Efficacy of surveillance bronchoscopy *versus* clinically indicated bronchoscopy for detection of acute lung transplant rejection: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
Due to the limited number of studies, it was not possible to statistically determine the superiority of either surveillance bronchoscopy or clinically indicated bronchoscopy over the other. Larger prospective studies are necessary to validate this. https://bit.ly/4dM4gxl

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Abstract

Background Acute allograft rejection after lung transplantation significantly increases the risk of developing bronchiolitis obliterans syndrome, a form of chronic lung allograft dysfunction and the leading cause of mortality beyond the initial post-transplantation year. There are two diagnostic approaches available for monitoring lung transplant recipients: clinically indicated bronchoscopy (CIB) and surveillance bronchoscopy (SB). The efficacy of both methods and their relative superiority in detecting acute rejection have not been conclusively determined.

Methods We systematically searched the MEDLINE, Embase, Cochrane and Scopus databases from inception until 10 October 2023 for prospective studies comparing the efficacy of SB and CIB. Meta-analysis using a random effects model was performed for three observational cohort studies, totalling 122 patients with 527 bronchoscopies.

Results Overall, neither SB nor CIB had a higher likelihood of detecting acute lung transplant rejection of any grade. Subsequent subgroup analyses showed no advantage for SB in detecting minimal rejection (grade A1), but an inverse association was observed for higher-grade rejection.

Conclusion In conclusion, our study found no significant difference in detecting acute lung transplant rejection between SB and CIB. However, due to the limited number of studies and small sample sizes, larger prospective studies are urgently needed to definitely determine whether there truly exists no difference between SB and CIB in detecting acute rejection, particularly A1 minimal rejection.

Introduction

Acute allograft rejection after lung transplantation significantly increases the risk of developing bronchiolitis obliterans syndrome (BOS), a form of chronic lung allograft dysfunction (CLAD) and the leading cause of mortality beyond the initial post-transplantation year [1]. The severity of acute rejection is often graded according to the revised classification by the International Society of Heart and Lung Transplantation (ISHLT), ranging from minimal (A1) to severe (A4) rejection based on the extent and nature of perivascular, interstitial and airspace infiltrates of mononuclear cells [2].

To identify acute cellular rejection at an early stage and minimise cellular damage through timely intervention, bronchoscopy with transbronchial lung biopsy is routinely used in the aftercare of lung transplant recipients in the first year post-transplant. In this period, triple immunosuppression is tapered from a maximal level early post-transplant to a maintenance immunosuppression at about 1 year post-transplant. The pace of tapering is influenced by the lack of evidence for allograft rejection. There are two primary approaches to detect acute cellular rejection: clinically indicated bronchoscopy (CIB), reserved

for symptomatic patients exhibiting significant declines in airway obstruction (forced expiratory volume in 1 s) or chest radiograph infiltrates, and surveillance bronchoscopy (SB), conducted at specific intervals post-transplantation, even in asymptomatic patients.

According to the recent ISHLT Bronchoalveolar Lavage (BAL) survey, 72 (86%) of 84 lung transplant centres across 25 countries worldwide adopt a SB approach [3]. However, the role of SB in screening asymptomatic patients for acute rejection remains a subject of debate [4, 5]. A primary argument against SB is that it may pose an unjustifiable procedural risk, particularly if it does not provide discernible benefits with regard to survival or the development of BOS. Recent studies suggest that CIB may be just as effective as SB in early detection of acute rejection allowing for successful treatment of such rejections. This adds to the ongoing discussion on the optimal approach [6]. The uncertainty and the lack of systematic reviews highlights the need for a critical evaluation of the diagnostic accuracy of both approaches and their potential impact on the incidence of CLAD and overall patient outcomes.

In light of this ongoing controversy, the primary objective of this systematic review and meta-analysis is to comprehensively compare the effectiveness of SB and CIB for detecting acute rejection in lung transplant recipients. By synthesising existing evidence on diagnostic outcomes, this study aims to provide valuable insights derived from available data that may inform clinical practice guidelines for the detection of acute rejection.

Methods

This systematic review and meta-analysis followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol was registered in the international prospective register of systematic reviews (PROSPERO) under the registration number CRD42023471338.

To be selected for analysis, studies had to: 1) include only adult lung transplant recipients (⩾18 years) with reasons for transplantation explicitly stated; 2) be published in English; 3) group patients based on whether they received CIB or SB; 4) grade detected rejection reactions according to the revised Working Formulation for the Classification of Pulmonary Allograft Rejection by the ISHLT; and 5) specify clinical inclusion criteria for the CIB cohort and a schedule for each bronchoscopy for the SB cohort.

Exclusion criteria encompassed studies that included re-transplanted patients or those who had undergone heart–lung transplantation, as well as studies characterised by a retrospective design.

We systematically searched the MEDLINE, Embase, Cochrane and Scopus databases from inception until 10 October 2023, combining keywords and MESH terms (supplementary figure S1).

The evaluation of studies for eligibility and data extraction was carried out independently by two authors (K. Fricke and N. Sievi). Disagreements were resolved through discussion or, when necessary, by involvement of a third reviewing author (F. Schmidt) to reach consensus. Data extraction was by one author (K. Fricke) and validated independently by another (N. Sievi). Extracted data encompassed study characteristics and participant demographics, focusing on the reasons for lung transplantation, the type of transplantation, and the numbers of SBs and CIBs per group (table 1).

Risk of bias assessment was independently conducted by two authors (K. Fricke and N. Sievi) using the Newcastle–Ottawa Scale (NOS), with a score range of 1 to 9. The certainty of evidence was evaluated across five categories: risk of bias, inconsistency, imprecision, indirectness and publication bias, employing the Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach.

Data were analysed using the STATA software package version 16.1 (Stata Corp., College Station, TX, USA) and presented as log odds ratios (OR) with 95% confidence interval (CI). Pooled data were obtained using a random effects model and statistical significance was set at a two-sided p-value of <0.05. Forest plots were utilised to present the results of individual studies and the pooled log OR. Statistical heterogeneity was assessed with the Higgins I^2 test.

Publication bias was assessed using Egger's linear regression test. Subgroup analyses were conducted based on the grade of rejection reaction, with subgroup 1 including grade A1 rejection reactions only and subgroup 2 including grade A2 to A4 rejection reactions.

TABLE 1 Summary of each study population

	Valentine *et al.* [6]	DeHoyos *et al.* [7]	Baz *et al.* [8]
Patients n	47	32	43
Age years, median (range)	47 (15–65)	NR	NR
Male %	57	NR	NR
Follow-up time months	12	6	13
ULLT/BLLT n	8/39	16/16	26/22
Top three primary reasons for lung transplant (n)	1) Cystic fibrosis (16) 2) Pulmonary fibrosis (15) 3) Emphysema (14)	1) Obstructive lung disease (10) 2) Interstitial lung disease (9) 3) Cystic fibrosis (7)	1) COPD (24) 2) Primary pulmonary hypertension (6) 3) Idiopathic pulmonary fibrosis (4)
SB regimen	6 weeks, 3, 6 and 12 months	3, 6, 9 and 12 months	First bronchoscopy during first 6 weeks, then after 3, 6, 9 and 12 months
Clinical indicators for CIB	Unexplained respiratory symptoms; signs or fever; 10% decline in FEV_1 or 20% decrease in FEF below baseline; delay in anticipated improvement of lung function; CXR changes	Significant change in pulmonary status of the patient suggesting infection and/or rejection	Hypoxaemia, fever, changes in CXR, decrease in airflow
Total SBs n	54	42	157
Total CIBs n	186	19	69

NR: not reported; ULLT: unilateral lung transplant; BLLT: bilateral lung transplant; SB: surveillance bronchoscopy; CIB: clinically indicated bronchoscopy; CXR: chest radiograph; FEV_1: forced expiratory volume in 1 s; FEF: forced mid-expiratory flow.

Results

The systematic search strategy, conducted in accordance with PRISMA guidelines, identified 4756 records. Following the application of inclusion and exclusion criteria, 37 studies were deemed eligible for full-text review (figure 1, and detailed reasons for study exclusion in supplementary figure S2). Only three studies were eligible for inclusion in this review, all of which were observational cohort studies with a cumulative enrolment of 122 patients who underwent a total of 527 bronchoscopies. Upon assessment of the included studies, a comprehensive evaluation of risk of bias was performed, employing the NOS. The results indicated an overall low risk of bias across all studies (supplementary figure S3).

Table 1 presents a summary of the main characteristics of each study cohort. Notably, the cohorts of De Hoyos *et al.* [7] and Baz *et al.* [8] demonstrated comparable numbers of unilateral and bilateral lung transplant patients, whereas the cohort of Valentine *et al.* [6] exhibited a significantly higher proportion of bilateral transplant recipients. All three studies uniformly implemented a SB regimen, commencing with regular bronchoscopies at 6 to 12 weeks post lung transplantation, followed by subsequent examinations at 6, 9 and 12 months. Analysis of SB and CIB revealed variations in their utilisation across studies. In the cohorts of De Hoyos *et al.* and Baz *et al.*, the total number of SBs exceeded twice that of CIBs, whereas Valentine *et al.*'s cohort displayed a threefold increase in CIBs compared to SBs.

To evaluate the efficacy of SB and CIB, a random effects model was employed to pool OR from each study. Neither SB nor CIB demonstrated a higher likelihood of detecting acute lung transplant rejection of any grade (OR 0.94, 95% CI 0.61–1.45; p=0.76; I^2=0%; figure 2a). Subgroup analysis, focusing solely on grade A1 rejection, revealed no statistically significant superiority for the detection of minimal rejection with SB (OR 2.11, 95% CI 0.67–6.64; p=0.20; I^2=55.6%; figure 2b). Conversely, an inverse association was observed when examining the detection of grade A2 and higher-grade lung transplant rejection with SB or CIB (OR 0.48; 95% CI 0.28–0.82; p=0.01; I^2=0%; figure 2c). Heterogeneity among studies was generally low, except in the grade A1 rejection subgroup analysis, where it reached substantial levels (I^2=55.6%, 95% CI 0.67–6.64). To assess the possibility of publication bias, Egger's test was conducted, yielding a p-value of 0.445, indicating no evidence of bias in the reported results.

Discussion

This systematic review and meta-analysis evaluated the role of SB and CIB in conjunction with transbronchial biopsy for screening lung transplant recipients for acute rejection. The review synthesised data from all three identified studies, encompassing observational cohorts with 122 patients with 253 SBs and 274 CIBs.

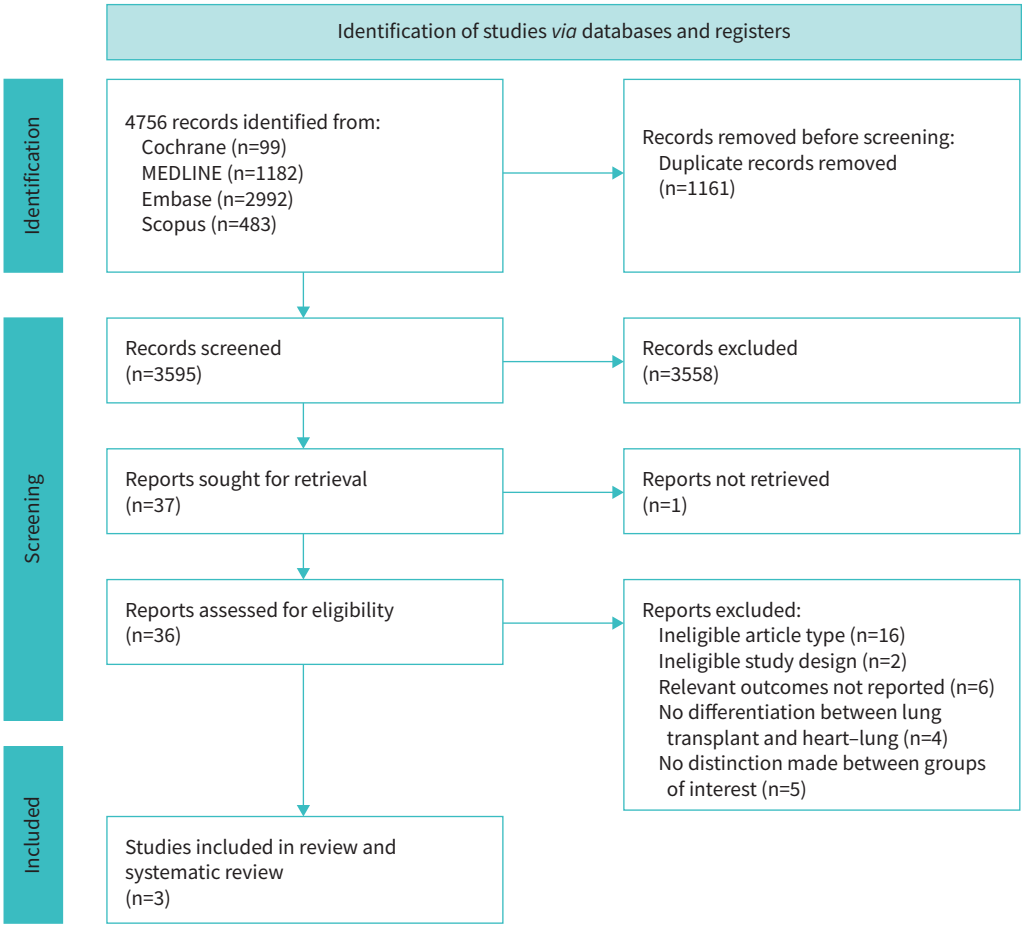

FIGURE 1 PRISMA 2020 flow diagram.

The main findings of our review revealed that there is no discernible superiority in diagnostic yield between SB and CIB when considering all grades of acute lung rejection. Conversely, the diagnostic yield of SB for grade A2–A4 acute rejection was less than half that of CIB. This difference is likely attributable to the fact that higher-grade rejections, by definition, manifest substantial immune responses, resulting in discernible signs and symptoms such as reduced lung function or increased body temperature, which warrant bronchoscopy.

With regard to grade A1 acute rejection, there was no statistically significant difference between the diagnostic yield of SB and that of CIB. This could be attributed to various factors, such as the limited number of studies, three in total, with a high heterogeneity, the relatively small sample size (122 patients) and the observational design of the studies. These factors emphasise the necessity for further research to clarify whether SB offers any discernible benefits in detecting A1 rejection.

SB and CIB have become essential screening tools for acute lung transplant rejection. The imperative to detect rejection promptly, optimise immunosuppression and prevent long-term complications has driven the adoption of these procedures. In particular, the SB approach has gained popularity among lung transplant centres globally, as shown by the recent ISHLT BAL survey. It found that 86% of lung transplant centres in 25 countries utilise the SB approach [3]. However, a lack of consensus on their frequency persists due to safety concerns and lack of scientific evidence from randomised trials. Bridging this gap is essential for establishing standardised guidelines that balance diagnostic efficacy and patient safety in post-transplant monitoring.

Data from the three available studies identified for inclusion in our meta-analysis were not able to corroborate findings in the scientific literature. To date, there are no randomised controlled trials investigating the efficacy and safety of SB against CIB. Moreover, the latest study included in our review was conducted 15 years ago [6].

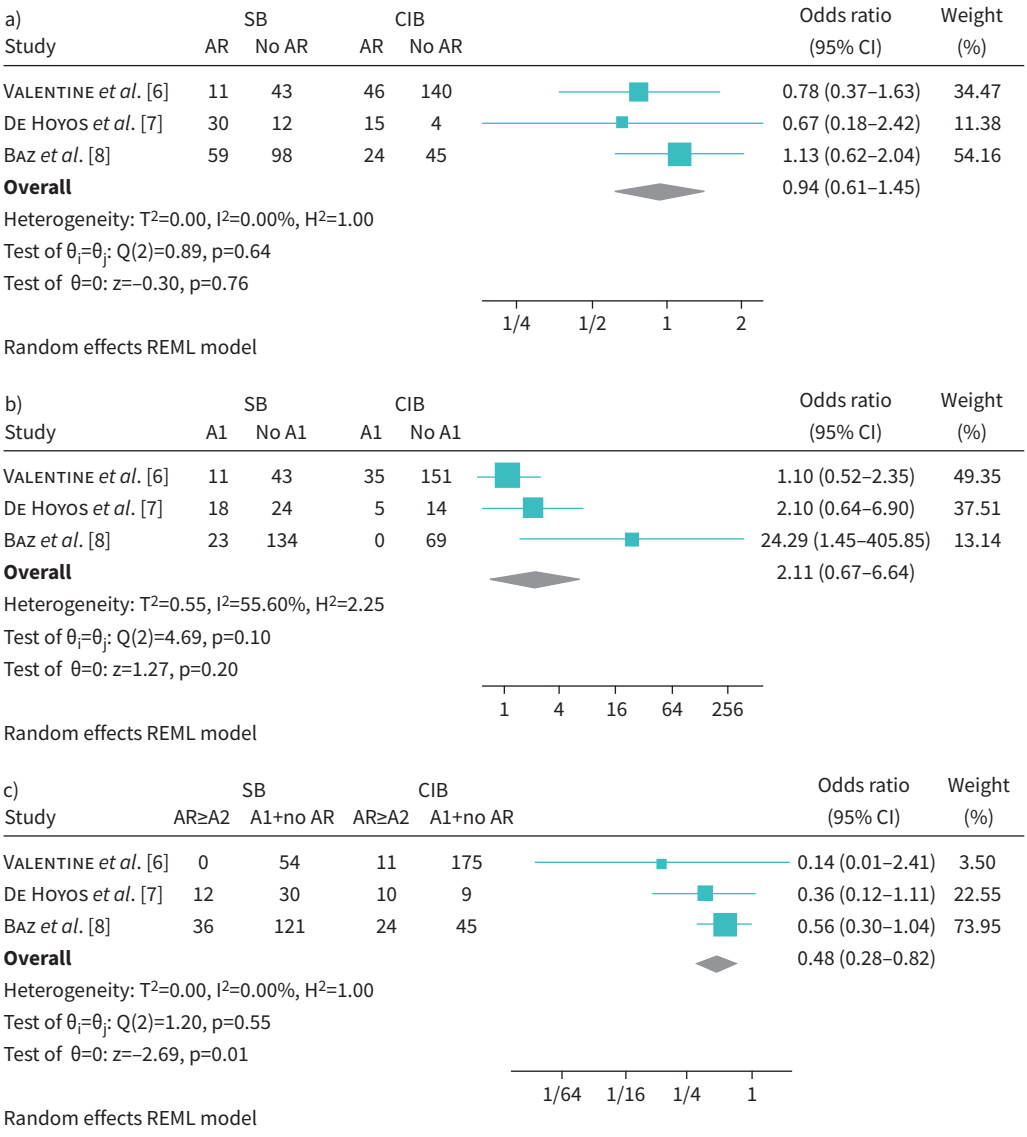

FIGURE 2 a) Overall detected numbers of acute rejection with SB and CIB. b) Detected numbers of A1 acute rejection with SB and CIB. c) Detected numbers of A2–A4 acute rejection with SB and CIB. SB: surveillance bronchoscopy; CIB: clinically indicated bronchoscopy; AR: acute rejection; CI: confidence interval.

McWilliams *et al*. [9], for instance, observed a comparable diagnostic yield between SB and CIB for overall acute rejections and noted an increased detection rate of grade A1 rejection with the use of SB. The authors recommend the use of SB, while also acknowledging the role of CIB in the diagnostic framework of lung transplant rejection. In contrast, Valentine *et al*. [6] observed comparable outcomes but concluded that relying solely on CIB could decrease the number of invasive bronchoscopies. They suggest that incorporating SB may be excessive, as CIB alone might suffice for detecting acute rejection, minimising unnecessary risks for patients. However, as Valentine *et al*. did not identify acute rejection episodes (grade A1 acute rejections) enabling treatment modifications through SB, their conclusion misses the feasibility of a more targeted approach, which could also reduce the number of future CIBs and therefore the complications with bronchoscopy.

As anticipated with any medical procedure, bronchoscopy was associated with some complications. Valentine *et al*. reported several complications within the SB group, including fever (18 cases out of 54), lung infiltrates (11 cases out of 54) and bleeding surpassing 100 mL (two cases out of 54). Baz *et al*. documented an overall complication rate of 4.4%, encompassing six instances of excessive bleeding (six out of 226), while De Hoyos *et al*. noted three pneumothoraces (three out of 66 cases). Unfortunately, a

clear differentiation between complications specific to the SB group and those observed in the CIB group was not made. The overall complication rate is expected to be consistent across both groups, with the higher frequency of bronchoscopies performed within the SB group being the primary factor contributing to a greater likelihood of complications.

The treatment of A1 rejection remains a topic of debate, with the prevailing consensus favouring treatment of grade A2 or higher acute rejection [1, 10]. Opponents of treatment argue that the lack of definitive evidence supporting its benefits, coupled with the risks associated with repeated bronchoscopy, such as bleeding, infection and arrhythmias, outweigh the advantages of early minimal rejection detection [11]. A cohort study with collected data from 1999 to 2017 found no significant increase in risk of CLAD or death for not treating A1 rejection in clinically stable patients in their first year post-transplant [12]. Hence, treatment of A1 rejection was not supported.

In contrast, advocates for treating A1 rejection argue for its direct association with BOS [13–15]. They claim that untreated A1 rejection may accelerate the onset of BOS. Preventing BOS in lung transplant recipients is crucial as it is strongly associated with acute vascular rejection and obliterative bronchiolitis [4]. CLAD-BOS, occurring in over 50% of recipients within 5 years, is the leading cause of late mortality and morbidity, significantly impacting the quality of life of transplant recipients. Therefore, effective prevention is essential to improve long-term outcomes and patient well-being. According to Hopkins *et al.* [15] and Khalifah *et al.* [14], close monitoring of patients with A1 rejection is advised due to its significant association with an increased risk of BOS development. Hopkins *et al.* [15] also propose managing rare cases of A1 rejection with steroid pulse therapy to limit progression to A2 rejection. When examining different stages of BOS, Hachem *et al.* [16] revealed that a solitary episode of minimal rejection significantly predicts BOS stages 1 and 2 but not stage 3 or mortality.

To the best of our knowledge, no previous study has comprehensively compared the efficacy of SB and CIB in their ability to detect acute lung transplant rejection. Rigorous search criteria were used and appropriate statistical analyses were done to evaluate the outcomes. Two of the included studies demonstrated good quality, as indicated by NOS scores of 9, while one study exhibited fair quality with a NOS score of 6. This discrepancy can be attributed, in part, to Valentine *et al.*'s exclusive enrolment of cytomegalovirus-positive patients in their SB cohort due to the patients' concurrent involvement in a multicentre trial [6].

The certainty of evidence for all three studies was assessed using the GRADE approach and was determined to be very low (supplementary figure S4). This was primarily due to the initial low certainty associated with observational cohort studies. Subsequent downgrades were attributed to a high level of imprecision, characterised by wide confidence intervals and cohort sizes below the recommended threshold of 2000 participants. Notably, risk of bias, inconsistency, indirectness and publication bias were all rated as low.

In this review, we discuss the roles of SB and CIB in the diagnostic framework for lung transplant recipients, particularly concerning the detection of A1 minimal rejection.

While our meta-analysis did not provide statistically significant evidence supporting the recommendation of SB, the low number of available studies and their lack of distinguishing safety outcomes for SB and CIB individually underscore the need for well-designed prospective studies. These are necessary to determine the efficacy of SB compared to CIB finally. SB could serve as a supplementary tool alongside CIB that enhances the diagnostic landscape, particularly the proactive identification of A1 minimal rejection. Concerning the framework of a SB plan, the ISHLT BAL survey revealed that the majority of programmes adhering to a SB protocol typically incorporate a bronchoscopy within the initial 6 weeks post-transplantation, followed by subsequent bronchoscopies at ~3 months (79.1%), 6 months (73.6%) and 12 months (80.2%) thereafter [3, 17, 18].

In this way, SB may be utilised within the diagnostic framework to identify minimal rejection reactions in lung transplant recipients during the first year post-transplant [19]. These reactions are associated with an elevated risk of developing CLAD in subsequent months and years [20]. Recognising this temporal distinction could offer a unique opportunity to identify cellular lung damage before the onset of symptoms, such as reduced lung function, providing a window for proactive intervention to mitigate cellular damage and potentially curtail the subsequent progression of CLAD.

To further enhance the ability to detect acute lung transplant rejection at its incipient stage, numerous promising biomarkers are under investigation. These biomarkers offer the potential for prompt and

minimally invasive detection, enabling intervention before the manifestation of overt signs and symptoms. One such area of research is the utilisation of circulating cell-free donor-derived DNA (dd-cfDNA) as a biomarker. This emerging approach leverages the detection of donor-specific DNA fragments in the recipient's circulation, providing a molecular signature indicative of graft injury [21]. Recent multicentre studies in lung transplant recipients have demonstrated the efficacy of dd-cfDNA in routine clinical care, highlighting its high negative predictive values for acute rejection and its potential as a noninvasive surveillance monitoring tool [22–24]. In addition to dd-cfDNA, another emerging biomarker of interest is the analysis of volatile organic compounds (VOCs) in exhaled breath. The identification and quantification of specific VOC profiles have shown promise in reflecting metabolic and inflammatory processes associated with allograft injury, offering an additional rapid and patient-centric diagnostic tool [25–27]. While these innovative biomarkers hold promise, the role of SB in the future of lung rejection monitoring remains crucial, serving as a complementary diagnostic tool to validate and further refine noninvasive approaches for comprehensive and effective post-transplant surveillance.

Our study has some limitations. The exclusion of non-English journal articles may have biased our findings. The limited number of studies, along with a small overall patient cohort and number of bronchoscopies could have compromised the identification of significant effects of SB and CIB on the detection of acute transplant rejection. The small sample size resulted in a downgrade of the certainty of evidence according to the GRADE approach. Additionally, studies involving patients with combined heart–lung transplantation were excluded as clinical signs and symptoms may be challenging to attribute solely to the lungs, potentially leading to misinterpretation and unnecessary bronchoscopy referrals. Some studies had missing data, specifically related to the distribution of the underlying diseases between SB and CIB, age and male-to-female ratio within the respective cohorts [7, 8]. Furthermore, one study group did not distinguish between each stage of acute transplant rejection as outlined by the International Society for Heart and Lung Transplantation criteria [7]. These data would have been beneficial for investigating a potential selection bias or conducting a subgroup analysis on each specific grade of acute rejection, instead of A1 and A2 or higher only.

In conclusion, this study could not show a statistically significant difference between the diagnostic yield of SB and CIB in detecting acute lung transplant rejection. It is important to note that only a very limited number of studies have attempted to compare the efficacy of SB *versus* CIB in this context, and most of them exhibit an older, observational design with small sample sizes. Consequently, the findings of our meta-analysis emphasise the need for larger prospective studies to definitely determine whether there truly exists no difference between SB and CIB in detecting acute rejection, particularly A1 minimal rejection. These prospective studies are essential to either corroborate our findings or ascertain if the lack of statistical significance was due to the limited sample size in previous research efforts.

Looking ahead, the future diagnostic landscape in post-transplant monitoring holds promise with the integration of novel biomarkers. Cell-free donor-derived DNA is poised to play a pivotal role, offering a noninvasive approach that can complement and expand the diagnostic capabilities of bronchoscopic procedures. The integration of such biomarkers into clinical practice has the potential to enhance diagnostic accuracy and advance patient-centric therapy, representing a significant step forward in the evolving field of lung transplant monitoring.

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