Title

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Journal

Annals of the American Thoracic Society, 13(6)

ISSN

2329-6933

Authors

Miele, Catherine H
Schwab, Kristin
Saggar, Rajeev
et al.

Publication Date

2016-06-01

DOI

10.1513/annalsats.201512-806oc

Peer reviewed

Lung Transplant Outcomes in Systemic Sclerosis with Significant Esophageal Dysfunction

A Comprehensive Single-Center Experience

Catherine H. Miele[1]*, Kristin Schwab[1]*, Rajeev Saggar[2], Erin Duffy[1,3], David Elashoff[1,3], Chi-Hong Tseng[1,3], Sam Weigt[1,4,5], Deepshikha Charan[1], Fereidoun Abtin[6], Jimmy Johannes[1,4,5], Ariss Derhovanessian[1,4,5], Jeffrey Conklin[7], Kevin Ghassemi[7], Dinesh Khanna[8], Osama Siddiqui[9], Abbas Ardehali[5], Curtis Hunter[5], Murray Kwon[5], Reshma Biniwale[5], Michelle Lo[1], Elizabeth Volkmann[10], David Torres Barba[1], John A. Belperio[1,4,5], David Sayah[4,5], Thomas Mahrer[11], Daniel E. Furst[10], Suzanne Kafaja[10], Philip Clements[8], Michael Shino[4,5], Aric Gregson[1], Bernard Kubak[1], Joseph P. Lynch 3rd[1,4], David Ross[1,4,5]*, and Rajan Saggar[1,4,5]*

[1]Department of Internal Medicine, David Geffen School of Medicine at the University of California Los Angeles; [3]Department of Medicine Statistics Core; [4]Department of Pulmonary and Critical Care Medicine; [5]Lung and Heart-Lung Transplant and Pulmonary Hypertension Programs, [6]Department of Radiology, [7]Department of Gastroenterology, and [10]Department of Rheumatology, University of California Los Angeles Medical Center, Los Angeles, California; [2]Department of Pulmonary and Critical Care Medicine, Banner University Medical Center, Phoenix, Arizona; [8]Department of Medicine, Scleroderma Program in the Division of Rheumatology, University of Michigan Health System, Ann Arbor, Michigan; [9]Department of Surgery, University of Maryland School of Medicine, Baltimore Maryland; and [11]Department of Medicine, Kaiser Permanente, Los Angeles, California

ORCID IDs: 0000-0003-1307-2364 (C.H.M.); 0000-0001-7021-8273 (D.S.).

Abstract

Rationale: Consideration of lung transplantation in patients with systemic sclerosis (SSc) remains guarded, often due to the concern for esophageal dysfunction and the associated potential for allograft injury and suboptimal post–lung transplantation outcomes.

Objectives: The purpose of this study was to systematically report our single-center experience regarding lung transplantation in the setting of SSc, with a particular focus on esophageal dysfunction.

Methods: We retrospectively reviewed all lung transplants at our center from January 1, 2000 through August 31, 2012 (n = 562), comparing the SSc group (n = 35) to the following lung transplant diagnostic subsets: all non-SSc (n = 527), non-SSc diffuse fibrotic lung disease (n = 264), and a non-SSc matched group (n = 109). We evaluated post–lung transplant outcomes, including survival, primary graft dysfunction, acute rejection, bronchiolitis obliterans syndrome, and microbiology of respiratory isolates. In addition, we defined severe esophageal dysfunction using esophageal manometry and esophageal morphometry criteria on the basis of chest computed tomography images. For patients with SSc referred for lung transplant but subsequently denied (n = 36), we queried the reason(s) for denial with respect to the concern for esophageal dysfunction.

Measurements and Main Results: The 1-, 3-, and 5-year post–lung transplant survival for SSc was 94, 77, and 70%, respectively, and similar to the other groups. The remaining post–lung transplant outcomes evaluated were also similar between SSc and the other groups. Approximately 60% of the SSc group had severe esophageal dysfunction. Pre–lung transplant chest computed tomography imaging demonstrated significantly abnormal esophageal morphometry for SSc when compared with the matched group. Importantly, esophageal dysfunction was the sole reason for lung transplant denial in a single case.

Conclusions: Relative to other lung transplant indications, our SSc group experienced comparable survival, primary graft dysfunction, acute rejection, bronchiolitis obliterans syndrome, and microbiology of respiratory isolates, despite the high prevalence of severe esophageal dysfunction. Esophageal dysfunction rarely precluded active listing for lung transplantation.

Keywords: scleroderma; lung transplantation; esophageal dysfunction; gastroesophageal reflux; acute rejection

(Received in original form December 10, 2015; accepted in final form March 10, 2016)

*These authors contributed equally.

Author Contributions: Conception and design: Rajeev Saggar., D.R., Rajan Saggar, S.W., C.H.M., K.S., E.D., D.K., A.A., C.H., M.K., R.B., J.A.B., D.S., T.M., D.E.F., S.K., P.C., M.S., A.G., B.K., J.P.L., A.D., and E.V. Analysis and interpretation: E.D., D.E., C.-H.T., C.H.M., K.S., D.C., S.W., A.D., Rajeev Saggar, Rajan Saggar, F.A., J.C., and K.G. Drafting of manuscript for important intellectual content: Rajeev Saggar, C.H.M., Rajan Saggar, J.J., S.W., E.D., K.S., M.L., D.T.B., and O.S.

Correspondence and requests for reprints should be addressed to Rajan Saggar, M.D., Associate Professor of Medicine, Director Medical Intensive Care Unit, Lung and Heart-Lung Transplant and Pulmonary Hypertension Programs, David Geffen School of Medicine, UCLA, 200 Medical Plaza #365B, Los Angeles, CA 90095. E-mail: rsaggar@mednet.ucla.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Ann Am Thorac Soc Vol 13, No 6, pp 793–802, Jun 2016

DOI: 10.1513/AnnalsATS.201512-806OC
Internet address: www.atsjournals.org

Pulmonary complications, particularly pulmonary arterial hypertension and pulmonary fibrosis, are the leading causes of death in patients with systemic sclerosis (SSc) (1). Nevertheless, consideration for lung transplantation for SSc is limited by the high prevalence of comorbid esophageal dysfunction, which likely increases the risk for allograft dysfunction (2). The reported post-transplant survival for SSc remains quite variable (45–73% 3-year survival) (3). Some have speculated that lung transplant centers with favorable post-transplant outcomes with patients with SSc may have more stringent selection criteria (3, 4), particularly regarding the extent of underlying esophageal dysfunction.

The intent of this manuscript is to extend the observations in our prior report (5) and comprehensively represent our center's experience with lung transplantation for adults with SSc, relative to all other lung transplant indications, with specific attention to associated esophageal dysfunction. We report SSc–lung transplant outcomes related to survival, primary graft dysfunction (PGD), acute rejection, bronchiolitis obliterans syndrome (BOS), and microbiology of respiratory isolates when compared with three distinct lung transplant groups, specifically non-SSc recipients, diffuse fibrotic lung disease, and a four-to-one matched group.

Methods

Study Design

We retrospectively reviewed the clinical data of all lung transplant recipients undergoing transplant between January 1, 2000 and August 31, 2012 at the University of California Los Angeles (UCLA). The first SSc–lung transplant was performed on February 18, 2003. All SSc diagnoses were confirmed based on existing criteria (6). The UCLA lung transplant protocols have been previously described (5). Pretransplant gastrointestinal-related management included extensive patient education and repeated clinical assessments, which incorporated the following: (*1*) lifestyle modifications, including dietary, positional, and "timing of oral ingestion" recommendations; (*2*) optimization of medical management (proton pump inhibition, histamine antagonists, promotility agents); and (*3*) a detailed review of prior "respiratory exacerbations," including a review of computed tomography (CT) chest radiology, the temporal relationship to gastroesophageal reflux (GER) symptomatology, and subsequent clinical course. These management strategies were used to the extent the multidisciplinary team was satisfied that the GER symptomatology was clinically quiescent or near quiescent before lung transplantation. Post-transplant feeding followed our general protocol, with nasogastric tube placement and advancing of diet as tolerated. We have no standard practice for partial fundoplication, gastrojejunal tube placement, or other preemptive post-transplant feeding strategies for patients with esophageal dysfunction.

Patients were categorized into groups as follows: (*1*) SSc, (*2*) non-SSc, (*3*) diffuse fibrotic lung disease, and (*4*) four-to-one matched group. The matched group was composed of non-SSc matched to SSc–lung transplant recipients through Greedy distance matching. Matching criteria included age, lung allocation score, transplant type, and pulmonary hypertension (*see* online supplement). The SSc–lung transplant–related outcomes were compared with those of the other groups.

Definitions of Lung Transplant–related Outcomes

Survival was measured as time to death or censor date (August 31, 2012). PGD, acute rejection, and BOS were defined and classified per established criteria (7–9) (*see* online supplement). All post-transplant respiratory microbiology was reviewed for the total cohort.

Esophageal Dysfunction Evaluation

SSc–lung transplant recipients underwent a battery of testing to assess esophageal function, including 24-hour dual pH probe study (±impedance), esophageal manometry, and/or upper endoscopy. Impedance testing was performed to assess for nonacid GER while on acid suppression during the pH probe study. This multimodal evaluation was not systematically attempted for any other patient group. The impedance and esophageal manometry assessments were independently reinterpreted by UCLA Gastroenterology (K.G., J.C.).

In addition, the chest CT examinations closest to and preceding the lung transplant date were reviewed (Rajan Saggar, J.J., F.A.) and the following esophageal morphometry parameters were collected for the SSc group and the diffuse fibrotic lung disease subgroup of the matched group (n = 52): (*1*) the presence of an air fluid level in the esophagus demonstrated on three or more sequential axial images, (*2*) the presence of a patulous esophagus, and (*3*) the maximum esophageal diameter on axial imaging (normal maximum esophageal diameter $\leqslant$ 15 mm) and maximum esophageal diameter location (infraaortic or supraaortic) (10). Severe esophageal dysfunction was defined either by esophageal morphometry as (*1*) the presence of air fluid level and esophageal dilatation (maximum esophageal diameter $\geqslant$ 20 mm) (10), or by esophageal manometry as (*2*) distal esophageal absent contractility (11).

We queried all patients with SSc referred for lung transplant during the study period but subsequently denied active lung transplant listing (n = 36) to query the basis for denial.

Statistical Analysis

Demographic and clinical characteristics were summarized as mean ± SD for continuous variables and frequency (%) for categorical variables.

Kaplan-Meier survival estimates were calculated for BOS-free and overall survival at 1, 3, and 5 years post-transplant. Log-rank tests were used to compare unadjusted survival estimates. Multivariate Cox proportional hazards regression models further assessed the association between SSc and transplant outcomes, adjusting for clinically relevant covariates.

The prevalence of grade 3 PGD at 72 hours post-transplant were compared between groups with chi-square tests. Chi-square or Fisher exact tests (in situations where at least one cell count was less than five) were used to compare the prevalence of post-transplant respiratory microbiologic isolates between groups.

Acute rejection was measured as a time-dependent sum of all prior acute rejection grades. Cumulative acute rejection scores at 1 year post-transplant were compared between groups using *t* tests. The association between SSc and clinically significant acute rejection (grade $\geqslant$ 2) as a repeated events outcome was evaluated by univariate Andersen Gill proportional hazards regression models.

The prevalence of air fluid level, patulous esophagus, maximum esophageal diameter, and maximum esophageal diameter location were compared between patients with SSc and the diffuse fibrotic lung disease subset of the matched group.

All analyses were performed in SAS v9.4 (SAS Institute Inc., Cary, NC). *See* online supplement for additional details.

Results

Baseline Patient Characteristics

A total of 562 lung transplants were performed at UCLA between January 1, 2000 and August 31, 2012. Thirty-five (6.2%) underwent transplant for SSc-associated pulmonary fibrosis with or without pulmonary hypertension, and 32 (91%) of the SSc group were bilateral lung transplant recipients (Table 1). The SSc group had near-equal distribution of sex and tended to be younger, whereas the non-SSc and diffuse fibrotic lung disease groups were predominantly men and older. A greater proportion of the SSc group, as compared with non-SSc and diffuse fibrotic lung disease groups, manifested pretransplant pulmonary hypertension. Where available, the lung allocation scores were similar between SSc and non-SSc groups. Notably, the four-to-one matched group (n = 109) was incompletely matched as a result of fewer non-SSc control subjects fulfilling all matching criteria.

Median follow-up duration for SSc (2.9 yr; interquartile range [IQR], 4.0) was similar to non-SSc (3.2 yr; IQR, 4.3) and diffuse fibrotic lung disease (2.7 yr; IQR, 3.7) but shorter than follow up for the matched group (3.8 yr; IQR, 4.7). Diffuse fibrotic lung disease was the most common transplant indication at our institution, representing 47% of all lung transplants during the study period. The compositions of the diagnoses in the total and matched groups are displayed in Table E1 in the online supplement.

Survival Analysis

Kaplan-Meier curves for survival after lung transplant revealed similar survival functions across groups (Figure 1). One-, 3-, and 5-year survival estimates for SSc were 0.94 (95% confidence interval [CI], 0.79–0.99), 0.77 (95% CI, 0.58–0.89), and 0.70 (95% CI, 0.47–0.85), respectively, and were similar to survival estimates of the non-SSc ($P = 0.31$), diffuse fibrotic lung disease ($P = 0.20$), and matched group ($P = 0.95$) (Table 2). In three univariate proportional hazards regression models, SSc was not associated with overall survival relative to non-SSc (hazard ratio [HR], 0.73; 95% CI, 0.40–1.34; $P = 0.31$), diffuse fibrotic lung disease (HR, 0.67; 95% CI, 0.36–1.25; $P = 0.21$), or the matched group (HR, 1.02; 95% CI, 0.52–2.00; $P = 0.95$).

Older age at transplant, higher pretransplant pulmonary artery wedge pressure, higher cumulative acute rejection score, and bilateral lung transplant status were each associated with a higher unadjusted rate of death (*see* Table E2). A multivariate analysis found that SSc (vs. non-SSc) was not associated with survival (HR, 0.83; 95% CI, 0.43–1.59; $P = 0.57$), but higher cumulative acute rejection score (HR, 1.10; 95% CI, 1.05–1.16; $P < 0.01$) and PGD grade 3 at 72 hours (HR, 1.57; 95% CI, 1.01–2.45; $P = 0.05$) were each associated with a higher rate of death, whereas bilateral lung transplant status (HR, 0.54; 95% CI, 0.30–0.98; $P = 0.04$) was associated with lower rate of death (Table 3).

Post–Lung Transplantation–related Outcomes

Primary graft dysfunction. Three of 35 patients with SSc experienced PGD grade 3 at 72 hours post-transplant, of which a single case required extracorporeal membrane oxygenation. The prevalence of PGD grade 3 at 72 hours for the total cohort was 11.7%, and there was no difference between the SSc (8.6%) and the non-SSc

Table 1. Characteristics of patients receiving lung transplant

	All Transplants (*n = 562*)		SSc (*n = 35*)		Non-SSc (*n = 527*)		DFLD (*n = 264*)		Matched Group (*n = 109*)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at transplant	58	10.7	50.7	9.5	58.5	10.6	61.8	7.9	53.9	8.6
BMI, kg/m^2	25.4	4.6	24.3	4.3	25.5	4.6	27	4.2	26	4.8
Mean PAP, mm Hg	26.7	10.9	32.9	12.5	26.2	10.7	24.6	9.4	31.2	13
PAWP, mm Hg	11.9	6.2	11.7	6.2	11.9	6.2	10.8	6.6	13.5	7
Cardiac output, L/min	5.6	−4.3	6.7	8	5.5	3.9	5.7	5.2	5.4	1.7
PVR, dyn s/cm^5	237	−197	381	335	227	180	218	141	297	274
Lung allocation score	47.9	−15.3	49.9	11	47.8	15.6	52.3	15.8	51	10.4
Cardiopulmonary bypass time, H	1.97	−1.78	3.26	1.41	1.89	1.77	1.68	1.79	3.15	1.38
Donor ischemic time, min	301	−79	325	82	299	79	294	78	318	84
	n	%	n	%	n	%	n	%	n	%
Male	329	−59	18	51	311	59	180	68	66	61
Female	233	−41	17	49	216	41	84	32	43	39
Single lung transplant	264	−47	3	9	261	50	159	60	12	11
Double lung transplant	298	−53	32	91	266	50	105	40	97	89
Pre–lung transplant PH										
Yes	232	−41	22	63	210	40	94	36	67	61
No	330	−59	13	37	317	60	170	64	42	39

Definition of abbreviations: BMI = body mass index; DFLD = diffuse fibrotic lung disease; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; SSc = systemic sclerosis.

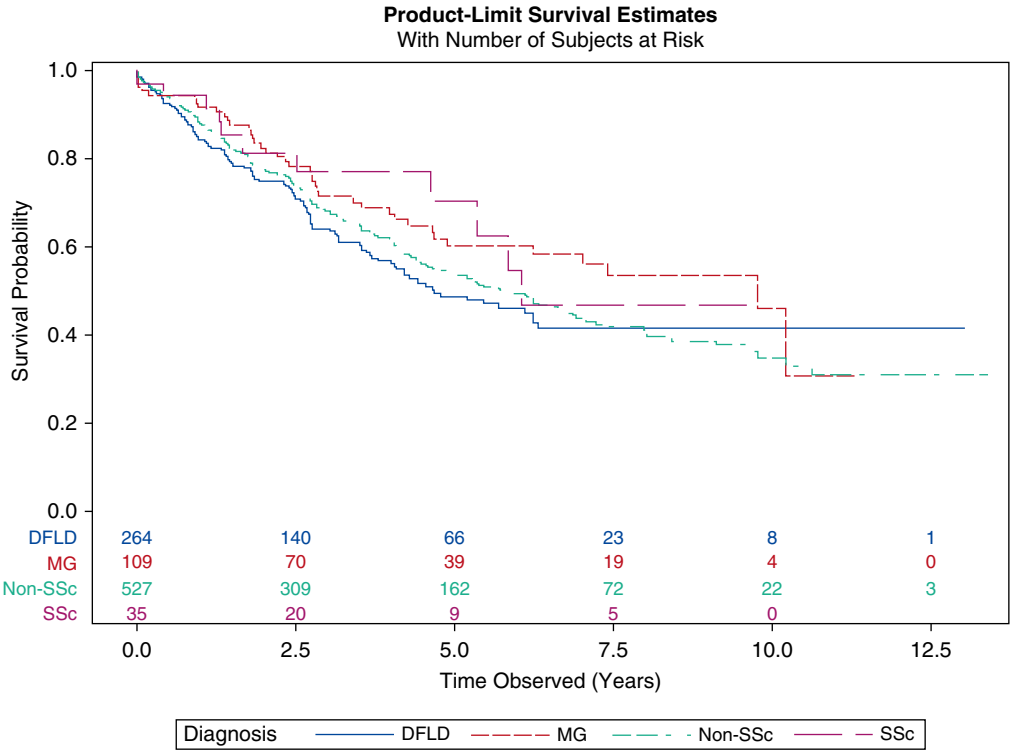

Figure 1. Product-limit survival estimates, with number of subjects at risk. Kaplan-Meier curves for post–lung transplant survival for all cohorts. Log-rank test systemic sclerosis (SSc) versus the following: non-SSc ($P = 0.31$), diffuse fibrotic lung disease (DLFD) ($P = 0.20$), and matched groups (MG) ($P = 0.95$).

(11.9%, $P = 0.50$), diffuse fibrotic lung disease (12.4%, $P = 0.49$), and matched groups (15.2%, $P = 0.41$) (Table 4). In a multivariate proportional hazards regression model, which included SSc diagnosis, age, sex, body mass index (BMI), pulmonary arterial wedge pressure, bypass time, accumulative acute rejection score, type of transplant (bilateral versus single), mean pulmonary artery pressure, lung allocation score, and year of transplant, for the total cohort, PGD grade 3 at 72 hours predicted overall mortality (HR, 1.57; 95% CI, 1.01–2.45; $P = 0.05$) (Table 3).

Acute rejection. The mean cumulative acute rejection scores at 1 year post-transplant were similar between the SSc (1.5 ± 2.05, mean $\pm$ SD) and non-SSc (1.14 ± 1.71, $P = 0.26$), diffuse fibrotic lung disease (1.25 ± 1.78, $P = 0.46$), and matched groups (0.95 ± 1.48, $P = 0.10$) (Table 4). In a proportional hazards regression model, SSc (vs. non-SSc) was not associated with a higher rate of acute rejection (HR, 1.15; 95% CI, 0.94–1.73; $P = 0.49$) or with clinically significant acute rejection (grade ≥ 2) (HR, 1.38; 95% CI, 0.81–2.35; $P = 0.23$).

A multivariate proportional hazards regression analysis of the total cohort adjusting for SSc diagnosis, age, sex, BMI, pulmonary capillary wedge pressure, transplant type (bilateral vs. single), PGD grade, mean pulmonary arterial pressure, lung allocation score, and year of transplant showed a strong association between the cumulative acute rejection score and BOS-free survival (HR, 1.16; 95% CI, 1.10–1.22; $P < 0.01$) as well as overall mortality (HR, 1.10; 95% CI, 1.05–1.16; $P < 0.01$).

BOS-free survival. During the post-transplant observation period, BOS developed in 12 patients in the SSc, 198 in the non-SSc, 94 in the diffuse fibrotic lung disease, and 51 in the matched patient groups. Kaplan-Meier curves and log-rank tests for BOS-free survival revealed similar pairwise BOS-free survival functions between the SSc group and non-SSc ($P = 0.57$), diffuse fibrotic lung disease ($P = 0.62$), and matched ($P = 0.55$) groups (Figure 2).

The 5-year BOS-free survival estimate for SSc was 0.56 (95% CI, 0.31–0.76), compared with non-SSc (0.47; 95% CI,

Table 2. Post–lung transplant Kaplan-Meier survival estimates for all cohorts at 1, 3, and 5 years

	1-Year Survival Survival Estimate (95% CI)	3-Year Survival Survival Estimate (95% CI)	5-Year Survival Survival Estimate (95% CI)	Pairwise Log-Rank Test
SSc	0.94 (0.79–0.91)	0.77 (0.58–0.89)	0.70 (0.47–0.85)	—
Non-SSc	0.88 (0.85–0.91)	0.68 (0.64–0.72)	0.54 (0.49–0.58)	0.31
DFLD	0.84 (0.79–0.88)	0.64 (0.57–0.70)	0.49 (0.41–0.56)	0.20
Matched group	0.92 (0.84–0.96)	0.71 (0.61–0.79)	0.60 (0.49–0.70)	0.95

Definition of abbreviations: CI = confidence interval; DFLD = diffuse fibrotic lung disease; SSc = systemic sclerosis.

Table 3. Multivariate proportional hazards regression model predicting survival

	HR	95% CI	*P* Value
SSc	0.83	0.43–1.59	0.57
Age by 10 years	1.11	0.92–1.34	0.29
PAWP, mm Hg	0.99	0.96–1.02	0.38
Cardiopulmonary bypass time	1.13	0.96–1.33	0.14
Time-dependent AR sum	1.10	1.05–1.16	<0.01
Transplant type, bilateral	0.54	0.30–0.98	0.04
PGD grade 3 at 72 h, yes vs no	1.57	1.01–2.45	0.05
BMI	0.99	0.96–1.03	0.72
Mean pulmonary artery pressure	0.99	0.97–1.01	0.29
Sex, male	1.11	0.83–1.48	0.48
Lung allocation score, high vs. low	1.22	0.82–1.80	0.32
Lung allocation score, missing vs. low	0.91	0.57–1.44	0.69
Year of transplant	0.97	0.89–1.06	0.51

Definition of abbreviations: AR = acute rejection; BMI = body mass index; CI = confidence interval; HR = hazard ratio; PAWP = pulmonary artery wedge pressure; PGD = primary graft dysfunction; SSc = systemic sclerosis.

0.41–0.52), diffuse fibrotic lung disease (0.49; 95% CI, 0.41–0.57), and matched groups (0.48; 95% CI, 0.36–0.59). The SSc group experienced similar estimated BOS-free survival at 3 years (0.71; 95% CI, 0.47–0.85) and 5 years (0.56; 95% CI, 0.31–0.76) compared with non-SSc, diffuse fibrotic lung disease, and matched groups. In three univariate proportional hazards regression models, SSc was not associated with BOS-free survival relative to non-SSc (HR, 0.85; 95% CI, 0.46–1.57; $P = 0.61$), diffuse fibrotic lung disease (HR, 0.84; 95% CI, 0.45–1.57; $P = 0.58$), or matched groups (HR, 0.81; 95% CI, 0.42–1.56; $P = 0.53$).

A multivariate proportional hazards regression model adjusting for age, sex, BMI, pulmonary capillary wedge pressure, accumulative acute rejection score, type of transplant (bilateral versus single), PGD grade, mean pulmonary artery pressure, lung allocation score, and year of transplant found no association between SSc and BOS-free survival (HR, 0.90; 95% CI, 0.49–1.65; $P = 0.72$) (Table E3). Cumulative acute rejection score (HR, 1.16; 95% CI, 1.10–1.22; $P < 0.01$) was the only variable associated with BOS-free survival. Higher pre–lung transplant BMI (HR, 1.04; 95% CI, 1.01–1.08; $P = 0.02$) and lower pre–lung transplant pulmonary artery wedge pressure (HR, 0.92; 95% CI, 0.94–1.00; $P = 0.03$) were the only variables associated with BOS-free survival.

Respiratory Microbiology after Lung Transplantation

The prevalence of gram-negative and gram-positive bacteria, *Mycobacterium* species, viral pathogens, and molds from respiratory microbiologic isolates obtained by bronchoalveolar lavage were similar between SSc and the other groups (Table 5).

Evaluation for Esophageal Dysfunction

The full battery of pre–lung transplant esophageal testing was not completed for all recipients with SSc; nonetheless, all available data are reported in Figure 3. In contrast, esophageal morphometry parameters obtained from chest CT scans were available for all SSc (n = 35) and the diffuse fibrotic lung disease subgroup of the matched group (n = 52).

Multimodal Esophageal Evaluation

Twenty-six SSc–lung transplant recipients underwent 24-hour pH probe (±impedance) testing. Fourteen studies were conducted on acid suppression with a mean ± SD DeMeester score of 16.1 ± 15.6; of these, 42% had an abnormal DeMeester score (>14.7). Twelve studies were conducted off acid suppression with a mean ± SD DeMeester score of 53.1 ± 55.1; of these, 93% had an abnormal DeMeester score. Overall, 63% of the studied SSc group had a DeMeester score greater than 14.7, and of those, 29% were on acid suppression.

Fourteen (40%) SSc–lung transplant recipients underwent esophageal manometry. Thirteen (93%) of those studied had significant distal esophageal dysmotility, with seven (57%) and six (43%) demonstrating severe dysmotility and absent contractility, respectively. A single SSc–lung transplant had normal peristalsis.

Twenty-two SSc–lung transplant recipients underwent upper endoscopy, of whom 2 had evidence for gross esophagitis; the other 20 had no evidence for esophagitis.

Esophageal Morphometry by CT of the Chest: Air Fluid Level, Patulous Esophagus, and Maximal Esophageal Diameter

In the SSc group, 20 (57%) had an esophageal air fluid level (Figure E1), 26 (74%) had patulous esophagus, and 19 (54%) had both air fluid level and patulous esophagus. In contrast, the diffuse fibrotic lung disease subgroup of the matched group had a significantly lower frequency of air fluid level (10%, $P < 0.001$) and patulous

Table 4. Spectrum of post–lung transplantation outcomes

	PGD 3 at 72h		Cumulative AR Score at 1 Year		3-Year BOS-Free Survival (%) Survival Estimate (95% CI)	5-Year BOS-Free Survival (%) Survival Estimate (95% CI)
	% of Cohort	*P* Value	Score (SD)	*P* Value		
SSc	8.6	—	1.50 (2.05)	—	71 (47–85)	56 (31–76)
Non-SSc	11.9	0.5	1.14 (1.71)	0.26	62 (57–67)	47 (41–53)
DFLD	12.4	0.49	1.25 (1.78)	0.46	59 (51–67)	49 (41–57)
Matched group	15.2	0.41	0.95 (1.48)	0.1	63 (52–72)	48 (36–59)

Definition of abbreviations: AR = acute rejection; BOS = bronchiolitis obliterans syndrome; CI = confidence interval; DFLD = diffuse fibrotic lung disease; PGD = primary graft dysfunction; SSc = systemic sclerosis.

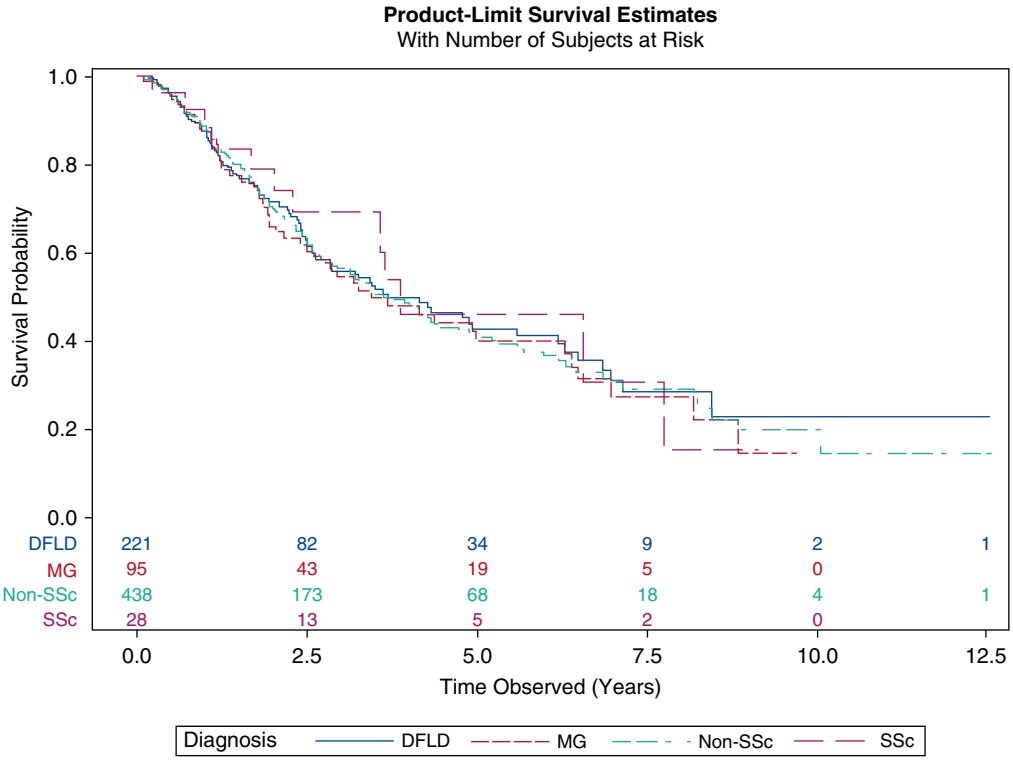

Figure 2. Product-limit survival estimates, with number of subjects at risk. Kaplan-Meier curves for post–lung transplantation bronchiolitis obliterans syndrome–free survival for all cohorts. Log-rank test systemic sclerosis (SSc) versus the following: non-SSc ($P = 0.57$), diffuse fibrotic lung disease (DFLD) ($P = 0.62$), and matched groups (MG) ($P = 0.55$).

esophagus (21%, $P < 0.001$). Within the SSc group, all 11 cases with air fluid level and patulous esophagus and available impedance data demonstrated a characteristic impedance spectrum compatible with air fluid level (12).

Compared with the diffuse fibrotic lung disease subgroup of the matched group, the SSc group had a higher mean maximum esophageal diameter (25.0 ± 11.4 mm vs. 15.2 ± 7.6 mm, $P < 0.001$) and higher prevalence of significantly abnormal maximum esophageal diameter (⩾20 mm; 66 vs. 17%; $P < 0.001$) (Table 6, Figure E2). In addition, the maximum esophageal diameter location was more often in the distal esophagus (infraaortic as opposed to supraaortic) in the SSc group compared with the diffuse fibrotic lung disease subgroup of the matched group ($P = 0.035$).

Severe esophageal dysfunction by morphometry criteria was significantly more frequent in the SSc group (55%) compared with the diffuse fibrotic lung disease subgroup of the matched group (8%, $P < 0.001$). Furthermore, the overall survival for the SSc subgroup (n = 19) with severe esophageal dysfunction by either morphometry or manometry criteria was similar to the SSc subgroup (n = 16) without severe esophageal function ($P = 0.43$, Figure E3).

Table 5. Prevalence of positive bacterial bronchoalveolar lavage isolates across the cohorts during the 12-year study period

Group (n)	Gram-Negative Bacteria			Gram-Positive Bacteria		
	n	%	*P* Value	n	%	*P* Value
SSc (35)	11	31	—	11	31	—
Non-SSc (527)	233	44	0.14	163	31	0.95
DFLD (264)	98	37	0.51	74	28	0.68
Matched group (109)	49	45	0.16	41	38	0.51

Definition of abbreviations: DFLD = diffuse fibrotic lung disease; SSc = systemic sclerosis.

Referral to Lung Transplant Consideration without Subsequent Transplant

Of the 36 patients with SSc who were referred for but denied lung transplant at our center during the study period, 5 denials were in part due to significant SSc-related esophageal disease. Four of these five denials were due to multifactorial concerns, of which esophageal disease was a contributory factor; in one patient, esophageal disease was the only reason for not offering lung transplant. The additional factors that precluded lung transplant candidacy for the remaining 31 SSc–lung transplant are shown in Figure 4.

Discussion

Lung transplant recipients with SSc at our center demonstrated survival comparable to non-SSc, diffuse fibrotic lung disease, and

	pH probe	Peristalsis	Esophagitis	AFL	PE	MED
1		*				
2	-	-				
3	*	*	-			
4						
5	*	*				
6		-				
7	*	**	-			
8	-	-	-			
9	-	-				
10	*	-	-			
11	*	**				
12	*	*				
13		-				
14		*	-			
15	-	-	-			
16	-	-	-			
17		-				
18	-	-	-			
19		-				
20	*	*				
21		-				
22	-	-	-			
23	*	-				
24	*	-	-			
25	*	-	-			
26	-	-				
27		-	-			
28	-	-				
29		-				
30		**	-			
31		*				
32	*	**				
33		**				
34		**				
35	*	-				

Figure 3. Comprehensive results of available gastrointestinal testing and computed tomography (CT) chest imaging for the systemic sclerosis (SSc) cohort (n = 35) before lung transplantation (n = 35); each row represents an individual lung transplant recipient with SSc. (−) implies the study was not performed before lung transplantation *Shaded boxes* imply the study was abnormal; *open boxes* imply the study was normal (if the study was performed). pH probe: abnormal is DeMeester score > 14.7; *off acid suppression; the absence of * implies the study was done on acid suppression. Peristalsis (as assessed by esophageal manometry): *severe esophageal dysmotility; **esophageal aperistalsis. Esophagitis: abnormal implies upper endoscopy findings consistent with reflux esophagitis. Air fluid level (AFL): abnormal is the presence of AFL by CT chest imaging. Patulous esophagus (PE): abnormal is presence of a patulous esophagus by CT chest imaging. Maximum esophageal diameter (MED): abnormal is MED ⩾ 15 mm by CT chest imaging.

matched groups, despite a high prevalence (∼60%) of severe esophageal dysfunction. In addition, we did not find SSc to be independently associated with overall survival or BOS-freesurvival.

We also demonstrated that our SSc group had similar outcomes across the entire post-transplant spectrum, including PGD, acute rejection, and BOS. PGD grade 3 at 72 hours affected 11.7% of the total cohort and 8.6% of the SSc group, which is consistent with a prior Lung Transplant Outcomes Group report (13). In addition, the cumulative acute rejection score was no different in SSc compared with other groups. Importantly, in this study, we found that SSc was not independently associated with acute rejection.

This finding is in contrast to our prior report (5), which suggested increased acute rejection in lung transplant for patients with SSc. However, the time-dependent method of acute rejection analysis, the increased size of our SSc group, and the size and relevance of the comparison groups argue in favor of our current conclusion. As expected, the cumulative acute rejection score did demonstrate a strong multivariate association with BOS-free survival and overall mortality for the total cohort, consistent with existing literature (9).

There were no differences in overall BOS-free survival between SSc and the other groups. Interestingly, the overall BOS-3–free survival for SSc was 96%, and, notably, only a single patient with SSc experienced BOS-3 physiology (which occurred in the first year post–lung transplant) during the study period. Importantly, our entire lung transplant cohort displayed a BOS frequency of 53% at 5 years, consistent with the 49% noted in a recent International Society for Heart and Lung Transplantation report (14).

These post-transplant outcomes for the SSc group should be interpreted in the context of the severity of pretransplant esophageal dysfunction. Exclusion of significant esophageal disease is recommended by the International Society for Heart and Lung Transplantation guidelines (15), given the association between GER and up-regulation of alloreactivity in the post-transplant setting, as evidenced by prior animal (16) and non-SSc human data (17). As such, it is of interest that our SSc group did not experience inferior post-transplant outcomes given the high frequency of severe esophageal dysfunction.

Table 6. Prevalence of severe esophageal dysfunction

	SSc (%)	Matched Cohort w/DFLD (%)	*P* Value
Severe esophageal dysfunction*	54	8	<0.0001
MED† ⩾ 20 mm	69	17	<0.0001
Esophageal AFL†	57	10	<0.0001
Both MED ⩾ 20 mm and AFL	54	8	<0.0001
Aperistalsis on manometry	17	—	—

Definition of abbreviations: AFL = air fluid level; DFLD = diffuse fibrotic lung disease; MED = maximal esophageal diameter; SSc = systemic sclerosis.
Prevalence of severe esophageal dysfunction between the SSc group and the diffuse fibrotic lung disease subgroup of the matched group.
*Severe esophageal dysfunction was defined as either aperistalsis by manometry or the combination of MED ⩾ 20 mm and AFL.
†MED and AFL were assessed by pre–lung transplant computed tomography chest imaging.

In a prior report, Sottile and coworkers also concluded that their SSc group had post-transplant survival comparable to a non-connective tissue disease (CTD) pulmonary fibrosis control (4). Surprisingly, their SSc and control groups were indistinguishable on the basis of the frequency of esophageal dysfunction as determined by DeMeester scoring or manometry. In support of these findings, however, prior work by Murphy and coworkers compared the esophageal testing of SSc and non-CTD groups with esophagitis and similarly observed no differences in DeMeester scoring (18). Nevertheless, compared with non-CTD, the SSc group was discernable by markedly prolonged acid clearance (despite paradoxically fewer reflux events), a direct consequence of the distal esophageal absent contractility and retained esophageal fluid (i.e., air fluid level) that is characteristic of SSc (18).

Importantly, in contrast to DeMeester scoring, prolonged acid clearance has been demonstrated by several authors to be the main determinant of end-organ damage (i.e., esophagitis [19] and aspiration [20]) related to GER, consequently rendering patients with SSc with severe esophageal dysfunction at particularly increased risk for recurrent aspiration in the post-transplant setting.

In an effort to best represent the extent of prolonged acid clearance and the risk for recurrent aspiration resulting from esophageal dysfunction in our SSc group, we defined severe esophageal dysfunction as distal esophageal absent contractility, demonstrated either by manometry (gold standard [11]) or CT chest imaging–based morphometry (presence of esophageal air fluid level and maximum esophageal diameter ⩾ 20 mm). We resorted to esophageal morphometry as the best available surrogate for esophageal manometry, given that manometry was only available in 40% of our SSc group.

The morphometry-based definition is anchored in prior work by Stevens and coworkers (21) in which all patients with SSc with radiographic evidence for distal esophageal dilatation (i.e., increased

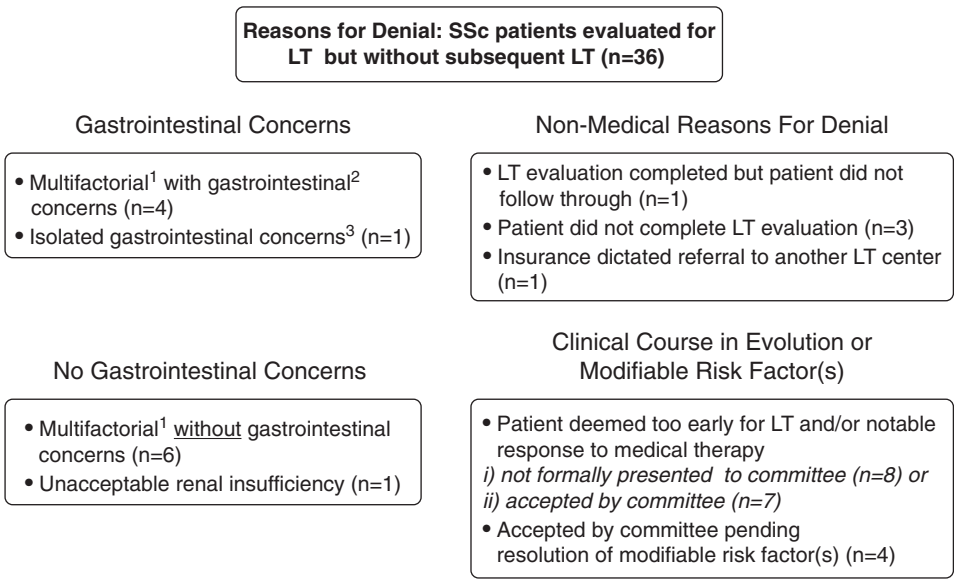

Figure 4. The reasons for lung transplantation (LT) denial for the 36 patients with systemic sclerosis (SSc) referred to the University of California Los Angeles Lung Transplant Program over the 12-year study period. [1]Multifactorial includes one or more of the following: age, prior pectus deformity surgery, moderate to severe aortic stenosis, renal insufficiency, body mass index ⩾ 40, restrictive cardiomyopathy, history of papillary thyroid cancer, abnormal neuropsychiatric testing, multiple prior transient ischemic attacks, recurrent lower extremity ischemic ulceration. [2]Gastrointestinal concerns included one or more of the following: clinically uncontrolled gastroesophageal reflux despite optimal medical therapy and lifestyle modifications, recurrent esophageal dilation due to achalasia, severe gastric dysmotility. [3]This patient had recurrent episodes of clinically overt aspiration pneumonia requiring hospitalization despite optimal medical therapy for gastroesophageal reflux.

maximum esophageal diameter) and retained esophageal fluid (i.e., air fluid level) displayed manometry findings consistent with esophageal absent contractility. Importantly, a maximum esophageal diameter of 20 mm or more and the presence of air fluid level by CT chest are demonstrated in only 0.2 and 1% of normal subjects, respectively, further supporting these conservative criteria for defining severe esophageal dysfunction.

On the basis of our definition, 60% of the SSc–lung transplant group met criteria for severe esophageal dysfunction. The overall survival of this SSc subgroup (n = 19) was no different than the SSc subgroup (n = 16) without severe esophageal dysfunction. In our SSc–lung transplant group, ~80% had abnormal maximum esophageal diameter (≥15 mm), ~70% had maximum esophageal diameter greater than or equal to 20 mm, and ~60% had air fluid level, all supporting abnormal esophageal morphometry and motility.

Because prior investigators have suggested that the most appropriate comparator diagnostic group for SSc–lung transplant is diffuse fibrotic lung disease (22), we compared the pretransplant CT chest imaging of SSc–lung transplant to the diffuse fibrotic lung disease subgroup from our matched group. We discovered the SSc–lung transplant group had significantly increased maximum esophageal diameter, frequency of maximum esophageal diameter in the infraaortic location (i.e., distal esophagus), frequency of air fluid level, and frequency of patulous esophagus when compared with this subgroup, further corroborating distinctly abnormal SSc-related esophageal morphometry and our definition for severe esophageal dysfunction.

Given the strong predisposition to marked prolonged acid clearance in SSc and subsequent end-organ damage (i.e., aspiration) likely to be most evident in our SSc group with severe esophageal dysfunction, one may have expected to find suboptimal post–lung transplant allograft function. One possible explanation for the lack of obvious extraesophageal post-transplant manifestations may be related to secondary or compensatory proximal esophageal contractions that likely result from distal esophageal dilatation (18, 23). This hypothesis merits further study to clarify the proximal esophageal and upper esophageal sphincter responses to the distal esophageal dilatation that is characteristic of SSc.

In the post–lung transplant setting of chronic acid suppression and immunosuppression and provided the constant risk for aspiration in SSc, we also evaluated the frequency of all post-transplant microbiologic isolates with a focus on organisms most associated with aspiration pneumonia, including gram-positive cocci, gram-negative rods (24), and *Mycobacterium* species (25, 26). Despite significant esophageal dysfunction in SSc, there was no microbiologic evidence post–lung transplant to suggest increased aspiration or differential colonization compared with the other groups.

To assess for a selection bias in offering lung transplant to patients with SSc at our institution, we reviewed all SSc referrals for lung transplant consideration to specifically determine how pretransplant esophageal disease affected transplant candidacy. Of the 36 referrals with SSc who were not offered lung transplant at our institution during the 12-year study period, a gastrointestinal concern was part of a multifactorial list of concerns in 4 patients with SSc and was the only concern for a single patient with SSc. This one patient suffered from recurrent, clinically overt aspiration pneumonia requiring repeated hospitalization despite maximal medical therapy for esophageal dysfunction. These findings suggest that SSc–lung transplant referrals to the UCLA lung transplant program are rarely being denied on the basis of concerns related to esophageal disease.

The assessment of esophageal dysfunction and its role in lung transplant candidacy at UCLA is strongly based on clinical assessment, with consideration of the total burden of gastrointestinal disease on the basis of the battery of pretransplant testing (5). Since our prior proposed algorithm for the consideration of SSc for lung transplant, our current approach to severe esophageal dysfunction remains unaltered (5). As such, regardless of the objective findings on the basis of formal pretransplant esophageal testing, the principal determinant of SSc–lung transplant candidacy at our center is the demonstration of quiescence (or near quiescence) of GER symptomatology with optimal medical management, often established only after repeated multidisciplinary clinical assessments. In addition, our immediate and early post-transplant feeding regimen for SSc–lung transplant recipients is no different from the regimen we apply for patients without SSc and, importantly, does not include protocolized enteral feeding, (gastro)jejunostomy placement, or fundoplication.

Our SSc pretransplant clinical assessment and approach to esophageal dysfunction as well as the subsequent post-transplant survival are reminiscent of the experience reported by the transplant group at the University of California, San Francisco (4). In contrast, the lack of a coordinated, multidisciplinary approach to the clinical assessment of esophageal dysfunction in the pre–lung transplant setting may, in part, explain the increased 1-year mortality post–lung transplant reported by Bernstein and coworkers (27) for SSc compared with diffuse fibrotic lung disease in a recent nationwide cohort study based on the United Network for Organ Sharing database.

To our knowledge, this is one of the largest and most comprehensive single-center reports of lung transplant for SSc. Our experience is the first to incorporate the following detailed assessments: a comparison of SSc to the entire lung transplant experience, primary graft dysfunction grade at 72 hours, post-transplant microbiologic isolates, an account of referred patients with SSc subsequently denied lung transplant, and an analysis of pretransplant CT chest parameters supporting abnormal esophageal morphometry and severe esophageal dysfunction.

Limitations

Our study has several limitations. The retrospective study design is prone to bias, including selection bias and the issue of missing data. Our definition for severe esophageal dysfunction required morphometry assessments based on pre–lung transplant CT chest imaging because manometry (gold standard) was not performed in all lung transplant recipients. As SSc–lung transplant remains an uncommon indication for lung transplant, our sample size was relatively small, which raises the potential for type II error; nonetheless, this report represents one of the largest reported single-center SSc–lung transplant experiences to date.

Conclusions

In this retrospective, single-center study, we found that post–lung transplant SSc survival and other relevant outcomes, including primary graft dysfunction, acute rejection, BOS, and microbiology of respiratory isolates, were no different in comparison to the non-SSc, diffuse fibrotic lung disease, and matched groups. Similar outcomes were observed despite severe esophageal dysfunction demonstrated in the SSc group. Furthermore, esophageal dysfunction was uncommonly the only reason or among a list of multifactorial reasons for lung transplant denial.

Esophageal morphometry may be an interesting noninvasive marker of esophageal dysfunction in patients pre–lung transplant and warrants further study. Future studies of lung transplant for patients with SSc should focus on a battery of pre–lung transplant esophageal testing that best objectively reflects prolonged acid clearance and the risk for recurrent aspiration. We believe this report will provide a strong foundation on which to consider the patient with SSc with advanced lung disease for lung transplant, even in the setting of severe esophageal dysfunction. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the nursing coordinators and assistants of the UCLA Lung Transplant and Pulmonary Hypertension Programs.

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