Possible baseline lung allograft dysfunction within the first year defines a high-risk and potentially reversible state after lung transplantation

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Possible BLAD, defined by the failure to reach normal FEV_1 and FVC>LLN during the first year, identifies a high-risk but potentially modifiable state, while achievement of normal baseline lung allograft function confers a strong survival benefit https://bit.ly/3QJCZES

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Abstract

Background Baseline lung allograft dysfunction (BLAD) has been associated with impaired long-term outcomes. However, BLAD within the first post-transplant year represents a potentially dynamic state. This is the first study evaluating a provisional Possible BLAD state, investigating risk factors and evolution to normal baseline lung function or confirmed BLAD.

Methods Possible BLAD was defined as failure to reach baseline forced expiratory volume in 1 s and forced vital capacity (FVC) ⩾lower limit of normal within the first post-transplant year. Association of Possible BLAD and BLAD with allograft failure was investigated using multivariate time-dependent Cox regression analysis.

Results Among lung allograft recipients in the Munich Lung Transplant cohort, Possible BLAD occurred in a substantial share of lung allograft recipients. Possible BLAD was independently associated with a markedly increased risk of allograft failure (HR 4.76, 95% CI 2.64–8.61). Patients who recovered from Possible BLAD to normal baseline lung function had similar survival compared to lung allograft recipients directly reaching normal baseline lung function. A four-item clinical score at timepoint of first spirometry predicted recovery from possible BLAD (area under the curve (AUC) 0.83 for double lung allograft recipients, AUC 0.88 for single lung allograft recipients).

Conclusion Possible BLAD is associated with a markedly increased risk of mortality. A share of patients with Possible BLAD may recover to normal baseline lung function, while others progress to BLAD. Possible BLAD characterisation improves early risk stratification and might provide further insight into modifiable mechanisms underlying impaired allograft performance.

Introduction

Lung transplantation represents an established last-line therapeutic option for patients with end-stage irreversible lung diseases. Despite substantial advances, long-term outcomes after lung transplantation remain limited [1]. A central determinant of long-term outcome after lung transplantation is the level of lung function achieved after the early post-transplant recovery phase [2].

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Baseline lung function after transplantation evolves dynamically, typically improving over the first months and often continuing to increase throughout the first post-transplant year [3]. As a result, a definitive baseline is frequently established only later, despite clinically relevant and potentially modifiable processes occurring predominantly during this early period and strongly influencing ultimate baseline lung function [4]. The term baseline lung allograft dysfunction (BLAD) has been introduced to describe a state of abnormally low peak lung function after transplant that is associated with markedly increased mortality [5–7]. However, impaired lung function early after transplantation is not uniformly irreversible. While some patients recover and ultimately reach a normal baseline, others remain persistently impaired, indicating that early abnormalities in baseline development represent a dynamic rather than a fixed condition [3]. As baseline lung function typically evolves over the first post-transplant year, a definitive classification can only be made later, although clinically relevant processes affecting baseline development occur much earlier.

In this context, the transplant community discusses an early, provisional stage of impaired baseline development during the first year after lung transplantation. Recognising abnormal baseline lung function within the first post-transplant year as a provisional phenotype, here referred to as Possible BLAD, defines a critical early window for risk stratification and potential intervention, with important implications for long-term outcomes after lung transplantation. We aimed to operationalise impaired early baseline lung function as a provisional phenotype as Possible BLAD and examined its association with mortality, subsequent recovery to normal baseline lung function, or persistence of BLAD in a large, single-centre cohort of lung transplant recipients. Furthermore, we aimed to systematically evaluate longitudinal baseline lung function trajectories, with a specific focus on abnormal baseline development within the first post-transplant year.

Materials and methods

Ethics

This study was approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich (approval number 21-0020). Informed consent requirements were waived due to the retrospective nature of the analysis.

Patient selection and study design

We retrospectively reviewed clinical characteristics and lung function trajectories of all adult patients receiving lung transplantation at the LMU University Hospital Munich, Germany between 1 January 2010 and 31 December 2018. Patients were followed up until death, re-transplantation or administrative censoring on 1 August 2024. Lung allograft recipients with too few pulmonary function testing data to calculate a baseline forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were excluded from the study.

Lung function measurements

Spirometry and lung volume measurements were performed using pulmonary function testing devices of Jäger, Würzburg, Germany, in accordance with European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines [8]. Routine pulmonary function tests were typically conducted at standardised intervals every 3 months and when clinically indicated. Baseline FEV_1 and FVC were established for each patient, analogously defined by the ISHLT 2019 chronic lung allograft dysfunction (CLAD) classification criterion, as the mean of the two best lung function measurements at least 3 weeks apart. No imputation of missing spirometric measurements was performed. Demographic characteristics were extracted from institutional electronic medical records.

Definition of BLAD, CLAD and spirometric obstruction

BLAD was defined as failure to reach a baseline FEV_1 and Baseline FVC $\geqslant$lower limit of normal (LLN) according to Global Lung Function Initiative (GLI) 2021 reference equations [9]. Possible BLAD was defined as BLAD within 3 to 12 months after lung transplantation within the first year. CLAD was defined according to the ISHLT 2019 consensus definition. Obstruction was defined as FEV_1/FVC<LLN according to the GLI 2021 reference equations.

Outcomes

The primary end-point was allograft survival, defined as time from transplantation to either death or lung re-transplantation, whichever occurred first.

Statistics

Lung function data are presented as median and range. Right-censored data were analysed using time-dependent Cox regression statistics. Variables changing over time such as BLAD status or spirometric obstruction were treated as time-dependent variables. Factors associated with recovery from Possible

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BLAD or BLAD were analysed using logistic regression statistics. Data analysis was performed with GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) and SPSS Statistics 31.0 (IBM Corp., Armonk, NY, USA) and with Python 3.10 and the scientific computing packages numpy (v1.22.3), pandas (v1.4.2), matplotlib (v3.5.2), seaborn (v0.11.2), lifelines (v0.27.0) and scipy (v1.8.0). Used statistical tests and models are indicated in the respective tables and figures.

Results

551 lung allograft recipients transplanted between 2010 and 2018 were screened and 333 double lung allograft (DLTX) recipients and 149 single lung allograft (SLTX) recipients included. 69 patients were excluded due to insufficient spirometry data to establish a baseline FEV_1 (supplementary figure S1).

Baseline characteristics of the study cohort are summarised in supplementary table S1.

Based on the BLAD classification framework (figure 1a), lung allograft recipients initially remain in an indeterminate state until a post-transplant baseline lung function is established. Once baseline FEV_1 and FVC measurements become available, patients are classified as having Normal baseline lung function if both values are ⩾LLN. Failure to reach these criteria within 3 to 12 months post-transplant results in classification as Possible BLAD. Persistence of impaired lung function beyond 1 year after transplantation leads to the designation of BLAD. Importantly, baseline lung function evolves dynamically, and patients classified as Possible BLAD or BLAD may still recover lung function to ⩾LLN, allowing reclassification as normal baseline lung allograft function. Representative longitudinal lung function trajectories illustrating these classification pathways are shown in figure 1b, demonstrating the heterogeneity of post-transplant lung function development, including early attainment of normal baseline function, delayed recovery after an initial Possible BLAD phase and sustained impairment progressing to BLAD without subsequent recovery.

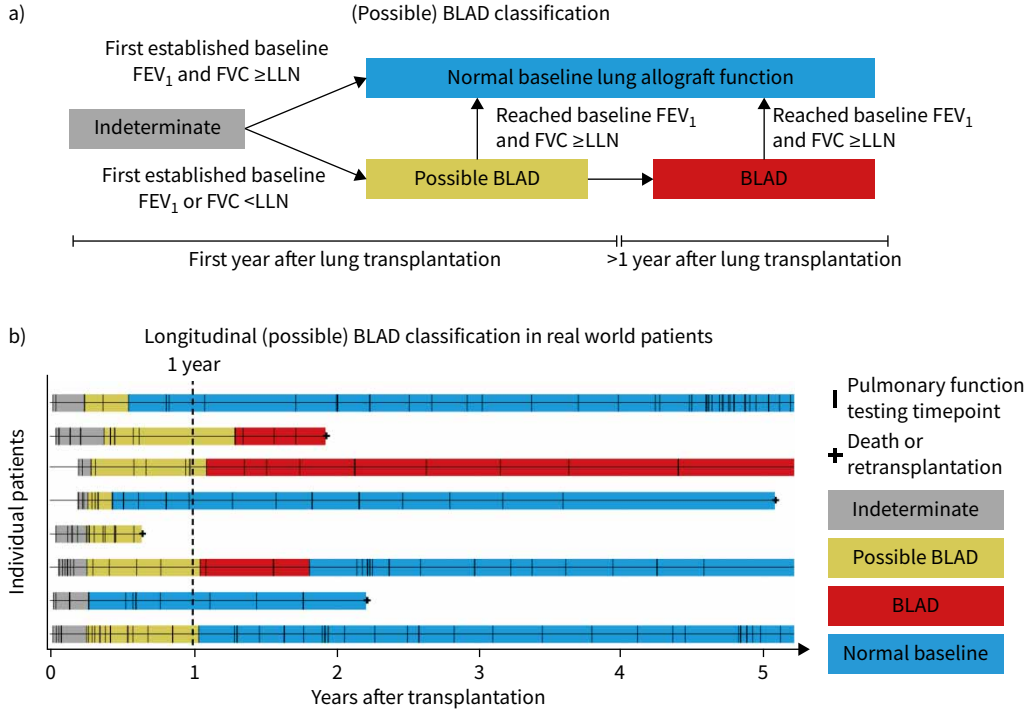


FIGURE 1 Scheme of (Possible) BLAD classification. a) After establishment of a first baseline lung function, baseline forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) ⩾ lower limit of normal (LLN) define normal baseline lung allograft function, while FEV_1 or FVC<LLN define Possible BLAD within the first year after transplantation. Until sufficient data are available to establish a baseline lung function, BLAD state remains indeterminate. Impairment persisting beyond 1 year after transplantation leads to classification as BLAD, whereas recovery to ⩾LLN leads to reclassification as normal. b) Representative longitudinal lung function trajectories illustrating transitions between classification states over time. Coloured bars indicate classified BLAD states, vertical ticks denote pulmonary function tests. BLAD: baseline lung allograft dysfunction.

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To further characterise these dynamics, transitions between BLAD states were analysed separately for SLTX and DLTX recipients (figure 2). Among SLTX recipients, only a small minority directly achieved normal baseline lung allograft function (22 out of 149), whereas most patients were initially classified as Possible BLAD (124 out of 149) and subsequently transitioned to confirmed BLAD. Recovery from Possible BLAD was uncommon (16 out of 124). In DLTX recipients, a substantial proportion directly achieved normal baseline lung allograft function (93 out of 333), while others initially fulfilled criteria for Possible BLAD (230 out of 333). Among these, a subset recovered to normal baseline lung function without progressing to BLAD (84 out of 230).

Depicting FEV_1 and FVC trajectories in DLTX and SLTX recipients, split by 1) directly achieving normal baseline lung function, 2) recovering from Possible BLAD to normal baseline lung function over time and 3) remaining in BLAD state showed that FEV_1 and FVC develop immensely within the first year after lung transplantation (figure 3). This effect was more pronounced in DLTX recipients.

We next evaluated the association between Possible BLAD and BLAD, and allograft failure (death or re-transplantation) using multivariable time-dependent Cox regression analysis (table 1). BLAD classification was modelled as a time-dependent covariate and adjusted for established risk factors, including transplant type, CLAD, airflow obstruction, diagnosis and recipient age. Mortality risk was already markedly elevated during the Possible BLAD state within the first post-transplant year (HR 4.76, 95% CI 2.64–8.61; p<0.001), even exceeding the risk observed in confirmed BLAD beyond 1 year (HR 1.53, 95% CI 1.12–2.10; p=0.008).

Given that patients may recover lung function after an initial Possible BLAD or BLAD state, we assessed the survival impact of achieving normal baseline lung allograft function (table 2). Both direct attainment of normal baseline lung function and recovery after prior impairment were associated with significantly lower mortality compared with remaining in the Possible BLAD or BLAD states. Direct establishment of normal baseline lung function was associated with reduced mortality (HR 0.57, 95% CI 0.40–0.82; p=0.002), as was recovery from prior Possible BLAD or BLAD (HR 0.50, 95% CI 0.35–0.71; p<0.001).

Given the predictive significance of recovering from BLAD, we next assessed factors associated with recovery from Possible BLAD or BLAD. Firstly, SLTX recipients who did not directly reach normal baseline lung allograft function (n=123 out of 149) were less likely to recover from BLAD (OR 0.21, 95% CI 0.121–0.365, p<0.001), compared to DLTX recipients who did not directly reach normal baseline lung allograft function (n=124 out of 333).

In DLTX recipients, recovery from Possible BLAD or BLAD was associated with higher first post-transplant FEV_1 z-score (multivariable OR 6.874, 95% CI 3.052–15.484; p<0.001), as did higher first FVC z-score (OR 3.102, 95% CI 1.389–6.927; p<0.006) (table 3). DLTX recipients with higher transplant age and COPD as transplant indication were more likely to recover compared to recipients with interstitial lung disease.

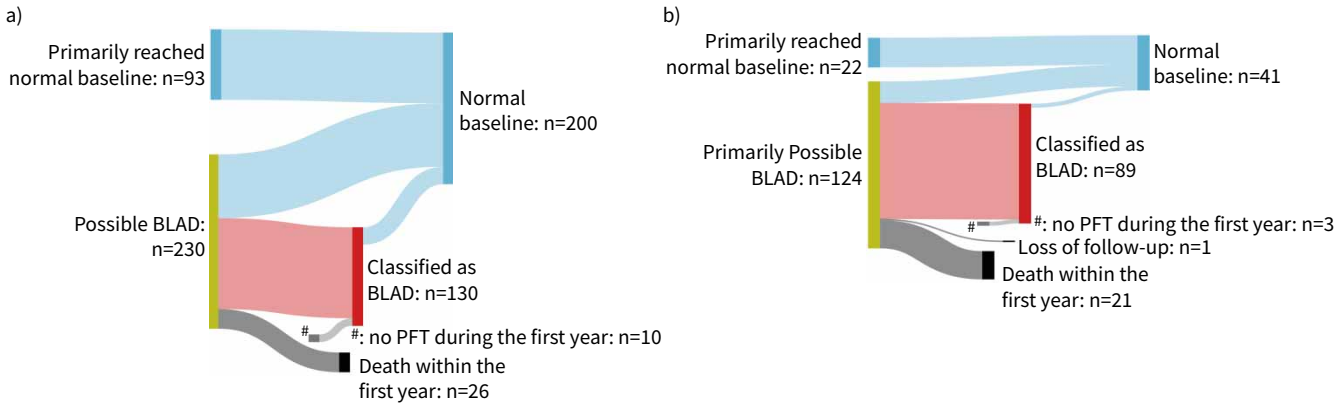


FIGURE 2 Alluvial diagram of transition of (Possible) BLAD states to normal baseline lung allograft function in a) double (DLTX) and b) single lung allograft (SLTX) recipients. Double lung recipients more frequently directly achieved normal baseline function or regained normal baseline function, whereas single lung recipients predominantly progressed to BLAD. BLAD: baseline lung allograft dysfunction; PFT: pulmonary function test.

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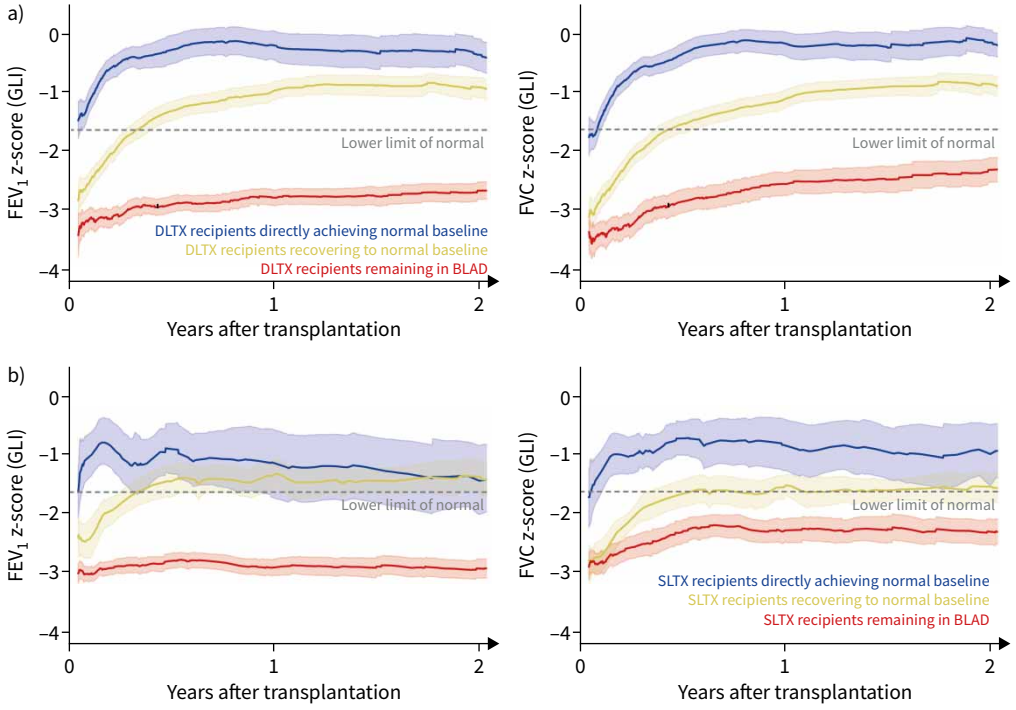


FIGURE 3 Forced expiratory volume in 1s (FEV_1) and forced vital capacity (FVC) trajectories in a) double (DLTX) and b) single lung allograft (SLTX) recipients stratified by BLAD (re-)classification. FEV_1 and FVC improvement occurred mainly within the first year and was more pronounced in DLTX. Longitudinal FEV_1 and FVC values are plotted as Global Lung Function Initiative (GLI)-based z-scores. BLAD: baseline lung allograft dysfunction.

In SLTX recipients, recovery was likewise associated with first spirometry performance. A first FEV_1 z-score higher than −2.5 independently predicted recovery (multivariable OR 6.879, 95% CI 1.149–41.183; p=0.035), as did a FVC z-score higher than −2.5 (multivariable OR 8.009, 95% CI: 1.303–49.234, p=0.025) (table 4). In contrast to DLTX recipients, COPD as transplant indication was independently associated with a markedly lower likelihood of recovery (OR 0.033, 95% CI 0.004–0.29; p=0.002).

To translate these predictors into a clinically applicable framework, we constructed simple recovery scores based on variables associated with recovery in the multivariable models. For DLTX recipients, the DLTX Possible BLAD score incorporated four variables assessed at the time of first spirometry 3 months after transplantation: underlying diagnosis of COPD or emphysema, transplant age ⩾58 years, first FEV_1 z-score> −2.5, and first FVC z-score > −2.5. Each variable contributed one point, resulting in a total score ranging from 0 to 4. The score demonstrated good discrimination for predicting recovery to normal baseline lung function (area under the curve (AUC) 0.83, figure 4a).

For SLTX recipients, a similar SLTX Possible BLAD score was derived. The score included underlying diagnosis other than COPD or emphysema, transplant age ⩾61 years, first FEV_1 z-score > −2.5, and first FVC z-score > −2.5. Each variable contributed one point, resulting in a total score ranging from 0 to 4. This score also showed good predictive performance for recovery (AUC 0.88, figure 4b).

In DLTX recipients, increasing score values were associated with a progressively higher probability of recovery, with the highest scores showing high positive predictive values, while low scores were associated with high negative predictive values, indicating persistent impairment (supplementary table S2). A similar pattern was observed in SLTX recipients, supporting the potential utility of these simple scores for early risk stratification among patients presenting with Possible BLAD (supplementary table S3).

Discussion

In this retrospective analysis of lung function trajectories of lung allograft recipients, we demonstrate that baseline lung function development is a dynamic process with major prognostic implications. We

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TABLE 1 Lung allograft survival analysis differentiating of the "Possible BLAD" and "BLAD" states by multivariate time-dependent Cox regression analysis

		Multivariable Cox regression analysis		
Variable/Category	**n**	**Hazard ratio**	**95% confidence interval**	**p-value**
Transplant				
Double lung transplantation	333		reference	
Single lung transplantation	**149**	**1.532**	**1.123–2.092**	**0.007**
(Possible) BLAD				
No BLAD	¶		reference	
Possible BLAD	¶	**4.762**	**2.636–8.605**	**<0.001**
BLAD	¶	**1.533**	**1.118–2.102**	**0.008**
CLAD				
No CLAD			reference	
CLAD		**3.258**	**2.42–4.385**	**<0.001**
Obstruction[#]				
FEV_1/FVC⩾LLN % predicted	¶		reference	
FEV_1/FVC<LLN % predicted	¶	1.013	0.752–1.365	0.931
Diagnosis				
Interstitial lung disease	238		reference	
Pulmonary vascular diseases	16	0.884	0.382–2.045	0.773
Cystic fibrosis/bronchiectasis	75	1.030	0.68–1.561	0.887
COPD/emphysema	128	1.216	0.889–1.663	0.222
Redo transplantation	17	1.591	0.899–2.817	0.111
Other	8	0.407	0.128–1.289	0.126
Transplant age				
38–50 years	115		reference	
<38 years	47	1.186	0.753–1.866	0.462
51–57 years	112	1.134	0.764–1.682	0.533
58–61 years	90	0.805	0.521–1.242	0.327
>61 years	118	1.037	0.716–1.501	0.848

Bold values indicate statistical significance. BLAD: baseline lung allograft dysfunction; CLAD: chronic lung allograft dysfunction; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal. [#]: modelled as time-dependent covariate. [¶]: modelled as time-dependent covariate; category membership may change over time, hence baseline absolute counts (n) are not applicable.

demonstrate the applicability of a Possible BLAD/BLAD classification framework, showing that failure to achieve normal baseline lung function is associated with substantially increased risk of allograft failure, already within the first post-transplant year. Baseline lung function is not immediately established after transplantation but evolves at least over the first year. This highlights that early post-transplant spirometry should not be interpreted as definitive, but rather as part of a longitudinal trajectory towards baseline lung allograft function.

Importantly, the Possible BLAD state within the first year emerged as a particularly high-risk phase. Patients classified as Possible BLAD exhibited a markedly increased mortality risk, exceeding even that observed in patients with BLAD beyond one year.

We have noted a particularly high hazard ratio for mortality in the Possible BLAD state. One possible explanation for the particularly high mortality associated with the Possible BLAD state is that early adverse events after transplantation may primarily manifest through impaired baseline development rather than through measurable lung function decline. During the first post-transplant year, a wide range of complications including severe infection, pleural complications, early alloimmune injury, primary graft dysfunction sequelae or systemic complications may impair physiological recovery of the graft [10–12]. Because a stable baseline has not yet been established, these events may not present as a decline from prior lung function but instead as a failure to achieve normal baseline lung function in the first place. Consequently, morbidity and mortality related to these early events may be captured within the Possible BLAD state. In contrast, once a normal baseline has been established, comparable injurious processes are more likely to present as a subsequent decline in lung function and therefore become classified as CLAD or FEV_1 declines of other causes rather than BLAD. This may partly explain why the relative mortality signal observed during the Possible BLAD phase appears particularly pronounced. Possible BLAD likely

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TABLE 2 Evaluation of lung allograft survival advantages of directly reaching normal baseline lung function compared with lung allograft recipients recovering from prior "Possible BLAD" or "BLAD" states by multivariate time-dependent Cox regression analysis

		Multivariable Cox regression analysis		
Variable/category	**n**	**Hazard ratio**	**95% confidence interval**	**p-value**
Transplant type				
Double lung transplantation	333		reference	
Single lung transplantation	**149**	**1.492**	**1.09–2.044**	**0.013**
(Possible) BLAD classification				
BLAD/Possible BLAD	¶		reference	
Normal lung allograft function, directly established	¶	**0.569**	**0.395–0.82**	**0.002**
Normal lung allograft function, recovered from (Possible) BLAD	¶	**0.499**	**0.351–0.708**	**<0.001**
CLAD				
No CLAD			reference	
CLAD		**3.192**	**2.363–4.311**	**<0.001**
Obstruction#				
FEV_1/FVC⩾LLN % predicted	¶		reference	
FEV_1/FVC<LLN % predicted	¶	0.986	0.727–1.337	0.927
Diagnosis				
Interstitial lung disease	238		reference	
Pulmonary vascular diseases	16	0.841	0.364–1.946	0.686
Cystic fibrosis/bronchiectasis	75	1.001	0.662–1.515	0.994
COPD/emphysema	128	1.224	0.893–1.677	0.209
Redo transplantation	17	1.505	0.851–2.663	0.160
Other	8	0.396	0.125–1.257	0.116
Transplant age				
38–50 years	115		reference	
<38 years	47	1.162	0.738–1.83	0.517
51–57 years	112	1.165	0.786–1.728	0.447
58–61 years	90	0.814	0.527–1.258	0.354
>61 years	118	1.038	0.718–1.501	0.841

Bold values indicate statistical significance. BLAD: baseline lung allograft dysfunction; CLAD: chronic lung allograft dysfunction; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal. #: modelled as time-dependent covariate. ¶: modelled as time-dependent covariate; category membership may change over time, hence baseline absolute counts (n) are not applicable.

represents a heterogeneous clinical state with multiple potential etiologic contributors. Early post-transplant factors such as primary graft dysfunction, acute cellular or antibody-mediated rejection, infections and differences in immunosuppressive regimens may contribute to impaired baseline lung function and may also influence subsequent recovery and survival. Disentangling these potentially reversible and irreversible causes represents an important focus for future research.

Previous studies have reported BLAD prevalences of around 30–40% among DLTX recipients, generally referring to the status at the end of follow-up [5, 6, 13, 14]. In our cohort, similar overall prevalences of BLAD were observed. As such, the high prevalence of Possible BLAD during the first year highlights the dynamic nature of baseline lung function recovery [3]. While many patients initially classified as Possible BLAD progressed to confirmed BLAD, a subset, particularly among DLTX recipients, recovered to normal baseline lung function. Notably, recovery of normal baseline lung function was associated with a substantial survival benefit, irrespective of whether it was achieved directly or after prior impairment. These findings underscore that impaired baseline lung function neither necessarily represents an irreversible state nor can be seen as a risk factor after lung function is recovered.

Clear differences between SLTX and DLTX recipients were observed: SLTX recipients rarely achieved normal baseline lung function directly and showed limited recovery once BLAD was established. In contrast, DLTX recipients more frequently achieved normal baseline lung function and demonstrated higher recovery rates from both Possible BLAD and BLAD. These differences likely reflect fundamental physiological and mechanical constraints inherent to single lung transplantation.

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TABLE 3 Factor associated with recovering from Possible BLAD or "BLAD" states by univariate and multivariate logistic regression in double lung allograft recipients that did not directly reach normal baseline lung allograft function (n=230)

		Univariable logistic regression analysis			Multivariable logistic regression analysis		
Variable/category	**n**	**Odds ratio**	**95% confidence interval**	**p-value**	**Odds ratio**	**95% confidence interval**	**p-value**
Sex							
Male	114		reference			reference	
Female	116	1.64	0.972–2.764	0.064	1.762	0.882–3.522	0.109
Diagnosis							
Interstitial lung disease	113		reference			reference	
Pulmonary vascular diseases	14	0.780	0.246–2.477	0.674	0.621	0.140–2.756	0.531
Cystic fibrosis/bronchiectasis	55	1.087	0.567–2.085	0.801	1.312	0.435–3.961	0.630
COPD/emphysema	**37**	**4.369**	**1.888–10.11**	**0.001**	**3.09**	**1.107–8.623**	**0.031**
Redo transplantation	8	0.201	0.024–1.685	0.139	0.68	0.056–8.227	0.762
Other	3	2.809	0.247–31.883	0.405	4.674	0.089–76.97	0.578
Transplant age							
38–50 years	75		reference			reference	
<38 years	59	0.943	0.467–1.905	0.870	1.582	0.533–4.691	0.409
51–57 years	39	1.507	0.69–3.291	0.304	2.005	0.702–5.724	0.194
58–61 years	**33**	**2.776**	**1.189–6.481**	**0.018**	**3.106**	**1.013–9.524**	**0.047**
>61 years	**24**	**3.172**	**1.205–8.349**	**0.019**	2.975	0.829–10.679	0.094
First spirometry							
First FEV_1 z-scor e ⩽ −2.5	109		reference			reference	
First FEV_1 z-score > −2.5	**121**	**14.061**	**7.361–26.858**	**<0.001**	**6.874**	**3.052–15.484**	**<0.001**
First FVC z-score ⩽ −2.5	114		reference			reference	
First FVC z-score > −2.5	**116**	**8.586**	**4.725–15.601**	**<0.001**	**3.102**	**1.389–6.927**	**0.006**
First FEV_1 (continuously)[#]	230	**9.914**	**5.539–17.745**	**<0.001**			
First FVC (continuously)[#]	230	**4.128**	**2.761–6.173**	**<0.001**			

Bold values indicate statistical significance. BLAD: baseline lung allograft dysfunction; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: by increment in z-score.

TABLE 4 Factor associated with recovering from Possible BLAD or "BLAD" states by univariate and multivariate logistic regression in single lung allograft recipients that did not directly reach normal baseline lung allograft function (n=123)

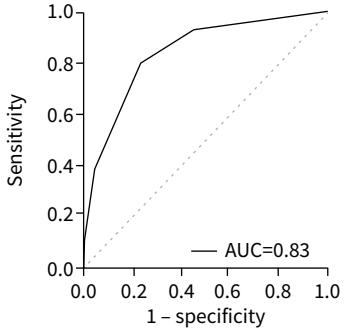
		Univariable logistic regression analysis			Multivariable logistic regression analysis		
Variable/category	**n**	**Odds ratio**	**95% confidence interval**	**p-value**	**Odds ratio**	**95% confidence interval**	**p-value**
Sex							
Male	66		reference			reference	
Female	57	0.816	0.304–2.194	0.687	0.691	0.178–2.681	0.594
Diagnosis							
Interstitial lung disease	58		reference			reference	
COPD/emphysema	**53**	**0.046**	**0.006–0.363**	**0.003**	**0.033**	**0.004–0.29**	**0.002**
Other	12	0.219	0.026–1.833	0.161	0.176	0.017–1.883	0.151
Transplant age							
⩽61 years	58		reference			reference	
>61 years	**66**	**2.800**	**0.94–8.337**	**0.064**	1.211	0.289–5.069	0.793
First spirometry, 3 months after transplantation							
First FEV_1 z-score ⩽ −2.5	75		reference			reference	
First FEV_1 z-score > −2.5	**48**	**20.016**	**4.359–91.905**	**<0.001**	**6.879**	**1.149–41.183**	**0.035**
First FVC z-score ⩽ −2.5	56		reference			reference	
First FVC z-score > −2.5	**67**	**9.18**	**2.018–41.756**	**0.004**	**8.009**	**1.303–49.234**	**0.025**
First FEV_1 (continuously)[#]	**123**	**32.305**	**6.709–155.547**	**<0.001**			
First FVC (continuously)[#]	**123**	**2.029**	**1.104–3.731**	**0.023**			

Bold values indicate statistical significance. BLAD: baseline lung allograft dysfunction; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: by increment in z-score.

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a)
Assessed at the timepoint of first spirometry 3 months after lung transplantation

Underlying diagnosis COPD/emphysema	+1
Transplant age ≥58 years	+1
First FEV_1 z-score >−2.5	+1
First FVC z-score >−2.5	+1
sum	



b)
Assessed at the timepoint of first spirometry 3 months after lung transplantation

Underlying diagnosis any other than COPD/emphysema	+1
Transplant age ≥61 years	+1
First FEV_1 z-score >−2.5	+1
First FVC z-score >−2.5	+1
sum	

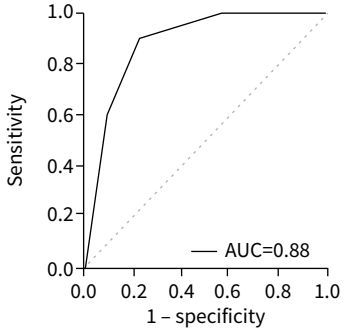


FIGURE 4 Score for prediction of recovery from Possible BLAD in double (DLTX) and single lung allograft (SLTX) recipients. Clinical risk scores to predict recovery to normal baseline lung function among patients presenting with Possible BLAD or BLAD at the time of first spirometry 3 months after transplantation. a) DLTX Possible BLAD score for double lung transplant recipients. One point is assigned for each of the following variables: underlying diagnosis COPD or emphysema, transplant age ⩾58 years, first forced expiratory volume in 1s (FEV_1) z-score > −2.5 and first forced vital capacity (FVC) z-score > −2.5. The total score ranges from 0 to 4. Receiver operating characteristic (ROC) analysis demonstrated good discrimination for recovery (area under the curve (AUC) 0.83). b) SLTX Possible BLAD score for single lung transplant recipients. One point is assigned for each of the following variables: underlying diagnosis other than COPD or emphysema, transplant age ⩾61 years, first FEV_1 z-score> −2.5 and first FVC z-score > −2.5. The total score ranges from 0 to 4. ROC analysis demonstrated good discrimination for recovery (AUC 0.88). BLAD: baseline lung allograft dysfunction.

This study has several limitations. Its retrospective, single-centre design limits external validity. Centre-specific surveillance management strategies, perioperative protocols and rehabilitation pathways, and local thresholds for diagnostic or therapeutic interventions practices may limit generalisability to other transplant programmes. At our centre, spirometry surveillance at 3-month intervals and routine rehabilitation were applied consistently during the study period, supporting internal comparability of longitudinal trajectories. Nevertheless, these standardised local practices may influence the incidence, timing and recovery patterns of Possible BLAD and may limit generalisability.

Furthermore, baseline establishment is inherently subject to interval censoring, as spirometric assessments were performed at predefined clinical intervals rather than continuously. Consequently, the exact timing of transition between classification states may have been misclassified. Also, missingness of pulmonary function tests might be informative due to severe complications prohibiting pulmonary function testing at certain timepoints. Patients with fewer or delayed spirometry measurements may have appeared to achieve normal baseline lung function later, potentially introducing timing bias in transition and survival analyses. Here, alternative approaches for assessing pulmonary function trajectories, including time-weighted averages or trajectory-based modelling, may provide complementary information. However, these methods are less directly aligned with current consensus definitions and may be less practical for routine clinical use.

Also notably, patients with insufficient spirometry data were excluded because Possible BLAD classification requires adequate pulmonary function follow-up to establish baseline FEV_1 and FVC. Consequently, very early post-transplant mortality is not captured by the framework of Possible BLAD.

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Still, recovery from Possible BLAD was clearly associated with early post-transplant lung function, particularly higher initial FEV_1. While this association may appear intuitive, it provides clinically relevant stratification, identifying a distinct high-risk subgroup for BLAD. Conversely, patients with moderate impairment retain meaningful recovery potential. Incorporating early spirometric performance into risk models could therefore enable enrichment of BLAD cohorts at an earlier stage and improve selection for interventional trials.

Based on our observations, we derived simple clinical scores to estimate the likelihood of recovery among patients presenting with Possible BLAD. These scores integrate readily available clinical variables assessed at the time of the first post-transplant spirometry, including early spirometric performance, transplant indication and recipient age. To do so, first FEV_1 and FVC z-scores were categorised with a clinically usable threshold of −2.5 that reflects clinically relevant impairment. Despite their simplicity, both scores demonstrated good discrimination for recovery in DLTX and SLTX recipients. Such tools may support early clinical risk stratification by identifying patients with a high probability of spontaneous recovery *versus* those at higher risk of persistent BLAD.

Patients with low scores may represent an enriched population for intensified monitoring or early interventional studies aimed at preserving or restoring baseline lung function. Since the score was derived and assessed in the same retrospective single-centre cohort without internal or external validation, its performance may be optimistic and affected by overfitting. Therefore, the scores should be interpreted cautiously. Therefore, the reported AUC values represent apparent performance and may be optimistic due to overfitting. Since the scores were developed using the full available cohort, *post hoc* cross-validation would not provide truly independent validation and could overstate model robustness.

Still, possible BLAD state represents a potential window for intervention, during which intensified surveillance, diagnostic evaluation, or targeted therapeutic strategies may be most effective. Rather than serving solely as a descriptive category, Possible BLAD may function as an early warning signal prompting proactive clinical management and inclusion criteria for interventional studies in BLAD.

Conclusions

In conclusion, our findings establish early post-transplant lung function development, particularly within the first year, as a critical determinant of long-term outcome after lung transplantation. Possible BLAD identifies a high-risk but potentially modifiable state, while achievement of normal baseline lung allograft function confers a strong survival benefit. These results support incorporating dynamic baseline lung function trajectories into post-transplant risk stratification and motivate future studies targeting early interventions in patients with Possible BLAD.

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Provenance: Submitted article, peer reviewed.

Ethics statement: This study was approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich (approval number 21-0020). Informed consent requirements were waived due to the retrospective nature of the analysis.

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