Feasibility of transbronchial lung cryobiopsy in patients with veno-venous extracorporeal membrane oxygenation support

Shiyao Wang [1,4], Guowu Zhou[1,4], Yingying Feng[1], Yi Zhang[1], Ye Tian[1], Sichao Gu[1], Xiaojing Wu[1], Meiyuan Li[1], Yiming Feng[1], Dan Wang[1], Ying Li[1], Zheng Tian[1], Ling Zhao[2], Min Li[1], Wenhui Chen[1,3], Xu Huang[1] and Qingyuan Zhan[1]

[1]Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China–Japan Friendship Hospital, National Center for Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China. [2]Department of Pathology, China–Japan Friendship Hospital, Beijing, China. [3]Department of Lung Transplantation, Center of Respiratory Medicine, China–Japan Friendship Hospital, Beijing, China. [4]Both authors contributed equally.

Corresponding author: Qingyuan Zhan (drzhanqy@163.com)

Shareable abstract (@ERSpublications)
The case series demonstrated performing TBLC in VV-ECMO-supported patients with acute hypoxaemic respiratory failure might be generally safe with appropriate bleeding prophylaxis and contributes to identifying underlying aetiologies of patients https://bit.ly/3CcVTKa

Cite this article as: Wang S, Zhou G, Feng Y, *et al*. Feasibility of transbronchial lung cryobiopsy in patients with veno-venous extracorporeal membrane oxygenation support. *ERJ Open Res* 2022; 8: 00383-2022 [DOI: 10.1183/23120541.00383-2022].

Received: 29 July 2022
Accepted: 21 Sept 2022

Abstract

Background Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is essential life support in patients with severe acute hypoxaemic respiratory failure. However, biopsies should be considered for some patients with unknown aetiology. This study aims to evaluate the feasibility of transbronchial lung cryobiopsy (TBLC) in such patients.

Methods All patients with acute hypoxaemic respiratory failure of unknown aetiology who underwent TBLC with VV-ECMO support were retrospectively reviewed. Patients' characteristics, ventilation settings, procedure parameters, complications, pathological diagnosis and survival were summarised and analysed.

Results Eight female and five male patients with VV-ECMO support underwent TBLC. The median age was 58 (interquartile range (IQR) 38–67) years old. Concurrent diseases were present in 10 of the 13 patients, seven of which were immunosuppressed. The median time between biopsy and VV-ECMO establishment was 2.0 (IQR 0.5–6.5) days. No patient died from the procedure. Neither pneumothorax nor severe bleeding occurred in any of the patients. Five of the 13 patients experienced moderate bleeding, and all bleeding events were successfully controlled with prophylactic balloon blockers. Pathological diagnosis by TBLC was obtained in all patients, and the diagnosis of diffuse alveolar damage was made in nine of them.

Conclusions In patients with VV-ECMO support, the TBLC procedure is generally safe when standardised bleeding prophylaxis is in place. TBLC contributes to identifying underlying aetiologies in patients with acute hypoxaemic respiratory failure of unknown aetiology.

Introduction

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is a life-saving initiative for patients with severe acute hypoxaemic respiratory failure [1]. It allows sufficient rest to the lungs, providing a valuable diagnostic and therapeutic window for determining the aetiology of acute respiratory failure and subsequent treatment. Pneumonia and non-pulmonary sepsis remain the most common causes of acute hypoxaemic respiratory failure [2]. However, for atypical cases, such as drug-induced lung injury, organising pneumonia, acute exacerbation of interstitial lung disease and malignancy, it could be difficult to obtain definitive diagnosis with routine assessments such as pathogenic detection or bronchoalveolar lavage fluid (BALF) analysis. Previous studies have shown that access to pathology may improve the prognosis of patients with acute respiratory failure of unknown aetiology [3–5]. For patients under VV-ECMO support, lung biopsy is still recommended to clarify the diagnosis as much as possible, as VV-ECMO itself is only a means of support, not a treatment [6].

In terms of biopsy choice, previous studies have primarily focused on surgical lung biopsy (SLB) in patients on extracorporeal membrane oxygenation (ECMO) support, whose complications mainly include haemopneumothorax and persistent bronchopleural fistula. However, the complications reported vary in different studies [7, 8]. As a new biopsy method, transbronchial lung cryobiopsy (TBLC) has been increasingly utilised in patients with diffuse pulmonary infiltrations [9–12]. Our previous work has shown the potential clinical benefit of TBLC in critically ill patients with acute hypoxaemic respiratory failure and demonstrated good safety profile of TBLC with acceptable risk of airway bleeding [13, 14]. However, the safety and pathological diagnostic yield of TBLC in VV-ECMO-supported patients with acute hypoxaemic respiratory failure are still unclear. Therefore, we reported a case series of patients who underwent TBLC with VV-ECMO support to demonstrate the feasibility of TBLC in such settings.

Methods

Patients

13 consecutive patients who underwent TBLC with VV-ECMO support were retrospectively reviewed in the medical intensive care unit (MICU) of a tertiary medical centre between 1 January 2019, and 30 June 2022. All patients were admitted with acute hypoxaemic respiratory failure. Initial assessments failed to identify the cause of pulmonary infiltration, such as pulmonary infection, heart failure or diffuse alveolar haemorrhage, by laboratory tests and BALF analysis. Lung biopsy was not considered in patients with a combination of the following conditions: significant haemodynamic instability, uncorrectable coagulopathy, severe pulmonary hypertension, acute coronary syndrome, intermediate–high-risk acute pulmonary embolism, acute phase of stroke, severe emphysema, aortic dissection and massive gastrointestinal bleeding. Based on the clinical conditions, imaging and safety considerations, the procedure of TBLC and biopsy site was decided collectively by multidisciplinary discussion. The multidisciplinary team consisted of respiratory and critical care medicine physicians, respiratory interventionalists, radiologists, pathologists and rheumatologists. This study was approved by the Institutional Review Board of China–Japan Friendship Hospital (2022-KY-031), and all patients had signed informed consent prior to the procedure.

Procedure

All patients underwent TBLC at bedside with the standardised process (figure 1). Coagulation indicators and platelet counts were carefully verified prior to the procedure. In general, platelet counts $<50\times10^9$ per L, prolongation of prothrombin time (PT) beyond 3 s and activated partial thromboplastin time (aPTT) beyond 15 s were considered as relative contraindications. Blood products were given if necessary. Unfractionated heparin (UFH) was stopped at least 4 hours before the TBLC procedure. Then the activated clotting time (ACT) of peripheral blood was monitored.

The procedure would begin once the ACT was within the acceptable range (<120 s). All patients were intubated and fully sedated (Richmond Agitation–Sedation Scale −4 to −5) with analgesics, anaesthetics and muscle relaxants. During the procedure, we applied pressure-controlled ventilation while setting positive end-expiratory pressure to zero and fraction of inspired oxygen to 1.0. Mechanical ventilation was not interrupted during the whole procedure. The femoro-jugular configuration of VV-ECMO was applied in all patients. Sweep gas flow and blood flow of VV-ECMO were not routinely altered prior to the procedure but could be temporarily increased to maintain oxygenation if there was a drop in oxygen saturation during the procedure. Endobronchial balloon blockers (CRE balloon; Boston Scientific Microvasive, Natick, MA, USA) were introduced first by bronchoscopy to the opening of the target segment. Radial probe endobronchial ultrasound (RP-EBUS) was used to identify the appropriate biopsy site during the procedure. Next, a cryoprobe (1.9 mm or 2.4 mm; ERBE, Solingen, Germany) was delivered to the target site using the distance confirmed on RP-EBUS. After positioning the cryoprobe, the cryobiopsy was performed (freeze time: 3–6 s) using carbon dioxide as the cryogen. After completion, the bronchial balloon blocker was immediately inflated (0.5–1 atmosphere) to stop bleeding, with each inflation lasting ∼2 minutes. Then the balloon blocker was slowly and carefully deflated, with pausing to observe whether bleeding emerged. Two to three specimens would be obtained from one pulmonary segment, and two pulmonary segments were selected for biopsy for each patient if available. In total, two to six biopsy specimens were obtained from each patient, and then the size of each specimen was measured. The procedure would be aborted if any moderate bleeding event occurred.

After the procedure, the balloon blockers were withdrawn only when ACT returned to the level previously achieved during VV-ECMO support, and no active airway bleeding was observed.

The pathology specimens collected were examined by experienced pulmonary pathologists. A second pathologist was consulted in complex cases, and discrepancies were resolved by discussion and reaching consensus.

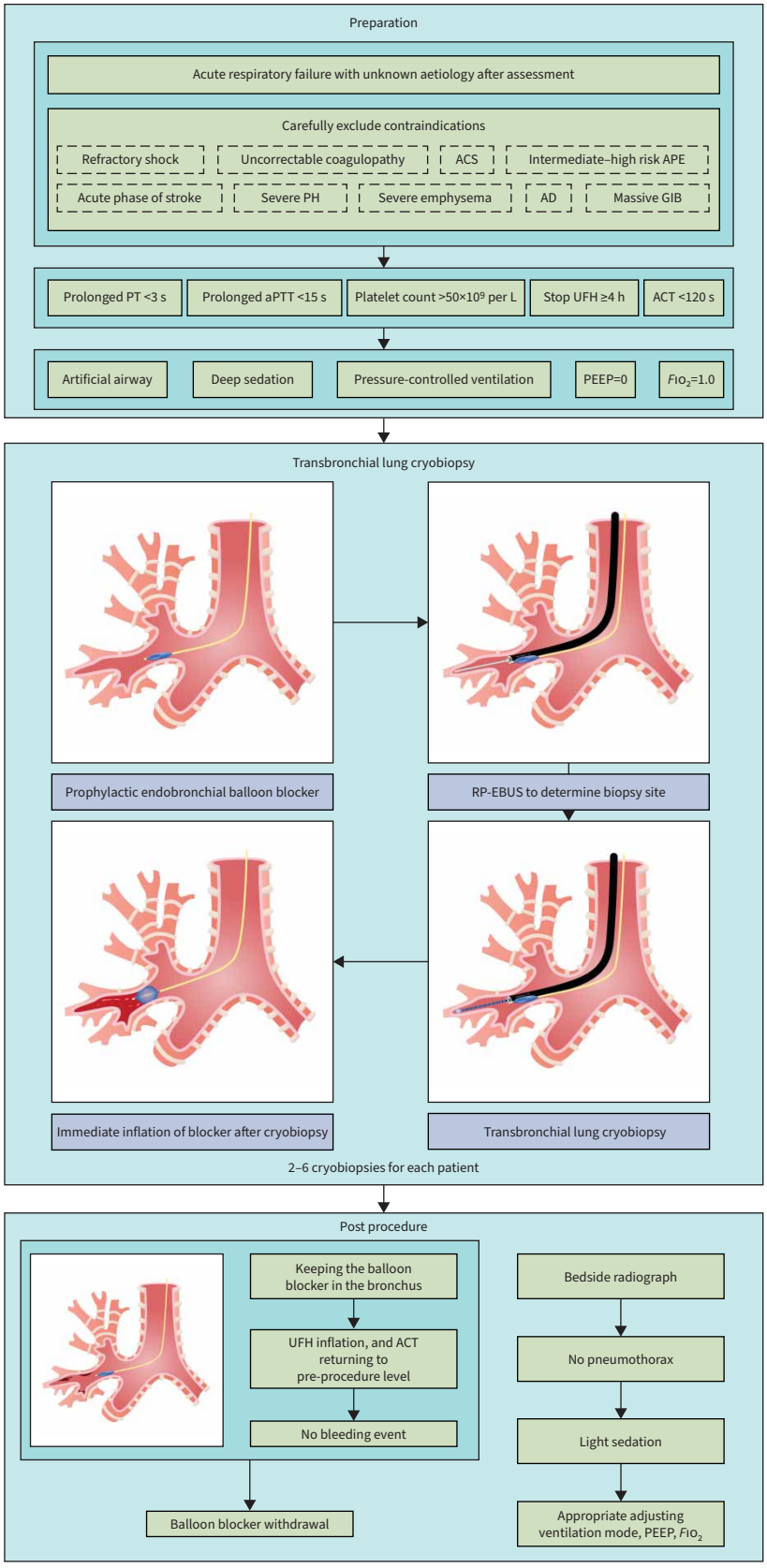

FIGURE 1 The standardised process for transbronchial lung cryobiopsy (TBLC) in veno-venous extracorporeal membrane oxygenation (VV-ECMO)-supported patients. ACT: activated clotting time; ACS: acute coronary

syndrome; AD: aortic dissection; APE: acute pulmonary embolism: aPTT: prothrombin time; F_{IO_2}: inspiratory oxygen fraction; GIB: gastrointestinal bleeding; PEEP: positive end-expiratory pressure; PH: pulmonary hypertension; PT: prothrombin time; RP-EBUS: radial probe endobronchial ultrasound; UFH: unfractionated heparin.

Complications and survival

The severity of bleeding was graded on a scale of four: Grade 0, no bleeding; Grade 1, mild bleeding (suction is needed for clearance, but no other endoscopic procedures are required); Grade 2, moderate bleeding (endoscopic procedures such as bronchial occlusion-collapse or ice-cold saline instillations are necessary); Grade 3, severe bleeding (the patient is haemodynamically unstable or has respiratory instability and may need to undergo surgical tamponade or blood transfusions) [15]. A bedside post-procedure radiograph was performed to rule out pneumothorax. Blood transfusions in 3 following days and 28-day survival from MICU admission were obtained from the patient's medical records.

Results

Clinical characteristics

Of the 13 patients who underwent TBLC with VV-ECMO support, eight were female and five were male. The median age was 58 (IQR 38–67) years. Most patients (76.9%, 10 out of 13) had underlying diseases. Seven of them were immunosuppressed, including three patients after lung transplantation, one patient after allogeneic haematopoietic stem cell transplantation, one patient with multiple sclerosis on glucocorticoids, one patient with erythema nodosum on glucocorticoids, and one patient with undifferentiated connective tissue disease treated with glucocorticoids and immunosuppressants. The median time from biopsy to symptoms onset was 20 (IQR 13–31) days, and the median time from VV-ECMO establishment was 2.0 (IQR 0.5–6.5) days. All patients were supported by pressure-controlled ventilation, except for two patients who were supported by high-flow nasal cannula (HFNC). According to the standardised operating procedure, patients supported by HFNC also received tracheal intubation prior to biopsy. The median levels of PT, aPTT and platelet count before biopsy were 15.9 (IQR 14.5–17.6) seconds, 50.8 (IQR 44.6–58.6) seconds and 111 (IQR 71–162) $\times 10^9$ per L, respectively.

Procedure-associated complications

A 2.4-mm cryoprobe was used during TBLC in all but one patient, for whom a 1.9-mm cryoprobe was used instead. The median number of biopsy specimens was 4.0 (IQR 2.5–5.0). The median long and short diameters of the specimens obtained were 5.2 mm (IQR 4.4–5.8 mm) and 3.7 mm (IQR 3.2–4.0 mm), respectively. Five of the 13 patients had a slight increase in VV-ECMO blood flow (median 0.3 L, IQR 0.3–0.6 L) during the procedure due to a decrease in oxygen saturation. All these patients had their VV-ECMO settings restored to pre-procedure levels after the procedure. No patient died directly from the procedure. Pneumothorax and severe bleeding events did not occur in any of the patients. Moderate bleeding occurred in five of the 13 (38.5%) patients, and all bleeding events were successfully controlled with prophylactic balloon blockers. The remaining eight patients had mild bleeding events, which did not affect the continuation of the procedures. Nine patients received red blood cell transfusion within 3 days after the procedure, with a median dose of 2 (0–3) units.

Diagnosis and survival

Pathological diagnosis was obtained in all patients by TBLC. Nine (69.2%) patients were diagnosed with diffuse alveolar damage (DAD) of different phases, three patients were diagnosed with organising pneumonia and one patient with nonspecific interstitial pneumonia. Interestingly, among the patients diagnosed with DAD, viral inclusion bodies were found in biopsy specimens in two patients. In one of these patients, immunohistochemical staining suggested human cytomegalovirus (CMV) infection, but CMV nucleic acid was not detected in the patient on initial BALF analysis after admission. In the other patient, human coronavirus 229E (HCoV-229E) was detected by microbial next-generation sequencing in repeated BALF analysis, and the diagnosis of severe community-acquired pneumonia due to HCoV-229E was established. Six of the 13 patients died within 28 days of MICU admission. The causes of death included uncontrollable underlying diseases (n=4), acute pulmonary embolism (n=1) and septic shock (n=1).

Clinical characteristics, complications, pathological diagnostic yields and survival of each patient who underwent TBLC with VV-ECMO support are summarised in table 1.

https://doi.org/10.1183/23120541.00383-2022

TABLE 1 Clinical characteristics, complications, pathological diagnosis and survival of patients who underwent transbronchial lung cryobiopsy with veno-venous extracorporeal membrane oxygenation (VV-ECMO) support

Case	Sex/age years	Comorbidities	Days from symptoms onset to biopsy	Days on VV-ECMO prior to biopsy	Ventilation settings before biopsy (except VV-ECMO)	Probe size/ sample number/ average size mm	Complications	Transfusion in the 3 following days (units)	Pathological diagnosis	28-day survival
1	F/39	Multiple sclerosis with GC	23	1	PCV (PC 14 cmH_2O, PEEP 11 cmH_2O, F_{IO_2} 0.35)	2.4 mm/2/5.5×4.5	Moderate bleeding	2	Proliferative and fibrotic phase of DAD	No
2	M/68	Membranous nephropathy without GC	29	5	HFNC, F_{IO_2} 0.40	2.4 mm/4/5.3×4.0	Mild bleeding	4	Exudative and proliferative phase of DAD, with viral inclusion bodies	Yes
3	F/66	None	12	7	HFNC, F_{IO_2} 0.30	2.4 mm/4/4.0×3.7	Mild bleeding	0	NSIP	Yes
4	M/67	Erythema nodosum with GC	50	0	PCV (PC 12 cmH_2O, PEEP 4 cmH_2O, F_{IO_2} 0.40)	2.4 mm/5/6.2×3.8	Mild bleeding	2	Fibrotic phase of DAD	No
5	F/34	Post allo-HSCT with anti-rejection therapy	30	0	PCV (PC 14 cmH_2O, PEEP 12 cmH_2O, F_{IO_2} 0.70)	2.4 mm/5/4.6×3.4	Mild bleeding	4	Exudative and proliferative phase of DAD	No
6	F/58	Glomerulonephritis without GC	20	1	PCV (PC 12 cmH_2O, PEEP 8 cmH_2O, F_{IO_2} 0.40)	2.4 mm/5/4.3×3.7	Mild bleeding	0	OP	Yes
7	F/24	None	32	0	PCV (PC 20 cmH_2O, PEEP 3 cmH_2O, F_{IO_2} 0.30)	2.4 mm/5/5.2×4.0	Moderate bleeding	2	Exudative and proliferative phase of DAD	No
8	M/67	Post LT with anti-rejection therapy	17	3	PCV (PC 15 cmH_2O, PEEP 10 cmH_2O, F_{IO_2} 0.50)	2.4 mm/2/3.0×3.0	Moderate bleeding	0	OP	Yes
9	F/62	ILD	14	1	PCV (PC 8 cmH_2O, PEEP 10 cmH_2O, F_{IO_2} 0.30)	2.4 mm/6/5.0×3.0	Mild bleeding	2	Proliferative and fibrotic phase of DAD	No
10	M/36	None	36	22	PCV (PC 15 cmH_2O, PEEP 4 cmH_2O, F_{IO_2} 0.60)	2.4 mm/4/4.5×2.5	Moderate bleeding	2	Fibrotic phase of DAD	No

Continued

https://doi.org/10.1183/23120541.00383-2022

TABLE 1 Continued

Case	Sex/age years	Comorbidities	Days from symptoms onset to biopsy	Days on VV-ECMO prior to biopsy	Ventilation settings before biopsy (except VV-ECMO)	Probe size/ sample number/ average size mm	Complications	Transfusion in the 3 following days (units)	Pathological diagnosis	28-day survival
11	F/39	Unclassified connective tissue disease with GC and immunosuppressants	17	6	PCV (PC 10 cmH_2O, PEEP 8 cmH_2O, F_{IO_2} 0.35)	2.4 mm/2/6.0×3.5	Moderate bleeding	2	Proliferative phase of DAD, with viral inclusion bodies	Yes
12	F/54	Post LT (within 1 month) with anti-rejection therapy	7	10 (started before LT)	PCV (PC 14 cmH_2O, PEEP 8 cmH_2O, F_{IO_2} 0.30)	2.4 mm/3/5.6×5.0	Mild bleeding	4	OP	No
13	M/63	Post LT with anti-rejection therapy	6	2	PCV (PC 14 cmH_2O, PEEP 8 cmH_2O, F_{IO_2} 0.40)	1.9 mm/4/6.5×3.8	Mild bleeding	0	Exudative and proliferative phase of DAD	Yes

F: female; M: male; PCV: pressure control ventilation; PC: pressure control above PEEP; PEEP: positive end-expiratory pressure; FiO_2: fraction of inspired oxygen; DAD: diffuse alveolar damage; GC: glucocorticoid; HFNC: high-flow nasal cannula oxygen therapy; NSIP: nonspecific interstitial pneumonia; allo-HSCT: allogeneic haematopoietic stem cell transplantation; OP: organising pneumonia; LT: lung transplantation; ILD: interstitial lung disease.

Discussion

ECMO-managing physicians always need to weigh the risks and benefits of performing invasive procedures on ECMO-supported patients. Our study demonstrated the safety and pathological diagnostic value of performing TBLC in VV-ECMO-supported patients with acute hypoxaemic respiratory failure of unknown aetiology.

ECMO is a crucial form of extracorporeal life support. But for certain diseases of specific aetiology, ECMO is only supportive treatment instead of an aetiology-specific one, whereas the treatment of the underlying disease is the key to withdrawing ECMO support. Therefore, for respiratory failure of which the aetiology is not clear from conventional assessment, additional measures are needed to confirm the diagnosis, even on ECMO support. Previous studies have supported lung biopsy (SLB) in critically ill patients with acute respiratory failure of unknown causes to clarify the aetiology [3–5]. The Extracorporeal Life Support Organisation (ELSO) guidelines recommended SLB over transbronchial lung biopsy (TBLB) in VV-ECMO-supported patients, primarily due to the risk of airway bleeding [6]. Most previously reported VV-ECMO-supported lung biopsies were done using SLB [7, 8]. Apart from our cases, only six transbronchial biopsies under VV-ECMO support were reported previously, four *via* cup forceps and two *via* cryoprobes [16].

In a case series of five patients who underwent SLB with ECMO support, two patients were reported to require blood transfusion due to bleeding. No patient required reoperation, and none had air leak after operation [7]. However, in another case series of ECMO-supported patients with suspected acute interstitial pneumonia who received SLB, severe post-operative complications were reported in all patients [8]. One patient presented with recurrent pneumothorax, one presented with bronchopleural fistula, and one presented with bronchopleural fistula with a persistent pneumothorax and massive haemothorax. In a study of ECMO-supported adult patients receiving thoracic surgery, 72% (13 out of 18) had excessive post-operative bleeding, 67% (12 out of 18) required excessive inotropes and 56% (10 out of 18) required renal replacement therapy [17]. In summary, the overall risk of SLB in ECMO-supported patients is still relatively high, and more studies are warranted to clarify its safety profile. For TBLB and TBLC in VV-ECMO-supported patients, only one case series has been reported previously [16]. The four patients who underwent TBLB required less blood transfusion within 3 post-procedure days than the four patients who underwent SLB. One patient who underwent TBLC without discontinuation of anticoagulation therapy did not require blood transfusions afterwards, while the other patient who did not initiate anticoagulation therapy needed more blood transfusions within 3 days of TBLC. In our study, 38.5% (5 out of 13) of VV-ECMO-supported patients who underwent TBLC suffered from moderate bleeding during TBLC, suggesting that airway bleeding remains the predominant complication.

Because of the potential high risk of airway bleeding in ECMO-supported patients undergoing TBLC, multiple approaches are used to prevent the complication. ELSO guidelines recommend lung biopsy within the first week of ECMO support initiation [6]. Our study has strictly followed the recommendations of the guidelines. In addition, three of our patients received TBLC immediately after the extracorporeal circulation was established, when anticoagulation had not been initiated, to minimise the impact of anticoagulation on the procedure. For patients who have commenced anticoagulation, we recommend discontinuing anticoagulation before TBLC. Based on the half-life of UFH, we recommend performing TBLC at least 4 hours after stopping anticoagulation therapy, with an extension to 6 hours if feasible. In addition, monitoring ACT allows for rapid determination of the patient's bleeding tendency at the bedside before the procedure. We applied an ACT monitor to guide the TBLC in our study. RP-EBUS has a wide range of applications in transbronchial biopsy. Besides locating the biopsy target, RP-EBUS can also identify the presence of significant arteries adjacent to the biopsy site. Previous studies showed that RP-EBUS in TBLC reduced the risk of airway bleeding [18, 19]. Therefore, we recommend using RP-EBUS to locate the biopsy target and to probe the vessels when performing TBLC in VV-ECMO-supported patients. The use of prophylactic balloon blockers remains controversial in TBLC procedures. However, most previous studies had shown that the application of prophylactic balloon blockers resulted in an acceptable rate of bleeding complications in TBLC [20–23], and some studies have demonstrated that prophylactic use of balloon blockers reduced the incidence of airway bleeding [24]. Based on the relatively high incidence of moderate bleeding events in our study, we believe that the routine application of prophylactic balloon blockers in TBLC performance is necessary. And for patients who developed moderate bleeding, we recommend delaying withdrawal of balloon blockers until the patient's anticoagulation treatment is relaunched without new onset of airway bleeding events.

In this case series, 69.2% (9 out of 13) of patients were diagnosed with DAD, which is the most common pathological diagnosis in patients with critical acute hypoxaemic respiratory failure. As the gold standard

for the diagnosis of diffuse lung disease, the role of SLB in non-ECMO-supported critically ill patients with acute respiratory failure of unknown aetiologies has been repeatedly described. In these patients, the diagnostic yield of SLB for DAD was reported to be between 35 and 80% [3, 4, 25–27]. Our study demonstrated that the diagnostic efficacy of TBLC for patients with acute hypoxaemic respiratory failure of unknown aetiologies had been comparable to that of SLB. In VV-ECMO-supported patients, both our study and previous studies revealed no change in the sensitivity of either biopsy for the diagnosis of DAD [8, 16]. This implies that even in the presence of VV-ECMO support, necessary biopsies could and should be performed to clarify the underlying diagnosis. It is worth mentioning that although all patients in this study were initially thought to have non-infectious diseases, some patients were found to have viral pneumonia. Previous studies have found similar results, regardless of the method of biopsy [3, 4, 25, 27–29]. In addition, it is also notable that four patients in our study had TBLC indicating a fibrotic phase of DAD, including two patients with a combined proliferative phase of DAD, but none of these four patients survived. This suggests that regardless of the aetiology, the appearance of irreversible pulmonary fibrosis secondary to lung injury suggests significantly affected prognosis. Therefore, in some patients with critical respiratory failure who may have developed pulmonary fibrosis over a long period of time, TBLC may help clinicians determine whether the patient's disease is potentially reversible and assist in decision-making regarding emergent lung transplantation or withdrawal of VV-ECMO support, which is essential in the management of patients with ECMO support.

We acknowledge that our study has some limitations. First, this is an observational study conducted at a single centre with a small sample size. Second, we did not compare the differences in safety profile and diagnostic yield of different biopsies in VV-ECMO-supported patients, as our centre has limited experience in performing TBLB and SLB in such patients. However, for some diseases previously thought to require SLB for confirmed diagnosis, such as idiopathic pulmonary fibrosis, there is a growing body of evidence that supports TBLC to achieve close diagnostic yields [30]. Although ELSO mainly recommended SLB for VV-ECMO-supported patients [6], our study revealed that TBLC was not inferior to SLB in diagnostic yield and had acceptable safety profile. More research is needed to elucidate the optimal lung biopsy means for VV-ECMO-supported patients in the future.

Conclusions

This study demonstrated that the overall safety of TBLC in VV-ECMO-supported patients with acute hypoxaemic respiratory failure is acceptable, but given the potential risk of airway bleeding, appropriate prophylaxis needs to be given, such as ACT monitoring, RP-EBUS positioning and prophylactic application of balloon blockers. At the same time, TBLC could offer a decent pathological diagnostic yield for this group of patients in determining the underlying aetiologies. Further studies are still warranted.

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors thank Min Liu from the Department of Radiology, China–Japan Friendship Hospital, and colleagues from the Department of Rheumatology, China–Japan Friendship Hospital, for participating in multiple disciplinary discussions. The authors also thank H. Weng (Peking Union Medical College) for her advice on refining the wording of this manuscript.

Conflict of interest: All the authors state that there are no conflicts of interest related to this study.

Support statement: This study was supported by National High Level Hospital Clinical Research Funding (2022-NHLHCRF-LX-01-01) and Special Project of Clinical and Translational Medicine, Chinese Academy of Medical Sciences (2021-I2M-C&T-B-088). The research was designed, conducted and analysed by the authors independently of the funding sources. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. *JAMA* 2018; 319: 698–710.
2 Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. *Lancet* 2021; 398: 622–637.
3 Gerard L, Bidoul T, Castanares-Zapatero D, *et al.* Open lung biopsy in nonresolving acute respiratory distress syndrome commonly identifies corticosteroid-sensitive pathologies, associated with better outcome. *Crit Care Med* 2018; 46: 907–914.
4 Lim SY, Suh GY, Choi JC, *et al.* Usefulness of open lung biopsy in mechanically ventilated patients with undiagnosed diffuse pulmonary infiltrates: influence of comorbidities and organ dysfunction. *Crit Care* 2007; 11: R93.

5 Papazian L, Doddoli C, Chetaille B, *et al.* A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. *Crit Care Med* 2007; 35: 755–762.
6 Extracorporeal Life Support Organization (ELSO). Guidelines for Adult Respiratory Failure. 2014. www.elso.org/Portals/0/IGD/Archive/FileManager/989d4d4d14cusersshyerdocumentselsoguidelinesforadultrespiratoryfailure1.3.pdf Date last accessed: 18 April 2018.
7 Rozé H, Thumerel M, Ouattara A, *et al.* Feasibility of bedside open lung biopsy in patients treated with extracorporeal membrane oxygenation. *Intensive Care Med* 2014; 40: 1789–1790.
8 Gonçalves-Venade G, Lacerda-Príncipe N, Roncon-Albuquerque R Jr, *et al.* Extracorporeal membrane oxygenation for refractory severe respiratory failure in acute interstitial pneumonia. *Artif Organs* 2018; 42: 569–574.
9 Colby TV, Tomassetti S, Cavazza A, *et al.* Transbronchial cryobiopsy in diffuse lung disease: update for the pathologist. *Arch Pathol Lab Med* 2017; 141: 891–900.
10 Hetzel J, Maldonado F, Ravaglia C, *et al.* Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the cryobiopsy working group on safety and utility and a call for standardization of the procedure. *Respiration* 2018; 95: 188–200.
11 Troy LK, Grainge C, Corte TJ, *et al.* Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med* 2020; 8: 171–181.
12 Zhou G, Ren Y, Li J, *et al.* Safety and diagnostic efficacy of cone beam computed tomography-guided transbronchial cryobiopsy for interstitial lung disease: a cohort study. *Eur Respir J* 2020; 56: 2000724.
13 Zhou G, Feng Y, Wang S, *et al.* Transbronchial lung cryobiopsy may be of value for nonresolving acute respiratory distress syndrome: case series and systematic literature review. *BMC Pulm Med* 2020; 20: 183.
14 Wang S, Feng Y, Zhang Y, *et al.* Transbronchial lung biopsy versus transbronchial lung cryobiopsy in critically ill patients with undiagnosed acute hypoxemic respiratory failure: a comparative study. *BMC Pulm Med* 2022; 22: 177.
15 Ravaglia C, Bonifazi M, Wells AU, *et al.* Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. *Respiration* 2016; 91: 215–227.
16 Lipps KM, Bharat A, Walter JM. Lung biopsy in patients with acute respiratory distress syndrome supported on extracorporeal membrane oxygenation: a 2 year experience. *ASAIO J* 2019; 65: e92–e94.
17 Joshi V, Harvey C, Nakas A, *et al.* The need for thoracic surgery in adult patients receiving extracorporeal membrane oxygenation: a 16-year experience. *Perfusion* 2013; 28: 328–332.
18 Inomata M, Kuse N, Awano N, *et al.* Utility of radial endobronchial ultrasonography combined with transbronchial lung cryobiopsy in patients with diffuse parenchymal lung diseases: a multicentre prospective study. *BMJ Open Respir Res* 2021; 8: e000826.
19 Berim IG, Saeed AI, Awab A, *et al.* Radial probe ultrasound-guided cryobiopsy. *J Bronchology Interv Pulmonol* 2017; 24: 170–173.
20 Pajares V, Núñez-Delgado M, Bonet G, *et al.* Transbronchial biopsy results according to diffuse interstitial lung disease classification. Cryobiopsy versus forceps: MULTICRIO study. *PLoS ONE* 2020; 15: e0239114.
21 Hackner K, Stadler A, Schragel F, *et al.* Transbronchial lung cryobiopsy: prospective safety evaluation and 90-day mortality after a standardized examination protocol. *Ther Adv Respir Dis* 2022; 16: 17534666221077562.
22 Kuse N, Inomata M, Awano N, *et al.* Management and utility of transbronchial lung cryobiopsy in Japan. *Respir Investig* 2019; 57: 245–251.
23 Inomata M, Kuse N, Awano N, *et al.* Prospective multicentre study on the safety and utility of transbronchial lung cryobiopsy with endobronchial balloon. *ERJ Open Res* 2020; 6: 00008-2020.
24 Dhooria S, Mehta RM, Srinivasan A, *et al.* The safety and efficacy of different methods for obtaining transbronchial lung cryobiopsy in diffuse lung diseases. *Clin Respir J* 2018; 12: 1711–1720.
25 Donaldson LH, Gill AJ, Hibbert M. Utility of surgical lung biopsy in critically ill patients with diffuse pulmonary infiltrates: a retrospective review. *Intern Med J* 2016; 46: 1306–1310.
26 Ortiz G, Garay M, Mendoza D, *et al.* Impact and safety of open lung biopsy in patients with acute respiratory distress syndrome (ARDS). *Med Intensiva (Engl Ed)* 2019; 43: 139–146.
27 Philipponnet C, Cassagnes L, Pereira B, *et al.* Diagnostic yield and therapeutic impact of open lung biopsy in the critically ill patient. *PLoS ONE* 2018; 13: e0196795.
28 Matta A, Gupta E, Swank Z, *et al.* The use of transbronchial cryobiopsy for diffuse parenchymal lung disease in critically ill patients with acute hypoxemic respiratory failure: a case series. *Clin Respir J* 2021; 15: 788–793.
29 Ghiani A, Neurohr C. Diagnostic yield, safety, and impact of transbronchial lung biopsy in mechanically ventilated, critically ill patients: a retrospective study. *BMC Pulm Med* 2021; 21: 15.
30 Raghu G, Remy-Jardin M, Richeldi L, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2022; 205: e18–e47.