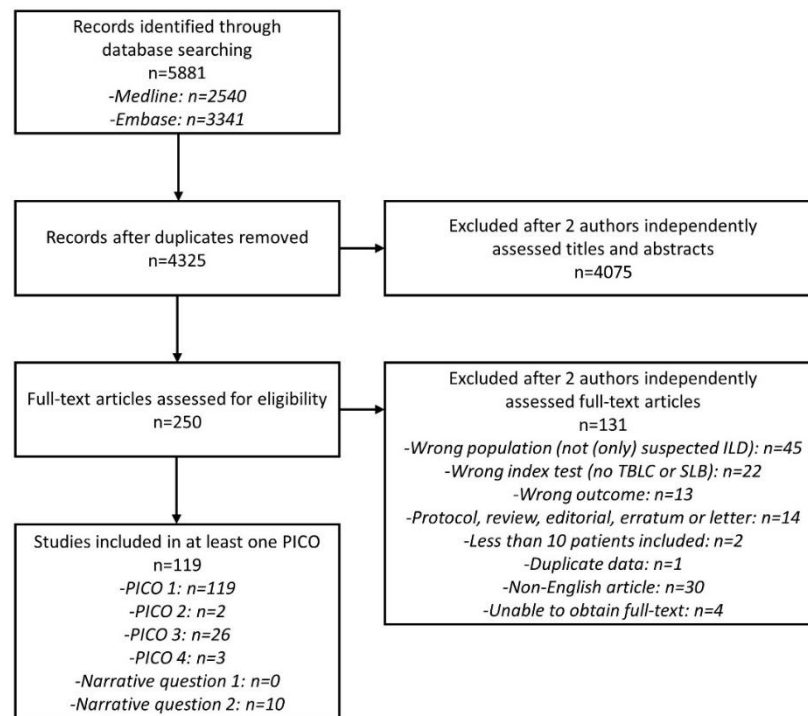


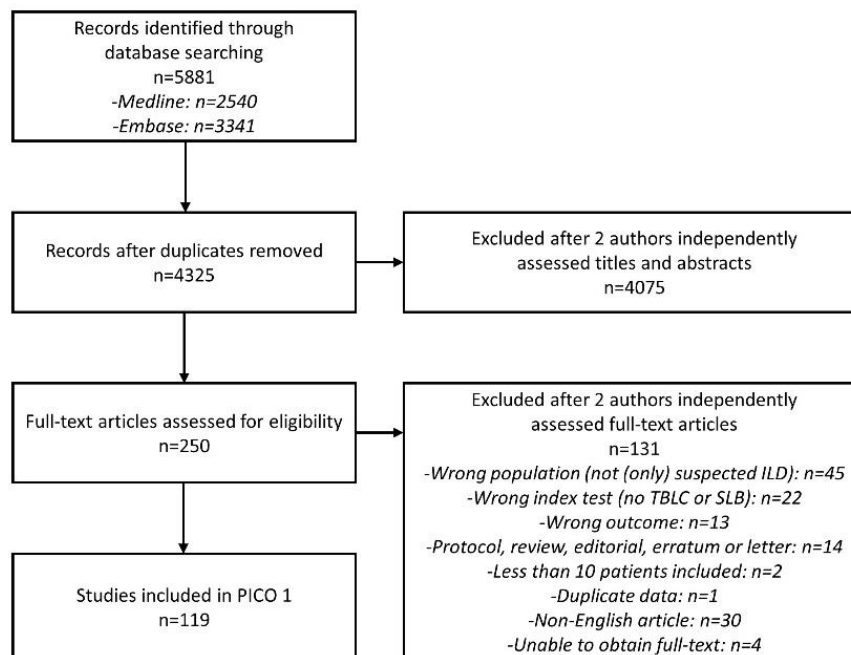
Appendix 5: Included studies per guideline question

Overall flowchart:



Flowchart PICO question 1:

In patients with undiagnosed ILD considered eligible to undergo SLB, is TBLC a valid replacement test?



Final included PICO question 1 (n=119):

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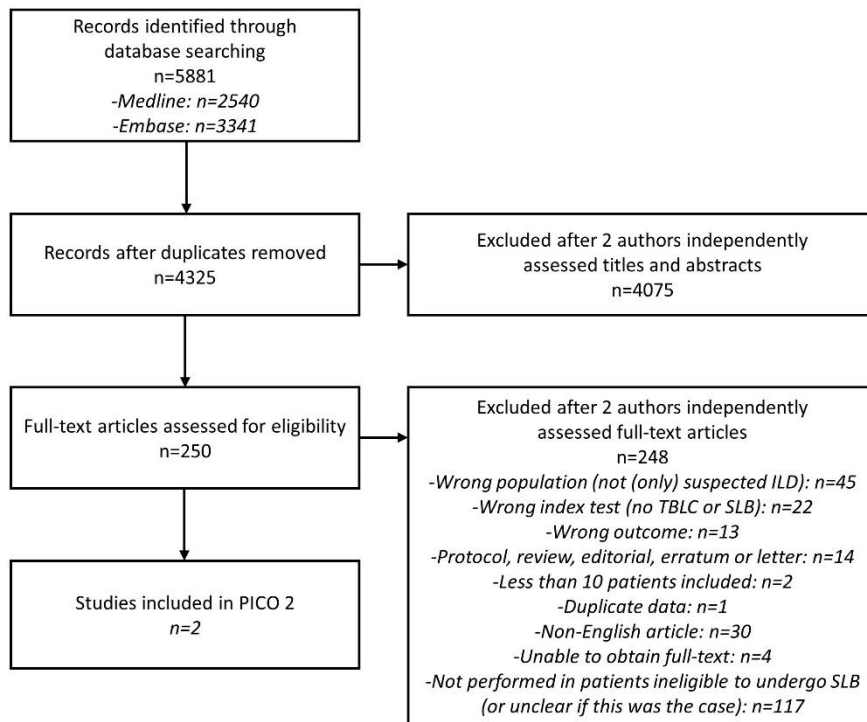
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Flowchart PICO question 2:

In patients with undiagnosed ILD not considered eligible to undergo SLB, does TBLC increase the diagnostic confidence of the multidisciplinary team discussion?

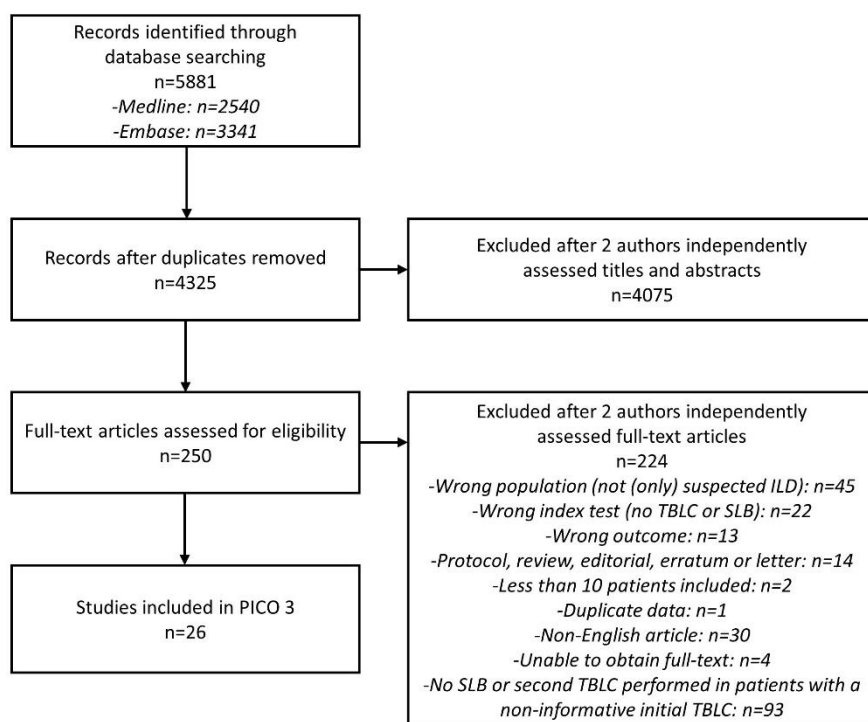


Final included PICO question 2 (n=2):

1. Bondue B, Schlossmacher P, Allou N, Gazaille V, Taton O, Gevenois PA, Vandergheynst F, Remmelink M, Leduc D. Trans-bronchial lung cryobiopsy in patients at high-risk of complications. BMC pulm 2021; 21(1): 135.
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Flowchart PICO question 3:

In patients with undiagnosed ILD and a non-informative TBLC, is step-up SLB or second TBLC a valid add-on test?



Final included PICO question 3 (n=26):

1. Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, Hetzel M. Transbronchial cryobiopsy: A new tool for lung biopsies. *Respiration* 2009; 78(2): 203-208.
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10. Hetzel J, Wells AU, Costabel U, Colby TV, Walsh SLF, Verschakelen J, Cavazza A, Tomassetti S, Ravaglia C, Bockeler M, Spengler W, Kreuter M, Eberhardt R, Darwiche K, Torrego A, Pajares V, Muche R, Musterle R, Horger M, Fend F, Warth A, Heusel CP, Piciucchi S, Dubini A, Theegarten D, Franquet T, Lerma E, Poletti V, Hantschel M. Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicentre trial. *European Respiratory Journal* 2020; 56(6): 12.
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12. Kronborg-White S, Sritharan SS, Madsen LB, Folkersen B, Voldby N, Poletti V, Rasmussen TR, Bendstrup E. Integration of cryobiopsies for interstitial lung disease diagnosis is a valid and safe diagnostic strategy-experiences based on 250 biopsy procedures. *Journal of Thoracic Disease* 2021; 13(3): 1455-1465.
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CM, Vachier I, Molinari N, Bourdin A. Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases. *Am J Respir Crit Care Med* 2019; 199(10): 1249-1256.

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22. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, Mahar A, Myers JL, Lai S, Mulyadi E, Torzillo PJ, Phillips MJ, Jo HE, Webster SE, Lin QT, Rhodes JE, Salamonsen M, Wrobel JP, Harris B, Don G, Wu PJC, Ng BJ, Oldmeadow C, Raghu G, Lau EMT, Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance I. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med* 2020; 8(2): 171-181.

23. Turan D, Ugur Chousein EG, Koc AS, Cortuk M, Yildirim Z, Demirkol B, Ozgul MA, Cinarka H, Akalin N, Yardimci AH, Cetinkaya E. Transbronchial cryobiopsy for diagnosing parenchymal lung diseases: real-life experience from a tertiary referral center. *Sarcoidosis Vasc Diffuse Lung Dis* 2021; 38(1): e2021004.

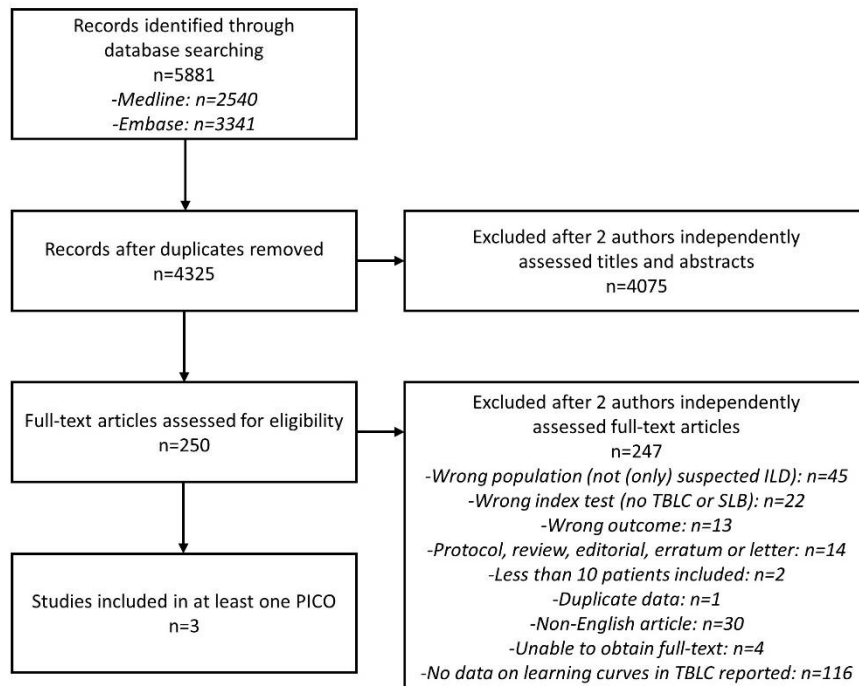
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Flowchart PICO question 4:

Is formal training in TBLC recommended to optimize diagnostic yield and minimize adverse events in patients with undiagnosed ILD?

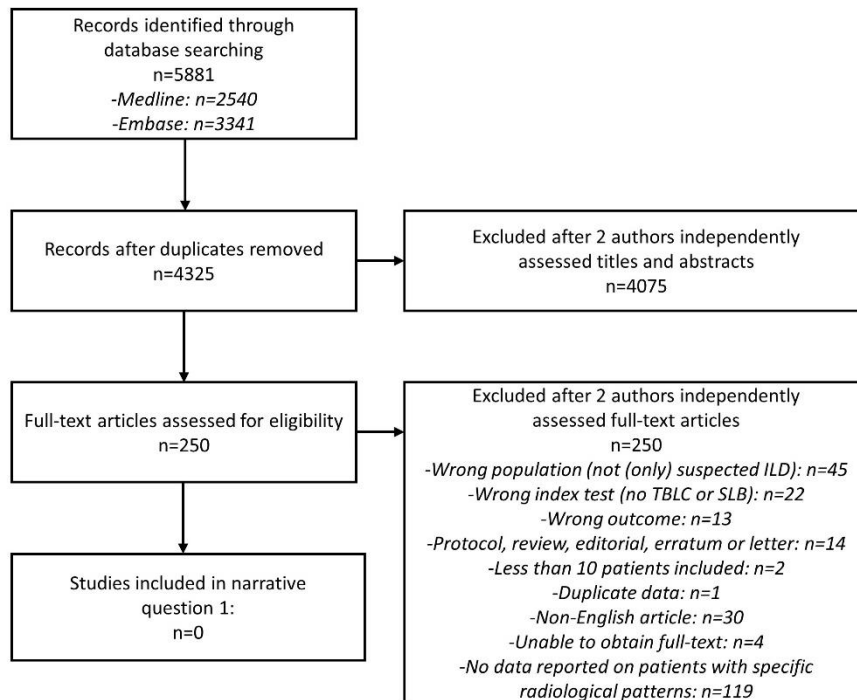


Final included PICO question 4 (n=3):

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3. Kronborg-White S, Folkersen B, Rasmussen TR, Voldby N, Madsen LB, Rasmussen F, Poletti V, Bendstrup E. Introduction of cryobiopsies in the diagnostics of interstitial lung diseases - experiences in a referral center. Eur Clin Respir J 2017; 4(1): 1274099.

Flowchart narrative question 1:

Are there specific HRCT findings which would lead to TBLC as the first choice for biopsy?

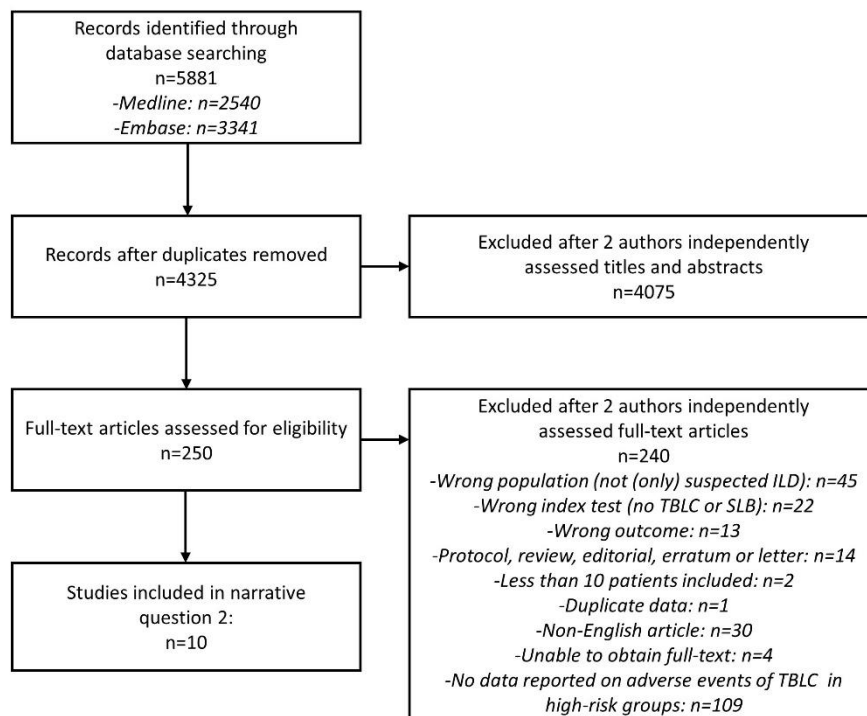


Final included narrative question 1 (n=0):

No studies included.

Flowchart narrative question 2:

What are the procedural risks of TBLC in patients with undiagnosed ILD?



Final included narrative question 2 (n=10):

1. Bondue B, Schlossmacher P, Allou N, Gazaille V, Taton O, Gevenois PA, Vanderghyest F, Rummelink M, Leduc D. Trans-bronchial lung cryobiopsy in patients at high-risk of complications. BMC pulm 2021; 21(1): 135.
2. Cooley J, Balestra R, Aragaki-Nakahodo AA, Caudell Stamper DN, Sriprasart T, Swank Z, Baughman RP, Benzaquen S. Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. Respir Med 2018; 140: 71-76.
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4. Hetzel J, Eberhardt R, Petermann C, Gesierich W, Darwiche K, Hagmeyer L, Muche R, Kreuter M, Lewis R, Ehab A, Boeckeler M, Haentschel M. Bleeding risk of transbronchial cryobiopsy compared to transbronchial forceps biopsy in interstitial lung disease - a prospective, randomized, multicentre cross-over trial. Respiratory Research 2019; 20(1): 140.
5. Kronborg-White S, Sriharan SS, Madsen LB, Folkersen B, Voldby N, Poletti V, Rasmussen TR, Bendstrup E. Integration of cryobiopsies for interstitial lung disease diagnosis is a valid and safe diagnostic strategy- experiences based on 250 biopsy procedures. Journal of Thoracic Disease 2021; 13(3): 1455-1465.

6. Kropski JA, Pritchett JM, Mason WR, Sivarajan L, Gleaves LA, Johnson JE, Lancaster LH, Lawson WE, Blackwell TS, Steele MP, Loyd JE, Rickman OB. Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. *PLoS ONE* 2013; 8(11): e78674.
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10. She S, Steinfort DP, Ing AJ, Williamson JP, Leong P, Irving LB, Jennings BR, Saghaie T. Transbronchial Cryobiopsy in Interstitial Lung Disease: Safety of a Standardized Procedure. *J Bronchology Interv Pulmonol* 2020; 27(1): 36-41.