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SHORT COMMUNICATION

Pathologists' experience and routine practice in high-volume lung transplant centers: An international survey

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Abbreviation: AI, Artificial intelligence; ACR, Acute cellular rejection; BAL, Bronchoalveolar lavage; CLAD, Chronic lung allograft dysfunction; dd-cfDNA, Donor-derived cell-free DNA; ESOT, European Society for Organ Transplantation; ISHLT, International Society for Heart and Lung Transplantation; TBB, Transbronchial biopsy

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Lung allograft pathology encompasses a wide spectrum of disorders, with new entities and emerging diagnostic technologies. The main goal of this study was to document pathologists' current global practices and highlight areas of consensus and divergence worldwide. A 24-item survey was distributed to transplant centers and responses were received from 35 specialists (51% European, 49% non-European). Most centers used both surveillance and symptom-driven assessments (77%), mainly with transbronchial biopsies (86%) and bronchoalveolar lavage (83%). Non-European centers were more likely to adopt digital pathology (OR 3.03), to use donor-derived cell-free DNA (dd-cfDNA) (OR 2.94), and supported large airway sampling (OR 2.27). Larger centers used dd-cfDNA (OR 2.75) more frequently and consider large airway sampling (OR 2.18). Responders largely supported standardized reporting (86%), reintroducing grade AX (94%), and independent bronchial lesion scoring (82%). Most endorsed an "indeterminate" category for acute and chronic rejection. These findings reflect evolving practices in the field and will inform the ongoing revision of the Lung Allograft Pathology Working Classification.
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Introduction

Lung transplantation is a life-saving procedure for end-stage pulmonary diseases but remains challenged by both immune- and non-immune-mediated complications. Despite significant advances in surgical techniques, perioperative care, and immunosuppressive therapies, long-term graft survival remains limited due to a complex interplay of these factors, which profoundly affect graft function. The International Society for Heart and Lung Transplantation (ISHLT) established standardized grading criteria for acute and chronic rejection, ensuring consistent interpretation and guiding therapeutic decisions.[1] However, over the past two decades, novel pathological entities, ambiguous lesions, and advanced diagnostic technologies have emerged, highlighting the need for updated guidelines. To address this, the four leaders of the ongoing Working Classification of Lung Allograft Pathology (F.C., D.H., D.L., G.W.) designed a survey to assess current practices, challenges, and evolving concepts in lung transplant pathology, with the aim of identifying unmet needs to appropriately formulate critical questions and recommendations for each topic.

Materials and methods

A 24-question survey, including multiple-choice, Likert-scale, and open-ended items, was developed to assess biopsy practices, classification proposals, new diagnostic tools, and reporting standardization (Table S1).

The survey was divided into key sections: center characteristics, biopsy practices, classification refinements, large airway sampling, technological advancements, and reporting standardization. Pathologists were asked about preferred diagnostic techniques, grading difficulties, and the relevance of digital pathology and artificial intelligence (AI) in routine practice.

To ensure clarity and relevance, the survey underwent multiple rounds of review by lung transplant experts. Pilot testing was conducted by the study leaders to refine question phrasing and format. The final version was optimized for clear responses and ease of completion. The survey was distributed via ISHLT and direct invitations to professionals from high-volume lung transplant centers. Responses were collected electronically using Google forms over a one-

month period and entered into a spreadsheet for statistical analysis (details are reported in the **Supplemental file**).

Results

Thirty-five lung transplant specialists participated in the survey, representing institutions from Europe (51%), North America (43%), and other regions. Most specialists worked in high-volume centers (≥50 transplants/year). Biopsy strategies included a both surveillance and on clinical demand (77%), on clinical demand only (17%), and per surveillance protocol (6%). Transbronchial biopsy (TBB) (86%) and bronchoalveolar lavage (BAL) (83%) were the most commonly used tools, followed by transbronchial-endobronchial biopsies (37%) and cryobiopsies (20%) (Figure 1). BAL was primarily employed for infection detection (94%).

Fifty-four percent of respondents considered the sampling of large airway biopsies valuable, primarily via endobronchial biopsies (94%); in particular, most of them (82%) recommended independent grading of bronchial lesions, recognizing differences in pathology between small and large airways (Figure 1).

Nearly all (94%) specialists supported reintroduction of the AX grade for inadequately sampled lung parenchyma, while 60% supported the creation of an "indeterminate" acute cellular rejection (ACR) category, reflecting recognition of the diagnostic challenges due to artifacts or concurrent conditions. Similarly, 63% agreed with the introduction of an "indeterminate category" for chronic rejection as well, in cases where a definite interpretation of fibrosing airway remodeling (e.g. obliterative bronchiolitis) or interstitium (e.g. restrictive allograft syndrome) is challenging (Figure 2).

Digital pathology was available in 89% of centers, with 46% routinely using it for clinical and research purposes (Figure 2). AI-assisted analysis was viewed as useful for ACR (43%) but had limited perceived benefit for chronic rejection (5%). Donor-derived cell-free DNA (dd-cfDNA), available in 40% of centers, was considered mainly a tool for research (64%), with 49% considering it complementary to biopsy (Figure 2). Eighty-six percent supported a synoptic standardized pathology report to improve diagnostic accuracy and comparability across centers. Interestingly, logistic regression revealed differences between European and non-European centers, as well as between large and small centers for several survey items (Table 1).

Discussion

This survey highlights the on-going importance of TBB and BAL in post-lung transplant monitoring and grading of rejection. While cryobiopsies may offer larger and better-preserved tissue samples thus enhancing diagnostic yield in lung transplant setting,[2] TBBs remain the preferred method due to their well-established safety profile, consistent procedural standardization, and validated role in grading rejection according to international consensus guidelines.[3]

The support for an "indeterminate" category highlights the need for more refined diagnostic classifications. The term "indeterminate for rejection" is used across solid organ transplantation (e.g. Banff classification of kidney, pancreas) to describe cases where histopathologic, immunologic, or clinical findings raise suspicion of rejection but fail to fulfill established diagnostic criteria.[4, 5] This category typically includes borderline or difficult to

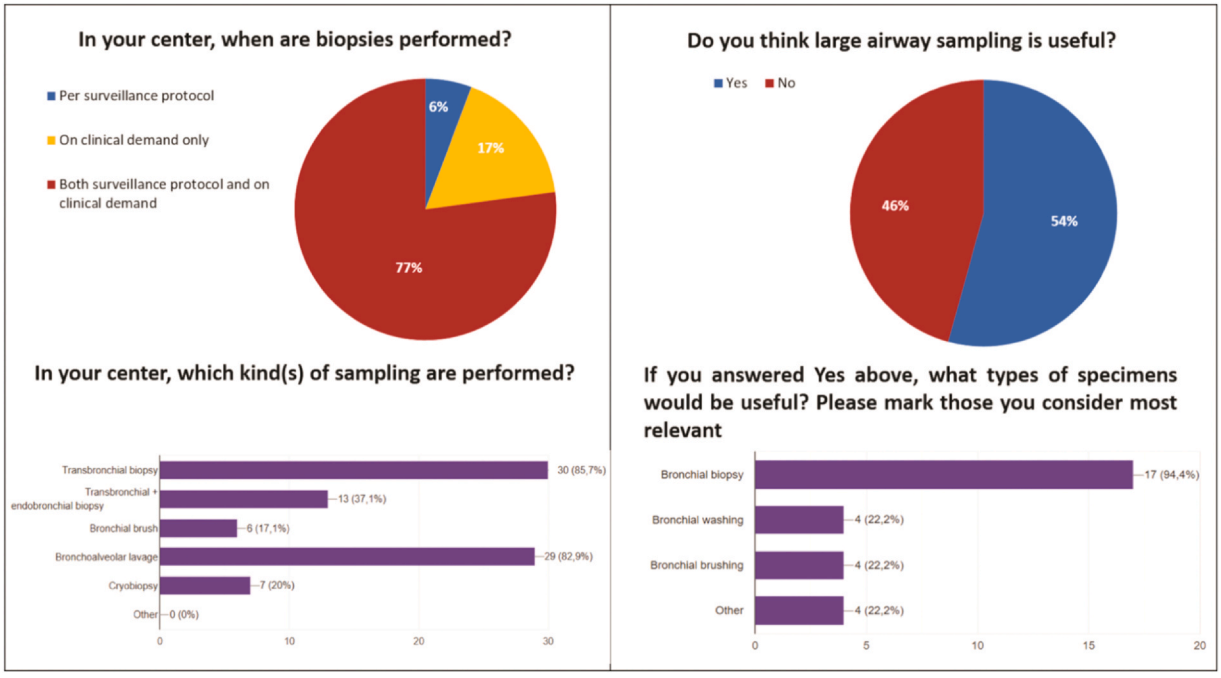

Figure 1 Distribution and perceived usefulness of large airway biopsy sampling among centers. Pie and bar charts showing the distribution of the most frequently used biopsy types across participating centers and respondents' opinions on the clinical utility of large airway sampling.

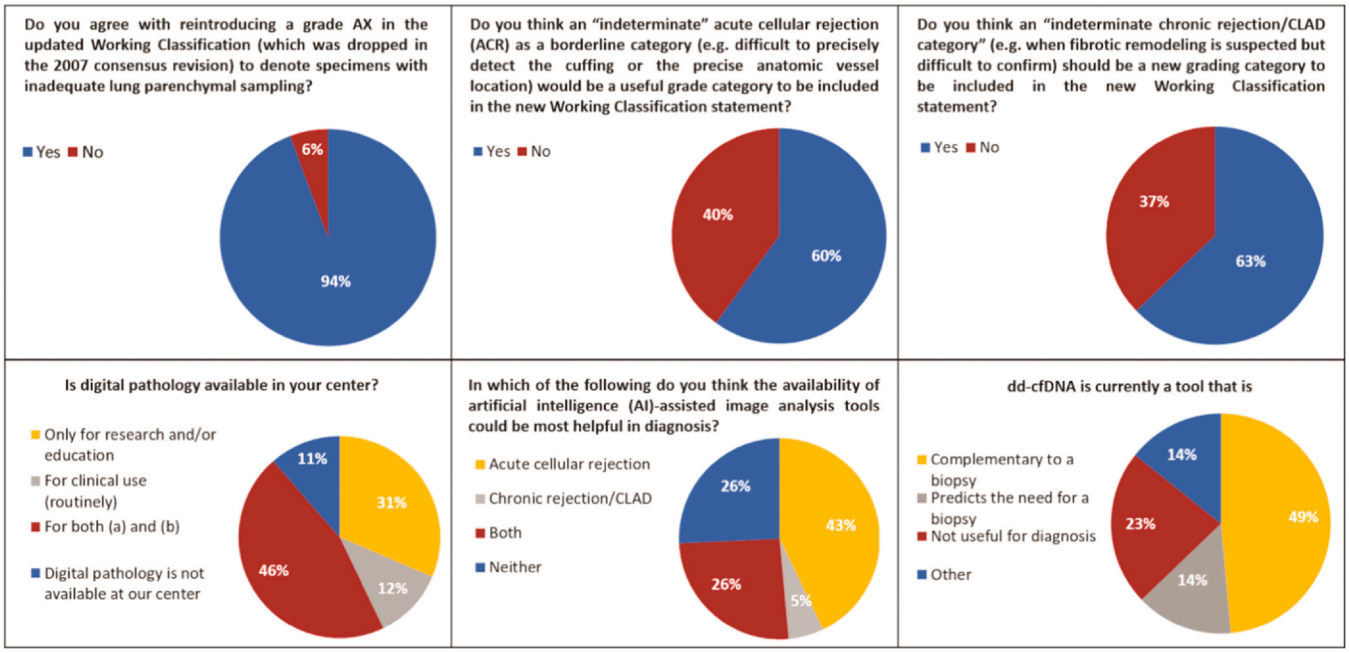

Figure 2 Key challenges and emerging tools in lung transplant pathology. Pie charts illustrating respondents' views on the most critical challenges in lung transplant pathology. Topics addressed include the reintroduction of grade AX into diagnostic criteria, the adoption of indeterminate categories for acute and chronic rejection, and the current diffusion and perceived usefulness of novel technologies such as digital pathology, artificial intelligence (AI), and donor-derived cell-free DNA (dd-cfDNA).

interpret lesions (due to crush artifact or limited sampling) such as the presence of minimal inflammatory infiltrates or fibrotic remodeling that do not meet thresholds for definite acute or chronic rejection. The introduction of an indeterminate grade could enable a more accurate assessment of rejection, helping to prevent both overestimation and underestimation, each of which can negatively impact on the clinical management of the graft. Clearly, the inclusion of such a category highlights the need for multidisciplinary discussion, together with strict follow-up and long-term monitoring of the recipient. Despite wide confidence intervals, the odds ratios suggested consistent trends: non-European and large centers were more aligned with proposed classification improvements and technological integration. The nearly universal support for AX reintroduction and synoptic reporting indicates a strong field-wide momentum toward standardization and diagnostic clarity.

The role of large airway sampling warrants careful consideration, particularly in light of the fact that more than half respondents in our survey, especially those from non-European and larger LT centers, expressed support for its use. Existing literature also suggests that phenotypic changes in the large airways may precede classical small airway lesions, underscoring the need for their standardized evaluation in post-transplant surveillance.[6, 7] Regarding advanced diagnostic tools, the potential of AI and dd-cfDNA is acknowledged, however, their current application

Table 1 Logistic Regression Analysis of Survey Responses by Region and Transplant Center Size

Variable	Group	Crude OR (95% CI)	Adjusted OR (95% CI)
Large airway sampling	Non-EU vs EU	2.27 (0.59–9.09)	2.00 (0.19–3.12)
	Large vs Small centers	2.18 (0.53–9.02)	1.85 (0.32–5.36)
Digital pathology	Non-EU vs EU	3.03 (0.74–12.50)	3.57 (0.54–9.09)
	Large vs Small centers	0.55 (0.13–2.33)	0.41 (0.11–1.84)
dd-cfDNA usage	Non-EU vs EU	2.94 (0.72–12.50)	2.50 (0.14–3.03)
	Large vs Small centers	2.75 (0.59–12.85)	2.25 (0.33–7.12)
Synoptic template	Non-EU vs EU	0.58 (0.08–4.00)	0.53 (0.09–4.55)
	Large vs Small centers	1.33 (0.19–9.31)	1.54 (0.22–10.54)
Reintroduction AX grade	Non-EU vs EU	n.c.*	n.c.*
	Large vs Small centers	2.00 (0.11–35.09)	1.27 (0.06–17.60)

The table shows the raw and adjusted odds ratios (ORs) for the main variables included in the survey, highlighting the association between geographic region (European vs Non-European), transplant center volume (Large centers: ≥50 lung transplants/year vs small centers: < 50 lung transplants/year) with the answers given to the questionnaire questions.

* OR is not calculable as all non-European respondents answered yes.

Abbreviations: CI: confidence interval; EU: European; OR: odds ratio.

remains limited and characterized by regional and institutional variability in lung transplant pathology practice. Notably, non-European centers demonstrated a greater inclination toward incorporating advanced diagnostic tools such as digital pathology and dd-cfDNA. The European centers appeared more cautious, reflecting the recent recommendation issued by the European Society for Organ Transplantation (ESOT) that supports its use primarily in selected clinical scenarios rather than for universal surveillance tool.[8] It is plausible that dd-cfDNA may gain greater relevance as a contributory diagnostic tool if performed systematically during follow-up, allowing for longitudinal monitoring over time, similar to other adjunctive biomarkers. These findings highlight the need to tailor revisions of the Lung Allograft Pathology Working Classification to reflect both universal consensus and region-specific practice patterns. Standardization, improved grading systems, and the cautious integration of novel technologies are crucial for advancing the field.

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.

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Appendix A. Supporting information

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2025.100415.

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