Prognostic validation of the 2019 International Society for Heart and Lung Transplantation chronic lung allograft dysfunction states in lung transplant recipients

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Analysing CLAD states in a simulated prospective assessment in >10 000 pulmonary function tests from 482 lung allograft recipients, "Possible" CLAD emerged as the earliest CLAD stage independently associated with mortality https://bit.ly/4aRG8J0

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Abstract

Background The 2019 ISHLT consensus chronic lung allograft dysfunction (CLAD) definition introduced a standardised classification for CLAD into Potential, Possible, Probable and Definite stages, based on the degree and persistence of forced expiratory volume in 1 s (FEV_1) decline. While Probable and Definite CLAD have been associated with graft loss, the significance of earlier stages remains unclear. This study aimed to validate the 2019 ISHLT CLAD classification system under simulated prospective conditions and to define their prognostic and clinical relevance.

Methods In 482 lung allograft recipients with measurable baseline FEV_1, CLAD states were assigned longitudinally for 10 312 pulmonary function tests according to ISHLT 2019 criteria. Each CLAD state was modelled as a time-dependent covariate to assess mortality risk in multivariable Cox regression analysis. Transitions between CLAD stages were evaluated by Kaplan–Meier and Cox regression models.

Results Possible CLAD was the earliest stage independently associated with increased mortality (HR 2.8, 95% CI 1.7–4.5), similar to Probable and Definite CLAD (HR 3.5 (1.8–7.6) and 3.5 (2.4–5.2), respectively). Most lung allograft recipients with Possible CLAD progressed to Probable/Definite CLAD, confirming its clinical importance. In contrast, Potential CLAD frequently resolved and was not associated with increased mortality, identifying it as an early but reversible warning signal.

Conclusion Potential CLAD shows uncertain prognostic significance, underscoring the need for biomarkers to identify patients at risk of progression. Possible CLAD is independently linked to increased mortality and defines the earliest actionable stage of chronic allograft dysfunction, for timely intervention.

Introduction

Lung transplantation represents a last-line therapeutic option for end-stage lung diseases. Long-term survival is limited, especially when compared with other solid-organ transplants [1]. The development of chronic lung allograft dysfunction (CLAD) is regarded as the major factor limiting long-term survival [1–3]. CLAD is defined as a sustained loss of ⩾20% in forced expiratory volume in 1 s (FEV_1) from the post-transplant baseline, after exclusion and treatment of other identifiable causes such as infection, airway complications or pleural effusion.

Since its first description, CLAD has been recognised as a heterogeneous entity encompassing multiple clinical phenotypes and temporal patterns of progression. To improve diagnostic consistency, the International Society for Heart and Lung Transplantation (ISHLT) published an updated consensus classification in 2019 [4]. This guideline introduced a stepwise framework with four diagnostic states – Potential, Possible, Probable and Definite CLAD – based on the magnitude and persistence of FEV_1 decline over time. While intended to standardise early recognition and reporting and to account for transient declines, the prognostic validity and real-world applicability of these stages remain incompletely understood.

The clinical relevance of the intermediate CLAD stages has recently become a focus of investigation. The multicentre CTOT-20 study by Todd *et al.* [5] demonstrated that Probable CLAD is a strong predictor of graft loss, with most affected patients (~80%) progressing to Definite CLAD. In their editorial to the research article by Todd *et al.*, Combs and Dilling [6] emphasised that Probable CLAD might be a sufficient criterion to warrant inclusion in clinical trials and early therapeutic intervention. However, neither of these studies systematically addressed the earlier stages Potential and Possible CLAD in a longitudinal manner.

In daily practice, clinicians must interpret serial lung function data without the benefit of hindsight. Declines that later recover are often indistinguishable at onset from those that progress to irreversible dysfunction. Retrospective classification, which re-labels reversible episodes as No CLAD, may therefore exaggerate the apparent risk associated with early states. Conversely, prospective application of the ISHLT 2019 definitions reflects true clinical decision-making but has rarely been evaluated in large datasets, given the immense efforts needed assessing the etiology of every single FEV_1 decline in a patient trajectory and attributing it to CLAD or a differential diagnosis [7, 8]. Distinguishing transient from prognostically relevant decline is crucial, as overdiagnosis may prompt unnecessary interventions, whereas under-recognition delays therapy during the narrow window when allograft injury may still be reversible.

Single lung transplant recipients represent an additional high-risk subgroup, as they rely on one allograft only and thus experience amplified variability in spirometry measurements [8]. Whether early functional declines carry similar prognostic weight in single *versus* double lung transplantation remains uncertain [9]. Also, the interaction with baseline allograft dysfunction, defined by subnormal baseline FEV_1, warrants clarification, as it may predispose patients to earlier or more severe CLAD progression [10, 11].

Against this background, we aimed to evaluate longitudinal lung function trajectories and CLAD progression in a large, single-centre cohort of lung transplant recipients according to the 2019 ISHLT classification with each single FEV_1 decline of $\geqslant$10% from baseline graded into Potential, Possible, Probable or Definite CLAD after excluding other causes of FEV_1 decline according to the extent and persistence of decline [4]. Classification was applied in a simulated prospective manner to mirror real-world clinical evaluation.

By validating the ISHLT 2019 classification across thousands of pulmonary function tests (PFTs), this study aims to delineate the prognostic and diagnostic significance of CLAD states Potential CLAD, Possible CLAD, Probable CLAD and Definite CLAD in a large-scale dataset with focus on the diagnostic intermittent states and to provide practical clinical implications for their use in risk stratification, surveillance and early therapeutic intervention after lung transplantation.

Materials and methods

Ethics

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

Patient selection and study design

We retrospectively reviewed all adult patients who underwent single or double lung transplantation at the LMU University Hospital, Munich, Germany, between 1 January 2010 and 31 December 2018. Patients were followed until death, re-transplantation or administrative censoring on 1 August 2024. Recipients were excluded if insufficient PFT data were available to define a baseline FEV_1.

Lung function measurements

Spirometry and lung volume measurements were performed using body plethysmography systems (Jäger, Würzburg, Germany) in accordance with European Respiratory Society (ERS)/American Thoracic Society

(ATS) guidelines [12]. Routine PFTs were typically conducted at standardised intervals every 3 months, or earlier if clinically indicated. Baseline FEV_1 was established for each patient as defined by the ISHLT 2019 CLAD classification criteria. Pulmonary function data were supplemented by demographic characteristics, underlying diagnosis, transplant type and available histopathological reports. All data were extracted from institutional electronic medical records.

Outcomes

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

CLAD definitions

CLAD staging was performed in accordance with the 2019 consensus report of the International Society for Heart and Lung Transplantation (ISHLT) [3]. All CLAD classifications were assigned after thorough exclusion of alternative causes for lung function decline, including infection, airway complications and pleural pathology.

Baseline FEV_1 was defined as the mean of the two highest post-transplant FEV_1 values recorded at least 3 weeks apart. All subsequent FEV_1 measurements were expressed as a percentage of this individual baseline. CLAD stages were classified as follows: Potential CLAD was defined as a single FEV_1 decline <90% of baseline FEV_1. Possible CLAD was defined as one or more FEV_1 declines below 80% of baseline FEV_1 within 3 weeks. Probable CLAD was defined as two or more pulmonary function measurements with an FEV_1 of <80% of baseline FEV_1 >3 weeks and <3 months apart. Definite CLAD was defined as two or more pulmonary function measurements with an FEV_1 of ⩽80% of baseline FEV_1 at least 3 months apart. Further details are described in the supplementary methods. An illustration of these staging criteria is provided in supplementary figure S1.

CLAD status was not assigned at a single timepoint but was evaluated dynamically over time based on the magnitude and persistence of unexplained FEV_1 decline after exclusion of alternative causes, following the 2019 ISHLT consensus definition. The observation of each PFT with an FEV_1 decline of >10% or >20% from baseline FEV_1 triggered structured diagnostic evaluation. CLAD states were assigned in a time-resolved manner at each PFT. Early CLAD states were intentionally treated as intermediate diagnostic states within an evolving disease process rather than as established chronic dysfunction.

To reflect real-world clinical assessment, CLAD state evolution was evaluated in a time-resolved manner, with states allowed to progress or regress dynamically over follow-up. To simulate prospective clinical assessment, CLAD adjudication was performed by experienced lung transplant physicians in a time-resolved manner using only information available up to the respective PFT indicating an FEV_1 decline. Using this procedure, each patient was assigned to the No CLAD state. At each PFT date, the state was updated and reassigned to one of the following states of No CLAD, Potential CLAD, Possible CLAD, Probable CLAD or Definite CLAD based on if there was a FEV_1 decline and the CLAD adjudication.

For survival analysis, CLAD state was modelled as a time-dependent covariate to account for temporal variation in classification. In the primary analysis, CLAD staging was applied in a simulated prospective manner, meaning only data available up to each timepoint were used to assign CLAD states, closely reflecting real-world clinical decision-making (figure 1).

To assess the influence of classification approach on prognostic interpretation, we also performed a retrospective, time-resolved CLAD classification, which allowed reclassification of transient FEV_1 declines based on future recovery. Analyses associated with the retrospective time-resolved CLAD classification are reported in supplementary figure S2.

Statistics

Lung function data are presented as median and range. Right-censored survival data were analysed using Kaplan–Meier estimators. Furthermore, transition rates from the diagnosis of a first Potential CLAD or Possible CLAD to Probable CLAD or to Definite CLAD were analysed using Kaplan–Meier estimators. Timepoint of Potential or Possible CLAD was defined by the PFT observing the 10% or 20% FEV_1 loss from baseline FEV_1. Here, time of diagnosis of Probable or Definitive CLAD was defined as the second pulmonary function measurement that established this diagnosis.

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

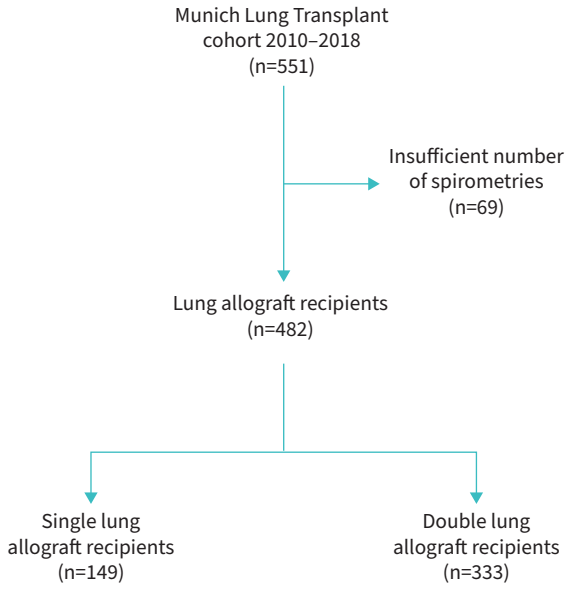


FIGURE 1 Study flow chart derived from patients undergoing lung transplantation at the Munich Lung Transplant programme between 2010 and 2018. Patients with an insufficient number of available spirometry measurements were excluded. The study population comprised 482 lung allograft recipients, including 149 single lung and 333 double lung transplant recipients.

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

A total of 551 lung allograft recipients were screened for inclusion. 69 patients were excluded due to insufficient spirometry data to establish a baseline FEV_1, defined as the absence of at least two PFTs spaced ⩾21 days apart. The final study population included 482 lung allograft recipients with a total of 10 312 FEV_1 measurements available for CLAD state classification (figure 1). Baseline characteristics of the included lung allograft recipients are summarised in table 1.

CLAD classification was performed according to the 2019 ISHLT consensus criteria using a simulated prospective time-resolved approach (figure 2a). At each timepoint, only historical spirometry data were used to assign CLAD states, with the possibility of downgrading previously assigned states if subsequent lung function recovered. This resulted in dynamic state transitions over time, including rare instances of reversion from Possible to Potential or No CLAD (figure 2b). CLAD state proportions over time are depicted in supplementary Figure S3.

Among the 482 patients, 324 lung allograft recipients experienced at least one episode of Potential CLAD, and 233 experienced an episode of Possible CLAD. Notably, the likelihood of progression from Potential to Probable or Definite CLAD was significantly higher in single lung transplant recipients compared to double lung recipients (hazard ratio (HR) 2.3, 95% confidence interval (CI) 1.6–3.4; figure 3a). In contrast, transition from Possible to Probable or Definite CLAD occurred swiftly and with similar frequency in both transplant groups (HR 1.3, 95% CI 0.9–1.8; figure 3b).

CLAD states were analysed as time-dependent covariates in univariate and multivariable Cox regression models, with allograft survival (death or re-transplantation) as the primary outcome. In the simulated prospective classification, Possible, Probable and Definite CLAD were each independently associated with increased mortality with adjusted HR of 2.78 (95% CI 1.72–4.51, p<0.001), 3.46 (95% CI 1.57–7.62, p=0.002) and 3.53 (95% CI 2.40–5.20, p<0.001), respectively (table 2). In contrast, Potential CLAD was not significantly associated with increased mortality in the prospective CLAD state classification (HR 1.19, 95% CI 0.81–1.73, p=0.38) (table 2) after adjusting for known confounder like transplant indication, transplant type, obstruction seen in spirometry and transplant age.

TABLE 1 Baseline demographics of lung allograft recipients

	Double lung allograft recipients	Single lung allograft recipients	p-value
Cohort size, n	333	149	
Age at transplantation years, median (range)	50 (39–57)	62 (59–64)	<0.001[#]
Sex			
Female, n/N (%)	158/333 (47%)	66/149 (44%)	0.521[¶]
Male, n/N (%)	175/333 (53%)	83/149 (56%)	0.521[¶]
Underlying disease, n/N (%)			
COPD/emphysema	67/333 (20%)	61/149 (41%)	<0.001[¶]
Interstitial lung disease	162/333 (49%)	76/149 (51%)	<0.001[¶]
Cystic fibrosis/bronchiectasis	75/333 (23%)	0	<0.001[¶]
Pulmonary hypertension	16/333 (5%)	0	<0.001[¶]
Redo lung transplant	9/333 (3%)	8/149 (5%)	<0.001[¶]
Others	4/333 (1%)	4/149 (3%)	<0.001[¶]
Overall baseline lung function, median (range)			
FEV_1, L	2.63 (2.17–3.26)	1.83 (1.43–2.34)	<0.001[#]
FVC, L	3.3 (2.74–4.1)	2.7 (2.21–3.39)	<0.001[#]
TLC, L	5.97 (5.1–6.97)	6.14 (4.65–7.26)	0.866[#]
FEV_1 % pred	0.86 (0.72–1.03)	0.65 (0.55–0.79)	<0.001[#]
FVC % pred	0.87 (0.74–1.03)	0.78 (0.65–0.88)	<0.001[#]
TLC % pred	1.01 (0.88–1.15)	0.96 (0.79–1.25)	0.585[#]
Transbronchial biopsies, n/N (%)			
Observed acute cellular rejections	59/333 (18%)	22/149 (15%)	0.423[¶]
Observed lymphocytic bronchiolitis	210/333 (63%)	87/149 (58%)	0.330[¶]

Of note, 69 patients were excluded from the chronic lung allograft dysfunction (CLAD) classification as they did not reach a measurable baseline FEV_1. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity. [#]: Mann–Whitney U-test; [¶]: Chi-squared test for categorical data (Fisher exact test for two cells (>25%)).

A comparison analysis using a retrospective time-resolved CLAD classification was conducted to assess the influence of classification method on prognostic interpretation. In this model, CLAD states were assigned using the full set of spirometry data available across follow-up, allowing for reclassification of early lung function declines that qualified at this timepoint as CLAD state that later resolved. The full results of this analysis are presented in supplementary Figure S2 and Table S1. Here, in contrast to the prospective approach, Potential CLAD in the retrospective model was significantly associated with increased mortality (adjusted HR 3.02, 95% CI 2.04–4.48, p<0.001).

Discussion

In this study, we applied the ISHLT 2019 CLAD consensus definition [4] to a large single-centre cohort using a simulated prospective time-resolved approach with over 10 000 PFTs of 482 lung transplant recipients.

This effort represents one of the most comprehensive spirometry-based CLAD state classifications to date and allowed dynamic tracking of CLAD state transitions over time and evaluation of their prognostic value. Our analysis showed that Possible CLAD was the earliest CLAD state independently associated with increased mortality, while Potential CLAD was frequently reversible and not associated with adverse outcomes when classified in real time.

A key aspect of this study is the distinction between CLAD as a confirmed disease state and earlier diagnostic stages observed. Early CLAD stages, like Potential, Possible and Probable CLAD, reflect diagnostic states at a time when the future trajectory of lung function cannot yet be determined. This distinction mirrors real-world clinical practice, where clinicians evaluating an unexplained decline in FEV_1 cannot know whether the decline will persist, progress or resolve. The ISHLT 2019 framework accommodates this uncertainty.

The evolution of CLAD states in our cohort followed a plausible and temporally ordered trajectory (figure 1). Most patients with Possible CLAD progressed within weeks to Probable or Definite CLAD, aligning with the 2019 ISHLT framework (figure 2b). Conversely, a significant proportion of Potential CLAD

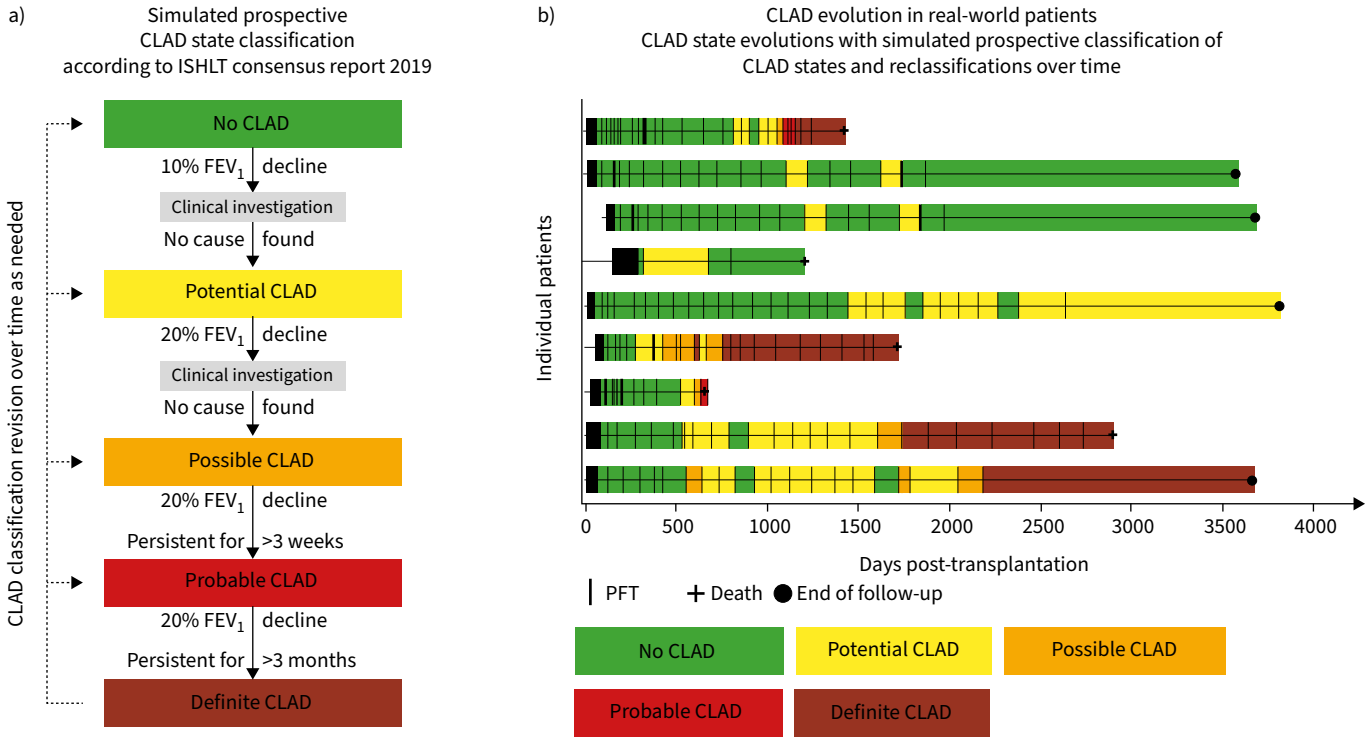


FIGURE 2 Chronic lung allograft dysfunction (CLAD) evolution in lung allograft recipients. a) A simulated prospective time-resolved CLAD classification according to the 2019 ISHLT consensus document was performed considering only data available up to the timepoint of classification. If lung function declines classified as *e.g.* Possible CLAD (unexpectedly) resolved, classification was revised. b) Depiction of CLAD state evolution using this classification, also showing revision of CLAD states after (unexpected) improvements of lung function in some patients.

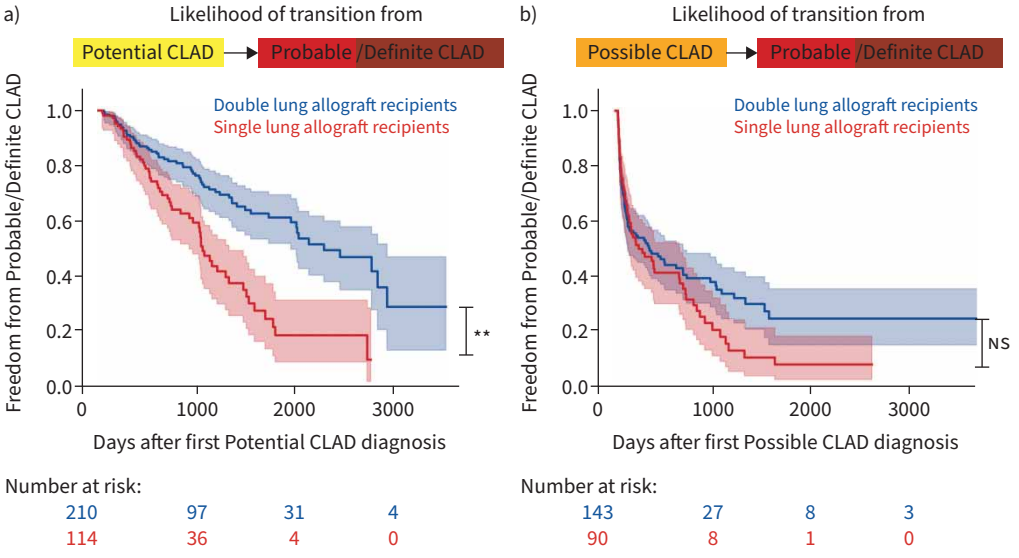


FIGURE 3 Single lung allograft recipients have a higher risk to transition from their first Potential CLAD diagnosis to Probable CLAD or Definite CLAD diagnosis. a) 210 double lung allograft recipients and 114 single lung allograft recipients experienced at least one potential CLAD event. The risk of transitioning later into a probable or definite CLAD state was higher in single lung allograft recipients (HR 2.3, 95% CI 1.6–3.4), shown here using Kaplan–Meier estimates. b) Transition from Possible CLAD to Probable/Definite CLAD was swift and occurred in most lung allograft recipients with no substantial difference between single and double lung allograft recipients (HR 1.3, 95% CI 0.9–1.8). CLAD: chronic lung allograft dysfunction. **p<0.01; NS: nonsignificant.

TABLE 2 Lung allograft survival analysis by univariate and multivariate time-dependent Cox regression analysis using a simulated prospective classification of chronic lung allograft dysfunction (CLAD) states

Variable	n	Univariable Cox regression analysis			Multivariable Cox regression analysis		
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Transplant type							
Double lung transplantation	333		reference			reference	
Single lung transplantation	**149**	**2.172**	**1.678–2.812**	**<0.001**	**1.597**	**1.196–2.134**	**0.002**
CLAD[#] simulated prospective classification							
No CLAD	[¶]		reference			reference	
Potential CLAD	[¶]	1.378	0.955–1.987	0.087	1.185	0.812–1.728	0.380
Possible CLAD	[¶]	**3.602**	**2.278–5.696**	**<0.001**	**2.782**	**1.718–4.507**	**<0.001**
Probable CLAD	[¶]	**4.480**	**3.135–6.404**	**<0.001**	**3.460**	**1.570–7.622**	**0.002**
Definite CLAD	[¶]	**4.542**	**2.099–9.826**	**<0.001**	**3.532**	**2.401–5.195**	**<0.001**
Obstruction[#]							
FEV_1/FVC ≥70% predicted	[¶]		reference			reference	
FEV_1/FVC <70% predicted	[¶]	**1.954**	**1.519–2.515**	**<0.001**	1.223	0.915–1.636	0.174
Diagnosis							
Interstitial lung disease	238		reference			reference	
Pulmonary vascular diseases	16	0.791	0.348–1.799	0.576	1.027	0.446–2.363	0.950
Cystic fibrosis/bronchiectasis	75	0.806	0.542–1.201	0.289	1.099	0.725–1.664	0.657
COPD/emphysema	**128**	**1.461**	**1.053–1.879**	**0.020**	1.182	0.864–1.618	0.295
Redo transplantation	**17**	**2.405**	**1.379–4.194**	**0.002**	**1.848**	**1.048–3.256**	**0.034**
Other	8	0.561	0.178–1.767	0.323	0.442	0.139–1.40	0.165
Transplant age							
38–50 years	115		reference			reference	
<38 years	47	0.612	0.357–1.050	0.075	0.962	0.590–1.567	0.876
51–57 years	112	0.996	0.693–1.431	0.981	1.154	0.733–1.817	0.536
58–61 years	90	1.090	0.748–1.589	0.654	0.978	0.606–1.58	0.929
>61 years	118	0.932	0.651–1.335	0.701	0.872	0.548–1.388	0.564

Bold data indicates significant difference to reference. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: modelled as time-dependent covariate; [¶]: modelled as time-dependent covariate; category membership may change over time, hence baseline absolute counts (n) are not applicable.

events resolved spontaneously or after treatment of confounding conditions (figure 2a), supporting its designation as an early warning signal rather than a disease-defining state. Our findings confirm the practical utility of the staged CLAD model.

The identification of Possible CLAD as the earliest prognostically significant stage has direct implications for clinical care. This state should prompt expedited diagnostic workup, closer monitoring and consideration of early intervention strategies. Potential CLAD, historically also referred to as 0-p CLAD and related to the upcoming concept of acute lung allograft dysfunction, has been associated with CLAD [13, 14], but not been assessed as mortality risk factors in context with the 2019 Consensus Classification. In contrast to Possible CLAD, Potential CLAD events should alert clinicians to early dysfunction but warrant a more conservative approach focused on surveillance and diagnostic workup. The magnitude of the FEV_1 declines seem to be a key determinant of prognostic significance after lung transplantation. This is reflected by the Potential CLAD (>10% FEV_1 decline) and Possible CLAD (>20% FEV_1 decline) thresholds.

Our side-by-side comparison of simulated prospective and retrospective CLAD classification reveals critical methodological insight: retrospective classification, by reassigning patients who recovered from early declines to the No CLAD group, overestimates the risk associated with early stages like Potential CLAD. This discrepancy illustrates a key limitation of retrospective adjudication: FEV_1 declines that initially qualified as Potential CLAD but later reversed were excluded from CLAD classification altogether, artificially enriching the Potential CLAD group with only those patients who ultimately had poor outcomes. Notably, the hazard ratios for Possible CLAD, Probable CLAD and Definite CLAD were also higher in the retrospective model compared to the prospective model, suggesting a similar bias towards worse outcomes when future information is used to refine classification. Prospective classification more faithfully mirrors clinical reality and provides a more accurate estimate of the prognostic impact of each CLAD state. For this reason, all primary analyses in this study were based on prospective classification.

Our results confirm and extend the findings of the Todd *et al*. study[5], which highlighted Probable CLAD as a strong predictor of graft loss. Building on this, we demonstrate that Possible CLAD also carries a substantial independent risk and should be considered a clinically actionable state, despite diagnostic workup varying between centres [15]. The editorial commentary by Combs and Dilling [6] emphasised the trial relevance of Probable CLAD; our data suggest that Possible CLAD may in fact offer an even (slightly) earlier window for screening and intervention. Moreover, our study is among the first to systematically assess Potential CLAD and to do so within a real-time classification framework.

Our findings support the use of Possible CLAD as a pragmatic end-point or inclusion criterion in future interventional trials. Because this state is both identifiable in real time and associated with poor outcomes, it offers a valuable opportunity to intervene before irreversible decline, while the same is overall not true for Potential CLAD. Trial designs that rely solely on Definite CLAD as an end-point may miss this earlier and potentially modifiable disease stage. Importantly, this does not imply that Possible CLAD represents established chronic disease, but rather that it marks the earliest diagnostic state at which the risk of progression to definitive chronic dysfunction becomes clinically meaningful.

We observed that single lung transplant recipients faced a significantly higher risk of progressing from Potential to Probable/Definite CLAD. This may reflect the greater vulnerability of a single allograft, where a decline in function cannot be compensated for by a second lung. Notably, single lung allograft recipients were significantly more likely to transition from Potential CLAD to advanced CLAD stages. However, lung function measurements in these showed increased variability and reduced prognostic discrimination of spirometry-based thresholds in prior studies [8], highlighting this important limitation of applying the ISHLT 2019 CLAD framework in single lung transplantation.

While spirometry remains the cornerstone of CLAD monitoring, our data highlight the limitations of relying solely on FEV_1 trajectories to predict outcomes. Potential CLAD represents a heterogeneous state with variable outcomes, suggesting the need for additional risk stratification tools. Biomarkers, including imaging features, bronchoalveolar lavage profiles, and molecular signatures, may help distinguish between patients likely to progress and those with transient dysfunction [16]. Integration of physiological and biologic data may ultimately improve early detection and personalised management of chronic allograft dysfunction.

A major strength of this study is the exhaustive manual classification of over 10 000 PFTs according to the ISHLT 2019 framework, enabling granular time-resolved CLAD state tracking. The large cohort and rigorous methodology lend robustness to our findings. Nonetheless, several limitations should be noted. First, the retrospective and single-centre design make this study vulnerable to centre-specific effects, residual confounding and selection bias. Second, PFT data availability was naturally not uniform across all timepoints, raising the possibility of informative censoring due to indication-driven testing. As spirometry is performed at discrete and variably spaced timepoints, the apparent onset may be influenced by testing intensity rather than true biological dynamics, which further supports the use of staged thresholds rather than continuous decline modelling.

Conclusions

In conclusion, prospective application of the ISHLT 2019 CLAD classification system in a large real-world cohort demonstrates that Possible CLAD is the earliest stage independently associated with mortality. Potential CLAD often reflects reversible or nonprogressive dysfunction and should not be considered prognostically definitive in the absence of additional risk markers. These findings refine the clinical interpretation of early FEV_1 declines, support the use of Possible CLAD in risk stratification and trial design, and underscore the importance of context-aware classification when assessing graft function over time.

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Provenance: Submitted article, peer reviewed.

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

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