Parametric Response Mapping as an Imaging Biomarker in Lung Transplant Recipients

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Abstract

Rationale: The predominant cause of chronic lung allograft failure is small airway obstruction arising from bronchiolitis obliterans. However, clinical methodologies for evaluating presence and degree of small airway disease are lacking.

Objectives: To determine if parametric response mapping (PRM), a novel computed tomography voxel-wise methodology, can offer insight into chronic allograft failure phenotypes and provide prognostic information following spirometric decline.

Methods: PRM-based computed tomography metrics quantifying functional small airways disease (PRM^{fSAD}) and parenchymal disease (PRM^{PD}) were compared between bilateral lung transplant recipients with irreversible spirometric decline and control subjects matched by time post-transplant ($n = 22$). PRM^{fSAD} at spirometric decline was evaluated as a prognostic marker for mortality in a cohort study via multivariable restricted mean models ($n = 52$).

Measurements and Main Results: Patients presenting with an isolated decline in FEV₁ (FEV₁ First) had significantly higher PRM^{fSAD} than control subjects (28% vs. 15%; $P = 0.005$), whereas patients with concurrent decline in FEV₁ and FVC had significantly higher PRM^{PD} than control subjects (39% vs. 20%; $P = 0.02$). Over 8.3 years of follow-up, FEV₁ First patients with PRM^{fSAD} greater than or equal to 30% at spirometric decline lived on average 2.6 years less than those with PRM^{fSAD} less than 30% ($P = 0.004$). In this group, PRM^{fSAD} greater than or equal to 30% was the strongest predictor of survival in a multivariable model including bronchiolitis obliterans syndrome grade and baseline FEV_{1%} predicted ($P = 0.04$).

Conclusions: PRM is a novel imaging tool for lung transplant recipients presenting with spirometric decline. Quantifying underlying small airway obstruction via PRM^{fSAD} helps further stratify the risk of death in patients with diverse spirometric decline patterns.

Keywords: bronchiolitis obliterans syndrome; chronic lung allograft dysfunction; parametric response mapping; computed tomography of the chest; prognosis

Chronic allograft failure, the major cause of poor long-term survival in patients undergoing lung transplantation, presents predominantly as obstructive airflow limitation by spirometry, termed bronchiolitis obliterans syndrome (BOS). Functional small airways disease (fSAD)

secondary to fibrotic obliteration or bronchiolitis obliterans (BO) is the primary driver of this clinical spirometric decline (1). However, there is growing awareness that chronic lung allograft dysfunction is a heterogeneous disorder with pathologic processes including BO and interstitial

or parenchymal fibrosis in varying combinations and severity within an individual (2–4). Diverse physiologic decline patterns have been shown to provide prognostic information; isolated decline in FEV₁ as compared with concurrent FEV₁ and FVC fall on

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At a Glance Commentary

Scientific Knowledge on the

Subject: Bronchiolitis obliterans syndrome is diagnosed by spirometry, and clinical tools are lacking to identify the degree of small airway obstruction and gauge prognosis for individual patients. Recent data suggest that lung allograft rejection has multiple pathophysiologic origins with different clinical phenotypes.

What This Study Adds to the

Field: Quantification of functional small airways disease by parametric response mapping, a novel computed tomography-based biomarker, in lung transplant recipients with spirometric decline offers pathophysiologic information of chronic rejection phenotype. Functional small airways disease levels greater than or equal to 30% as measured by parametric response mapping identify patients with significantly shorter survival.

spirometry is associated with superior survival suggesting that patients with fSAD versus parenchymal disease have heterogeneous outcomes (5, 6). In patients with BOS, the degree of airflow obstruction by spirometry is also linked to survival (7, 8). Hence, a clinical methodology to quantitate fSAD and to differentiate underlying phenotypes would have significant impact on care of lung transplant recipients.

Small airways, the predominant histologic target of fibrotic remodeling in a chronically rejecting lung allograft, have been termed the “silent zone” of the lung secondary to difficulty in evaluating small airway pathology (9). Transbronchial biopsies fail to adequately sample small airways and have limited sensitivity in diagnosing BO in lung transplant recipients (10, 11). Similarly, routine radiographic imaging techniques cannot easily visualize small airways, although some direct and indirect signs of bronchiolar disease have been proposed on high-resolution computed tomography (HRCT) chest imaging. These findings, including air trapping and bronchiectasis, have limited sensitivity and specificity for a diagnosis of BOS and

provide no prognostic information (12–14).

Parametric response mapping (PRM) is a voxel-based methodology for image analysis that has been demonstrated to be effective in improving the diagnostic ability of radiographic methodologies, such as magnetic resonance imaging and CT scans in various organs and disease states (15–19). In the lung, comparison of inspiratory and expiratory images on a voxel-by-voxel basis by image coregistration has been shown to provide a quantitative measure of fSAD in patients with chronic obstructive pulmonary disease (16, 20–22). This unique ability to quantitate fSAD on CT chest images suggests that PRM can potentially be used as an imaging biomarker for evaluation of BO in lung allografts. In this study, we investigate the PRM signature of lung transplant recipients with spirometric decline and demonstrate the utility of this methodology to evaluate disease phenotype and survival.

Methods

Patient Population

Bilateral lung transplant recipients at the University of Michigan Health System between 1991 and 2014 were included in the study group. Many patients included in our previous analysis of spirometric function following lung transplantation (6) were also included in this study, now with a longer follow-up period. Patients were managed in line with a standard clinical algorithm (23). Baseline FEV₁

was defined according to International Society for Heart and Lung Transplantation (ISHLT) guidelines as the average of the two highest FEV₁ values obtained greater than or equal to 3 weeks apart post-transplant (24). FVC baseline was similarly defined as the average of the two highest FVC values obtained greater than or equal to 3 weeks apart post-transplant (6). Persistent spirometric decline was defined as a decline in FEV₁ and/or FVC to less than 80% of the respective post-transplant baseline as measured by two consecutive FEV₁ and/or FVC values greater than or equal to 3 weeks apart. Patients were assigned to the two spirometric decline pattern groups, FEV₁ First or Concurrent, as previously described (6). Briefly, FEV₁ First was defined as a persistent fall in FEV₁ with a preserved FVC at the time of spirometric decline. Concurrent decline pattern was defined as a fall in both FEV₁ and FVC to less than 80% of the respective post-transplant baselines on the same date (6). A simple algorithm outlining the criteria for development of persistent spirometric decline and its various patterns is provided in Figure 1. BOS grade was defined per ISHLT guidelines (25). Time of death was assessed up to October 21, 2015; all other data were censored.

Computed Tomography

CT data were obtained as whole-lung volumetric CT scans at full inspiration (total lung capacity) and incremental scans at relaxed expiration (functional residual capacity) on General Electric 64-detector scanners (General Electric, Boston, MA) and reconstructed using a bone reconstruction kernel. Slice thicknesses were 1.25 mm for all scans, with incremental scans acquired

Figure 1. An algorithm outlining the definitions of baseline spirometric function, persistent spirometric decline, and categorization of decline type.

with 1-cm gaps. All CT scans were checked for Hounsfield unit (HU) drift and if necessary corrected based on aortic blood (50 HU) and central air (−1,000 HU) as previously described (26).

Parametric Response Mapping

PRM was applied to all paired CT scans and has been previously described (17). Briefly, lungs from both paired CT scans were segmented from the thoracic cavity using an in-house algorithm written in Matlab (The MathWorks, Inc., Natick, MA). The whole-lung inspiratory CT scan was spatially aligned to the incremental expiratory CT scan using Elastix, an open source image registration algorithm (27, 28). This process allows the paired images to share the same geometric space, where each voxel, the smallest unit of volume in a three-dimensional image dataset, consists of HU values at inspiration and expiration. Each voxel was classified based on a scheme of three predetermined thresholds as previously described (17). In brief, voxels with values greater than or equal to 950 HU and less than −810 HU at inspiration and greater than or equal to −856 HU at expiration were classified normal (PRM^{Normal}, green voxels), greater than or equal to 950 HU and less than −810 HU at inspiration and less than −856 at expiration were functional small airways disease (PRM^{FSD}, yellow voxels), and greater than or equal to −810 HU at inspiration were parenchymal disease (PRM^{PD}, purple voxels). The relative lung volumes, calculated as the sum of all voxels within a class normalized to the sum of all

voxels within the expiratory lungs multiplied by 100, were used as global measures.

Statistical Analysis

Statistical analyses were performed using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). In the case-control analysis, continuous variables were compared using linear mixed models with a random effect for matched pair (29), which corresponds to a matched pair Student's *t* test when case/control status is the only predictor in the model. Logistic and multinomial random effects models, with a random effect for matched pair (30), were used to compare binary and categorical predictors between matched cases and control subjects. For matched pair comparisons of PRM values, Wilcoxon signed rank tests were done (31). Multivariable linear mixed models (29), stratified by spirometric decline group of the case and including a random effect for matched pair, were used to describe associations between PRM values and case status adjusted for age, baseline FEV₁ % predicted, and baseline FVC % predicted.

Demographics of the retrospectively followed lung transplant recipients with persistent FEV₁ decline are reported as mean ± SD for continuous predictors or count (percent) for categorical predictors, stratified by availability of PRM data. Demographic differences between patients with versus without available PRM data were compared using chi-square (32) or Fisher exact (33) tests for categorical descriptors, as appropriate, or two-sample

Student's *t* tests for continuous descriptors (34). Associations between clinical risk factors for BOS occurring before spirometric decline and PRM^{FSD} values at spirometric decline ($\geq$ or $<$ 30%), adjusted for time to spirometric decline, were assessed using negative binomial regression for count-oriented outcomes or logistic regression for binary outcomes (35). Survival curves were estimated using the Kaplan-Meier method (36) with two-sample comparisons conducted using both restricted mean (RM) tests (37) and log-rank tests (38–40). Multivariable censored survival regression analysis was conducted using the RM model framework (41).

Results

Spirometric Decline Patterns Are Associated with Distinct PRM Signatures

We first investigated the application of PRM to patients with spirometric decline in a case-control fashion. Cases were defined as bilateral lung transplant recipients experiencing a persistent spirometric decline (Figure 1) in the absence of obvious confounders in concordance with ISHLT guidelines (25). Cases were restricted to patients with irreversible lung function decline as defined by no improvement in FEV₁ to greater than or equal to 80% of the post-transplant baseline during the entire study period (*n* = 22). Control subjects (CT scans obtained from patients with stable pulmonary function) were matched to cases by time from transplantation to CT scan.

Table 1. Demographics of FEV₁ First and Concurrent Decline Groups as Compared with their Matched Control Subjects*

	FEV ₁ First Group (<i>n</i> = 15)	Control Group (<i>n</i> = 15)	<i>P</i> Value	Concurrent Group (<i>n</i> = 7)	Control Group (<i>n</i> = 7)	<i>P</i> Value
Age at transplant, yr	39 ± 18	50 ± 9	0.04	46 ± 12	46 ± 13	0.93
Male	10 (67)	11 (73)	0.66	4 (57)	4 (57)	1
Baseline FEV ₁ , % predicted	90 ± 20	103 ± 19	0.08	93 ± 13	87 ± 13	0.41
Baseline FVC, % predicted	82 ± 14	93 ± 12	0.03	86 ± 14	82 ± 15	0.64
LAS score	44 ± 15	47 ± 16	0.69	44 ± 13	36 ± 4	0.20
LAS			1.00 [†]			1.00 [†]
Group A	5 (33)	2 (13)		2 (29)	5 (71)	
Group B	0 (0)	0 (0)		1 (14)	0 (0)	
Group C	8 (53)	2 (13)		1 (14)	2 (29)	
Group D	2 (13)	11 (73)		3 (43)	0 (0)	

Definition of abbreviation: LAS = lung allocation score.

*Continuous predictors reported as mean ± SD; categorical as *n* (%).

[†]Negligible number of patients in LAS group B, so no comparisons were performed for that group. Otherwise, mixed model analysis was used for overall LAS diagnosis group comparisons for groups A, C, and D.

Figure 2. Bar plots demonstrating distribution of parametric response mapping (PRM) of functional small airways disease (PRM^{fSAD}) and PRM of parenchymal disease (PRM^{PD}) in lung transplant recipients with irreversible spirometric decline by decline group status and respective control subjects. (A) Patients presenting with isolated decline in FEV₁ (FEV₁ First group) had significantly more PRM^{fSAD} compared with their matched control subjects (28 ± 3% vs. 15 ± 3%; $P = 0.005$). No significant difference was noted in PRM^{PD} values ($n = 15$ per group). (B) Patients presenting with simultaneous decline in both FEV₁ and FVC (Concurrent group) had significantly higher PRM^{PD} compared with their matched control subjects (39 ± 6% vs. 20 ± 2%; $P = 0.02$). No significant difference was noted in PRM^{fSAD} values between Concurrent patients and their matched control subjects ($n = 7$ per group). * $P < 0.05$. Data are presented as mean ± SEM.

The average time from spirometric decline to CT scan was 4 days (range, −59 to 73 d) in the FEV₁ First group and −7 (range, −49 to 37 d) in the Concurrent group.

Sixty-eight percent (15 of 22) of cases had an FEV₁ First decline pattern, whereas 32% (7 of 22) had a Concurrent spirometric decline pattern. Demographics for the cases in each group and their respective control groups are shown in Table 1. FEV₁ First patients were younger than their respective control subjects (39 ± 18 yr vs. 50 ± 9 yr; $P = 0.04$) and had a lower baseline FVC % predicted post-transplant (82 ± 14% vs. 93 ± 12%; $P = 0.03$). Concurrent group patients were not significantly different from their matched control subjects.

Quantification of fSAD (PRM^{fSAD}, yellow) and parenchymal disease (PRM^{PD}, purple) obtained by PRM was compared

between spirometric decline groups and their respective control subjects (Figure 2). PRM measurements revealed significantly higher fSAD in the FEV₁ First group as compared with stable matched control subjects (Wilcoxon signed rank test, $P = 0.005$). No difference was seen in PRM^{PD} between FEV₁ First cases and control subjects. In contrast, Concurrent group patients were found to have significantly more PRM^{PD} than their control group (Wilcoxon signed rank test, $P = 0.02$) and as a group had PRM^{fSAD} values comparable with those of control subjects.

In a model that controlled for age, baseline FEV_{1%} predicted, and baseline FVC % predicted, FEV₁ First patients continued to have significantly more PRM^{fSAD} than their respective control group (30% vs. 18%; $P = 0.03$) (Table 2).

Similarly, Concurrent patients had significantly more PRM^{PD} than their respective control subjects after adjusting for these variables (34% vs. 15%; $P = 0.02$) (Table 3). Representative cross-sectional HRCT images and associated PRM images from a control, FEV₁ First, and Concurrent patient, respectively, are shown in Figure 3.

Quantitative Assessment of fSAD by PRM Predicts Survival in Patients with Spirometric Decline

To evaluate if PRM values at the onset of spirometric decline can provide prognostic information, a retrospective analysis of the prospective cohort of 287 bilateral lung transplant recipients at the University of Michigan from 1991 to 2014 was performed (Figure 4). The study group included all patients with persistent spirometric decline who had a CT chest in the time range of 30 days before to 60 days after spirometric decline that was available for PRM analysis ($n = 64$). Demographics of patients with and without PRM data available were not significantly different (Table 4). The clinical information at the time of each patient's spirometric decline event was closely reviewed. Patients with confounding factors responsible for the spirometric decline event were removed from the cohort ($n = 12$). Confounding conditions included acute abdominal process ($n = 1$), acute rejection that eventually improved ($n = 1$), bronchial stenosis ($n = 1$), drug toxicity ($n = 2$), flare of connective tissue disease ($n = 1$), neuromuscular weakness ($n = 2$), organizing pneumonia ($n = 1$), and volume overload ($n = 3$). Thus, 52 patients comprised the final study group with persistent spirometric decline. Of those,

Table 2. Multivariate Analysis to Investigate Clinical Predictors of PRM Values in Case/Control Pairs where Case has FEV₁ First Pattern of Spirometric Decline

	PRM ^{fSAD}			PRM ^{PD}		
	Estimate* (%)	SE	P Value	Estimate* (%)	SE	P Value
Intercept	17.9	3.9	<0.001	15.9	2.7	<0.001
FEV ₁ First group (vs. control)	11.7	5.1	0.03	1.0	3.7	0.80
Age (per 10-yr increase)	−0.8	1.8	0.64	0.5	1.2	0.72
Baseline FEV _{1%} predicted (per 10% change)	−2.2	2.1	0.32	−0.1	1.5	0.95
Baseline FVC % predicted (per 10% change)	2.1	3.2	0.51	−1.8	2.3	0.45

Definition of abbreviations: FEV₁ First pattern = patients presenting with isolated decline in FEV₁; fSAD = functional small airways disease; PD = parenchymal disease; PRM = parametric response mapping.

*Estimate for intercept reflects average PRM^{fSAD} or PRM^{PD} for a control patient who is 45 years of age and has a baseline FEV₁ and FVC of 95% predicted. All other estimates reflect the change in PRM^{fSAD} and PRM^{PD} based on unit change of the predictor.

Table 3. Multivariate Analysis to Investigate Clinical Predictors of PRM Values in Case/Control Pairs where Case has Concurrent Pattern of Spirometric Decline

	PRM ^{fSAD}			PRM ^{PD}		
	Estimate* (%)	SE	P Value	Estimate* (%)	SE	P Value
Intercept	22.0	8.3	0.03	14.7	6.0	0.04
Concurrent group (vs. control)	−5.3	9.7	0.60	19.2	4.8	0.02
Age (per 10-yr increase)	3.2	4.4	0.48	3.6	2.6	0.22
Baseline FEV ₁ % predicted (per 10% change)	−1.3	6.2	0.84	4.7	4.1	0.27
Baseline FVC % predicted (per 10% change)	3.5	5.5	0.54	−6.5	4.4	0.18

Definition of abbreviations: Concurrent pattern = patients presenting with simultaneous decline in both FEV₁ and FVC; fSAD = functional small airways disease; PD = parenchymal disease; PRM = parametric response mapping.

*Estimate for intercept reflects average PRM^{fSAD} or PRM^{PD} for a control patient who is 45 years of age and has a baseline FEV₁ and FVC of 95% predicted. All other estimates reflect the change in PRM^{fSAD} and PRM^{PD} based on unit change of the predictor.

75% (39 of 52) had an FEV₁ First decline pattern, and 25% (13/52) had a Concurrent decline pattern.

The distributions of PRM^{fSAD} and PRM^{PD} obtained at the time of spirometric decline are shown in Figure 5. FEV₁ First patients had an average PRM^{fSAD} value of 21% (95% confidence interval [CI], 18–25%). Concurrent group patients had an average PRM^{PD} of 35% (95% CI, 27–42%). To investigate quantitative fSAD as a survival predictor, a threshold PRM^{fSAD} value of 30% was selected because it marked the first quartile and hence identified the 25% of patients with the highest PRM^{fSAD} values. Sex, recipient age, baseline FEV₁ and FVC % predicted, and BOS grade at spirometric decline were not significantly different between patients with PRM^{fSAD} greater than or equal to 30% versus those with PRM^{fSAD} less than 30% (data not shown). However, patients with PRM^{fSAD} greater than or equal to 30% had more episodes of acute rejection (average 1.77 vs. 0.9 episodes; $P = 0.02$) and were more likely to have a history of lymphocytic bronchitis (54% vs. 23%; $P = 0.04$) as compared with patients with low PRM^{fSAD} (Table 5). There was no significant difference in history of bronchoalveolar lavage neutrophilia, history of *Pseudomonas* colonization or infection, history of *Aspergillus fumigatus* colonization or infection, history of cytomegalovirus pneumonitis, or history of community-acquired respiratory virus infection between patients with low versus high PRM^{fSAD}.

Kaplan-Meier survival curves based on spirometric decline group status and PRM^{fSAD} values are shown in Figure 6. PRM^{fSAD} was found to be a significant predictor of survival in FEV₁ First patients

(RM, $P = 0.004$; log-rank, $P = 0.038$). Over 8.3 years of follow-up, FEV₁ First patients with PRM^{fSAD} greater than or equal to 30% (10 of 39 patients; 26%) at the time of

spirometric decline lived an average of 2.50 years as compared with 5.12 years in patients with PRM^{fSAD} less than 30% (average difference, 2.6 yr; 95% CI,

Figure 3. Inspiratory and expiratory high-resolution computed tomography images with associated parametric response mapping (PRM) images from representative scans are shown for a control, FEV₁ First (presenting with isolated decline in FEV₁), and Concurrent (presenting with simultaneous decline in both FEV₁ and FVC) patient, respectively. Normal lung tissue is shown in green, functional small airways disease is yellow, and parenchymal disease is purple. HRCT = high-resolution computed tomography.

Figure 4. CONSORT (Consolidated Standards of Reporting Trials) diagram delineating study cohort. Concurrent decline = simultaneous decline in both FEV₁ and FVC; FEV₁ First = isolated decline in FEV₁; PRM = parametric response mapping.

0.83–4.41 yr). A multivariable analysis was performed using RM regression as shown in Table 6. In a model adjusted for age, baseline FEV₁ % predicted, baseline FVC % predicted, and BOS grade at spirometric decline, PRM^{fSAD} greater than or equal to 30% in FEV₁ First patients was the only significant predictor of survival; those with PRM^{fSAD} greater than or equal to 30% lived lifetimes that were 48% shorter over the follow-up period (95% CI, 23–97% shorter; $P = 0.04$).

PRM^{fSAD} was also evaluated as a predictor of survival in Concurrent patients and subsequently in all patients regardless

of spirometric decline pattern. Interestingly, even in Concurrent patients, PRM^{fSAD} continued to be a significant predictor of survival (RM $P = 0.005$; log-rank, $P = 0.029$). Over 5.1 years of follow-up, Concurrent patients with PRM^{fSAD} greater than or equal to 30% lived an average of only 0.27 years as compared with Concurrent patients with PRM^{fSAD} less than 30% who lived an average of 2.31 years (Figure 6B; average difference 2.04 yr; 95% CI, 0.61–3.47 yr). All three patients in the Concurrent spirometric decline group with PRM^{fSAD} greater than or equal to 30% died within 4 months of their spirometric decline (range, 82–119 d).

In the entire cohort including both FEV₁ First and Concurrent patients, those with PRM^{fSAD} greater than or equal to 30% had a significantly shorter average survival following spirometric decline (RM, $P = 0.001$; log-rank, $P = 0.018$) (Figure 6C). Those with PRM^{fSAD} greater than or equal to 30% lived an average of 1.98 of 8.3 follow-up years compared with those with PRM^{fSAD} less than 30% who lived on average 4.63 years in the same follow-up period (average difference, 2.65 yr; 95% CI, 1.03–4.27 yr).

To determine if spirometric and radiographic parameters can be combined to provide prognostic information, we compared survival of patients categorized by their spirometric decline pattern and further by PRM^{fSAD} in the FEV₁ First group. Figure 7 demonstrates survival in patients with an FEV₁ First pattern of decline with PRM^{fSAD} less than 30%, FEV₁ First pattern of decline with PRM^{fSAD} greater than or equal to 30%, and Concurrent patients. Although FEV₁ First patients with PRM^{fSAD} values of less than 30% had longer survival than both patients with PRM^{fSAD} greater than or equal to 30% in the FEV₁ First group ($P = 0.004$) and the Concurrent group ($P = 0.0005$), no significant difference in

survival was noted between Concurrent and FEV₁ First patients with high PRM^{fSAD} ($P = 0.42$). Thus, PRM^{fSAD} greater than or equal to 30% was found to identify patients in the FEV₁ First group who had a prognosis as poor as those presenting with Concurrent spirometric decline. Figure 8 outlines a useful clinical algorithm to predict survival following spirometric decline with the application of PRM data.

Discussion

In this study, we evaluate the application of PRM, a voxel-wise image analysis technique, in a lung transplant population to quantify small airway obstruction and offer prognostic information. We demonstrate that PRM-based evaluation of chest CT images provides a unique signature in patients with diverse spirometric decline patterns after lung transplantation. Patients who presented with isolated FEV₁ decline have significantly higher PRM^{fSAD} than their control subjects matched by time post-transplant, whereas patients with Concurrent decline have higher PRM^{PD}. Furthermore, we demonstrate that degree of fSAD as assessed by PRM is a robust predictor of survival with significantly poorer survival noted in patients with PRM^{fSAD} values greater than or equal to 30% at the onset of spirometric decline. We have shown that PRM can offer unique rejection signatures and predict survival after onset of chronic rejection in lung transplant recipients.

This study is the first to demonstrate the utility of PRM as a prognostic measure in a lung transplant population with spirometric decline. We demonstrate that higher PRM^{fSAD} at the time of spirometric decline onset predicts significantly worse survival. In the FEV₁ First cohort, patients with PRM^{fSAD} greater than or equal to 30%

Table 4. Demographics of Lung Transplant Recipients with Persistent Spirometric Decline stratified by Availability of PRM Data*

	PRM Data Available (n = 64)	PRM Data Unavailable (n = 55)	P Value
Age at transplant, yr	44 ± 15	45 ± 10	0.52
Male	37 (58)	24 (44)	0.17
Baseline FEV ₁ , % predicted	86 ± 19	89 ± 28	0.59
Baseline FVC, % predicted	81 ± 16	85 ± 22	0.26

Definition of abbreviation: PRM = parametric response mapping.

*Continuous predictors reported as mean ± SD; categorical as n (%).

Figure 5. Distribution of parametric response mapping (PRM) of functional small airways disease (PRM^{fSAD}) (A) and PRM of parenchymal disease (PRM^{PD}) (B) at the time of spirometric decline stratified by FEV₁ First (presenting with isolated decline in FEV₁) and Concurrent (presenting with simultaneous decline in both FEV₁ and FVC) (n = 13) group status.

had an average survival of only 2.5 years compared with 5.12 years in patients with PRM^{fSAD} less than 30%. Significant variability has been described in the rate of spirometric decline and survival in patients presenting with chronic allograft failure, underscoring the need to identify prognostic markers that can be used in guiding therapeutic interventions and in time consideration of retransplantation (8, 42, 43). In patients with BOS, clinical factors, such as early versus late and rapid versus gradual onset, have been associated with abrupt decline and mortality (8, 43). Similarly, spirometric variables, such as higher BOS grade at onset and progression to higher BOS grades, have been shown to portend a poor prognosis (7, 8). PRM^{fSAD}

represents the first quantitative radiographic measure of small airway obstruction, which has been demonstrated to correlate with survival in lung allograft recipients presenting with spirometric decline. In a recent investigation, PRM^{fSAD} was shown to increase over time after BOS onset, thus further demonstrating the correlation of this measure with disease severity (44).

Illustrated in Figure 9 are representative HRCT images and PRM analyses from a patient before and after BOS onset demonstrating progressive increase in PRM^{fSAD} values over time. It is also important to note that in patients with isolated FEV₁ decline pattern, PRM^{fSAD} greater than or equal to 30% was

found to be the only significant predictor of survival in a model adjusting for age, baseline FEV₁% predicted, baseline FVC % predicted, and BOS grade at spirometric decline. Thus PRM methodology offers a simple radiographic biomarker of disease severity with a predictive ability that is more robust than physiology alone. Furthermore, because chest CT scans are routinely performed in lung transplant recipients when spirometry declines to exclude causes of decline other than chronic rejection, PRM can have wide clinical applicability.

A significant contribution of this study is that it provides a novel approach of combining physiologic and radiographic phenotyping for prognostication and

Table 5. Presence of Key Clinical Characteristics Stratified by PRM^{fSAD}

	PRM ^{fSAD} ≥30% (n = 13)	PRM ^{fSAD} <30% (n = 39)	P Value*
BAL neutrophilia >20% (at least 3 mo post-transplant), n (%)	10 (77)	25 (64)	0.40
Number of acute rejection episodes before persistent spirometric decline†	1.77 (1.24)	0.9 (1.12)	0.02
Any history of acute cellular rejection, n (%)	11 (85)	21 (54)	0.06
Any history of lymphocytic bronchitis, n (%)	7 (54)	9 (23)	0.04
History of <i>Pseudomonas</i> colonization or infection, n (%)	6 (46)	14 (36)	0.54
History of <i>Aspergillus fumigatus</i> colonization or infection, n (%)	5 (39)	12 (31)	0.60
History of CMV pneumonitis, n (%)	3 (23)	9 (23)	0.97
History of community-acquired respiratory viral infection, n (%)	3 (23)	3 (8)	0.15
Azithromycin use before persistent spirometric decline, n (%)	4 (31)	7 (18)	0.35

Definition of abbreviations: BAL = bronchoalveolar lavage; CMV = cytomegalovirus; fSAD = functional small airways disease; PRM = parametric response mapping.

*Adjusted for time from transplant to spirometric decline.

†Mean (SD).

Figure 6. Survival following spirometric decline in various patient cohorts stratified by parametric response mapping (PRM) of functional small airways disease (PRM^{fSAD}). (A) FEV₁ First patients (presenting with isolated decline in FEV₁) with PRM^{fSAD} greater than or equal to 30% have significantly shorter average survival than patients with PRM^{fSAD} less than 30% (2.50 ± 0.6 vs. 5.12 ± 0.7 yr; restricted mean [RM], *P* = 0.004; log-rank, *P* = 0.038). (B) Concurrent patients (presenting with simultaneous decline in both FEV₁ and FVC) with PRM^{fSAD} greater than or equal to 30% similarly had significantly shorter average survival than those with PRM^{fSAD} less than 30% (0.27 ± 0.03 vs. 2.31 ± 0.7 yr; RM, *P* = 0.005; log-rank, *P* = 0.029). (C) PRM^{fSAD} greater than or equal to 30% is a key prognostic indicator in all patients regardless of spirometric decline pattern (RM, *P* = 0.001; log-rank, *P* = 0.018).

patient stratification. Spirometry is the most commonly used modality for routine graft function monitoring after lung transplantation, and recent investigations have highlighted diverse patterns of spirometric decline that correlate with survival (5, 6). Two specific physiologic patterns based on spirometry have emerged: patients who present with an initial fall in FEV₁ alone, and those who suffer concomitant decline in FEV₁ and FVC. Although patients with concomitant

Table 6. Multivariable Restricted Mean Analysis Evaluating Impact of Clinical Variables on Survival in the FEV₁ First Group (n = 39)

	Estimate*	Lower Bound	Upper Bound	P Value
Intercept	5.24	3.91	7.02	<0.001
PRM ^{fSAD} ≥30%	0.48	0.23	0.97	0.04
Age (per 10-yr interval)	1.06	0.91	1.25	0.47
Baseline FEV ₁ % predicted (per 10% increase)	0.90	0.75	1.07	0.21
Baseline FVC % predicted (per 10% increase)	1.12	0.91	1.37	0.30
BOS grade at spirometric decline	0.82	0.54	1.25	0.35

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; FEV₁ First = patients presenting with isolated decline in FEV₁; fSAD = functional small airways disease; PRM = parametric response mapping.
*Estimate for intercept reflects the average time lived following spirometric decline for a 45-year-old lung transplant recipient with FEV₁ and FVC baseline % predicted of 95%, who at the time of spirometric decline has BOS grade 1 and PRM^{fSAD} less than 30%.

Figure 7. Survival stratified by spirometric decline pattern and parametric response mapping (PRM) of functional small airways disease (PRM^{fSAD}). FEV₁ First patients (presenting with isolated decline in FEV₁) with PRM^{fSAD} greater than or equal to 30% have an average survival similar to Concurrent patients (presenting with simultaneous decline in both FEV₁ and FVC) (2.5 ± 0.6 vs. 1.8 ± 0.6 yr; average difference, 0.67 yr; $P = 0.42$). FEV₁ First patients with PRM^{fSAD} less than 30% on average live longer than both Concurrent patients ($P = 0.0005$) and FEV₁ First patients with PRM^{fSAD} greater than or equal to 30% ($P = 0.004$). Open circles are censoring events (at the last patient visit).

decline in FEV₁ and FVC comprise the lesser proportion ($\sim 30\%$), this decline pattern has been shown to portend a very poor long-term outcome (6). The more predominant decline pattern is that of FEV₁ alone, and we now demonstrate that assessment of fSAD by PRM can provide additional important prognostic information in these patients at the time of disease onset. Patients with FEV₁

First decline pattern and PRM^{fSAD} greater than or equal to 30% had very poor survival, similar to that noted in patients with a Concurrent spirometric decline pattern. This ability to predict prognosis by spirometry and PRM as shown in Figure 8 has relevance in strategizing therapeutic options, such as retransplantation, and in patient stratification for clinical trials.

Figure 8. Prognostic stratification by spirometric decline pattern and computed tomography-based parametric response mapping of functional small airways disease (PRM^{fSAD}) in lung transplant recipients. Concurrent pattern = simultaneous decline in both FEV₁ and FVC; FEV₁ First pattern = isolated decline in FEV₁.

Distinct PRM signatures were noted in patients with FEV₁ First versus Concurrent spirometric decline patterns. Patients who presented with Concurrent decline in FEV₁ and FVC had significantly more PRM^{PD} than their matched control group. This finding similarly fits well with what is known regarding pathophysiology of restrictive chronic lung allograft dysfunction, which has not yet been rigorously defined (2, 3, 5, 25). These patients are generally described to have radiographic interstitial or alveolar changes and histologic evidence of parenchymal and pleural fibrosis (2, 3, 5). It is important to note that PRM^{PD} does not imply the presence of restrictive chronic lung allograft dysfunction with certainty; PRM^{PD} reflects any process that results in hyperattenuation or increased parenchymal density, which could include infection, pulmonary edema, organizing pneumonia, and so forth. These various processes must be excluded before an elevated PRM^{PD} can be attributed to restrictive chronic lung allograft dysfunction. It has also been postulated that the Concurrent group may also include patients with very severe obstruction leading to premature airway closure and a resultant drop in FVC (45); fibrotic airway narrowing and obstruction has been demonstrated in the lungs of patients with restrictive chronic lung allograft dysfunction (4).

Interestingly, although patients with Concurrent spirometric decline typically have higher PRM^{PD}, 23% (3 of 13) of the Concurrent patients in our larger cohort had PRM^{fSAD} values greater than or equal to 30%, suggesting significant fSAD. Furthermore, in the Concurrent patients in our cohort, PRM^{fSAD} greater than or equal to 30% predicted death within 4 months suggesting that even in patients with a Concurrent spirometric decline pattern, PRM^{fSAD} may prove very useful to the clinician in identifying rejection phenotype. However, because of the small sample size in the Concurrent group, these findings must be confirmed in a larger cohort.

Our study is limited by its retrospective study design and evaluation of PRM at a single time point. However, the demonstration of utility of PRM in predicting prognosis and evaluating disease phenotype in lung transplant recipients provides the foundation for future

Figure 9. Serial parametric response mapping (PRM) images from a patient with bronchiolitis obliterans syndrome (BOS). The *left column* shows high-resolution computed tomography (HRCT) and PRM images from a time point approximately 1 year before BOS onset. At this time point, the patient had low PRM of functional small airways disease (PRM^{fSAD}) of 12%. Images in the *middle column* were obtained approximately 2 months following BOS onset; PRM^{fSAD} has increased to 48%. In the *right column*, a scan obtained 20 months after the onset of BOS, PRM^{fSAD} demonstrated further increase at 54%. Normal lung tissue is shown in *green*, and functional small airway disease is *yellow*.

prospective multicentric longitudinal studies to investigate use of this novel radiographic methodology in monitoring graft health in lung transplant recipients.

Assessment of the amount of fSAD present in a healthy lung transplant patient population with baseline graft function also requires further study. In a

prior study evaluating the utility of PRM to quantify fSAD and aid in BOS diagnosis in a hematopoietic stem cell transplant population, nontransplanted healthy nonsmoking control subjects had an average PRM^{fSAD} value of 8.4% (17). In a cohort of current or previous smokers with normal FEV₁ and Global Initiative for Chronic Obstructive Lung Disease stage 0, Bhatt and colleagues (20) found average PRM^{fSAD} values of 12.4%. The average PRM^{fSAD} of our control groups were 15.3% and 18.8%, respectively, for our FEV₁ First and Concurrent control groups. Interestingly, similar findings were noted in the evaluation of a European cohort where mean PRM^{fSAD} values in a normal lung transplant cohort were noted to be higher than those expected for nontransplanted normal subjects (44). Because a lung allograft is subjected to various insults unique to transplantation, such as ischemia reperfusion injury, immune insults, denervation, and lack of bronchial circulation, it is possible that perhaps a higher threshold for normal PRM^{fSAD} will have to be considered in this population. A prospective analysis of serial PRM data over time in a transplant population would be better able to address this finding.

In summary, we have offered a view of the PRM landscape in a group of lung transplant recipients with persistent spirometric decline. We demonstrate that PRM, a quantitative imaging application, can offer insight into chronic lung allograft dysfunction phenotypes and provide prognostic information that has relevance in clinical care and future clinical trials. ■

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