Transbronchial Lung Cryobiopsy May be of Value for Nonresolving Acute Respiratory Distress Syndrome: Case series and Systematic literature Review

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Abstract

Background: Identifying pathologic features is helpful for the management of nonresolving acute respiratory distress syndrome (ARDS). Transbronchial lung cryobiopsy (TBLC) is a novel biopsy technique that may have comparable utility to surgical biopsy. The aim of this study was to assess the value of TBLC in patients with nonresolving ARDS. Methods: All patients with nonresolving ARDS who underwent TBLC from January 2019 to August 2019 in a tertiary medical ICU were included. In addition, a literature search of TBLC for ARDS was performed by searching PubMed, EMBASE, ATS/ERS/APSR meeting abstracts, clinicaltrial.gov, and Google Scholar. Data on complications, histologic diagnosis, management changes, and outcomes were analyzed. Results: Five patients (three women and two men) underwent TBLC. None of the patients developed pneumothorax although in two patients massive bleeding occurred, which was controlled by continuous occlusion using bronchial blockers. There were no procedure-related deaths. Diffuse alveolar damage (DAD) and alternative histologic patterns were found in two and three patients, respectively, resulting in management changes in all cases. Literature search yielded four studies, which together with the present study resulted in data from 25 cases in which TBLC was used in nonresolving ARDS. The summary diagnostic yield was 92% (23/25). Only 44% (11/25) of cases were proven to be DAD. TBLC contributed to management changes in 80% of patients (20/25). Procedure-related complications consisted of pneumothorax (16%, 4/25), significant bleeding (12%, 3/25), and persistent air leak (8%, 2/25). There were no procedure-related deaths. The follow-up survival rate was 61.9% (13/21). Conclusions: Given its acceptable safety profile and high diagnostic yield, TBLC may be of value in selected patients with nonresolving ARDS.

Background

Acute respiratory distress syndrome (ARDS) is common in critically ill patients. The majority of studies report a high rate of morbidity and a mortality rate in the range of 35–60% (1,2). The Berlin definition of ARDS takes into account clinical and radiological criteria in the diagnosis and classification without considering pathologic findings (3). Diffuse alveolar damage (DAD) is a typical pathological finding in ARDS (4), but it is not seen in all ARDS patients nor is it specific to the disease. Studies have shown that only 43-45% of ARDS patients had DAD (5-8). Identifying the pathologic pattern in nonresolving ARDS can facilitate treatment decision-making and improve outcomes (6,8).

When the inciting event that results in ARDS is unclear or when an alternative diagnosis is under consideration, surgical lung biopsy (SLB) is one of the most common procedures to obtain a histologic diagnosis. Several studies have shown a positive impact of the histologic results of SLB in patients with nonresolving ARDS (6,8). However, SLB is performed in only 4–7% of patients with ARDS (6,9) due to the high surgery risk and poor conditions of most patients who are candidates for the procedure. Moreover, the complication rate of SLB is about 30%, with complications including persistent air leak and bleeding (9). The use of less invasive procedures, such as transbronchial lung biopsy (TBLB), in clinical practice has been limited due to difficulties in obtaining adequate tissue to provide confident pathologic results (the diagnostic yield is <35%) (9,10). Transbronchial lung cryobiopsy (TBLC) is an alternative technique

that has been widely used for the diagnosis of diffuse parenchymal lung disease (DPLD) (11). The sample sizes are significantly larger than those obtained with TBLB, and the diagnostic yield approaches that of SLB with lower complication rates (12,13). These observations suggest that TBLC may be an alternative procedure to SLB in patients with nonresolving ARDS, with potential benefits including adequate tissue to identify pathologies and less invasiveness. However, to the best of our knowledge, the use of TBLC in nonresolving ARDS has been examined in only a few case reports. Thus, in this study we assessed the use of TBLC in nonresolving ARDS based on 25 cases from our institute and literature review.

Methods

Patients

TBLC was conducted in the event of persistent respiratory failure after ongoing lung infection was ruled out by previous bronchoalveolar lavage (BAL) or when an alternative diagnosis was suspected based on the patient's history, clinical and radiologic presentation. The hospital records of all ARDS patients who underwent TBLC from January 2019 to August 2019 in our 26-bed tertiary medical ICU were reviewed. The inclusion criteria were as follows: Age ≥18 years at the time of TBLC, findings consistent with the Berlin ARDS definition, and ARDS characterized as mild, moderate, or severe, as described in the Berlin definition, at the time of diagnosis and biopsy.

TBLC procedure

Five patients with ARDS underwent TBLC (Figure 1). In four patients, the procedure was performed at the ICU bedside through an endotracheal tube (ETT), with the patient under deep sedation and supported by pressure control ventilation (F_iO_2 100%, PEEP 0 cmH_2O) or combined with extracorporeal membrane oxygenation (ECMO). The fifth patient received TBLC in a hybrid cone beam computed tomography (CBCT) OR. The procedure was conducted using rigid bronchoscopy with the patient under general anesthesia and ventilated by high-frequency jet respirator (F_iO_2 100%, respiratory rate 60 bpm, tidal volume 500 mL). In the four bedside procedures, the bronchoscopy was first introduced through the nasal route to the lower airway after releasing the balloon on the ETT. Next, a long guidewire was inserted to target lobe through bronchoscopy working channel. Bronchoscopy was then pulled out alone and reinserted through the ETT. Then, a bronchial blocker with a guide channel was introduced along the guidewire to target lobe. Radial probe endobronchial ultrasound (RP-EBUS) (EU-ME1, Olympus, Tokyo, Japan) was used to identify the proper biopsy site (Figure 1A). Under the guidance of pre-procedure CT images, the bronchoscope was advanced into the potential target bronchi as far as possible and then retracted 1–2 cm. When the surrounding RP-EBUS showed heterogeneous echo without vascular presentation, the depth of the probe was marked. A 2.4 mm cryoprobe (ERBE, Solingen, Germany) was inserted to the same position (Figure 1B). Cryobiopsy was performed (freeze time: 4 s) following probe

positioning, using carbon dioxide as the cryogen (Figure 1D). After each biopsy, the bronchial balloon blocker (CRE balloon, Boston Scientific Microvasive, Natick, MA, USA) was immediately filled (0.5-1 atm) to stop the bleeding (Figure 1E). Two to five biopsies were performed in each patient and the sizes of the obtained samples were measured. For patient who underwent TBLC in the hybrid OR, flexible bronchoscopy and bronchial blocker were inserted through a rigid bronchoscope. Prior to TBLC, CBCT images (Artis Zee III ceiling, Siemens AG, Munich, Germany) were acquired to determine the exact position of the cryoprobe (Figure 1C2), which was placed under RP-EBUS guidance.

In patients with ECMO, the plan was to stop treatment with unfractionated heparin (UFH) 4 h before TBLC and then monitor the activated clotting time of whole blood (ACT). TBLC was performed when the ACT had decreased to within an acceptable range. After the procedure, the bronchial blocker was not removed until UFH had been reinitiated (Figure 1F) and the ACT had recovered to the level previously achieved during ECMO with no active bleeding.

Outcomes

Patients routinely underwent a post-procedure chest X-ray to screen for pneumothorax. Bleeding severity was graded on a scale of 4: no bleeding, mild bleeding (requiring suction to clear but no other endoscopic procedures), moderate bleeding (requiring endoscopic procedures such as bronchial occlusion-collapse and/or instillation of ice-cold saline) and severe bleeding (causing hemodynamic or respiratory instability, requiring tamponade or other surgical interventions, transfusions) (14). Other complications, if any, were recorded.

Data on pathological diagnosis, treatment changes after TBLC and survival outcomes were obtained from the patient's medical records.

Literature search strategy

A literature search of PubMed, EMBASE, ATS meeting abstracts, ERS meeting abstracts, APSR meeting abstracts, clinicaltrial.gov, and Google Scholar ending on November 25, 2019 was conducted using the following terms: "acute respiratory distress syndrome" or "ARDS," and "cryobiopsy" or "cryoprobe," without restrictions on language or publication year. The retrieved papers were read in their entirety to assess their appropriateness for this study of the value of TBLC in ARDS. Data on the characteristics of the TBLC procedure, related complications, pathological diagnosis, treatment changes and patient survival outcomes were extracted and summary proportions were calculated based on individual cases.

Results

Patient characteristics

Five patients (three women and two men) with nonresolving ARDS underwent TBLC at our hospital. Their average age was 53 years (range: 31–68 years). The characteristics of these patients are summarized in Table 1. Four of them had underlying disease, including multiple sclerosis, nephrotic syndrome, impaired glucose tolerance and advanced lung adenocarcinoma. Four of the patients were diagnosed with severe ARDS and one with moderate ARDS according to the Berlin definition. All four patients with severe ARDS received mechanical ventilation (MV) support, including two in combination with veno-venous ECMO. UFH was used in patients with ECMO but was stopped 4 h before TBLC in one patient. In the other (patient 1), because flow-through ECMO decreased significantly after UFH was stopped, heparin use was continued until 30 min before the biopsy procedure. Respiratory support in patients with moderate ARDS consisted of high-flow nasal cannula oxygen therapy (HFNC).

TBLC procedure

All TBLC procedures were successfully performed using a 2.4 mm cryoprobe (freeze time: 4 s). A mean of 3.2 samples (range: 2–4 samples) were obtained from one (1 patient) or two (4 patients) lung segments. The samples had a mean size of 27.1 mm^2 (surface area) and were deemed satisfactory for use in histopathology and tissue culture (Figure 2). The patient with moderate ARDS successfully recovered from general anesthesia and was placed on HFNC after TBLC. None of the patients experienced significant oxygenation state changes before or after the procedure. No patient developed pneumothorax but two patients suffered massive bleeding, which ceased after 2 and 3 h, respectively, in response to tamponades using bronchial blockers. There was no incident of hemodynamic instability. Three other patients had mild bleeding. There were no procedure-related deaths. The bronchial balloon blockers in patients with ECMO were removed after comfirming no active bleeding following the reinitiation of UFH.

Outcomes

Histopathological diagnosis in the five patients included a fibrotic phase of DAD with underlying infection (n=1), proliferative phase of DAD with cytomegalovirus inclusions (n=1), foreign body granulomas (n=1), fibrotic non-specific interstitial pneumonia (n=1) and organizing pneumonia (OP) (n=1). One patient had an *Acinetobacter baumanii* infection, confirmed by tissue culture. Management changes (such as in antibiotic and steroid usage (Table 1)) were made in all patients after multidisciplinary discussion, based on the clinical condition, laboratory data, BAL results of the patient, and the pathological pattern of TBLC. Three patients improved and subsequently underwent rehabilitation treatments. Two patients died, one due to pulmonary embolism and the other to septic shock.

Systematic review

Four studies (2 meeting abstracts, 1 published letter and 1 published paper) met the inclusion criteria (15–18) (Figure 3). The patients in two studies (15,18) overlapped such that three previous investigations of 20 patients with nonresolving ARDS who underwent TBLC were included (15-17). Thus, together with our five patients, a total of 25 patients who met the criteria of the Berlin definition of ARDS were included in our larger study. The characteristics of these four studies are summarized in Table 2. All studies were retrospective case series. In the study of Dincer *et al*. (15), the five patients with ARDS were on MV and a mean of five specimens were obtained from each patient. A specific histopathological diagnosis was made and contributed to management changes in all patients. The pathological pattern included two cases of DAD and three alternative diagnoses. There were no procedure-related complications. Four of the five patients survived. Cooley *et al*. (16) reviewed 11 cases of ARDS in patients under MV support. The diagnostic yield of TBLC was 82% (9/11), including four cases of DAD. TBLC resulted in management changes in eight patients. Complications included pneumothorax (n=4), persistent air leak (n=2), and significant bleeding (n=1). Six patients survived. Las Heras *et al*. (17) reported on four ARDS patients, and a specific histopathological diagnosis was made in each case, including DAD (n=3) and another pattern (n=1). TBLC contributed to management changes in two patients. There were no incidents of pneumothorax, significant bleeding or procedure-related death. The survival outcome was not available.

According to the summary proportions from these four studies, the diagnostic yield of TBLC for nonresolving ARDS was 92% (23/25). DAD was diagnosed in 44% (11/25) of patients; the remainder had other diagnoses. TBLC contributed to management changes in 80% (20/25) of patients. Procedure-related complications included pneumothorax (16%, 4/25), significant bleeding (12%, 3/25) and persistent air leak (8%, 2/25). The rate of significant bleeding was 8.7% (2/23) in patients without ECMO. There were no procedure-related deaths. The follow-up survival rate was 61.9% (13/21).

Discussion

We assessed the safety and value of TBLC for ARDS in five patients with nonresolving ARDS at our hospital and then in a larger study that also included all patients from previous studies.

TBLC was most often used in patients with DPLD. A recent study (13) indicated that the diagnostic yield of TBLC was comparable to that of SLB, with a high level of diagnostic agreement between the two procedures. However, the safety and potential value of TBLC in ARDS has not been established. A literature search of this topic was conducted and resulted in the identification of only three independent studies with a total of 20 patients (15–17). Our combined analyses suggested that complications of TBLC in ARDS are acceptable and similar to those reported for TBLC used in DPLD during the stable stage (12). One of the most important advantages of this novel technique over SLB is the superior safety profile. The overall complication rate of SLB is about 30%, most of which (71%) are persistent air leaks (19); this rate of complications is significantly higher than that for TBLC (8%). Persistent air leak is a serious condition in ARDS patients, especially for those with positive pressure ventilation. It is difficult to clinically manage patients with persistent air leak. Another advantage of TBLC over SLB is that patient and ventilation conditions may be easier to manage, and the requirement for surgeon skill may be lower.

Finally, the cost of TBLC is much lower than that of SLB (20). In our country (China), the overall cost of TBLC is about 10,000 yuan compared to about 50,000 yuan for SLB.

However, ARDS is defined only according to clinical and radiological criteria without consideration of the pathological findings, which are known to be heterogenous. Identifying specific pathological patterns is an important determinant of treatment. Gerard et al. (6) reported that 57% (29/51) of patients who underwent SLB had pathologies other than DAD. Moreover, 37% (19/51) of the patients had a steroid-sensitive pathologic disease pattern (OP, acute interstitial pneumonia, acute exacerbation of usual interstitial pneumonia, eosinophilic pneumonia, pneumocystis pneumonia, alveolar hemorrhage and amiodarone toxicity); these patients had significantly better outcomes than patients with steroid-resistant pathologies (in-hospital mortality rate: 37% vs. 65%; 180-day mortality rate: 37% vs. 75%). In our study based on the combined data of reported cases, the summary diagnostic yield of TBLC was 92%, and 56% of patients had a diagnosis other than DAD, which led to management changes in 80% of patients (similar to SLB) (19). These results indicate that TBLC may be an alternative biopsy method to SLB for patients with nonresolving ARDS.

Patients with ARDS typically have complex underlying conditions that increase the difficulty and risk of TBLC. ECMO is an important life support method for patients with severe ARDS. The majority of these patients receive UFH to prevent thrombus formation and maintain normal ECMO operation, although the risk for procedure-related bleeding is higher. The use of TBLC in ARDS patients on ECMO was not previously described. However, our study included two patients with severe ARDS who were on ECMO support in whom TBLC was successfully performed. One suffered from procedure-related massive bleeding, which was successfully stopped by 3 h of continuous occlusion using bronchial blockers. Thus, in patients with ECMO, TBLC should be performed after controlling for the bleeding risk and thrombogenesis, and bronchial blockers should be placed prophylactically. The rate of significant bleeding was 8.7% (2/23) in patients without ECMO.

The safety of TBLC depends to a large extent on the location of the cryoprobe (21). A distance of <1 cm to the pleura is associated with a significantly higher risk for pneumothorax, and a biopsy obtained too proximal to the middle third of the lung increases the risk for severe bleeding. RP-EBUS can identify diffuse lung lesions and their surrounding vessels and encouraging results have been obtained using RP-EBUS-guided TBLC in patients with ILD (22,23). Our study is the first to describe the use of RP-EBUS-guided TBLC in ARDS. Four patients with severe ARDS underwent ICU bedside TBLC guided only by RP-EBUS. The patient with moderate ARDS underwent TBLC in a hybrid OR with the combined guidance of CBCT and RP-EBUS. None of the patients developed pneumothorax but two had massive bleeding. Thus, the value of RP-EBUS guidance requires further investigations in larger populations.

By including all patients from current and previous studies, our study was the largest case series to preliminarily assess the safety and value of TBLC in ARDS. However, it had several limitations. First, it was a retrospective study, although the results support the need for a prospective controlled study with a larger population. Second, the procedure protocols were not identical between studies. Further

investigations should be performed based on a standard TBLC protocol for patients with ARDS. Third, the results were limited by the small sample size, and strong support for the routine use of TBLC in patients with nonresolving ARDS is still lacking. TBLC should be performed after multidisciplinary discussion with consideration of the clinical condition, laboratory data of patient, and of other non-invasive methods. The cost/benefit ratio and effectiveness should also be considered.

Conclusion

The complications of TBLC in patients with ARDS were acceptable. The procedure had a high diagnostic yield and led to a re-evaluation of the diagnosis as well as changes in patient management. TBLC may be of value in select patients with nonresolving ARDS. Further investigations with a prospective design and a larger number of patients are required to confirm the value of TBLC for nonresolving ARDS.

List Of Abbreviations

ARDS, acute respiratory distress syndrome; ILD, interstitial lung disease; SLB, surgical lung biopsy; ETT, endotracheal tube; OR, operating room; TBLB, transbronchial lung biopsy; TBLC, Transbronchial lung cryobiopsy; RP-EBUS, radial probe endobronchial ultrasound; ACT, activated clotting time of whole blood; UFH, unfractionated heparin; PCV, pressure control ventilation; PEEP, positive end expiratory pressure; PC, pressure control above PEEP; ECMO, extracorporeal membrane oxygenation; RP-EBUS, radial probe endobronchial ultrasound; CBCT, cone beam computed tomography; DAD, diffuse alveolar damage; HFNC, high-flow nasal cannula oxygen therapy; CMV, cytomegalovirus; NSIP, non-specific interstitial pneumonia; OP, organized pneumonia; COP, cryptogenic organizing pneumonia.

Declarations

Ethics approval and consent to participate:

The Institutional Ethics Committee (China-Japan Friendship Hospital) approved this study. The written informed consent from the patients or their next of kin was obtained.

Consent for publication:

The consent for publication from the patients or their next of kin was obtained.

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

All authors declared no competing interest existed in this study.

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Author contributions:

GZ analyzed and interpreted the patient data and was a major contributor in writing the manuscript. YF and SW contributed to the acquisition and analysis. YZ, YT and XW contributed to substantively revised the manuscript. LZ performed the histological examination of the specimens. DW, YL and ZT contributed to the literature search and analysis. QZ contributed to the conception and design of the work. All authors read and approved the final manuscript.

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Figures

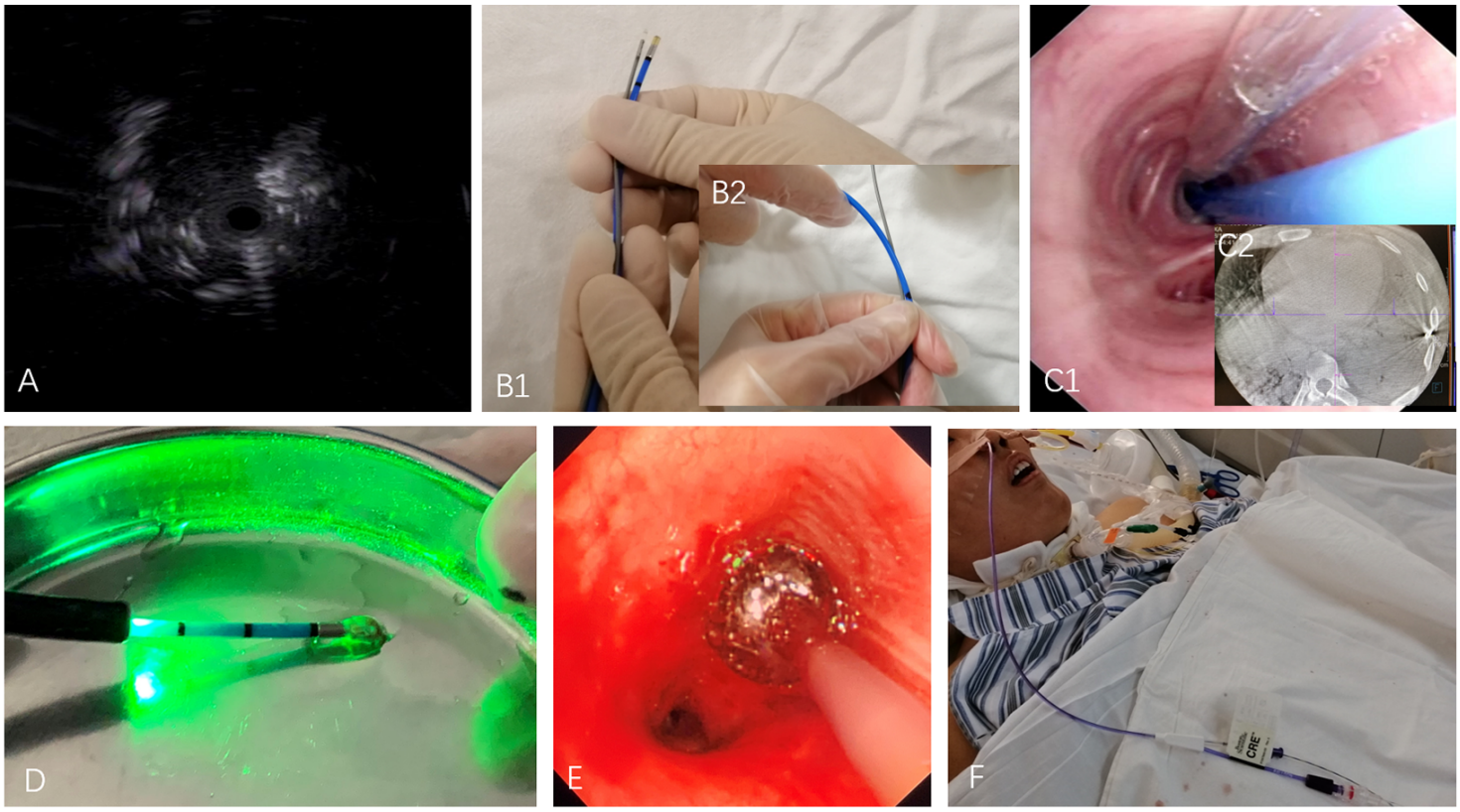

Figure 1

Radial probe endobronchial ultrasound (RP-EBUS) guided transbronchial lung cryobiopsy (TBLC) for acute respiratory distress syndrome (ARDS). (A) RP-EBUS screening the target biopsy position. (B) Marking the biopsy distance on cryoprobe compared to that of RP-EBUS. (C1) Prophylactically placing bronchial blocker and inserting cryoprobe in the target segment. (C2) Combined guidance with cone beam CT after placing cryoprobe in patient 5. (D) Transbronchial lung cryobiopsy was done after freezing 4 s. (E) Bronchial blocker was filled to stop bleeding. (F) Bronchial blocker was continuously placed in target bronchi for the patients with massive bleeding.

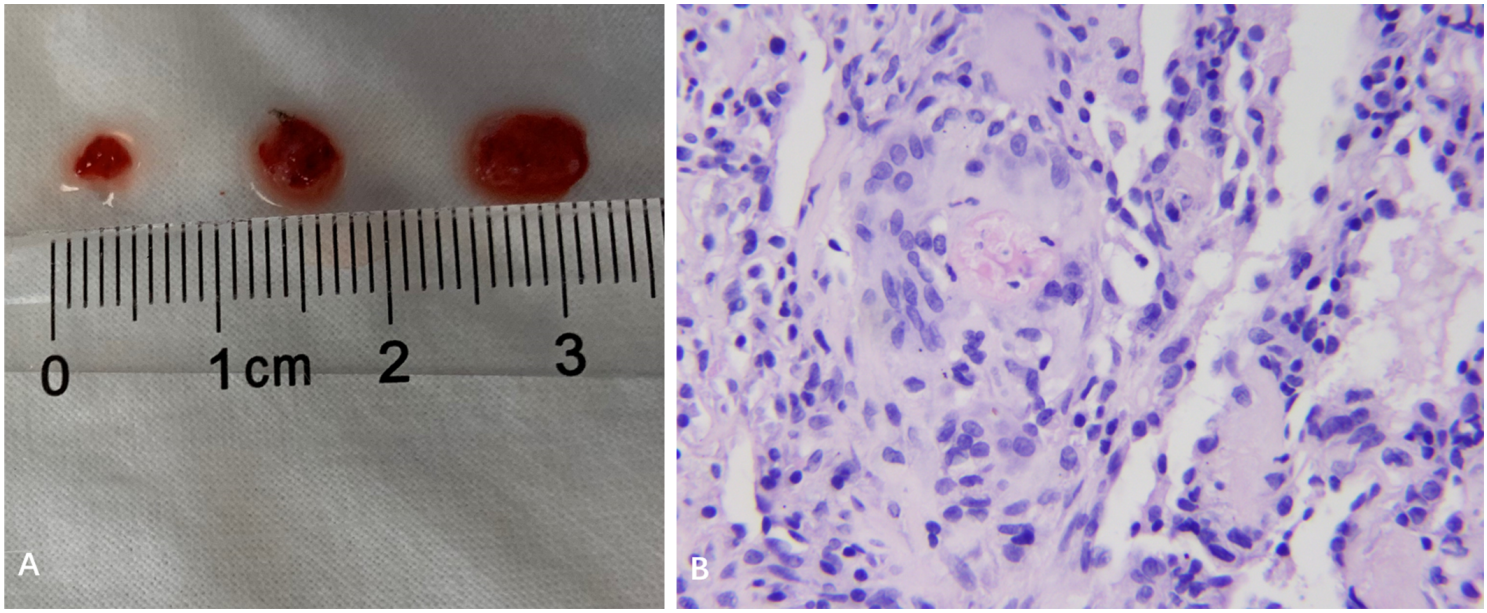

Figure 2

Specimens and histology obtained by transbronchial lung cryobiopsy for acute respiratory distress syndrome. (A) Gross specimens and their sizes. (B) Histologic diagnosis of foreign body granulomas in patient 3.

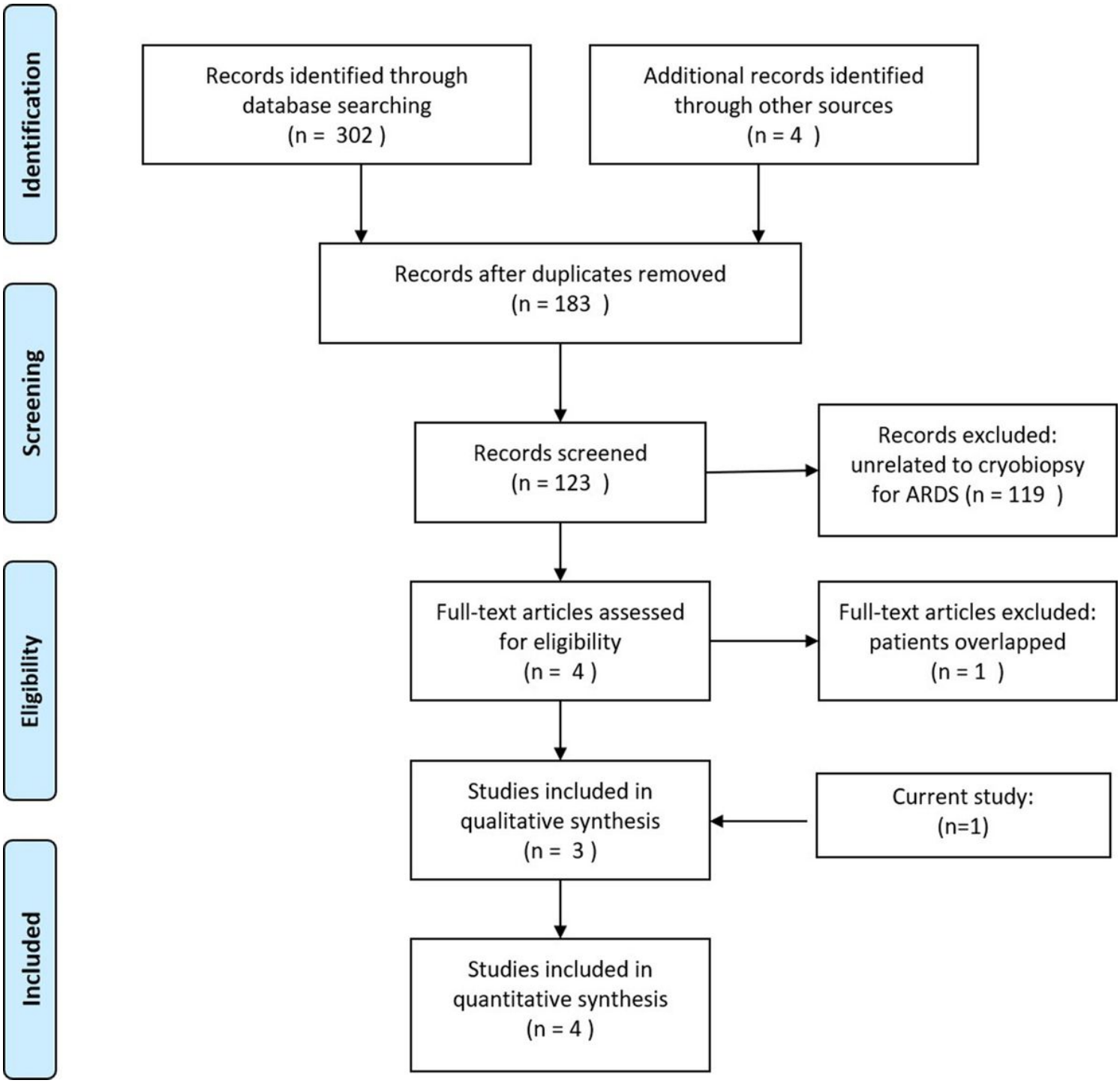

Figure 3

Flow diagram of the literature search and study selection process.

Supplementary Files

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