Lung transplantation for interstitial lung disease

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Shareable abstract (@ERSpublications)
This review outlines the appropriate timing and indications for lung transplant referral for patients with ILD and provides readers with an understanding of the risk factors and comorbidities associated with adverse outcomes post lung transplant in ILD. https://bit.ly/3ClxQMd

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Abstract

Interstitial lung diseases (ILDs) are now the most common indication for lung transplant internationally. Given that many lung transplant candidates with idiopathic pulmonary fibrosis are older, referral to a pulmonary rehabilitation programme is important to help mitigate the adverse outcomes associated with frailty. Despite this increase many patients with ILD who would potentially benefit from lung transplant are either not referred or referred too late. Particularly relevant in ILD which may have prominent extra-pulmonary manifestations is a multidisciplinary assessment of comorbidities which may impact on post lung transplant outcomes. Particular challenges in lung transplant for ILD are increasing age, comorbidities, donor lung sizing and the risk–benefit balance of single *versus* bilateral lung transplant. Evidence is continuing to evolve for lung transplant in rarer ILDs, including surfactant protein associated ILD and TERT mutations. Unfortunately, the number of potential lung transplant recipients exceeds available donor organs and some patients will die without transplant. Palliative care is an important aspect of managing patients on an active lung transplant list to help optimise physical and psychological symptoms associated with uncertainty on an active lung transplant list.

Educational aims

- To understand appropriate timing and indications for lung transplant referral for patients with ILD.
- To understand risk factors and comorbidities associated with adverse outcomes post lung transplant in ILD.

Introduction

Interstitial lung disease (ILD) encompasses a heterogenous group of lung diseases affecting the lung parenchyma, with idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILD and hypersensitivity pneumonitis (HP) being among the most common [1, 2]. Prognosis and disease behaviour can be variable depending on the underlying lung disease but many display progressive respiratory failure despite medical management [2]. Lung transplantation may be a suitable treatment option for a selected sub-group of these patients with the aim of increasing life expectancy and improving symptoms [3]. The number of lung transplants performed for ILD has increased with time, having first exceeded COPD as the leading indication for lung transplant in 2007. This has been paralleled by an increase in the age of lung transplant recipients [4]. In the most recent International Society for Heart and Lung Transplantation (ISHLT) registry report 32.4% of all transplants were performed for IPF and 8.1% for non-IPF ILD. In the era 1995–2018 2.4% of lung transplants were for sarcoidosis, and 0.9% for connective tissue disease-associated ILD (CTD-ILD) [4]. The median survival for all lung transplant recipients has increased over time with most recent median survival estimated at 6.2 years for all recipients, 5.2 years for IPF and 6.7 years for non-IPF ILD [4]. Similar observations were noted in a single-centre UK study assessing lung transplant outcomes for ILD which demonstrated statistically significant increase in patient age at transplant with increase over time [5]. IPF was the most common indication for lung transplant for ILD in

this group at 65%, followed by fibrotic nonspecific interstitial pneumonia 8.1%, sarcoidosis 7.4%, chronic HP 6% and CTD-ILD 6% and other causes accounting for 6.7% [5].

Lung transplant referral

Correctly identifying the optimal timing of lung transplant referral in patients with ILDs is challenging. The lung transplant referral and assessment process are complex, requiring a multifaceted multidisciplinary team assessment that firstly a patient is sick enough to need a lung transplant and secondly that a lung transplant is anatomically and technically possible, but also that they are well enough from a general health perspective to survive a lung transplant and thereafter have a good survival length and reasonable quality of life [3]. Thus, important components of a lung transplant assessment include assessing the severity of lung disease and high-risk features, anatomy, presence and severity of comorbidities, exercise capacity and frailty, nutritional status, social supports and psychosocial circumstances, and health related behaviours such as treatment adherence [3]. Given the complexities and time required to assess a patient for transplant and evaluate their comorbidities, potential lung transplant candidates should ideally be referred for consideration of lung transplant before they meet the criteria for lung transplant listing. This allows the opportunity for work-up, patient education, psychological support and also the opportunity to navigate potentially modifiable barriers to lung transplant such a comorbidities, body mass index (BMI) and nutritional status [3]. Evaluating the risk associated with comorbidities and whether these are prohibitive, and maintaining health and physical activity while on an active lung transplant list remain challenging and often raise difficult ethical predicaments [3]. Important ethical considerations in lung transplantation include utility (maximising the benefit from the scare resource that is suitable lungs for transplant), justice (using medical urgency to allocate organs) and respect for persons [3]. The ISHLT has produced consensus guidelines outlining contraindications to lung transplant and factors associated with increased risk and adverse outcomes (table 1). Internationally, differences exist among transplant centres in relation to candidate selection due to a variety of factors including donor organ availability, centre experience, national policy and strategy for utilising a scare resource [3].

While a potential lung transplant candidate may not have one absolute contraindication to lung transplant, it is critical to not consider comorbidities in isolation, but to consider the summative effect of multiple comorbidities and risk factors for a poor outcome and how these combine together [3, 6]. Cantu *et al*. [6] have demonstrated a statistically significant increase in risk of mortality, length of hospital stay and risk of discharge to a nursing facility moving from low (<3 comorbidities) to medium (3–6 comorbidities) and high risk (>6 comorbidities). Thus, lung transplant candidacy requires a nuanced assessment of the risk profile of the individual patient. Additional complicating factors that play into timing include the trajectory of underlying lung disease (*e.g.* rapidly progressive) and candidates that are likely to wait for a longer period of time for transplant (*e.g.* due to high antibodies or extremes of height) [3]. Table 1 summarises ISHLT contraindications and risk factors for poor outcome with lung transplant [3].

Timing of lung transplant referral

Due to the progressive and unpredictable behaviour of IPF in particular with acute exacerbations the recommendation of the ISHLT consensus for lung transplant remains that potential lung transplant candidates with IPF should be referred early for lung transplant evaluation before they meet criteria for lung transplant listing [3] (table 2). Prognostication in ILD is challenging, however; features associated with worse outcome include a usual interstitial pneumonia (UIP) pattern on chest computed tomography, progressive fibrosing ILD, pneumothorax, development of pulmonary hypertension (PH) and right ventricular failure. As a result ISHLT consensus guidelines recommend referral to a lung transplant programme at the time of diagnosis of definite or probable radiological UIP, histological UIP, any ILD with forced vital capacity (FVC) <80% or diffusing capacity of the lung for carbon monoxide (D_{LCO}) <40%, any ILD with an oxygen requirement at rest or on exertion, and any ILD with any one of the following in the last 2 years: decline in FVC ⩾10%, D_{LCO} ⩾5% or FVC ⩾5% with symptomatic or radiographic progression. For Inflammatory ILDs the ISHLT recommendation for timing of referral is progression of disease on either imaging or pulmonary function tests despite maximum medical therapy. For CTD-ILD and familial ILD, early referral is recommended to allow for assessment and management of extrapulmonary manifestations. The difference between referral and listing criteria are summarised in table 2. While a number of potential biomarkers and prognostication tools exist to predict outcome in ILD in general these are not in widespread clinical use nor consistently validated to predict treatment response or outcome. Referral for each patient will need to be individualised considering comorbidities and disease trajectory.

Patients with combined pulmonary fibrosis and emphysema (CPFE) in particular require special consideration given that decline in FVC is less reliable and thus attention must be paid to evidence of

TABLE 1 ISHLT lung transplant contraindications

Absolute contraindication	Lack of willingness or acceptance of transplant
	Malignancy with a high risk of recurrence or death related to cancer
	eGFR <40 mL·min^{-1}·1.73 m^{-2} (unless being considered for multi-organ transplant)
	Acute coronary syndrome or myocardial infarction within 30 days (excluding demand ischaemia)
	Stroke within 30 days
	Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant
	Acute liver failure
	Acute renal failure with rising creatinine or on dialysis and low likelihood or recovery
	Septic shock
	Active extrapulmonary or disseminated infection
	Active tuberculosis infection
	HIV infection with detectable viral load
	Limited function status (*e.g.* non-ambulatory) with poor potential for post-transplant rehabilitation
	Progressive cognitive impairment
	Repeated episodes of non-adherence without evidence of improvement
	Active substance use/dependence (tobacco use, vaping, marijuana smoking, intravenous drug use)
	Severe uncontrolled medical condition expected to limit survival after transplant
Risk factors with high or substantially increased risk	Age >70 years
Candidates with these conditions may be considered in centres with expertise specific to the condition	Severe coronary artery disease requiring coronary artery bypass graft at transplant
	Reduced left ventricular ejection fraction <40%
	Significant cerebrovascular disease
	Severe oesophageal dysmotility
When more than one of these risk factors are present, they are thought to be possibly multiplicative in terms of increasing risk of adverse outcomes	Untreatable haematological disorders including bleeding, thrombophilia, severe bone marrow dysfunction
	BMI ⩾35 kg·m^{-2}
	BMI <16 kg·m^{-2}
	Limited functional status with potential for post-transplant rehabilitation
	Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems
	Unreliable support system or caregiving plan
	Lack of understanding of disease and/or transplant despite teaching
	Mycobacterium abscessus infection
	Lomentospora prolificans infection
	Burkholderia cenocepacia or *gladioli* infection
	Hepatitis B or C infection with detectable viral or liver fibrosis
	Chest wall or spinal deformity expected to cause restriction after transplant
	Extracorporeal life support
	Retransplant <1 year following initial lung transplant
	Retransplant for restrictive CLAD
	Retransplant for AMR as aetiology for CLAD
Risk factors	Age 65–70 years
While acceptable for lung transplant to consider patients with these risk factors, multiple together may increase risk for adverse post-transplant outcome	eGFR 40–60 mL·min^{-1}·1.73 m^{-2}
	Mild to moderate coronary artery disease
	Severe coronary artery disease that can be revascularised *via* PCI prior to transplant
	Patients with prior coronary artery bypass graft
	Reduced left ventricular ejection fraction 40–50%
	Peripheral vascular disease
	Connective tissue diseases (scleroderma, lupus, inflammatory myopathies)
	Severe gastro-oesophageal reflux disease
	Oesophageal dysmotility
	Thrombocytopenia, leukopenia, or anaemia with high likelihood of persistence after transplant
	Osteoporosis
	BMI 30–34.9 kg·m^{-2}
	BMI 16–17 kg·m^{-2}
	Frailty
	Hypoalbuminaemia
	Diabetes on insulin that is poorly controlled
	Edible marijuana use
	Scedosporium apiospermum infection
	HIV infection with undetectable viral load
	Previous thoracic surgery
	Prior pleurodesis
	Mechanical ventilation
	Retransplant >1 year for obstructive CLAD

ISHLT: International Society for Heart and Lung Transplantation; eGFR: estimated glomerular filtration rate; BMI: body mass index; CLAD: chronic lung allograft dysfunction; AMR: antibody mediated rejection; PCI: percutaneous coronary intervention. Reproduced and modified from [3] with permission.

TABLE 2 Lung transplant referral and listing criteria (ISHLT)

Timing of referral	Timing of listing
At time of diagnosis of histopathological UIP	Hospitalisation for respiratory decline, pneumothorax or acute exacerbation
At time of diagnosis of radiographic probable or definite UIP pattern	Desaturation to <88% on 6MWT or >50 m decline in 6MWD over 6 months
Any ILD with FVC <80% or D_{LCO} <40% predicted	Pulmonary hypertension on right heart catheterisation or echocardiography
Any ILD with relative decline in pulmonary function over the past 2 years: FVC ⩾10% D_{LCO} ⩾5% FVC ⩾5% with symptomatic or radiographic progression	Any ILD with one of the following in the last 6 months: Absolute ↓ FVC >10% Absolute ↓ D_{LCO} >10% Absolute ↓ FVC >5% with radiographic progression
Any resting or exertional oxygen requirement	
For inflammatory ILDs, disease progression despite treatment (imaging or pulmonary function test)	
CTD-ILD or familial ILD early referral recommended as extrapulmonary disease may require additional evaluation[#]	

Referral or listing should be considered if meeting any one criterion. ISHLT: International Society for Heart and Lung Transplantation; UIP: usual interstitial pneumonia; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; ILD: interstitial lung disease; CTD: connective tissue disease; 6MWT: 6-min walk test; 6MWD: 6-min walk distance. [#]: earlier referral is recommended for patients with CTD or familial idiopathic pulmonary fibrosis to address potential extrapulmonary manifestations. Reproduced and modified from [3] with permission.

disease progression on computed tomography, decline in D_{LCO} or the development of PH. Patients with non-IPF ILD including chronic HP, CTD-ILD and unclassifiable ILD may also have a progressive course with behaviour similar to IPF [3]. Thus, in these patients with non-IPF ILD disease trajectory and predictors of survival such as FVC and D_{LCO} decline, hospitalisation, oxygen use, pneumothorax and development of PH should factor into timing of referral and listing [3] (table 2).

Pre-transplant considerations

ISHLT guidelines advise that lung transplant should be considered in potential candidates with a >50% chance of death from their underlying lung disease within 2 years if lung transplantation is not performed and a >80% likelihood of 5-year post-transplant survival from a comorbidities and general medical perspective assuming that the transplanted lung functions well [3]. Many factors contribute to post-transplant outcome and survival including age, malignancy and comorbidities (gastro-oesophageal reflux disease (GORD), diabetes, PH) and many of these are prevalent in patients with ILD [4, 7, 8]. Factors that may impact on lung transplant outcomes in patients with ILD are discussed in the following sections.

Age

An age limit for lung transplantation is controversial. In early lung transplant guidelines age over 65 years in association with poor physiological reserve was considered a relative contraindication to lung transplant [4]. The age of lung transplant recipients has increased with time and in the US 30% of waiting list patients are over 65 years [9]. Much of this increase in age has been driven by increasing transplants in older patients with IPF. While some studies have demonstrated an acceptable short-term survival in older recipients, one needs to bear in mind that these patients are highly selected with minimal comorbidities and thus the results are skewed by selection bias [4, 10]. Additionally, there are important ethical considerations in organ transplantation. This includes how one allocates a scare resource. The general population has expressed a preference to allocate solid organs for transplant to younger patients in the first instance [11]. While there is no absolute age limit on lung transplantation, older transplant recipients have worse long-term survival compared to younger recipients [12].

Native lung complications

A single lung transplant may be performed in patients with ILD due a variety of reasons. There is the potential for the development of complications related to the native lung. Among the complications that have been reported are pneumothorax in up to 29.4%, which does not appear to impact on outcome [13, 14]. Similarly high rates of native lung pulmonary aspergillosis have been reported (11.8%) and have been reported to be associated with a higher risk of mortality compared to aspergillus pulmonary infection in bilateral lung transplant [14, 15]. Single lung transplant recipients may also experience acute exacerbations of native lung ILD (8.9%) [14].

Weight

High or low BMI is a significant risk factor for primary graft dysfunction and early mortality post lung transplantation [16]. Primary graft dysfunction is an acute lung injury affecting the lung transplant within 72 h and is a significant cause of death in the early-phase post lung transplant. Adipose tissue may produce cytokines which worsen lung injury. Malnutrition is often due to the increased calorific requirements due to the chronic illness and it can alter immune function and be caused by disease severity [17]. Current guidelines advise that a BMI greater than 35 $kg \cdot m^{-2}$ or less than 16 $kg \cdot m^{-2}$ confer high or substantially increased risk, while those with a BMI of 30–34.9 $kg \cdot m^{-2}$ or 16–17 $kg \cdot m^{-2}$ are associated with unfavourable implications for short- and long-term outcomes post-transplant [3, 18, 19]. There is an increased rate of primary graft dysfunction in individuals who are obese in comparison to patients falling within normal and overweight BMI [20]. Patients who are obese should be encouraged to lose weight as this correlates with improvements in post-transplant survival [21]. BMI may not be an accurate measure of body composition, and alternative biomarkers are currently being reviewed to better risk-stratify candidates [22].

Frailty

Frailty, deconditioning, reduced functional status and sarcopenia impact both pre-transplant outcomes and post-transplant outcomes [23–26]. Frailty is common in advanced ILD and accounts for 30% of candidates with restrictive lung disease [24–26]. Frailty and sarcopenia lead to poor outcomes post-transplant and a careful review of patients with advanced ILD should be initially undertaken at ILD centres, including a dietician and physiotherapist. Pulmonary rehabilitation has been associated with improved outcomes and is a requirement to be undertaken at most lung transplant centres [27, 28]. Previous work has demonstrated that for every one point worsening in short physical performance battery there was a 20% increase in risk for death post lung transplant, and frail recipients had 12.2% absolute increased risk of death within the first year post lung transplant [23].

GORD

GORD has been suggested to be implicated in progression of progressive fibrosing ILD through micro aspiration, the development of bronchiolitis obliterans syndrome, and may also result in acute exacerbations. It has been demonstrated in 90% of patients with IPF, and suggested to be involved in its pathogenesis [29, 30]. While medical management may be sufficient in some patients, anti-reflux surgery has been shown to improve outcomes. One study examining laparoscopic fundoplication *versus* medical management for patients with IPF found the patients managed surgically had fewer exacerbations, hospitalisations and deaths [31]. GORD is also a significant co-morbidity in many patients with CTD-ILD. Most notably in those with scleroderma, which when combined with the high prevalence of oesophageal dysmotility and/or gastroparesis seen in this cohort poses a significant challenge amongst transplant candidates. Reflux and oesophageal dysmotility need to be thoroughly investigated due to its association with early allograft injury, rejection and chronic lung allograft dysfunction (CLAD) [32–34]. In patients who require it pre- or early post-transplant fundoplication mitigates the risk and should be done in cases where benefit will be derived [31, 35].

Coronary artery disease

There is a significantly higher incidence of cardiovascular disease in patients with ILDs, likely due to inflammation, endothelial injury, lipid injury and treatments especially for systemic lupus erythematous and rheumatoid arthritis; it is associated with an increase in mortality [36–39]. A carefully selected group of patients with coronary artery disease may be suitable for lung transplantation; some candidates undergo revascularisation procedures but they will require a close monitoring of symptoms post-transplant. Over 80% of patients with ILD at 5 years post lung transplant will have hypertension. This can result in end organ damage and increased morbidity and mortality over time [3]. Hyperlipidaemia occurs in over 63% of patients with ILD at 5 years. ISHLT registry data have also reported over 30% of patients develop diabetes mellitus post-transplant [3].

Mortality

Outcomes post lung transplant for IPF, although improving, are still inferior to transplantation for other organ groups due to infections or CLAD [4]. There are a number of other complications that may occur in post transplant recipients highlighted in table 3. CLAD, infection and malignancy are the three most common causes of death in patients with a lung transplantation after 5–10 years, with prevalence rates of 18–27.8% [40, 41]. Lung transplant recipients experience higher rates of cancer in general compared to the general population [41, 42]. The most common cancers in lung transplant recipients include non-melanoma skin cancer, lung cancer and post-transplant lymphoproliferative disorder [41–43]. Malignancy is probably due to chronic immunosuppression over many years, higher immunosuppression protocols for lung transplant recipients and loss of innate anti-tumour surveillance mechanisms making these patients higher

TABLE 3 Morbidity and mortality post lung transplant for interstitial lung disease (ILD)

Primary graft dysfunction	↑ Risk in sarcoidosis
Bleeding/haemothorax	↑ Risk in sarcoidosis ↑ Risk in pleuroparenchymal fibroelastosis
Anastomotic issues and/or dehiscence	↑ Risk with pre-transplant steroids
Phrenic nerve injury	Incidence rate 3–9% in LTR
Chronic kidney disease	Rates of up to 35.8% in ILD patients 5 years post-transplant ~2.7% of these patients are on dialysis
Diabetes	Prevalence 25–30% in first year post lung transplant Up to 40% at 5 years
Hypertension	Prevalence >80% at 5 years post lung transplant
Skin cancer	Non-melanoma skin cancer – most common cancer post lung transplant
Post transplant lymphoproliferative disorder	Incidence 1.8–7.9% post lung transplant Patients with pSS have a 15–20-fold risk of malignant lymphoid disorders
Osteoporosis	High rates of osteopenia and osteoporosis post lung transplant
Lung cancer	6-fold increased risk of lung cancer 10% SLTRs with IPF develop native lung cancer
Coronary artery disease	↑ Prevalence
Dyslipidaemia	63% prevalence at 5 years post lung transplant
Cytomegalovirus	↑ Risk with increasing age ↑ TERT mutations
***Aspergillus* lung disease**	↑ Risk native lung *Aspergillus*
Cytopenia	↑ TERT mutations ↑ 30–60% Sjogren's LTRs
Gastrointestinal	↑ Risk gastroparesis, GORD, oesophageal dysmotility, SIBO in particular in scleroderma ↑ Risk xerostomia, dysgeusia, GORD, abnormal liver function in pSS LTR
Venous thromboembolism	Incidence of pulmonary embolism 5–15% Incidence of DVT 20–45% 8-fold increase in risk of pulmonary embolism in pSS, 4-fold increase in risk of DVT
Chronic lung allograft dysfunction	↑ risk TERT mutations

LTR: lung transplant recipient; pSS: primary Sjogren's syndrome; SLTRs: single lung transplant recipients; IPF: idiopathic pulmonary fibrosis; TERT: telomerase reverse transcriptase; GORD: gastro-oesophageal reflux disease; SIBO: small intestinal bacterial overgrowth; DVT: deep vein thrombosis. Information from [3, 4, 42, 57, 63, 65, 69, 72, 74, 76–78].

risk [41]. Increased rates of lung cancer have been reported in patients with ILD including IPF and it can be very difficult to identify lung cancer pre-transplant in patients with extensive fibrosis and parenchymal destruction [44]. On occasion lung cancer is identified on native lung explant at the time of lung transplant for ILD that was not identified pre-transplant. A prevalence of approximately 1–2% has been reported in some studies and being most frequently observed in lung transplant for ILD followed by COPD [44–46]. Lung cancer at the time of lung transplant is challenging to manage and associated with a particularly poor survival with lung cancer being the cause of death in the majority of cases [44, 46, 47]. *De novo* lung cancer can also develop post lung transplant. It is more frequently observed in single lung transplant recipients and recipients who underwent a lung transplant for ILD and is associated with a poor prognosis [46, 48].

Size matching

Size matching donor lung to a recipient is an important aspect of lung transplant, with an impact on post-transplant outcomes [4]. This can be particularly challenging with ILD patients who have a small chest cavity that can result in increased complexity in size matching [49]. Results have been variable as to whether undersizing or oversizing is preferable. ISHLT registry data did not demonstrate worse outcomes with lung undersizing in ILD [4]. Franz *et al*. [49] reported significantly better survival and lower rates of primary graft dysfunction (PGD) with undersized lungs compared to oversized in lung transplant recipients with ILD. Complications may arise due to sizing issues such as pneumothorax and pleural effusions if the lung is too small and atelectasis if the lung is too big [50].

Single versus *bilateral lung transplant*

As lung transplant has evolved over time there has been a transition towards a majority of lung transplants internationally now being bilateral [4]. In the most recent ISHLT registry report 81% of lung transplants were bilateral [4]. Single or bilateral lung transplant may be an appropriate option in patients with ILD. Factors such a recipient age, anatomy, presence of concomitant PH, donor organ availability and rate of

disease progression may all play a role in procedure choice [51, 52]. Previous studies have identified a better median survival in patients with IPF undergoing bilateral lung transplant (65.2 months) compared to single lung transplant (50.4 months) [53]. However, this needs to be considered in the context that patients with ILD undergoing bilateral lung transplant wait significantly longer on a lung transplant list than patients with ILD undergoing single lung transplant (240 *versus* 150 days) [54]. However, a study of United Network for Organ Sharing data of patients with IPF listed concurrently for single or bilateral lung transplant did not demonstrate any statistically significant difference in actuarial graft survival with bilateral compared to single lung transplant. Additionally patients with IPF listed for bilateral lung transplant only have been demonstrated to have an increased risk of death on an active lung transplant list and to be less likely to receive a lung transplant [51, 55]. Thus, in patients who are rapidly deteriorating or difficult to match [56], there is merit to listing a patient for a single in preference to a bilateral lung transplant to increase the opportunity for transplantation [51, 55]. Single lung transplant may also be a more appropriate option for older lung transplant recipients given the lower morbidity and similar early mortality but lower 5-year survival in this group, who may not tolerate a bilateral lung transplant [52].

Sarcoidosis

Patients with sarcoidosis may need additional evaluation to examine the extent of other organ involvement [57]. In particular, investigations are required to ascertain possible cardiac involvement and to screen for conductive infiltrative cardiac disease [58]. If cardiac disease is found then a heart–lung transplantation may be the required surgery. Long-standing treatment of disease with glucocorticoids and possibly other immunotherapy is also a concern given their side effect profiles over time. Most studies have reported similar outcomes post lung transplant for sarcoidosis compared to other groups of lung transplant recipients, with a median survival of years 9.7 years [57, 59]. Sarcoidosis with a fibrosis phenotype had worse one-year survival post lung transplant compared to sarcoidosis with other phenotypes [57]. Higher rates of PGD and greater difficulty explanting the native lungs with resultant post-operative risk of haemothorax have been reported in lung transplant for sarcoidosis [57, 60]. Recurrence of sarcoidosis post lung transplant has been reported and may even necessitate considering re-transplant. In one study this occurred in 14% of patients at a mean time of 15 months post-transplant [56].

CPFE

Patients with CPFE have been demonstrated to have a high prevalence of co-existent PH and higher rates of death or lung transplant compared to patients with IPF alone [61]. Higher rates of PGD, acute rejections and CLAD have been observed post lung transplant in patients with CPFE compared to IPF with similar overall survival [62].

CTD-ILD

Lung transplant for CTD-ILD constituted 0.9% of lung transplants in the ISHLT 2019 registry data, with rheumatoid arthritis and undifferentiated CTD being the two most common CTD-ILDs [4]. Lung transplant for CTD-ILD may be contentious due to medical and surgical risk factors including GORD, oesophageal dysmotility, extrapulmonary manifestations (cardiac, renal, venous thromboembolism risk, cancer risk, musculoskeletal, neurological, skin and vascular) and the increased risk associated with concomitant PH. Particular concerns exist around the presence of oesophageal dysmotility and GORD and the resultant risk for aspiration and its association with increased risk of CLAD [63, 64]. Multidisciplinary team involvement in evaluation of these patients is recommended including rheumatology assessment of disease activity and extrapulmonary manifestations [63]. ISHLT have produced additional guidelines for patients with CTD-ILD being referred for lung transplant with uncontrolled extrapulmonary disease and severe swallowing/oesophageal dysfunction being considered absolute contraindications [63]. In particular due to the risks of severe infections and impaired wound healing with some medications used to managed CTD they are not recommended to be used while patients are on an active lung transplant list. This includes tumour necrosis factor inhibitors, tocilizumab, infliximab, adalimumab, certolizumab, golimumab, secukinumab, ixekizumab and ustekinumab [65].

Pleuroparenchymal fibroelastosis

Idiopathic pleuroparenchymal fibroelastosis (PPFE) is a rare form of ILD manifesting with fibrosis and elastosis affecting the pleura and subpleural lung tissue with prominent features including platythorax, low BMI and upper lobe predominant disease. PPFE may also arise secondary to other conditions such a radiotherapy, chemotherapy or stem cell transplant [66, 67]. Treatment options are limited to potentially nintedanib to slow disease progression [68]. PPFE represents a particular challenge for lung transplant due to the associated anatomy including platythorax which may result in persistent restriction even after a lung transplant. A single centre retrospective French study assessed lung transplant outcome in 31 patients with idiopathic and secondary PPFE confirmed on explant [69]. The authors noted that parietal adhesions were

present in 53%, delayed chest closure was required in 15 patients and lung volume reduction was required in nine patients [69]. There was a high early mortality rate (death within 90 days of lung transplant) at 32%. Weaning from mechanical ventilation with a median ventilation time of 10 days and 57.7% requiring tracheostomy to wean from ventilatory support. Rates of severe PGD (grade 3) at 72 h were high at 55.6% and rates of re-intervention for bleeding were high at 35.5% [69]. Survival was poor at 90 days (67.7%), 1 year (57.9%), 2 years (42.6%) and 5 years (38.3%) post lung transplant and the median survival was 21 months [69]. This high mortality rate is similar to the outcomes reported in single centre Italian case series of six patients where they reported a median survival of 10 months after lung transplant [70]. These results are in contrast to a Japanese study which reported in-hospital mortality of 3% and a median survival of 3093 days in a cohort of patients transplanted for PPFE, however, the patients in the French study had more severe disease and more severe anatomical distortion than those in the Japanese study [71]. There were also higher rates of lobar transplant in the Japanese study, and in the French cohort patients with PPFE who had a lobar transplant had a better median survival (54 months).

Surfactant protein associated ILD

Surfactant protein associated ILDs are rare genetic surfactant disorders with a variety of presentations from neonatal presentation with respiratory distress to adult ILD [72]. There is no specific treatment, however, lung transplant may be a potential option. A recent French retrospective multi-centre observational study reported a median survival of 8.6 years post lung transplant in an adult cohort (n=20) aged older than 18 years with SFTPA1, SFTPA2 and SFTPC associated ILD [72]. Of note two patients had a pre-transplant history of lung cancer and two were diagnosed with lung cancer post lung transplant. Thus, close lung cancer surveillance pre- and post-transplant is required given the association between surfactant protein mutations and lung cancer [73]. It also merits consideration of whether bilateral lung transplant should be the treatment of choice to reduce the risk of developing a native lung cancer post-transplant [72].

Telomere disorders

Telomeres are a group of repetitive nucleotide sequences at the end of a chromosome that protect the genome during active cell division. If mutations of these telomeres occur, then patients are a risk of pulmonary fibrosis, liver cirrhosis, bone marrow disorders and cancers [74]. Patients with a telomere disorders with a length<10th percentile are found in 25% of patients with sporadic mutation and 37% of familial IPF [75]. Early studies on patients with telomere disorders and with telomere shortening is associated with earlier age at presentation, a more rapid course of symptoms and a poor response to immunosuppression [76]. Reduced telomere length is linked to worse post-transplant survival outcomes and higher rates of primary graft dysfunction and CLAD [77]. However, due to differences in methodology in studies, a recent review reports no firm conclusions can be made and better quality studies are required in looking at transplant outcomes [78]. However, testing for telomere length at the ILD centre is very useful and may help to determine prognosis, aid in risk-stratifying candidates and help predict post-transplant complications.

Post-COVID ILD

Since the COVID-19 pandemic, post-COVID-19 pulmonary fibrosis and post-COVID acute respiratory distress syndrome (ARDS) have emerged as a lung transplant indication in selected patients [79–81]. The available evidence suggests waiting 4–8 weeks from disease onset before lung transplant referral to allow for potential lung recovery; however, many centres will wait for more than 8 weeks [80, 82]. Short-term survival data suggests a similar 1 year survival for COVID-19 associated ARDS and COVID-19 associated pulmonary fibrosis compared to other groups of lung transplant recipients at 88% and 84% respectively [79].

Acute exacerbations and mechanical ventilation

The prognosis post-acute exacerbation (AE) of IPF is poor, with in-hospital mortality of 50%, and as high as >90% in patients who require mechanical ventilation and median survival post an exacerbation is only 3–4 months [83]. However, there is concern that transplantation in patients with AE-ILD could increase early post-transplant complications or death as well as lead to long-term issues with graft function. As such, the role of lung transplantation in AE-ILD is controversial. Two previous studies evaluating lung transplantation during AE-ILD reported differing results, with one showing no difference in post-transplant overall survival for patients transplanted with an AE-ILD [84, 85] and another showing worse survival for those specifically with IPF transplanted while inpatient with an AE-ILD [86].

Immunosuppression pre transplant

Chronic high doses of corticosteroids may impair wound healing, increase risk of anastomotic dehiscence and of steroid-induced diabetes mellitus and infections [87]. Most lung transplant programmes consider

maintenance programmes >20 mg daily of steroids to be a contraindication and discussion with local ILD centres with the transplant programmes policies are necessary [63, 65, 87].

PH pre transplant

PH is frequently observed in patients with ILD. The presence of co-existent PH in patients with ILD has been demonstrated to be associated with increased disease severity, poorer outcomes, reduced exercise tolerance, increased need for supplemental oxygen, increased risk of acute exacerbations and increased risk of death in patients waiting for lung transplant [88]. Studies have reported varying prevalence of PH in patients with ILD, varying depending on the underlying ILD and severity of illness. Previous studies have reported a prevalence of PH in IPF of 8–15% at the time of diagnosis of IPF, prevalence of 29–46% at the time of lung transplant assessment and up to 86% at the time of lung transplantation [88, 89]. It remains controversial as to whether a single lung transplant is appropriate in patients with ILD and PH due to concern that a single lung transplant will result in increased blood flow through the transplanted lung in the setting of increased pressure in the native lung with resultant PGD. Previous work reported reduced survival in patients with an mPAP $\geqslant$40 mmHg who had a single lung transplant compared to those with a mean pulmonary arterial pressure (mPAP) <40 mmHg, with a survival difference not being observed in patients who underwent a bilateral lung transplant [90]. Various thresholds of mPAP have been suggested above which bilateral lung transplant should be performed [91]. However, despite this, a number of studies have reported no statistically significant difference in outcomes for patients with single lung transplant and group 3 PH [92]. However, patients with advanced lung disease and moderate or severe PH undergoing lung transplant did have increased rates of nitric oxide use without evidence of increased rates of PGD [93].

A recent Delphi consensus suggested a low index of suspicion and early screening for PH in patients with ILD which may prompt an early lung transplant referral given the increased mortality associated with PH [94].

Palliative care

Patients with advanced lung failure waiting for lung transplant typically have significant physical and psychological symptoms affecting their quality of life including dyspnoea and the uncertainty over whether they will receive a suitable donor organ [95, 96]. Despite the multiple potential benefits of palliative care in managing these patients while on an active lung transplant list, palliative care referral is uncommon with one study finding only a 20.7% referral rate to palliative [97]. Many patients are only referred at a late stage when they are close to death or delisting [95]. A variety of factors may contribute to this including lack of knowledge and misconceptions around the role of palliative care [95, 97]. Importantly, palliative care involvement in managing lung transplant candidates is safe and effective without inhibiting lung transplant eligibility [97].

ILD patients are often referred to transplant centres too late or not at all, thus denying patients an opportunity to be considered for lung transplant [98], and in a Czech study up to two thirds of eligible patients were never referred to lung transplant [99].

Conclusion

Lung transplant offers great potential for patients with advanced fibrotic lung disease to improve their symptoms and quality of life. It is important to be aware of the need to identify suitable patients who would benefit from the surgery early and for all referring teams to understand the complexity of this population as it may directly affect their candidacy, perioperative survival and post-transplant management. Identifying suitable candidates early prior to advanced disease progression should occur concurrent with management at the ILD centre, focusing on trying to stabilise their overall clinical status and optimising their candidacy for lung transplantation. Recognition of overall survival and commonly occurring comorbidities is necessary, so that from the start patients and caregivers are aware of issues that may occur and the need for lifelong monitoring of the graft. Early referral to palliative care for patients with advanced lung failure and ILD progression allows provision of support for the symptoms patients may have, as well as additional emotional support. Challenges remain at transplant centres with donor organ shortages and there is continuing opportunity in exploring the use of marginal lungs with ex-vivo lung perfusion and how expanded criteria for donor lungs can be used in these sicker patient groups. Transplant centres are managing patients who are now sicker, older, higher risk, have increased oxygen requirements and evidence of PH with added potential complex connective tissue disease-associated disease and upper gastrointestinal disorders that have an impact on perioperative and postoperative outcomes. They have the difficult task of trying to manage these complications potentially alongside other comorbidities, and of trying to personalise post-transplant care immunosuppression by protecting the lung allograft against infection and rejection.

Key points

- Interstitial lung diseases are now the most common indication for lung transplant.
- Potentially suitable candidates should be referred early for consideration for lung transplant to allow for work-up and for potentially modifiable barriers to be addressed.
- It is important to consider co-existent comorbidities and how they might impact on lung transplant.

Self-evaluation questions

1. Which one of the following is the most common indication for lung transplant?
    a) Sarcoidosis
    b) Chronic hypersensitivity pneumonitis
    c) Idiopathic pulmonary fibrosis
    d) Connective tissue disease associated ILD
2. Which two of the following are associated with a substantially increased risk of death post lung transplant?
    a) Age over 60 years
    b) Frailty with limited functional status
    c) *Pseudomonas aeruginosa* in sputum
    d) Mild gastro-oesophageal reflux disease
3. Which of the following two patients with ILD would be appropriate for referral to a lung transplant team?
    a) A 58-year-old male with IPF with a FVC of 80% predicted who is smoking 20 cigarettes per day.
    b) A 73-year-old male with chronic HP on dialysis for chronic kidney disease, poor exercise, BMI 15 $kg \cdot m^{-2}$ and an FVC of 50% pred.
    c) A 64-year-old female with CTD-ILD who is on 2 L oxygen on ambulation with a 12% drop in FVC in the last 6 months.
    d) A 52-year-old male with unclassifiable ILD with a 15% decline in FVC and 10% decline in D_{LCO} in the last 6 months.
4. Which of the following are common comorbidities post lung transplant?
    a) Chronic kidney disease
    b) Skin cancer
    c) Osteoporosis
    d) Hypertension
    e) Dyslipidaemia

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References

1 Maher TM. Interstitial lung disease: a review. *JAMA* 2024; 331: 1655–1665.
2 Cottin V, Hirani NA, Hotchkin DL, *et al.* Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; 27: 180076.
3 Leard LE, Holm AM, Valapour M, *et al.* Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2021; 40: 1349–1379.
4 Chambers DC, Cherikh WS, Harhay MO, *et al.* The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult lung and heart-lung transplantation report-2019; focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019; 38: 1042–1055.
5 Leong SW, Bos S, Lordan JL, *et al.* Lung transplantation for interstitial lung disease: evolution over three decades. *BMJ Open Respir Res* 2023; 10: e001387.
6 Cantu E, Jin D, McCurry M, *et al.* Transplanting candidates with stacked risks negatively affects outcomes. *J Heart Lung Transplant* 2023; 42: 1455–1463.
7 Lederer DJ, Wilt JS, D'Ovidio F, *et al.* Obesity and underweight are associated with an increased risk of death after lung transplantation. *Am J Respir Crit Care Med* 2009; 180: 887–895.
8 Sheikh SI, Hayes D, Jr, Kirkby SE, *et al.* Age-dependent gender disparities in post lung transplant survival among patients with idiopathic pulmonary fibrosis. *Ann Thorac Surg* 2017; 103: 441–446.
9 Valapour M, Lehr CJ, Skeans MA, *et al*. OPTN/SRTR 2019 annual data report: lung. *Am J Transplant* 2021; 21: Suppl. 2, 441–520.
10 Hayanga AJ, Aboagye JK, Hayanga HE, *et al.* Contemporary analysis of early outcomes after lung transplantation in the elderly using a national registry. *J Heart Lung Transplant* 2015; 34: 182–188.
11 Tong A, Howard K, Jan S, *et al.* Community preferences for the allocation of solid organs for transplantation: a systematic review. *Transplantation* 2010; 89: 796–805.
12 Lehr CJ, Blackstone EH, McCurry KR, *et al.* Extremes of age decrease survival in adults after lung transplant. *Chest* 2020; 157: 907–915.

13 Gonzalez FJ, Alvarez E, Moreno P, *et al.* The influence of the native lung on early outcomes and survival after single lung transplantation. *PLoS One* 2021; 16: e0249758.
14 Watanabe T, Hirama T, Onodera K, *et al.* Native-lung complications following single-lung transplantation for interstitial lung disease: an in-depth analysis. *BMC Pulm Med* 2024; 24: 202.
15 Singh N, Husain S. *Aspergillus* infections after lung transplantation: clinical differences in type of transplant and implications for management. *J Heart Lung Transplant* 2003; 22: 258–266.
16 Fernandez R, Safaeinili N, Kurihara C, *et al.* Association of body mass index with lung transplantation survival in the United States following implementation of the lung allocation score. *J Thorac Cardiovasc Surg* 2018; 155: 1871–9.e3.
17 Bennett RM, Reilly JP, Diamond JM, *et al.* Body mass index and mortality following primary graft dysfunction: a lung transplant outcomes group study. *JHLT Open* 2024; 5: 100107.
18 Jomphe V, Mailhot G, Damphousse V, *et al.* The impact of waiting list BMI changes on the short-term outcomes of lung transplantation. *Transplantation* 2018; 102: 318–325.
19 Upala S, Panichsillapakit T, Wijarnpreecha K, *et al.* Underweight and obesity increase the risk of mortality after lung transplantation: a systematic review and meta-analysis. *Transpl Int* 2016; 3: 285–296.
20 Chandrashekaran S, Keller CA, Kremers WK, *et al.* Weight loss prior to lung transplantation is associated with improved survival. *J Heart Lung Transplant* 2015; 34: 651–657.
21 Clausen ES, Frankel C, Palmer SM, *et al.* Pre-transplant weight loss and clinical outcomes after lung transplantation. *J Heart Lung Transplant* 2018; 37: 1443–1447.
22 Emsley C, King S, Nyulasi I, *et al.* A GLIMmer of insight into lung transplant nutrition: Enhanced detection of malnutrition in lung transplant patients using the GLIM criteria. *Clin Nutr* 2021; 40: 2521–2526.
23 Singer JP, Diamond JM, Anderson MR, *et al.* Frailty phenotypes and mortality after lung transplantation- a prospective cohort study. *Am J Transplant* 2018; 18: 1995–2004.
24 Singer JP, Diamond JM, Gries CJ, *et al.* Frailty phenotypes, disability and outcomes in adult candidates for lung transplantation. *Am J Respir Crit Care Med* 2015; 192: 1325–1334.
25 Castleberry AW, Englum BR, Snyder LD, *et al.* The utility of preoperative six-minute-walk distance in lung transplant transplantation. *Am J Respir Crit Care Med* 2015; 192: 843–852.
26 Rozenberg D, Mathur S, Wickerson L, *et al.* Frailty and clinical benefits with lung transplantation. *J Heart Lung Transplant* 2018; 37: 1245–1253.
27 Li M, Mathur S, Chowdhury NA, *et al.* Pulmonary rehabilitation in lung transplant candidates. *J Heart Lung Transplant* 2013; 32: 626–632.
28 Wickerson L, Rozenberg D, Janaudis-Ferreira T, *et al.* Physical rehabilitation for lung transplant candidates and recipients: an evidence informed clinical approach. *World J Transplant* 2016; 6: 517–531.
29 Tobin RW, Pope CE, Pellegrini CA, *et al.* Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998; 158: 1804–1808.
30 Lee JS, Collard HR, Raghu G, *et al.* Does chronic microaspiration cause idiopathic pulmonary fibrosis? *Am J Respir Crit Care Med* 2010; 123: 304–311.
31 Raghu G, Pellegrini CA, Yow E, *et al.* Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial. *Lancet Respir Med* 2018; 6: 707–714.
32 Hartwig MG, Anderson DJ, Onaitis MW, *et al*. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. *Ann Thorac Surg* 2011; 92: 462–469.
33 Lo W-K, Burakoff R, Goldberg HJ, *et al*. Pre-transplant impedance measures of reflux are associated with early allograft injury after lung transplantation. *J Heart Lung Transplant* 2015; 34: 26–35.
34 Lo WK, Goldberg HJ, Wee J, *et al.* Both pre-transplant and early post-transplant antireflux surgery prevent development of early allograft injury after lung transplantation. *J Gastrointest Surg* 2016; 20: 111–118.
35 Biswas Roy S, Elnahas S, Serrone R, *et al.* Early fundoplication is associated with slower decline in lung function after lung transplantation in patients with gastroesophageal reflux disease. *J Thorac Cardiovasc Surg* 2018; 155: 2762–2771.
36 Clarson LE, Bajpai R, Whittle R, *et al.* Interstitial lung disease is a risk factor for ischaemic heart disease and myocardial infarction. *Heart* 2020; 106: 916–922.
37 Hubbard RB, Smith C, Le Jeune I, *et al.* The association between idiopathic pulmonary fibrosis and vascular disease: a population based study. *Am J Respir Crit Care Med* 2008; 178: 1257–1261.
38 Mantel A, Holmqvist M, Jernberg T, *et al.* Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short term outcome. *Eur Heart J* 2015; 36: 3413–3422.
39 Asanuma Y, Oeser A, Shintani AK, *et al.* Premature coronary artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; 349: 2407–2415.
40 Yusen RD, Edwards LB, Dipchand AI, *et al.* The registry of the International Society for Heart and Lung Transplantation: thirty third annual adult lung and heart-lung transplant report-2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant* 2016; 35: 1170–1184.
41 Shtraichman O, Ahya VN. Malignancy after lung transplantation. *Ann Transl Med* 2020; 8: 416.

42 Engels EA, Pfeiffer RM, Fraumeni JF, Jr, *et al.* Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* 2011; 306: 1891–1901.
43 Rashtak S, Dierkhising RA, Kremers WK, *et al.* Incidence and risk factors for skin cancer following lung transplantation. *J Am Acad Dermatol* 2015; 72: 92–98.
44 Mondoñedo JR, Huang T, Lin J, *et al.* Explanted malignancies after lung transplantation: the University of Michigan experience. *Interact Cardiovasc Thorac Surg* 2022; 35: ivac203.
45 Panchabhai TS, Arrossi AV, Patil PD, *et al.* Unexpected neoplasms in lungs explanted from lung transplant recipients: a single-center experience and review of literature. *Transplant Proc* 2018; 50: 234–240.
46 Ahmad U, Hakim AH, Tang A, *et al.* Patterns of recurrence and overall survival in incidental lung cancer in explanted lungs. *Ann Thorac Surg* 2019; 107: 891–896.
47 Grewal AS, Padera RF, Boukedes S, *et al.* Prevalence and outcome of lung cancer in lung transplant recipients. *Respir Med* 2015; 109: 427–433.
48 Tseng SC, Gagne SM, Hatabu H, *et al.* Lung cancer in lung transplant recipients: clinical, radiologic, and pathologic characteristics and treatment outcome. *J Comput Assist Tomogr* 2023; 47: 590–597.
49 Franz M, Tavil S, de Manna ND, *et al.* Oversizing lung allografts deteriorates outcomes in patients with pulmonary fibrosis. *J Heart Lung Transplant* 2024; 43: 1126–1134.
50 DeFreitas MR, McAdams HP, Azfar Ali H, *et al.* Complications of lung transplantation: update on imaging manifestations and management. *Radiol Cardiothorac Imaging* 2021; 3: e190252.
51 Chauhan D, Karanam AB, Merlo A, *et al.* Post-transplant survival in idiopathic pulmonary fibrosis patients concurrently listed for single and double lung transplantation. *J Heart Lung Transplant* 2016; 35: 657–660.
52 Weingarten N, Mehta AC, Budev M, *et al.* Single *vs* double lung transplantation in older adults: a propensity-matched analysis. *Chest* 2024; 167: 518–528.
53 Schaffer JM, Singh SK, Reitz BA, *et al.* Single- *vs* double-lung transplantation in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis since the implementation of lung allocation based on medical need. *JAMA* 2015; 313: 936–948.
54 De Oliveira NC, Osaki S, Maloney J, *et al.* Lung transplant for interstitial lung disease: outcomes for single versus bilateral lung transplantation. *Interact Cardiovasc Thorac Surg* 2012; 14: 263–267.
55 Nathan SD, Shlobin OA, Ahmad S, *et al.* Comparison of wait times and mortality for idiopathic pulmonary fibrosis patients listed for single or bilateral lung transplantation. *J Heart Lung Transplant* 2010; 29: 1165–1171.
56 Schultz HH, Andersen CB, Steinbruuchel D, *et al.* Recurrence of sarcoid granulomas in lung transplant recipients is common and does not affect overall survival. *Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31: 149–153.
57 Le Pavec J, Valeyre D, Gazengel P, *et al.* Lung transplantation for sarcoidosis: outcome and prognostic factors. *Eur Respir J* 2021; 58: 2003358.
58 Shlobin OA, Nathan SD. Management of end-stage sarcoidosis: pulmonary hypertension and lung transplantation. *Eur Respir J* 2012; 39: 1520–1533.
59 Walker S, Mikhail G, Banner N, *et al.* Medium term results of lung transplantation for end stage pulmonary sarcoidosis. *Thorax* 1998; 53: 281–284.
60 Liu Y, Liu Y, Su L, *et al.* Recipient-related clinical risk factors for primary graft dysfunction after lung transplantation: a systematic review and meta-analysis. *PLoS One* 2014; 9: e92773.
61 Kim HJ, Snyder LD, Neely ML, *et al.* Clinical outcomes of patients with combined idiopathic pulmonary fibrosis and emphysema in the IPF-PRO registry. *Lung* 2022; 200: 21–29.
62 Takahashi T, Terada Y, Pasque MK, *et al.* Clinical features and outcomes of combined pulmonary fibrosis and emphysema after lung transplantation. *Chest* 2021; 160: 1743–1750.
63 Crespo MM, Lease ED, Sole A, *et al.* ISHLT consensus document on lung transplantation in patients with connective tissue disease: Part I: Epidemiology, assessment of extrapulmonary conditions, candidate evaluation, selection criteria, and pathology statements. *J Heart Lung Transplant* 2021; 40: 1251–1266.
64 Tangaroonsanti A, Lee AS, Crowell MD, *et al.* Impaired esophageal motility and clearance post-lung transplant: risk for chronic allograft failure. *Clin Transl Gastroenterol* 2017; 8: e102.
65 Crespo MM, Claridge T, Domsic RT, *et al.* ISHLT consensus document on lung transplantation in patients with connective tissue disease: Part III: Pharmacology, medical and surgical management of post-transplant extrapulmonary conditions statements. *J Heart Lung Transplant* 2021; 40: 1279–1300.
66 Bondeelle L, Gras J, Michonneau D, *et al.* Pleuroparenchymal fibroelastosis after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2020; 55: 982–986.
67 Beynat-Mouterde C, Beltramo G, Lezmi G, *et al.* Pleuroparenchymal fibroelastosis as a late complication of chemotherapy agents. *Eur Respir J* 2014; 44: 523–527.
68 Nasser M, Si-Mohamed S, Turquier S, *et al.* Nintedanib in idiopathic and secondary pleuroparenchymal fibroelastosis. *Orphanet J Rare Dis* 2021; 16: 419.
69 Clermidy H, Mercier O, Brioude G, *et al.* Outcomes of lung transplantation for pleuroparenchymal fibroelastosis: a French multicentric retrospective study. *J Heart Lung Transplant* 2024; 43: 1727–1736.

70 Faccioli E, Verzeletti V, Giraudo C, *et al.* Lung transplantation for pleuroparenchymal fibroelastosis: a single-center experience with revision of literature. *Biomedicines* 2023; 11: 1505.
71 Shiiya H, Nakajima J, Date H, *et al.* Outcomes of lung transplantation for idiopathic pleuroparenchymal fibroelastosis. *Surg Today* 2021; 51: 1276–1284.
72 Bermudez J, Nathan N, Coiffard B, *et al.* Outcome of lung transplantation for adults with interstitial lung disease associated with genetic disorders of the surfactant system. *ERJ Open Res* 2023; 9: 00240-2023.
73 Selman M, Lin HM, Montaño M, *et al.* Surfactant protein A and B genetic variants predispose to idiopathic pulmonary fibrosis. *Hum Genet* 2003; 113: 542–550.
74 Hannan SJ, Iasella CJ, Sutton RM, *et al.* Lung transplant recipients with telomere-mediated pulmonary fibrosis have increased risk for hematologic complications. *Am J Transplant* 2023; 23: 1590–1602.
75 Cronkhite JT, Xing C, Raghu G, *et al.* Telomere length shortening in familial and sporadic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; 178: 729–737.
76 Newton CA, Zhang D, Oldham JM, *et al.* Telomere length and use of immunosuppressive medications in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019; 200: 336–347.
77 Newton CA, Kozlitina J, Lines JR, *et al.* Telomere length in patients with pulmonary fibrosis associated with chronic lung allograft dysfunction and post lung transplantation survival. *Am J Respir Crit Care Med* 2017; 36: 845–853.
78 Bordas-Martinez J, Miedema JR, Mathot BJ, *et al.* Outcomes of lung transplantation in patients with telomere-related forms of progressive fibrosing interstitial lung disease pulmonary fibrosis: a systematic review. *JHLT Open* 2024; 3: 100054.
79 Tasoudis P, Lobo LJ, Coakley RD, *et al.* Outcomes following lung transplant for COVID-19–related complications in the US. *JAMA Surg* 2023; 158: 1159–1166.
80 Bharat A, Querrey M, Markov NS, *et al.* Lung transplantation for patients with severe COVID-19. *Sci Transl Med* 2020; 12: eabe4282.
81 Cerier E, Lung K, Kurihara C, *et al.* Lung transplantation in coronavirus-19 patients: what we have learned so far. *Clin Chest Med* 2023; 44: 347–357.
82 King CS, Mannem H, Kukreja J, *et al.* Lung transplantation for patients with COVID-19. *Chest* 2022; 161: 169–178.
83 Collard HR, Ryerson CJ, Corte TJ, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016; 194: 265–275.
84 Dotan Y, Vaidy A, Shapiro WB, *et al.* Effect of acute exacerbation of idiopathic pulmonary fibrosis on lung transplantation outcome. *Chest* 2018; 154: 818–826.
85 Guidot DM, Weber JM, Swaminathan AC, *et al.* Lung transplantation during acute exacerbations of interstitial lung disease and post-transplant survival. *JHLT Open* 2023; 2: 100011.
86 Chizinga M, Machuca TN, Shahmohammadi A, *et al.* Lung transplantation for acute exacerbation of interstitial lung disease. *Thorax* 2022; 77: 364–369.
87 McAnally KJ, Valentine VG, LaPlace SG, *et al.* Effect of pre-transplantation prednisolone on survival after lung transplantation. *J Heart Lung Transplant* 2006; 25: 67–74.
88 Shorr AF, Wainright JL, Cors CS, *et al.* Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. *Eur Respir J* 2007; 30: 715–721.
89 Kimura M, Taniguchi H, Kondoh Y, *et al.* Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. *Respiration* 2013; 85: 456–463.
90 Nasir BS, Mulvihill MS, Barac YD, *et al.* Single lung transplantation in patients with severe secondary pulmonary hypertension. *J Heart Lung Transplant* 2019; 38: 939–948.
91 Conte JV, Borja MJ, Patel CB, *et al.* Lung transplantation for primary and secondary pulmonary hypertension. *Ann Thorac Surg* 2001; 72: 1673–1680.
92 Huerd SS, Hodges TN, Grover FL, *et al.* Secondary pulmonary hypertension does not adversely affect outcome after single lung transplantation. *J Thorac Cardiovasc Surg* 2000; 119: 458–465.
93 Julliard WA, Meyer KC, De Oliveira NC, *et al.* The presence or severity of pulmonary hypertension does not affect outcomes for single-lung transplantation. *Thorax* 2016; 71: 478–480.
94 Rahaghi FF, Kolaitis NA, Adegunsoye A, *et al.* screening strategies for pulmonary hypertension in patients with interstitial lung disease: a multidisciplinary Delphi study. *Chest* 2022; 162: 145–155.
95 Pawlow PC, Doherty CL, Blumenthal NP, *et al.* An integrative review of the role of palliative care in lung transplantation. *Prog Transplant* 2020; 30: 147–154.
96 Scully BB, Nolley EP, Bush EL. Palliative care in lung transplantation. *Ann Palliat Med* 2022; 11: 927–935.
97 Colman R, Singer LG, Barua R, *et al.* Outcomes of lung transplant candidates referred for co-management by palliative care: A retrospective case series. *Palliat Med* 2015; 29: 429–435.
98 Deri O, Ovadia D, Huszti E, *et al.* Referral rates and barriers to lung transplantation based on pulmonary function criteria in interstitial lung diseases: a retrospective cohort study. *Ther Adv Respir Dis* 2024; 18; 17534666231221750.

99 Sterclova M, Doubkova M, Sykorova L, *et al.* Adherence to the ISHLT protocol for the referral of patients with idiopathic pulmonary fibrosis to the transplantation center among of Czech centers for interstitial lung diseases. *Pulm Med* 2024; 2024: 5918042.

Suggested answers

1. c.
2. a, b.
3. c, d.
4. a, b, c, d, e.