Survival and early outcomes following lung transplantation for interstitial lung disease associated with non-scleroderma connective tissue disease: a national cohort study

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Abstract

Objective

The progressive decline in interstitial lung disease associated with non-scleroderma connective tissue disease (ILD-NSCTD) is linked to poor prognosis and frequently results in respiratory failure. Lung transplantation (LTx) offers a viable treatment option, yet its outcomes in ILD-NSCTD remain contentious, particularly across different subtypes.

Methods

This retrospective cohort study included patients with idiopathic pulmonary fibrosis (IPF) (n=11,610) and ILD-NSCTD (n=610) listed in the United Network for Organ Sharing (UNOS) database who underwent lung transplantation between May 5, 2005, and December 31, 2022. We used the Kaplan-Meier method to evaluate cumulative survival rates and logistic regression to assess the risk of post-operative complications.

Results

Compared to IPF patients, those with ILD-NSCTD are generally younger, with a lower proportion of male and white patients. After propensity matching, overall survival rates remained similar between the groups (log-rank, p=0.953). However, ILD-NSCTD was associated with a significantly higher risk of post-operative stroke (adjusted OR 1.75, 95% CI 1.12-2.74, p=0.015) and longer post-operative hospital stays (p<0.001). Subgroup analyses yielded consistent results. Finally, infection was identified as the leading cause of death.

Conclusion

Compared to IPF, patients with ILD-NSCTD have a significantly higher risk of post-operative stroke and extended hospital stays, potentially due to complications inherent to ILD-NSCTD. However, the underlying causes of these outcomes remain unclear. Despite these differences, short-term and long-term survival rates are comparable between the two groups, with consistent findings across various ILD-NSCTD subgroups. Therefore, ILD-NSCTD should not be regarded as a relative contraindication for lung transplantation. Nonetheless, the influence of extra-pulmonary complications in ILD-NSCTD patients requires further investigation.

Key words

connective tissue disease, interstitial lung disease, scleroderma, lung transplantation, idiopathic pulmonary fibrosis

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Introduction

Connective tissue disease (CTD) is a systemic disorder affecting multiple organs, including systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), polymyositis/dermatomyositis (PM/DM), Sjögren's syndrome (SS), rheumatoid arthritis (RA), and systemic sclerosis (SSc). The lung is frequently involved in CTD, often presenting as interstitial lung disease (ILD). Although CTD-associated ILD (CTD-ILD) and idiopathic interstitial pneumonias, such as idiopathic pulmonary fibrosis (IPF), share similar clinical and pathological features, their treatment strategies and prognoses differ significantly (1).

Pulmonary progression in CTD is often linked to poor prognosis, leading to respiratory failure and death (2, 3). For patients with end-stage CTD-ILD complicated by severe respiratory failure, lung transplantation (LTx) may be the only viable treatment. However, unlike IPF, CTD often affects other extrapulmonary systems, such as gastroesophageal reflux (GER), renal insufficiency, and myositis (1), raising concerns about the suitability of LTx. Consequently, some lung transplant centres consider CTD a relative contraindication, resulting in fewer CTD-ILD patients undergoing LTx compared to those with IPF. As of 2006, the International Society for Heart and Lung Transplantation (ISHLT) guidelines still listed CTD-ILD as a rare indication for LTx, representing only 0.5% of cases (4). Despite advances in surgical techniques and a significant increase in LTx procedures over the past 30 years, CTD patients continue to comprise only 0.9% of recipients (5).

ILD is a common manifestation across various CTDs (6-8), and studies have shown that CTD patients hospitalised with ILD have a ten-fold higher mortality risk compared to those without pulmonary involvement (9). For these patients, LTx may be the only effective treatment. However, research on LTx outcomes in CTD-ILD patients is limited and often contradictory, with few studies addressing specific CTD subtypes. This scarcity of data hinders informed decision-making for LTx in end-stage CTD-ILD patients. To address this gap, our study leverages multicentre data from the UNOS database (2005-2022) to systematically analyse post-operative complications and long-term survival in CTD-ILD patients undergoing LTx.

Methods

Study population

We conducted a retrospective cohort study using data from the United Network for Organ Sharing (UNOS) database, including patients who underwent lung transplantation between May 5, 2005 (the start of the lung allocation score era), and December 31, 2022. The study group comprised patients with CTD-ILD, including lupus, MCTD, PM, SS, SSc and RA, Since there were only two patients with SSc, we did not include this population in the study. Therefore, we defined the cohort of CTD-ILD as ILD-NSCTD. while the control group included patients with IPF. Exclusion criteria were as follows: (1) missing survival data, (2) paediatric transplants, (3) multi-organ transplants, (4) repeat transplants, and (5) lobar transplants, (6). less data systemic sclerosis. The Institutional Review Board of the First Affiliated Hospital of Guangzhou Medical University determined that formal review was not required for this study.

Clinical characteristics

We collected data on recipient characteristics, including age, gender, ethnicity, body mass index (BMI), preoperative diabetes status, preoperative dialysis status, lung allocation score (LAS), type of lung transplant, human leukocyte antigen (HLA) mismatch, pre-transplant medical condition, life support Extracorporeal Membrane Oxygenation (ECMO), waitlist days, and donor characteristics such as age, gender, diabetes status, and ischaemic time.

Outcome events

The primary outcome was overall survival, defined as the time from transplantation to death. Secondary outcomes included the length of hospital stay, use of ECMO at 72 hours postoperatively, acute rejection episodes, ventilator support, and post-operative

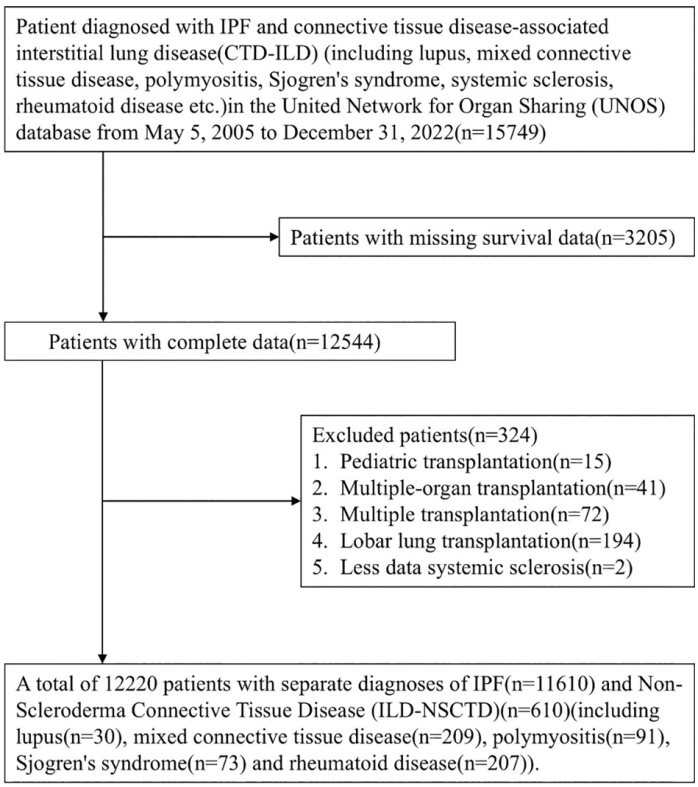

Fig. 1. Flow chart of the study.

complications such as airway dehiscence, dialysis, and stroke. Survival rates were calculated at 90 days, 1 year, 5 years, and 10 years, alongside the causes of death.

Statistical methods

Continuous variables were summarised as medians with interquartile ranges (IQR), and categorical variables as frequencies and percentages. T-tests or Kruskal-Wallis tests were used for inter-group tests for continuous variables, and Chi-square tests were used for component tests for categorical variables. Univariable and multivariable mixed-effects logistic regression was performed to assess post-operative risks in ILD-NSCTD patients compared to IPF patients. Based on established biological knowledge, we preselected covariates for multivariable models, including age, gender, ethnicity, BMI, diabetes status, pre-transplant dialysis, lung allocation score, type of lung transplant, HLA mismatch, pre-transplant medical condition, life support ECMO, waitlist days, and donor characteristics (age, gender, BMI, diabetes status, and ischaemic time).

Overall survival was analysed using the Kaplan-Meier method and log-rank test. To control confounding among patients with different primary diseases undergoing lung transplantation, we employed a Cox proportional hazards model and conducted a 3:1 propensity score matching analysis as a sensitivity analysis. All analyses were performed using Stata 17 software (StataCorp LP, College Station, TX).

Results

Overall cohort

The patient inclusion and exclusion process is illustrated in Figure 1. The final analysis included 12,220 patients from the UNOS database between May 5, 2005, and December 31, 2022. Of these, 11,610 patients (95.01%) had IPF, and 610 patients (4.99%) had ILD-NSCTD. Specifically, the ILD-NSCTD group comprised 30 patients with lupus (0.25%), 209 with MCTD (1.71%), 91 with PM (0.75%), 73 with SS (0.60%), and 207 with RA (1.70%).

Clinical and sociodemographic characteristics

ILD-NSCTD patients were younger (median age 58 [IQR 49–64] years vs 64 [IQR 58–68] years, $p<0.001$), had a lower proportion of males (38.36% *vs*. 74.12%, $p<0.001$), and a lower proportion of white patients (51.48% *vs*. 81.53%, $p<0.001$) compared to IPF patients. ILD-NSCTD patients also had a lower BMI (median 26.91 [IQR 23.48–29.69] *vs*. 27.26 [IQR 24.43–29.76], $p=0.010$), a higher lung allocation score (median 46.03 [IQR 39.89–62.51] *vs*. 45.15 [IQR 38.75–60.68], $p=0.029$), a higher proportion of bilateral sequential lung transplants (77.05% *vs*. 60.20%, $p<0.001$), a lower need for ECMO support (3.93% *vs*. 5.25%, $p=0.005$), and a longer waiting time (median 47 [IQR 16–163] days *vs*. 34 [IQR 11–97] days, $p<0.001$). Regarding donor characteristics, ILD-NSCTD patients had a lower proportion of male donors (44.26% *vs*. 58.18%, $p<0.001$) and a longer ischaemic time (median 5.30 [IQR 4.25–6.57] hours *vs*. 5.17 [IQR 4.13–6.23] hours, $p=0.019$). No significant differences were observed in recipient diabetes, pre-transplant dialysis, HLA mismatch, pre-transplant medical condition, or donor age, BMI, and diabetes status (Table I).

Outcomes after lung transplantation

ILD-NSCTD patients had a higher incidence of post-operative stroke compared to IPF patients (3.93% *vs*. 2.30%, $p=0.034$; Table II). Univariate analysis (OR 1.74, 95% CI 1.14–2.66, $p=0.011$) and multivariate analysis (OR 1.75, 95% CI 1.12–2.74, $p=0.015$; Table III) confirmed this elevated risk.

Additionally, a higher proportion of ILD-NSCTD patients required ECMO at 72 hours post-operatively (9.18% *vs*. 4.16%, $p<0.001$) and mechanical ventilation for ≥5 days (29.34% *vs*. 19.31%, $p<0.001$). Univariate analysis showed increased risks for these outcomes (OR 1.67, 95% CI 1.24–2.24, $p=0.001$ and OR 2.09, 95% CI 1.18–3.71, $p=0.012$, respectively). However, multivariate analyses revealed no significant differe–ces compared to IPF (OR 1.24, 95% CI 0.89–1.73, $p=0.201$ and OR 1.63, 95% CI 0.90-2.96, $p=0.108$, respectively).

There were no significant differences in rates of post-operative airway dehiscence, post-operative dialysis, or acute rejection between the groups. Both

univariate and multivariate analyses showed similar risks for these complications in ILD-NSCTD and IPF patients.

Survival

Unadjusted analysis revealed no significant differences in overall survival rates at 90 days, 1 year, 5 years, and 10 years between ILD-NSCTD and IPF patients (log-rank, p=0.147, Fig. 2A). After propensity score matching, survival rates remained similar (log-rank, p=0.953, Fig. 2B). Survival was better with bilateral sequential transplantation than with single-lung transplantation, but no statistically significant differences were seen between the ILD-NSCTD and IPF groups (Fig. 3).

Infection was the leading cause of death post-lung transplantation in both groups, with a higher incidence in ILD-NSCTD patients compared to IPF patients (26.67% *vs*. 18.67%, p=0.005, Table II). It is worth noting that IPF patients is much more likely to die from malignant than ILD-NSCTD patients (13.25% *vs*. 4.15%, p<0.001, Table II).

Subgroup analysis

Patients with lupus, MCTD, PM, SS, and RA were significantly younger than IPF patients (median ages 52.5 [IQR 40–62], 55 [IQR 46–63], 53 [IQR 46–59], 60 [IQR 51–64], and 61 [IQR 55–66] years, respectively, p<0.001, Supplementary Table S1). The proportion of males was lower in all ILD-NSCTD subgroups (lupus 10.00%, MCTD 30.62%, PM 48.35%, SS 24.66%, and RA 50.72% *vs*. IPF 74.12%, p<0.001). Most patients in the MCTD, SS, RA, and PM subgroups were White (p<0.001). SS patients had the lowest BMI (median 25.13 [IQR 22.91–28.49], p=0.003). Lupus and MCTD patients had higher rates of bilateral sequential lung transplantation (83.33% and 81.34%, p<0.001). SS patients had the longest median waiting time (94 [IQR 27–219] days), followed by lupus and MCTD patients. A higher proportion of lupus patients required ICU care pre-transplant (p=0.026). Lupus, MCTD, and SS patients had a smaller proportion of male donors (33.33%, 38.76%, and 36.99%, respectively, p<0.001) and longer ischaemic times (p=0.033). No significant differences were observed in recipient diabetes, pre-transplant dialysis, HLA mismatch, lung allocation score, pre-transplant medical condition, donor age, or BMI among the subgroups.

Post-operatively, lupus, MCTD, and PM patients had higher probabilities of requiring dialysis (16.67%, 10.53%, and 10.99%, respectively, p=0.009, Suppl. Table S2). Lupus patients had a higher incidence of stroke (10.00%, p=0.022). MCTD and RA patients had higher ECMO support requirements (12.44% and 8.21%, p<0.001). The median length of hospital stay post-transplant was longest for lupus patients (24.5 [IQR 12.5–38.5] days), followed by MCTD (19 [IQR 13–37] days) and PM (19 [IQR 14–38] days) patients (p<0.001). Lupus patients also had the highest proportion of ventilator support lasting ≥5 days (40.00%, p<0.001).

Five-year survival rates were 52.84% for lupus, 53.75% for MCTD, 60.10% for PM, 65.04% for SS, and 62.78% for RA, compared to 54.24% for IPF patients. Survival analysis showed no significant differences in overall survival at 90 days, 1 year, 5 years, and 10 years between ILD-NSCTD subgroups and IPF patients (p=0.416, Fig. 4). Infection remained the leading cause of death in all groups, with RA patients showing a significantly higher infection-related mortality post-lung transplantation compared to IPF patients (35.48% *vs*. 18.67%, p=0.009, Suppl. Table S2).

Table I. Recipient-donor characteristics of ILD-NSCTD and IPF patients and procedural details.

	ILD-NSCTD	IPF	*p*-value
n	610 (4.99%)	11610 (95.01%)	
Recipient characteristics			
Age, year (IQR)	58 (49 to 64)	64 (58 to 68)	<0.001
Male	234 (38.36%)	8605 (74.12%)	<0.001
Ethnicity			<0.001
White	314 (51.48%)	9466 (81.53%)	
Black	152 (24.92%)	634 (5.46%)	
Asian	36 (5.90%)	318 (2.74%)	
Other/missing	108 (17.70%)	1192 (10.27%)	
BMI, kg/m^2 (IQR)	26.91 (23.48 to 29.69)	27.26 (24.43 to 29.76)	0.010
Diabetes	98 (16.07%)	2239 (19.29%)	0.080
Pre-transplant Dialysis	1 (0.16%)	23 (0.20%)	0.361
Lung allocation score	46.03 (39.89 to 62.51)	45.15 (38.75 to 60.68)	0.029
Type of lung transplant			<0.001
Bilateral sequential	470 (77.05%)	6989 (60.20%)	
Single right	59 (9.67%)	2151 (18.53%)	
Single left	81 (13.28%)	2470 (21.27%)	
HLA mismatch ≥5	389 (63.77%)	7188 (61.91%)	0.527
Medical condition before transplant			
In ICU	93 (15.25%)	1414 (12.18%)	0.074
Hospitalised not in ICU	61 (10.00%)	1265 (10.90%)	
Not hospitalised	456 (74.75%)	8931 (76.93%)	
Life support ECMO	24 (3.93%)	610 (5.25%)	0.005
Waitlist days (IQR)	47 (16 to 163)	34 (11 to 97)	<0.001
Donor characteristics			
Age, years (IQR)	35 (24 to 48)	33 (23 to 47)	0.083
Male	270 (44.26%)	6755 (58.18%)	<0.001
BMI, kg/m^2 (IQR)	25.60 (22.49 to 29.15)	25.54 (22.58 to 29.26)	0.801
Diabetes	45 (7.38%)	931 (8.02%)	0.081
Ischaemic time (hours) (IQR)	5.30 (4.25 to 6.57)	5.17 (4.13 to 6.23)	0.019

ILD-NSCTD: interstitial lung disease associated with non-scleroderma connective tissue disease; IPF: idiopathic pulmonary fibrosis; IQR: interquartile range; BMI: body mass index; HLA: human leukocyte antigen; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation.

Discussion

Lung transplantation is the only effective treatment for end-stage CTD-ILD. However, due to the multisystem involvement of CTDs, some transplant centres consider CTD-ILD a relative contraindication. Potential adverse outcomes include gastroesophageal reflux disease (which may lead to bronchi-

Table II. Outcomes after lung transplant in patients with ILD-NSCTD and IPF.

	ILD-NSCTD	IPF	*p*-value
n	610	11610	
Post-operative airway dehiscence	11 (1.80%)	181 (1.56%)	0.503
Post-operative dialysis	51 (8.36%)	742 (6.39%)	0.138
Post-operative stroke	24 (3.93%)	267 (2.30%)	0.034
Acute rejection episode	43 (7.05%)	918 (7.91%)	0.466
Length of stay Tx to discharge (IQR)	19 (13 to 34)	16 (11 to 27)	<0.001
ECMO at 72 hours	56 (9.18%)	483 (4.16%)	<0.001
Ventilator support			<0.001
None	13 (2.13%)	340 (2.93%)	
<48h	290 (47.54%)	6853 (59.03%)	
48h-5 days	119 (19.51%)	1937 (16.68%)	
≥5 days	179 (29.34%)	2242 (19.31%)	
Unknow/missing	9 (1.48%)	238 (2.05%)	
Long-term survival			
90-day survival, % (95%CI)	93.19% (90.84%-94.96%)	94.45% (94.01%-94.86%)	
1-year survival, % (95% CI)	85.80% (82.62%-88.43%)	86.58% (85.93%-87.21%)	
5-year survival, % (95% CI)	58.99% (53.77%-63.83%)	54.24% (53.17%-55.30%)	
10-year survival, % (95%CI)	28.69% (20.47%-37.43%)	25.74% (24.55%-26.94%)	
Median survival, years (95% CI)	6.55 (5.75-7.55)	5.60 (5.45-5.82)	0.147
Long-term survival in single lung transplant			
90-day survival, % (95%CI)	90.94% (85.19%-94.54%)	93.17% (92.51%-93.78%)	
1-year survival, % (95% CI)	81.48% (74.29%-86.83%)	83.12% (82.14%-84.05%)	
5-year survival, % (95% CI)	50.89% (41.62%-59.42%)	46.84% (45.46%-48.22%)	
10-year survival, % (95%CI)	21.03% (11.79%-32.07%)	18.39% (17.18%-19.64%)	
Median survival, years (95% CI)	5.18 (3.68-7.14)	4.60 (4.44-4.78)	0.361
Long-term survival in bilateral sequential lung transplant			
90-day survival, % (95%CI)	93.41% (90.76%-95.32%)	93.53% (92.94%-94.06%)	
1-year survival, % (95% CI)	86.63% (83.10%-89.47%)	86.11% (85.29%-86.89%)	
5-year survival, % (95% CI)	61.71% (55.77%-67.09%)	58.48% (57.17%-59.77%)	
10-year survival, % (95%CI)	35.34% (26.10%-44.68%)	33.73% (32.17%-35.30%)	
Median survival, years (95% CI)	6.78 (6.08-8.48)	6.66 (6.41-6.90)	0.368
Cause of death			0.001
Graft failure	30 (13.82%)	921 (15.37%)	0.536
Infection	57 (26.67%)	1,119 (18.67%)	0.005
Cardio- or cerebrovascular	22 (10.14%)	601 (10.03%)	0.957
Pulmonary	40 (18.43%)	987 (16.47%)	0.444
Haemorrhage	7 (3.23%)	79 (1.32%)	0.018
Malignancy	9 (4.15%)	794 (13.25%)	<0.001
Multiple-organ failure	11 (5.07%)	256 (4.27%)	0.569
Renal failure	4 (1.84%)	81 (1.35%)	0.540
Other	3 7 (17.05%)	1156 (19.29%)	0.412

The *p*-values reflect the outcomes of Pearson's chi-square test or Fisher's exact test as applicable, except for the comparison of median survival, which was assessed using the log-rank test.
[a] *p*-values for cause of death represent the overall chi-square test, while the individual *p*-values compare each cause as a binary variable.

olitis obliterans syndrome), renal disease (complicating the management of post-transplant immunosuppressants and antibiotics), and extrapulmonary conditions such as myositis (affecting immunosuppression and rehabilitation). These concerns contribute to ongoing debate regarding the suitability of lung transplantation for CTD patients. As a result, CTD patients undergo lung transplantation at lower rates compared to other diseases, and there is variability among transplant centres in candidate selection and evaluation. The potential adverse outcomes of transplantation, particularly early post-operative recovery, remain inconclusive (1, 10, 11).

Our findings indicate that ILD-NSCTD patients exhibit similar survival rates to IPF patients. Post-operative complications such as the need for dialysis, airway dehiscence, and acute rejection are also comparable. Although ILD-NSCTD patients have a higher incidence of ECMO use at 72 hours post-surgery and require respiratory support for more than five days, multivariable-adjusted risks are similar between the two groups. However, ILD-NSCTD patients have a significantly higher risk of post-operative stroke and prolonged hospital stays.

Given the characteristics of autoimmune diseases, ILD-NSCTD patients are younger, with a higher proportion of females and a lower proportion of non-whites compared to IPF patients (12-14). These differences reflect the accurate selection of these populations in the UNOS database. Despite a higher incidence of extrapulmonary complications, such as oesophageal motility disorders and renal failure, ILD-NSCTD patients showed no significant differences in pre-transplant variables compared to IPF patients, suggesting a high degree of selectivity. This implies that ILD-NSCTD candidates may be selected based on factors that equalise survival and other post-transplant outcomes, at least partially. For example, ILD-

Table III. Additional outcomes after lung transplant for patients with ILD-NSCTD *vs*. IPF .

Outcome	OR	95% CI	p-value
Post-operative airway dehiscence	1.15	(0.62-2.13)	0.646
Post-operative dialysis	1.34	(0.99-1.80)	0.054
Post-operative stroke	1.74	(1.14-2.66)	0.011
Acute rejection episode	0.88	(0.64-1.21)	0.447
ECMO at 72 hours	1.67	(1.24-2.24)	0.001
Ventilator support			
<48h	1.11	(0.63-1.95)	0.725
48h-5 days	1.61	(0.90-2.88)	0.111
≥5 days	2.09	(1.18-3.71)	0.012
[a]Adjusted			
Post-operative airway dehiscence	1.31	(0.68-2.52)	0.414
Post-operative dialysis	1.21	(0.88-1.66)	0.235
Post-operative stroke	1.75	(1.12-2.74)	0.015
Acute rejection episode	0.74	(0.53-1.04)	0.079
ECMO at 72 hours	1.24	(0.89-1.73)	0.201
Ventilator support			
<48h	1.14	(0.64-2.04)	0.661
48h-5 days	1.42	(0.78-2.60)	0.256
≥5 days	1.63	(0.90-2.96)	0.108

OR: odds ratio; CI: confidence interval; ECMO: extracorporeal membrane oxygenation.
[a] Multivariable models are adjusted for age, sex, race, body mass index, diabetes, pre-transplant dialysis, lung allocation score, type of transplant, HLA mismatch, medical condition before transplant, life support ECMO, waitlist days waitlist days and donors' age, BMI, diabetes and ischaemic time.

NSCTD patients rarely exhibit significant renal insufficiency, are relatively younger, and have fewer comorbidities. To mitigate potential biases arising from differences in baseline characteristics, we conducted a 3:1 propensity score matching analysis. The analysis revealed no significant differences in overall survival rates at 90 days, 1 year, 5 years, and 10 years between ILD-NSCTD and IPF patients, as well as across lung transplant types, consistent with recent findings from several large centres (15-17). These results align with those observed in various single-centre datasets worldwide (18-20). Although ILD-NSCTD and IPF share similar pathological processes, lung transplantation fundamentally improves these processes.

However, the pathogenesis of ILD-NSCTD and IPF differs significantly, as do their pre-transplant treatment regimens. The diverse extrapulmonary complications associated with ILD-NSCTD present significant challenges for post-transplant management, complicating the assessment of their impact on prognosis. For example, Ju *et al*. found a significantly higher incidence of primary graft dysfunction (PGD) in CTD-ILD patients compared to IPF patients (90.3% *vs*. 70.4%, p=0.03) (19). Yang *et al*. reported that PGD and ICU duration were independent contributors to survival outcomes in age- and sex-adjusted analyses (20). Conversely, Park *et al*. reported no significant difference in the incidence of PGD between CTD-ILD and IPF patients (18). Moreover, Prieto-Peña *et al*. found a lower incidence of acute graft rejection in CTD-ILD patients compared to IPF patients, while chronic graft rejection showed no significant difference (21). Multicentre studies have similarly found no significant differences in PGD, acute rejection, or chronic rejection between the two groups (15).

Our findings support these observations, showing no significant differences in ECMO use at 72 hours post-surgery or in the need for prolonged respiratory support between ILD-NSCTD and IPF patients. However, ILD-NSCTD patients have a notably higher risk of post-operative stroke and extended hospital stays, likely related to the nature of the disease. ILD-NSCTD is often a chronic inflammatory condi-

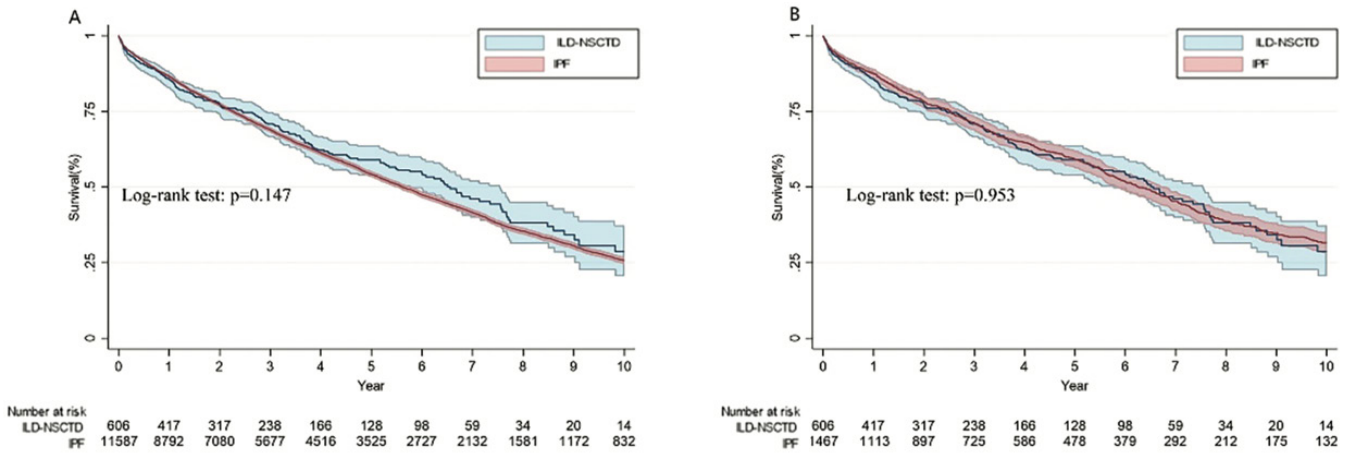

Fig. 2. Kaplan-Meier survival curves for lung transplant recipients with ILD-NSCTD and IPF.
A: Kaplan-Meier survival curves for lung transplant recipients with ILD-NSCTD and IPF, unadjusted.
B: adjusted. The unadjusted and adjusted models showed no significant difference in overall survival rates between patients with ILD-NSCTD and IPF after lung transplantation.
ILD-NSCTD: interstitial lung disease associated with non-scleroderma connective tissue disease; IPF: idiopathic pulmonary fibrosis.

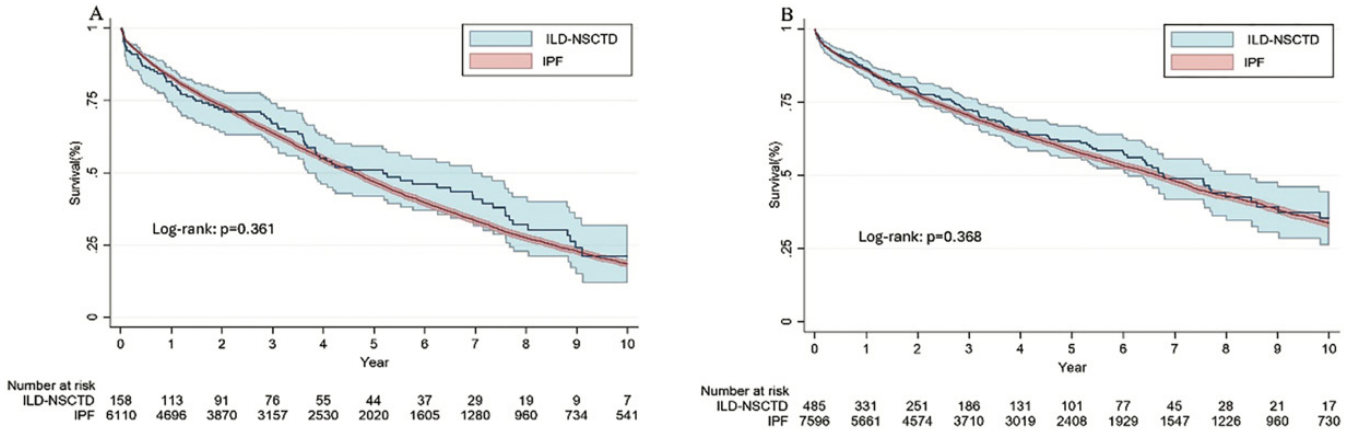

Fig. 3. Kaplan-Meier survival curves for lung transplant recipients with ILD-NSCTD and IPF in different transplantation types.
A: Kaplan-Meier survival curves for single lung transplant recipients with ILD-NSCTD and IPF.
B: Kaplan-Meier survival curves for bilateral sequential lung transplant recipients with ILD-NSCTD and IPF. The were no significant difference in overall survival rates between patients with ILD-NSCTD and IPF both in single lung transplant and bilateral sequential lung transplant.
ILD-NSCTD: interstitial lung disease associated with non-scleroderma connective tissue disease; IPF: idiopathic pulmonary fibrosis.

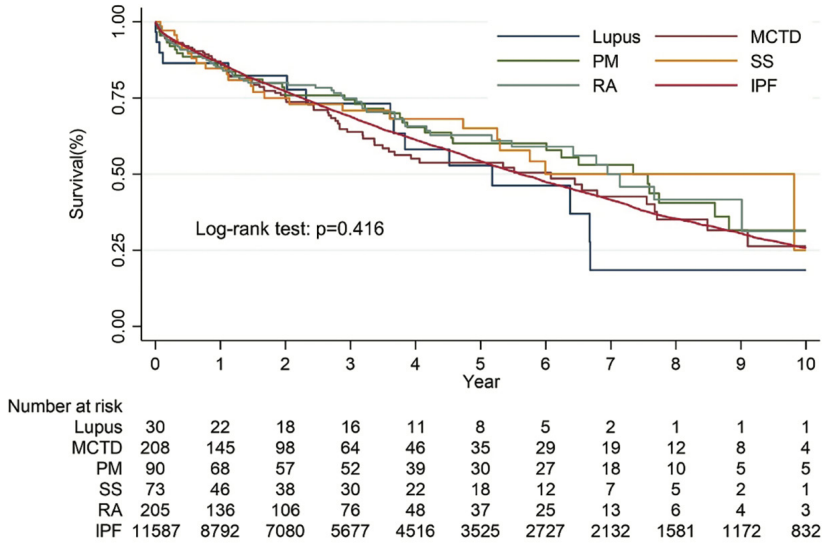

Fig. 4. Kaplan-Meier survival curves for lung transplant recipients by thoracic diagnosis. There were no significant differences in overall survival between ILD-NSCTD subgroups and IPF.
MCTD: mixed connective tissue disease; PM: polymyositis; SS: Sjogren's syndrome; RA: rheumatoid disease; IPF: idiopathic pulmonary fibrosis.

tion caused by immune system abnormalities, leading to a hypercoagulable state or vasculitis due to autoantibody-mediated vascular damage (22), increasing stroke risk. Additionally, prolonged hospital stays may result from extracorporeal complications such as oesophageal motility disorders, necessitating the placement of feeding tubes or gastrojejunostomy tubes for enteral nutrition before discharge. However, these data were not captured in the UNOS registry, making it difficult to rule out other factors, such as inconsistencies in diagnostic and treatment protocols across transplant centres.

Our cause-of-death analysis indicates that infection is the leading cause of mortality post-lung transplantation in both ILD-NSCTD and IPF patients, with ILD-NSCTD patients showing a higher probability of infection-related death (26.67% *vs*. 18.67%, p=0.005). Previous studies have demonstrated that CTD patients are at increased risk of respiratory failure due to their susceptibility to respiratory infections (23). In fact, infectious pneumonia is the most common cause of respiratory failure in CTD patients admitted to intensive care units (24). This increased risk may be attributed to immune dysregulation, prolonged immunosuppressive therapy, and a high incidence of aspiration, particularly in systemic sclerosis (SSc) or polymyositis/dermatomyositis (PM/DM) patients. Early post-operative infection prevention is therefore crucial for ILD-NSCTD patients. It is interesting to note that the percentage of deaths from malignancy is significantly higher in IPF patients than in ILD-NSCTD, and in fact, transplant recipients are significantly more likely to develop cancer than the general population (25), and in the most recent report of the ISHLT, cancer was the second most common cause of death in patients between 5 and 10 years post-transplantation (17.3%) and in patients more than 10 years post-operatively (17.9%) (26), and the cause of death was similar in IPF patients, and then ILD-NSCTD was much lower than this, even though previous studies have shown a high association between rheumatic diseases and malignancy (27), which we suspect is related to a high degree of selection of this population, including different autoimmune statuses of the patients and a generally younger age prior to transplantation compared to IPF.

Despite shared clinical and pathological features across CTDs, significant differences exist in the prevalence and patterns of ILD among CTD subtypes. For instance, lupus has a low prevalence of ILD (4–13%), while systemic sclerosis shows a high prevalence (up to 91% in some studies). The prevalence in other

CTDs, such as RA, SS, MCTD, and idiopathic inflammatory myopathies, falls between these extremes (22). Our subgroup analysis revealed similar demographic characteristics and overall survival rates among ILD-NSCTD subgroups. However, lupus patients had the highest risk of stroke, consistent with previous research indicating that lupus patients are at higher risk for stroke and myocardial infarction (28). RA patients had the highest risk of infection-related mortality, supported by evidence showing that high-dose prednisone increases infection risk in RA-ILD patients (29).

Our study has several limitations. First, there is some missing data across sociodemographic, clinical, and outcome variables, though this is unlikely to significantly affect ILD-NSCTD patients. The UNOS database also lacks information on specific outcomes relevant to ILD-NSCTD, such as PGD incidence, gastrointestinal or oesophageal complications, and comorbidities. This omission limits our ability to conduct a more detailed analysis.

In addition, there were only two patients with SSc combined with ILD that we could retrieve in our database, so limiting our analysis of this population, although previous studies have demonstrated that carefully screened patients SSc combined with ILD have similar short- and long-term survival compared to patients with ILD-NSCTD (30). Moreover, although this is the largest study on lung transplantation for ILD-NSCTD to date, the limited number of ILD-NSCTD patients may reduce the power to detect small differences compared to IPF patients. Finally, we could not verify each subject's diagnosis through medical record review. Despite this, multidisciplinary discussions at participating medical centres ensured accurate diagnoses based on established criteria.

Conclusion

Compared to IPF patients, those with ILD-NSCTD have a significantly higher risk of post-operative stroke and prolonged hospital stays, likely due to comorbidities associated with ILD-NSCTD, though the exact causes remain unclear. Despite these differences, both groups demonstrate comparable short-term and long-term survival rates, with consistent outcomes across various ILD-NSCTD subgroups.

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