criterion for BOS 0-p provides useful predictive information regarding the risk of development of BOS or death in single-lung recipients. The predictive value of this criterion is higher in patients with underlying restriction and is superior to the FEF_{25-75%} criterion.

Keywords: bronchiolitis obliterans syndrome; diagnosis; lung transplantation; staging

Bronchiolitis obliterans is the major complication limiting outcomes in lung transplantation (1–3). Its clinical correlate, bronchiolitis obliterans syndrome (BOS), is defined as a fall in FEV₁ of greater than 20% from baseline determined by the average of two measurements made at least 3 weeks apart (4). Development of BOS is associated with progressive irreversible decline in lung function with a poor response to therapeutic interventions (1, 2). This feature, and the knowledge that pathogenesis of BO involves progressive fibroproliferation (2, 5), underscores the need for early intervention and the need to develop predictors of this disease.

Implementation of increasingly sensitive criteria for identifying early decline in pulmonary function may allow the prediction of BOS. As such, a potential-BOS stage (BOS 0-p), defined by a

10 to 19% decrease in FEV₁ and/or by a 25% or greater decrease in forced expiratory flow, midexpiratory phase (FEF_{25-75%}), from baseline was added to the original staging system in 2001 (4). In bilateral lung transplant recipients, the FEV₁ but not the FEF_{25-75%} criterion for BOS 0-p was shown to be a reasonable predictor of BOS (6). However, the role of various criteria of BOS 0-p in predicting recipients with BOS remains to be established in single-lung transplant (SLT) recipients. This population is of particular interest because spirometric criteria, such as FEV₁ and FEF_{25-75%}, are influenced by degree and nature of native lung pathology (7).

This study provides novel data defining the ability of both FEV₁ and FEF_{25-75%} criteria for BOS 0-p to predict development of BOS in a large cohort of SLT recipients. Some of these results have been previously reported in the form of an abstract (8).

METHODS

Patients

The study group comprised 197 consecutive SLT recipients who were alive 3 months post-transplantation and had post-transplant pulmonary functions available. The study was approved by the University of Michigan Institutional Review Board. All patients were followed by a standardized protocol as previously described (9). Pulmonary function testing was performed following standards established by the American Thoracic Society at each clinic visit (10).

Definition of BOS

Baseline FEV₁ and FEF_{25-75%} were determined according to the published guidelines (4). The criterion for BOS was met when two consecutive FEV₁ values at least 3 weeks apart fell below 80% of baseline FEV₁. Therefore, BOS diagnosis included stages 1, 2, and 3. Medical records of the patients during this time period were reviewed to exclude confounding variables, including infection, acute rejection, bronchial stenosis, and recurrence of primary disease or any other factors that might explain this decline in lung function. The date of onset of BOS was defined as the date of the first of the two FEV₁ measurements used to establish the diagnosis.

Definition of BOS 0-p

BOS 0-p was determined by the FEV₁ and the FEF_{25-75%} criteria, as defined by the new guidelines (4), using a similar method as described above. A modified FEF_{25-75%} criterion for stage 0-p as defined by Hachem and others (6) in the bilateral lung transplant population was also analyzed. This modified FEF_{25-75%} redefines the baseline FEF_{25-75%} as the average of the two FEF_{25-75%} measurements obtained with the two highest FEV₁ measurements (6).

Data Analysis

Correlated times to event were analyzed using years-of-life-saved statistics (11). Kaplan-Meier methodology was used to estimate sensitivity, specificity, and positive predictive value (PPV) curves for relating the diagnosis of BOS 0-p by various criteria to development of BOS. These diagnostic curves are functions of the time between meeting, or not meeting, the BOS 0-p and BOS criteria as well as the available follow-up window. The appropriate patient population, event time scale, and follow-up time scale used to construct sensitivity, specificity, and PPV

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curves using the Kaplan-Meier method are detailed further in Table 1. These same measures were compared between subgroups of SLT recipients with underlying obstructive or restrictive lung disease using log-rank tests.

To avoid bias from dependent censoring, we studied time to BOS or death in forward-looking analyses of PPV curves. In estimating sensitivity and specificity curves, patients were always alive during the study window; therefore, dependent censoring from death as a competing endpoint was not an issue.

RESULTS

Primary indications for transplantation for SLT included emphysema with or without α_1 -antitrypsin deficiency ($n = 151$; 77%) and interstitial lung diseases ($n = 34$; 18%). The remainder of the patients ($n = 12$) underwent SLT for miscellaneous indications. The dataset included 15,118 spirometric observations, with a mean number of 77 ± 98 observations per patient. Median follow-up time was 5.4 years (95% confidence interval [CI], 4.6–6.9).

The median time from transplantation to the onset of BOS or death was 2.27 years (95% CI, 1.84–2.71). The median time from transplant to the onset of BOS 0-p as defined by FEV₁ or death was 1.84 years (95% CI, 1.53–2.68) (Figure 1); over the first 5 years of follow-up, this endpoint was observed 65 days earlier on average than the combined death/BOS endpoint (95% CI, 18–149 days; $p = 0.13$). The median time from transplant to the onset of BOS 0-p as defined by the FEF_{25–75%} or death was 1.39 years (95% CI, 1.18–1.61) (Figure 1), observed during the first 5 years of follow-up 237 days earlier on average than the combined death/BOS endpoint (95% CI, 161–313 days; $p = 2.4 \times 10^{-8}$) and 172 days earlier than the combined death/BOS 0-p as defined by the FEV₁ endpoint (95% CI, 81–262 days; $p = 0.0003$). The median time from transplant to the onset of BOS 0-p as defined by the modified FEF_{25–75%} was 1.59 years (95% CI, 1.33–1.97) (Figure 1), observed during the first 5 years of follow-up 158 days earlier on average than the combined death/BOS endpoint (95% CI, 69–246 days; $p = 0.0007$), 93 days earlier than the combined death/BOS 0-p as defined by the FEV₁ endpoint (95% CI, 3–188 days; $p = 0.06$), and 79 days later on average than the combined death/BOS 0-p as defined by the FEF_{25–75%} endpoint.

The sensitivity curves of BOS 0-p by each criterion and the combinations thereof are illustrated in Figure 2. The most sensitive criterion was the combined criteria of meeting either the FEV₁ or the FEF_{25–75%} criterion. BOS 0-p defined by FEV₁ was the second most sensitive criterion followed by BOS 0-p defined by FEF_{25–75%}. The probability of testing positive for BOS 0-p in patients with BOS (i.e., sensitivity) is expected to increase as longer time periods elapse before onset of BOS. Indeed, 52, 71, and 84% of patients with BOS had met the BOS FEV₁ 0-p criterion within 1, 2, and 4 years before the onset of BOS, respectively. Over a specific time period—for example, within 2 years

before onset of BOS—the sensitivity of FEV₁ and FEF_{25–75%} criteria were 71 and 60%, respectively.

The specificity curves of BOS 0-p criteria are shown in Figure 3. In this case, we examined the population of patients alive and free of BOS during follow-up and calculated the probability that they had not met BOS 0-p within t units of time from their last pulmonary function test. So, for example, if a patient had not met the BOS criteria during follow-up, there was a 93% chance that he or she did not meet the BOS 0-p criterion as defined by FEV₁ within the last year. Similarly, there was a 79% chance that the patient did not meet the BOS 0-p criterion as defined by FEV₁ within the last 4 years. The criterion defined by meeting FEV₁ and FEF_{25–75%} criteria was found to be most specific, followed by BOS 0-p defined by FEV₁.

As expected, the PPVs increased as follow-up times after meeting BOS 0-p increased (Figure 4). Within 1 year of meeting BOS 0-p as defined by FEV₁, the probability of meeting BOS was 56%, and by 4 years, this probability had risen to 86%. The strongest positive PPVs were observed in those patients who met either the FEV₁ or both the FEV₁ and FEF_{25–75%} BOS 0-p criteria.

Figure 5 compares sensitivity, specificity, and PPV curves in patients with underlying obstructive lung disease as opposed to those with underlying restrictive lung disease. The sensitivity curve for BOS 0-p FEF_{25–75%} was higher in the group with restrictive lung disease ($p = 0.04$; Figure 5A). The specificity (Figure 5B) and PPV curves (Figure 5C) for the BOS 0-p FEV₁ were significantly higher for patients with underlying restrictive lung disease ($p = 0.05$ and 0.01, respectively).

DISCUSSION

BOS affects up to 60% of lung transplant recipients by 5 years after surgery (1, 2, 12) and is the major cause of mortality after the first year of transplantation (3). Recent advances in understanding pathogenesis point to fibroproliferation as a final common pathway leading to airway obliteration and progressive airflow obstruction (2). As such, an early marker of disease is essential in both treating patients and devising clinical trials with early intervention. Early changes in pulmonary function can be one such marker. Although BOS 0-p, encompassing early changes in FEV₁ and FEF_{25–75%}, has been proposed, there is a paucity of studies validating the usefulness of this new stage in SLT recipients, a population that comprises more than half of all lung transplant recipients (3).

This study examined the relationship over time between BOS 0-p and development of BOS in a large cohort of SLT recipients and the effect of native lung physiology on this prediction. We demonstrate the following in SLT recipients: (1) the FEV₁ criterion of BOS 0-p provides the best combination of sensitivity, specificity, and PPV over different time periods investigated; (2) the FEF_{25–75%} criterion lacks sensitivity and specificity as a

TABLE 1. OUTLINE OF KAPLAN-MEIER ELEMENTS THAT WERE USED TO ESTIMATE SENSITIVITY, SPECIFICITY, AND POSITIVE PREDICTIVE VALUE CURVES

Probability Measurement	Patient Population	Event Time Scale	Follow-up Time Scale
Sensitivity*	BOS criteria met	Time preceding BOS that BOS 0-p was met	Time preceding BOS that transplant was done
Specificity	Never met BOS criteria and alive at end of study	Time before last pulmonary function test that BOS 0-p was met	Time preceding last pulmonary function test that transplant was done
Positive predictive value*	BOS stage 0-p criteria met	Time between BOS 0-p and BOS or death	Time between BOS 0-p and last follow-up time

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; BOS 0-p = potential bronchiolitis obliterans syndrome stage.

*Note that Kaplan-Meier estimates were subtracted from 1 in these cases to get the desired probabilities.

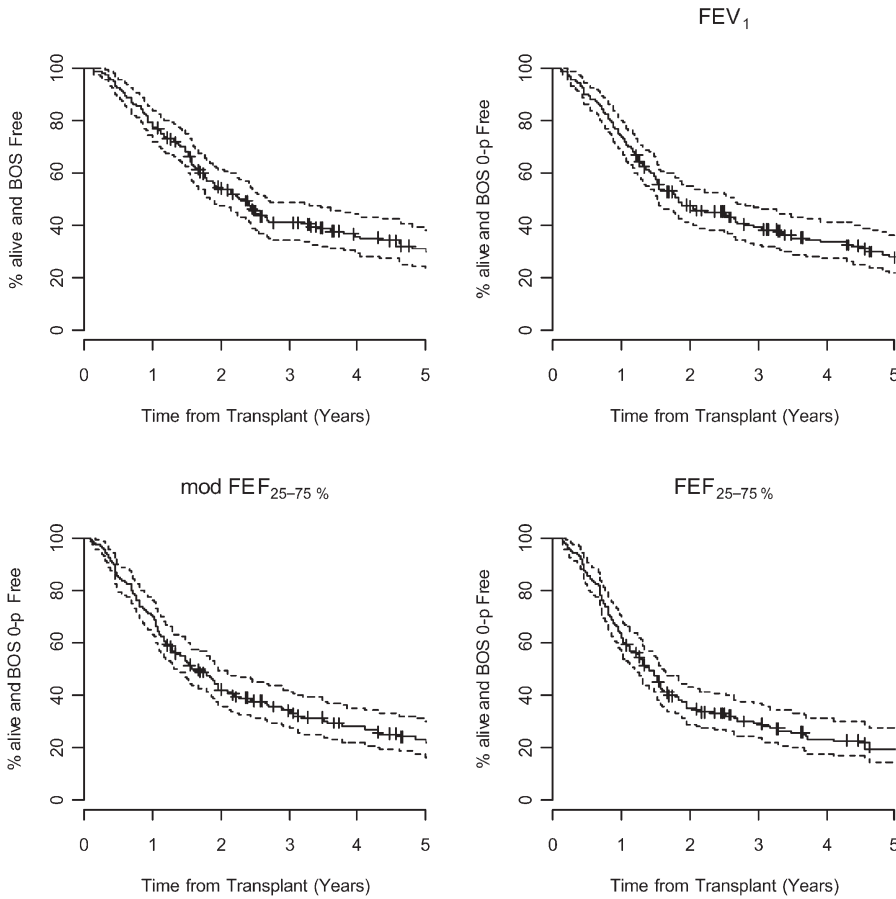


Figure 1. Freedom from bronchiolitis obliterans syndrome (BOS) and potential BOS stage (BOS 0-p) by each criterion from the time of transplantation.

predictor; and (3) native restrictive physiology increases the diagnostic utility of the FEV₁ variable.

An important and clinically relevant finding of our study is the demonstration that development of BOS 0-p FEV₁ in SLT recipients provides useful prognostic information about subsequent development of BOS or death. This is of significant clinical relevance because predictive ability of the FEV₁ criterion has not been adequately studied previously in SLT recipients. In addition, the BOS 0-p FEV₁ criterion exhibited reasonable specificity and sensitivity. The combination of either the FEV₁ or the

FEF_{25-75%} criterion was associated with highest sensitivity but was less specific and predictive. The meeting of both FEV₁ and FEF_{25-75%} criteria was most strongly predictive of development of BOS or death; however, its utility is limited by its low sensitivity.

Importantly, we document that, in SLT recipients, BOS-0 p diagnosis by FEF_{25-75%} is associated with lower sensitivity, specificity, and PPV than the FEV₁ criterion. Although in heart-lung and bilateral lung transplant recipients, an FEF_{25-75%} threshold of less than 70% of baseline has been shown to be a sensitive predictor of BOS (13, 14), a recent study found an unacceptably

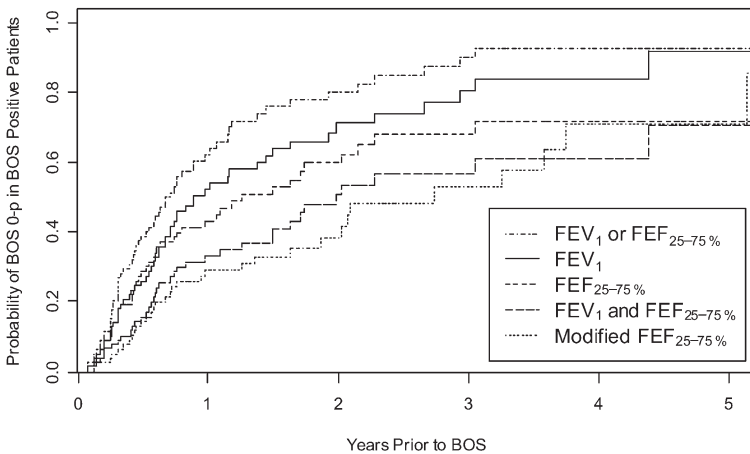


Figure 2. Sensitivity curves of BOS 0-p by each criterion in single-lung transplant recipients. The sensitivity curve as a function of time, *t*, is defined as the probability of having BOS 0-p at *t* units of time before onset of BOS among patients who ultimately develop BOS. The time along the horizontal axis indicates the length of the time before meeting the BOS criterion.

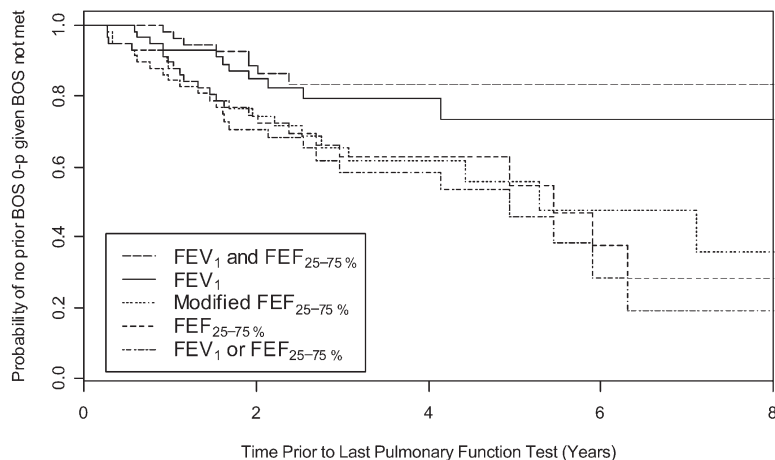


Figure 3. Specificity curves of BOS 0-p by each criterion over time in single-lung transplant recipients. The specificity curve as a function of time, t , is defined as the probability of not meeting BOS 0-p criteria within the previous t units of time from the last pulmonary function test among patients who were not diagnosed with BOS. The time on the horizontal axis is the length of time before the last observed pulmonary function test.

low specificity and PPV of the BOS 0-p $FEF_{25-75\%}$ criterion in bilateral lung transplant recipients (6). In SLT recipients, measurement of $FEF_{25-75\%}$ has been associated with higher degree of variability (7, 15). A study of 43 SLT recipients during a median follow-up of 16 months reported a sensitivity of the BOS 0-p $FEF_{25-75\%}$ of 80% and a specificity of 82.6% for subsequently detecting BOS stage (16). The differences in findings regarding predictive ability of the $FEF_{25-75\%}$ criterion may reflect the larger sample size of our study, the longer follow-up time, and differing statistical techniques used.

Another intriguing finding of our study is that SLT recipients with underlying restrictive physiology demonstrated a higher specificity and predictive ability of the BOS 0-p FEV_1 criterion in suggesting subsequent development of BOS. It can be expected that the native lung physiology will influence the diagnostic ability of criteria based on pulmonary function testing because of the contribution of the native lung (7). However, because of the small sample size of our restrictive group, these results will need to be confirmed in a larger cohort of patients.

A unique feature of our study is that we have examined sensitivity, specificity, and PPVs as functions of follow-up time and time between development of BOS 0-p and BOS. As such, we provide a more complete picture of the diagnostic ability of BOS 0-p. Our analyses indicate that sensitivity, specificity, and PPV vary significantly as functions of study-specific parameters, such as follow-up time and time to development of BOS in the cohort studied. Using our approach to the analysis of sensitivity,

specificity, and PPV is akin to estimating complete survival curves as opposed to the limited approach of estimating survival at a single point in time. It is difficult to describe negative predictive value using BOS 0-p (or any time-dependent testing measure) because patients negative for BOS 0-p at one point in time may change to BOS 0-p positive during subsequent follow-up. As such, it is difficult to identify a solid BOS 0-p-negative population and still maintain additional follow-up time to define a negative predictive value.

In summary, the FEV_1 criterion for BOS 0-p provides useful predictive information regarding the subsequent course of pulmonary function and the risk of development of BOS or death in SLT recipients. The predictive value of this criterion is higher in patients with underlying restrictive physiology and is superior to the $FEF_{25-75\%}$ criterion of BOS 0-p. These data demonstrate the need to be vigilant about onset of BOS 0-p in SLT recipients. Further studies to document if early intervention at the onset of this stage changes the natural history of disease are warranted. Additional studies of factors that influence operating characteristics of BOS-related diagnostic tests also would be useful in making clinical predictions. Knowledge of the sensitivity, specificity, and PPV of this criterion over time can be used in clinical decision making as well as for designing clinical trials targeting early disease. We would suggest that the BOS 0-p designation is a preferable criterion for triggering initiation of therapies in clinical trials of possible disease-modifying agents.

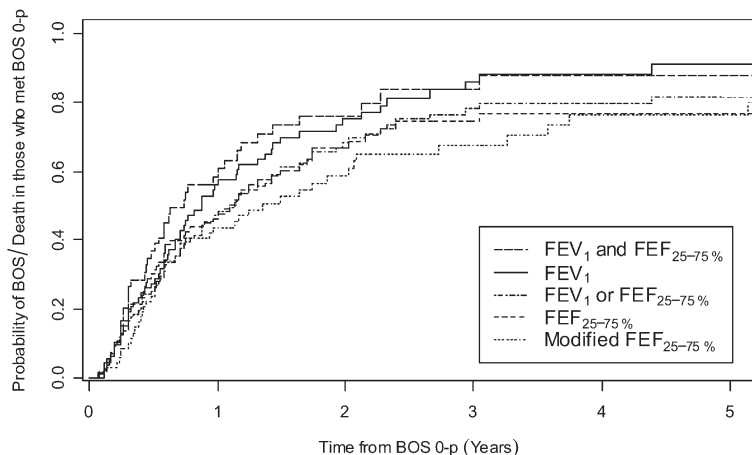


Figure 4. Positive predictive value of BOS 0-p by each criterion over time in single-lung transplant recipients (freedom from BOS or death after the onset of BOS 0-p).

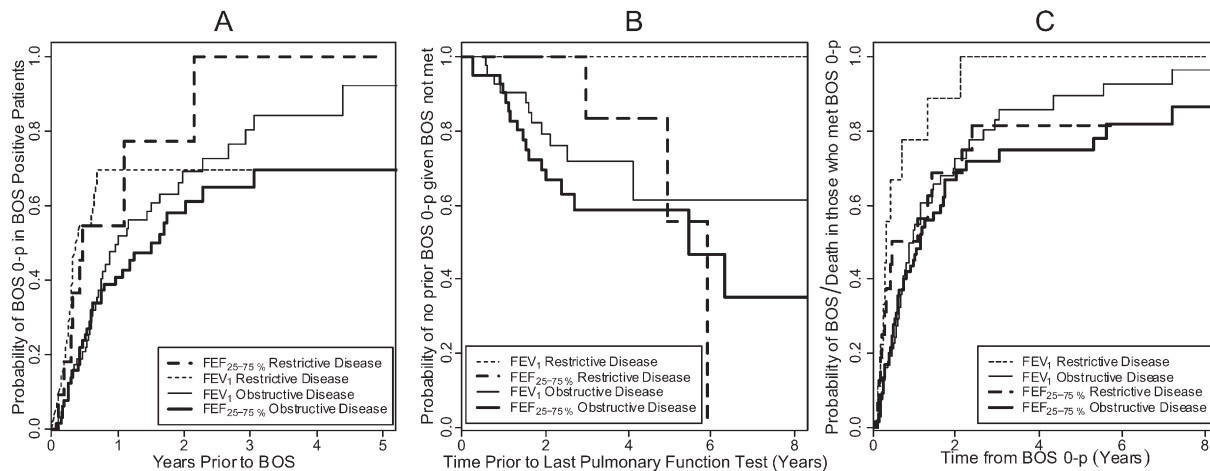


Figure 5. Sensitivity (A), specificity (B), and positive predictive value (C) for obstructive (solid lines) and restrictive (dashed lines) lung disease for BOS 0-p defined by both FEV₁ (thin lines) and FEV_{25-75%} (bold lines) criteria. The sensitivity for obstructive versus restrictive lung disease was not significantly different for BOS 0-p FEV₁ ($p = 0.24$), but was significantly different for BOS 0-p FEV_{25-75%} ($p = 0.04$). The specificity for obstructive versus restrictive lung disease was significantly different for BOS 0-p FEV₁ ($p = 0.05$), but was not significantly different for BOS 0-p FEV_{25-75%} ($p = 0.31$). The positive predictive values for obstructive versus restrictive lung disease was significantly different for BOS 0-p FEV₁ ($p = 0.01$), but was not significantly different for BOS 0-p FEV_{25-75%} ($p = 0.44$).

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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