ISHLT CONSENSUS STATEMENT

Baseline Lung Allograft Dysfunction: Definition, Timing, and Implications for Outcomes—an ISHLT Consensus Document[1]

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KEYWORDS:
Baseline lung allograft dysfunction; Lung transplantation; Chronic lung allograft dysfunction; Survival

The leading cause of graft loss in lung transplant recipients is chronic lung allograft dysfunction (CLAD), where lung function, as measured by the forced expiratory volume in 1 s (FEV1), deteriorates from the established post-transplant baseline. There has been less emphasis on the actual value of the baseline lung function, specifically on whether it is subnormal and how severely subnormal it is. Low baseline lung function was originally studied as a potential contributor to outcomes almost 2 decades ago, but it is not captured by the current CLAD diagnostic system and

Abbreviations: CLAD, chronic lung allograft dysfunction; FEV1, forced expiratory volume in 1 second; BLAD, baseline lung allograft dysfunction; ISHLT, International Society for Heart and Lung Transplantation; LLN, lower limit of normal; GLI, Global Lung Function Initiative; DLCO, diffusion limitation for carbon monoxide; BLAD-iFEV, BLAD with an isolated low FEV1; BLAD-iFVC, BLAD with an isolated low FVC; BLAD-FEV1&FVC, BLAD with both low FEV1 and FVC; VATS, video-assisted thoracoscopic surgery; ALAD, acute lung allograft dysfunction; ECMO, extracorporeal membrane oxygenation; GERD, gastroesophageal reflux disease; HRCT, high resolution computed tomography; BAL, bronchoalveolar lavage; NT-proBNP, N-terminal B-type natriuretic peptide; SPPB, Short Physical Performance Battery; COPD, chronic obstructive pulmonary disease; HRQL, health-related quality of life; SF-36, Short Form Health Survey

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https://doi.org/10.1016/j.healun.2026.05.034

hence has not been a focus for clinical improvement or research. The central questions about low baseline function were whether it was independently associated with poorer survival, whether it has additive effects when it coexists with CLAD, and whether poor baseline function itself increases the risk of CLAD. In 2018, baseline lung allograft dysfunction (BLAD) was proposed as a construct and terminology to facilitate the study of these associations.[1] The specific definition and construct implementation, however, varied over subsequent publications. Some lung transplant experts have expressed concern about the ultimate utility of the BLAD construct and whether it could foster expectations among commissioners, insurers, and regulators about achieving normal post-transplant lung function. Concern has also been expressed that framing lung function as subnormal may unnecessarily unsettle patients, resulting in stigmatization potentially without individual detrimental consequences. The role of this consensus document then is to clearly define the utility of the construct, to standardize the definition for future clinical and research use, and to summarize what is known about its potential risk factors, causes, and association with outcomes.

METHODOLOGY

After an approved application to the International Society for Heart and Lung Transplantation (ISHLT) Standards & Guidelines Committee in June 2024, and a call for applications via ISHLT*connect*, a multidisciplinary group of 17 contributors was established in July 2024. A panel of 17 international experts was selected from 95 applicants, ensuring balanced representation in gender (9 women, 8 men), geography (4 continents), and career stage (4 early-career members). Selection prioritized candidates with relevant publications or experience in the field.

Delphi consensus process

A structured Delphi process was conducted to develop expert consensus on a series of statements through iterative rounds of surveys. Each expert was asked to rate their level of agreement with each statement using a 5-point Likert scale: "strongly agree" (+2), "agree" (+1), "neither agree nor disagree"(0), "disagree" (−1), and "strongly disagree" (−2). A response of “I do not feel qualified to answer this” was also available and these were excluded from the sum of votes for an individual statement. Only completed surveys with all statements graded were included in the analysis. All surveys were conducted anonymously, and, after each round, summarized results were shared with participants to inform the next stage of evaluation. Agreement was defined based on the proportion of “strongly agree” and “agree” among total votes or by the mean agreement score. To determine consensus for each statement, 1 of the 2 following conditions had to be met: at least 75% of responses had to indicate agreement, or the mean agreement score for the statement had to be equal to or greater than 1.00, with a standard deviation of less than 1.00.[2]

In Round 1 of the Delphi-Process, conducted in October 2024, experts evaluated 20 statements. A total of 320 individual adjudications of statements were submitted, accompanied by 95 qualitative comments. Sixty-five percent of the first round of responses indicated either agreement or strong agreement, and 4 of the statements met the formal criteria for consensus (appendix 2). Round 2 took place in January and February 2025, the latter with 2 clarified statements. Based on feedback from the first round, 20 revised statements were presented. This round yielded 302 adjudications and 92% of responses indicating either agreement or strong agreement. Eighteen statements met both the quantitative and distributional criteria for consensus. Thirty-five comments were provided in round 2. Round 3, held March to April 2025, focused on one clarified statement from the previous round. This final round included 16 adjudications. Results had an overall agreement rate of 81%. The mean agreement scores for this statement exceeded 1.00, and standard deviation was below the 1.00 threshold, thus confirming full consensus. Overall, the Delphi-Process achieved a 97% participation rate by working group members. In the final stage, the consensus statements were translated into 17 actionable recommendations, which are presented in this document.

Systematic literature search

An information specialist developed and executed a comprehensive search strategy to identify all relevant literature on baseline lung allograft dysfunction (appendix 2). The search included studies specifically focused on BLAD, as well as those addressing baseline lung function following lung transplantation in relation to any clinical

outcome. Only English-language publications involving human subjects were included, with no restrictions on publication date. The search was conducted across multiple databases, including MEDLINE, Web of Science, Embase, Google Scholar, and the Cochrane Database of Systematic Reviews (see Supplementary Material).

The initial search was carried out on October 22, 2024, and was repeated on September 12, 2025. Exclusion criteria comprised case reports, case series, non-human studies, reviews, and conference abstracts. Screening was managed using the Covidence online platform (www.covidence.org). All screening tasks were performed independently by 2 task force members, with discrepancies resolved by a third reviewer. The identification and selection process were documented using a PRISMA flow diagram (Figure 1), in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[3] Literature searches yielded 43 eligible references (appendix 2).

SECTION I. DEFINITION

BLAD refers to a state of objectively measurable, abnormally low peak lung function following transplantation. In the existing literature, BLAD has been defined in the context of spirometry, reflecting the summative effects of transplant type (bilateral, single, or lobar), allocation (size-, ethnicity-, sex-, or age-matching), underlying pulmonary disease (obstructive versus restrictive), abnormalities of the extra-pulmonary respiratory mechanics (diaphragmatic dysfunction, chest wall abnormalities), and damage to the donor/allograft tissue itself (Summary of key studies in Table 1). The current concept of BLAD is thus inclusive, representing peak baseline lung function relative to a recipient's normal predicted threshold. It reflects a physiologic state of poor function with multiple potential causes, rather than primary allograft process with a single underlying pathophysiology, and it is distinct from CLAD in this way. Recommendations proposed and endorsed by our working group are summarized in Table 2, along with the percent agreement from the most updated statements in the Delphi surveys.

Consensus definition of baseline lung allograft dysfunction (BLAD)

We define BLAD as failure to reach normal post-transplant lung function based on the recipient's predicted values, where the normal threshold is defined as a baseline FEV1 and baseline forced vital capacity (FVC) ≥ the lower limit of normal (LLN) or ≥ 80% predicted, by 1-year post-transplant and beyond. The baseline is calculated by averaging the 2 best/highest FEV1 measurements taken at least 3 weeks apart [aligning with the ISHLT FEV1 baseline for CLAD], and the FVC values from the same dates.[4] This definition implies that if *either* baseline FEV1 *or* baseline FVC are < LLN or 80% predicted, the patient meets the definition of BLAD, with subtypes being specified [isolated low FEV1, isolated low FVC, low FEV1, and FVC) and grading of severity.

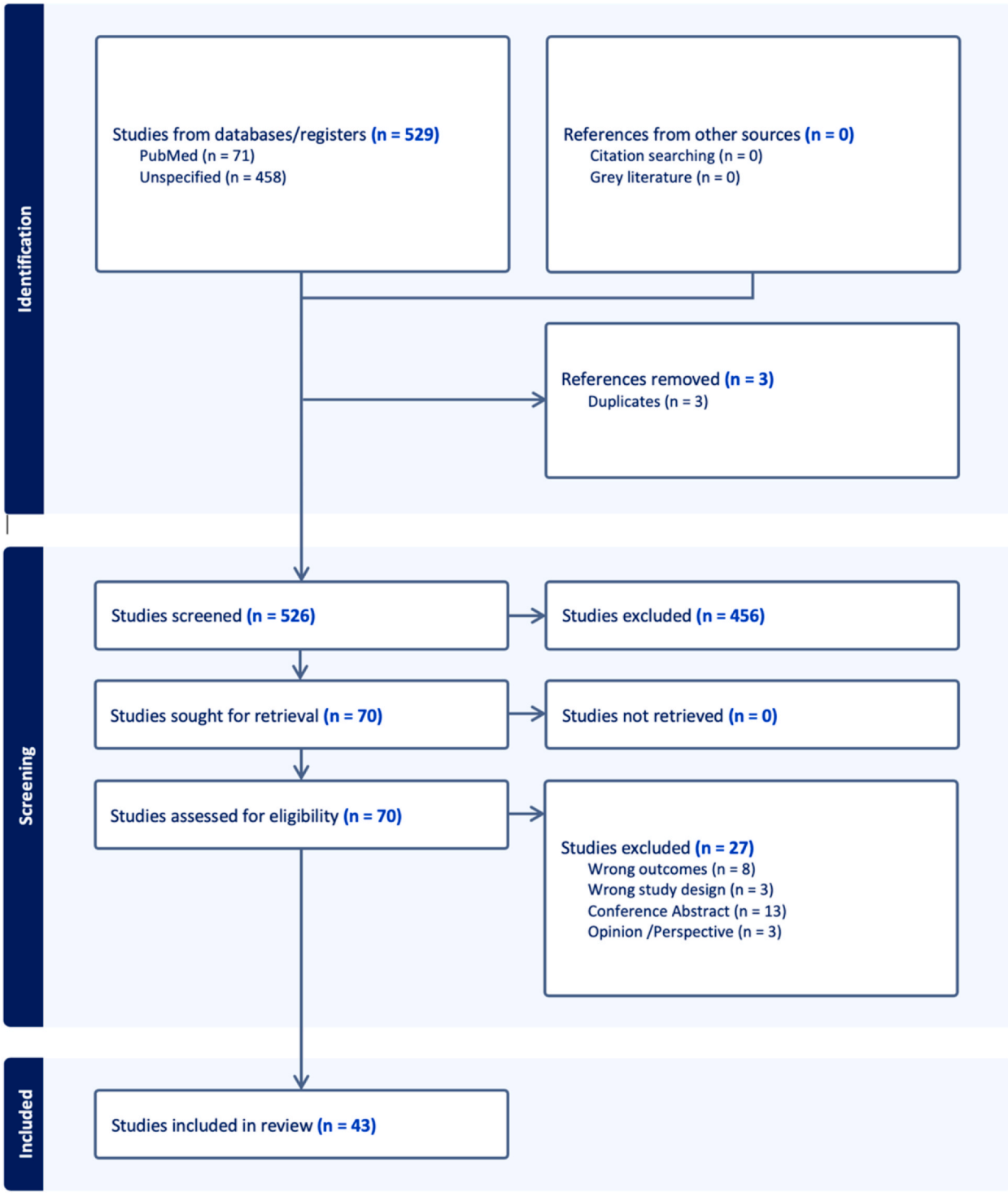
Definition of baseline lung function

Most studies have utilized spirometry, specifically the FEV1 and FVC, to define BLAD and used reference values from the normal population. Some studies have defined baseline function as 2 consecutive FEV1 values, which differs from the ISHLT CLAD baseline definition which uses the average of the 2 highest FEV1 values separated by at least 3 weeks, regardless of whether they are consecutive (Table 1).[4] Utilizing the same method as calculating the ISHLT CLAD baseline simplifies implementation by eliminating the need for separate BLAD and CLAD baseline values. Additionally, the CLAD consensus documents have established that the baseline FVC values should correspond with the baseline FEV1 measurements on the same test. Moving forward, the BLAD baseline will be aligned with the 2019 CLAD consensus document and precedents for consistency and ease of application. The average of the 2 measurements must exceed the predicted threshold, not the individual values.

Reference values to define normal lung function

Three factors are important to consider for BLAD designation with respect to a patient's reference values as follows: 1) the choice of reference equations; 2) the selection of the normal threshold; and 3) whether donor or recipient values should be used.

Figure 1 PRISMA diagram depicting the literature search strategy.



First, the choice of reference equations used to calculate predicted normal values could potentially influence the classification of post-transplant lung function as normal or subnormal. Various reference equations have been used in the published literature.[1,5] The Global Lung Function Initiative (GLI) equations are based on the largest cohort of healthy individuals (n = 97,759) with various ethnicities and apply to an age group of 3 to 95 years.[6] More

Table 1 Studies of BLAD and Other Low Baseline Function Constructs: Definitions, Prevalence, and Study Characteristics

Authors	Country	Single vs. multicenter	Bilateral, n	Unilateral, n	Reference values	Definition of Baseline	Definition of BLAD	BLAD Prevalence %
Burton et al. 2007[10]	Denmark	Single	123*	225*	Quartiles of a LTx cohort	ISHLT CLAD baseline	FEV1 lowest quartile (< 1.9-2.3L)	25%
Liu et al. 2018[1]	Canada	Single	178	-	Crapo 1981	2 consecutive	FEV1 or FVC < 80 % predicted	42%
Mohanka et al. 2020[17]	US	Single	157	-	Not reported	average of 2 highest in first year	FVC < 80% predicted,	49%
Paraskeva et al. 2021[5]	Australia	Single	217**	-	Hankinson 1991	ISHLT baseline	At 1 year: FEV1 or FVC < 80 %	49% (36% after 1 year)
Li et al. 2021[18]	Canada	Single	446	-	Crapo 1981	2 consecutive	FEV1 or FVC < 80 % predicted	40%
Darley et al. 2022[15]	Canada	Single	1259	-	Quanjer 2012 Stanojevic 2017	maximum value	Maximum DLCO < 75 % predicted	40%
Darley et al. 2023[11]	Australia	Single	237	16	Quanjer 2012 Oostveen 2013	2 consecutive	FEV1 or FVC < 80 % predicted	35%
Gottlieb et al. 2023[19]	Germany	Single	1170	-	Quanjer 1993	ISHLT baseline	FEV1 and FVC < 80 % predicted,	17%
Keller et al. 2024[12]	US	Multi	172	-	Not reported	2 consecutive	FEV1 or FVC < 80 % predicted	40% (16% obstructive)
Gerckens et al. 2024[20]	Germany	Single	-	141	Not reported	Not reported.	FEV1 or FVC < 60 % predicted	43%
Yamaguchi et al. 2024[14]	Japan	Single	38	-	Japanese Respiratory Society 2023	2 consecutive	FEV1 or FVC < 80 % predicted	55%
Choi et al. 2024[21]	Canada	Single	82	-	Gutierrez 2004	ISHLT baseline	FEV1 < 80% predicted	12%

BLAD, baseline lung allograft dysfunction; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ISHLT, international Society of Heart and Lung Transplantation; DLCO, Diffusion Capacity of the Lungs for Carbon Monoxide; LTx, lung transplantation

*3-month survivors

**1-year survivors

recently, race-neutral GLI reference equations have been introduced.[7] The GLI reference values have already been widely adopted in most lung transplantation centers worldwide; however, the number of centers using the lower limit of normal could still be expanded.[8] Most modern lung function interpretations favor using these equations, which provide a predicted normal value, a percent predicted, and a lower limit of normal.[9] Only one study has proposed nomograms of baseline FEV1 specifically after lung transplantation, either single or bilateral, based on a single-center analysis from which percentiles were derived.[10] All other studies have relied on reference values from various normal populations; in some cases, the sources of these reference values were not specified. For these reasons, our group favors the use of the GLI race-neutral equations for reference values.

Second, the normal threshold must be specified. Most published studies of BLAD have utilized a threshold of ≥ 80% predicted for defining FEV1 and FVC as normal.[1,5,11,12] Although using percent-predicted thresholds has been common practice, it can lead to misclassification—especially in older patients.[13] Current evidence indicates that using the lower limit of normal (LLN), as defined by the GLI, provides a more accurate and preferred method

Table 2 Consensus-Based Delphi Recommendations for Defining BLAD

#	Recommendation	% agreement
1	BLAD is a state of abnormally low baseline lung function after lung transplant.	100
2	The proposed definition of BLAD should apply to all lung transplant recipients, including adult and pediatric recipients of single, lobar, or size-mismatched organs.	88
3	The baseline used for BLAD designation is the same as the ISHLT baseline for CLAD diagnosis, i.e., the average of the 2 highest post-operative FEV1 values separated by a minimum of 3 weeks, and the corresponding FVC values obtained at the same time as the baseline FEV1 measurements.	88
4	BLAD designation should be based on **recipient** LLN (GLI reference values), where possible, but can be based on <80%-predicted if LLN values are not available. A single approach should be selected and clarified for a given population or analysis.	100
5	The BLAD definition should be based on spirometry.	100
6	"Suspected BLAD" can be diagnosed in the absence of spirometry if there is convincing evidence of significantly impaired baseline lung function such as need for chronic ventilation or supplemental oxygen.	94
7	BLAD is the failure of the baseline FEV1 **or** baseline FVC **or** BOTH to reach normal thresholds. BLAD can be sub-grouped as follows: BLAD-isolated FEV1 [BLAD-iFEV1]; BLAD-isolated FVC [BLAD-iFVC]; and BLAD-FEV1&FVC.	81
	Baseline FVC ≥ LLN / **Baseline FVC < LLN**	
	Baseline FEV1 ≥ LLN: Normal/No BLAD / **BLAD-iFVC**	
	Baseline FEV1 < LLN: **BLAD-iFEV1** / **BLAD-FEV1&FVC**	
8	Baseline lung function is reached at the time of the first of the 2 FEV1 measurements used for baseline calculation.	100
9	BLAD is best assessed at 1-year post-transplant and beyond.	100
10	A "possible BLAD" diagnosis can be assigned between 3-months and 1-year post-transplant.	100
11	BLAD assessment should be performed uniformly for all patients in a research study.	100
13	Whether and how BLAD should be adjusted for recipient-donor size mismatch should be a focus of future studies of BLAD.	100
14	BLAD can be phenotyped into obstructive and non-obstructive using the FEV1/FVC ratio (obstructive phenotype defined as FEV1/FVC ratio <LLN or < 0.7 if LLN is not available).	80
15	Grading of BLAD should be based on the FEV1%-predicted and align numerically with CLAD grade cutoffs:	94
	BLAD grade / **Spirometric criteria**	
	Normal/No BLAD: FEV1 **and** FVC ≥ LLN predicted	
	BLAD (any grade): FEV1 **or** FVC **or** both < LLN	
	BLAD grade 1, mild: FEV1 ≥ 65 predicted*	
	BLAD grade 2, moderate: FEV1 ≥ 50% < 65% predicted	
	BLAD grade 3, severe: FEV1 < 50% predicted	

BLAD, baseline lung allograft dysfunction; CLAD, chronic lung allograft dysfunction; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ISHLT, international Society of Heart and Lung Transplantation; LLN, lower limit of normal; GLI, Global Lung Initiative

*Patients with BLAD-iFVC may have an FEV1 > 80% predicted.

for distinguishing between normal and subnormal results compared to the fixed 80% predicted threshold.[9] Consequently, the consensus working group favors the use of LLN primarily for the diagnosis of BLAD. However, recognizing that LLN values may not always be feasible for certain laboratories or historical cohorts, the use of 80%-predicted thresholds is acceptable when LLN values are unavailable.

Third, a key consideration in defining normal reference values is whether to base them on the recipient or the donor. A central goal of lung transplantation is to optimize lung function for a given recipient, through appropriate donor selection, allocation, and minimization of complications. While donor physiology does play a role, post-transplant recipient lung function, as a percentage of what would be predicted for this recipient, was shown to be a determinant of both short- and long-term outcomes following transplantation (see Table 1). Therefore, we recommend that spirometric values should be assessed in reference to recipient anthropometrics.

With the use of LLN according to GLI reference values is most robust, using the LLN (or 80% if LLN is not available) may not currently represent the perfect cut-off, but it is the most objective and universally available. For this reason, the working group chose to adopt this cut-off for the present first consensus document on this definition. Future studies may provide new insights.

Tests to define normal lung function

Almost all studies have utilized spirometry, specifically the FEV1 and FVC, to define BLAD[1,5,10–12,14] (Table 1). One study evaluated diffusing capacity of the lungs for carbon monoxide (DLCO)[15]—while 2 studies evaluated oscillometry.[11,16] Although lung function can be assessed through various modalities, including spirometry, lung volumes, gas exchange, and other methods, our consensus group advocates for a definition using spirometry alone to facilitate the simplest, most practical solution for widespread implementation and one that is analogous to CLAD diagnosis. Ideally, all lung transplant patients should also undergo full pulmonary function testing, including static lung volumes, however we opted for spirometry as the basis of the definition because it is in routine use worldwide in all centers.

In cases where spirometry is not feasible, but where there is clear evidence of post-transplant lung dysfunction—such as chronic respiratory failure requiring either supplemental oxygen or mechanical ventilation—the term "suspected BLAD" is proposed. This label indicates clinical suspicion of poor baseline function, while acknowledging that it remains unconfirmed without spirometry or before a baseline is available.

Subtypes of BLAD based on spirometry

Most published papers on BLAD to date have designated BLAD when either baseline FEV1 or baseline FVC or both are low (Table 1).[1,5,12,14,20] We note that the exact definitions of the FEV1 and FVC baselines were different between these studies and also different from the proposed definition of baseline in this document. Reported prevalence rates of BLAD in prior studies ranged from approximately 35% to 55%, indicating that a substantial proportion of patients after lung transplantation do not achieve normal values measured by spirometry for FEV1 or FVC. One study designated BLAD when both baseline FEV1 and baseline FVC were low, rather than either/or,[19] resulting in a lower prevalence of BLAD (< 30%). Other studies that defined BLAD solely on the basis of FEV1 reported an intermediate prevalence of 30% to 40%.[10,21–23]

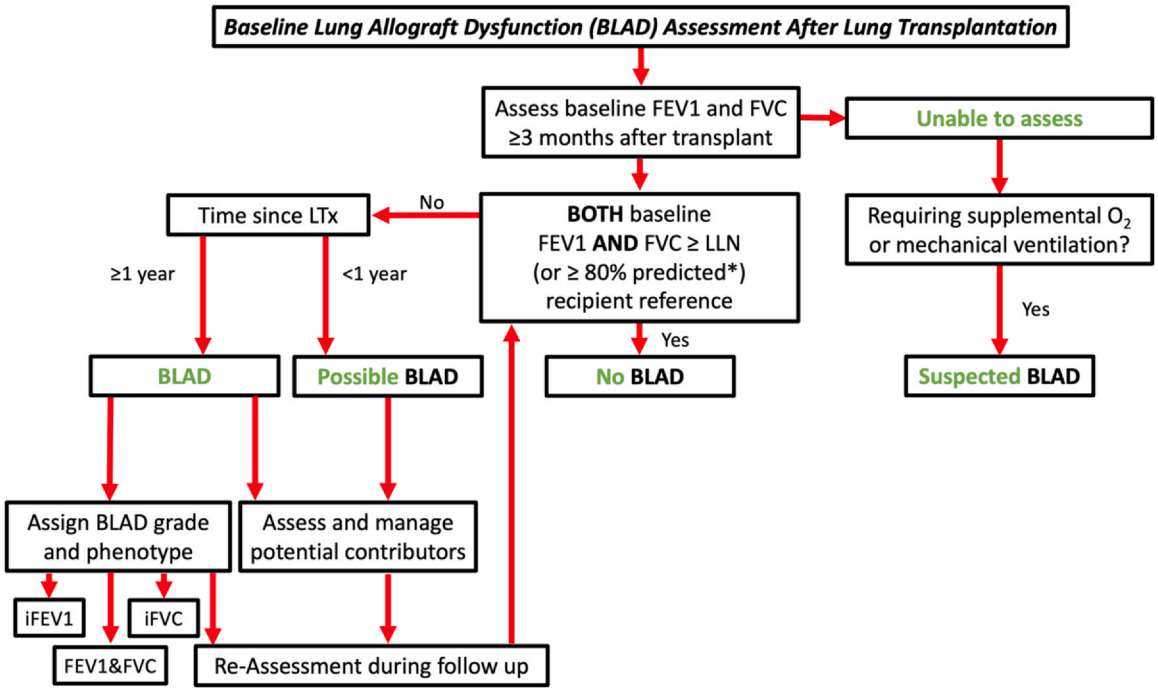
The definition proposed by our expert group strives to strike a balance. This definition is inclusive, with patients meeting criteria when either the baseline FEV1, baseline FVC, or both are abnormally low (Table 2). We herein acknowledge that different combinations of low FEV1 or FVC may have different prognostic or even etiologic associations. We propose these can be classified as: BLAD with an isolated low FEV1 (BLAD-iFEV1); BLAD with an isolated low FVC (BLAD-iFVC); and BLAD with both low FEV1 and low FVC (BLAD-FEV1&FVC) (Table 2, Figure 2). BLAD-FEV1, defined by a low FEV1 irrespective of FVC, has also been described in the literature.[10,21] Dedicated studies exploring these BLAD subtypes are needed to provide deeper insights into their significance.

Timing of BLAD designation

The course of post-transplant lung function is highly variable among transplant recipients. Baseline lung function is a dynamic value, which can either plateau or continue to increase over time. In contrast, declines in lung function compared to the baseline signify acute lung allograft dysfunction or CLAD. Consequently, some patients will start with normal lung function, others with subnormal function that eventually improves, and some with abnormally low lung function that never normalizes.

Time-to-baseline can be assessed in patients when spirometry data are available, and a baseline can be established. This implies that the theoretically earliest time point at which the status of BLAD can be assessed is several weeks after surgery when the patient is able to produce lung function. However, the literature includes studies describing normalization of lung function after video-assisted thoracoscopic surgery (VATS) already at the time of hospital discharge, whereas normalization after open thoracotomy required roughly 4 months.[24] Estimates of the median time to baseline in the published studies have varied from 255 to 551 days, meaning a proportion of

Figure 2 Flowchart for the assessment of BLAD. BLAD, baseline lung allograft dysfunction; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; iFEV1, BLAD with isolated FEV1 < LLN; iFVC, BLAD with isolated FVC < LLN; FEV1&FVC, BLAD with both FEV1 and FVC below LLN. *if LLN not available



patients take longer than 1 year to reach their baseline. In the available studies of BLAD, the time point for reaching baseline was not consistently defined, and in some cases, no definition was provided.

We propose that baseline lung function is reached at the time of the first of the 2 FEV1 measurements used for baseline calculation. Based on published studies, many patients reach their baseline by 1-year post-transplant and some beyond. Therefore, 1-year post-transplant reflects a logical and relatively stable time point at which, and after which, designation of BLAD vs normal lung function can be assessed.[25] However, while we propose for the sake of clinical and research feasibility that BLAD status can be best assigned at 1-year, patients' lung function can continue to improve to the point where they no longer meet criteria after that point. Prior to 1 year, a diagnosis of possible BLAD may be assigned. BLAD is best conceptualized as a dynamic state that can normalize at any time post-transplant and is best assessed with as much time as possible post-transplant and using as much lung function data as is available. It is crucial for research studies to clearly define the specific time point at which BLAD is evaluated.

BLAD phenotyping

BLAD phenotypes have not been well studied with respect to the impact on prognostic relationships or distinct etiologies. We propose categorization of BLAD into cases defined as follows: an isolated low baseline FEV1 (BLAD-iFEV1); isolated low baseline FVC (BLAD-iFVC); and a combination of both low FEV1 and FVC (BLAD-FEV1 &FVC). These should be further researched (Table 3).

Obstructive physiology vs. non-obstructive physiology in BLAD may be relevant.[5,12] Obstructive physiology may suggest airway-related limitation to lung function; restrictive changes should be confirmed using static lung volumes, including total lung capacity. However, this requires further study. Obstructive and restrictive patterns will likely have strong correlations to the BLAD-iFEV1, BLAD-iFVC, and BLAD-FEV1&FVC categories and need further study in the future.

Table 3 Consensus-Based Delphi Recommendations for Etiologies of BLAD

	Statement	% agreement
12	Lower donated tissue volume (size mismatch, single lung transplants, and lobar transplants) can be a cause of BLAD.	88
16	BLAD can be the result of intrinsic pulmonary or extrapulmonary causes (such as size mismatch or diaphragm dysfunction), or a combination of causes.	100
17	BLAD can be secondary to one or multiple identified causes or it can also be idiopathic without clearly identifiable secondary causes.	100

BLAD grading

BLAD severity has been examined in some publications and appears to have a dose-dependent effect on the risk of death or graft loss, with lower baseline lung function being associated with higher risk.[1,5,12] This risk relationship is likely continuous. However, to facilitate clinical utilization as well as the ability to study BLAD severity, we propose a grading schema similar to the CLAD grading approach (Table 3).[4] A key distinction is that the grading percentages are referring to population values rather than percent of the baseline value. We chose not to include a fourth grade (FEV1%-predicted < 35%) as this scenario is expected to be rare, unlike the analogous FEV1%-of-baseline in CLAD category in CLAD. Case studies are presented in Figure 3.

Differentiation from other forms of graft dysfunction (ALAD and CLAD) and trajectories of BLAD

In contrast to BLAD, where the baseline is expected to rise or plateau after lung transplantation, a decline in lung function at any time is classified as acute lung allograft dysfunction (ALAD) or, if persistent despite appropriate treatment of potential causes, as CLAD. Due to the nature of the construct, the only possible change in BLAD classification that can occur is to change from BLAD to normal function, if a patient's lung function reaches normal threshold, they no longer meet criteria. Patients cannot go from normal function to BLAD, given this patient has already reached normal function in the past and given this would reflect a deterioration or loss in function, which would meet criteria for either ALAD or CLAD. Similarly, changes in BLAD grade can only be upwards (3-2, 2-1, etc.), as patients improve. BLAD grade cannot worsen, as this would indicate a previous higher baseline and a progressive loss in keeping with a different physiologic graft dysfunction syndrome.

SECTION II. CAUSES AND INVESTIGATIONS

Causes

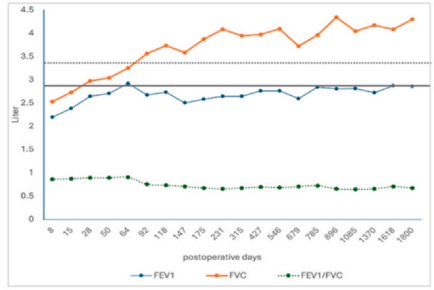
The cause of BLAD can be multifactorial. The working group proposed and endorsed several statements specific to BLAD etiologies that are summarized in Table 3. Notably, the working group agreed that etiologies may originate within and/or outside the allograft. The working group elected to develop a construct that encompasses all cases of poor graft function after lung transplantation, regardless of the presumed underlying etiology. This inclusive approach was chosen for the following reasons:

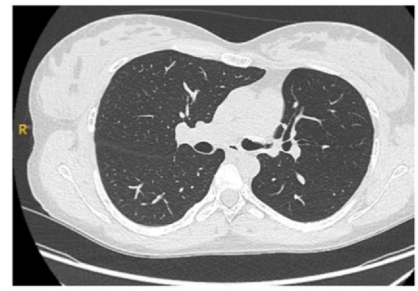
- Lung allograft function reflects the combined contribution of the transplanted lung and the entire respiratory system (including extrapulmonary factors).
- Precise causal attribution is often difficult, particularly in the presence of subtle changes (e.g., pleural disease, central airway complications, neuromuscular weakness, or obesity).
- Multiple coexisting abnormalities are common and may lead to misclassification if only a single predominant cause is assigned.

This inclusive approach also aligns with the upcoming definition of acute lung allograft dysfunction (ALAD), which applies the ALAD label to all cases with new acute lung dysfunction irrespective of cause. This alignment will facilitate the implementation of these 2 constructs. We fully intend that this decision be revisited with

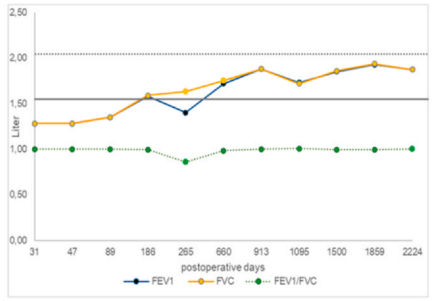
Figure 3 A-C. Case studies. BLAD, baseline lung allograft dysfunction; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; BLAD-FEV1&FVC, BLAD with both FEV1 and FVC below LLN, BLAD-iFEV1

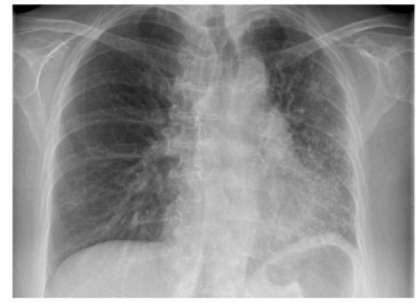
A 28-year-old female, 5 years after bilateral lung transplantation for cystic fibrosis. There was a moderate suture stenosis on the left main bronchus that was dilated several times. At one year post transplant, the baseline spirometry shows an FEV_1 of 2.62 L and an FVC of 3.91 L, resulting in an FEV_1/FVC of 0,84. At 5 years posttransplant, these values were 2.71 L, 4.14 L and 0,65 respectively. The recipient's lower limit of normal (LLN) reference values are: FEV_1 2.9 L (solid line; predicted 3.6L), FVC 3.41 L (dotted line; predicted 4,24L) and FEV_1/FVC 0.74 (predicted 0.85). Based on these values ,this case should be classified as BLAD-iFEV1, grade 1.



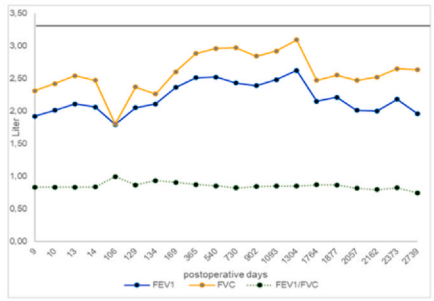


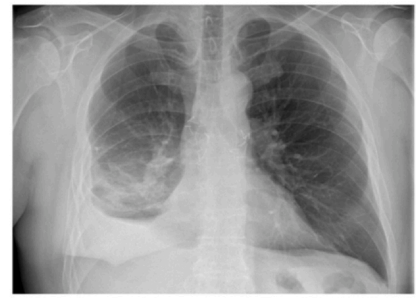
A 74-year-old female, 6 years after unilateral right-sided lung transplantation for idiopathic pulmonary fibrosis. Her baseline spirometry shows an FEV_1 of 1.89 L and an FVC of 1.90 L, resulting in an FEV_1/FVC ratio of 0.99. The recipient's lower limit of normal (LLN) reference values are: FEV_1 1.54 L (solid line; predicted 2.23 L), FVC 2.04 L (dotted line; predicted 2.91 L), and an FEV_1/FVC LLN of 0.65. Based on these values, this case should be classified as BLAD-iFVC, grade 1.





A 60-year-old male, 7.5 years after bilateral lung transplantation. His baseline spirometry shows an FEV_1 of 2.57 L and an FVC of 3.03 L, resulting in an FEV_1/FVC ratio of 0.84. The recipient's lower limit of normal (LLN) reference values are: FEV_1 3.35 L (solid line; predicted 4.44 L), FVC 4.43 L (not shown; predicted 5.77 L), and an FEV_1/FVC LLN of 0.77. Based on these values, this case should be classified as BLAD-FEV_1&FVC, grade 2.





subsequent iterations of the definition. In contrast to the definition of CLAD, which is intended to reflect an airway/parenchymal lung disease and requires exclusion of other causes of dysfunction, BLAD in its current understanding shows no uniform pathological correlate or pattern.

The potential causes described below were generated through literature review and clinical expertise of the working group. Notably, BLAD can be idiopathic, meaning no contributing factors can be identified. In other cases, one or more abnormalities may still be present, but it is difficult to determine whether they are the cause of the dysfunction.

Overall, the literature regarding possible causes is rather limited, and with respect to potential etiology, it is neither comprehensive nor consistent in terms of the definitions used throughout the papers. Some explanations for BLAD are described in transplantation-specific retrospective single-center studies, while others are based on the theoretical considerations of the authors of this consensus document. Appendix 3 also proposes criteria from the literature that can serve as a basis for a definition to be used in scientific studies investigating the causes of BLAD.

Allograft-specific etiologies

Factors affecting the allograft itself include donor characteristics, perioperative conditions, and post-operative factors and complications. Donor-related factors that may impact allograft function include advanced donor age and heavy donor smoking history.[1,26–29] Lower donated tissue volume, such as a donor-recipient size mismatch,

single lung transplantation, and/or lobar lung transplantation are additional causes of BLAD. Perioperative factors potentially contributing to BLAD development include prolonged ischemia time, longer operative time, and significant intraoperative bleeding.[1,5,14,17] Post-operative conditions that may contribute to BLAD include severe primary graft dysfunction[18,30,31] e.g., hemothorax with need for re-thoracotomy, aspiration and the requirement for prolonged mechanical ventilation[5,14] and/or the need for salvage post-transplant extracorporeal membrane oxygenation (ECMO), all of which likely indicate diminished allograft function. Other post-operative complications that may contribute to BLAD include infections, airway complications[19] such as airway stenosis, early acute cellular and/or antibody-mediated rejection, and abnormal allograft perfusion.[32] Table 4A summarizes these etiologies, along with proposed clinical investigations.

Etiologies external to the allograft

Extrapulmonary causes that could contribute to BLAD can either originate within the thoracic cavity or be extra-thoracic. The recipient thoracic cavity can be limited by deformities of the chest wall, including kyphosis, pectus excavatum, and chest wall rigidity as seen in patients with severe skin graft-versus-host disease. Interstitial lung disease as an indication for lung transplant has been linked with a higher risk of BLAD may be related to the chest wall and/or to the generally smaller donated long volume[1,33] as has recipient obesity at the time of transplant.[12] Additional risk factors for BLAD may include prolonged intensive care unit or hospital length of stay, although the mechanism for this association may be multifactorial and include extrapulmonary etiologies, including neuromuscular weakness and physical deconditioning. Other etiologies include diaphragm dysfunction,[34] pleural complications such as pleural effusion, empyema, and secondary fibrothorax/pleural fibrosis, as well as other causes of a restrictive thoracic wall. Lastly, allograft injury caused by gastroesophageal reflux disease (GERD) and (micro)aspiration might result in a lower baseline lung function following transplantation.[35] Additionally, these causes may contribute to allograft dysfunction through either direct or indirect injury. Table 4B summarizes these etiologies with the proposed investigations and notes for existing literature evidence.

Investigations

The goal of investigations into BLAD etiologies is to better understand the cause(s) and to address those for which an intervention is possible. Given the limited published data about assessment of BLAD, this document proposes considerations that have been described in other contexts regarding post-transplant allograft dysfunction or in the general care of lung transplant recipients. As BLAD is defined by spirometry, spirometry is not included here though it could be used to monitor change over time. Full lung function testing, including body plethysmography and diffusion limitation can help to better understand a patient's lung physiology, with plethysmography able to identify the physiological mild hyperinflation observed in some patients after bilateral and combined heart–lung transplantation resulting in reduced vital capacity.[36] While there is no evidence to mandate all the listed investigations, many are non-invasive and can be done in parallel to quickly identify potential treatments. Notably, any results should be considered in conjunction with other clinical findings and diagnostic tests to ensure a comprehensive and accurate evaluation of BLAD, both in its underlying causes and in its consequences. These investigations are included with the relevant etiologies in Tables 4A 4B.

Clinical history of donor and recipient

The clinical history of the donor, including donor age, smoking history, lung size, and prior lung disease or injury, can provide insights into potential BLAD etiologies. Small chest cavity due to native lung diseases like pulmonary fibrosis and other restrictive lung diseases make a diagnosis of BLAD more likely.

Specific allograft factors, such as lower donated lung tissue volume resulting from lobar resection, size reduction, or single lung transplant can contribute to BLAD.[10,37–39] Perioperative events, including prolonged ischemia time, longer operative time, and significant intraoperative bleeding should be noted. Early post-operative events, including severe primary graft dysfunction, prolonged mechanical ventilation, and ECMO, can contribute to BLAD.[18,40]

Additional clinical history of the recipient includes a history of infections, acute rejection episodes, and medication adherence concerns (especially for immunosuppressive drugs). If information on exposures to

Table 4A Potential BLAD Etiologies and Investigations Within the Allograft

Category	Potential etiology originating within the allograft	Possible investigations	Literature
Donor-related factors	Advanced donor age Heavy donor smoking history Donor-recipient size mismatch Aspiration Donor lung disease	Clinical history of donor	1,26–29,68
Allograft-related factors	Lower donated tissue volume Size mismatch Single lung transplant Lobar lung transplant	Clinical history of donor and recipient	10,37–39,69
Perioperative factors	Prolonged ischemic time Longer operative time Significant intraoperative bleeding	Clinical history of recipient transplant	1,5,14,17,70,71
Early post-operative factors	Severe primary graft dysfunction Prolonged post-operative mechanical ventilation or ECMO	Clinical history of recipient	5,14,18,30,32,72
Post-transplant factors	Infection	Clinical history of recipient, sputum/lavage samples for microbiology	No transplant-specific references
	Airway complications (especially obstructive)	Bronchoscopy	19,73,74
	Reflux and aspiration	GastroscopypH/impedance testing	23,35,75
	Persistent rejection (cellular or antibody-mediated)	Bronchoscopy with transbronchial biopsy, screening for anti-HLA antibodies	67,76
	Vascular complications	Computed tomography scan with intravascular contrast, angiogram, perfusion scan	32
	Hyperinflation leading to low FVC	Body phlethysmography	36
	Parenchymal opacities not otherwise associated with abnormalities above	Computed tomography scan of the chest	No transplant-specific references

ECMO, extracorporeal membrane oxygenation

environmental pollutants or allergens is available, this should be noted as well. Smoking history, GERD, and comorbidities, including pre-transplant pulmonary hypertension and cardiac dysfunction or disease are also relevant.

Imaging studies

Several imaging studies may aid in the investigations for BLAD.[31,32,41] Chest X-ray may identify infiltrates or opacities, bronchial wall thickening, pleural effusion, hyperinflation, atelectasis, or poor expansion. Abnormalities seen on chest X-ray should have additional follow-up with high-resolution CT (HRCT). HRCT can be instrumental in assessing BLAD etiologies as it provides detailed visualization of lung parenchyma, airway anatomy, and vascular structures.

Additionally, thoracic ultrasound is a non-invasive tool useful in evaluating pleural effusions, diaphragm dysfunction, and lung consolidation. It helps assess diaphragm movement, which is critical in post-transplant patients at risk of phrenic nerve injury or neuromuscular dysfunction.[42,43] Bedside ultrasound is particularly valuable for real-time assessment in critically ill patients.

Bronchoscopy

Bronchoscopy plays a crucial role in evaluating BLAD after lung transplantation. It aids in diagnosing potentially reversible causes of subnormal early lung function, including infection, acute rejection, and airway complications.

Table 4B Summary of BLAD Etiologies and Investigations Outside of the Allograft

Category	Potential etiology originating outside of the allograft	Possible Investigations	Literature support
Recipient chest wall/ muscles	Surgical incision type	History Physical exam	24,77
	Kyphoscoliosis Pectus excavatum Kyphosis Chest wall rigidity	Physical exam Chest X-ray Chest CT	No transplant-specific references
	Recipient chest restriction due to underlying disease	Recipient history Total lung capacity Chest imaging	1,33,78,79
	Recipient obesity	Physical exam including anthropometric measurements, chest imaging	12
	Recipient deconditioning and neuromuscular weakness	Frailty assessment	No transplant-specific references
	Diaphragm dysfunction	Chest ultrasound Chest X-ray CT chest Fluoroscopy Mean inspiratory pressure	34,42,43
Recipient pleura	Pleural effusion Empyema Secondary fibrothorax	Thoracic Ultrasound Chest X-ray CT chest	11,80
Other	Cardiac causes	ECG NT-proBNP Echocardiography	No transplant-specific references
	Idiopathic	All above	No transplant-specific references

CT, computed tomography; ECG, electrocardiogram; NT-proBNP, n-terminal pro-brain natriuretic peptide

Bronchoalveolar lavage (BAL) is performed to collect samples for microbial analysis, assessing for bacterial, viral, or fungal infections.[44,45] Cytological examination of BAL fluid may reveal increased neutrophils, lymphocytes, or eosinophils, suggesting infection, rejection, or allograft dysfunction. If available in the local facilities, it might be reasonable to test a BAL sample for pepsinogen A,[46] bile acids,[35] and lipid laden macrophages, as they all are recognized markers of aspiration, a risk factor for graft dysfunction.[47–49]

Transbronchial biopsies can help detect acute cellular rejection, antibody-mediated rejection, acute lung injury, or organizing pneumonia, which, if severe or recurrent, could contribute to BLAD.

In addition to diagnostic purposes, bronchoscopy can be therapeutic, allowing for airway clearance, foreign body removal, or dilation of strictures if present. Serial bronchoscopies may be performed in patients with persistent symptoms or progressive allograft dysfunction to identify new or additional causes of BLAD.

Cardiac evaluation

Cardiac evaluation, including ECG and echocardiogram, may help to identify potential underlying causes, such as heart failure,[50] which may contribute to BLAD through fluid overload. Additionally, measuring N-terminal pro B-type natriuretic peptide (NT-proBNP) is a useful indicator of cardiac overload, providing further insight into the degree of heart strain. However, it is important to note that NT-proBNP levels may be influenced by other confounding factors, such as renal insufficiency, which could lead to inaccurate readings and complicate the clinical interpretation. Finally, an echocardiogram provides useful information about left and right ventricular function, as well as valve function, and might indicate pulmonary hypertension,[51] though the prevalence of post-transplant pulmonary hypertension and the relationship to BLAD are unknown.

Frailty assessment

Frailty is defined as an aging syndrome with increased vulnerability to adverse health events, whether medical or surgical. It is a complex state associated with comorbidities and disabilities.[52] There is no single standard to define frailty, and several screening tools have been developed in the geriatric populations with expansion to transplant recipients. Frailty may plausibly be a risk factor for BLAD, due to muscular weakness, but existing data on this relationship is limited. Frailty in lung transplant patients may be assessed using validated tools, most commonly: the Fried frailty phenotype,[53] the Frailty Index,[54] and the Short Physical Performance Battery (SPPB).[55] All 3 are established in the literature; the SPPB is often preferred for its practicality and accuracy. While a significant proportion of lung transplant candidates are deemed frail,[56] many of these patients do not meet the frailty criteria after lung transplant.[57,58] A prospective, multicenter cohort study involving more than 300 lung transplant candidates identified an association between frailty and 1-year post-transplant mortality.[58] Wilson et al., in a retrospective cohort analysis, demonstrated a lower 1-year and 3-year survival rate post-transplant in frail lung transplant candidates compared to others.[59] Despite this direct correlation with mortality, frailty may be a modifiable risk factor that can be addressed through rehabilitation programs[60–63] and improvements in frailty scores have been observed within the first months post-transplant (in varying ways depending on the scale used).[64–66] The relationship between post-transplant frailty and lung function, however, remains unclear and is an important field for future research.

BLAD biomarkers

One of the future challenges is identification of rapidly accessible and highly reliable biomarkers for allograft dysfunction. Biomarker identification is an active area of research for CLAD—identifying patients at risk, associating biomarkers with prognosis, and finding biomarkers responsive to therapy. At present, however, there are no validated biomarkers for BLAD-subtypes. A multicenter U.S.-based study investigated the potential role of cell-free DNA for assessing BLAD, but the authors did not find any significant association between the level of donor-derived cell-free DNA and the presence of BLAD. A follow-up study from this same cohort noted that DSA, even without clinical antibody-mediated rejection, were associated with BLAD.[67] As BLAD has many potential etiologies, it may be that the role of biomarkers will be to help identify causes, particularly treatable ones like rejection, rather than to identify BLAD itself.

SECTION III. OUTCOMES IN PATIENTS WITH BLAD

BLAD and all-cause mortality

Several studies have measured the association between baseline lung function and risk of future all-cause mortality. As BLAD represents decreased pulmonary physiological reserve and increased vulnerability to insults, these studies have generally shown that normalization of baseline spirometry, either measured at a fixed time point of 12-months following transplant or at achievement of best post-transplant lung function at baseline at any time point, confers a protective effect against death or retransplantation.[1,5,12] Conversely, these studies demonstrate that failure to achieve a normal baseline (i.e., BLAD) is associated with increased risk of death in some studies and graft loss in others compared to normalization of lung function; this effect is dose-dependent, with worse baseline dysfunction conferring a higher risk of death. These findings align with previous evidence indicating that greater physiological reserve following lung transplantation is associated with improved recipient outcomes.[10,39] More recent studies have further highlighted that reduced peak performance in other lung function parameters, relative to normative values, is also associated with increased mortality.[11,16] A single study by Yamaguchi et al. did not support the association between BLAD and mortality, though this may have been impacted by small numbers and short follow-up time.[14]

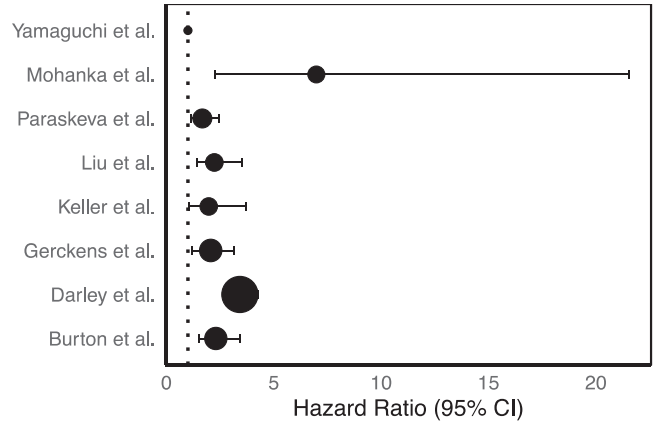
Table 5 summarizes the main findings of studies examining the association between BLAD and mortality, with Fig. 4 highlighting effect sizes.

Table 5 Studies Measuring the Association Between BLAD, Death, and CLAD

Authors	Follow-up	Number	Exclusions	BLAD definition	Cumulative incidence of BLAD	BLAD and mortality association	BLAD grade and mortality association	BLAD and CLAD association
Liu et al[1]	6.4 years	178	Single lung Lobar Heart lung	Peak FEV_1 or FVC <80% predicted*	42%	56% vs 27% HR 2.23 $p < 0.001$ Death	Yes	47% vs 36% HR 1.25 p=0.36
Paraskeva et al[6]	6.8 years	217	Single lung Survival < 3mo Anastomotic narrowing	FEV_1 or FVC < 80% predicted at 12 months*	49%	67% vs 45% aHR 1.66, p=0.009 Death or retransplant	Yes	70% vs 59% aHR 1.54 p=0.016
Keller et al[12]	2.4 years	173	Single lung	Peak FEV_1 or FVC <80%predicted* (no 20% recent increase in FEV_1)	40% 30.9% at 12 months	HR 1.97 p= 0.03 Death	Yes	HR 1.60 p=0.13
Yamaguchi et al[14]	2.4 years	38	Single lung	Peak FEV_1 or FVC < 80% predicted*	55%	Not significant	Not studied	12% vs 10% HR Not Reported p=0.58
Gerckens et al[20]	7.5 years	214 Double, 141 Single	No baseline available, re-do transplant	Single lung FEV1 or FVC < 60% predicted	43% single 44% double	77% vs 50% HR 2.06 p < 0.005; Death or retransplant	Not studied	44% vs 48% HR Not Reported p=0.15
Darley et al[15]	20 years (Median follow-up 4.3 years)	1259 Double	Single Lung	Baseline DLCO <75%, Baseline FEV1 <80% Predicted	40%	Low DLCO aHR 3.42, p < 0.001; Low FEV1 aHR 1.77, p < 0.001; Death or retransplant	Not studied	Low Baseline DLCO aHR 1.29 p=0.005 Low Baseline FEV1 aHR 1.41 p=0.01
Ramendra et al[74]	Not reported	309 Double, 178 Single	Heart–Lung, Re-transplant	Baseline FEV1 < 80% predicted	58%	Not reported	Not studied	HR 1.26 p=NS
Burton et al. 2009[10]	12 years (Median follow-up time not reported)	103 Double 225 Single 18 Heart–Lung	< 3-month survival	Baseline FEV1 (per liter change)	N/A	Not reported	Not studied	1 L FEV1 Reduction Outcome: Freedom-from-BOS aHR 2.33 $p < 0.001$
Mohanka et al.[17]	3 years	157 Double	< 3-month survival	FVC < 80% Predicted	50%	46% vs 19% Death	Yes	FVC 60%-80% HR 2.85 $p < 0.05$ FVC <60% HR 7.9 $p < 0.001$

HR, hazard ratio; aHR, adjusted hazard ratio; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; BLAD, baseline lung allograft dysfunction

Figure 4 Forest plot summarizing the association between BLAD and mortality in studies which measured effect sizes. Horizontal lines represent the 95% confidence intervals (CIs) for the estimated hazard ratio (HR). The vertical dashed line at HR 1.0 indicates the null hypothesis (no increased or decreased risk). Points to the right of this line suggest an increased risk of death. The circle symbol size indicates the relative cohort size. The hazard ratio reflects the measured risk



Implications of simultaneous BLAD and CLAD

Studies have demonstrated that both BLAD and CLAD, when considered independently, are associated with reduced survival following lung transplantation. One investigation reported that among patients diagnosed with the BOS phenotype of CLAD, those who received bilateral lung transplants showed a trend toward improved survival compared to single lung recipients—an effect speculated to be related to differences in baseline allograft function.[81] Concurrent BLAD and CLAD may represent a more severe CLAD sub-phenotype with a potentially greater negative impact on post-CLAD survival. This hypothesis warrants further investigation.

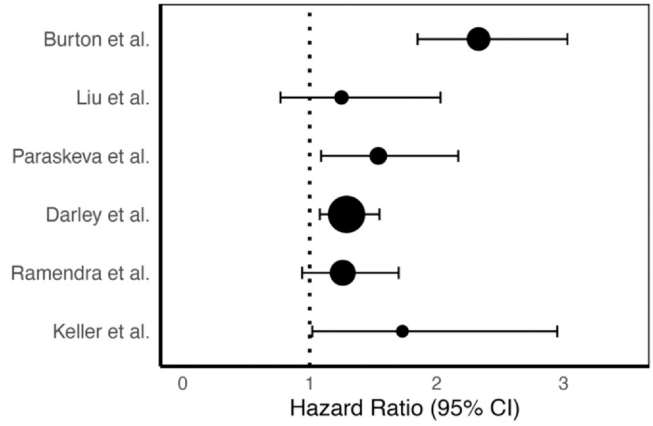
BLAD and future onset of CLAD

A key priority in lung transplantation is to better understand the relationship between 2 forms of persistent allograft dysfunction: BLAD, defined by subnormal baseline allograft function, and CLAD, characterized by progressive and sustained decline from baseline. Efforts to assess the association between these conditions have been hampered by historical inconsistencies in their definitions and in the statistical methods used to explore their relationship.

Early observational studies explored how different transplant types (single, bilateral, heart–lung) might influence future CLAD risk, using baseline allograft function as a reference point. Notably, Burton et al. were the first to examine the link between transplant type and cause-specific risk of BOS, adjusting for baseline FEV1, which they defined as the average of the 2 highest recorded values.[10] An independent inverse relationship was identified between baseline FEV1 and the development of BOS, within a statistical model that treated death prior to BOS onset as a competing risk. Subsequent work by Burton et al. emphasized that baseline FEV1 should be considered a key confounding variable when assessing both freedom from BOS and its cumulative incidence.[82] In a retrospective study of 220 patients transplanted for chronic obstructive pulmonary disease (COPD), recipients of bilateral lung transplants were significantly less likely to develop BOS (Grade ≥1) at 3 and 5 years post-transplant compared to those who received single lung transplants.[81] One study found that CLAD had a strong association with mortality in patients with normal baseline lung function (HR 5.1), but also to a lesser extent in BLAD patients (HR 1.8).[83]

A number of studies aimed to directly measure the association between BLAD and CLAD and the results yielded conflicting findings (Table 5). Liu et al. investigated 178 bilateral lung transplant recipients (75 with BLAD) and did not detect an association between the presence of BLAD and the future risk of CLAD.[1] In a multicenter, prospective cohort study including 173 bilateral lung transplant recipients, Keller et al. also found no association between BLAD and CLAD.[12] Similarly, Gerckens et al., in a retrospective single-center analysis including 141 single lung transplant recipients, of whom 43% met the criteria for BLAD, found no association with future CLAD.[20]

Figure 5 Forest plot summarizing the association between BLAD and CLAD. The horizontal lines represent the 95% confidence intervals (CIs) for the estimated hazard ratio (HR). The vertical dashed line at HR 1.0 indicates the null hypothesis (no increased or decreased risk). Points to the right of this line suggest an increased risk of CLAD. The circle symbol size represents the cohort size



Other cohort studies, in which CLAD was not the primary outcome of the study, did not report significant associations with CLAD.[75] In contrast, Darley et al. investigated the relationship between both the DLCO and the spirometric trajectory, and the future risk of CLAD in 1259 bilateral lung transplant recipients.[15] In a multivariable, landmark time-to-event model, low baseline spirometric indices were independently associated with future CLAD risk. Paraskeva et al. performed a retrospective cohort study of 217 bilateral lung transplant recipients, with subnormal cases defined by spirometric indices at the 12-month post-transplant time-point.[5] In this study, the presence of BLAD was also independently associated with future CLAD risk.

One study investigated whether BLAD might act as a mediating state linking early allograft injury to the later development of CLAD. In a cohort of 446 bilateral lung transplant recipients, Li et al. found that, while high-grade primary graft dysfunction was associated with the development of BLAD, it was not linked to subsequent CLAD.[18] Although several studies have reported a positive correlation between BLAD and CLAD, a definitive relationship between the two has yet to be established (Figure 5). The effect may arise because even a modest decline represents a disproportionately large percentage change from baseline. Further research is needed to clarify this association. The proposed definition of BLAD, developed by the ISHLT consensus working group, offers a foundation for global standardization of this potential predictor state in relation to long-term transplant outcomes. Another recent study shows that BLAD is a dynamic early post-transplant state with markedly different recovery (higher in bilateral recipients with COPD) and mortality patterns in single versus double lung transplant recipients, and that while BLAD increases mortality risk, chronic lung allograft dysfunction (CLAD) remains the strongest predictor of death once normal baseline lung function is achieved.[83]

BLAD and the relationship to future CLAD phenotypes

Another important consideration is that the pattern of physiological abnormality in BLAD may influence the subsequent classification of CLAD phenotypes. Under the current CLAD classification, obstructive physiology is defined by a forced expiratory ratio below 0.7 at CLAD onset. Subnormal baseline lung function, as seen in BLAD, may reduce the accuracy of CLAD phenotyping and increase the proportion of recipients who remain unclassified under existing ISHLT criteria. Consequently, accurate identification of obstructive CLAD is most reliable when there is clear evidence of progression from normal spirometry (forced expiratory ratio > 0.7) to physiologic obstruction (forced expiratory ratio < 0.7) and may allow better phenotyping in cases of impaired baseline spirometry. CLAD can also be challenging or even impossible to diagnose in the presence of major abnormalities or confounders. Future iterations of the ISHLT CLAD consensus statement may need to refine physiologic classifications to account for changes from individual baseline function.

BLAD and health-related quality of life (HRQL)

BLAD may also be associated with poorer patient-centered outcomes. One study evaluated the relationship between BLAD, health-related quality of life (HRQL), and exercise capacity.[84] In this single-center cohort of 264 lung transplant recipients, BLAD was linked to lower scores on the 36-Item Short Form Health Survey (SF-36) at 1-year post-transplant, indicating a perceived decline in quality of life. Additionally, BLAD was associated with shorter distances on the 6-minute walk test, reflecting impaired exercise capacity and reduced physiological performance.

SECTION IV. PEDIATRIC CONSIDERATIONS

It is the primary goal of lung transplantation in children to restore pulmonary function, aiming to increase survival and improve health-related quality of life.[85] As in adults after lung transplant, overall post-transplant outcomes in children remain inferior compared to results after other solid organ pediatric transplant procedures. CLAD is the most frequent cause for morbidity and mortality in pediatric lung transplant recipients, limiting its success. However, classifying pediatric lung transplant recipients according to the international CLAD consensus definition is challenging as somatic growth throughout childhood is not appropriately accounted for by absolute pulmonary function values.[86] Furthermore, infants and younger children are unable to reliably perform spirometry.[87] Thus, CLAD diagnosis in children < 6 years of age is mostly attempted by using CT chest imaging, although no international consensus exists on the matter.

As in adults, some pediatric lung transplant recipients never achieve normal pulmonary function parameters post-transplant, a phenomenon that has been recognized but not investigated or defined in pediatric patients to date. The systematic literature search presented in this document retrieved no studies in children. Therefore, there is a complete lack of evidence on the association of BLAD and survival, allograft survival, and development of CLAD in children following lung transplantation.

There are several limitations of the BLAD definition construct proposed in this document as it pertains to pediatric lung recipients. First, as it is based on spirometry values, the definition is not applicable to infants and children younger than 6 years of age who are unable to reliably perform spirometry. At experienced pediatric centers with highly skilled pulmonary laboratory technicians, spirometry could be attempted in children < 6 years of age with the appropriate training, but it will remain an important limitation in this population, as it will with CLAD. Second, the increases in spirometry that occur with normal somatic growth of pediatric donor lungs may pose challenges in assigning BLAD status, though these can still be compared to reference age-appropriate values. Finally, the GLI values do not apply in children below the age of 5. Impaired gas exchange and the need for respiratory support as alternative diagnostic criteria, in the absence of available spirometry, may also be applicable in children. As such, surrogate markers are especially needed in the younger pediatric cohort, predominately chest imaging.

Currently, 6 pediatric lung transplant programs in North America will conduct a retrospective multicenter study to investigate the frequency of BLAD in the pediatric population, using this ISHLT consensus definition once it is formally available, and its association with overall survival, allograft survival, and the development of CLAD (Wai Wong, MD, Boston Children's Hospital, MA, USA). The results of this first study on pediatric BLAD are eagerly awaited by the international pediatric lung transplant community.

SECTION V. LIMITATIONS OF THE BLAD CONSTRUCT

There are important limitations to note about BLAD as a research construct. Although assessing baseline using lung function over the first year post-transplant allows for a common and stable assessment timepoint, maximum lung function may be reached at later timepoints. Allowing patients as much time as possible to reach normal lung function will likely result in the most stable classification. For this reason, treating lung function normalization as a time-varying single event—where patients first reach the specific normal threshold of FEV1 AND FVC ≥ LLN or 80% predicted—is likely the most accurate way to study it. In this way, time spent in BLAD physiologic range is considered "time at risk", allowing patients to change classes (BLAD to normal) and still contribute to the hazard function. Researchers also need to consider the competing risk of death in their analysis.

It is also important to clarify that BLAD is not a lung disease in the same sense as CLAD, which represents a complication of allograft tissue. Rather, BLAD is intended to describe a syndrome characterized by abnormally low peak lung function after lung transplantation in relation to the predicted value, irrespective of the etiology, be it within or outside the allograft. It is possible that some causes of poor baseline function, such as severe primary graft dysfunction, may have stronger prognostic associations than others, such as donor-recipient undersizing when transplanting for interstitial lung disease, though this requires dedicated study. The goal of this framework is to provide a common language that captures known risk associations and facilitates investigation by clinicians and researchers. Most importantly, the intent of the BLAD construct is not to replace thoughtful investigation of patients with poor function, but in fact to prompt these investigations.

The timepoints at which BLAD status is assigned are a matter of debate. Our proposal in this document is based on a combination of what is clinically logical. As noted, baseline function as a time-varying covariate can overcome this challenge, but makes the construct more difficult to implement and study. Similarly, time to baseline may be an important independent parameter to study, as patients that require longer to improve and normalize their lung function may have differential outcomes compared to those who normalize earlier.

Finally, many lung transplant recipients exhibit lower-than-expected FEV1 and FVC in relation to reference values from the healthy population, and mild or borderline impairments may not necessarily be associated with adverse outcomes. The GLI project was designed to establish reference values for a healthy population. Individuals with respiratory diseases or a history of smoking were, understandably, excluded from the GLI-dataset.[6] By definition, the GLI-reference values may not be applicable to lung transplant recipients.

SECTION VI. FUTURE RESEARCH CONSIDERATIONS

A key aspect of proposing a common international definition of BLAD is to harmonize and focus future research efforts. During the development of this document, our group identified some important areas of future study.

First, it will be key to investigate the lung function trajectory following BLAD designation, particularly the natural course of FEV1 stability or decline over time and how it relates to BLAD severity, phenotype, and risk of CLAD. The etiologic and prognostic associations with individual BLAD phenotypes—BLAD-iFEV1, BLAD-iFVC, BLAD-FEV1&FVC, as well as the presence of obstruction and the characteristics of the flow-volume loop—are also important areas for future study.

It will be important to investigate cases of BLAD where no clear cause is present or attributable as the source of dysfunction, given this may suggest a primary disorder of the lung parenchyma. The presence of tissue changes on pathology or other complementary testing is worth additional study. This may also pave the way for dedicated studies of specific causes of BLAD—i.e., large airway complications or severe undersizing—to assess whether the prognostic associations of poor lung function are variable among these groups. This approach requires a systematic diagnostic work-up and will require more rigorous definition of the various etiologies. More broadly, systematic studies of clearly defined etiologies in large cohorts should provide a more accurate picture of the frequency distribution of causes and future consensus documents may include a diagnostic algorithm.

Equally important are patient-related outcomes. Research should explore how BLAD affects quality of life, including the psychological, social, and functional dimensions of living with a lower-than-expected graft function. Additionally, the impact of BLAD on the ability to return to work or resume normal daily activities after lung transplantation remains underexplored. Exercise capacity is another crucial outcome that reflects both physical health and functional status. Studies assessing changes in exercise tolerance and the mechanisms limiting performance in BLAD patients could provide a better understanding of disease burden and help tailor rehabilitation programs. Finally, the role of patient-reported outcomes forming part of the BLAD definition itself is an area worthy of study.

With insights gained from BLAD phenotyping and the presence of preexisting subnormal spirometry, the criteria for CLAD phenotyping may need to be revised. Obstruction may be defined in the future as a decline in the FEV1/FVC ratio from baseline. Restriction may be defined as a decline in TLC, while the FEV1/FVC ratio may either remain stable or increase significantly. To confirm the diagnosis of restrictive allograft syndrome, persistent opacities on chest X-ray or chest CT must also be present.[88]

Because GLI reference values are based on healthy cohorts rather than patients after thoracic surgery, the BLAD cut-off used for lung transplant recipients may need recalibration. Further research should refine these

thresholds and determine the clinical significance of specific BLAD grades. In the future, a different definition for single lung transplant recipients may be developed.

BLAD could also potentially be considered as a study endpoint in preventative or interventional trials, particularly those focused on early perioperative outcomes such as PGD.

Preventive and treatment strategies for BLAD need further investigation. Research should aim to identify modifiable risk factors, biomarkers for early detection, and protective interventions—whether pharmacological, immunological, or lifestyle-related—that could increase the likelihood of lung function normalization. Treatment options for established BLAD remain limited and largely empirical, consisting mainly of the correction of observed abnormalities. Future trials are needed to evaluate targeted therapies—pharmacologic and non-pharmacologic interventions like respiratory therapy and structured exercise programs—aimed at optimizing post-transplant lung function, improving symptoms, and reducing the likelihood of CLAD onset and BLAD-associated risk of death.

SECTION VII. CONCLUSIONS

This ISHLT consensus statement defines BLAD as failure to achieve normal post-transplant lung function, with the normal threshold defined as an FEV1 and FVC greater than or equal to the lower limit of normal (LLN) or 80% predicted—by ≥ 1-year post-transplant, using the average of the 2 best measurements separated by at least 3 weeks. BLAD can involve isolated low FEV1 (BLAD-iFEV1), isolated low FVC (BLAD-iFVC), or both (BLAD-FEV1& FVC), with severity graded by FEV1 % predicted. The Delphi consensus process involving 17 international experts yielded 17 recommendations, emphasizing standardized definitions, phenotyping, and timing of assessment. The document was developed through a systematic literature search and international expert consensus using the Delphi process.

BLAD can arise from allograft-related causes (e.g., donor–recipient size mismatch, airway complications, allo-immune mechanisms, severe primary graft dysfunction) or factors external to the allograft (e.g., chest wall deformities, diaphragm dysfunction, obesity, pleural complications). The document proposes targeted investigations—including spirometry, imaging, bronchoscopy, cardiac evaluation, and clinical assessment—to identify reversible contributors.

We recognize that subnormal lung function may still allow patients to lead normal lives compared to patients who reach normal function. However, existing studies indicate that these patients face reduced survival and potential interference with CLAD diagnosis. BLAD provides an additional dimension of clinical and scientific insight in lung transplant follow-up care. Our intention is for this construct to trigger further evaluation, reflection, and investigation so that we can assess strategies to improve baseline function across all lung transplant populations. This process naturally involves discussion with patients, as is routinely done in lung transplant follow-up care. Pediatric definitions remain challenging due to patient and lung growth and feasibility of spirometry.

The consensus highlights research priorities: refining the relationship between BLAD and CLAD, characterizing the causes of BLAD and the individual prognostic associations (including where no cause is identifiable), and developing prevention/treatment strategies. While not a disease like CLAD, BLAD is a clinical state warranting standardization to guide prognosis, research, and potential interventions.

ACKNOWLEDGMENTS

The authors would like to express our sincere gratitude to Dr. Maarten Engel of the Erasmus University Medical Library for his invaluable support in developing and executing the comprehensive search strategy, and to Charlotte Sybrecht, Hannover Medical School for her essential contributions in designing the Delphi surveys and analyzing the results.

APPENDIX A. SUPPORTING INFORMATION

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2026.05.034.

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