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Survival after lung transplantation in systemic sclerosis. A systematic review

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Summary
Background: Lung transplantation is a life-saving option for systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) and interstitial lung disease (SSc-ILD) patients. However, some programs may be concerned about the possibility of excess post-transplantation mortality related to the extra-pulmonary manifestations of SSc. The objective of this study was to evaluate survival of SSc patients post-lung transplantation. We secondarily evaluated SSc lung transplant recipient characteristics (age, sex, and type of SSc lung disease), and discussed post-lung transplantation survival of SSc patients and non-SSc patients (idiopathic PAH, and ILD).
Methods: A systematic review of MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials and CINAHL (all inception to 2012) was performed to identify studies evaluating post-lung transplant survival in SSc compared to PAH and ILD patients. Two reviewers independently abstracted study and survival data.
Results: Two hundred twenty-six citations were screened to identify 7 observational studies reporting SSc patients who underwent single lung, double lung, or heart-lung transplantation. Mean age at transplantation ranged 46–53 years. SSc post-transplantation survival ranged 69%

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—91% at 30-days, 69%—85% at 6-months, 59%—93% at 1-year, 49%—80% at 2-years, and 46%—79% at 3-years. Causes of death included graft failure, infection, cardiac events, hemorrhagic stroke, respiratory failure, malignancy, pulmonary hypertension, complications of bronchiolitis obliterans syndrome, anesthetic complication, and scleroderma renal crisis. There were no reports of recurrence of SSc in the lung allograft.
Conclusion: The short-term and intermediate-term survival post-lung transplantation are similar to IPAH and ILD patients requiring lung transplantation.

Introduction

Systemic sclerosis (SSc, scleroderma) is a disease characterized by immune activation and inflammation that leads to vasculopathy and fibrosis. It can affect the skin, blood vessels, and internal organs. The internal organs most commonly affected are kidney, gastrointestinal tract, and lung. Over the past decade, the use of angiotensin-converting enzyme inhibitors has greatly reduced the burden of renal complications, making lung disease the leading cause of morbidity and mortality in SSc patients [1]. The two principal manifestations of SSc lung disease are pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) [2].

PAH is a lethal disease characterized by elevated pulmonary artery pressure that leads to dyspnea, heart failure, and death. In the setting of SSc, the prevalence of PAH ranges from 5% to 12% [3—5], and is a leading cause of death [6,7]. Historically, SSc-PAH had a median survival of 12 months [6]. In the modern treatment era, the median survival has improved to 3—4.9 years [5,8,9]. Similarly, idiopathic pulmonary arterial hypertension (IPAH) historically has a median survival of 2.8 years [10]. In the modern treatment era, 3-year survival has improved to 76%—85% [9,11,12]. The use of PAH-specific therapies (endothelin receptor antagonists, phosphodiesterase 5 inhibitors and prostaglandin analogues) used alone or in combination, has resulted in improvements in six-minute walk distance, functional class, cardiac hemodynamics, quality of life and time to clinical worsening [13]. Yet none of these treatments are curative.

ILD also portends a poor prognosis, with mean survival of 2—5 years from the time of diagnosis [14]. Estimated mortality rates are 64.3 deaths per million men and 58.4 deaths per million women [15]. Prognostic factors for survival in SSc-PAH, SSc-ILD and IPAH include baseline mean pulmonary artery pressure, sex, functional class and signs of right heart failure [16].

Lung transplantation is performed to prolong survival and to improve the quality of life for patients with end stage lung disease [17]. Nearly three decades have passed since the procedure was first introduced, and this extended experience has led to improvements in outcomes for lung transplant recipients. Despite the recent increase in the number of patients undergoing lung transplantation over the past decade, patients with systemic autoimmune rheumatic disease, such as SSc, are often denied transplantation because of concerns about the short- and long-term outcomes [18].

However, very little is known about the survival of SSc patients, who undergo lung transplantation. The objective of this study was to evaluate survival of SSc patients' post-lung transplantation through a systematic review of the literature. We secondarily evaluated SSc lung transplant recipient characteristics such as age, sex and SSc lung disease type, and discussed post-lung transplantation survival of non-SSc patients (idiopathic PAH, and ILD).

Methods

Data sources and searches

An investigator (IYK) and an information specialist from the University Health Network library services independently performed the literature search. Studies were identified using Ovid MEDLINE (1986—2012), EMBASE (inception to January 2012) Cochrane Central Registry of Controlled Trials (inception to 2012) and CINAHL (inception to 2012). The following keywords, alone or in combination, with mapping of term to subject heading were used in the database search: "scleroderma", "systemic sclerosis", "lung transplantation", "pulmonary fibrosis", and "pulmonary hypertension". No language, publication date or publication status restrictions were imposed. The results of the 2 independent searches were compared to ensure completeness.

Study selection

Titles and abstracts were screened to identify studies reporting survival post-lung transplantation in SSc patients. Studies were included if they reported 1) human SSc patients (classified as SSc using the American College of Rheumatology classification criteria [19], or physician-based diagnosis), 2) lung transplantation (single lung, double lung or heart lung transplantation), and 3) reported survival as an outcome. The primary outcome for this study was death from all causes. Studies were ineligible if they included 1) only individuals aged <16 years, 2) lung transplantation for indications other than SSc-PAH or SSc-ILD, 3) patients with another rheumatic disease (rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease), or 4) were animal studies. The reference lists of selected articles were hand searched for relevant publications.

Data abstraction

Two reviewers (IYK, AK) independently abstracted data using standardized, pilot tested forms. The reviewers were

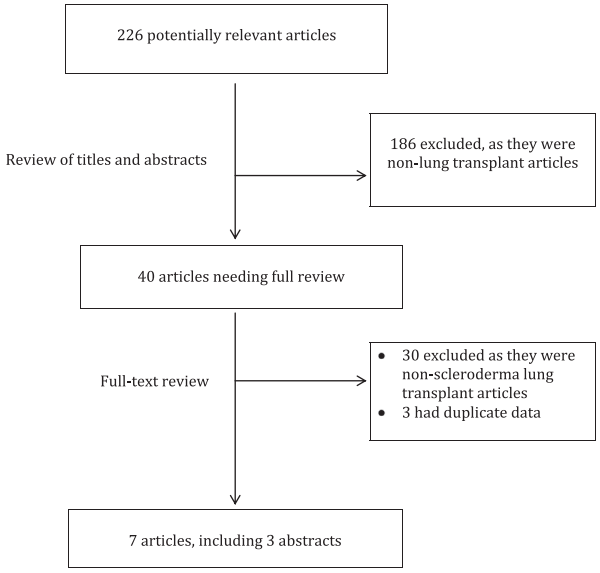

Figure 1 Flow diagram of systematic review.

blinded to the names of authors, institutions and journals when performing data abstraction. Data collection included study design, age, sex, sample size, type of lung transplantation, 6-month, 1-, 2- and 3-year survival data. Death was defined as all-cause mortality. Survival data were taken directly from the text, tables or Kaplan Meier figures. All disagreements were resolved through consensus.

Reporting of this study is compliant with the PRISMA statement [20].

Results

Search results

Two hundred twenty-six citations were identified. Screening of titles and abstracts resulted in the exclusion of 186 citations, leaving 40 citations for full review. Detailed review of these 40 citations identified 7 papers or abstracts that reported post-lung transplant survival in SSc patients. No randomized controlled trials were identified. Fig. 1.

SSc and lung transplant studies

Seven studies report approximately 186 SSc patients who underwent lung transplantation (55 single lung, 50 double lung, 2 heart-lung transplant, remaining not reported). Five studies report outcomes in US centers, 1 study reports outcomes in 1 center in Canada, and 1 study reports outcomes in 1 center in Israel. There is some overlap in cohorts between studies precluding the ability to identify unique patients, unique events, and subsequently precluding meta-analysis of the data. Study characteristics are summarized in Table 1.

Shitrit et al. report 7 SSc patients (5 females and 2 males) who underwent lung transplantation at Rabin Medical Centre, Beilinson Campus, Israel between January 1997 and September 2006. The median age of the patients was 52 years. All the patients had ILD, and were positive for anti-Scl-70 antibodies. All patients underwent single-lung transplantation (SLT). The median time to transplantation from diagnosis of pulmonary disease was 23 months. Following a median follow-up of 12 months, the survival of patients with SSc (88%) was similar to non-scleroderma lung transplantation (84%) at the same center.

Massad et al. report a retrospective, multicenter cohort of 47 SSc patients who underwent lung transplantation at 23 U.S centers between 1987 and 2004, and were reported to the United Network for Organ Sharing. Women constituted 57% of the patients and the mean age was 46 years. Twenty-seven (57%) patients received single lung transplant, and the remaining received double lung transplant. The Kaplan Meier 1- and 3-year survival rates were 67.6% and 45.9%, respectively. The survival estimates were not statistically significant compared to 10,070 patients who underwent transplant for other lung conditions during the same period (75.5% and 58.8%, respectively, $p = 0.25$).

Saggar et al. retrospectively evaluated lung transplant recipients who underwent lung transplant between January

Table 1 Demographic characteristics of systemic sclerosis patients who have undergone lung transplantation.

Reference	*N*	Mean age	Sex female:male	PAH (%)	ILD (%)	Type of lung transplant
Massad 2005	47	46	27:20	NA	NA	27 SLT 20 DLT
Schachna 2006	29	46.6	16:13	11	15	9 DLT 18 SLT 2 HLT
Shitrit 2009	7	52	5:2	6 (84)	7 (100)	7 SLT
Saggar 2010	15	53.2	4:11	2	6	1 SLT 14 DLT
Crespo 2011	67	49	NR	NR	NR	NR
Sottile 2011	22	NR	NR	NR	22 (100)	NR
Pakhale 2002	9	NR	5:4	NR	NR	7 DLT 2 SLT

PAH Pulmonary arterial hypertension, ILD Interstitial lung disease, SLT Single lung transplant, DLT Double lung transplant, HLT Heart lung transplant.

1, 2003 and December 31, 2007 at the University of California Los Angeles (UCLA), CA, USA. Inclusion criteria for transplant listing included age ≤60 years, SSc diagnosis ≥5 years, and baseline six minute walk distance ≥100 m. Exclusion criteria included symptomatic esophageal stricture or upper gastrointestinal ulcer, esophageal atonia or achalasia, or abnormal gastric emptying (<25% clearance at 90 min post ingestion) despite aggressive medical therapy. A total of 243 lung transplants were performed during this period, out of which 15 were for SSc and 38 were for IPF patients. All lung transplants for SSc were double lung transplants, except for one who underwent single lung transplant. Apart from a younger SSc cohort (53.2 versus 58.8 years; $p = 0.02$) the two groups were well matched. During a median follow up of 632 days (SSc) and 788 days (IPF), the post-lung transplant survival (78.6% versus 71.1%) was no different [21].

Schachna et al. report a retrospective cohort of all patients who underwent lung transplantation between December 1, 1989 and June 30, 2002 at the Johns Hopkins Hospital and the University of Pittsburgh Medical Center. A total of 689 lung transplantations were performed at the 2 centers during the study period. Survival following lung transplantation was examined among 29 patients with SSc as compared to 70 patients with ILD, and 38 patients with IPAH. The primary outcome was all-cause mortality. Cumulative survival at 6 months post-transplantation was 69% in the SSc group, compared with 80% in the ILD group and 79% in the IPAH group. Over the following 18 months, there was convergence in the survival rates such that cumulative survival at 2-years was comparable at 64%, among all 3 groups [22].

Crespo et al. report a retrospective cohort study of patients who underwent lung transplant between July 1989 and December 2010 at the University of Pittsburgh Medical Center. They compared 67 patients with SSc to 223 patients controlled for era, age and disease (non-SSc). The average age was 49 years. Kaplan—Meier survival for SSc patients at 30 days, 1- and 5- years were 91%, 73% and 46%, compared with non-SSc survival estimates of 95%, 86% and 52%. Overall mortality for SSc patients was 11% compared to 13% for non-SSc patients (time frame not specified) [23].

Pakhale et al. retrospectively reported the outcomes of 9 SSc patients from 415 patients who underwent lung transplantation at the Toronto General Hospital, Toronto, Canada between November 1983 and January 2001. Five patients were females and four were males and their mean age was 47 years. Seven received double lung transplantation and two received single lung transplantation. Survival at 30 days was 88.9%. The median survival time was 46 months (range 1—116 months) [24].

Sottile et al. retrospectively reported 22 SSc patients who underwent lung transplantation at University of California San Francisco, USA between 1998 and 2010. These patients were matched by age and sex to 30 patients with ILD and 11 patients with IPAH. The primary outcome was post-transplant survival. In the SSc group, 6-month, 12-month and 36- month survival was 85%, 79% and 68% compared to 90%, 83% and 69% in the ILD group. In IPAH, survival was 90% at 6-months, 12-months and 36-months. Survival was not statistically different across all groups ($p = 0.4$) [25].

Post-lung transplant survival

Survival data across studies are summarized in Table 2. Causes of death included graft failure [18,26], infection [18,26], cardiac events [18], hemorrhagic stroke [18], respiratory failure [18], malignancy, pulmonary hypertension [18], complications of bronchiolitis obliterans syndrome [21], scleroderma renal crisis [21], anesthetic complication [21]. There were no reports of recurrence of SSc in the lung allograft. The inclusion criteria for each study are summarized in Table 3.

Discussion

Lung transplantation is a potentially life-saving option for SSc patients with end stage lung disease. Our systematic review indicates that SSc post-lung transplant survival is good. Some lung transplant programs have expressed concern about the possibility of excess post-transplantation mortality related to the extra-pulmonary manifestations of SSc [21]. The results of this review suggest that this is possibly not the case. Furthermore, there has been a progressive improvement in survival rates over time. Indeed, there has been a substantial decrease in 30-day mortality for PAH patients post-lung transplantation over the past 2 decades [28]. The SSc patients have kept pace with the overall cohort of patients with time. The observed improvement in SSc post-lung transplant survival is likely attributable to increasing experience across centers resulting in improvements in perioperative and post-lung transplant care over time. However, within the SSc group, there was considerable variability in survival estimates (e.g. 67.6%—93.4% survival at 1-year post-transplantation) [18,21]. The study with the best survival outcomes had more stringent recipient selection criteria [21]. It is likely that these patients were highly selected, and thus had the best survival outcomes, compared to the other studies. Furthermore, the presented data suggests that there possibly are no differences between groups, but is not conclusive. Definitive conclusions cannot be drawn based on these studies. Studies with larger samples or even more studies, which can be included in a meta-analysis, are needed to definitively answer this important question.

The comparability of SSc post-lung transplant survival in relation to non-SSc (IPAH and ILD) lung transplant survival is controversial. Two studies demonstrate comparable survival between SSc and non-SSc lung transplant recipients [22,26], one study demonstrates better survival in among non-SSc lung transplant recipients [18], and one study [21] demonstrates better survival among the SSc lung transplant recipients. The reasons for these discrepancies are unclear. The first reason may relate to the processes of access to lung transplantation. Very few studies have characterized SSc patients referred for lung transplant assessment, those deemed unsuitable for transplantation, those who refuse lung transplantation, those considered too early to be listed, those who die before their assessment or die on the transplant list. Waiting list mortality has been reported to be highest among connective tissue disease (CTD) associated PAH patients [28]. SSc pre-transplant disease

Table 2 Survival post-lung transplantation in systemic sclerosis.

Reference	*N*	30 day survival		6-month survival		1-year survival		2-year survival		3-year survival	
		SSc	Non-SSc	SSc	Non SSc	SSc	Non-SSc	SSc	Non-SSc	SSc	Non-SSc
Pakhale 2002	9	88.9%	NA	NR	NA	NR	NA	NR	NA	NR	NA
Massad 2005	47	85%	NR	NR	NR	67.6%	75.5%	58%	66.5%	45.9%	58.8%
Schachna 2006	29	69%	80% ILD 79% IPAH	69%	80% ILD 79% IPAH	59%	59% ILD 74% IPAH	52%	37% ILD 58% IPAH	NR	NR
Shitrit 2009	7	NR	NR	NR	NR	88%	84%	NR	NR	73%	NR
Saggar 2010	15	NR	NR	NR	NR	93.4%	86.9%	80%	71.1%	NR	NR
Crespo 2011	67	91%	95%	NR	NR	73%	86%	NR	NR	NR	NR
Sottile 2011	22	NR	NR	85%	90% ILD 90% IPAH	79%	83% ILD 90% IPAH	NR	NR	68%	69% ILD 90% IPAH

SSc Systemic sclerosis, Non-SSc Non systemic sclerosis, ILD Interstitial lung disease, IPAH Idiopathic pulmonary arterial hypertension, NA Not applicable, NR Not reported.

manifestations, disease severity, patient preferences and socio-economic factors all may impact post-lung transplant prognosis. As such, discrepancies could reflect how the cohorts were matched or how potential confounders were accounted for. The small sample sizes make control of relevant prognostic factors problematic.

Second, the combined effect of SSc manifestations and post-operative morbidity may also impact survival.

Table 3 Summary of inclusion criteria.

		Saggar	Schachna	Shitrit	Massad	Crespo[a]	Phakle[a]	Sottile[a]
General								
Adherence to established guidelines		✓	✓	NR	NR	NR	NR	NR
Age		≤60 yrs.	NR	NR	NR	NR	NR	NR
SSc diagnosis		≥5 yrs.	NR	NR	NR	NR	NR	NR
Baseline 6MWT		≥100 m (with oxygen)	NR	NR	NR	NR	NR	NR
FVC		NR	<55%	NR	NR	NR	NR	NR
Gastrointestinal								
Absence	Severe gastroesophageal reflux	NR	✓	NR	✓	NR	NR	NR
	Oesophageal stricture	✓	NR	NR	NR	NR	NR	NR
	Active UGI ulceration	✓	NR	NR	NR	NR	NR	NR
	Oesophagealperistalsis	✓	NR	NR	NR	NR	NR	NR
	Abnormal gastric emptying	✓	NR	NR	NR	NR	NR	NR
	Chronic GI bleed	✓	NR	NR	NR	NR	NR	NR
Skin								
Chest induration score								
Absence	Non-healing wounds	NR	✓	NR	NR	NR	NR	NR
	Open skin wounds	NR	✓	NR	✓	NR	NR	NR
	Severe sclerosis of chest wall	NR	✓	NR	NR	NR	NR	NR
	Rapidly progressive diffuse skin thickening	✓	NR	NR	NR	NR	NR	NR
	Active digital ulcerations	✓	NR	NR	NR	NR	NR	NR
	Active myositis	✓	NR	NR	NR	NR	NR	NR
	Progressive myopathy	✓	NR	NR	NR	NR	NR	NR
Renal								
Creatinine clearance		>50 ml/min	>50 ml/min	NR	>50 ml/min	NR	NR	NR
Time between last renal crisis & active listing for LT		Min of 5 yrs.	NR	NR	NR	NR	NR	NR
Cardiac								
Absence	Left heart failure	✓	NR	NR	NR	NR	NR	NR
	CAD	✓	NR	NR	NR	NR	NR	NR
	Overt right heart failure	✓	NR	NR	NR	NR	NR	NR

NR Not reported.
[a] Abstract.

Gastroparesis (as measured by delayed gastric emptying on nuclear gastric emptying studies) and gastroesophageal reflux are common in lung transplant recipients, and are associated with the development of bronchiolitis obliterans syndrome (BOS) in the lung allograft [29,30]. The presence and extent of gastroesophageal reflux may increase concern for graft refection [27] SSc-ILD patients have more reflux episodes and more reflux reaching the proximal esophagus compared with SSc patients without ILD [31]. This could possibly also explain some of the variability in results post transplant for SSc-ILD versus SSc-PAH. Other SSc-related morbidity that should be considered includes the occurrence of infection, gastrointestinal complications (aspiration, reflux, need for feeding tube), and renal complications including need for dialysis. An improved understanding of the occurrence, management and possible prevention of these post-lung transplant co-morbidities will likely improve lung allograft outcomes and survival.

A third reason for the discrepancies in survival estimates between SSc and non-SSc lung transplant recipients may be due to biased case-ascertainment (related to classification versus diagnosis of SSc [19], or insufficient characterization of the etiology of lung disease.) It may be that there are survival differences across SSc-PAH, SSc-ILD, SSc with combined PAH and ILD, IPAH and ILD. Mixing of these subgroups as 'cases' and 'controls' may bias the survival estimates. Future investigators should report the criteria by which each subgroup was classified, and outcomes for each of the subgroups under study.

We have also found that very little is known about long-term SSc post-lung transplant survival. The studies we have identified only report short-term (30-day and 6-month), and intermediate-term (1-, 2-, 3-year) survival. Long-term survival data are needed. It has been reported that long-term post-lung transplant survival (10-year) in CTD-PAH is 69%, and is better than IPAH post-lung transplant survival [28]. There were no reports of recurrence of SSc in the lung allograft. It should be noted that simply not reported does not preclude such a possibility. It might be difficult to distinguish graft rejection from SSc, since both are characterized by vascular damage, inflammation and fibrosis.

There are a few limitations to consider in our systematic review. The only recipient characteristics, which we evaluated, were age, sex and the type of SSc lung disease. We feel that there is a scope for future investigators to evaluate further recipient characteristics such as disease duration, time to lung transplant, type of SSc, other organ system involvement, especially gastrointestinal tract. All of the studies were retrospective observational studies; hence there may be selection bias and the potential for missing data in these studies. All of the studies had small sample sizes, and were limited in longitudinal follow-up. These limitations are not insurmountable. A more significant issue is that the publications may contain overlapping cohorts of the same patients [32]. For example, the study reported by Massad et al. includes all US patients with an identified diagnosis of SSc. It may be that some patients are counted multiple times. As a result there is insufficient scientific basis for combining these studies as a meta-analysis. However, the descriptive systematic review is worthwhile and interesting. Our study synthesizes the current state of knowledge, and lays the groundwork for future research. We have found that there is a significant gap in understanding the determinants of post-lung transplantation survival in SSc patients. Review of the United Network for Organ Sharing (UNOS) or the International Society for Heart and Lung Transplantation (ISHLT) databases may further answer these questions. However, these databases only contain information on transplanted patients and not those with SSc that were referred for transplant or refuse transplant. Future researchers need to clearly delineate the access process for lung transplantation in SSc patients: who gets referred for assessment, who gets listed and finally who undergoes lung transplantation [32]. Undoubtedly, the assessment process can result in selection bias and impact post transplant survival. Investigators should report clinically relevant outcomes post-lung transplant in SSc such as the occurrence of acute rejection, infection, bronchiolitis obliterans syndrome, renal dysfunction and dialysis, gastroparesis, and need for tube feeding.

Gastroesophageal reflux and altered motility are common among patients with SSc and post-lung transplantation population [29]. This is of potential clinical importance as both gastroesophageal reflux and aspiration may be modifiable. There is increasing consideration of early anti-reflux measures [26,33—35] in these patients. The occurrence of these co-morbidities will impact survival and the quality of life post-transplantation.

In conclusion, there remains a small body of literature on the topic of lung transplantation in patients with SSc. This study reviews several articles and compares the results of these papers. Based on these studies, the short-term and intermediate-term survival post-lung transplantation are similar to IPAH and ILD patients requiring lung transplantation.

Conflict of interest statement

None of the authors have funding sources or financial conflicts relating to this paper to disclose.

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