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Lung Transplantation for Scleroderma-related Lung Disease

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Abstract

Lung transplantation for scleroderma-related lung disease is controversial due to extra-pulmonary organ involvement that may threaten allograft and patient survival after transplant surgery. Despite concerns, several lung transplant programs do offer lung transplantation to patients with scleroderma-related lung disease. In this review, we evaluate the scleroderma-related extra-pulmonary organ involvement that may result in poorer outcomes after lung transplantation as well as the existing evidence on survival, freedom from bronchiolitis obliterans syndrome (BOS), and other important clinical outcomes after lung transplantation. Among the nine studies reviewed, comprising 226 subjects, survival and freedom from BOS appears to be similar for subjects undergoing lung transplantation for scleroderma compared to non-scleroderma lung diseases. Although scleroderma is a systemic disease with several unique potential threats to allograft and patient survival, lung transplantation appears to be a reasonable intervention for this patient population.

Keywords

Scleroderma; systemic sclerosis; lung transplantation; survival; bronchiolitis obliterans syndrome; acute rejection; gastroesophageal reflux; GERD; scleroderma renal crisis; interstitial lung disease; pulmonary arterial hypertension; idiopathic pulmonary fibrosis; Nissen fundoplication

Introduction

Scleroderma is an incurable connective tissue disease characterized by fibrosis of the skin and internal organs. Also called systemic sclerosis, it most commonly affects the heart, lungs, proximal gastrointestinal system, and kidneys.¹ The incidence of scleroderma ranges from 0.6 to 122 per million persons per year² and its prevalence ranges from 7–489 persons affected per million.² There are three general patterns of clinical presentation (diffuse cutaneous, limited cutaneous, sine; Table 1). Although efforts are underway, there are still no consistently effective anti-fibrotic treatments available.³ Therefore, management is focuses predominantly on organ specific symptoms and mitigation of complications.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

Claire B. Richardson and Jonathan P Singer have reported no conflicts of interest.

Today, pulmonary diseases account for the majority of scleroderma-attributable mortality.^{4,5} Until the 1980s, however, scleroderma renal crisis was the most frequent cause of death.⁶ The advent of angiotensin-converting enzyme inhibitors (ACE-inhibitors) in the late 1970s dramatically reduced scleroderma renal crisis and, as a result, mortality.⁷ Subsequently, pulmonary involvement has emerged as the dominant cause of scleroderma-attributable mortality.⁶ The lack of effective anti-fibrotic therapies has led some to consider lung transplantation for patients with end-stage scleroderma-related lung disease.

This paper will review scleroderma-related lung disease, why lung transplantation for scleroderma-related lung disease is controversial, and the existing evidence evaluating key clinical outcomes such as allograft and patient survival after lung transplantation.

Scleroderma-related lung disease

Scleroderma-related lung disease manifests as pulmonary fibrosis, pulmonary arterial hypertension, or a combination of both. Today, scleroderma-related lung disease accounts for 45–61% of scleroderma-related deaths.^{4–6,8}

Nearly 40% of patients with scleroderma have clinically significant interstitial lung disease (ILD), which most commonly manifests as non-specific interstitial pneumonia.^{9–11} Within scleroderma, those with diffuse cutaneous disease are more likely to have clinically significant ILD than those with limited disease.¹² Although immunosuppressive agents may slow disease progression for some, response to therapy is unpredictable. First line agents may include mycophenolate mofetil¹³ or cyclophosphamide; other options include azathioprine and rituximab. Close monitoring for response to therapy and stopping of the agent if no response is identified are important for patient safety.

Pulmonary arterial hypertension (PAH) is also common in scleroderma. A retrospective study of 619 patients with scleroderma identified isolated PAH in 19%; an additional 18% had PAH and suspected ILD overlap (based on a restrictive pattern on pulmonary function testing).¹⁰ PAH is a poor prognostic indicator. Indeed, in those with scleroderma related PAH, 3-year transplant free survival range between 46–52% while those without PAH have a 5-year transplant-free survival of 80%.^{14–16} PAH-directed therapies, including ambrisentan and intravenous epoprostenol, do not impact mortality or distance walked in six-minutes as significantly as for those with idiopathic PAH.^{17–23}

Combined ILD and PAH carries a particularly poor prognosis; in one cohort study, 3-year survival was 39% compared to 64% in those with isolated PAH ($p < 0.01$).²⁴

Lung transplantation for scleroderma-related lung disease is controversial

Although lung transplantation is a well-accepted therapeutic intervention for other types of ILD and pulmonary hypertension, the extrapulmonary involvement of scleroderma including esophageal dysmotility, risk of scleroderma renal crisis, and malnutrition are considered potential threats to patient and allograft survival after transplantation.

Esophageal dysmotility and acid reflux

Scleroderma-related fibrosis affects the proximal gastrointestinal tract in approximately 90% of patients.²⁵ The clinical impact of this fibrosis includes esophageal dysmotility, gastroesophageal reflux disease (GERD), and delayed gastric emptying. All of these factors increase the risk of macro- and micro-aspiration.^{26–28} Macro-aspiration with resultant pneumonitis or pneumonia may pose immediate threats to allograft and patient survival. Micro-aspiration is also an established risk factor for the development of bronchiolitis obliterans syndrome (BOS), the most common form of chronic allograft rejection.^{29–33} One potential mechanism by which aspiration may cause BOS is through the activation of the innate immune system.³⁴ In addition, esophageal dysmotility makes some anti-reflux interventions such as Nissen fundoplication complicated. Indeed, while reducing retrograde refluxate, the fundoplication may impede antegrade emptying of the esophagus, paradoxically increasing the risk of aspiration.³⁵

Scleroderma Renal Crisis

Scleroderma renal crisis is defined as an abrupt onset of renal failure often accompanied by mild to severe hypertension. It occurs in 5–15% of patients, and may result in permanent dialysis or death.^{36,37} Up to 39% of patients with scleroderma renal crisis require permanent dialysis or die as a result of the episode, despite use of ACE-inhibitors.³⁸ While widespread use of ACE-inhibitors has reduced its incidence, scleroderma renal crisis presents theoretical challenges in the perioperative period after lung transplantation. For instance, studies have demonstrated an association between increasing daily doses of corticosteroids (15mg of prednisone per day) and scleroderma renal crisis.^{37,39–41} During allograft implantation, high doses of corticosteroid are used as a component of most induction regimens, and are also frequently used as a first line therapy for acute cellular rejection. Furthermore, calcineurin inhibitors, part of many program's immunosuppressive maintenance regimens, may cause irreversible glomerular efferent arteriolar vasospasm as well as irreversible glomerular fibrosis.^{42–44} Thus, pre-existing scleroderma renal involvement or scleroderma renal crisis may require adjustments to calcineurin-inhibitor dosing or even its use, which may threaten long-term allograft survival.

Additional concerns

In addition to esophageal involvement, gastric and small bowel fibrosis may result in inconsistent absorption, leading to concerns of potential malabsorption or oral medication and malnutrition in these patients.

Finally, fibrosis of the chest wall may impair wound healing after transplant surgery.

Lung transplantation for scleroderma-related lung disease: the existing evidence

Despite the concerns discussed above, several lung transplant centers do offer transplantation to patients with scleroderma. In all, nine studies reporting outcomes after lung transplantation for patients with scleroderma-related lung diseases have been published.^{45–53} Combined, these retrospective cohort studies include 226 subjects and

provide a reasonable evidence base from which to evaluate key measures of transplant efficacy. These studies were predominantly single-center studies with sample sizes ranging from 9 to 67 subjects (Table 2); all but one compared subjects with scleroderma to non-scleroderma cohorts. Survival, freedom from BOS, and acute rejection were the most frequently evaluated outcomes.

Survival after lung transplantation

All nine studies reported survival estimates after lung transplantation, although the specific time points evaluated varied (Table 2). Generally, 1-year survival estimates range from 68%–93%, 3-year survival from 67–83%, and 5-year survival from 46%–76%. The reasons for the wide range of survival estimates are not known but may include patient selection, center specific approaches to management after lung transplantation, and chance differences due to small sample sizes. Importantly, however, all nine studies found that survival after lung transplantation for scleroderma-related lung disease was similar to that of their non-scleroderma comparison cohorts.

Few studies characterized esophageal dysfunction before lung transplantation, although some reported that patients with GERD or proximal gastrointestinal pathology were routinely declined for lung transplantation.^{48–50,52} An exception is the study by Sottile et al. which evaluated survival and freedom from BOS in subjects with scleroderma-related lung disease, some of whom had well-characterized esophageal dysfunction. At the authors' center (UC San Francisco), severe esophageal dysmotility, as measured by high-resolution manometry and pH testing, is not a contraindication to lung transplantation. Scleroderma patients are accepted for transplantation if they demonstrate no clinical evidence of aspiration and their symptoms of GERD are controlled by medications.

In the Sottile study, 23 subjects with scleroderma-related lung disease were age and gender matched in a 1:2 fashion to subjects with non-connective tissue disease related ILD (nCTD-ILD). Of 23 subjects, 12 had pre-operative high resolution manometry and pH testing performed. Normal motility, "mild nonspecific dysmotility", and aperistalsis were each found in three subjects, two subjects had "severe nonspecific dysmotility," and one had nutcracker esophagus. The subjects with scleroderma had 1- and 3-year survival estimates of 83%, which was similar to the nCTD-ILD group. In a subgroup analysis of the 12 subjects with esophageal evaluation prior to transplant, esophageal dysmotility did not impact survival (1- and 3-year survival rates of 86% and 86% vs 96% and 83% for nCTD-ILD; $p=0.99$). While the authors could not identify a specific reason for the excellent medium term survival outcomes, a pro-active multi-disciplinary education focused on aspiration prevention before and after transplantation may have contributed. Patients adhere to strict lifestyle modifications: they must finish eating and drinking a minimum of three hours prior to lying down for the evening, must sleep on a medi-wedge, and take proton-pump inhibitors. Further, in the perioperative period speech and swallow therapists familiar with scleroderma evaluate swallowing and risk for aspiration and teach swallow-specific strengthening exercises.

The use of percutaneous feeding tubes is variable, although feeding is always jejunal. At UC San Francisco, percutaneous feeding tubes are used only when the above approaches fail to

mitigate aspiration; other approaches include the routine insertion of percutaneous feeding for a minimum of six months after transplantation. If aspiration symptoms persist beyond these measures, surgical interventions, including 270° Nissen fundoplication or, for severe dysmotility, Roux-en-Y anastomosis, are considered on a case-by-case basis.

In sum, the available evidence for nearly 230 patients with scleroderma related lung disease suggests survival after lung transplantation is equivalent to other commonly accepted disease indications.

Freedom from Bronchiolitis Obliterans Syndrome

Four studies, comprising 152 subjects, reported on freedom from BOS.^{45,47,49,52} These studies reported 1-year freedom from BOS ranging from 70–100%, two-year freedom from BOS ranging from 63–92%, and three years from 52–75%. Three of these studies found freedom from BOS was equivalent in subjects with scleroderma compared to non-scleroderma groups.^{47,49,52} The fourth study reported a trend towards increased freedom from BOS in scleroderma compared to the non-scleroderma group (95% vs. 92% at 1-year, 78% vs. 61% at 5-years) but did not perform tests of statistical significance. Sottile et al. reported the highest freedom from BOS with 1-, 3-, and 5-year estimates of 100%, 79%, and 79% respectively, despite providing lung transplantation to subjects with severe esophageal dysmotility. Interestingly, Saggar et al. reported the lowest freedom from BOS with 1-, 2-, and 3-year estimates at 70%, 63% and 52% respectively. Clinically, the approach to evaluating and managing proximal gastrointestinal pathology before and after lung transplantation are similar at the centers represented in the Sottile and Saggar studies, so an explanation for the different freedom from BOS estimates requires further investigation.

Despite these encouraging findings, no study evaluated the mechanisms underpinning equivalent survival and freedom from BOS after transplantation in subjects with scleroderma compared to non-scleroderma cohorts. Therefore, any explanation for these observations is speculative. It may be possible that heightened awareness of risk of aspiration results in rigorous pre- and postoperative counseling, lifestyle modification, the use of pro-motility agents and other interventions aimed at reducing aspiration risk. This multi-pronged approach may mitigate any potential increased risk of aspiration in those with scleroderma.

Another explanation may be that gastroesophageal reflux and risk of aspiration is common after lung transplantation even in those *without* scleroderma. Indeed, one study found that 57% of lung transplant candidates have elevated acid exposure times, and 36% have esophageal hypo- or dysmotility measured by high-resolution manometry.⁵⁴ Another study of lung transplant candidates identified nearly 80% had esophageal dysmotility to some degree and nearly 40% had gastroesophageal reflux.⁵⁵ After lung transplantation, vagal injury and medications may further exacerbate these problems. Thus, while aspiration may be a risk to patient and allograft survival after lung transplantation, this risk very well may not be limited to patients with scleroderma.

For patients without scleroderma, small studies have demonstrated that Nissen and Dor fundoplication improve allograft function and reduce episodes of pneumonia, acute rejection, and BOS.^{33,56} While these procedures may be more difficult in scleroderma, anti-

reflux surgical interventions tailored to scleroderma may also be considered. For example, roux-en-Y gastric bypass has been found to improve gastroesophageal reflux disease quality of life scores with fewer complications than other commonly performed anti-reflux surgeries.⁵⁷ Our center also uses partial (i.e. 270°) Nissen fundoplication or percutaneous gastrojejunostomy tube placement with jejunal feeds for those with scleroderma-related gastroesophageal reflux and aspiration that is refractory to medical management.

Acute Cellular Rejection

Six of nine studies reported acute rejection outcomes; however, the variation in allograft surveillance protocols, reporting of rejection results, and methods of comparison varied substantially.^{45,47–49,51,52} Four studies reported the incidence of acute rejection was similar in those with scleroderma compared to those without scleroderma.^{45,47,48,51} Saggar et al., however, reported that those with scleroderma had a higher one-year cumulative incidence of ISHLT grade A2 acute rejection compared to those with IPF (62% versus 22%; $p=0.007$).^{49,58} Contrarily, Sottile et al. reported a lower incidence rate of grade A2 rejection in those with scleroderma compared to those with non-connective tissue disease-related ILD (1.4 versus 2.4 episodes per patient-year; $p=0.05$).⁵² Although there is substantial heterogeneity, the preponderance of the data suggest those with scleroderma are not at increased risk of acute rejection following lung transplantation.

Single vs. Bilateral Transplantation

Both single and bilateral lung transplantation for scleroderma are common. Eight of nine studies provided information on transplant type. In five studies, single lung transplantation was more common ($n = 103$), while bilateral lung transplantation was more common in three ($n = 99$). Only Massad et al., however, compared survival by transplant type; in that study of 47 subjects, one-year survival was 62% for single-lung recipients and 75% for bilateral lung transplant recipients ($p = 0.95$). In general, little information is provided in the published literature on the clinical decisions driving the choice to provide single or bilateral lung transplantation.

Other

Renal complications of transplantation were mentioned in only a few studies. Crespo et al. cited 1-year freedom from dialysis as 87% in scleroderma and 98% in non-scleroderma.⁴⁵ Since this information was presented only in abstract form, lacking statistical significance testing as well as other clinical details, limited conclusions can be drawn from this data. Furthermore, Rosas et al. found mean serum creatinine at follow up to be similar between scleroderma (1.55 ; at a mean of 18 ± 7 month after transplantation) and the IPF/PAH comparison cohort (1.15 ; 21 ± 4 month after transplantation) ($p = 0.15$). Death from scleroderma renal crisis appears to be rare; only one death due to scleroderma renal crisis has been reported at 481 days after transplantation.⁴⁹

No studies evaluated the effect of malnutrition or malabsorption on lung transplant outcomes.

Conclusion

Scleroderma is a systemic disease that may cause life-threatening pulmonary fibrosis, pulmonary arterial hypertension, or both. The involvement of the proximal gastrointestinal system with resultant esophageal dysmotility and risk of aspiration has tempered may centers' enthusiasm for considering lung transplantation in this population. The existing evidence, however, demonstrates that patients undergoing lung transplantation for scleroderma-related lung diseases achieve patient and allograft survival equivalent to comparable patients without scleroderma.

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Table 1

Typical Clinical patterns of Scleroderma

	Limited Cutaneous	Diffuse Cutaneous	Sine	
Skin involvement	<ul style="list-style-type: none"> Hands, distal forearm, face, neck + Nail fold capillary loops 	<ul style="list-style-type: none"> Hands, distal forearm, face, neck Chest, abdomen, upper arms, shoulders Nail fold capillary dilatation and capillary destruction. 	<ul style="list-style-type: none"> None + Nail fold capillary abnormalities 	
Internal organ involvement	<ul style="list-style-type: none"> <i>Pulmonary</i>: pulmonary arterial hypertension > interstitial lung disease <i>GI</i>: dysmotility, esophageal reflux, malabsorption <i>Renal</i>: minimal <i>Cardiac</i>: minimal <i>Vascular</i>: Raynaud's phenomenon, cutaneous telangiectasia 	<ul style="list-style-type: none"> <i>Pulmonary</i>: interstitial lung disease > pulmonary arterial hypertension <i>GI</i>: dysmotility, esophageal reflux, malabsorption <i>Renal</i>: + fibrosis, + risk of renal crisis, <i>Cardiac</i>: cardiomegaly 	<ul style="list-style-type: none"> <i>Pulmonary</i>: Lung fibrosis and late pulmonary arterial hypertension <i>GI</i>: dysmotility, esophageal reflux, malabsorption <i>Renal</i>: renal crisis <i>Cardiac</i>: similar to limited and diffuse 	
Antibodies	<ul style="list-style-type: none"> Anti-centromere antibodies Pm/Scl Anti-Th/To U1-RNP 	<ul style="list-style-type: none"> Anti-topoisomerase I Anti-RNA polymerase-I, II, III U3-RNP 	<ul style="list-style-type: none"> Anti-centromere antibody Anti-topoisomerase I Anti-RNA polymerase-I, II, or III 	
Other	Characterized by the CREST syndrome: Calcinosis cutis, Raynaud Phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia			

Table 2

Clinical outcomes after lung transplantation for scleroderma related lung disease

Study	n	Transplant type	Comparison group?	Survival After Transplant	Freedom from BOS	Acute cellular rejection	Other
Crespo et al., 2012 * Abstract	67	n/a	Non-Scl = 223	30 day: 91% vs. 95% 1-year: 73% vs. 86% 5-year: 46% vs. 52% Scl overall: 1-year: 75% 3-year: 67% 5-years: 50% Comparison of SLT only: Scl vs. COPD: 1-year: 80% vs. 76% (p=NS) 5-year: 52% vs. 47% (p=NS) Scl vs. IPF: 1-year: 80% vs. 71% (p=NS) 5-year: 52% vs. 49% (p=NS)	Grade 1 6 months: 98% vs. 98% 1-year: 95% vs. 92% 2-year: 92% vs. 79% 5-year: 78% vs. 61%	Grade A3 or A4 3 month: 15% vs. 17% 6 month: 18% vs. 21% 1-year: 18% vs. 24%	Freedom from dialysis 1 yr: 87% vs. 98%
Kubo et al., 2001 * Abstract	12	BLT = 2 SLT = 10	COPD = 105 IPF = 21		n/a	n/a	Causes of death: Bacterial pneumonia (3 patients), PGF (1), PE (1), metastatic cholangiocarcinoma (1). No significant difference in FEV ₁ at one year
Massad et al., 2005	47	BLT = 20 SLT = 27	All non-Scleroderma recipients from U.S. national registry undergoing transplantation during the same time period	30 day mortality 15% 1-yr by transplant type BLT: 75% (p=NS) SLT: 61.9% (p=NS) Scl vs. Non-Scl 1-year: 67% vs. 75% (p=0.252) *Note: 37 patients used for survival analysis	1-year 89% vs. 91% (p=NS) *Data available from only 27 Scl subjects	1-year acute rejection 48% vs. 56.6% (p=NS) *Data available from only 23 Scl subjects *Method for diagnosing acute rejection not provided	Cause of early death: Graft failure (2), Cardiac event (2), Bacterial infection (1) Hemorrhagic stroke (1)
Rosas et al., 2000	9	BLT = 1 SLT = 7 HLT = 1	IPF = 12 PPH = 10	4-year Scl: 76.2% Non-Scl: 69.2% (p=NS)	n/a	Mean annual incidence rate: 0.14 vs. 0.47 (p=NS) *Method for diagnosing acute rejection not provided	Infection mean annual incidence rate: <i>Viral</i> : 0.17 vs. 0.29 (p=NS) <i>Bacterial</i> : 0.17 vs. 1.4 (p=NS) <i>Fungal</i> : 0.99 vs. 0.36 (p=NS) Serum Creatinine 1.55 vs. 1.15 (p=NS)
Saggat et al., 2010	15	BLT = 14 SLT = 1	IPF = 38	Scl vs. IPF 1-year: 6.6% vs. 13.1% (p=0.62) *adjusted for age	1-year: 70% vs. 88% 2-years: 63% vs. 84% 3-years: 52% vs. 60% (p=0.29)	A2 62% vs. 22% (p=0.01) HR 2.91; p=0.007	Infection at 1-year 20% vs. 17% (p=0.54) Causes of death: BOS (1), SRC (1), complications of anesthesia (1) Pulmonary Function: No significant difference at 1 year for FEV ₁ , FVC, or FEV ₁ /FVC
Schachna et al., 2006	29	BLT = 9 SLT = 18 HLT = 2	IPF = 70 IPAH = 38	Scl vs. IPF 6-month: 69% vs. 80% 2-year: 62% vs. 67% (p=NS) Scl vs. IPAH 6-month: 69% vs. 79%	n/a	n/a	Note: Higher proportion of SLT in IPF and IPAH than Scl. Cause of early death: PGF (4) Bacterial pneumonia (3)

Study	n	Transplant type	Comparison group?	Survival After Transplant	Freedom from BOS	Acute cellular rejection	Other
				2-year: 62% vs. 63% (p=NS)			
Shitrit et al., 2009	54	BLT = 17 SLT = 37	n/a	2-year: 72% 5-year: 55%	n/a	Rejection rates reportedly similar but data not provided.	Infection rates reportedly similar: data not provided. Study was single center study of 7 subjects <i>and</i> meta-analysis of additional 47 subjects.
Sottile et al., 2013	23	BLT = 23	nCTD-ILD =46	1-year: 83% vs. 91% 3-year: 83% vs. 77% 5-year: 76% vs. 64% (p=0.99)	1-year: 100% vs. 96% 3-year: 79% vs. 83% 5-year: 79% vs. 75% (p=0.87)	Episodes of A2 per patient year Scl 1.4 vs. 2.4 nCTD-ILD (P=0.05)	Esophageal dysfunction, and Nissen fundoplication were not associated with death (P=0.72) or BOS (P=0.46)
Yazdani et al.	17	BLT = 13 SLT = 3 HL = 1	RA-ILD = 10 IPF = 53	Scl vs. RA-ILD 1-year: 82% vs. 67% (p=NS) Scl vs. IPF 1-year: 82% vs. 69% (p=NS)	n/a	n/a	n/a

Scl = Scleroderma; Non-Scl = Lung transplant recipients without Scleroderma; BMI = Body Mass Index; BLT = Bilateral Lung Transplant; SLT = Single Lung Transplant, HLT = Heart Lung Transplant; OB = Obliterative Bronchiolitis; PE = Pulmonary Embolism; COPD = Chronic obstructive pulmonary disease; IPF = Idiopathic pulmonary fibrosis; PGF = Primary Graft Failure; NS = Not statistically significant (p > 0.05); PPH = Primary Pulmonary Hypertension; HR = Hazard Ratio; SRC = Scleroderma Renal Crisis; IPAH = Idiopathic Pulmonary Arterial Hypertension; nCTD-ILD = non-Connective Tissue Disease-related Interstitial Lung Disease; RA-ILD = Rheumatoid Arthritis-related Interstitial Lung Disease; n/a = not available