

Appendix 11: Narrative question 2 evidence synthesis

Tables and figures included in this appendix:

Table 1: Studies reporting on complication or mortality rates in patients at high procedural risk only

Table 2: Studies comparing complication or mortality rates in subgroups of patients at high versus low procedural risk

Table 1: Studies reporting on complication or mortality rates of TBLC in patients with ILD at high procedural risk only

First author Year Country	Specification of high risk group	Total number of patients at high procedural risk undergoing TBLC	Complications: Pneumothorax	Complications: Bleeding	Complications: Other	Mortality
Matta A , 2021 USA	-Critically ill patients with acute hypoxemic respiratory failure	n=17	<i>Pneumothorax:</i> -n=6 (35.3%) <i>Pneumothorax requiring drainage:</i> -n=5 (29.4%) <i>Pneumothorax with persistent air leak (> 5 days):</i> -n=4 (23.5%)	<i>Moderate bleeding:</i> -n=1 (5.9%) <i>Severe bleeding:</i> -n=0 (0%)	<i>Moderate hemorrhage:</i> -n= 1 (5.9%) <i>Severe hemorrhage:</i> -n=0 (0%)	<i>Mortality at 8 days:</i> -n=8 (47.1%)
Ravaglia C 2019 Italy	-Patients with FVC <50% and/or DLCO <35%	n=31	<i>Pneumothorax:</i> -n=6 (19.4%) <i>Pneumothorax requiring drainage:</i> -n=5 (16.1%)	<i>Mild bleeding:</i> -n=2 (6.4%) <i>Moderate bleeding:</i> -n=4 (12.9%) <i>Severe bleeding:</i> -n=0 (0%)	Other (empyema) -n=1 (3.2%)	NR
She S 2020 Australia	-Patients with DLCO <40%	n=15	“In our cohort, 15 (12.4%) patients had a diffusing capacity of the lungs for carbon monoxide <40%, but we did not note differences in the rate of complications in this subgroup.” No further details were reported.			NR

Legend:

Abbreviations: DLCO = diffusing capacity for carbon monoxide. FVC = forced vital capacity. ILD = interstitial lung disease. NR = not reported. TBLC = transbronchial lung cryobiopsy.

Table 2: Studies comparing complication or mortality rates of TBLC in subgroups of patients with ILD at high versus low procedural risk

First author Year Country	Specification of high risk group and low risk group	Total number of patients undergoing TBLC per subgroup	Complications: Pneumothorax	Complications: Bleeding	Complications: Other	Mortality
Bondue B 2021 Belgium	<p><i>Risk:</i></p> <ul style="list-style-type: none"> -High-risk patients (defined as presence of any of the following: age ≥ 75-years, BMI ≥ 35, sPAP by echocardiography ≥ 45 mmHg, FVC $< 50\%$, DLCO $< 30\%$, and/or significant cardiac comorbidities with reduced heart ejection fraction) -Low-risk patients (not fulfilling the definition of high-risk) <p><i>Additional subgroups:</i></p> <ul style="list-style-type: none"> -Subgroup of BMI ≥ 35 versus low risk patients -Subgroup of severe pulmonary impairment (FVC $< 50\%$ or DLCO $< 30\%$) versus low risk patients 	<p><i>High-risk patients:</i></p> <ul style="list-style-type: none"> -n=38 (40%) -n=15 BMI ≥ 35 -n=15 severe pulmonary impairment -n=4 sPAP ≥ 45 mmHg -n=4 ≥ 75-year-old -n=3 cardiac comorbidities) <p><i>Low-risk patients:</i></p> <ul style="list-style-type: none"> -n=58 (60%) <p><i>Subgroup of BMI ≥ 35:</i></p> <ul style="list-style-type: none"> -n=15 <p><i>Subgroup of severe pulmonary impairment:</i></p> <ul style="list-style-type: none"> -n=15 	<p><i>Pneumothorax:</i></p> <ul style="list-style-type: none"> -n=5 (13.2%) in high-risk patients -n=12 (20.7%) in low-risk patients -p=0.419 <p>-n=1 (6.7%) in the subgroup of patients with BMI ≥ 35 (p=0.206 compared to low-risk patients)</p> <p>-n=1 (6.7%) in the subgroup of patients with severe pulmonary impairment (p=0.316 compared to low-risk patients)</p> <p><i>Pneumothorax requiring drainage:</i></p> <ul style="list-style-type: none"> -n=3 (7.9%) in high-risk patients -n=6 (10.3%) in low-risk patients -p=0.687 	<p><i>Mild bleeding:</i></p> <ul style="list-style-type: none"> -n=24 (63.2%) in high-risk patients -n=36 (62.1%) in low-risk patients -p=0.914 <p><i>Moderate bleeding:</i></p> <ul style="list-style-type: none"> -n=11 (28.9%) in high-risk patients -n=17 (29.3%) in low-risk patients -p=0.969 <p><i>Severe bleeding:</i></p> <ul style="list-style-type: none"> -n=1 (2.6%) in high-risk patients -n=3 (5.2%) in low-risk patients -p=0.542 -no difference for sub-groups BMI ≥ 35 and severe pulmonary impairment (no numbers reported) 	<p><i>Median hospital stay:</i></p> <ul style="list-style-type: none"> -1 day (range 1-12) in high-risk patients -1 day (range 1-107) in low-risk patients -p=0.675 <p><i>Other complications:</i></p> <ul style="list-style-type: none"> -n=0 in high-risk patients -n=3 in low-risk patients (n=1: acute exacerbation, n=1: empyema, n=1: seizure 24 hours after procedure) 	<p><i>Mortality:</i></p> <ul style="list-style-type: none"> -n=1 (2.6%) in high-risk patients (possible acute embolic and/or coronary event) -n=0 (0%) in low-risk patients
Cooley J 2018 USA	<p><i>Hospitalization:</i></p> <ul style="list-style-type: none"> -Hospitalized patients -Outpatients <p><i>(Patients were hospitalized for respiratory failure, fatigue or acute kidney injury)</i></p>	<p><i>Hospitalized patients:</i></p> <ul style="list-style-type: none"> -n=17 (11%) -n=15 due to respiratory failure -n=1 due to fatigue -n=1 due to kidney injury <p><i>Outpatients:</i></p> <ul style="list-style-type: none"> -n=142 (89%) 	<p><i>Pneumothorax:</i></p> <ul style="list-style-type: none"> -n=4 (23.5%) in hospitalized patients -n=14 (9.9%) in outpatients -p=0.11 <p><i>Persistent air leak:</i></p> <ul style="list-style-type: none"> -n=1 (5.9%) in hospitalized patients -n=1 (0.7%) in outpatients -p=0.20 	NR	<p><i>ICU transfer within 48 h:</i></p> <ul style="list-style-type: none"> -n=2 (11.8%) in hospitalized patients -n=3 (2.1%) in outpatients -p=0.09 	<p><i>Mortality at 30 days:</i></p> <ul style="list-style-type: none"> -n=1 (5.9%) in hospitalized patients -n=2 (1.4%) in outpatients -p=0.29
Gershman E, 2015 Germany	<p><i>Risk:</i></p> <ul style="list-style-type: none"> -Post-lung-transplantation patients -Immunocompromised patients -Other (non-high-risk) patients with DLD 	<p><i>Post-lung-transplantation:</i></p> <ul style="list-style-type: none"> -n= 146 (49%) <p><i>Immunocompromised:</i></p> <ul style="list-style-type: none"> -n= 18 (6%) <p><i>Other patients with DLD:</i></p> <ul style="list-style-type: none"> -n=139 (46%) 	<p><i>Pneumothorax:</i></p> <ul style="list-style-type: none"> -n=5 (3.4%) in post-lung-transplantation -n=2 (11.1%) in immunocompromised -n=8 (5.8%) in other DLD patients -p-value NR <p><i>Pneumothorax requiring drainage:</i></p> <ul style="list-style-type: none"> -n=1 (0.7%) in post-lung-transplantation -n=2 (11.1%) in immunocompromised -n=3 (2.2%) in other DLD patients -p-value NR 	<p><i>Bleeding:</i></p> <ul style="list-style-type: none"> -n=6 (4.1%) in post-lung-transplantation -n=3 (16.6%) in immunocompromised -n=7 (5.0%) in other DLD patients -p-value NR 	<p><i>Hospitalization:</i></p> <ul style="list-style-type: none"> -n=3 (2.1%) in post-lung-transplantation -n=1 (5.6%) in immunocompromised -n=6 (4.3%) in other DLD patients -p-value NR 	NR
Hetzel J 2019 Germany	<p><i>Age:</i></p> <ul style="list-style-type: none"> -Age < 65 years -Age ≥ 65 years <p><i>Aspirin use:</i></p> <ul style="list-style-type: none"> -Aspirin use -No aspirin use 	<p><i>Age < 65 years:</i></p> <ul style="list-style-type: none"> -n=160 (46%) <p><i>Age ≥ 65 years:</i></p> <ul style="list-style-type: none"> -n=189 (54%) <p><i>Aspirin use:</i></p> <ul style="list-style-type: none"> -n=51 (14%) 	-NR	<p><i>Moderate/severe bleeding:</i></p> <ul style="list-style-type: none"> -n=17 (10.6%) in patients < 65 years -n=38 (20.1%) in patients ≥ 65 years -p=0.018 <ul style="list-style-type: none"> -n=13 (25.5%) in patients with aspirin use -n=45 (14.9%) in patients with no aspirin use 	NR	NR

		No aspirin use: -n=303 (86%)		-p=0.067		
Kronborg-White S, 2021 Denmark	Anticoagulant therapy: -Anticoagulant therapy -No anticoagulant therapy (All patients ceased individual anticoagulant treatment before the procedure according to national guidelines)	Anticoagulant therapy: -n= 86 -n=64: Acetyl salicylic acid -n=13: Thrombocyte inhibitors -n=15: New oral anticoagulants -n=18: Vitamin K antagonists No anticoagulant therapy: -n=164	NR	Moderate or severe bleeding: -n=19 (22.1%) in anticoagulant therapy -n=36 (22.0%) in no anticoagulant therapy -p=0.98	NR	NR
Kropski JA, 2013 USA	Hospitalization: -Hospitalized patients -Outpatients (Reasons for hospitalization NR; unclear if this is related to respiratory state)	Hospitalized patients: -n=4 (11%) Outpatients: -n= 33 (89%)	Pneumothorax: -n=0 (0%) in hospitalized patients -n=0 (0%) in outpatients	Bleeding: -n=0 (0%) in hospitalized patients -n=0 (0%) in outpatients	Other complications: -n=1 (25.0%) for hospitalized patients (n=1: ICU admission for post-procedural hypoxemia for 1 day) -n=1 (3.0%) for outpatients (n=1: hospitalization for hemoptysis)	NR
Pannu J 2019 USA	Hospitalization: -Hospitalized patients -Outpatients (Reasons for hospitalization NR; unclear if this is related to respiratory state)	Hospitalized patients: -n=8 (4.1%) Outpatients: -n=189 (95.9%)	NR	NR	NR	Mortality at 30 days: -n=2 (25%) in hospitalized patients -n=2 (1.1%) in outpatients -p-value NR

Legend:

Abbreviations: BMI = body mass index. DLCO = diffusing capacity for carbon monoxide. DLD = diffuse lung disease. FVC = forced vital capacity. ICU = intensive care unit. ILD = interstitial lung disease. NR = not reported. sPAP = systolic pulmonary artery pressure. TBLC = transbronchial lung cryobiopsy.