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Incremental clinical impact of transbronchial cryobiopsy in lung transplant recipients: a paired comparative study

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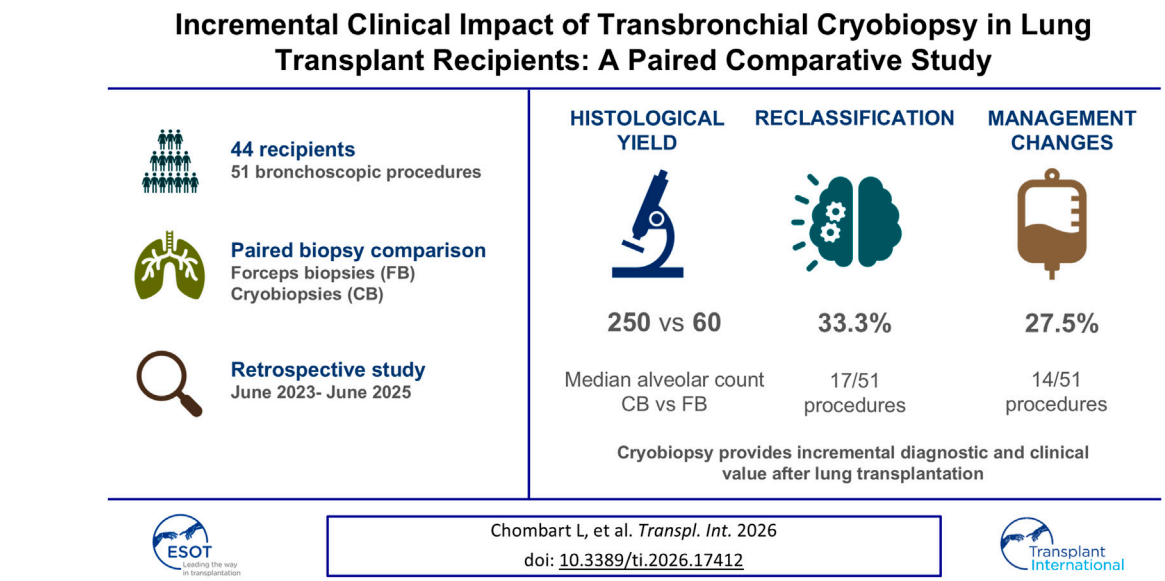
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Although transbronchial cryobiopsy (CB) improves tissue sampling compared with forceps biopsy (FB) after lung transplantation, the extent to which this translates into clinically meaningful diagnostic and therapeutic consequences remains uncertain. We conducted a single-center retrospective paired comparative study of lung transplant recipients undergoing bronchoscopy with both FB and CB during the same procedure. Diagnostic reclassification, clinical management changes, histological sample quality, and procedural safety were assessed. CB findings were associated with diagnostic reclassification in 17/51 procedures (33.3%, 95% CI 20.8%–46.2%) and management changes in 14/51 (27.5%, 95% CI 15.7%–39.6%), including treatment modifications and potentially avoided repeat bronchoscopies. Discordances included higher rejection grades, alternative diagnoses, and contributive CB after non-contributive FB. CB yielded more alveoli than FB (median 250 [185–338] vs. 60 [42–100]; $p < 0.0001$). No grade 3–4 bleeding occurred; grade ≥2 bleeding occurred in three procedures (6%) with each technique. Pneumothorax occurred in seven procedures (13.7%) and could not be attributed to either technique. CB provided additional histological findings associated with changes in clinical decision-making. Whether these changes improve patient outcomes remains uncertain.

KEYWORDS
acute rejection, clinical impact, cryobiopsy, forceps biopsy, lung transplantation

Introduction

Lung transplantation requires repeated bronchoscopic and histological evaluation to detect acute rejection, infection, and other forms of allograft injury [1]. Transbronchial forceps biopsy (FB) remains the standard sampling technique for post-transplant surveillance and diagnostic assessment and is currently incorporated into ISHLT rejection grading systems [2]. However, conventional FB is limited by small specimen size, crush artefacts, variable representation of vascular and bronchiolar structures, imperfect sensitivity for clinically relevant lesions, and substantial interobserver variability in histological interpretation [3–5]. Transbronchial cryobiopsy (CB) has



GRAPHICAL ABSTRACT

emerged as an alternative bronchoscopic sampling technique capable of obtaining larger and better-preserved tissue specimens. Accumulating evidence from comparative, randomized, and meta-analytic studies suggests that CB improves tissue adequacy and increases detection of acute rejection and other pathological processes compared with conventional FB [5–9]. Nevertheless, the precise clinical implications of discordant findings between FB and CB remain incompletely characterized in routine lung transplant practice. We therefore conducted a paired comparative study of FB and CB in lung transplant recipients undergoing bronchoscopic evaluation.

Materials and methods

Study design and population

Between June 2023 and June 2025, we conducted a single-center, retrospective, paired comparative study at Bordeaux University Hospital, including lung transplant recipients who underwent bronchoscopy with both conventional transbronchial FB and CB during the same procedure. Bronchoscopies were performed either as routine surveillance procedures (approximately 3 months post-transplantation) or for clinical indications. Clinical, bronchoscopic, histopathological, and procedural data were retrospectively collected from electronic medical records. Patients under 18 years of age were excluded. All procedures in which both FB and CB were performed during the same session were screened for eligibility between June 2023 and June 2025. Patients younger than 18 years were excluded. No *a priori* sample size calculation was performed. The study selection is illustrated in Supplementary Figure S1. The study was approved by the Bordeaux University Hospital Ethics Committee (approval number: CER-BDX 2024-226) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Bronchoscopy procedure

All bronchoscopies were performed as inpatient procedures under general anesthesia in the bronchoscopy unit. Flexible bronchoscopes (PENTAX®, EB-1575K; 2.2-mm working channel) were introduced through an endotracheal tube with a minimal internal diameter of 8 mm, allowing simultaneous placement of a bronchial blocker. Procedures began with bronchoalveolar lavage (BAL) using 100–150 mL of normal saline, followed sequentially by CB and FB performed according to current recommendations. This fixed, non-randomized sampling sequence reflected routine procedural practice at our institution. FB and CB samples were obtained unilaterally from a single lobe, targeting at least two different segments. Biopsy sites were selected based on chest CT findings, with a preference for lower lobes. A bronchial blocker was prophylactically positioned in the targeted main bronchus prior to biopsy acquisition. Fluoroscopic guidance was used for both forceps and cryoprobe positioning. Instruments were advanced toward the pleura and then withdrawn by approximately 1–2 cm before sampling. Six FB specimens and four CB specimens were obtained during each procedure. FB was performed using flexible forceps (Micro-Tech®, UK), with specimens immediately fixed in formalin. CB was performed using a flexible 1.1-mm cryoprobe (Erbe®, Elektromedizin GmbH, Tübingen, Germany) with carbon dioxide cryogen. Freezing time ranged from 3 to 5 s before *en bloc* removal of the bronchoscope and cryoprobe. A Fogarty® 6-Fr bronchial blocker, previously positioned in the sampled segment, was immediately inflated after specimen retrieval to minimize bleeding. Cryobiopsy samples were immediately fixed in formalin.

Abbreviations: BAL, Bronchoalveolar lavage; CB, Cryobiopsy; CT, Computed Tomography; FB, Forceps biopsy; IQR, Interquartile range; ISHLT, International Society for Heart and Lung Transplantation; LTR, Lung transplant recipients.

Histopathological assessment

Histopathological interpretation was performed according to routine clinical practice at our institution. All specimens were evaluated by a single pathologist. Each sample was analyzed separately. Acute rejection and airway inflammation were graded in accordance with ISHLT criteria. Alternative diagnoses were also recorded. Non-contributive specimens were defined differently depending on the analysis objective: For clinical impact analyses, non-contributive specimens were defined based on the pathologist's report. For agreement analyses, non-contributive specimens were defined using structural criteria, specifically the absence of histological features required for grading. Histological sample quality was assessed by comparing alveolar yield between FB and CB in procedures where both techniques provided contributive specimens. Alveolar yield was assessed as the total number of alveoli obtained per procedure, summing all specimens collected with each biopsy technique.

Assessment of clinical management changes

Clinical management changes were retrospectively assessed from medical records by a resident physician, with uncertain cases adjudicated by a senior lung transplant physician. No independent adjudication committee was involved. Management decisions were made in routine clinical practice based on histopathological findings and clinical context, without a predefined treatment algorithm. Changes potentially attributable to additional CB findings included treatment initiation or escalation, treatment modification for alternative diagnoses, and potential avoidance of repeat bronchoscopy. At our center, repeat bronchoscopy is generally considered after non-contributive biopsies, although no formal protocol mandates it. When FB was non-contributive, but CB provided interpretable histology, the decision not to repeat bronchoscopy was classified as a diagnostic management modification.

Study objectives

The primary objective was to determine the clinical impact of cryobiopsy relative to forceps biopsy in lung transplant recipients.

Secondary objectives included the assessment of histological agreement for acute rejection and airway inflammation grading, specimen quality, and procedural safety.

Statistical analysis

Continuous variables are presented as medians [interquartile ranges (IQR)] and categorical variables as counts and percentages. Paired continuous variables were compared using the Wilcoxon signed-rank test, and paired categorical data were summarized using contingency tables. Agreement in acute rejection (A grade) and airway inflammation (B grade) was assessed using contingency tables and Cohen's kappa coefficients, both including and excluding non-contributive specimens. Unweighted kappa was used when non-ordinal categories were included, whereas quadratic weighted kappa was used for interpretable ordinal grades. The 95% confidence intervals (CIs) for kappa coefficients were estimated using percentile bootstrap resampling (10,000 iterations). Analyses were performed at the procedure level. To account for repeated procedures within recipients, 95% CIs for diagnostic reclassification and clinical management changes were estimated using patient-level cluster bootstrap resampling (10,000 iterations). A sensitivity analysis restricted to the earliest procedure per recipient was also performed. All analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

TABLE 1 Baseline patient characteristics and bronchoscopy indications.

Characteristic	Value
Number of patients	44
Number of procedures	51
Patient-level characteristics (n = 44)	
Age, median [IQR], years	58 [53–62]
Female sex, n (%)	25 (57%)
Underlying disease, n (%)	
– Emphysema	22 (50%)
– Interstitial lung disease	15 (34%)
– Pulmonary hypertension	4 (9%)
– Other	3 (7%)
Procedure-level characteristics (n = 51)	
Time from transplantation, median [IQR], days	84 [72–107]
Bronchoscopy indication, n (%)	
– Surveillance	37 (73%)
– Clinically indicated	14 (27%)

Results

Study population

A total of 51 bronchoscopic procedures were performed in 44 lung transplant recipients. Seven recipients underwent two bronchoscopic procedures each, whereas the remaining 37 recipients underwent a single procedure. The median age was 58 years [53–62], and 25 patients (57%) were female. The main underlying diseases leading to transplantation were emphysema (n = 22, 50%), interstitial lung disease (n = 15, 34%), pulmonary hypertension (n = 4, 9%), and other conditions (n = 3, 7%). At the procedure level, the median time from transplantation was 84 days [72–107]. Bronchoscopies were performed as part of routine surveillance in 37 cases (73%) (Table 1).

Clinical impact of cryobiopsy

CB findings led to a change in diagnostic assessment in 17 of 51 procedures (33.3%, 95% CI 20.8%–46.2%)), through three

mechanisms: diagnostic reclassification of acute rejection, identification of alternative diagnoses, and conversion of non-contributive FB into contributive CB.

Acute rejection and airway inflammation reclassification

Among the 10 procedures in which CB identified acute cellular rejection (A grade ≥1) and/or airway inflammation (B1R), diagnostic reclassification compared with FB occurred in 8 cases (80%), including reclassifications from A0 to A1 (n = 2), A0 to A2 (n = 4), A1B0 to A2B1R (n = 1), and A0B0 to A0B1R (n = 1) (Supplementary Table S1).

Alternative diagnoses

Cryobiopsy identified alternative diagnoses in 7 procedures (13.7%), including organizing pneumonia (n = 3), granulomatous lesions (n = 2), obliterative bronchiolitis (n = 1), and acute bronchiolitis (n = 1). Among these, 5 diagnoses were discordant with forceps biopsy findings and had been interpreted as normal on forceps biopsy, including organizing pneumonia (n = 2), granulomatous lesions (n = 2), and obliterative bronchiolitis (n = 1) (Supplementary Table S2).

Non-contributive sampling

Non-contributive specimens were defined based on the pathologist's report and analyzed separately, as they reflect the ability to reach a diagnostic interpretation rather than structural sample adequacy. FB was non-contributive in 5 of 51 procedures (9.8%). In 4 of these cases, CB yielded contributive histology, all interpreted as normal, whereas one procedure remained non-contributive with both techniques (Supplementary Table S3).

Management changes

Overall, CB led to a change in clinical management in 14 of 51 procedures (27.5%, 95% CI 15.7%–39.6%). These changes consisted of corticosteroid pulse therapy for acute rejection (n = 7), initiation of treatment for alternative diagnoses, including organizing pneumonia (n = 2) and obliterative bronchiolitis (n = 1), as well as avoidance of repeat bronchoscopy in cases with non-contributive forceps biopsy and normal cryobiopsy findings (n = 4) (Table 2). In addition, 3 procedures showed discordant findings between forceps biopsy and cryobiopsy without impacting clinical management, including 1 case reclassified from A1B0 to A2B1R and 2 cases reclassified from normal findings to granulomatous lesions (Figure 1). In a sensitivity analysis restricted to the first procedure for each recipient (n = 44), diagnostic reclassification occurred in 12/44 procedures (27.3%), compared with 17/51 (33.3%) in the overall cohort. Clinical management modifications occurred in 9/44 procedures (20.5%), compared with 14/51 (27.5%) in the overall cohort (Supplementary Table S4). Both proportions were lower after excluding repeated procedures.

TABLE 2 Clinical management changes following cryobiopsy.

Type of management change	n
Treatment escalation for acute rejection	7
Treatment initiation/modification for alternative diagnosis	3
Avoidance of repeat bronchoscopy	4
Total	14

Diagnostic agreement patterns

Diagnostic agreement for acute rejection (A grades) and airway inflammation (B grades) was assessed using paired contingency analyses and heatmap visualization. For this analysis, non-contributive specimens were defined using structural criteria corresponding to the absence of histological features required for grading.

Primary analysis (including non-contributive specimens)

Acute rejection grading (A grades)

Agreement between FB and CB for A-grade classifications, including non-contributive specimens and alternative diagnoses as separate categories, yielded an unweighted Cohen's kappa of 0.306 (95% bootstrap CI 0.067–0.536; 10,000 resamples) (Supplementary Table S5). Concordance was mainly observed for A0 classifications, whereas discrepancies were frequent for abnormal findings. Most discordances involving rejection grades corresponded to upward reclassification from A0 to A1 or A2 on CB. In addition, non-contributive specimens were more frequent with FB than with CB, contributing substantially to overall discordance between techniques. These patterns are illustrated in the heatmap of A-grade agreement (Figure 2A).

Airway inflammation grading (B grades)

Agreement between FB and CB for airway inflammation classifications, including non-contributive specimens and alternative diagnoses as separate categories, yielded an unweighted Cohen's kappa of 0.162 (95% bootstrap CI 0.024–0.311; 10,000 resamples). Non-contributive specimens were markedly more frequent with FB (38/51, 74.5%) than with CB (13/51, 25.5%). Among the 38 non-contributive forceps biopsies, CB yielded contributive results in 26 cases (68%), including 20 classified as B0, 2 as B1R, and 4 as alternative diagnoses (Supplementary Table S6). These findings suggest that discordance between techniques was largely driven by differences in bronchiolar sampling adequacy. This is reflected in the heatmap of B-grade agreement (Figure 2B), showing a high proportion of non-contributive forceps biopsies.

Secondary analysis (excluding non-contributive specimens)

To assess agreement among interpretable samples, a secondary analysis was performed after excluding non-contributive specimens.

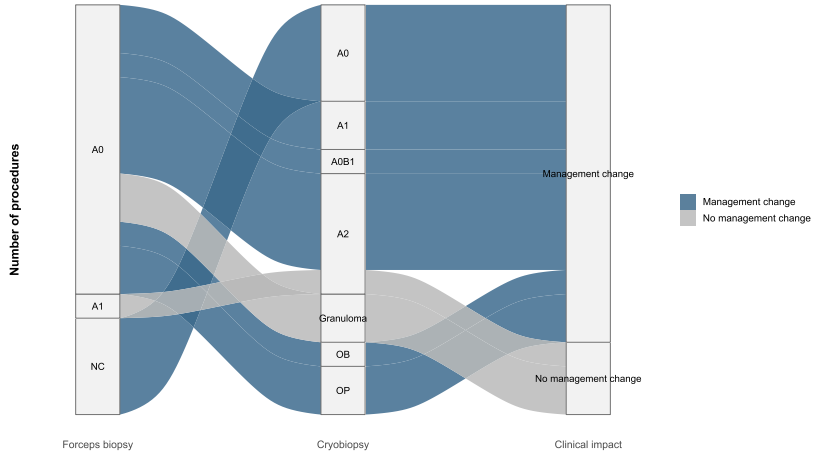


FIGURE 1
Alluvial representation of diagnostic reclassification and management changes following cryobiopsy.

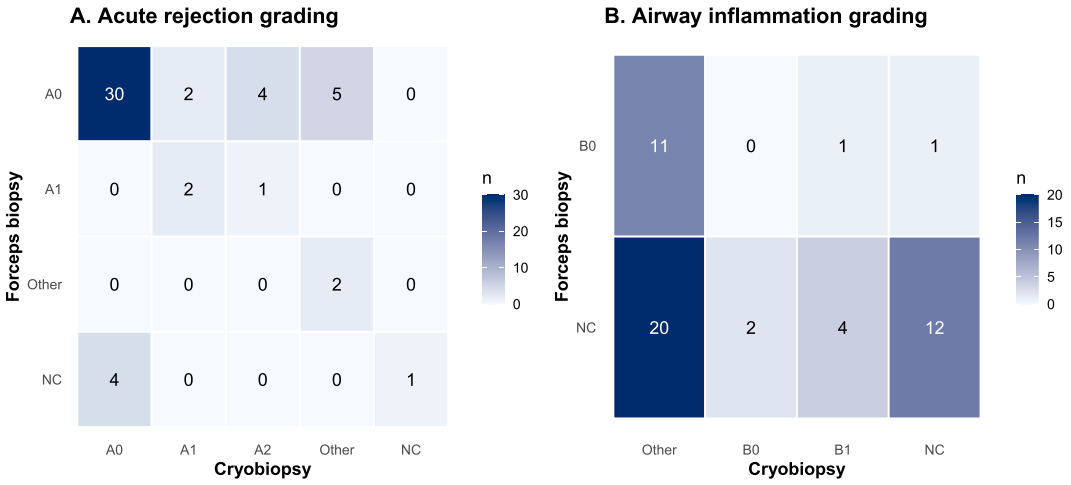


FIGURE 2
Agreement between forceps biopsy and cryobiopsy for A and B grades. **(A)** Acute rejection grading. **(B)** Airway inflammation grading.

A grades

Among the 46 procedures with contributive samples for both techniques, 39 had interpretable ordinal A grades (A0 - A2) for both techniques. In these 39 paired samples, quadratic weighted Cohen's kappa was 0.235 (95% bootstrap CI 0.000–0.574; 10,000 resamples). Concordance was primarily observed for A0 grades, whereas discrepancies for abnormal findings predominantly favored higher-grade or alternative diagnoses on CB (Supplementary Table S7).

B grades

Among the 12 procedures with contributive specimens for both techniques, 11 showed concordant B0 classifications (91.7%), while CB identified an alternative diagnosis in one case (Supplementary Table S8). As all pairs with interpretable B grades were classified as B0 by both techniques, there was no variability in B grades, making weighted Cohen's kappa inapplicable. Consequently, this analysis does not allow meaningful assessment of agreement in airway inflammation grading.

Histological sample quality

Histological sample quality was assessed among procedures with contributive specimens for both techniques by comparing alveolar yield between forceps biopsy (FB) and cryobiopsy (CB). Among the 46 procedures with contributive samples for both techniques, CB yielded a significantly higher number of alveoli than FB, with a median of 250 [185–338] versus 60 [42–100], respectively ($p < 0.0001$, Wilcoxon signed-rank test). Thus, CB yielded approximately four times as many alveoli as FB per procedure, despite requiring fewer specimens (4 vs. 6). The median paired gain in alveolar count (CB − FB) was +180 [113–274] alveoli per procedure. At the individual procedure level, CB provided a higher alveolar count than FB in 43 of 46 procedures (93.5%). These findings are illustrated in Figure 3 and summarized in Supplementary Table S9.

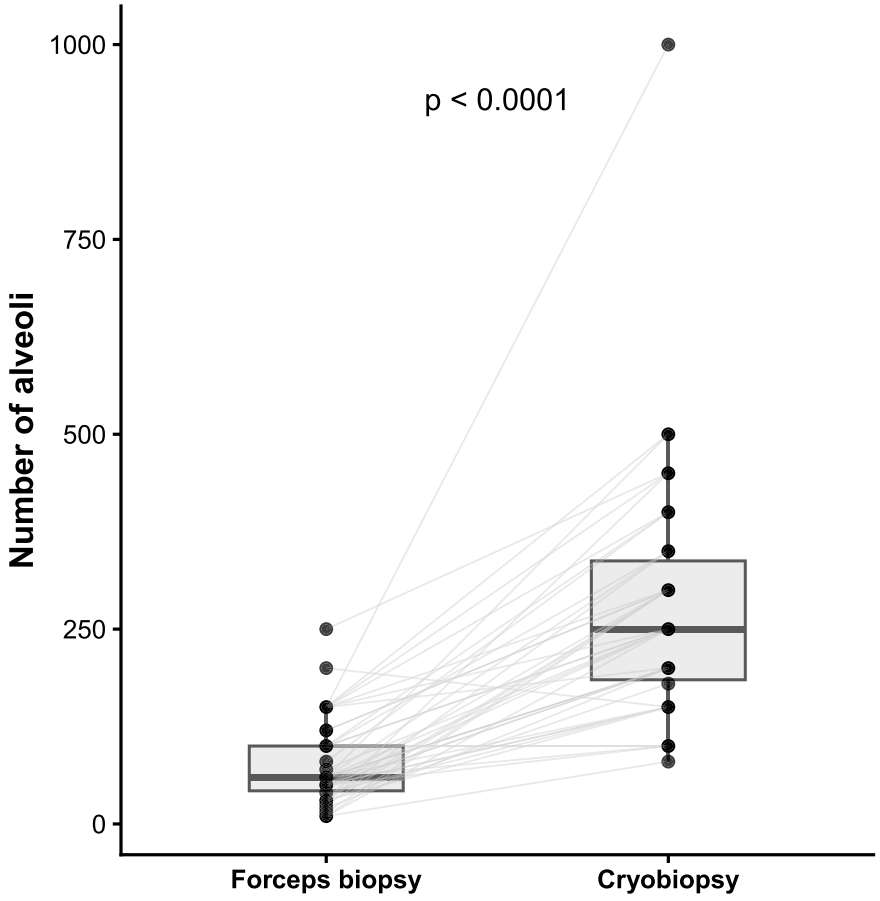


FIGURE 3
Paired comparison of alveolar yield between forceps biopsy and cryobiopsy.

Procedural safety

Procedure-related complications were recorded for all 51 procedures. No grade 3–4 bleeding events occurred with either technique. Bleeding severity was analyzed using paired comparisons. The distribution of bleeding grades appeared similar between FB and CB. No bleeding occurred in 39 procedures (76%) with FB and 36 procedures (71%) with CB. Grade 1 bleeding was observed in 9 (18%) and 12 (24%) procedures, respectively, whereas grade ≥2 bleeding occurred in 3 procedures (6%) with both techniques, with no difference observed on paired analysis (McNemar test, p = 1.00) (Table 3; Supplementary Table S10). Pneumothorax occurred in 7 of 51 procedures (13.7%). Because FB and CB were performed during the same bronchoscopy, pneumothorax events could not be attributed to a specific biopsy modality. Chest tube drainage was required in one case, whereas six cases were managed conservatively (Table 3).

Discussion

In this paired study of lung transplant recipients undergoing both transbronchial forceps biopsy (FB) and cryobiopsy (CB) during the same procedure, additional histological findings obtained by CB were associated with changes in clinical management in 14 of 51 procedures (27.5%). These included therapeutic modifications in 10 procedures (19.6%) and decisions not to repeat bronchoscopy following non-contributive FB findings in four procedures (7.8%). CB also provided greater alveolar yield, reduced non-contributive sampling, and identified additional histological abnormalities. These findings suggest that the potential clinical relevance of CB extends beyond its established advantages in tissue acquisition, although the benefit of the resulting management decisions remains uncertain. Previous studies have established the technical and diagnostic advantages of CB over conventional FB in lung transplantation. Early prospective and comparative studies demonstrated larger specimens, better architectural preservation, improved alveolar and vascular representation, and fewer non-diagnostic biopsies [5, 6]. Steinack et al. reported increased detection of acute rejection and associated therapeutic modifications with CB [7], while the prospective randomized trial by Loor et al. demonstrated higher detection of clinically significant rejection grades, particularly ≥A2 rejection [8]. These findings were further supported by a recent meta-analysis including 11 studies and 915 patients, demonstrating improved detection of both acute and chronic rejection with CB compared with FB [9]. Most

TABLE 3 Procedure-related complications.

Complication	FB (n = 51)	CB (n = 51)	Overall (n = 51)
Bleeding severity, n (%)			
No bleeding	39 (76%)	36 (71%)	-
Grade 1	9 (18%)	12 (24%)	-
Grade ≥2	3 (6%)	3 (6%)	-
Pneumothorax, n (%)			
Pneumothorax	-	-	7 (13.7%)
Conservative management	-	-	6 (11.8%)
Chest tube required	-	-	1 (2.0%)

FB: forceps biopsy; CB: cryobiopsy. Bleeding severity was assessed separately for each technique. Pneumothorax was recorded at the procedure level and could not be attributed to either technique because both were performed during the same bronchoscopy.

recently, the multicenter randomized FROSTBITE-2 trial reported a diagnostic yield of 96.0% with CB compared with 88.7% with FB among lung transplant recipients, while maintaining an excellent safety profile [10]. Against this background, our study provides complementary real-world data focusing specifically on the frequency and nature of clinical management decisions associated with additional CB findings. Although therapeutic modifications have previously been described, our findings further characterize their occurrence in routine clinical practice. Importantly, these observed decisions should not be interpreted as evidence of improved diagnostic accuracy or patient outcomes. The direction of histological discordances is particularly relevant. In our cohort, discrepancies in acute rejection grading predominantly involved higher grades on CB than on FB. Although larger and better-preserved specimens may increase the detection of focal rejection, the absence of an independent diagnostic reference standard prevents us from distinguishing underdetection by FB from potential overdiagnosis by CB. This limitation is particularly important because seven patients received corticosteroid pulse therapy following additional CB findings. Without independent diagnostic confirmation or subsequent outcome assessment, the appropriateness and clinical benefit of these treatments cannot be established. The spatial heterogeneity of lung allograft injury may partly explain the observed discordances, as rejection and airway-centered lesions can be focal or patchy. Similar sampling limitations have been highlighted in previous comparative and randomized studies [7, 8]. Beyond acute rejection, CB identified additional pathological findings, including organizing pneumonia, bronchiolitis obliterans, and granulomatous lesions that were not detected by paired FB specimens. Previous studies have similarly reported improved identification of infectious, inflammatory, and airway-centered abnormalities with CB [6, 7]. The meta-analysis by Luo et al. also suggested improved detection of chronic rejection [9]. These findings support the potential contribution of CB to a broader histopathological assessment of lung allograft injury. However, whether increased detection of these abnormalities improves clinical management or long-term outcomes remains uncertain. Another relevant finding concerns non-contributive biopsies. Montero et al. reported a reduction in non-diagnostic specimens from 21.9% with FB to 2.5% with CB [6], while previous studies have highlighted substantial interobserver variability in lung allograft histopathology, even with improved tissue quality [7]. In our study, we distinguished biopsies considered non-contributive by the pathologist from structurally inadequate specimens lacking the anatomical features required for rejection grading. This distinction allowed us to assess clinical impact and histological agreement using definitions appropriate to each objective. In four procedures, contributive CB findings were associated with decisions not to repeat bronchoscopy after non-contributive FB. However, because repeat bronchoscopy was not systematically mandated by protocol, these cases represent potentially avoided procedures rather than definitively prevented interventions. Procedural safety remains an important consideration. Previous studies, including randomized trials and meta-analyses, have supported the feasibility of CB when appropriate protective strategies are used [9, 11]. In our cohort, pneumothorax occurred in seven procedures (13.7%), a higher rate than the 6.3% reported by Steinack et al [7]. Nevertheless, only one patient (2.0%) required chest tube drainage, while the remaining cases were managed conservatively. Differences in procedural protocols, sampling strategies, and patient populations may contribute to variability in reported complication rates. Importantly, because FB and CB were performed during the same bronchoscopy, pneumothorax could not be attributed to either technique individually. Similarly, the limited number of bleeding events precludes conclusions regarding comparative safety. Our findings therefore characterize complications associated with the combined procedure rather than establishing the independent safety profile of CB. Several limitations should be acknowledged. First, this was a small, single-center retrospective study, predominantly involving surveillance bronchoscopies performed early after transplantation (median 84 days). Seven recipients underwent repeated procedures, introducing potential within-patient correlation. In the sensitivity analysis restricted to one procedure per recipient, diagnostic reclassification decreased from 33.3% to 27.3%, while management modifications decreased from 27.5% to 20.5%. Although additional findings and associated management changes remained frequent, these differences indicate that the estimated clinical impact was sensitive to the inclusion of repeated procedures. Second, the paired design does not eliminate potential sampling bias. CB and FB specimens were

obtained from different sites, and CB was systematically performed before FB without randomization. Spatial heterogeneity, bleeding, or local tissue disruption following CB may therefore have influenced subsequent FB sampling. Histopathological assessment was performed by a single pathologist without blinded independent review, introducing potential interpretation bias. Furthermore, the absence of an independent reference standard prevents validation of discordant diagnoses. Third, clinical management changes were retrospectively identified from medical records and reflected decisions made with knowledge of both biopsy results, without a predefined treatment algorithm or independent adjudication committee. Consequently, the primary endpoint captures observed clinical decision-making rather than independently validated clinical benefit. The study was also underpowered to assess differences in uncommon complications, particularly bleeding, for which only two discordant pairs were available. Finally, all procedures were performed in hospitalized patients under general anesthesia, with fluoroscopic guidance and prophylactic bronchial blocker placement, potentially limiting generalizability to other procedural settings. Long-term outcomes, including CLAD progression and survival, were not assessed. In conclusion, CB provided additional histological information associated with changes in clinical management in more than one-quarter of procedures. These findings suggest a potential clinical role beyond improved tissue sampling, although the diagnostic accuracy and clinical benefit of CB-driven management decisions remain to be established. Prospective multicenter studies incorporating independent diagnostic validation and long-term outcomes are warranted.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Bordeaux University Hospital Ethics Committee (approval number: CER-BDX 2024-226). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LC, CB, and XD participated in research design, the performance of the research, the data analysis, the writing of the paper and in review and editing. HB, CB, AR, YB, JM, EB, MG, PS, and CV participated in the performance of the research and in review and editing.

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Conflict of interest

CB was employed by Menarini, pulmonX and Boehringer. PS was employed by Vitalaire for a presentation, and by SOS Oxygène and Alizée for attendance at a congress. XD was employed by Menarini (honorarium for educational presentation), by Boerhinger for participation in advisory board, and received travel support for attendance at scientific meetings from SOS Oxygène and Sanofi.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.17412/full#supplementary-material

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