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PROGNOSTIC SIGNIFICANCE OF EARLY PULMONARY FUNCTION CHANGES AFTER THE ONSET OF CHRONIC LUNG ALLOGRAFT DYSFUNCTION

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Abstract

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 FEV1 and FVC over the first 18 months following 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; differentiated to R-CLAD (n=65) or BOS (n=151). The course of FEV1 and FVC after CLAD was described. Cox proportional hazards models were used to evaluate the impact of a 10% decline in FEV1 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, experienced the greatest losses in FEV1 and FVC within the first 6 months after onset. Moreover, a decline in FEV1 or FVC of 10% within the first six months after CLAD was associated with a significant increase in the hazard for graft loss after that time (HR=3.17, 95% CI 1.56-6.42, p=0.001 and HR=2.80, 95% CI 1.66-4.70, p<0.001, respectively), an effect observed in both BOS and R-CLAD.

Conclusions: We demonstrate early physiological changes after CLAD are independently associated with graft loss. This suggests lung function changes after CLAD, specifically a 10% decline in FEV1 or FVC, could be a surrogate measure of graft survival.

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INTRODUCTION

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 the forced expiratory volume in one second (FEV1) relative to the highest posttransplant 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 two phenotypes conferring distinct prognoses(4-9). Work by our group and others used spirometry to distinguish physiological CLAD phenotypes demonstrating patients with a decrement in forced vital capacity (FVC) along with FEV1 at CLAD onset, which suggests a restrictive ventilatory defect (restrictive CLAD, 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 FEV1 after CLAD demonstrating the greatest decline occurs in the first six months following CLAD onset. However, this 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, this work predated the current understanding of CLAD phenotypes and as such did not consider differences in FEV1 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 BOS phenotype suggested that while both FEV1 and FVC decline over time after BOS onset, only FVC decline was associated with shorter patient survival(11). In a series of 24 patients with a restrictive CLAD phenotype, Verleden et al reported all subjects experienced FEV1 loss over follow up although details regarding the precise estimates of loss were not described(12).

Additional studies are needed to better define the natural history of pulmonary function changes within BOS and R-CLAD and clarify the prognostic significance of such changes. Precise information on FEV1 and FVC after CLAD including correlation with survival could identify useful surrogate endpoints from which to assess the effectiveness of CLAD treatments. We sought to: 1) Describe changes in FEV1 and FVC after CLAD and compare these measures in BOS and R-CLAD, and 2) determine if a decline in FEV1 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:

The cohort consisted of 216 adult, first, bilateral lung recipients with CLAD at Duke (Figure 1). Cohort derivation was previously described(5). According to published methods, patients

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were considered as R-CLAD if they demonstrated FVC loss at CLAD onset or BOS if FVC was preserved(5). Sixty-five patients met criteria for R-CLAD, while the remaining 151 were BOS. As our study focused on physiologic changes after CLAD, subjects were excluded if they did not have at least one 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 as described in the supplement. Patients with CLAD were managed at physician discretion. Management may include augmented immunosuppression (i.e. anti-thymocyte globulin and/or alemtuzumab). Azithromycin is also utilized at physician discretion and may be initiated prior to CLAD. Ethics approval was obtained from the Duke Institutional Review Board.

Analyses:

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Descriptive statistics were used to describe patient characteristics. Continuous variables are presented as medians (Q1, Q3) and categorical variables as counts (proportions). Patient characteristics were compared between the R-CLAD and BOS groups using the Wilcoxon or Fischer's exact test as appropriate. To describe changes in FEV1 and FVC after CLAD, split-time jitter scatter plots of absolute and percent-drop 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 $100 * [(post-CLAD \text{ absolute FEV1 or FVC} - CLAD \text{ onset absolute FEV1 or FVC}) / CLAD \text{ onset absolute FEV1 or FVC}]$. The median (Q1, Q3) of the absolute and percent-drop in each PFT measure were also reported.

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We tested the hypothesis that a 10% decline in FEV1 or FVC within the first six months after CLAD onset is associated with an increased risk of graft loss (defined as death or retransplantation) beyond that six 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 FEV1 or FVC as compared with the CLAD onset value within the first 6 months following CLAD diagnosis. The relationship between a 10% decline in FEV1 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 (n=181) were included in this landmark analysis.

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The Cox model was adjusted for CLAD phenotype (BOS reference), CLAD onset timing (early onset, defined as CLAD within two 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 prior to vs. on or after 1/1/2005), 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 on graft loss as detailed in the supplement.

The landmark analytic method necessarily resulted in the exclusion of 32 patients due to death within six months of CLAD onset. The majority of these patients experienced a 10% FEV1 or FVC decline prior to 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 FEV1 or FVC within 6 months after CLAD diagnosis. All analyses were performed using R 3.3.3.

RESULTS

Cohort Characteristics

Table 1 describes the cohort characteristics. The median number of PFTs from CLAD onset to 18 months post CLAD was 7 (4, 9) and was similar in BOS (7 [4, 9]) and R-CLAD (6 [3, 8]). Considering all CLAD patients, median FEV1 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 FEV1 and FVC values at diagnosis when compared to those with BOS (FEV1 1.52 and FVC 2.12 liters in R-CLAD vs. 1.99 and 2.97 liters in BOS, $p < 0.001$ for both). Most patients (68.5%) received azithromycin after CLAD. Forty-four (20.7%) underwent treatment with alemtuzumab while 59 (27.7%) were treated with anti-thymocyte globulin. The majority of the augmented immunosuppression use was within 6 months of CLAD onset. Fifty-two (34.9%) patients with BOS and forty-three (67%) with R-CLAD died over the 18 month follow up.

Physiologic Progression after CLAD

Patients with CLAD experienced a median absolute (percent) decline in FEV1 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) declines in FEV1 of 80 mL (5.7%) and FVC of 40 mL (1.7%) (6-12 month interval) and 50 mL (3.7%) and 60 mL (2.4%) (12-18 month interval) were observed (Table 2, Figure 2). Tables S1 and S2 describe the *cumulative* FEV1 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 experienced the greatest losses in FEV1 and FVC in the 6 months following diagnosis. While both R-CLAD and BOS patients experienced similar median declines in FEV1 during this interval (345 mL vs. 320 mL), the median decline in FVC was larger 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 CT scan performed near the time of CLAD onset (n=52), we observed similar median declines in FEV1 when stratifying patients by the presence or absence of parenchymal opacities (350 mL vs. 345mL), while the median absolute and percent decline in FVC was

somewhat larger in patients with versus those without opacities (350mL, 20.3% vs. 270mL, 9.8%) (Table S3) Regardless of CLAD phenotype, the absolute and percent decline in both FEV1 and FVC were more pronounced among patients who experienced graft loss within 18 months post CLAD (Table 3, Figure 2).

Pattern and Reversibility of Early Physiologic Declines after CLAD

We defined an early physiologic decline as a 10% decline in FEV1 or FVC relative to the CLAD onset value within the first six months after CLAD onset. 161 patients experienced an early physiologic decline after CLAD (155 met the FEV1 threshold while 106 met the FVC threshold). In general, patient demographics were similar across the strata of FEV1 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 (Table S4)

Among patients experiencing an early physiologic decline after CLAD, the most common pattern of decline was a concurrent drop in FEV1 and FVC (occurring in 74/161, 46%) (Figure S1) The next most frequent patterns were an isolated FEV1 decline (55/161, 34.2%) and an FVC decline occurring after FEV1 decline (22/161, 13.7%). This suggests FEV1 declines 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% FEV1 or FVC decline was sustained on the next measured PFT. The majority (71.6%) of patients experiencing a threshold FEV1 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 one 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 one 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.

Impact of Early Physiologic Decline after CLAD on Graft Survival

We next 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% or greater decline in FEV1 or FVC within the first 6 months after CLAD and graft loss. A decline in FEV1 or FVC of 10% within the first six months after CLAD onset was associated with a significant increase in the hazard of future graft loss (unadjusted HR=3.17, 95% CI 1.56-6.42, p=0.001 and HR=2.80, 95% CI 1.66-4.70, p<0.001, respectively). This finding was true whether CLAD was of BOS or R-CLAD phenotype at onset. Notably an early 10% decline in FEV1 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 1.36-5.89, $p=0.005$ and adjusted HR 2.39, 95%CI 1.40-4.08, $p=0.001$, respectively) (Table 4).

To understand if FEV1 and FVC decline are independently or collinearly associated with graft loss, the Cox model for FEV1 decline was adjusted for FVC decline and vice versa. The effect estimate for each PFT measure attenuated after adjustment for the other suggesting the two variables do not contain completely independent information about risk (Table 4). While the confidence interval for the FEV1 effect estimate crossed one after adjustment for FVC, the estimate for FVC remained statistically significant even after adjustment for FEV1 (adjusted HR 1.87, 95% CI 1.05-3.33, p -value 0.034).

Importantly, the results of our time-dependent Cox model were consistent with those observed in the landmark analysis. Specifically, the occurrence of a 10% decline in FEV1 or FVC was associated with a nearly four to five fold increase in the hazards for graft loss (unadjusted HR 5.50, 95%CI 2.89-10.47, p -value <0.001 for FEV1 decline, HR 3.91, 95%CI 2.51-6.09, p -value <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 (Table S5)

DISCUSSION

This study provides a longitudinal description of FEV1 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 FEV1 and FVC occur 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 physiological changes after CLAD with longer-term graft outcomes. We showed that patients experiencing a 10% decline in FEV1 or FVC in the first 6 months after CLAD are at increased risk for graft loss independent of CLAD phenotype at diagnosis or timing of CLAD onset relative to transplantation.

Our data suggesting the greatest FEV1 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 FEV1 of 12% in the first 6 months after CLAD, compared with a 4% and 3% decline in the 6-12 month and 12-18 month intervals after CLAD, respectively (10). As this prior cohort was largely comprised of single lung recipients with native lung emphysema, our work provides an important extension of these earlier observations by investigating the course of FEV1 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 physiological changes attributable to CLAD.

An innovation of our work includes discerning the course of FEV1 and FVC within the phenotypes of BOS and R-CLAD. In particular, this is novel related to R-CLAD as there are no prior comprehensive descriptions of physiologic progression after R-CLAD onset. We demonstrated patients with R-CLAD enter CLAD with lower FEV1 and FVC values when compared to BOS yet both groups experience similar absolute declines in FEV1 and FVC

over the first 6 months after diagnosis. Thus, the percent decline in FEV1 and FVC in this interval is much larger in patients with R-CLAD than in BOS. While prior data within R-CLAD are unavailable, our observation that both FEV1 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 reported nearly all patients experienced a decline in FVC over follow up and most experienced further FEV1 deterioration with progression of BOS grade at the time of FVC decline(11). In keeping with this idea, we demonstrate the most common pattern of early PFT progression after CLAD onset is concurrent FEV1 and FVC decline.

Prior 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 physiological 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, for example FVC decline in patients with idiopathic pulmonary fibrosis (IPF)(14, 15). We demonstrate early physiologic changes after CLAD, whether in FEV1 or FVC, provide 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 FEV1 and FVC decline with regard to the risk of graft loss after CLAD. However, our findings suggesting an early FVC decline of 10% remains independently associated with longer-term graft loss after CLAD even after adjustment for FEV1 decline adds to prior observations regarding the potential prognostic value of FVC monitoring after CLAD(11).

The precise estimates of longitudinal change in FEV1 and FVC after CLAD in addition to the impact of early PFT decline on longer-term post CLAD graft outcomes presented herein are essential to guiding the rational design of CLAD treatment trials. Our findings demonstrating early physiological changes after CLAD correlate with longer-term CLAD outcomes suggest a decline in either FEV1 or FVC of 10% within 6 months after CLAD onset could be an attractive surrogate clinical endpoint for an interventional CLAD trial as this decline associates with later graft loss. Our data also suggest the same endpoint 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 prior treatments. While controversy exists regarding the use of physiological endpoints 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 to enabling pivotal clinical trials employing FVC decline as the primary endpoint(18, 19).

An important 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 time, 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 six 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 trial implications including consideration of composite endpoints that include both physiological decline and death or, for endpoints focused only on physiological 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. Additionally, while our analysis is strengthened by a focus on bilateral lung recipients, it also limits 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. While there are inherent limitations of 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 demonstrate the greatest losses in FEV1 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 FEV1 or FVC change may be a reasonable surrogate endpoint 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CLAD	Chronic lung allograft dysfunction
FEV1	Forced expiratory volume in one second
BOS	Bronchiolitis obliterans syndrome
FVC	Forced vital capacity

R-CLAD	Restrictive chronic lung allograft dysfunction
PFT	Pulmonary function test
IPF	Idiopathic pulmonary fibrosis

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HIGHLIGHTS

- The greatest loss in FEV1 and FVC occurs in the first 6 months after CLAD onset.
- Early physiological changes after CLAD provide independent prognostic information.
- These observations held true whether CLAD was of BOS or R-CLAD phenotype at onset.
- Our data supports a physiologic surrogate endpoint for use in CLAD clinical trials.

Figure 1.

Consort diagram describing study cohort derivation for the pulmonary function and survival analyses. * The derivation of the CLAD cohort has been previously detailed(5). CLAD is defined as a sustained 20% decline in FEV1 as compared to the average of the two best posttransplant FEV1s measured at least three weeks apart in the absence of other clinical confounders.. † At CLAD onset, patients were considered to have restrictive CLAD (R-CLAD) if the 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 two FVCs associated with the two PFTs used in FEV₁ baseline calculation for CLAD diagnosis.

Figure 2.

Absolute change in FEV1 (panels A and B) and FVC (panels C and D) in liters over 18 months following CLAD diagnosis. Line plots in panels A and B are stratified by physiologic CLAD phenotype at CLAD onset (R-CLAD, red; BOS, blue) while those in B and D are stratified by physiologic CLAD phenotype at diagnosis (R-CLAD, red or BOS, blue) 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, experienced the greatest losses in FEV1 and FVC during the first 6 months after CLAD onset after which time pulmonary function loss is attenuated. The decline in both FEV1 and FVC is more pronounced among patients who experiencing graft loss, as defined by death or retransplantation, within 18 months post CLAD.

Figure 3.

Kaplan-Meier curves describing the relationship between a 10% or greater decline in FEV1 (panels A and B) or FVC (panels C and 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 while panels B and D are stratified by physiological CLAD phenotype at CLAD onset (R-CLAD, red or BOS, blue). A decline in FEV1 or FVC of 10% within the first six 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.

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* (R-CLAD vs. BOS)
<i>At Time of Transplant</i>				
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
Prior to 01/01/2005	119 (55.9%)	30 (46.9%)	89 (59.7%)	
On or After 01/01/2005	94 (44.1%)	34(53.1%)	60 (40.3%)	
<i>At Time of CLAD</i>				
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 [†]	70 (32.9%)	21 (32.8%)	49 (32.9%)	0.999
PFT Measurements				
FEV1 (Liters)	1.85(1.31, 2.37)	1.52(1.17- 1.97)	2.00(1.51-2.55)	< 0.001
FEV1 Ratio [‡]	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 [§]	0.86 (0.77, 0.93)	0.73(0.63-0.75)	0.91(0.85-0.96)	< 0.001
<i>Treatment after CLAD</i>				
Alemtuzumab				
Received at anytime	44 (20.7%)	9 (14.1%)	36 (24.2%)	0.104
Received in first 6months	29 (13.6%)	8 (12.5%)	21 (14.1%)	0.831
Antithymocyte globulin				
Received at anytime	59 (27.7%)	19 (29.7%)	40 (26.8%)	0.739
Received in first 6months	44 (20.7%)	17 (26.6%)	27 (18.1%)	0.196
Azithromycin				
Received at anytime	146 (68.5%)	37 (57.8%)	109 (73.2%)	0.036

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

[†] Early onset CLAD was defined according to prior literature as the onset of CLAD within two years of transplantation.

[‡] Ratio of the FEV1 at CLAD onset to the average of the two best post transplant FEV1 values.

[§] Ratio of the FVC at CLAD onset to the average of the two FVC values that paired with the two best post transplant FEV1 values.

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

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Table 2.

Absolute and percent change in FEV1 or FVC in each 6-month interval following CLAD diagnosis, up to 18 months post CLAD. Data are presented for the overall CLAD cohort and as stratified by the physiologic phenotype at CLAD onset.

	All CLAD (N = 213)	R-CLAD (N = 64)	BOS (N =149)
Absolute Change in FEV1 (mL)*			
CLAD onset to 6 months [†]	−330.0 (−630.0, −160.0)	−345.0 (−630.0, −160.0)	−320.0 (−600.0, −160.0)
6 months to 12 months [†]	−85.0 (−275.0, 67.5)	0.0 (−172.5, 80.0)	−90.0 (−280.0, 55.0)
12 months to 18 months [†]	−50.0 (−190.0, 50.0)	−50.0 (−300.0, 30.0)	−50.0 (−180.0, 50.0)
Percent Change in FEV1*			
CLAD onset to 6 months	−18.7 (−34.8, −8.7)	−25.4 (−36.3, −12.0)	−17.6 (−34.4, −7.3)
6 months to 12 months	−5.7 (−19.1, 4.3)	0.0 (−15.1, 9.0)	−6.6 (−19.1, 3.3)
12 months 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)*			
CLAD onset to 6 months	−270.0 (−580.0, −90.0)	−335.0 (−655.0, −117.5)	−240.0 (−550.0, −90.0)
6 months to 12 months	−40.0 (−310.0, 107.5)	15.0 (−202.5, 200.0)	−70.0 (−317.5, 90.0)
12 months 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*			
CLAD onset to 6 months	−9.8 (−23.6, −3.5)	−18.0 (−29.2, −6.0)	−8.0 (−19.6, −2.5)
6 months to 12 months	−1.7 (−13.6, 4.6)	0.7 (−14.3, 8.3)	−2.3 (−13.4, 3.2)
12 months to 18 months	−2.4 (−8.0, 2.8)	−3.9 (−17.4, 1.0)	−2.2 (−7.2, 2.8)

* Post-baseline PFT measures defined as minimum observe value in window; percent-change = 100*[(Time2 PFT–Time1 PFT)/Time1 PFT] and reported as median (Q1–Q3) liters.

[†] All subjects contributed at least one 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 one PFT in the 6 to 12 month interval or 12 to 18 month interval, respectively.

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

Table 3.

Absolute and percent change in FEV1 or FVC in each 6-month interval following CLAD diagnosis, up to 18 months post CLAD. Data are presented stratified by the physiologic phenotype at CLAD diagnosis and graft status at 18 months after CLAD (alive vs. dead).

	R-CLAD Dead ‡ (N =43)	R-CLAD Alive‡ (N = 21)	BOS Dead ‡ (N = 52)	BOS Alive ‡ (N =97)
Absolute Change in FEV1 (mL)*				
CLAD onset to 6 months ‡	-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 months to 12 months ‡	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 months to 18 months ‡	-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 FEV1*				
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 months 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 months 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)*				
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 months 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 months 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*				
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 months 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 months 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)

* Post-baseline PFT measures defined as minimum observe value in window; percent-change = $100 * [(Time2 \text{ PFT} - Time1 \text{ PFT}) / Time1 \text{ PFT}]$ and reported as median (Q1–Q3) liters.

‡ All subjects contributed at least one 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 one PFT in the 6 to 12 month interval or 12 to 18 month interval, respectively.

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

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

Table 4.

Results of a Cox model constructed to examine the impact of early physiological decline, defined as a greater than or equal to 10% decline in FEV1 or FVC within 6 months of CLAD diagnosis, on graft loss at 18 months post CLAD *.

	10% Decline in FEV1 (Reached/Not = 125/56)		10% Decline in FVC (Reached/Not = 81/100)	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Univariate Association				
PFT Decline [†]	3.17(1.56 - 6.42)	0.001	2.80(1.66 - 4.70)	<0.001
Adjusted for CLAD Phenotype[‡]				
PFT Decline	3.15 (1.55 - 6.38)	0.001	2.61(1.55 - 4.41)	<0.001
Interaction with CLAD Phenotype[§]				
PFT Decline among RCLAD	3.21(0.95 - 10.85)	0.972	3.17(1.17 - 8.60)	0.651
PFT Decline among BOS	3.12(1.31 - 7.42)		2.41(1.30 - 4.50)	
Adjusted for Early Onset CLAD				
PFT Decline	2.88(1.40 - 5.91)	0.004	2.62(1.55 - 4.43)	<0.001
Interaction with Early Onset CLAD[§]				
PFT Decline among RCLAD	2.07(0.49 - 8.79)	0.622	1.95 (0.84 - 4.52)	0.395
PFT Decline among BOS	3.15(1.39 - 7.15)		3.10(1.60 - 6.00)	
Adjusted for Treatment^{**} within 6 months of CLAD Diagnosis				
PFT Decline	3.26(1.60 - 6.64)	0.001	2.80(1.66 - 4.70)	<0.001
Interaction with Treatment within 6 months of CLAD Diagnosis				
PFT Decline among patients treated	---	---	3.16(1.17 - 8.56)	0.775
PFT Decline among patients not treated	---		2.67 (1.45 - 4.90)	
Adjusted for Transplant Era^{***}				
PFT Decline	3.17(1.56 - 6.42)	0.001	2.79 (1.66 - 4.69)	<0.001
Interaction with Transplant Era				
Transplant Occurred Prior to 01/01/2005	---	---	3.35 (1.45 - 7.78)	0.582
Transplant Occurred On or After 01/01/2005	---		2.48(1.28 - 4.80)	

	10% Decline in FEV1 (Reached/Not = 125/56)		10% Decline in FVC (Reached/Not = 81/100)	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Adjusted for CLAD Phenotype, Early Onset, Treatment, and Transplant Era				
PFT Decline	2.83(1.36 - 5.89)	0.005	2.39 (1.40 - 4.08)	0.001
Adjusted for Other PFT Measure				
PFT Decline	2.16(1.00 - 4.68)	0.051	2.10(1.19 - 3.71)	0.010
Adjusted for Other PFT Measure, CLAD Phenotype, Early Onset, Treatment, and Transplant Era				
PFT Decline	2.06(0.93 - 4.54)	0.074	1.87(1.05 - 3.33)	0.034

* Follow-up censored at 18 months; follow-up landmarked at 6 months.

[†] Post-baseline PFT measures defined as minimum observe value in window; percent -drop = 100*[(post-baseline PFT –baseline PFT)/baseline PFT]; decline defined as percent-drop – cutoff level.

[‡] CLAD Phenotypes: RCLAD = restrictive CLAD and BOS = bronchiolitis obliterans syndrome.

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

// Early onset CLAD was defined according to prior literature as the onset of CLAD within two years of transplantation.

** Treatment defined as any treatment with Alemtuzumab or Anti-thymoglobulin within 6 months of CLAD diagnosis.

*** Transplant era defined as date of transplantation occurring prior to or on or after 1/1/2005.

--- Indicates regression coefficients were not estimable due to insufficient sample size in some group combinations.

HR = hazard ratio; CI = confidence interval.