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Mapping acute lung allograft dysfunction of unknown cause after lung transplantation: Insights from clinical and radiological patterns

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KEYWORDS:
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Follow-up

BACKGROUND: Acute lung allograft dysfunction (ALAD) is a recently defined post-transplant clinical entity characterized by acute, potentially reversible graft dysfunction. The aim of this study was to describe the clinical and radiological features of ALAD in which no identifiable underlying cause could be recognized, hereafter referred to as idiopathic ALAD (i-ALAD).

METHODS: Among all bronchoscopies with bronchoalveolar lavage and transbronchial lung biopsy performed in a single-center cohort of lung transplant recipients between 2013 and 2024 (n = 497), we retrospectively identified episodes of i-ALAD. These patients were subsequently evaluated for clinical characteristics and high-resolution computed tomography (HRCT) findings. For exploratory purposes, imaging findings were compared with those of a cohort of lung transplant recipients with biopsy-proven acute cellular rejection (ACR).

RESULTS: Among 158 lung transplant recipients, 20 cases of i-ALAD were identified, corresponding to an incidence of 12.4%. ALAD was reversible in most patients, although 2 progressed to chronic lung allograft dysfunction (CLAD). Six patients (30%) met criteria for baseline lung allograft dysfunction (BLAD), and 6 had a history of recurrent ACR. HRCT most frequently demonstrated bronchial wall thickening (85%), smooth interlobular septal thickening, and pulmonary micronodules (80%), with characteristic lobar distribution patterns. Compared with ACR, i-ALAD was associated with a significantly higher prevalence of bronchiectasis/bronchiolectasis, air trapping, and pleural effusion.

CONCLUSIONS: ALAD is a relatively frequent and potentially reversible complication after lung transplantation but may represent a risk factor for subsequent CLAD development. Distinctive HRCT features may assist in identifying ALAD of unknown cause and stratifying patients according to the

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risk of disease progression. Prospective, multicenter studies are warranted to validate these findings and further refine the clinical and radiological characterization of i-ALAD.
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Background

Lung transplantation (LTX) is an established therapeutic option for selected patients with end-stage pulmonary diseases, offering improved survival and quality of life. Despite advances in surgical techniques and immunosuppressive strategies, lung transplant recipients remain vulnerable to a range of alloimmune and non-alloimmune complications. Infections, acute cellular rejection (ACR), and antibody-mediated rejection (AMR) represent the most common acute complications and may lead to significant, potentially severe, allograft dysfunction. Importantly, these events are also recognized risk factors for the subsequent development of chronic lung allograft dysfunction (CLAD).

In this context, the concept of acute lung allograft dysfunction (ALAD) was introduced as a novel clinical entity during the 2024 International Society for Heart and Lung Transplantation (ISHLT) International Congress, with a dedicated consensus document currently in preparation.[1] ALAD refers to acute lung injury occurring after LTX that may either resolve or progress to CLAD. According to the proposed—yet unpublished—definition, ALAD is characterized by a reversible deterioration in lung allograft function lasting less than 3 months and occurring at least 72 hours after LTX. Functional decline is defined by a reduction of more than 10% in forced expiratory volume in one second (FEV_1) and/or worsening oxygenation.

ALAD may be further classified based on the presence or absence of an identifiable underlying cause. When an etiological factor—such as ACR, AMR, or infection—is identified, the condition is referred to as ALAD with a detected cause. However, far less is known about ALAD cases in which no identifiable cause can be recognized, and, to date, data describing the radiological presentation of this subgroup remain limited.

The aim of this single-center retrospective study was to describe the clinical and high-resolution computed tomography (HRCT) features of a cohort of lung transplant recipients with ALAD in which no identifiable cause can be recognized, hereafter referred to as idiopathic ALAD, with the objective of improving characterization of this emerging entity and exploring potential associations with comorbidities, as well as pre- and post-transplant clinical variables.

Materials and methods

Study population

Among patients who underwent LTX at the Transplant Center of the University Hospital of Siena between January 1, 2013, and December 31, 2024 (n = 158), we identified 20 patients who met the diagnostic criteria for ALAD in whom no identifiable underlying cause could be recognized. For the purposes of the present study, and pending the standardized classification expected to be proposed in the forthcoming ISHLT consensus statement, these cases were operationally defined as i-ALAD.

Diagnostic criteria of ALAD included worsening oxygenation and/or a decline in $FEV_1 \geq 10\%$ from the highest value recorded in the preceding 3-6 months and/or the presence of new radiological abnormalities, in the absence of any identifiable cause of graft dysfunction.

The diagnosis of i-ALAD was retrospectively established through a comprehensive review of clinical, functional, radiological, histopathological, and microbiological data.

The study cohort was identified from all bronchoscopies with bronchoalveolar lavage (BAL) and transbronchial lung biopsy performed in 158 lung transplant recipients between 2013 and 2024 (n = 497). Procedures were excluded if biopsy specimens were considered non-diagnostic for histopathological assessment. In accordance with ISHLT recommendations, a biopsy was deemed adequate when it contained at least 5 fragments of well-expanded alveolated lung parenchyma, each including bronchioles and at least 100 alveoli, allowing reliable assessment of perivascular and/or interstitial infiltrates, with at least 1 to 2 bronchioles available for airway grading.

Availability of a HRCT performed prior to the bronchoscopic procedure was required for inclusion. Additional exclusion criteria included the identification of an alternative diagnosis, positive microbiological results, or procedures performed in the absence of clinical, functional, or radiological deterioration.

Through this stepwise selection process, 20 episodes fulfilling the predefined criteria for idiopathic acute lung allograft dysfunction (i-ALAD) were identified, corresponding to 20 individual patients (Figure 1).

The presence of bronchial stenosis was not considered an exclusion criterion, provided that it was stable on bronchoscopic examination and not deemed responsible for the observed clinical, functional, or radiological deterioration.

All patients provided written informed consent for participation in the study (Protocol Respir1).

Immunosuppressive protocol

The institutional immunosuppressive protocol included basiliximab induction therapy and maintenance immunosuppression

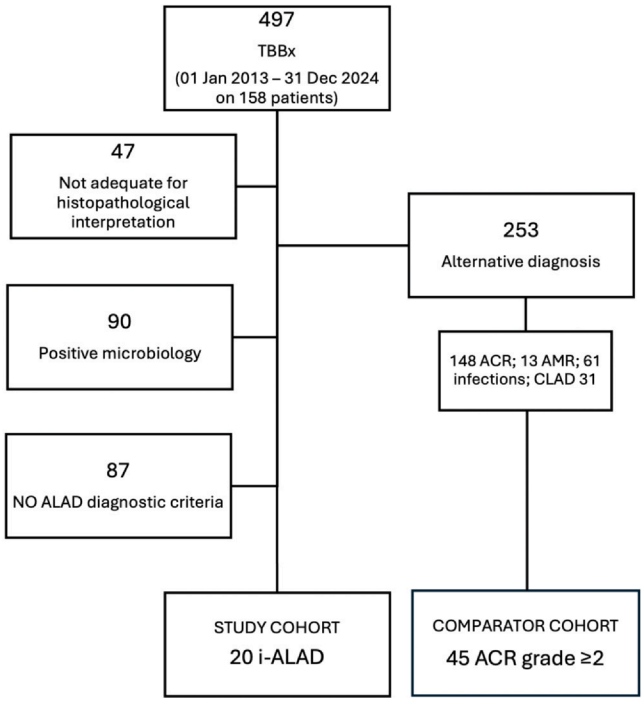

Figure 1 Flow diagram adopted for the retrospective identification of patients with i-ALAD ($n = 20$) and ACR of grade ≥2 with HRCT available ($n = 45$).

with prednisone, cyclosporine or tacrolimus, and mycophenolate mofetil. In frail patients or those at high risk of infection, mycophenolate mofetil was withheld. Mycophenolic acid was used in cases of intolerance to mycophenolate mofetil. Everolimus was introduced after 3-6 months post-transplant in patients with renal dysfunction—together with tacrolimus minimization—or in those with concomitant malignancies.

Clinical data collection

For the entire cohort, pre-transplant variables collected included age, body mass index (BMI), smoking history, underlying lung disease, comorbidities, waiting-list time, and the use of extracorporeal membrane oxygenation (ECMO) as a bridge to transplantation.

Intraoperative and postoperative variables included transplant type (single or bilateral), graft ischemia time, requirement for blood transfusions, and significant hypotension, defined as a cardiac index < 2.2 L/min/m² and systolic blood pressure < 90 mmHg or the need for vasoactive agents to maintain these values. Additional variables collected were the use of intraoperative and postoperative ECMO, duration of invasive mechanical ventilation (for patients undergoing tracheostomy, the interval from transplantation to tracheostomy was considered), severity of primary graft dysfunction (PGD) at 72 hours,[2] duration of vasoactive drug therapy, duration of inhaled nitric oxide (NO) therapy, length of intensive care unit (ICU) stay, total post-transplant hospital length of stay, and the immunosuppressive regimen.

Baseline lung allograft dysfunction (BLAD) was defined as both FEV_1 and FVC remaining below 80% of predicted values in 2 consecutive tests performed at least 3 weeks apart by 1-year post transplant.[3,4]

i-ALAD characterization and outcomes

For each patient with i-ALAD, the following data were collected: time from transplantation to the i-ALAD event; history of refractory ACR, defined as more than 1 episode within the first year post-transplant or more than 3 episodes overall; AMR; prior infections; and i-ALAD outcome, including progression to CLAD.

Based on spirometric data, recovery was defined as improvement of lung function to the pre-i-ALAD baseline, whereas stabilization was defined as persistently reduced lung function without further decline.

Radiological analysis

HRCT scans were reviewed for all i-ALAD patients by a thoracic radiologist with expertise in LTX. The presence or absence of the following findings was assessed: mosaic attenuation, air trapping, large airway stenosis, bronchial wall thickening, peribronchial cuffing, tree-in-bud pattern, micronodules, bronchiectasis, bronchiolectasis, intralobular ground-glass opacities, peribronchial ground-glass opacities, crazy paving, irregular and smooth interlobular septal thickening, organizing pneumonia, peripheral consolidation, architectural distortion, volume loss, hilar retraction, pleural effusion, pleural thickening, and lymph node enlargement. For each radiological feature, lung distribution (upper, middle, and lower lobes) and severity (graded on a 4-point scale) were recorded.

CT examinations were performed without intravenous contrast using a high-resolution protocol with volumetric acquisition and submillimeter collimation. Scans were acquired at full inspiration in the supine position.

In all i-ALAD patients, inspiratory scans were complemented by low-dose expiratory imaging to assess air trapping. In 5 of the 45 patients with ACR, expiratory scans could not be adequately obtained because of patient-related factors or the presence of post-transplant cardiopulmonary support devices.

Multiplanar reconstructions and maximum-intensity projections were used to evaluate nodules and micronodules, while minimum-intensity projection reconstructions were employed to enhance visualization of airway abnormalities.

Comparative cohort

Clinical and radiological findings in patients with i-ALAD were compared with those of a cohort of lung transplant recipients from the same institution with histologically proven ACR of grade ≥2 ($n = 45$). This comparison group was selected from the 497 bronchoscopies with BAL and transbronchial lung biopsy performed between 2013 and 2024 and was limited to patients for whom a high-resolution

chest CT performed immediately before bronchoscopy was available (Figure 1).

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 10 for Windows. Given the non-normal distribution of the data, non-parametric tests were applied. A 2-sided p value ≤ 0.05 was considered statistically significant. Between-group comparisons were conducted using the Mann-Whitney U test, while differences in prevalence in contingency tables were assessed using Fisher's exact test or the χ^2 test, as appropriate. Data are reported as median with interquartile range (25th-75th percentile), unless otherwise specified.

Results

General characteristics

The study population comprised 20 patients (14 males and 6 females) with a age of 52.3 years (IQR 35.6-60.6). Seventeen patients underwent bilateral LTX and 3 single LTX. The underlying indications for transplantation were pulmonary fibrosis ($n = 7$, 35%), cystic fibrosis ($n = 6$, 30%), chronic obstructive pulmonary disease ($n = 3$, 15%), and other conditions in 4 patients (20%), including post-ARDS pulmonary fibrosis, Langerhans cell histiocytosis, bronchiectasis, and systemic sclerosis-associated interstitial lung disease.

BMI was 21 kg/m² (IQR 19-23), and 13 patients (65%) had a history of smoking. Waiting time on the transplant list was 291 (61.5-707.75) days. Three patients (15%) required (ECMO) as a bridge to transplantation (Table 1).

The mean ischemia time was 260 min (IQR 240-307.5) for the first lung and 410 min (IQR 380-465) for the second lung. Intraoperative ECMO was used in 6 patients (30%), and in 5 cases (25%) it was continued postoperatively.

All patients received induction therapy with basiliximab and maintenance immunosuppression with prednisone and tacrolimus; mycophenolate mofetil was used in 14 patients (70%). None of the i-ALAD patients were receiving mycophenolic acid or everolimus.

Significant hypotension requiring vasoactive support occurred in 15 patients (75%) during the immediate postoperative period, with a mean duration of 60 hours (IQR 24-96). Blood transfusions were required in 10 patients (50%). Prolonged invasive mechanical ventilation (> 96 hours) was necessary in 12 patients (60%), and tracheostomy was performed in 5 (25%) because of difficult weaning. Inhaled NO therapy was required in 12 patients (60%), with a mean duration of 24 hours (IQR 0-48).

PGD developed in 15 patients (75%), including 6 cases of grade 1, 5 of grade 2, and 4 of grade 3. The median ICU stay was 9 days (IQR 7-18), and the median total hospital stay was 40.5 days (IQR 30.8-53.5) (Table 1).

Characteristics of i-ALAD

Idiopathic ALAD developed within the first year after transplantation in 14 patients (70%), with a mean interval from LTX to ALAD of 113 (87.5-315.25). Four patients (20%) had a history of refractory ACR, 3 (15%) had prior donor-specific antibody potivity (none was found positive at the time of i-ALAD), 6 (30%) had prior bacterial infection (with negative BAL cultures at the time of i-ALAD diagnosis), and 6 patients (30%) met criteria for BLAD. Only 2 patients had no other pre-existing conditions (Table 2).

In 14 patients, i-ALAD was diagnosed based on spirometric decline compared with the preceding 3-6 months, whereas in 6 patients the diagnosis was prompted by worsening oxygenation. At least 1 radiological abnormality was identified in all cases.

Six patients were already receiving azithromycin at the time of i-ALAD diagnosis, while 11 initiated azithromycin following the acute event. All patients received an increase in corticosteroid dosage for ALAD treatment: those developing ALAD within the first year post-transplant received steroid pulses (10 mg/kg/day for 3 consecutive days), whereas patients at longer intervals from transplantation were treated with prednisone at a dose of 1 mg/kg administered 7-15 days, followed by a gradual tapering of about 20% every 15-30 days.

Regarding outcomes, pulmonary function stabilized in 9 patients (45%), and complete recovery within 3 months was observed in an additional 9 patients (45%). In 2 cases (10%), i-ALAD progressed to CLAD. Notably, 2 i-ALAD episodes occurred after a diagnosis of CLAD, and both resulted in stabilization (Table 2). Among patients who initially recovered, 7 later developed CLAD after a median of 226 days (IQR 40-812) from the ALAD episode.

Radiological analysis

The most frequent HRCT finding was bronchial wall thickening (85%), followed by smooth interlobular septal thickening and pulmonary micronodules (both 80%). Other common abnormalities included bronchiolectasis (75%), air trapping, bronchiectasis, and peripheral consolidations (each 65%), as well as irregular septal thickening and intralobular ground-glass opacities (55%). Pleural effusion was present in 70% of cases; in all patients, extensive diagnostic work-up failed to identify an attributable cause, and fluid overload was excluded. All patients underwent thoracentesis with cytological, biochemical, and microbiological analyses, all patients also received comprehensive cardiological evaluation, including cardiac ultrasound (Figure 1 supplement reports chest imaging of 5 patients with grade 3-4 pleural effusion before i-ALAD, at the time of the i-ALAD event, and during follow-up). In 2 cases the pleural effusion was already present prior to the diagnosis of i-ALAD, whereas in the remaining cases pleural effusion developed concomitantly with the i-ALAD episode. In all cases pleural effusion was associated with other

Table 1 Pre-operative, Intra-operative, and Post-operative Data of i-ALAD and ACR Patients

	i-ALAD	ACR	*p*-value
Number	20	42	
Age	52.33 (35.55-60.63)	51.56 (4.43-61.48)	0.91
Smoke history	13 (65%)	22 (53.4%)	0.87
BMI	21 (19-23)	23 (20-26)	0.053
Diagnosis			
• Pulmonary fibrosis	7 (35%)	14 (33.3%)	0.07
• COPD	3 (15%)	14 (33.3%)	
• Cystic fibrosis	6 (30%)	13 (30.9%)	
• Other diagnosis	4 (20%)	1 (2.3%)	
Comorbidities			
• Diabetes mellitus	6 (30%)	21 (50%)	0.17
• Arterial hypertension	7 (35%)	17 (40.4%)	0.78
• Hypercholesterolemia	4 (20%)	15 (35.7%)	0.25
• Osteoporosis	14 (70%)	29 (69%)	> 0.99
Time on the waiting list (days)	291 (61.5-707.75)	202 (85-646)	0.71
pre-LTX ECMO (Bridge)	3 (15%)	2 (4.7%)	0.31
LTX procedure			
• Single LTX	3 (15%)	17 (40.5%)	0.07
• Bilateral LTX	17 (85%)	25 (59.5%)	
Ischemic Time			
• 1° Lung (minutes)	260 (240-307.5)	254 (230-300)	0.52
• 2° Lung (if bilateral LTX) (minutes)	410 (380-465)	360 (242-430)	0.02*
Induction therapy (basiliximab or thymoglobulin)	20 (100%)	39 (92.8%)	0.54
CNI therapy			
• Cyclosporine	0 (0%)	13 (31%)	0.005*
• Tacrolimus	20(100%)	29 (69%)	
Mycophenolate mophetil	14 (70%)	25 (59.5%)	0.57
Severe hypotension/hemodynamic decompensation	15 (75%)	27 (64.2%)	0.56
Vasoactive amines (hours)	60 (24-96)	60 (18-96)	0.87
Blood transfusion	10 (50%)	9 (24.4%)	0.03*
IMV > 96 hours	12 (60%)	15 (35.7%)	0.10
Tracheostomy	5 (25%)	5 (11.9%)	0.26
NO inhalation	12 (60%)	37 (88%)	0.02*
NO inhalation (hours)	24 (0-48)	24 (0-54)	0.36
Intra-operative ECMO	6 (30%)	6 (14.3%)	0.17
Post-operative ECMO	5 (25%)	1 (2.3%)	0.01
PGD at 72 h			
• All Grades	15 (75%)	23 (54.8%)	0.16
• Grade 1	6 (40%)	9 (39.1%)	0.60
• Grade 2	5 (33.33%)	10 (43.5%)	
• Grade 3	4 (26.67%)	4 (17.4%)	
ICU stay (days)	9 (7-18)	7 (6-11)	0.66
Total in-hospital stay (days)	40.5 (30.75-53.5)	35 (30-49)	0.67
Total in-hospital stay (days)	40.5 (30.75-53.5)	35 (30-49)	0.67
PFTs			
• FEV1 (% pred.)	61.0 (56.75-67.0)	55.5 (51.58-62.58)	0.83
• FVC (% pred.)	63.5 (54.0-85.25)	70 (58.55-75.0)	0.11
• FEV1/FVC	67 (63.25-85.55)	67.75 (56.68-74.85)	0.31
• TLC (% pred.)	82.50 (64.5-96.5)	93 (81.6-109.5)	0.23
• RV (% pred.)	110 (91.5-147.25)	153 (106.35-179.0	0.18
• DLCO (% pred.)	45 (34.85-63.50)	49.45 (38.75-55.1)	0.13
• KCO (% pred.)	72 (62.4-88.0)	69.2 (61.9-77.3	0.67

radiological abnormalities and was never an isolated finding. On follow-up, pleural effusion completely resolved in 4 of the 5 cases, while in 1 case it decreased in extent, showing signs of chronicity.

The prevalence of individual radiological findings is illustrated in Figure 2 (detailed CT data are provided in Supplementary Table 1). Representative CT images are shown in Figure 3.

Table 2 i-ALAD-Associated Conditions and Outcome

Number	20
i-ALAD in first year after LTx	14 (70%)
LTx to i-ALAD (days)	113 (87.5-315.25)
Pre- i-ALAD associated conditions	
• Refractary ACR	4 (20%)
• DSA positivity	3 (15%)
• Infections	6 (30%)
• BLAD	6 (30%)
• CLAD	2 (10%)
• None	2 (10%)
i-ALAD outcome	
• Stabilization	9 (45%)
• Recovery	9 (45%)
• CLAD	2 (10%)

With regard to distribution, abnormalities were predominantly located in the lower lobes (49.5%), followed by the upper lobes (33.2%) and middle lung fields (17.3%). Most findings were of mild to moderate severity, with grade 1 and grade 2 involvement accounting for 39.3% and 33.7% of observations, respectively; grade 3 and grade 4 changes were less frequent (16.8% and 10.2%).

An inverse lobar distribution pattern was observed for the most common findings: bronchial wall thickening predominated in the lower lobes, smooth septal thickening in the upper lobes, and micronodules were evenly distributed throughout the lungs.

Analyzing the cohort according to CLAD status, patients were subdivided into those with concurrent CLAD at the time of the i-ALAD episode, those who subsequently progressed to CLAD after i-ALAD, those who developed CLAD following initial stabilization or recovery after the i-ALAD episode, and those who achieved complete and sustained recovery after i-ALAD (Supplementary Table 2). Despite the small number of patients in each subgroup, an observation of potential interest is that pleural effusion was present in all patients who achieved complete and durable recovery. Patients with pre-existing CLAD at the time of i-ALAD and those who developed CLAD after the i-ALAD episode appeared to share certain radiological features, including micronodules, bronchiectasis, bronchiolectasis, and peripheral consolidations.

Comparison between i-ALAD and ACR

Clinical characteristics of patients with i-ALAD and those with histologically proven ACR grade ≥A2 are summarized in Table 1. Compared with ACR patients, individuals with i-ALAD had significantly longer ischemia times—particularly for the second lung in bilateral transplants—required a higher number of blood transfusions, and less frequently required inhaled NO therapy. The time from transplantation to the acute event (ACR or i-ALAD) was significantly shorter in ACR patients compared with i-ALAD (59 (26.7-218.5) vs 113 (87.5-315.25), $p = 0.004$).

All i-ALAD patients were receiving tacrolimus as their calcineurin inhibitor, whereas among ACR patients, 31% were treated with cyclosporine and 69% with tacrolimus. In 4 of the 45 ACR cases, acute rejection was diagnosed in the absence of clinical or functional deterioration; however, at least 1 radiological abnormality was present in all cases. Lymphocytic bronchitis/bronchiolitis (grade B) was observed in 1 patient in the i-ALAD group (A0B1R); by definition, all i-ALAD patients had an A0 grade. All patients included in the ACR group met the inclusion criterion of an A grade ≥2, with the following distribution: 14 A2B0, 8 A2B2R, 3 A2B1R, 3 A2Bx; 9 A3B0, 4 A3B2R, 2 A3B1R, and 2 A3Bx.

Donor-specific antibodies were detected in 4 of the 45 patients with grade ≥2 ACR; however, none fulfilled the histopathological criteria for AMR. In the i-ALAD group, 3 patients (15%) had a history of donor-specific antibody positivity, but none had detectable donor-specific antibodies at the time of the i-ALAD episode.

Spirometric data were available for 14 patients with i-ALAD and for 18 patients with grade ≥2 ACR. No

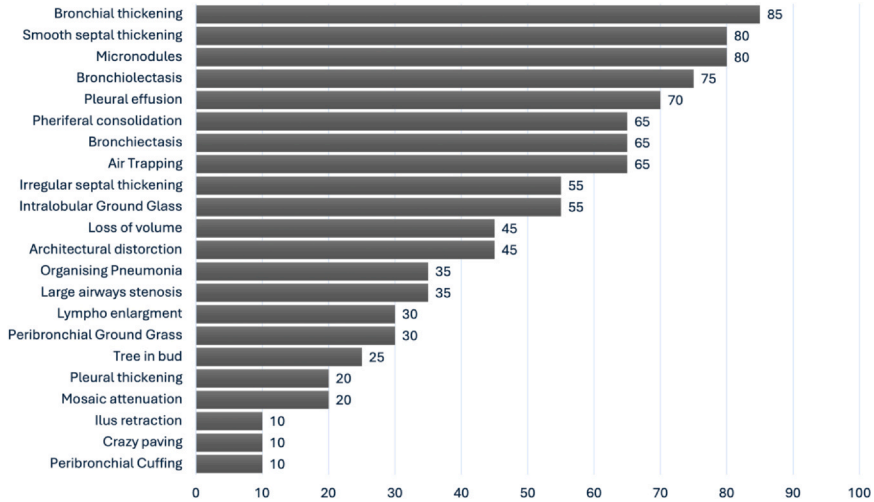

Figure 2 Radiological features of i-ALAD patients expressed as percentage.

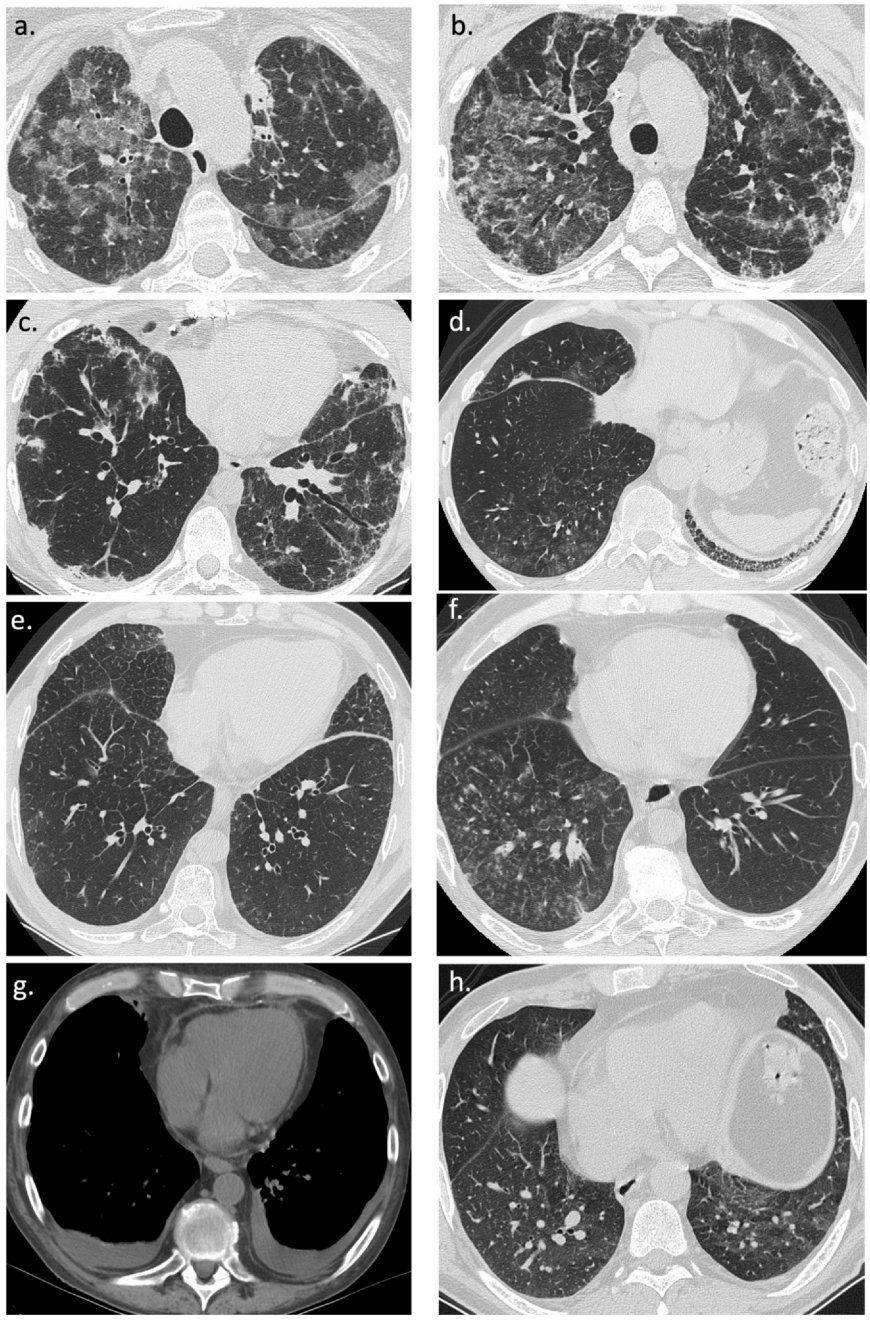

Figure 3 The main radiological characteristics of i-ALAD at CT scan. A: Intralobular ground-glass opacities in the upper lobes, accompanied by smooth intralobular septal thickening. B: intralobular ground-glass opacities in the upper lobes, accompanied by traction bronchiectasis and irregular septal thickening. C: basal subpleural consolidations associated with irregular septal thickening and traction bronchiectasis/bronchioloectasis. D: basal ground-glass micronodules on the right, associated with minimal smooth septal thickening. E: smooth interlobular septal thickening and bronchial wall thickening. F: Diffuse centrolobular ground-glass micronodules in the right lower lobe. G: Bilateral pleural effusion. H: Lobular air trapping in expiratory scans.

significant differences were observed between the 2 groups in terms of FEV_1, FVC, FEV_1/FVC, TLC, RV, DLCO, or KCO (Table 1).

Comparative radiological analysis revealed significant differences in the prevalence of pulmonary micronodules ($p = 0.0067$), bronchial wall thickening ($p < 0.0001$), septal thickening ($p = 0.0025$), bronchiectasis/bronchiolectasis ($p < 0.0001$), pleural effusion ($p = 0.015$), and air trapping ($p = 0.007$), all of which were more frequent in i-ALAD than in ACR patients (Table 3, Figure 4).

No statistically significant differences were observed for ground-glass opacities ($p = 0.17$), consolidations ($p = 0.26$), or crazy paving ($p = 0.22$).

Discussion

ALAD is a recently recognized clinical entity characterized by acute lung injury that may either resolve spontaneously or progress to CLAD. Its definition was first introduced at

Table 3 Radiological Characteristics at CT Scan of Patients With i-ALAD and With ACR (grade ≥A2)

Radiological features	i-ALAD ($n = 20$)	ACR (grade≥A2) ($n = 45$)	p-value
Ground glass	11 (55%)	16 (36%)	$p = 0.17$
Consolidations	11 (55%)	32 (71%)	$p = 0.26$
Micronodules	16 (80%)	19 (42%)	$p = 0.0067$
Bronchial thickening	17 (85%)	13 (29%)	$p < 0.0001$
Septal thickening (smooth or irregular)	18 (90%)	23 (51%)	$p = 0.0025$
Bronchiectasis/bronchiolectasis	15 (75%)	0 (0%)	$p < 0.0001$
Crazy paving	2 (10%)	1 (2.2%)	$p = 0.22$
Pleural effusion	14 (70%)	16 (36%)	$p = 0.015$
Air trapping	13 (65%)	9 (20%)	$p = 0.007$

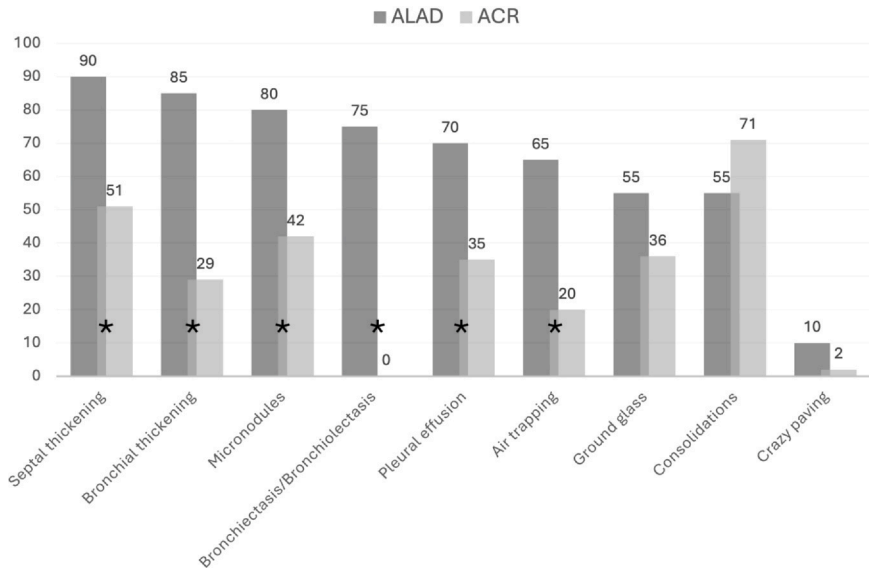

Figure 4 Different radiological features of patients with i-ALAD and with ACR (grade≥2). * = $p \leq 0.05$.

the 2024 ISHLT International Congress;[1] however, a formal consensus document has not yet been published.

ALAD is defined as a reversible decline in allograft function occurring at least 72 hours after LTX and lasting less than 3 months. Based on these criteria, ALAD is distinct from PGD, which by definition manifests within the first 72 hours post-transplantation.[2] ALAD must also be differentiated from BLAD, which reflects the inability to achieve adequate baseline lung function following transplantation.[3,4]

In our cohort, 6 patients (30%) also met criteria for BLAD, with both FEV_1 and FVC persistently below 80% of predicted values. The relationship between ALAD and BLAD remains poorly understood but warrants further investigation, given that BLAD has been associated with peri- and postoperative complications, reduced survival, and an increased risk of CLAD.[3–6] ALAD may occur in patients with BLAD and/or CLAD. Moreover, when ALAD develops in patients with established CLAD and lung function fails to return to baseline within 3 months, the episode is classified as progressive CLAD.

In this study, we retrospectively applied the proposed ALAD criteria to a cohort of lung transplant recipients at our center over a 10-year period, with the aim of describing the clinical and radiological characteristics of patients in whom no identifiable underlying cause could be recognized. We have arbitrarly designated these cases as idiopathic ALAD (i-ALAD), pending the standardized classification expected to be proposed in the forthcoming ISHLT consensus statement.

Among 497 bronchoscopies with transbronchial lung biopsy performed in 158 lung transplant recipients between 2013 and 2024, we identified 20 cases of i-ALAD, corresponding to an incidence of 12.4%. All included patients underwent bronchoscopy with BAL and transbronchial lung biopsy to exclude ALAD with an identifiable cause. Patients with a history of prior infection were excluded if BAL microbiology was positive, even in the absence of overt clinical or radiological signs of active infection. Given the retrospective nature of the study, assessing the contribution of colonization to the diagnosis of i-ALAD was challenging, and the risk of misclassifying ALAD with a detected cause as idiopathic was considered unacceptably high.

The requirement for lung biopsy represents a potential source of selection bias and may have led to an underestimation of the true incidence of i-ALAD. Nonetheless, transbronchial biopsy remains essential for excluding ACR,

which represents one of the most important and clinically relevant causes of ALAD and cannot be overlooked.

No patient experienced more than 1 episode of i-ALAD. Despite the long observation period, the observed frequency underscores that ALAD is not a rare complication and should not be underestimated; notably, its incidence appears comparable to that of other post-transplant complications.[7]

Analysis of baseline characteristics did not identify specific risk factors for the development of ALAD of unknown cause. Surgical variables—including ischemia times, transfusion requirements, and intraoperative ECMO use—were consistent with standard practice at our institution. Although 75% of patients had experienced PGD, only 20% were classified as grade 3.

Given the limited understanding of predisposing factors for ALAD of unknown cause, we also examined pre-existing conditions potentially associated with its development, including refractory ACR, AMR, prior infectious colonization, and established CLAD. In our cohort, 4 patients (20%) had a history of refractory ACR, 3 (15%) had previous DSA, 6 (30%) had prior bacterial colonization, and in 2 cases (10%), i-ALAD occurred after a diagnosis of CLAD. Only 2 patients had no other pre-existing conditions. In 1 case, mild lymphocytic bronchiolitis was observed on lung biopsy; however, this finding was considered an accompanying histopathological feature rather than the primary driver of the ALAD episode, as the severity of the clinical course of this patient and his radiological abnormalities appeared disproportionate to the limited pathological changes.

The clinical course of ALAD is heterogeneous, ranging from complete recovery or stabilization to progression toward CLAD. Persistent ALAD has also been proposed, and forthcoming consensus documents are expected to further define and characterize this entity. The role of targeted or empiric treatment is particularly relevant in ALAD, as many associated causes are potentially reversible. However, much less is currently known about the mechanisms underlying ALAD of unknown cause. While responsiveness to corticosteroid therapy could suggest the possible involvement of alloimmune mechanisms, such observations should be interpreted with caution. Although these considerations are of considerable interest, the design and scope of the present study do not allow any definitive conclusions to be drawn regarding the underlying pathophysiology of these episodes.

Our findings support the concept of ALAD of unknown cause as a potentially reversible condition, as most patients experienced either full recovery or stabilization of lung function. Only 2 patients progressed to CLAD. Notably, in 2 cases, i-ALAD occurred after CLAD had already been diagnosed, and both episodes ultimately stabilized.

To our knowledge, this study is the first to describe the high-resolution CT features of ALAD of unknown cause. Multiple concurrent abnormalities were frequently observed in individual patients. The most common findings included bronchial wall thickening, smooth interlobular septal thickening, pulmonary micronodules, bronchiectasis/bronchiolectasis, and air trapping. These abnormalities were generally diffusely distributed, although bronchial wall thickening predominated in the lower lobes, septal thickening in the upper lobes, and micronodules were evenly distributed. Several patients also presented with pleural effusion; in all cases, extensive diagnostic work-up failed to identify an attributable cause. Interpreting whether pleural effusion represents a causal factor or a consequence of i-ALAD is challenging. In the 2 cases in which pleural effusion predated the ALAD episode, it is evident that it was not the cause of clinical deterioration. In the remaining 3 cases, we do not believe it is possible to reliably distinguish cause from effect. Nevertheless, the observation of pleural effusion remains clinically relevant, as it suggests that, in selected cases, ALAD of unknown cause may present with pleural effusion on chest CT. Notably, pleural effusion was observed in all patients who achieved a complete and durable recovery after the ALAD episode.

Certain radiological findings—such as smooth septal and bronchial wall thickening and pleural effusion—may reflect an acute inflammatory process and, therefore, potential reversibility. In contrast, features such as broncho- and bronchiolectasis, fibrosis, and air trapping may indicate subacute or chronic fibrotic remodeling, potentially associated with an unfavorable prognosis and progression to CLAD.

When analyzing the cohort according to CLAD status and acknowledging the very small number of patients in each subgroup, a descriptive observation is that patients with pre-existing CLAD at the time of i-ALAD and those who subsequently developed CLAD appeared to share some radiological features, including micronodules, bronchiectasis, bronchiolectasis, and peripheral consolidations.

Significant differences emerged when comparing patients with ALAD of unknown cause to a cohort of patients with grade ≥2 ACR. Clinically, some differences were observed in perioperative variables; however, their role as risk factors for subsequent i-ALAD remains uncertain, and no definitive conclusions can be drawn. In contrast, radiological differences were more pronounced: pulmonary micronodules, bronchial wall thickening, septal thickening, bronchiectasis/bronchiolectasis, pleural effusion, and air trapping were more frequently observed in i-ALAD than in ACR.

These findings support the potential specificity of the radiological pattern associated with ALAD of unknown cause compared with ACR; however, they must be interpreted within the appropriate clinical context. The imaging appearance of ACR is often nonspecific(8), and HRCT alone should not be used to establish the differential diagnosis between these entities. Lung biopsy remains the diagnostic gold standard for ACR and a cornerstone in the evaluation of patients with suspected i-ALAD.

From a pathobiological perspective, the mechanisms underlying the development of idiopathic ALAD remain largely unknown. While the limited sample size of our study precludes any definitive interpretation, patients with ALAD of unknown cause more frequently had a history of prior blood transfusions compared with patients with ACR. This observation should be interpreted with caution and may reflect an associative finding rather than a causal relationship; nevertheless, it raises the hypothesis that allosensitization could potentially contribute in selected cases and warrants further investigation in larger cohorts.

This study has several limitations, including its retrospective, single-center design and the relatively small sample size, which may have affected data completeness and influenced the precision of the estimated incidence of ALAD of unknown cause. The descriptive nature of the study, together with the lack of a direct comparative analysis between ALAD of unknown cause and ALAD with a detected cause, represents an additional limitation. We also acknowledge that the forthcoming ISHLT consensus statement may adopt a different and more standardized nomenclature than that used in the present study.

Nevertheless, this is, to our knowledge, the first study specifically aimed at defining the clinical and radiological phenotype of ALAD of unknown cause and exploring potential associations with risk factors and long-term graft outcomes. Identification of characteristic imaging features may represent a first step toward improved phenotyping of ALAD and could be integrated with other diagnostic tools to stratify patients at risk of unfavorable outcomes or CLAD progression. Furthermore, these findings may inform future research into the pathophysiological mechanisms underlying ALAD of unknown cause and contribute to the identification of novel biomarkers.

Prospective, multicenter studies with larger cohorts will be essential to clarify the natural history, imaging characteristics, and prognostic implications of this newly described post-transplant complication.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Local Ethics Committee (Protocol Respir1, Prot n 15732, Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, Sezione: AREA VASTA SUD EST).

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Marco Guerrieri and David Bennett. Matteo Fanetti, Felice Perillo, Jean-Guillaume Starnini, Luca Luzzi, Chiara Catelli, Federico Franchi, Antonella Fossi, and Elena Bargagli participated to data collection. Chiara Piscitello, Francesco Gentili, Vito Di Martino, and Armando Perrella, performed radiological imaging collection, Cristiana Bellan evaluated pathological examinations, and Maria Antonietta Mazzei evaluated all CT scans. The first draft of the manuscript was written by Marco Guerrieri and David Bennett, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the images in Figure 3, panels A to H.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2026.100519.

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