OPEN

Health-related Quality of Life and Exercise Capacity in Double Lung Transplant Recipients With Baseline Lung Allograft Dysfunction

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Background. Baseline lung allograft dysfunction (BLAD) after lung transplant is associated with an increased risk of dying, but the association with health-related quality of life (HRQL) and exercise capacity is not known. We hypothesized that BLAD would be associated with reduced HRQL and 6-min walk distance (6MWD) at 1 y post–lung transplant. **Methods.** We analyzed patients who underwent lung transplants in our program from 2004 to 2018 who completed 1-y 36-item Short Form (SF-36) questionnaire and 6MWD testing. We secondarily analyzed the Beck Depression Inventory and Borg dyspnea scores in patients using the available data. We defined BLAD as a failure of both forced expiratory volume in 1 s and forced vital capacity to reach ≥80% predicted of a healthy reference population's lung function on 2 consecutive tests ≥3 wk apart at any time point posttransplant. We tested the relationship between BLAD status and SF-36 physical component summaries and 6MWD using least squares regression, adjusting for age at transplant, sex at birth, and primary lung disease. **Results.** Two hundred sixty-four patients were included, 96 (36%) of whom met the criteria for BLAD. Patients with interstitial lung disease as an indication for transplant and those who received older, female, and heavy smoking donors were at increased risk of BLAD. SF-36 physical component summary scores were lower in patients with BLAD (75 versus 85; $P = 0.0076$), as were 6MWD values (528 versus 572 m; $P = 0.0053$). BLAD was associated with lower SF-36 scores ($P = 0.0025$) and 6MWD ($P = 0.0008$) in adjusted regression models at 1 y posttransplant. We did not observe differences in Beck Depression Inventory or Borg scores. **Conclusions.** BLAD was associated with reduced HRQL and 6MWD scores at 1 y posttransplant in adjusted models. This suggests that poor posttransplant lung function could contribute to lower HRQL and exercise capacity in lung recipients and is worthy of further exploration in terms of causes, prevention, and treatment.

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The goal of lung transplantation is to restore normal lung function and, in doing so, improve the survival and quality of life of patients having end-stage lung disease. However, in up to 40% of patients, lung function does not reach normal levels, compared with the general population free from lung disease.[1] We previously described this condition as baseline lung allograft dysfunction (BLAD) and demonstrated its association with reduced survival after transplant, and these findings have subsequently been replicated in other single-center and multicenter studies, although definitions and assessment time points have varied.[2-4] It is likely that BLAD constitutes a final common physiologic state of multiple potential insults to the respiratory apparatus, including the lung parenchyma and airways, the diaphragms, or potentially just the physical state of the patient.[5] Despite these findings, the association between BLAD and health-related quality of life (HRQL) and physical functioning after lung transplantation remains unknown.

HRQL is an important outcome focusing on patients' lived experiences and the effect of symptoms on day-to-day life. These measures are often applied to patients with advanced lung disease, and in lung transplant candidates and recipients in particular, to understand their perceived quality of life at multiple time points pre- and posttransplant.[6-8] Lung transplant recipients have been shown to enjoy a significant quality of life benefit compared with their pretransplant baseline.[9-11] However, this benefit is mitigated or eliminated altogether in patients who develop posttransplant complications, such as

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primary graft dysfunction (PGD) or chronic lung allograft dysfunction (CLAD).[12,13] Similarly, improving exercise capacity is an important goal with lung transplant, and the 6MWD can be used in lung transplant patients as an indicator of exercise capacity.[14-16] 6MWD has been noted to be higher in double compared with single lung transplant recipients, suggesting it may have a relationship to baseline lung function.[17] Given this context, it is important to assess the association between BLAD and HRQL and exercise capacity.

The purpose of this study was to determine whether posttransplant BLAD is associated with a reduced HRQL and exercise capacity, as measured by SF-36 physical component summary (PCS) scores and 6MWD, compared with patients with normal lung function. We hypothesized BLAD would be associated with reduced HRQL and 6MWD in double lung transplant recipients.

PATIENTS AND METHODS

Patient Population

We reviewed all adult lung transplant recipients transplanted from January 1, 2004, to October 31, 2018, in the Edmonton lung transplant program. We stopped inclusion in October 2018 due to an electronic medical record transition, which resulted in a change in lung function reference equations and an interruption in questionnaire data collection. We excluded single lung, heart-lung, and lobar lung transplants to facilitate BLAD phenotyping, as our previous definition is only applicable to double lung transplant recipients to avoid confounding related to lower donated lung tissue volume. We excluded patients who had incomplete quality-of-life scores and 6-min walk distance (6MWD) test results at 1 y posttransplant. These are routinely measured at various time points in our program, but only in patients remaining in the Edmonton and Northern and Central Alberta health regions. Our program operates a hub-and-spoke model, performing transplants for patients across Western Canada (approximately 3.6 million km^2), including Northern British Columbia, the Northwest Territories, Southern Alberta, and all of Saskatchewan and Manitoba. Many of these patients return to their home programs for long-term follow-up by 3 mo posttransplant and while we continue to track them in our database in terms of survival, lung function, and some complications, they do not complete 1-y testing at our hospital. The results in this study focus on the sample population of 1-y survivors from Edmonton and Northern/Central Alberta. This study was approved by the health research ethics board of the University of Alberta (Pro00130721) and was conducted in compliance with the International Society for Heart and Lung Transplantation ethics statement.

BLAD Definition and Grades

Our main risk factor was BLAD. As per our previous definition, BLAD is the failure of both forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) to reach ≥80% predicted referent to normal population values in 2 consecutive spirometry tests >3 wk apart at any time point posttransplant. The reference equations in use over the study period were Crapo 81.[18] We graded BLAD based on the average of the best 2 FEV_1% predicted values: grade 0, ≥80% predicted; grade 1, <80% and ≥65% predicted; grade 2, <64% and ≥50% predicted; and grade 3, <50% predicted.[1]

Primary Endpoints: SF-36 PCS and 6MWD

Our primary interest was in HRQL as measured by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and exercise capacity as measured by 6MWD performance. The SF-36 is a generic HRQL questionnaire consisting of 8 dimensions: physical functioning, physical role limitations, bodily pain, general health perception, emotional role limitations, social functioning, energy/vitality, and mental health.[19] These 8 components all contribute to the PCS and mental component summary. For this study, we looked at the PCS, which scored out of 100, with a higher score indicating a better HRQL. The SF-36 PCS has been previously shown to be valid in lung transplant recipients.[7] A 4-point difference in the SF-36 is considered the minimal clinically important difference (MCID).[20] No respiratory-specific tools are tracked by our program, but the use of a generic tool such as SF-36 PCS has the advantage of contextualizing values with normal populations. We were also not able to use the lung transplant-specific tool, the Lung Transplant Quality of Life, as this was not published until 2019.[21]

The 6MWD test is a submaximal exercise test used as a clinical indicator of exercise capacity. The outcome of this test is to measure the maximum distance in meters patients can walk within a 6-min period. Patients are given standard encouragement and instruction. The MCID in 6MWD has typically been noted to be between 25 and 35 m in advanced lung diseases treated by transplant, including pulmonary fibrosis, pulmonary arterial hypertension, and chronic obstructive pulmonary disease.[22-24]

Both tests are administered before pretransplant physiotherapy, after pretransplant physiotherapy, and then posttransplant at 3 mo, 6 mo, 1 y, and annually until 5-y posttransplant in our program. Our pretransplant physiotherapy program consists of structured, daily therapy guided by physical and occupational therapists as per the best available evidence.[25] This totaled 6 wk in duration for the study, although it has been shortened to 4 wk in subsequent years to accommodate larger program volumes.

Secondary Endpoints: Beck Depression Inventory and Borg Dyspnea Scale

We also evaluate patients with the Beck Depression Inventory (second edition [BDI-II]) and the modified Borg category-ratio 10 (CR10) rating of perceived exertion (RPE) scores during their 6MWD testing at the time points indicated above. The BDI-II is a survey that quantifies depression symptoms, with increasing scores indicating worse severity of symptoms.[26] The MCID for the BDI-II has been cited at 5 points but may depend on baseline severity.[27,28] As well, we assess patients modified Borg CR10 RPE scores during their 6MWD tests, with increasing scores indicating worsening dyspnea from 0 to 10.[29] The MCID for the Borg RPE is a 1-point difference.[30]

Statistics

We presented continuous data using medians and interquartile ranges (IQRs) to facilitate similar treatment of normally and nonnormally distributed data. We compared the groups using Wilcoxon rank-sum tests. We compared dichotomous and categorical data using Fisher exact and Pearson chi-square tests, respectively. We modeled the association between BLAD status and the SF-36 PCS and 6MWD

using 2 separate least squares regression models, adjusting for age at transplant, sex at birth, and indication for transplant to account for the known associations of these covariates with posttransplant survival and to mirror the models from our previous work on the association between BLAD and survival.[1,31-33] We considered a 2-sided *P* value of 0.05 significant. All analyses were performed on JMP version 12 software (SAS Institute Inc, Cary, NC).

RESULTS

We performed 546 double lung transplants within the specified time frame of January 1, 2004, to October 31, 2018 (Figure 1). We excluded 282 patients due to incomplete SF-36 or 6MWD data due to patients either not surviving for 1 y or returning to their home programs as per our hub-and-spoke program design (see Patients and Methods section). This left a representative sample of 264 patients from the Edmonton and Northern/Central Alberta regions, 96 (36%) of whom were classified as having BLAD (Table 1). Recipients were majority male (68%), with a median body mass index of 25 kg/m^2 and having undergone transplant primarily for obstructive or interstitial lung disease. Cardiopulmonary bypass was the most common form of intraoperative support (although we note this has been largely replaced by extracorporeal membrane oxygenation in our program now), and interleukin 2 receptor antagonists were the main induction agent. Our program routinely uses triple-maintenance immunosuppression with tacrolimus, mycophenolic acid, and prednisone. The study cohort was similar to and representative of the overall cohort at our center over the study time frame (**Table S1, SDC,** http://links.lww.com/TXD/A731), with a similar proviso to most HRQL studies that this represents a cohort of conditional survivors.

Lung Function

The median FEV_1% predicted and FVC% predicted in the cohort were 92% and 92%, respectively (Table 1). BLAD was common in this cohort, with 36% of patients meeting our definition, which is similar to previous estimates. BLAD grade 1 was the most common, representing 78% of affected patients. BLAD was more common in patients who had undergone transplants for interstitial lung disease and in recipients of donors who were older, female, or heavy smokers (Table 1). A history of severe, grade 3 PGD at the 48- or 72-h time point was more common in patients with BLAD, as were longer durations of intubation, intensive care unit stay, and total hospital stay, as previously observed in our center and in other cohorts.[1,3] Note that the prevalence of BLAD in this study is likely not a true estimate of an overall posttransplant population at this center and elsewhere due to the restriction to 1-y survivors. As well, it is important to note that lung function parameters in patients with BLAD may actually overlap with the 80% threshold due to the requirement for both FEV_1 and FVC to be <80% by our definition,

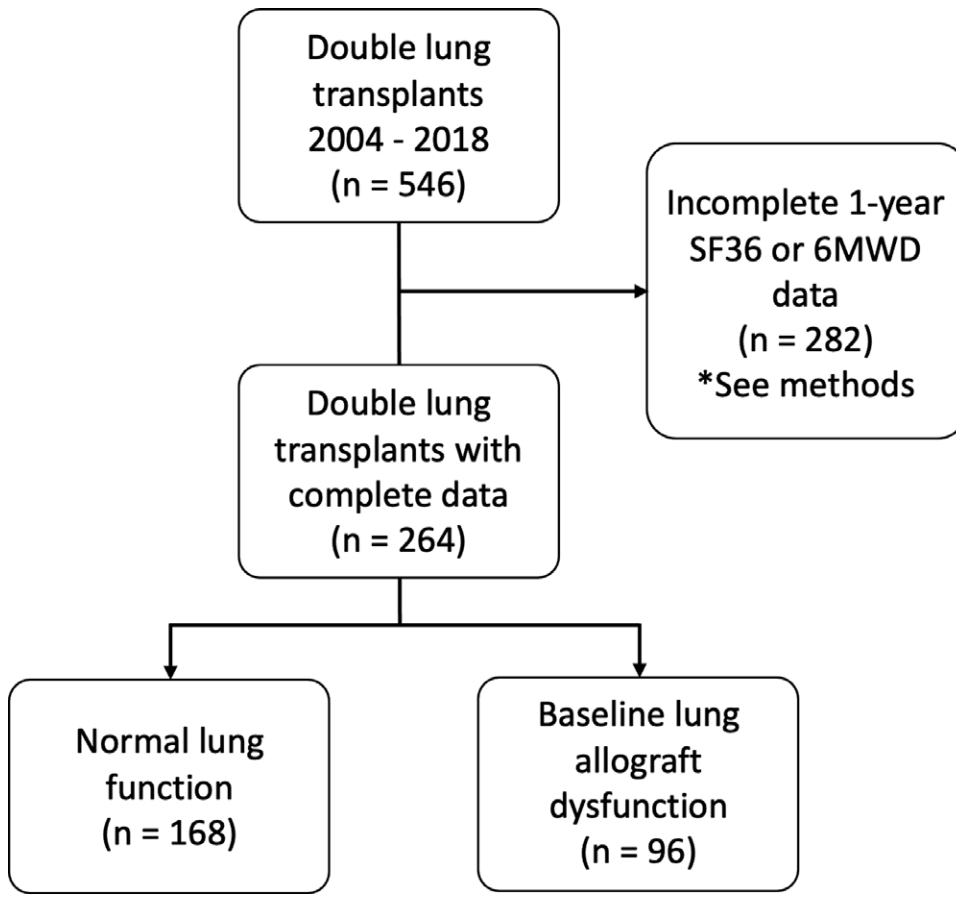

FIGURE 1. Study cohort. 6MWD, 6-min walk distance; SF-36, 36-item Short-Form questionnaire.

TABLE 1.

Baseline demographics of the cohort stratified by BLAD status

Characteristic	Overall (N = 264)	BLAD (N = 96)	Normal function (N = 168)	*P*
Recipient				
Age, y	57 (45–62)	57 (41–61)	57 (48–63)	0.2975
Female sex	84 (32)	24 (25)	72 (43)	0.0760
BMI, kg/m^2	25 (21–29)	26 (21–30)	24 (21–28)	0.1912
Diagnosis				0.0045
Bronchiectasis	40 (15)	15 (16)	25 (15)	
Interstitial lung disease	98 (37)	48 (50)	50 (30)	
Obstructive lung disease	115 (44)	29 (30)	86 (51)	
Pulmonary vascular disease	9 (3)	4 (4)	5 (3)	
Other	2 (1)	0 (0)	2 (1)	
Intraoperative support				0.8558
ECMO	25 (9)	8 (8)	17 (10)	
CPB	208 (79)	76 (79)	132 (79)	
None	28 (11)	11 (11)	17 (10)	
Induction therapy				0.5311
None	10 (4)	3 (3)	7 (4)	
IL-2RA	148 (56)	58 (60)	90 (53)	
ATG	106 (40)	35 (37)	71 (42)	
PGD grade at 48/72 h				0.0264
Grade 0	105 (40)	32 (33)	73 (44)	
Grade 1	81 (31)	26 (27)	55 (33)	
Grade 2	42 (16)	18 (19)	24 (14)	
Grade 3	35 (13)	20 (21)	15 (9)	
Intubation time, h, median (IQR)	53 (29–144)	104 (33–309)	46 (27–96)	<0.0001
Duration of ICU, d, median (IQR)	6 (4–12)	8 (5–20)	6 (4–9)	<0.0001
Duration of hospitalization, median (IQR)	23 (18–38)	31 (20–58)	21 (17–30)	<0.0001
Donor				
Age, y	37 (24–52)	44 (28–54)	34 (23–50)	0.0041
Female sex	126 (48)	58 (60)	68 (40)	0.0021
BMI, kg/m^2	25 (22–29)	26 (22–29)	25 (22–29)	0.3163
Smoking >20 pack-years	35 (13)	23 (24)	12 (7)	0.0002
Ischemic time, min	363 (262–442)	366 (285–450)	361 (253–427)	0.5290
Ethnicity				0.0671
White	202 (80)	79 (85)	123 (77)	
Black	6 (2)	0 (0)	6 (4)	
Asian	12 (5)	2 (2)	10 (6)	
Indigenous	14 (6)	6 (6)	8 (5)	
Other	19 (8)	6 (6)	13 (8)	
Lung function				
FEV_1, L	3.0 (2.5–3.6)	2.5 (2.0–3.3)	3.3 (2.9–4.4)	<0.0001
FEV_1% predicted	92 (79–107)	76 (66–82)	103 (92–115)	<0.0001
FVC, L	3.8 (3.0–4.4)	3.1 (2.6–3.8)	4.2 (3.3–4.7)	<0.0001
FVC% predicted	92 (79–103)	74 (66–83)	100 (91–109)	<0.0001
Time to baseline function, d	329 (102–711)	185 (78–475)	367 (134–814)	0.0031
BLAD grades				NA
1	–	75 (78)	–	
2	–	17 (18)	–	
3	–	3 (3)	–	

Counts are presented with percentages. Continuous values are expressed as medians with IQR (25th–75th).
ATG, antithymocyte globulin; BLAD, baseline lung allograft dysfunction; BMI, body mass index; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICU, intensive care unit; IL-2RA, interleukin 2 receptor antagonist; IQR, interquartile range; PGD, primary graft dysfunction.

meaning one or the other can be above the threshold in a given patient.

SF-36 PCS Scores and the Relationship With BLAD

HRQL scores, symptom scores, and 6MWD results are depicted in Table 2. Overall, SF-36 PCS results in the study population are depicted in Figure 2A. The median SF-36 PCS score was 80 (IQR, 60–95), similar to previous estimates (Figure 2A).[34] SF-36 PCS scores were lower in patients with BLAD than in those with normal lung function (75 [59–90] versus 85 [66–95]; $P = 0.0076$; Figure 3A). The same relationship was observed when analyzed by BLAD grade (Figure 4A),

TABLE 2.

Quality-of-life measures, 6MWD, and symptom scores at various time points, stratified by BLAD status

Measurement	Overall (N = 264)	BLAD (N = 96)	Normal function (N = 168)	*P*
SF-36 PCS				
Pre-Tx pre-physio, n = 243	19 (10–30)	20 (10–30)	18 (10–30)	0.7740
Pre-Tx post-physio, n = 211	20 (10–35)	20 (15–35)	23 (10–35)	0.9972
3-mo post-Tx, n = 227	70 (50–85)	70 (45–85)	75 (55–85)	0.1978
1-y post-Tx	80 (60–95)	75 (59–90)	85 (66–95)	0.0073
1-y benefit,[a] n = 243	60 (45–75)	58 (35–75)	63 (45–75)	0.0889
6MWD, m				
Pre-Tx pre-physio, n = 234	352 (258–428)	352 (233–413)	352 (264–440)	0.4897
Pre-Tx post-physio, n = 203	374 (277–475)	380 (286–449)	374 (264–484)	0.8174
3-mo post-Tx, n = 225	528 (444–599)	507 (438–591)	529 (452–602)	0.3528
1-y post-Tx	567 (480–653)	528 (437–616)	572 (504–660)	0.0065
1-y benefit,[a] n = 234	192 (78–286)	198 (92–305)	240 (132–308)	0.1927
Beck depression inventory				
Pre-Tx pre-physio, n = 230	12 (7–18)	13 (8–20)	12 (6–18)	0.2888
Pre-Tx post-physio, n = 202	9 (4–15)	9 (5–15)	9 (3–15)	0.3038
3-mo post-Tx, n = 199	5 (3–9)	4 (2–10)	5 (3–8)	0.6210
1-y post-Tx, n = 217	4 (2–8)	4 (1–8)	4 (2–8)	0.8154
1-y benefit,[a] n = 203	–2 (–4 to 0)	–8 (–12 to –4)	–7 (–13 to –2)	0.3196
Borg dyspnea scale				
Pre-Tx pre-physio, n = 230	7 (5–8)	6 (4–8)	7 (5–8)	0.3117
Pre-Tx post-physio, n = 201	6 (4–7)	6 (4–8)	6 (4–7)	0.5686
3-mo post-Tx, n = 213	4 (4–5)	4 (3–5)	4 (3–5)	0.2114
1-y post-Tx, n = 236	4 (2–6)	4 (3–7)	4 (2–5)	0.1725
1-y benefit,[a] n = 204	–2 (–5 to 0)	–1 (–5 to 1)	–3 (–5 to 0)	0.0558

Continuous values are expressed as medians with IQR (25th–75th).

[a]1-y value – Pre-Tx pre-physio value.

6MWD, 6-min walk distance; BLAD, baseline lung allograft dysfunction; IQR, interquartile range; PCS, physical component summary; physio, physiotherapy; SF-36, 36-item short form questionnaire; Tx, transplant.

with most of the reduction occurring in the more severely affected grade 3 group.

We used least squares regression to model the association between BLAD status and SF-36 PCS, adjusting for age at transplant, sex at birth, and primary diagnosis/indication for transplant. BLAD was associated with lower SF-36 PCS scores (β coefficient = 4.50 [SE = 1.47]; $P = 0.0025$) and had the strongest effect in the model via false discovery rate-corrected logworth contribution ($P = 0.0099$). To ensure the nonnormal distribution of the SF-36 data was not producing misleading results, we binned SF-36 values (0–19, 20–39, 40–59, 60–79, 80–100) and ran an ordinal regression model in which we found BLAD status was similarly associated with SF-36 scores ($P = 0.0027$).

6MWD Performance and the Relationship With BLAD

The median 6MWD in the cohort was 562 m (IQR, 484–639) similar to previous 1-y posttransplant estimates (Figure 2B).[35] 6MWD was lower in patients who developed BLAD than in patients who did not (528 m [IQR, 439–616] versus 572 m [IQR, 504–660]; $P = 0.0053$; Figure 3B). The same relationship held true when analyzed by BLAD grade (Figure 4B).

BLAD status was also associated with lower 6MWD scores in a least squares regression model adjusting for age at transplant, sex at birth, and indication for transplant (β coefficient = 30 [SE = 9]; $P = 0.0008$) and had the second strongest effect in the model via false discovery rate-corrected logworth contribution ($P = 0.0012$), with the most important effect being sex consistent with known association with 6MWD.[36]

SF-36 PCS and 6MWD Transplant Benefit and the Relationship With BLAD

We also assessed whether the 1-y HRQL and 6MWD transplant benefit—that is, the difference between 1-y values and pretransplant values before pretransplant physiotherapy—differed by BLAD status (Table 2). SF-36 transplant benefit was numerically but not statistically lower in patients with BLAD versus normal function (50 [35–70] versus 60 [39–70]; $P = 0.0889$), and similar results were observed for the 6MWD transplant benefit (198 m [IQR, 92–305] versus 240 m [IQR, 132–308]; $P = 0.1927$). The same was true of measuring transplant benefits compared with the pretransplant post-physiotherapy values.

BDI and Modified Borg CR10 RPE Dyspnea Scale

Finally, we analyzed the BDI-II scores, which quantifies depressive symptoms, and the Borg dyspnea scale, which quantifies breathlessness, although we acknowledge complete data on these elements was not a requirement for study inclusion (Table 2). BDI-II scores at 1 y posttransplant were not different in patients with BLAD compared with those with normal function (4 [IQR, 1.4–8] versus 4 [IQR, 2–8]; $P = 0.9448$, n = 218), and no difference was noted when analyzed by BLAD grade ($P = 0.6301$). Similarly, we noted no difference in Borg CR10 RPE scores (4 [IQR, 3–7] versus 4

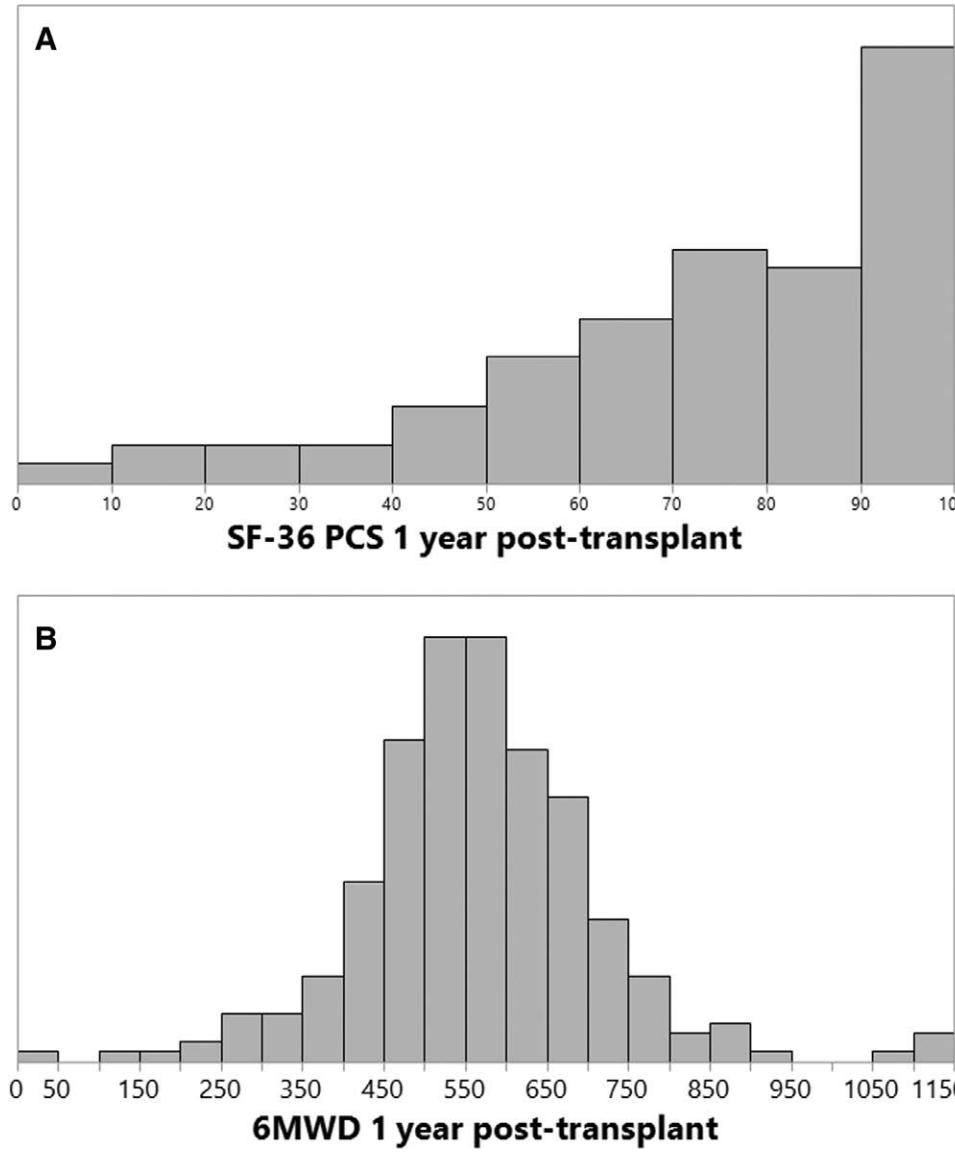

FIGURE 2. SF-36 PCS scores (A) and 6MWD scores (B) at 1 y posttransplant. 6MWD, 6-min walk distance; BLAD, baseline lung allograft dysfunction; PCS, physical component summary; SF-36, 36-item Short-Form questionnaire.

[IQR, 2–5]; $P = 0.1884$, n = 237), including when analyzed by BLAD grade ($P = 0.2856$).

DISCUSSION

We found BLAD was associated with lower HRQL and 6MWD scores in our cohort of double lung transplant recipients. These results suggest that BLAD may contribute to the patient-important outcomes of HRQL and exercise capacity, consistent with associations noted in other posttransplant complications such as PGD and CLAD.[12,37] This supports the concept of BLAD as an important posttransplant complication to identify, prevent, and treat.

The identified differences in HRQL and 6MWD are substantial and exceed previously described MCIDs in populations with the lung diseases that we are treating with transplant.[20,22-24] Lung transplantation has been shown to be associated with consistent and substantial improvements in HRQL, as measured by the SF-36 and other scores,[9-11] but BLAD may be functioning as a mediator—or at the very least a marker of a mediator—of that benefit. This is consistent with other serious lung function complications after transplant, such PGD and CLAD.[12,13] We note that a multicenter initiative in the United States has even been making efforts to develop a patient-centered definition of BLAD based not on lung function but on patient-reported outcomes.[38] 6MWD is also a recognized tool for measuring exercise capacity in lung transplant populations, and lung transplantation has been shown to produce meaningful exercise benefits.[14-16] Conditions that either cause, or are associated with, reductions in the exercise performance of lung transplant recipients are worth identifying, as improved exercise is a recognized patient-important outcome.[39] It should be noted that the exclusion of single, heart-lung, and lobar transplant recipients from this cohort means the study findings cannot be extrapolated to those groups. Single lung transplantation although has previously been associated with a reduced HRQL benefit compared with double lung

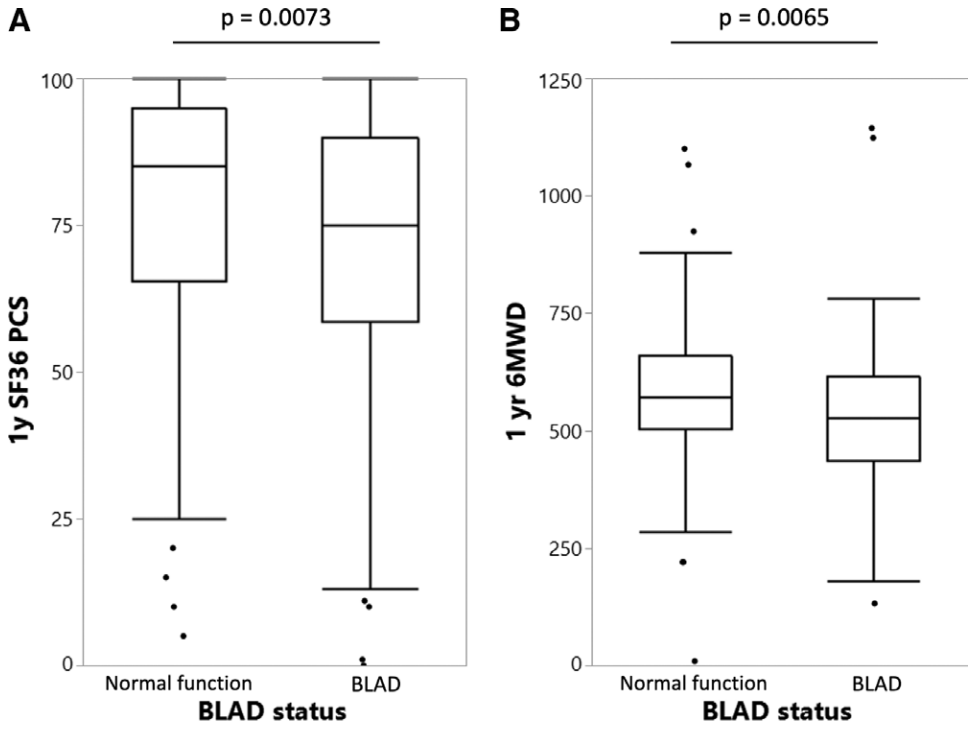

FIGURE 3. SF-36 PCS scores (A) and 6MWD scores (B) at 1 y posttransplant stratified by BLAD status. 6MWD, 6-min walk distance; BLAD, baseline lung allograft dysfunction; PCS, physical component summary; SF-36, 36-item Short-Form questionnaire.

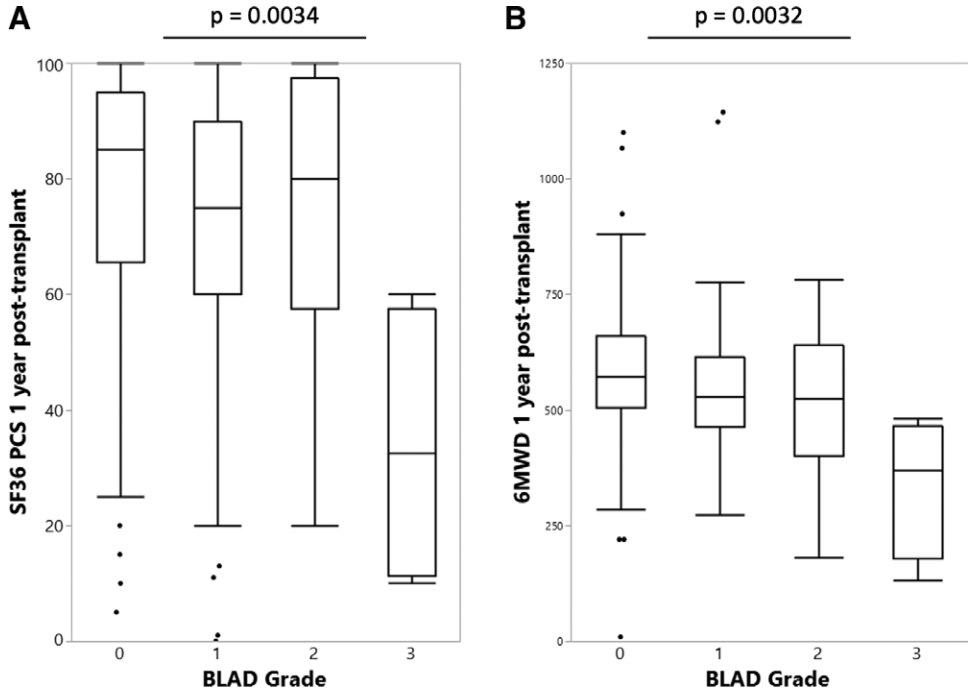

FIGURE 4. SF-36 PCS scores (A) and 6MWD scores (B) at 1 y posttransplant stratified by BLAD grade. 6MWD, 6-min walk distance; BLAD, baseline lung allograft dysfunction; PCS, physical component summary; SF-36, 36-item Short-Form questionnaire.

recipients, and it is plausible that the lower baseline function in that cohort (ie, spirometry <80% predicted) may partly account for that.[40]

It is also important to note that the presented associations do not necessarily demonstrate that BLAD *causes* the observed reductions in HRQL and exercise capacity. BLAD could potentially cause poor SF-36-PCS and 6MWD scores through poor exercise tolerance and pulmonary symptomatology, but alternative explanations are also plausible. Despite controlling for some important potential confounders, we cannot exclude the possibility that patients with BLAD have other comorbidities that contribute. Skeletal muscle strength, in particular, has been studied as a parameter that remains abnormal in posttransplant patients and one that does not

improve commensurate with lung function.[15] Recurrent and prolonged hospitalization over the first posttransplant year has prognostic implications and likely influences HRQL and exercise capacity as well.[41] Persistent inflammation—for instance, from infections—could potentially contribute. Other metabolic complications, such as renal failure, can also have serious implications for patient-important outcomes.[42] Finally, the long-term effects of critical illness are an important consideration in this context. PGD survivors have been shown to have an increased risk of BLAD, but the associated intensive care unit-acquired weakness can affect long-term physical functioning independent of respiratory function.[43]

The relationships among perioperative course, comorbidity, best achieved lung function, exercise capacity, and quality of life are likely to be complex in this patient cohort: comorbidity can affect HRQL and exercise, low lung function can increase the risk of complications, and accrued comorbidity, and comorbidity can in some instances affect lung function. CLAD is not easily diagnosable in the first posttransplant year, so it is difficult to estimate the degree to which it could contribute to observed differences in quality of life or exercise performance, but the contributions of episodes of acute lung allograft dysfunction to quality of life (and indeed to BLAD itself) certainly require further study. Analyses that attempt to tease apart the temporal sequence of posttransplant events in this population will need to be carefully done and ideally prospectively. For the time being, the study serves to establish the associations in our center and prompt further investigation.

The lack of difference in transplant benefit—the difference between 1-y and pretransplant values—both in SF-36 and 6MWD performance is notable, given the findings in the primary models. The lack of difference is not driven by different HRQL and 6MWD values at baseline, as these were similar (Table 2). Similarly, it does not appear to be driven by differences in indication for transplant, because the primary models were adjusted for this and because we did not note an association between indication for transplant and 1-y SF-36 PCS and 6MWD (data not shown). It is possible these comparisons are less robustly powered compared with the primary models due to missing data, and given a similar direction of effect, we suspect this may be the case.

The secondary comparisons of BDI and Borg CR10 RPE scores are also noteworthy. One-year Beck and Borg scores did not appear to differ significantly between patients with BLAD and normal function. The depression scores are potentially encouraging, as despite a negative association with quality of life and exercise capacity, this physiologic state does not appear to be associated with negative mental health scores. The similar Borg scores are also interesting, perhaps mainly that the Borg scores during 6MWD testing are actually more elevated than expected in the normal lung function group with a median value of 4, resulting in no detectable difference compared with patients with BLAD. This is consistent with previous observations of global noncardiopulmonary limitations to exercise after transplant, felt to relate to muscular limitations as sequelae of critical illness and medication toxicity, among other factors. Our data set does not clarify whether this known muscle dysfunction is more pronounced in patients with BLAD and whether it contributes to lower 6MWD scores without an increase in dyspnea but remains a thought-provoking future direction.

Finally, if BLAD is associated with reduced survival as well as reduced quality of life and exercise performance, it will be an important condition for developing preventative and therapeutic strategies for in the future. It is outside the scope of this work to postulate specifically what this could look like, and these developments will require more work on BLAD biology, the contributions of parenchymal and extraparenchymal contribution, and distinguishing cases with identifiable causes versus those without. However, it may be that the identification of persistently lower-than-normal lung function can prompt investigations to offer individualized, targeted therapies directed at potential causes in addition to more generalized supportive strategies such as prolonged physiotherapy. It may also be that some cases do not have therapeutic options—such as severely undersized patients—and in these situations, understanding BLAD and its contributions to lung transplant outcomes will simply help us to better prevent it through, for example, revisions to institutional size matching policies.

This study has limitations. First, the single-center design can introduce unwanted center-specific effects and would therefore benefit from replication in another center or ideally in a prospective multicenter cohort. However, we note that our cohort is similar to a general lung transplant cohort in other centers with similar volumes. Second, the requirement for complete SF-36 PCS and 6MWD data excluded a substantial number of patients, potentially introducing unwanted selection bias. These exclusions were overwhelmingly due to the nature of our hub-and-spoke program model, in which approximately half of our transplants are looked after by satellite programs closer to their home. However, we were reassured by the lack of substantial differences between the study cohort and the excluded 1-y survivors. Third, the lack of complete data on secondary elements such as the Beck and Borg CR10 RPE scores means that these findings are exploratory only. Fourth, it is important to remember that all quality-of-life studies (and many studies on BLAD and CLAD) contain an element of survivorship bias, as patients must survive long enough to complete quality-of-life scores (or produce lung function). Finally, subsequent to our initial publication defining BLAD, several other groups have published their experience using different definitions. Establishing an international consensus definition will be an important mission moving forward so we can mitigate different definitions as a source of variability in the presented associations and move forward with studying causes as well as prevention and treatment strategies.

BLAD was associated with lower HRQL and exercise testing scores at 1 y posttransplant compared with patients with normal lung function in this cohort of double lung transplant recipients. This supports the concept of BLAD as an important posttransplant complication. Future studies are needed to help identify how BLAD contributes to HRQL and exercise limitation, how to help prevent BLAD from occurring, and how to effectively intervene when it does, all with the goal of improving the quantity and quality of life for our lung transplant patients.

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