ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Prognostic significance of early pulmonary function changes after onset of chronic lung allograft dysfunction

Jamie L. Todd, MD,[a,b] Megan L. Neely, PhD,[b,c] C.A. Finlen Copeland, MSW,[a,b] Courtney W. Frankel, PT, MS,[a] John M. Reynolds, MD,[a] and Scott M. Palmer, MD, MHS[a,b]

From the [a]Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine; [b]Duke Clinical Research Institute; and the [c]Department of Biostatistics and Bioinformatics Duke University Medical Center, Durham, North Carolina, USA.

KEYWORDS:
chronic lung allograft dysfunction;
bronchiolitis obliterans syndrome;
lung transplantation;
pulmonary function

BACKGROUND: Chronic lung allograft dysfunction (CLAD), including the phenotypes of bronchiolitis obliterans syndrome (BOS) and restrictive CLAD (R-CLAD), represents the leading cause of late death after lung transplantation. Little is known, however, regarding the natural history or prognostic significance of pulmonary function changes after the onset of these conditions. We examined changes in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) over the first 18 months after CLAD. We also sought to determine whether lung function changes occurring early after CLAD impact longer term outcomes.

METHODS: We performed a retrospective analysis of 216 bilateral lung recipients with CLAD, which included those with R-CLAD ($n = 65$) or BOS ($n = 151$). The course of FEV_1 and FVC after CLAD was described. Cox proportional hazards models were used to evaluate the impact of a ≥10% decline in FEV_1 or FVC within the first 6 months of CLAD on graft loss after that time.

RESULTS: Lung recipients with CLAD, whether BOS or R-CLAD, had the largest decreases in FEV_1 and FVC within the first 6 months after onset. Moreover, a decline in FEV_1 or FVC of ≥10% within the first 6 months after CLAD was associated with a significantly increased hazard for graft loss after that time (hazard ratio [HR] = 3.17, 95% confidence interval [CI] 1.56 to 6.42, $p = 0.001$, and HR = 2.80, 95% CI 1.66 to 4.70, $p \leq 0.001$, respectively), an effect observed in both BOS and R-CLAD patients.

CONCLUSIONS: Early physiologic changes after CLAD were independently associated with graft loss. This suggests lung function changes after CLAD, specifically a ≥10% decline in FEV_1 or FVC, could be a surrogate measure of graft survival.

J Heart Lung Transplant 000;000:1−10

Chronic lung allograft dysfunction (CLAD) is the principal obstacle to improved long-term survival after lung transplantation.[1] CLAD is a condition of sustained lung function impairment recognized by a persistent decline in forced expiratory volume in 1 second (FEV_1) relative to the highest post-transplant baseline, after exclusion of confounding conditions.[2,3] Previously, bronchiolitis obliterans syndrome (BOS) was the most widely described CLAD phenotype; however, accumulating evidence suggests CLAD takes on at least 2 phenotypes conferring distinct

Reprint requests: Jamie L. Todd, MD, Department of Internal Medicine, Division of Pulmonary Allergy and Critical Care Medicine, DUMC Box 103002, MSRB II, Durham, NC 27710.
E-mail address: jamie.todd@dm.duke.edu

1053-2498/$ - see front matter
https://doi.org/10.1016/j.healun.2018.10.006

prognoses.[4–9] Work by our group and others used spirometry to distinguish physiologic CLAD phenotypes demonstrating patients with a decrement in forced vital capacity (FVC) along with FEV_1 at CLAD onset, which suggests a restrictive ventilatory defect (restrictive CLAD, or R-CLAD), have significantly worse survival after CLAD than patients with BOS, in whom FVC is preserved.[5,6]

Despite the importance of CLAD, there are relatively few data regarding the progression of pulmonary function after its onset. Lama et al described the course of FEV_1 after CLAD and found that the greatest decline occurs in the first 6 months after CLAD onset. However, their study cohort consisted predominantly (82%) of single lung transplant recipients, most with native lung emphysema.[10] Thus, it remains uncertain to what extent these observations were confounded by native lung disease, and the generalizability to bilateral lung recipients is unknown. Furthermore, their work predated the current understanding of CLAD phenotypes and, as such, did not consider differences in FEV_1 progression within BOS and R-CLAD.

Recent studies have begun to address the course of pulmonary function after CLAD in contemporary lung transplant cohorts. Work by Belloli and colleagues in 59 bilateral lung recipients with the BOS phenotype suggested that, although both FEV_1 and FVC declined over time after BOS onset, only FVC decline was associated with shorter patient survival.[11] In a series of 24 patients with the R-CLAD phenotype, Verleden et al reported all subjects had FEV_1 loss over follow-up, although details regarding the precise estimates of loss were not presented.[12]

Additional studies are needed to better define the natural history of pulmonary function changes within BOS and R-CLAD and to clarify the prognostic significance of such changes. Precise information on FEV_1 and FVC after CLAD, including correlation with survival, could identify useful surrogate end-points from which to assess the effectiveness of CLAD treatments. In this study we sought to: (1) describe changes in FEV_1 and FVC after CLAD and compare these measures in BOS and R-CLAD; and (2) determine whether a decline in FEV_1 or FVC in the first 6 months after CLAD diagnosis is associated with an increased risk of graft loss in BOS or R-CLAD.

Methods

Cohort

Our study cohort consisted of 216 adult, first, bilateral lung recipients with CLAD at the Duke University Medical Center (Figure 1). Cohort derivation was described in a previous study.[5] According to published methods, patients were considered R-CLAD if they demonstrated FVC loss at CLAD onset or BOS if FVC was preserved.[5] Sixty-five patients met the criteria for R-CLAD and the remaining 151 were BOS. As our study focused on physiologic changes after CLAD, subjects were excluded if they did not have at least 1 pulmonary function test (PFT) within 6 months of CLAD onset (1 R-CLAD, 2 BOS). The remaining 213 patients (64 R-CLAD, 149 BOS) were followed to death, retransplantation, or study censor at 18 months post-CLAD. All patients received similar clinical management (refer to Supplementary Material available online at www.jhltonline.org/). Patients with CLAD were managed at the physician's discretion. Management may include augmented immunosuppression (i.e., anti-thymocyte globulin and/or alemtuzumab). Azithromycin is also utilized with physician discretion and may be initiated before CLAD. Ethics approval was obtained from the institutional review board at Duke University.

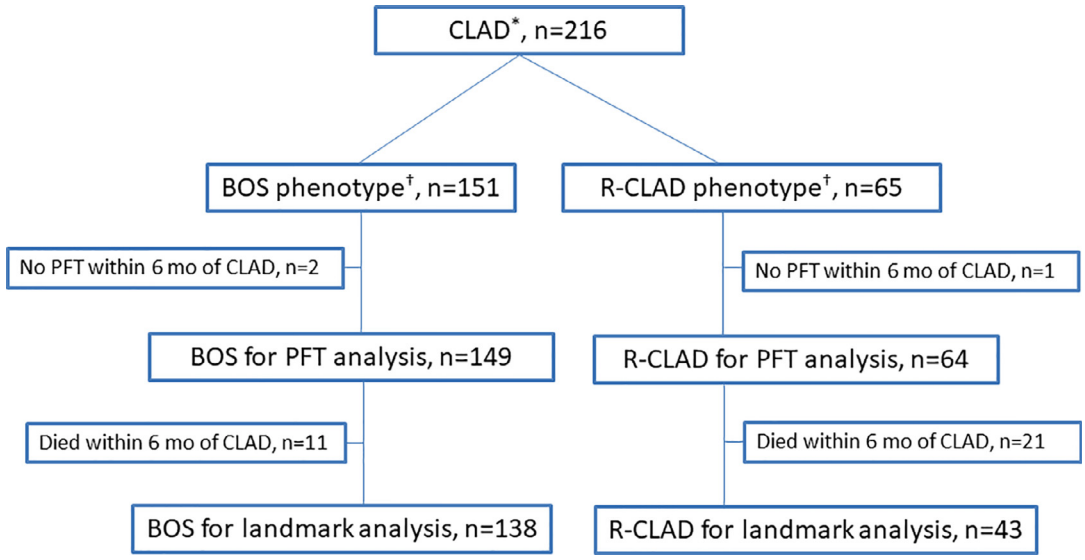

Figure 1 Consort diagram describing the study cohort derivation for the pulmonary function and survival analyses. Asterisk (*) indicates that derivation of the CLAD cohort has been detailed previously.[5] CLAD is defined as a sustained ≥20% decline in FEV_1 as compared with the average of the 2 best post-transplant FEV_1 values measured at least 3 weeks apart in the absence of other clinical confounders. Dagger (†) indicates that, at CLAD onset, patients were considered to have restrictive CLAD (R-CLAD) if CLAD-onset FVC/FVC_{Best} was <0.8; or, if this condition was not met, BOS. FVC_{Best} is defined as the average of the 2 FVCs associated with the 2 PFTs used in the FEV_1 baseline calculation for CLAD diagnosis.

Analyses

Descriptive statistics were used to describe patients' characteristics. Continuous variables are presented as median (Q1, Q3) and categorical variables as count (percent). Patients' characteristics were compared between the R-CLAD and BOS groups using Wilcoxon's test or Fisher's exact test, as appropriate. To describe changes in FEV_1 and FVC after CLAD, split-time jitter scatterplots of absolute and percent decline in each measurement as compared with the CLAD-onset value were created and stratified by CLAD phenotype (BOS vs R-CLAD) and by graft status, as assessed at 18 months post-CLAD (alive vs dead). PFT measures were plotted at 0 (e.g., CLAD onset), 6, 12, and 18 months post-CLAD diagnosis. The lowest observed absolute value collected within each time interval was used. The percent drop from CLAD onset was calculated as: $100 \times$ [(post-CLAD absolute FEV_1 or FVC − CLAD onset absolute FEV_1 or FVC) / CLAD onset absolute FEV_1 or FVC]. We also calculated the median (Q1, Q3) of the absolute and percent drop in each PFT measure.

We tested the hypothesis that a ≥10% decline in FEV_1 or FVC within the first 6 months after CLAD onset is associated with an increased risk of graft loss (defined as death or retransplantation) beyond that 6-month time period. To test this hypothesis, we used a landmark analytic method. We first created a binary indicator of early physiologic decline, defined as any occurrence of a ≥10% drop in FEV_1 or FVC compared with the CLAD-onset value within the first 6 months after CLAD diagnosis. The relationship between a ≥10% decline in FEV_1 or FVC during the first 6 months after CLAD and graft loss after 6 months was then considered using Kaplan–Meier and Cox proportional hazards models. Survival analyses were landmarked at 6 months post-CLAD, when the variable of interest (early physiologic decline) is known. As such, only patients still at risk for death after this time-point ($n = 181$) were included in this landmark analysis.

The Cox model was adjusted for CLAD phenotype (BOS reference), timing of CLAD onset (early onset, defined as CLAD within 2 years of transplantation[13] vs not), receipt of augmented immunosuppression (defined as receipt of alemtuzumab or anti-thymocyte globulin within 6 months of CLAD vs not), transplant era (defined as before vs on or after January 1, 2005), and the other PFT measure of interest. Given minimum clinically important differences in PFT measures have not been determined in lung transplantation, we also considered the impact of early physiologic declines that were smaller or greater than our chosen threshold for graft loss (refer to Supplementary Material online).

The landmark analytic method necessarily resulted in the exclusion of 32 patients due to death within 6 months of CLAD onset. The majority of these patients had a ≥10% FEV_1 or FVC decline before death ($n = 30$ and 25, respectively). Therefore, to complement the landmark analysis, we also constructed a time-dependent Cox model to examine the association of early physiologic decline and graft loss in all 213 patients in our cohort. Specifically, time to graft loss after CLAD was modeled as a function of a time-dependent binary indicator for the occurrence of any ≥10% decline in FEV_1 or FVC within 6 months after CLAD diagnosis. All analyses were performed using R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Cohort characteristics

Table 1 presents the characteristics of our study cohort. The median (Q1, Q3) PFTs from CLAD onset to 18 months post-CLAD was 7 (4, 9) and was similar for BOS (7 [4, 9]) and R-CLAD (6 [3, 8]) patients. When considering all CLAD patients, median FEV_1 and FVC at CLAD onset were 1.85 (1.31, 2.37) and 2.77 (2.12, 3.48) liters, respectively. Patients with R-CLAD had lower median FEV_1 and FVC values at diagnosis when compared to those with BOS (R-CLAD: FEV_1 1.52 liters and FVC 2.12 liters; BOS: 1.99 liters and 2.97 liters; $p < 0.001$ for both). Most patients (68.5%) received azithromycin after CLAD. Forty-four (20.7%) underwent treatment with alemtuzumab, whereas 59 (27.7%) were treated with anti-thymocyte globulin. Most of the augmented immunosuppression use was within 6 months of CLAD onset. Fifty-two (34.9%) patients with BOS and 43 (67%) with R-CLAD died over the 18-month follow-up period.

Physiologic progression after CLAD

Patients with CLAD had a median absolute (percent) decline in FEV_1 of 330 ml (18.7%) and in FVC of 270 ml (9.8%) within the first 6 months after CLAD. After 6 months, further median absolute (percent) decreases in FEV_1 of 80 ml (5.7%) and FVC of 40 ml (1.7%) (6- to 12-month interval) and 50 ml (3.7%) and 60 ml (2.4%) (12- to 18-month interval) were observed (Table 2 and Figure 2). Tables S1 and S2 (online) present the *cumulative* FEV_1 and FVC loss relative to the CLAD-onset value over 18 months.

When comparing PFT progression by CLAD phenotype, a similar pattern was observed in patients with R-CLAD or BOS as both groups had the greatest losses in FEV_1 and FVC in the 6 months after diagnosis. Although both R-CLAD and BOS patients had similar median declines in FEV_1 during this interval (345 ml vs 320 ml), the median decline in FVC was greater in patients with R-CLAD as compared to those with BOS (335 ml vs 240 ml) and represented a larger percent change (18% vs 8%) given the lower FVC at CLAD onset observed in R-CLAD (Table 2). In a subset of R-CLAD patients with a chest computed tomography (CT) scan performed near the time of CLAD onset ($n = 52$), we observed similar median declines in FEV_1 when stratifying patients by the presence or absence of parenchymal opacities (350 ml vs 345 ml), whereas the median absolute and percent decline in FVC was somewhat greater in patients with vs those without opacities (350 ml, 20.3% vs 270 ml, 9.8%) (see Table S3 online). Regardless of CLAD phenotype, the absolute and percent decline in both FEV_1 and FVC were more pronounced among patients who had graft loss within 18 months post-CLAD (Table 3 and Figure 2).

Pattern and reversibility of early physiologic declines after CLAD

We defined an early physiologic decline as a ≥10% decline in FEV_1 or FVC relative to the CLAD-onset value within the first 6 months after CLAD onset. One hundred sixty-one patients had an early physiologic decline after CLAD

Table 1 CLAD Cohort Characteristics Overall and Stratified by Physiologic Phenotype at CLAD Onset

Characteristic	Study cohort ($N = 213$)	R-CLAD ($n = 64$)	BOS ($n = 149$)	p-value[a] (R-CLAD vs BOS)
At time of transplant				
Age	55.0 (39.0, 61.0)	55.0 (39.8, 61.2)	55.0 (39.0, 61.0)	0.658
Female sex	90 (42.3%)	36 (56.2%)	54 (36.2%)	0.010
Race				0.462
Caucasian	187 (87.8%)	59 (92.2%)	128 (85.9%)	
African American	24 (11.3%)	5 (7.8%)	19 (12.8%)	
Other	2 (0.9%)	0 (0.0%)	2 (1.3%)	
Native lung disease				0.752
Obstructive	79 (37.1%)	22 (34.4%)	57 (38.3%)	
Restrictive	84 (39.4%)	28 (43.8%)	56 (37.6%)	
Cystic	43 (20.2%)	13 (20.3%)	30 (20.1%)	
Other	7 (3.3%)	1 (1.6%)	6 (4.0%)	
Transplant era				0.098
Before January 1, 2005	119 (55.9%)	30 (46.9%)	89 (59.7%)	
On or after January 1, 2005	94 (44.1%)	34 (53.1%)	60 (40.3%)	
At time of CLAD				
Timing of diagnosis (months)				
Complete distribution	36.6 (17.8, 58.3)	34.3 (15.3, 50.6)	39.2 (18.4, 63.7)	0.207
Early onset[b]	70 (32.9%)	21 (32.8%)	49 (32.9%)	0.999
PFT measurements				
FEV_1 (liters)	1.85 (1.31, 2.37)	1.52 (1.17, 1.97)	2.00 (1.51, 2.55)	<0.001
FEV_1 ratio[c]	0.74 (0.62, 0.77)	0.62 (0.53, 0.73)	0.76 (0.69, 0.78)	<0.001
FVC (liters)	2.77 (2.12, 3.48)	2.12 (1.54, 2.63)	3.12 (2.39, 3.81)	<0.001
FVC ratio[d]	0.86 (0.77, 0.93)	0.73 (0.63, 0.75)	0.91 (0.85, 0.96)	<0.001
Treatment after CLAD				
Alemtuzumab				
Received at any time	44 (20.7%)	9 (14.1%)	36 (24.2%)	0.104
Received in first 6 months	29 (13.6%)	8 (12.5%)	21 (14.1%)	0.831
Anti-thymocyte globulin				
Received at any time	59 (27.7%)	19 (29.7%)	40 (26.8%)	0.739
Received in first 6 months	44 (20.7%)	17 (26.6%)	27 (18.1%)	0.196
Azithromycin				
Received at any time	146 (68.5%)	37 (57.8%)	109 (73.2%)	0.036

BOS, bronchiolitis obliterans syndrome; R-CLAD, restrictive chronic lung allograft dysfunction.

[a]Continuous variables are reported as median (Q1, Q3) and compared using Wilcoxon's test; categorical variables are reported as count (column proportion) and compared using Fisher's exact test.

[b]Early-onset CLAD was defined according to previous literature as the onset of CLAD within 2 years of transplantation.

[c]Ratio of FEV_1 at CLAD onset to average of the 2 best post-transplant FEV_1 values.

[d]Ratio of FVC at CLAD onset to average of the 2 FVC values that paired with the 2 best post-transplant FEV_1 values.

(155 met the FEV_1 threshold, whereas 106 met the FVC threshold). In general, patients' demographics were similar across the strata of FEV_1 or FVC decline; however, we did observe numerical differences in the distribution of restrictive native lung disease, CLAD phenotype, and timing of CLAD onset relative to transplantation (see Table S4 online).

Among patients with early physiologic decline after CLAD, the most common pattern of decline was a concurrent drop in FEV_1 and FVC (occurring in 74 of 161, 46%) (see Figure S1 online). The next most frequent patterns were an isolated FEV_1 decline (55 of 161, 34.2%) and an FVC decline occurring after FEV_1 decline (22 of 161, 13.7%). This suggests FEV_1 declines of ≥10% occurring early after CLAD are generally concurrent with or prior to FVC drops of this magnitude, but rarely occur after an FVC decline.

To understand the potential reversibility of early physiologic declines after CLAD, we evaluated whether the initial ≥10% FEV_1 or FVC decline was sustained on the next measured PFT. The majority (71.6%) of patients with a threshold FEV_1 decline sustained this magnitude of decline on the very next measured PFT in the 6-month window. Further, 88.4% reached this threshold of decline at least 1 more time during follow-up, with a median of 42 days between events. Similarly, 67.0% of patients meeting the FVC decline threshold sustained this magnitude of decline on the next measured PFT in the 6-month window, with 86.8% reaching the FVC decline threshold at least 1 more time during follow-up (median of 42 days between events). These data suggest that, in the majority of patients, early physiologic declines after CLAD onset are sustained and even those with apparent short-term reversibility go on to deteriorate again within a relatively brief interval.

Table 2 Absolute and Percent Change in FEV_1 or FVC in Each 6-month Interval After CLAD Diagnosis up to 18 Months Post-CLAD

	All CLAD ($N = 213$)	R-CLAD ($n = 64$)	BOS ($n = 149$)
Absolute change in FEV_1 (ml)[a]			
CLAD onset to 6 months[b]	−330.0 (−630.0, −160.0)	−345.0 (−630.0, −160.0)	−320.0 (−600.0, −160.0)
6 to 12 months[b]	−85.0 (−275.0, 67.5)	0.0 (−172.5, 80.0)	−90.0 (−280.0, 55.0)
12 to 18 months[b]	−50.0 (−190.0, 50.0)	−50.0 (−300.0, 30.0)	−50.0 (−180.0, 50.0)
Percent change in FEV_1[a]			
CLAD onset to 6 months	−18.7 (−34.8, −8.7)	−25.4 (−36.3, −12.0)	−17.6 (−34.4, −7.3)
6 to 12 months	−5.7 (−19.1, 4.3)	0.0 (−15.1, 9.0)	−6.6 (−19.1, 3.3)
12 to 18 months	−3.7 (−12.4, 4.1)	−3.8 (−18.8, 4.5)	−3.0 (−10.9, 3.9)
Absolute change in FVC (ml)[a]			
CLAD onset to 6 months	−270.0 (−580.0, −90.0)	−335.0 (−655.0, −117.5)	−240.0 (−550.0, −90.0)
6 to 12 months	−40.0 (−310.0, 107.5)	15.0 (−202.5, 200.0)	−70.0 (−317.5, 90.0)
12 to 18 months	−60.0 (−245.0, 65.0)	−100.0 (−520.0, 20.0)	−50.0 (−215.0, 100.0)
Percent change in FVC[a]			
CLAD onset to 6 months	−9.8 (−23.6, −3.5)	−18.0 (−29.2, −6.0)	−8.0 (−19.6, −2.5)
6 to 12 months	−1.7 (−13.6, 4.6)	0.7 (−14.3, 8.3)	−2.3 (−13.4, 3.2)
12 to 18 months	−2.4 (−8.0, 2.8)	−3.9 (−17.4, 1.0)	−2.2 (−7.2, 2.8)

Data are presented for overall CLAD cohort and as stratified by physiologic phenotype at CLAD onset. BOS, bronchiolitis obliterans syndrome; R-CLAD, restrictive chronic lung allograft dysfunction.

[a]Post-baseline PFT measures defined as minimum observe value in window: percent change = 100 × [(Time2 PFT − Time1 PFT) / Time1 PFT], reported as median (Q1, Q3) liters.

[b]All subjects contributed at least 1 PFT to the CLAD onset in the 6-month interval. Because of patient deaths occurring over follow-up, 162 subjects (36 R-CLAD and 126 BOS) and 124 subjects (25 R-CLAD and 99 BOS) contributed at least 1 PFT in the 6- to 12-month interval or 12- to 18-month interval, respectively.

Impact of early physiologic decline after CLAD on graft survival

We then examined whether early physiologic declines after CLAD identify patients at risk for worse outcomes. Figure 3 illustrates Kaplan–Meier curves describing the relationship between a ≥10% decline in FEV_1 or FVC within the first 6 months after CLAD and graft loss. A decline in FEV_1 or FVC of ≥10% within the first 6 months after CLAD onset was associated with a significant increase in the hazard of future graft loss (unadjusted hazard ratio [HR] = 3.17, 95% confidence interval [CI] 1.56 to 6.42, $p = 0.001$, and HR = 2.80, 95% CI 1.66 to 4.70, $p < 0.001$, respectively). This finding held true whether CLAD was of BOS or R-CLAD phenotype at onset. Notably, an early ≥10% decline in FEV_1 or FVC after CLAD remained an independent risk factor for graft loss, even after adjustment for CLAD phenotype, CLAD-onset timing, transplant era, and receipt of augmented immunosuppression (adjusted HR = 2.83, 95% CI 1.36 to 5.89, $p = 0.005$, and adjusted HR = 2.39, 95% CI 1.40 to 4.08, $p = 0.001$, respectively) (Table 4).

To determine whether FEV_1 and FVC declines are independently or collinearly associated with graft loss, the Cox model for FEV_1 decline was adjusted for FVC decline and vice versa. The effect estimate for each PFT measure attenuated after adjustment for the other, suggesting the 2 variables do not contain completely independent information about risk (Table 4). Although the CI for the FEV_1 effect estimate crossed 1 after adjustment for FVC, the estimate for FVC remained statistically significant even after adjustment for FEV_1 (adjusted HR = 1.87, 95% CI 1.05 to 3.33, $p = 0.034$).

Importantly, the results of our time-dependent Cox model were consistent with those observed in the landmark analysis. Specifically, the presence of a ≥10% decline in FEV_1 or FVC was associated with a nearly 4- to 5-fold increase in the hazard for graft loss (unadjusted HR = 5.50, 95% CI 2.89 to 10.47, $p < 0.001$, for FEV_1 decline; HR = 3.91, 95% CI 2.51 to 6.09, $p < 0.001$, for FVC decline). This association remained significant with similar effect sizes, even after adjustment for CLAD phenotype at onset, timing of CLAD onset, receipt of augmented immunosuppression, and transplant era (see Table S5 online).

Discussion

In this study we have provided a longitudinal description of FEV_1 and FVC over the first 18 months after CLAD onset in a large cohort of bilateral lung transplant recipients, stratified by BOS or R-CLAD phenotype. We demonstrated the greatest declines in FEV_1 and FVC occurred within 6 months of CLAD diagnosis. This pattern was observed whether CLAD was of BOS or R-CLAD phenotype at onset. We next examined the association of early physiologic changes after CLAD with longer term graft outcomes. We showed that patients with a ≥10% decline in FEV_1 or FVC in the first 6 months after CLAD are at increased risk for graft loss independent of CLAD

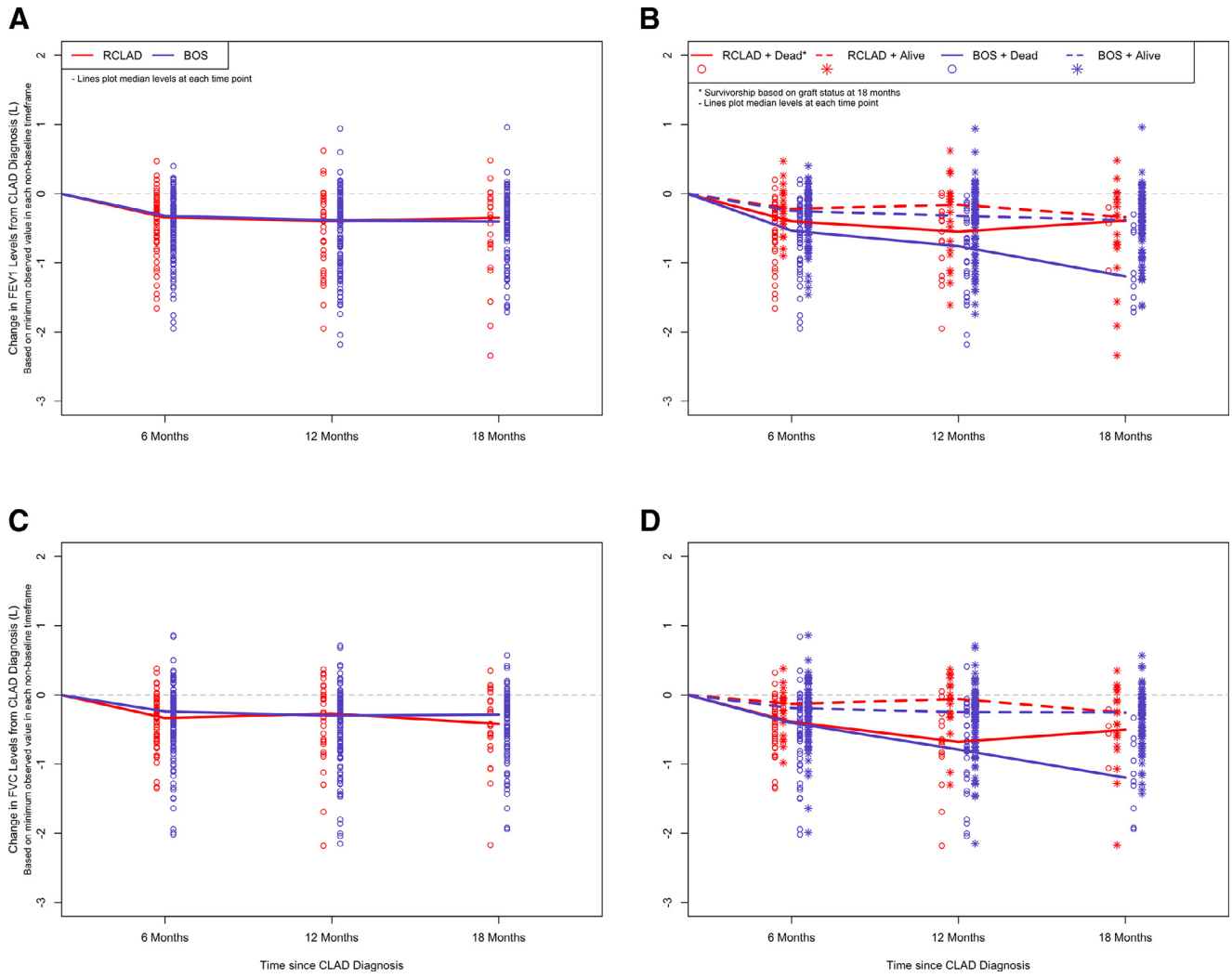

Figure 2 Absolute change in FEV_1 (A, B) and FVC (C, D), in liters, over the 18 months after CLAD diagnosis. Line plots in (A) and (B) are stratified by physiologic CLAD phenotype at CLAD onset (red: R-CLAD; blue: BOS), whereas those in (B) and (D) are stratified by physiologic CLAD phenotype at diagnosis (red: R-CLAD; blue: BOS) and by graft status as assessed at 18 months post-CLAD (alive, dashed line with individual data points plotted in stars vs dead, solid line with individual data points plotted in open circles). Bilateral lung recipients with CLAD, whether BOS or R-CLAD phenotype, had the largest losses in FEV_1 and FVC during the first 6 months after CLAD onset, after which pulmonary function loss attenuated. The decline in both FEV_1 and FVC is more pronounced among patients with graft loss, as defined by death or retransplantation, within 18 months post-CLAD.

phenotype at diagnosis or timing of CLAD onset relative to transplantation.

Our data suggesting the greatest FEV_1 decline occurs early after CLAD diagnosis is consistent with previous reports, including those of Lama and colleagues, who reported a mean decline in percent predicted FEV_1 of 12% in the first 6 months after CLAD, compared with 4% and 3% declines in the 6- to 12-month and 12- to 18-month intervals after CLAD, respectively.[10] As this previous cohort was largely comprised of single lung recipients with native lung emphysema, our work provides an important extension of those earlier observations by investigating the course of FEV_1 in a cohort of bilateral lung transplant recipients. This focus on bilateral recipients avoids potential confounding from native lung disease, thus allowing more precise estimates of physiologic changes attributable to CLAD.

An innovation of our work includes discerning the course of FEV_1 and FVC within the phenotypes of BOS and R-CLAD. In particular, this is novel in relation to R-CLAD, as there are no previous comprehensive descriptions of physiologic progression after R-CLAD onset. We demonstrated patients with R-CLAD enter CLAD with lower FEV_1 and FVC values when compared with BOS, yet both groups had similar absolute declines in FEV_1 and FVC over the first 6 months after diagnosis. Thus, the percent decline in FEV_1 and FVC in this interval was much larger in patients with R-CLAD than in BOS. Although previous data within R-CLAD are unavailable, our observation that both FEV_1 and FVC decline over time in patients specifically with BOS phenotype is consistent with work by Belloli and colleagues.[11] Their work examining 59 bilateral lung recipients with BOS demonstrated nearly all patients had a decline in FVC over follow-up and most experienced

Table 3 Absolute and Percent Change in FEV_1 or FVC in Each 6-month Interval After CLAD Diagnosis up to 18 Months Post-CLAD

	R-CLAD dead[c] ($n = 43$)	R-CLAD alive[c] ($n = 21$)	BOS dead[c] ($n = 52$)	BOS alive[c] ($n = 97$)
Absolute change in FEV_1 (ml)[a]				
CLAD onset to 6 months[b]	−400.0 (−705.0, −225.0)	−220.0 (−440.0, −20.0)	−535.0 (−962.5, −272.5)	−250.0 (−460.0, −70.0)
6 to 12 months[b]	0.0 (−145.0, 75.0)	10.0 (−180.0, 80.0)	−180.0 (−440.0, 10.0)	−70.0 (−240.0, 70.0)
12 to 18 months[b]	−155.0 (−510.0, 185.0)	−50.0 (−270.0, 20.0)	−210.0 (−355.0, −92.5)	−40.0 (−150.0, 60.0)
Percent change in FEV_1[a]				
CLAD onset to 6 months	−29.8 (−41.9, −17.5)	−12.6 (−23.0, −2.4)	−37.4 (−50.9, −17.7)	−12.6 (−20.0, −3.9)
6 to 12 months	−0.0 (−17.6, 9.5)	0.6 (−12.2, 7.4)	−15.4 (−37.6, 1.1)	−3.7 (−13.8, 3.4)
12 to 18 months	−9.2 (−39.0, 17.2)	−3.8 (−13.4, 1.6)	−14.1 (−20.4, −12.6)	−2.3 (−8.0, 4.3)
Absolute change in FVC (ml)[a]				
CLAD onset to 6 months	−390.0 (−685.0, −225.0)	−130.0 (−400.0, −40.0)	−405.0 (−705.0, −172.5)	−190.0 (−410.0, −50.0)
6 to 12 months	−70.0 (−300.0, 30.0)	70.0 (−30.0, 280.0)	−460.0 (−740.0, 20.0)	−40.0 (−240.0, 110.0)
12 to 18 months	−240.0 (−557.5, 102.5)	−100.0 (−380.0, 0.0)	−360.0 (−577.5, −165.0)	−40.0 (−140.0, 100.0)
Percent change in FVC[a]				
CLAD onset to 6 months	−20.7 (−29.9, −12.4)	−6.6 (−20.4, −2.2)	−14.3 (−29.2, −6.5)	−6.2 (−12.2, −1.0)
6 to 12 months	−3.8 (−16.2, 4.2)	4.7 (−1.7, 13.5)	−18.0 (−27.8, 1.3)	−1.5 (−7.9, 4.1)
12 to 18 months	−12.2 (−33.8, 7.3)	−3.9 (−10.3, −0.0)	−13.4 (−14.5, −8.8)	−1.7 (−5.6, 3.3)

Data are presented stratified by the physiologic phenotype at CLAD diagnosis and graft status at 18 months after CLAD (alive vs dead). BOS, bronchiolitis obliterans syndrome; R-CLAD, restrictive chronic lung allograft dysfunction.

[a]Post-baseline PFT measures defined as minimum observe value in window: percent change = 100 × [(Time2 PFT − Time1 PFT) / Time1 PFT], reported as median (Q1, Q3) liters.

[b]All subjects contributed at least 1 PFT to the CLAD onset in the 6-month interval. Because of patient deaths occurring over follow-up, 162 subjects (36 R-CLAD and 126 BOS) and 124 subjects (25 R-CLAD and 99 BOS) contributed at least 1 PFT in the 6- to 12-month interval or 12- to 18-month interval, respectively.

[c]Survivorship based on graft status, defined as death or retransplantation, assessed at 18 months post-CLAD diagnosis.

further FEV_1 deterioration with progression of BOS grade at the time of FVC decline.[11] In keeping with this idea, we have demonstrated the most common pattern of early PFT progression after CLAD onset is concurrent FEV_1 and FVC decline.

Previous work has established the impact of factors identifiable at CLAD onset on survival after CLAD, including CLAD phenotype and timing of CLAD onset relative to transplantation.[5,6,13] This study is the first to examine and place in context the prognostic implications of early physiologic changes after CLAD diagnosis. We focused our analysis on a 10% threshold PFT decline, as this limit has proven useful in identifying patients at increased risk for mortality in other respiratory diseases, such as FVC decline in patients with idiopathic pulmonary fibrosis (IPF).[14,15] We have demonstrated early physiologic changes after CLAD, whether in FEV_1 or FVC, providing useful prognostic information independent of factors previously known to be associated with post-CLAD graft loss. These findings are also independent of various treatment interventions given in the early period after CLAD. Not unexpectedly, we observed collinearity in FEV_1 and FVC decline with regard to the risk of graft loss after CLAD. However, our findings suggesting that an early FVC decline of ≥10% remains independently associated with longer term graft loss after CLAD, even after adjustment for FEV_1 decline, adds to previous observations regarding the potential prognostic value of FVC monitoring after CLAD.[11]

The precise estimates of longitudinal change in FEV_1 and FVC after CLAD in addition to the impact of early PFT decline on longer term post-CLAD graft outcomes presented here are essential to guiding the rational design of CLAD treatment trials. Our findings demonstrating early physiologic changes after CLAD correlate with longer term CLAD outcomes suggest a decline in either FEV_1 or FVC of ≥10% within 6 months after CLAD onset could be a useful surrogate clinical end-point for an interventional CLAD trial, as this decline associates with later graft loss. Our data also suggest the same end-point criteria could be applied in CLAD trials irrespective of the mix of R-CLAD, BOS, or early-onset CLAD patients comprising the cohort and irrespective of previous treatments. Although controversy exists regarding the use of physiologic end-points in pulmonary trials,[16,17] it is notable that a precise understanding of the natural history of FVC in untreated patients with IPF was critical in enabling pivotal clinical trials employing FVC decline as the primary end-point.[18,19]

A major confounder to estimating physiologic progression after CLAD is survivor bias. Indeed, one third of our BOS cohort and two thirds of our R-CLAD cohort died over the 18-month follow-up period, similar to survival observed in other contemporary studies evaluating outcomes after CLAD.[4,6,20] Accumulating deaths likely contributed to the attenuation in PFT decline observed in later intervals after CLAD. As such, we focused our survival analysis on PFT changes observed within the first 6 months of CLAD, an interval during which all patients had an available measurement. The high death rate within 18 months of CLAD onset brings to light additional clinical

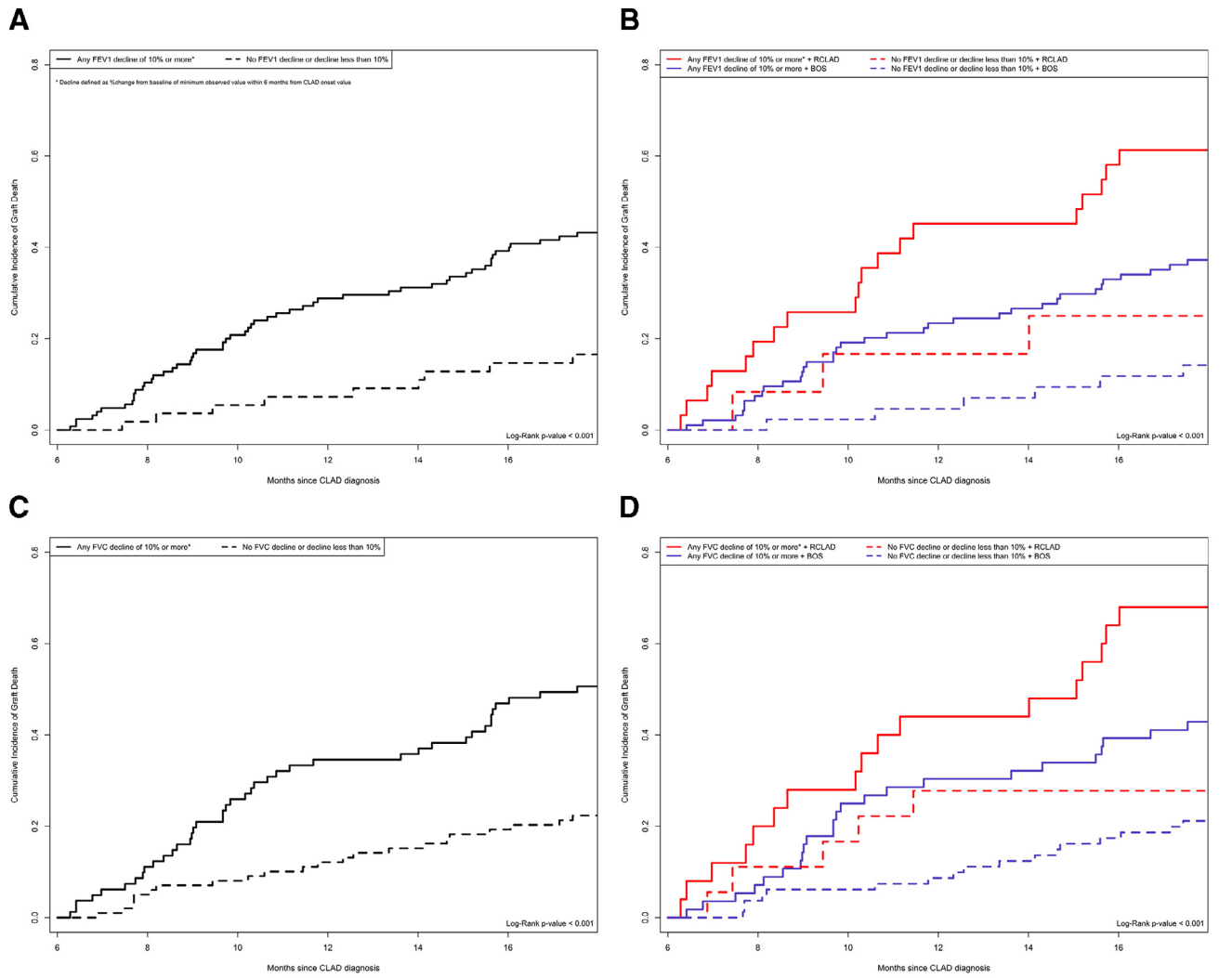

Figure 3 Kaplan–Meier curves describing the relationship between a ≥10% decline in FEV_1 (A, B) or FVC (C, D) within the first 6 months after CLAD diagnosis on 18-month post-CLAD survival. Panels (A) and (C) are reflective of the CLAD cohort as a whole, whereas (B) and (D) are stratified by physiologic CLAD phenotype at CLAD onset (red: R-CLAD; blue: BOS). A decline in FEV_1 or FVC of ≥10% within the first 6 months after CLAD was associated with worse post-CLAD survival after that time. This observation was consistent whether CLAD was of BOS phenotype or R-CLAD phenotype at onset.

trial implications, including consideration of composite end-points that include both physiologic decline and death or, for end-points focused only on physiologic changes, the need to impute PFT values for patients who die before study conclusion.

Although our study included a large cohort of lung recipients with CLAD who were phenotyped according to published methods, and closely followed with serial PFTs, it has inherent limitations. We recognize our results are single center in nature and should be corroborated by other centers. In addition, although our analysis was strengthened by a focus on bilateral lung recipients, it is also limited by the generalizability of these observations to single lung recipients. Finally, we acknowledge there is no consensus on the approach to defining a restrictive CLAD phenotype. Although there are inherent limitations with spirometry in determining restriction, several groups have now confirmed the impact of FVC loss at the time of CLAD onset on post-CLAD survival,[6,11] thus substantiating the importance of this spirometric distinction, irrespective of remaining uncertainties.

In conclusion, we have demonstrated that the greatest losses in FEV_1 and FVC occur within 6 months of CLAD onset, regardless of R-CLAD or BOS phenotype. Moreover, the severity of early lung function decline after CLAD is strongly associated with risk of graft loss, even after accounting for factors known to impact outcomes after CLAD. These data provide novel insights to guide the rational design of CLAD treatment studies, suggesting that 6-month FEV_1 or FVC change may be a reasonable surrogate end-point in trials enrolling newly diagnosed CLAD patients. Ultimately, well-designed, properly powered trials will be essential to translating recent advances in transplant biology into clinical practice and addressing the critical unmet need for effective CLAD treatments.

Table 4 Results of a Cox Model Constructed to Examine Impact of Early Physiologic Decline, Defined as a ≥10% Decline in FEV_1 or FVC Within 6 Months of CLAD Diagnosis, on Graft Loss at 18 Months Post-CLAD[a]

	10% decline in FEV_1 (reached/not reached: 125/56)		10% decline in FVC (reached/not reached: 81/100)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Univariate association				
PFT decline[b]	3.17 (1.56 to 6.42)	0.001	2.80 (1.66 to 4.70)	<0.001
Adjusted for CLAD phenotype[c]				
PFT decline	3.15 (1.55 to 6.38)	0.001	2.61 (1.55 to 4.41)	<0.001
Interaction with CLAD phenotype[d]				
PFT decline among R-CLAD	3.21 (0.95 to 10.85)	0.972	3.17 (1.17 to 8.60)	0.651
PFT decline among BOS	3.12 (1.31 to 7.42)		2.41 (1.30 to 4.50)	
Adjusted for early-onset CLAD[e]				
PFT decline	2.88 (1.40 to 5.91)	0.004	2.62 (1.55 to 4.43)	<0.001
Interaction with early-onset CLAD[d]				
PFT decline among R-CLAD	2.07 (0.49 to 8.79)	0.622	1.95 (0.84 to 4.52)	0.395
PFT decline among BOS	3.15 (1.39 to 7.15)		3.10 (1.60 to 6.00)	
Adjusted for treatment[e] within 6 months of CLAD diagnosis				
PFT decline	3.26 (1.60 to 6.64)	0.001	2.80 (1.66 to 4.70)	<0.001
Interaction with treatment[f] within 6 months of CLAD diagnosis				
PFT decline among patients treated	Not estimable[g]	Not estimable[g]	3.16 (1.17 to 8.56)	0.775
PFT decline among patients not treated	Not estimable[g]		2.67 (1.45 to 4.90)	
Adjusted for transplant era[h]				
PFT decline	3.17 (1.56 to 6.42)	0.001	2.79 (1.66 to 4.69)	<0.001
Interaction with transplant era				
Transplant occurred before January 1, 2005	Not estimable[g]	Not estimable[g]	3.35 (1.45 to 7.78)	0.582
Transplant occurred on or after January 1, 2005	Not estimable[g]		2.48 (1.28 to 4.80)	
Adjusted for CLAD phenotype, early onset, treatment, and transplant era				
PFT decline	2.83 (1.36 to 5.89)	0.005	2.39 (1.40 to 4.08)	0.001
Adjusted for other PFT measure				
PFT decline	2.16 (1.00 to 4.68)	0.051	2.10 (1.19 to 3.71)	0.010
Adjusted for other PFT measure, CLAD phenotype, early onset, treatment, and transplant era				
PFT decline	2.06 (0.93 to 4.54)	0.074	1.87 (1.05 to 3.33)	0.034

BOS, bronchiolitis obliterans syndrome; CI, confidence interval; HR, hazard ratio; R-CLAD, restrictive chronic lung allograft dysfunction.

[a]Follow-up censored at 18 months; follow-up landmarked at 6 months.

[b]Post-baseline PFT measures defined as minimum observed value in window: percent drop = 100 × [(post-baseline PFT − baseline PFT) / baseline PFT]; decline defined as percent drop ≤ cut-off level.

[c]CLAD phenotypes: R-CLAD and BOS.

[d]Represents the *p*-value for interaction between PFT decline and risk factor.

[e]Early-onset CLAD defined according to previous literature as the onset of CLAD within 2 years of transplantation.

[f]Treatment defined as any treatment with alemtuzumab or anti-thymoglobulin within 6 months of CLAD diagnosis.

[g]Regression coefficients not estimable due to insufficient sample size in some group combinations.

[h]Transplant era defined as date of transplantation either before or on/after January 1, 2005.

Disclosure statement

The authors have no conflicts of interest to disclose related to this work. This study was supported by a grant from the National Institutes of Health/National Institute of Allergy and Infectious Diseases (K23 AI125670 to J.L.T.). The funding source had no role in collection, analysis, or interpretation of the data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.healun.2018.10.006.

References

1. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart–lung transplant report—2012. J Heart Lung Transplant 2012;31:1073-86.
2. Sato M. Chronic lung allograft dysfunction after lung transplantation: the moving target. Gen Thorac Cardiovasc Surg 2013;61:67-78.
3. Verleden GM, Raghu G, Meyer KC, et al. A new classification system for chronic lung allograft dysfunction. J Heart Lung Transplant 2014;33:127-33.
4. Sato M, Waddell TK, Wagnetz U, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. J Heart Lung Transplant 2011;30:735-42.

5. Todd JL, Jain R, Pavlisko EN, et al. Impact of forced vital capacity loss on survival after the onset of chronic lung allograft dysfunction. Am J Respir Crit Care Med 2014;189:159-66.
6. DerHovanessian A, Todd JL, Zhang A, et al. Validation and refinement of chronic lung allograft dysfunction phenotypes in bilateral and single lung recipients. Ann Am Thorac Soc 2016;13:627-35.
7. Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 2002;21:297-310.
8. Kneidinger N, Milger K, Janitza S, et al. Lung volumes predict survival in patients with chronic lung allograft dysfunction. Eur Respir J 2017;49(4).
9. Suhling H, Dettmer S, Greer M, et al. Phenotyping chronic lung allograft dysfunction using body plethysmography and computed tomography. Am J Transplant 2016;16:3163-70.
10. Lama VN, Murray S, Lonigro RJ, et al. Course of FEV(1) after onset of bronchiolitis obliterans syndrome in lung transplant recipients. Am J Respir Crit Care Med 2007;175:1192-8.
11. Belloli EA, Wang X, Murray S, et al. Longitudinal forced vital capacity monitoring as a prognostic adjunct after lung transplantation. Am J Respir Crit Care Med 2015;192:209-18.
12. Verleden SE, de Jong PA, Ruttens D, et al. Functional and computed tomographic evolution and survival of restrictive allograft syndrome after lung transplantation. J Heart Lung Transplant 2014;33:270-7.
13. Finlen Copeland CA, Snyder LD, Zaas DW, et al. Survival after bronchiolitis obliterans syndrome among bilateral lung transplant recipients. Am J Respir Crit Care Med 2010;182:784-9.
14. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168:543-8.
15. Collard HR, King Jr TE, Bartelson BB, et al. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:538-42.
16. Raghu G, Collard HR, Anstrom KJ, et al. Idiopathic pulmonary fibrosis: clinically meaningful primary endpoints in phase 3 clinical trials. Am J Respir Crit Care Med 2012;185:1044-8.
17. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis—FDA review of pirfenidone and nintedanib. New Engl J Med 2015;372:1189-91.
18. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New Engl J Med 2014;370:2071-82.
19. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. New Engl J Med 2014;370:2083-92.
20. Verleden SE, Ruttens D, Vandermeulen E, et al. Predictors of survival in restrictive chronic lung allograft dysfunction after lung transplantation. J Heart Lung Transplant 2016;35:1078-84.