Transbronchial cryobiopsy for diffuse parenchymal lung disease: 30- and 90-day mortality

To the Editor:

Surgical lung biopsy (SLB) in diffuse parenchymal lung disease (DPLD) has been associated with significant in-hospital mortality (16% for non-elective patients, 1.7% for elective patients, overall 6.4%) [1, 2]. Overall 30-day mortality from SLB is reported at 1.5–4.5% from case series and 2.4% from a large European database [3]. Transbronchial cryobiopsy (TBC) has been proposed as a safer alternative to SLB for diagnosis of DPLD [4]. Existing studies on TBC report immediate procedural complications, but data on mortality at 30 and 90 days is sparse [2]. This is a report of 30- and 90-day mortality after TBC at a large volume interventional pulmonary practice in the USA examined in relation to indices of baseline disease severity. Individual case elements that led to practice changes are described. These descriptions elucidate clinical features potentially portending an increased risk of poor outcome.

We performed a retrospective review of consecutive patients who underwent TBC at Vanderbilt University Medical Center (VUMC) from 1 January 2012, to 31 March 2018 (IRB 180311). Electronic medical records and online obituaries were reviewed to collect data for mortality. Our procedural protocol has been described previously [5, 6].

Total of 197 patients underwent TBC, the majority for indeterminate DPLD (176, 89.3%). 11 patients (5.6%) underwent TBC as a part of a research study on familial interstitial lung disease (ILD) without clinical or radiological evidence of diffuse parenchymal lung disease at the time of biopsy and 10 (5.1%) for localised parenchymal lesions. Four patients died within 30 days (2.0%), and five patients died within 90 days of undergoing TBC (2.5%), all with underlying DPLD. These include one patient who died during the same hospitalisation (0.5% in-hospital mortality). All-cause 30-day mortality was 25% for inpatient procedures (two of eight total inpatients) and 1.1% for outpatient procedures (two of 189 total outpatients). Mortality increased to 1.67% at 90 days for outpatient procedures (three of 189 total outpatients). In our data following review of patient follow-up on EMR as well as obituaries, all patients were accounted for, ruling out any underestimation of mortality.

Among the patients who died, three patients underwent the procedure amidst acutely worsening dyspnoea with increased oxygen requirements, and two were inpatients. Two patients had bleeding complications during the procedure. Haemostasis was eventually obtained intra-procedure without recurrence during their course. However, both experienced severe hypoxaemic respiratory failures following this event. One patient had worsening hypoxaemia without bleeding complications. Two patients died of unknown causes on postoperative day 29 and 74 following an initial uneventful discharge from the hospital following the procedure (table 1).

While existing studies and meta-analyses report procedural mortality rates of 0.1–0.3%, our study suggests 30-day mortality after TBC is higher, confirming concerns raised about safety in advanced DPLD [2, 7]. All patients who died within 30 days of TBC had poor baseline lung function (diffusion capacity less than 35% of predicted). Patients, particularly at risk for death, were inpatients, patients amidst an acute decline and those with low baseline lung function. The occurrence of bleeding complications also predicted a higher risk of mortality.

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This study suggests 30- and 90-day mortality after transbronchial cryobiopsy is higher than reported, confirming concerns raised about safety in advanced diffuse lung disease. Keen attention towards patient selection and procedural planning is warranted. http://bit.ly/2ySoZNq

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TABLE 1 Demographics, baseline indices and characteristics of patients who died within 90 days of transbronchial cryobiopsy

Variable	% of total (n=197)	Case 1	Case 2	Case 3	Case 4	Case 5
Age at procedure years	61.28 (53.34–67.35)	72	54	62	50	71
Female	43.43% (86)	Yes	Yes	No	No	No
BMI	30.85 (26.55–35.30)	28	29.2	29.8	37.9	25.7
Inpatient	4% (8)	Yes	Yes	No	No	No
Smoking		Never	Yes	Yes	Never	Never
Never	43% (83)					
Current	45% (86)					
Former	12% (24)					
ASA Class		III	IV	IV	III	III
I	1% (1)					
II	19% (36)					
III	74% (140)					
IV	7% (11)					
V	0					
ECOG Performance Score		3	3	1	1	4
0	9% (17)					
1	56% (110)					
2	25% (49)					
3	10% (20)					
Charlson Comorbidity Index	2.0 (1.0–3.5)	3	1	5	1	1
FEV_1 % predicted	73.5 (60.0–85.80)	31	NA	60	101	85
FVC % predicted	71.0 (58.0–82.0)	24	NA	51	114	73
D_{LCO} % predicted	57.00 (43.00–67.00)	NA	NA	36	29	43
GAP index	3.00 (2.00–4.00)	7	NA	4	1	5
Pre-procedure oxygen requirement L·min^{-1}	0 (0.00–12.00)	6	2	0	3	0
Signs of recent decline pre procedure		Yes	Yes	No	Yes	No
Intraprocedural bleeding		No	Yes	No	Yes	No
Post-operative day of death		23	10	29	9	74

Data are presented as per cent value and frequencies in parentheses, or median (interquartile range) for continuous variables. BMI: body mass index; ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusion capacity of lung for carbon monoxide; GAP index: gender, age, physiology index; NA: not available.

Several practice changes were introduced in our biopsy selection criteria and technique following these events that are now a part of the standard protocol at VUMC. Following cases with bleeding complications, use of prophylactic bronchial blockade became a requirement for all TBC at VUMC [6]. It was acknowledged that the role of bronchial blocker is not only to achieve haemostasis but to prevent soiling of airways with blood that can cause exacerbation of the disease. Bronchial blocker is tested for leaks under saline before the procedure. Before the biopsy, the bronchial blocker is also used to serially occlude lobes that would be targeted for TBC, for 3–4 min, to assess for the adequacy of residual lung function if one lobe had to be occluded due to bleeding. All anticoagulants, antiplatelet agents, over the counter analgesics, vitamins, and herbal medications are recommended to be held at least 5 days before the procedure.

Following the analysis of this report, TBC is no longer offered to inpatients with acute DPLD exacerbations. All potential candidates are evaluated in an ambulatory setting by an interventional pulmonary attending. Indications, contraindications, and other less invasive alternatives for diagnosis are examined carefully in discussion with an ILD expert.

There are several limitations of this report. Our sample size is too small to allow statistical comparisons of baseline disease indices between patients who survived as compared to those who did not. We also acknowledge that this is a retrospective review from a single centre without the presence of a comparable control arm of SLB. However, we draw our comparison from the published 10-year nationwide outcomes of SLB [1, 3]. Being a single centre study limits the generalisability of our results like other recent reports [8, 9]. For instance, high prevalence of active smokers in our data, median GAP (gender, age, physiology) index and American Society of Anesthesiologists score of 3 (moderate risk for mortality) could have affected our mortality rates compared to other cohorts with different patient demographics. Our report should be looked at as a set of precautions that need to be considered by the proceduralist when deciding whether or not to biopsy.

We conclude that both TBC and SLB can be high-risk procedures and keen attention towards patient selection and procedure planning is warranted. We recommend transparent reporting of all outcomes after TBC for DPLD and encourage the DPLD and interventional pulmonology communities to collaborate on the establishment of a robust registry for TBC.

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References

1 Hutchinson JP, Fogarty AW, McKeever TM, *et al.* In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. *Am J Respir Crit Care Med* 2016; 193: 1161–1167.
2 DiBardino DM, Haas AR, Lanfranco AR, *et al.* High complication rate after introduction of transbronchial cryobiopsy into clinical practice at an academic medical center. *Ann Am Thorac Soc* 2017; 14: 851–857.
3 Hutchinson JP, McKeever TM, Fogarty AW, *et al.* Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008. *Eur Respir J* 2016; 48: 1453–1461.
4 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.
5 Lentz RJ, Taylor TM, Kropski JA, *et al.* Utility of flexible bronchoscopic cryobiopsy for diagnosis of diffuse parenchymal lung diseases. *J Bronchology Interv Pulmonol* 2018; 25: 88–96.
6 Lentz RJ, Argento AC, Colby TV, *et al.* Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. *J Thorac Dis* 2017; 9: 2186–2203.
7 Sethi J, Ali MS, Mohananey D, *et al.* Are Transbronchial Cryobiopsies Ready for Prime Time? *J Bronchology Interv Pulmonol* 2019; 26: 22–32.
8 Cooley J, Balestra R, Aragaki-Nakahodo AA, *et al.* Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. *Respir Med* 2018; 140: 71–76.
9 Ravaglia C, Wells AU, Tomassetti S, *et al.* Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients. *BMC Pulm Med* 2019; 19: 16.