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CONSENSUS STATEMENT

ISHLT consensus document on lung transplantation in patients with connective tissue disease: Part I: Epidemiology, assessment of extrapulmonary conditions, candidate evaluation, selection criteria, and pathology statements

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Patients with connective tissue disease (CTD) and advanced lung disease are often considered suboptimal candidates for lung transplantation (LTx) due to their underlying medical complexity and potential surgical risk. There is substantial variability across LTx centers regarding the evaluation and listing of these patients. The International Society for Heart and Lung Transplantation-supported consensus document on lung transplantation in patients with CTD standardization aims to clarify definitions of each disease state included under the term CTD, to describe the extrapulmonary manifestations of each disease requiring consideration before transplantation, and to outline the absolute contraindications to transplantation allowing risk stratification during the evaluation and selection of candidates for LTx.
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According to the 2019 International Society for Heart and Lung Transplantation (ISHLT) Registry report, the proportion of lung transplants performed in patients with end-stage lung disease related to connective tissue disease (CTD) is small (0.9%).[1] Among lung transplant (LTx) recipients with CTD, rheumatoid arthritis (RA)-lung disease is the most common (28.71%), followed by undifferentiated CTD (21.36%). Whether LTx is an acceptable treatment option for patients with CTD can be controversial due to medical and surgical risks. Particular concerns pertain to the potential risk for aspiration due to esophageal dysmotility, gastroesophageal reflux (GERD), and an association between the upper gastrointestinal (GI) pathology and an increased risk for early chronic lung allograft dysfunction (CLAD).[2] The 2014 ISHLT consensus document for the selection of LTx candidates suggests that patients with CTD can be acceptable candidates if there are no extrapulmonary contraindications for transplantation,[3] however there is substantial variability between LTx centers regarding the evaluation and listing of these patients.

The goals of this consensus paper are to clarify definitions of each disease state included under the term CTD, to describe the extrapulmonary manifestations of each disease requiring consideration prior to transplantation, and to outline the absolute contraindications to transplantation as determined by a Delphi consensus methodology.[4] The purpose of this effort is to allow for risk stratification during the evaluation and selection of candidates for LTx and heart-lung transplantation (HLTx). For this document, we classified disease states under the term of CTD as either:

- Systemic sclerosis (SSc)
- Sjögren's syndrome (SS)
- Rheumatoid arthritis (RA)
- Systemic lupus erythematosus (SLE)
- Inflammatory myopathies (polymyositis (PM), dermatomyositis (DM), and antisynthetase syndrome)
- Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA/Churg-Strauss syndrome) and microscopic polyangiitis (MPA)
- Mixed connective tissue disease (MCTD) and overlap syndromes

Methodology

In 2019, an expert Writing Committee was convened by the ISHLT with the aim to develop a consensus recommendations focusing on specific recommendations for LTx and heart-lung transplant (HLTx) in patients with CTD. After an open invitation to ISHLT members, an international workgroup was created. This consensus represents a collaborative effort from international experts in the specialties of Pulmonary, Pulmonary Hypertension, Pharmacy, Pathology, Nursing and Allied Health, and Rheumatology.

The Writing Committee was divided into 12 subgroups covering the following topics: (1) connective tissue disorders including definitions of disease states, extrapulmonary conditions, LTx evaluation, and contraindications for LTx, (2) CTD -related pulmonary hypertension and cardiomyopathy, (3) surgical management and unique challenges in patients with CTD, (4) Anesthetia considerations in the CTD population, (5) intensive care unit challenges and management in CTD transplant recipients, (6) pharmacology therapy of CTD: pre- and post-transplant, (7) surgical management of esophageal disorders in CTD transplant recipients, (8) post-transplant management of CTD transplant recipients, and (9) pathology of CTD as it pertains to LTx and HLTx. A comprehensive literature search and review was performed for each topic to answer the identified questions based on the published evidence and to provide guidance based on prevailing expert knowledge and experience. This consensus was divided in three parts to provide a comprehensive review of the salient topics within cardiothoracic transplantation of patients with CTD. Part I which is discussed here reviews the epidemiology, extrapulmonary conditions, pathology, candidate evaluation, and selection criteria considerations for transplantation for each CTD.

Recommendations regarding evaluation, testing, and absolute contraindications for transplantation were made based on voting by the members of the workforce. The strength of the workforce agreement was based on a Delphi method voting.[4] The voting range for each participant was from 0 to 9, with 0 as no agreement with the statement and 8 to 9 as high agreement. A consensus agreement was considered to be present when ≥80% of workforce members voted 8 or higher. The percentage of responders was also recorded. Based on poor agreement results for the proposed absolute contraindications in the first survey, a second-round survey was sent using the responder's comments from round I to

modify the statements for the round II survey. Of note, only nurses, pulmonologists, and surgeons who were directly involved in the LTx and HLTx clinical evaluation and selection were asked to respond to this second-round survey. For each statement on the round II survey, the agreement was also calculated as the percentage of respondents who endorsed at a level 8 or higher.

Connective tissue diseases: Assesment of extrapulmonary conditions, specific recommendations for lung transplant evaluation, and agreement strength

The involvement of a multidisciplinary team in the evaluation of these complex patients is strongly advised. Rheumatology evaluation is recommended to confirm disease diagnosis, assess disease activity, and evaluate for active extra-pulmonary disease. The workgroup's LTx evaluation recommendations specific for each CTD and the agreement strength are summarized below in Tables 1-6.

Systemic sclerosis

Systemic sclerosis (SSc) is a chronic autoimmune collagen vascular disease that often leads to life-threatening visceral involvement, including interstitial lung disease (ILD), cardiac disease, and renal disease.[5,6] Patients with SSc can have extrapulmonary clinical manifestations which can negatively impact the patient's transplant candidacy as summarized in Table 1.

Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic multi-system autoimmune inflammatory exocrinopathy.[19] Secondary Sjögren's syndrome may accompany other CTDs such as RA, SSc, SLE, and PM/DM. Lung involvement by SS is characterized by constrictive bronchiolitis and lymphoproliferative disease in approximately 9% to 20% of patients with primary SS (pSS).[20] SS patients have important extrapulmonary conditions that may be relevant in the evaluation and management of a potential LTx and HLTx candidate (Table 2).

Rheumatoid arthritis

RA is the most common systemic autoimmune disease, with an overall prevalence of 0.5% to1%.[40] Pulmonary manifestations of RA include ILD, airway disease, pleural disease, pulmonary vascular disease, and musculoskeletal involvement.[41,42] RA-lung disease is the second most common cause of death behind secondary cardiac disease.[43] RA also has other non-pulmonary clinical organ involvement, which can be relevant for lung transplant candidacy and post-transplant management. These concerning extrapulmonary conditions are included in Table 3.

Systemic lupus erythematosus

Pulmonary involvement in SLE includes ILD, pleural disorders, pulmonary hypertension, and diaphragmatic disorders. Shrinking lung syndrome (SLS) is a rare manifestation of SLE that is typically seen in women. However, if present, this uncommon complication of SLE could have serious implications for lung transplant candidacy. It is manifested by an elevated hemidiaphragm with evidence of restrictive pulmonary function testing. These patients are typically not noted to have a radiographically evident pleural or parenchymal disease on imaging.[50-52] Extrapulmonary conditions of SLE which can affect both LTx candidacy and post-transplant clinical outcomes are detailed in Table 4.

Polymyositis, Dermatomyositis, and antisynthetase syndrome

There are four primary types of inflammatory myopathies (IM), but it is PM, DM, and a subset of these termed *antisynthetase syndromes* that are associated with ILD. Antisynthetase syndrome has a much higher prevalence of ILD than the other IM, with ILD involvement in approximately 90% of cases.[70,71] The concerning extrapulmonary features of PM/DM which can be relevant during transplant candidate evaluation and listing are sumarized in Table 5.

ANCA-Associated Vasculitis

ANCA-associated vasculitis (AAV) includes GPA, EGPA/Churg-Strauss syndrome, and MPA.[87,88] Vasculitides are often classified by the type (arteriole, venule, etc.) and size (small, medium, or large) of the vessel (s) involved. GPA is the most common vasculitis for which lung transplantation has been reported. However, the multi-organ involvement in GPA can increase the complexity of a lung transplant candidate, which in turn makes the optimal timing of referral hard to define. Patients with AAV can develop granulomatous airway inflammation. Subglotic stenosis, the most common airway complication of vasculitis, can be very severe and requires adequate management before transplantation. A single area of focal stenosis is usually treatable[89]; however, multiple mass lesions, multiple areas of stenosis, or tracheobronchomalacia is more problematic.

The concerning extrapulmonary features of vasculitis to consider during LTx evaluation and listing are include in Table 6.

Mixed connective tissue disease

The definitive diagnosis of mixed connective tissue disease (MCTD) is often complicated because the characteristic overlapping features of SLE, SSc, RA, and IM, found in association with high titers of anti-U1 ribonucleoprotein (RNP) antibody, tend to occur sequentially. The extrapulmonary clinical manifestations in patients with CTD relevant for LTx evaluation and selection are primarily associated with the dominant disease of the overlapping CTD.

Table 1 Extrapulmonary Manifestations and Transplant Evaluation Specific to Systemic Sclerosis: Recommendations and Agreement Strength

Extrapulmonary manifestations(references)		Specific transplant evaluation (Testing agreement strength = 87%)
Cardiac [7]	• Myocarditis, congestive heart failure, pericarditis, or a conduction defect requiring treatment. • Occurs in 7% to 39% of patients.	• CMRI if an echocardiogram suggests restrictive cardiomyopathy, an abnormal rhythm on holter monitor, or suspected myocarditis. • Myocardial biopsy to confirm active inflammation.
VTE [8-11]	• Increased risk if antiphospholipid antibodies (aPLs) are present. • Occurs in 10% to 43% of patients.	• Hypercoagulable evaluation for risk of thrombophilia[a]. • Hematology evaluation for patients with APL to assess risk post-transplant.
Renal: Scleroderma renal crisis (SRC) [12-15]	• Risk factors include: rapid progression of skin fibrosis, diffuse cutaneous SSc, disease duration ≤ 4 years, presence of anti-RNA polymerase III antibodies, tendon friction rubs, anemia, and high-glucocorticoid use (prednisone >15 mg/day). • Occurs in 5% to 85% of patients. • Hypertension-induced acute renal failure has been reported in SSc kidney transplant recipients taken cyclosporine.	• Assess patients who are at risk for SRC post-transplant. • Check anti-RNA polymerase III antibodies
GI [16,17]	• Ineffective or absent esophageal peristalsis leading to GERD. Occurs in 75% to 80% of patients. • Gastroparesis. Affects up to 50% of patients. • Small intestinal bacterial overgrowth (SIBO) leading to malabsorption and malnutrition. Occurs in 30% to 60% of patients.	• A multidisciplinary approach with a gastroenterologist, nutritionist, and SLP. • Symptoms of GERD and gastrointestinal dysmotility should be assessed and documented. • Measurement of GERD with a 24-hour dual pH probe study with impedance testing and manometry. • CT chest imaging may reveal esophageal dysfunction such as dilation and the presence of air-fluid levels. • Evaluation by a thoracic surgeon for patients with severe GERD and esophageal dysfunction to assess whether the esophageal pathology is surgically salvageable and to guide the best indicated anti-reflux procedure pre- or post-LTx. • Assess oropharyngeal dysphagia and aspiration risk. • Nutritionist evaluation should include patient education on lifestyle modifications, diet, positional and timing of feeding post-LTx.
Vascular: Raynaud's phenomenon [18]	• Digital ischemia occurs as a result of secondary vasospasm due to compromised arterial supply due to thrombosis, vasculopathy, vasculitis, embolic, and traumatic. Occurs in up to 95% of patients with SSc. • Digital ulcers can be present in 30% to 50% of patients with SSc. • Digit(s) amputation due to ischemia can occur in 20% of patients.	• Rheumatology evaluation to assess RP severity and identify risk for significant vascular involvement and digital loss. • Measure the presence and number of vascular-insufficiency ulcers in the last 12 months and the timing to resolution. • Arterial-doppler studies of upper and lower limbs in patients with severe symptomatic RP and recurrent necrotic lesions.

Abbreviations: CT, computed tomography; GERD, gastroesophageal reflux disease; GI, gastrointestinal; LTx, lung transplant; MRI, magnetic resonance imaging; RP, raynaud's phenomenon; SRC, scleroderma renal crisis; SLP, speech and language pathologist; SSc, systemic sclerosis; VTE, venous thromboembolism.

[a]In those patients with a family or personal history of venous thromboembolism.

Survival and prognosis of patients with CTD after lung transplantation

Lung transplant (LTx) outcomes in patients with CTD have been reported in several case series. Transplant centers in both US and Europe have consistently reported that outcomes in patients undergoing LTx for SSc are comparable to those in patients transplanted for other ILD.[100-104] Despite the high frequency of severe esophageal dysmotility and GERD, patients with SSc do not appear to be at an increased risk for CLAD compared with other patients with ILD. Severe pulmonary arterial hypertension (PAH) and high body mass index (BMI) are high-risk factors for poor LTx survival in SSc.[102]

Table 2 Extrapulmonary Manifestations and Transplant Evaluation Specific to Primary Sjögren's Syndrome: Recommendations and Agreement Strength

Extrapulmonary manifestations(references)		Specific transplant evaluation (Testing agreement strength = 82%)
Oncologic/Hematologic [19-24]	• Patients with pSS have a 15-20-fold risk of developing malignant lymphoid disorders. • BCL occurs in 5% of patients, usually NHLs, with MALT being the predominant histology. • B-cell NHLs are identified in organs with active pSS, mostly the salivary glands. The nasopharynx, orbits, stomach, thyroid, and lung can also be affected. • Risk factors for BCL in patients with SS are detailed below[a]. • BCL is associated with an 8-fold risk of mortality among patients with pSS. • The potential impact of transplant-related immunosuppressive therapy on the development of new BCL following transplantation remains uncertain, as does the rate of relapse/recurrence of previously treated BCL and secondary carcinomas. • Cytopenias occur in 30% to 60% of patients with SS. Most common are anemia (20%), leukopenia (16%), and thrombocytopenia (13%) Severe thrombocytopenia ($<50 \times 10^9$/L) is found in less than 3% of patients. • Monoclonal gammopathy of undetermined significance (MGUS) has been reported in 10% to 15% of patients, and is associated with risk of developing multiple myeloma (MM).	• Screen for risk factors for development of BCL. • PET scan if ESSDAI index[b] $\geq$ 5 with 3 or more risk factors for BCL and further evaluation by rheumatology and oncology is warranted. • UPEP/SPEP if suspect paraproteinemias/dysproteinemias, MGUS, and MM. • Serum cryoglobulins.
Immunologic [25-27]	• Hypergammaglobulinemia occurs in 20% to 50% of patients with SS. • Hypogammaglobulinemia occurs in 5% to 20% of patients with SS. • Low IgG level has been associated with increased bacterial, fungal, and viral infections. • Low IgG has also been associated with shorter time to progression to post LTx bronchiolitis obliterans syndrome (BOS).	• Check immunoglobulins levels (IgG, IgA, IgM) particularly in patients who have been treated with rituximab or mycophenolate and for those patients who have had an autologous stem cell transplant to assess risk of infections post-transplant.
VTE [28-32]	• pSS is associated with an 8-fold increased of PE, 4-fold increased of DVT, and 7-fold increased risk of VTE.	• Hypercoagulable evaluation to assess patients at risk[c].
GI[33-35]	• GI manifesttaions of SS include xerostomia, dysgeusia, oropharyngeal dysphagia, esophegal reflux, constipation or diarrhea, and abnormal liver function test. Occurs un up to 60% of patients with SS. • Xerostomia can predispose to dental caries and periodontal disease and may also results in poor esophageal acid clearance, which in turn can predispose to esophageal abnormalities. • Atrophic gastritis and chronic pancreatiris can lead to dyspepsia. • Patients with SS are at risk for development of primary biliary cirrhosis. Occurs in 21% to 31% of patients with SS.	• A multidisciplinary approach with a gastroenterologist, nutritionist and SLP. • Symptoms of GERD, esophageal dysmotility, and oropharyngeal dysphagia and aspiration risk should be assessed. • Assess risk for dental caries, periodontal disease, salivary gland calculi and oral candidiasis.
Vasculitis: Dermatological[36]	• Occurs in 10% of patients. • Cutaneous vasculitis includes small vessel cutaneous vasculitis patients with palpable purpura of the lower extremities. • Multiple vessel vasculitis can present with large cutaneous ulcerations as well as visceral involvement mimicking polyarteristis nodosa.	• Rheumatology and dermatology evaluation when presence of cutaneous vasculitis.

(*continued on next page*)

Table 2 (*Continued*)

Extrapulmonary manifestations(references)		Specific transplant evaluation (Testing agreement strength = 82%)
Renal [37-39]	• Renal disease found in 4% to 5% of patients with SS is defined as proteinuria, >0.5 g/day, active sediment, distal renal tubular acidosis, tubular interstitial nephritis (TIN) or glomerulonephritis. • Biopsy data shows that TIN is the predominat lesion in 75% of patients with SS and renal disease with the remaining ~25% of patients having glomerular diasease.	• Nephrology evaluation is warranted when there is a high suspicion for SS-kidney involvement (history of hypertension, kidney stones, muscle weakness and/or polyuria). • Assess for RTA (UA, basic metabolic panel, and potassium level). • Random protein/creatinine if suspicion for TNI and GMN.

Abbreviations: BCL, B-cell lymphoma; DVT, deep vein thrombosis; ESSDAI, sjögren's syndrome disease activity index; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GMN, glomerulonephritis; HTN, hypertension; LTx, lung transplant; MALT, mucosa-associated lymphoid tissue; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PE, pulmonary embolism; PET, positron emission tomography; pSS, primary sjögren's syndrome; RTA, renal tubular acidosis; SS, sjögren's syndrome; SLP, speech and language pathologist; SPEP, serum protein electrophoresis; TIN, tubulointerstitial nephritis; UA, urinalysis; UPEP, urine protein electrophoresis; VTE, venous thromboembolism.

[a]Risk factors for development of BCL in pSS are: recurrent swelling of parotid glands; splenomegaly, lymphadenopathy, or both; purpura; score of >5 on the ESSDAI, rheumatoid factor, cryoglobulinemia; low C4 level; CD4 T cell lymphocytopenia, presence of ectopic germinal centers, focus score >3, germinal mutations in TNFAIDP3. TNFAIP3= tumor necrosis factor alpha—induced protein 3.

[b]ESSDAI= Sjögren's Syndrome Disease Activity Index. Scores range from 0 to 123, with a score of 5-13 indicating moderate activity and a score of ≥ 14 indicating high activity.

[c]In those patients with a family or personal history of venous thromboembolism.

Small, retrospective studies have shown that patients with RA have comparable short and long-term LTx outcomes compared with patients with other non-RA ILD.[105,106]

Few centers have reported the experience of LTx for SLE-associated pulmonary disease. Positive outcomes have been reported for a cohort of 6 patients transplanted for SLE-ILD or SLE-PAH with 3-year survival of 83% and no development of extra-pulmonary complications of SLE over a median follow up of 4-years.[107] In a larger, scientific registry of transplant recipients (SRTR)- based study of 275 patients who underwent LTx for non-scleroderma CTD, including 24 patients with SLE, there were no differences in survival, the occurrence of acute rejection, CLAD, or

Table 3 Extrapulmonary Manifestations and Transplant Evaluation Specific to Rheumatoid Arthritis: Recommendations and Agreement Strength

Extrapulmonary manifestations(references)		Specific transplant evaluation (Testing agreement strength = 81%)
Upper airway[44,45]	• Crycoarythenoid joint arthritis involvement manifest as hoarseness and inspiratory stridor. Occurs in 30% of patients. • Laryngeal involvement obstruction occurs in 13% to 75% of patients.	• Neck and chest CT scan and evaluation by OHNS for possible need of an indirect laryngoscopy, in symptomatic patients and those with high suspicion for RA-associated cricoarytenoid joint/laryngeal disease.
MSK involvement [46,47]	• Cervical spine involvement is common in RA and increases the risk for subluxation and spinal cord compression. • Severe erosive arthropathy can impact pre and post-transplant exercise capacity and LTx outcomes. • Occurs in 25% to 34% of patients.	• An axial skeleton MRI to assess atlantoaxial joint stability and risk for subluxation and spinal cord compression in symptomatic patients and those with high suspicion for atlantoaxial involvement.
Neurologic [48,49]	• Sensorimotor neuropathy or mononeuritis multiplex can affect patient's ability to participate in rehabilitation pre and post-transplant and contribute to deconditioning. • Occurs in 5% to 85% of patients.	• Neurology evaluation for patients with severe symptomatic sensorimotor neuropathy or mononeuritis multiplex.

Abbreviations: CT, computed tomography; LTx, lung transplant; MSK, musculoskeletal; MRI, magnetic resonance imaging; OHNS, otolaryngology head and neck surgery; RA, rheumatoid arthritis.

Table 4 Extrapulmonary Manifestations and Transplant Evaluation Specific for Systemic Lupus Erythematosus: Recommendations and Agreement Strength

Extrapulmonary manifestations(references)		Specific transplant evaluation (Testing agreement strength = 82%)
VTE[53-57]	• Anti-phospholipid antibodies (aPLs) are associated with risk for venous thromboembolism, aPLs occur in 35% of patients with SLE. • Kidney transplant recipients with anti-phospholipid syndrome (APS) have increased risk for allograft loss and APS associated clinical events in up to 27% of patients.	• Screening for the presence of anticardiolipin and APS. • Hematology evaluation for patients with APS.
Hematologic[58-63]	• Thrombocytopenia can occur in isolation or conjunction with other hematologic manifestations of SLE, including thrombotic thrombocytopenic purpura (TTP) or APS. • Occurs in 10% to 40% of patients.	• Hematology evaluation in patients with cytopenias.
Neurologic and Psychiatric[64,65]	• Neuropsychiatric systemic lupus erythematosus (NPSLE) can cause cognitive dysfunction, headache, mood disorder, cerebrovascular disease, transverse neuritis, seizures, polyneuropathy, anxiety, and psychosis. • Occurs in up to 80% of patients.	• Neurology and psychiatry evaluation in patients with NPSLR or patients with cognitive dysfunction, headache, mood disorder, cerebrovascular disease, seizures, polyneuropathy, anxiety, or psychosis. • Brain MRI, EEG, and neurocognitive testing based on neurology recommendations.
Renal[66]	• Lupus nephritis occurs in up to 50% of patients with SLE.	• A nephrology consultation for patients with a history of lupus nephritis for assessment of activity of diffuse or focal proliferative lupus nephritis and risk of recurrence.
Cardiac[67-69]	• Pericarditis, autoimmnune vasculitis, endocarditis, and myocarditis occur in up to 50% of patients with SLE. • Premature atherosclerosis. The incidence of myocardial infarction is 5 times higher than in the general population, and in young women. The age specific incidence is increased by a factor of up to 50.	• Cardiology evaluation when suspected SLE-related cardiac disease.

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; NPSLE, neuropsychiatric systemic lupus erythematosus; NCS, nerve conduction studies; SLE, systemic lupus erythematosus; SLS, shrinking lung syndrome.

extrapulmonary organ dysfunction compared with a cohort of 6,346 patients transplanted for idiopathic pulmonary fibrosis (IPF).[106]

Knowledge of LTx outcomes in patients with PM/DM is limited to a few case reports and retrospective review studies. The most extensive data available describes patients from the Organ Procurement Transplantation Network (OPTN) database, who underwent LTx between May 2005 and Sep 2016. Similar 30-day, 1-, and 5-year survival was found in PM/DM patients as compared to those transplanted for IPF.[108]

Very few case reports exist regarding LTx in patients with vasculitis. Published rates of vasculitis relapse following solid organ transplantation are highly variable, with only very few studies available on relapse after LTx. In a case report, a LTx recipient remained relapse-free for 1450 days post-transplant but required treatment with cyclophosphamide and rituximab in addition to post-transplant immunosuppression.[109]

Contraindications for lung and heart-lung transplantation in patients with CTD

Data regarding specific predictors of prognosis after cardiothoracic transplantation in CTD are limited. The consensus group recognizes that the paucity of evidence precludes any strong conclusions about LTx and HLTx contraindications in patients with CTD. A consensus agreement on absolute contraindication was considered to be present when ≥80% of workforce members voted 8 or higher. The relative contraindications were considered when no absolute contraindication agreement was present. While listing absolute and relative contraindications for lung transplantation, the group acknowledges that the willingness to accept any risk may vary between centers, depending on the center's expertise and the local need to ration the limited organ supply. The absolute and relative contraindications specific for each CTD and the agreement strength of the voting survey's questionaries are summarized below in Tables 7-12.

Table 5 Extrapulmonary Manifestations and Transplant Evaluation Specific of Polymyositis/Dermatomyositis: Recommendations and Agreement Strength

Extrapulmonary manifestations(references)		Specific transplant evaluation (Testing agreement strength = 92%)
Oncologic[72-80]	• There is an increased risk of cancer associated myositis (CAM), particularly in patients with DM, and occurs in 6% to 60% of patients . • Adenocarcinoma of the cervix, lung, ovaries, pancreas, bladder, and stomach accounts for 70% of the CAM. Southeast Asian patients are at risk of nasopharyngeal carcinoma. • Risk factors for CAM include: age older than 45, male sex, rapid onset of myositis (<4 weeks), cutaneous necrosis, and cutaneous vasculitis.	• Cancer screening for patients who have risk factors for CAM • Cancer screening for patients ≥40-year- old who have DM or patients ≥ 60-year-old who have PM, and those with a prior history of cancer. • CT scan of the chest, abdomen, and pelvis, given the increased risk for NHL, ovarian, lung, and pancreatic cancer. • A PET scan might be required for further assessment. • Endoscopic studies of the upper and lower GI tract according to the patient's age. • Obtain a pap-smear, testicular examination, mammography, and to check a CA-125 levels and transvaginal ultrasound in women at high risk for ovarian cancer.
Cardiac[81,82]	• Myocarditis can occur in 9% to 72% of patients.	• CMRI if the echocardiogram suggests restrictive cardiomyopathy, if there is an abnormal rhythm on Holter monitoring, or in the context of suspected myocarditis. • Myocardial biopsy to confirm active inflammation.
GI[83,84]	• Weakness of the striated muscle of the upper one-third of the esophagus and/or the oropharyngeal muscles can contribute to dysphagia, nasal regurgitation, dysphania, and/or aspiration. • Occurs in 32% to 84% of patients.	• Symptoms of GERD, esophageal dysmotility, and oropharyngeal dysphagia and aspiration risk should be assessed. A multidisciplinary approach with a gastroenterologist and SLP.
MSK [85,86]	• Myositis can cause severe muscle weakness and frailty, limiting rehabilitation potentials. Occurs in up to 45% of patients. • Involvement of the diaphragmatic and respiratory muscles can cause ventilator insufficiency with both inspiratory and expiratory dysfunction and hypercarbia.	• Assess frailty and rehabilitation potential pre- and post-transplant.

Abbreviations: CAM, cancer associated myositis; CMRI, cardiac magnetic resonance imaging; CT, computed tomography; DM, dermatomyositis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; MSK, musculoskeletal; NHL, non-Hodgkin's lymphoma ;PM, polymyositis; PET, positron emission tomography.

Summary and recommendations on lung transplantation in patients with CTD

Lung transplantation should be considered for CTD patients with advanced lung disease whose clinical status has progressively declined despite maximal medical therapy. Ideally, the candidate should be free of any other organ dysfunction or medical problem that would substantially jeopardize the outcome of transplantation. Early referral to a transplant center is recommended due to the medical complexity inherent to this particular patient population and to determine the potential risk and benefits of LTx. An earlier evaluation may identify modifiable risk factors that would influence a patient's candidacy for transplantation or their survival after lung transplantation.

SSc Recipient pulmonary phenotype proposal: Discussion and recommendations

Based on the extent of ILD and hemodynamic profiles, distinct SSc pulmonary phenotypes can be identified (Figure 1). Understanding outcomes as they relate to phenotypes may help understand outcomes. Goh and colleagues developed a staging system of SSc-associated ILD based on HRCT of the chest that defines ILD as "limited" (<20% of lung area) or

Table 6 Extrapulmonary Manifestations and Transplant Evaluation Specific to ANCA-Associated Vasculitis: Agreement Strength

Extrapulmonary Manifestations(references)		Specific Transplant Evaluation (Testing agreement strength = 83%)
Neurologic [90,91]	• ANCA-associated vasculitis (AAV) can cause a mixed sensorimotor neuropathy, and spinal cord lesions causing transverse myelitis. Other manifestations are psychiatric disorders like psychosis. • Occurs in 15% of patients with GPA and 70% of those with MPA.	• Complete neurologic exam and neurology consultation if suspected neurological involvement. • Assess extent of nerve involvement to improve the combined risk assessment. • EMG and NCS in patients with suspected vasculitic neuropathy to exclude other causes, such as chronic inflammatory demyelinating polyneuropathy (CIDP). • Spine MRI to assess for spinal involvement such as transverse myelitis. • A low threshold for psychiatry evaluation.
Renal [92-93]	• AAV places patients at a higher risk for early renal failure after transplantation due to disease associated with AAV. • Occurs in up to 75% of patients at high risk for relapse.	• Nephrology consultation on all GPA patients and those patients who have pretransplant renal involvement by AAV. • Assess risk factors for vasculitis (EGPA, GPA, or microscopic polyangiitis) relapse including the presence of pulmonary manifestations, anti-PR3 positivity, and ANCA positivity at transplant.
Rheumatologic [94-98]	• Vasculitis relapse after LTx and HLTx is highly variable. • Up to 33% of heart recipients have EGPA relapse after transplant. • Lung disease and anti-PR3 antibody seropositivity are predictors of relapse in up to 73% of patients.	• Rheumatology consultation to evaluate risk for vasculitis relapse after transplant.
Upper and Lower Airway[92,99]	• AAV can affect the sinus, upper and lower airway. Occurs in up to 50% of patients. • Tracheobronchial stenosis has a female and younger age preponderance. Symptoms range from non-specific dyspnea, wheeze or stridor. Occurs in 10% to 30% of patients.	• CT sinus if sinus involvement is suspected. • CT scan of the neck and chest if airway symptoms (i.e., inspiratory wheezing or stridor). • A bronchoscopy might be warranted to assess if tracheobronchial involvement and potential surgical transplant concerns.

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis; EMG, electromyography; GPA, Granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MRI, magnetic resonance imaging; NCS, nerve conduction studies; OHNS, otorhinolaryngology surgery; PET, positron emission tomography.

"extensive" (≥20% of lung area).[6] The 20% cutoff to classify ILD into categories has been associated with mortality differences in patients with SSc.[6] Pulmonary hypertension (PH) in SSc is often multifactorial as both pre and postcapillary PH may be present in an individual patient.[6,110,111] Combined ILD and PH in SSc have been associated with greater mortality compared to ILD or PAH alone.[101-116]

Recommendation: The working group proposes the following classification of pulmonary phenotypes in LTx and HLTx candidates with SSc as predominant ILD, predominant PAH, and combined ILD and PH (Table 13). Classifying SSc in pulmonary phenotypes as proposed above may allow better risk stratification of candidates for LTx. As more information about the association in SSc of ILD and PH with mortality emerges, the cutoff points of these criteria may be updated.

The team agreement strength voting on the proposed SSc pulmonary phenotypes groups was 91.83%.

Histopathological aspects of connective tissue disease

Although there has been increasing awareness of the pulmonary manifestations of CTD over the last several decades, specific histopathological features have yet to be established that provide diagnostic criterion of any of the rheumatologic disorders in the absence of clinical or serological findings. The histopathological findings can include one or more patterns: interstitial, airway, pleural and/or vascular alterations.

Table 7 Contraindications for Lung Transplant Specific to SSc: Absolute Agreement Strength

Absolute Agreement strength (≥80%)		Relative	
Rheumatologic	• Active and uncontrolled extrapulmonary manifestations SSc such as kidney or skin abnormalities (with skin necrosis, uncontrolled non-healing ulcers and secondary infections, or skin thickness impeding rehabilitation) despite maximal therapy. (94%)	Renal	• Poor renal function with CrCl <40 mL/min unless the patient a good candidate for combined lung-kidney transplant.
Gastrointestinal	• Severe swallowing dysfunction with recurrent aspiration, not amenable to therapy. In particular, we recommend avoiding transplantation in patients who have a Penetration Aspiration Scale of 4 or more on more than 1 consistency. (84%) • Severe underlying esophageal dysfunction by achalasia or complete aperistalsis with a DCI of <500 mmHg-s-cm (the Chicago classification of esophageal motility disorders, v3.0) and GERD that may not be surgically salvageable post-transplant or a patient's unwillingness to be NPO with jejunal feedings and comply with dietary modifications after transplant, including diet, tube-feeding, position, and timing. (88%)	Gastrointestinal	• Severe symptomatic gastroparesis as defined by a nuclear medicine gastric emptying test of >35% retention at 4 hours despite maximal medical and surgical therapy. • History of chronic gastrointestinal bleeding (GAVE or "watermelon stomach"). • Barrett's esophagus with high grade dysplasia. • Patulous/dilated esophagus seen on chest CT scan. • History of small intestinal bacterial overgrowth (SIBO) which is NOT well managed on medical therapy. • History of small bowel hypomotility and intestinal pseudo-obstruction.
Cardiac	• Active myocarditis with refractory systolic heart failure despite maximal therapy and not a candidate for combined lung-heart transplant. (98%)	Vascular	• Complicated Raynaud phenomenon not responsive to maximal medical therapy or associated severe digital ulcers, with prolonged wound healing and active infection.

Abbreviations: CT, computed tomography; CrCl, creatinine clearance; DCI, Distal Contractile Integral; GERD, gastroesophageal reflux; NPO, nil per os; SSc, systemic sclerosis.

Explanted specimens, though limited, provide a unique opportunity to study this complicated ILD pathology and to correlate the pathology with imaging studies and the clinical course of a particular disease. With this, a clearer picture of how morphology may predict or correlate with the clinical course becomes feasible. Further, given the histopathologic overlap of pulmonary manifestations of many connective tissue diseases with both acute cellular rejection (i.e., lymphocytic inflammation) and antibody-mediated rejection (AMR) (i.e., capillaritis, organizing pneumonia pattern with neutrophils) and obliterative bronchiolitis in the transplanted lung, an understanding of the patient's CTD may be helpful in the evolution of the patient's post-transplant course for evidence of acute cellular rejection,

Table 8 Contraindications for Lung Transplant Specific to SS: Absolute Agreement Strength

Absolute agreement strength (≥80%)		Relative	
Gastrointestinal	• Severe oropharyngeal dysphagia with recurrent aspiration, not amenable to swallow therapy. In particular, we recommend *not* proceeding with transplant in patients who have a Penetration Aspiration Scale of 4 or more on more than 1 consistency. (80%)	Rheumatologic	• Active SS.
Hematologic	• Patients who are <2-year disease-free interval after treatment of low-grade B-cell lymphoma (MALT & marginal zone lymphoma) and <5-year disease-free interval after treatment of diffuse BCL. (86%.)	Hematologic/oncologic	• Patients who are ≥2-year disease-free interval after treatment of low-grade B-cell lymphoma (MALT & marginal zone lymphoma). • Patients who are ≥5-year disease-free after treatment of diffuse BCL. • Presence of MGUS.

Abbreviations: BCL, B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; MGUS, monoclonal gammopathy of undetermined significance; SS, Sjögren's syndrome.

Table 9 Contraindications for Lung Transplant Specific to RA: Absolute Agreement Strength

Absolute Agreement strength (≥80%)		Relative	
Musculoskeletal/ Neurologic	• Severe unstable atlantoaxial joint with high risk for subluxation and spinal cord compression. (88%) • Symptomatic arthropathy despite optimal disease-modifying anti-rheumatic drug therapy (DMARD) impeding ambulation, and inability to perform pre-and post-transplant pulmonary rehabilitation. (82%)	Musculoskeletal/ Neurologic	• Severe pre-transplant frailty.
		Rheumatologic	• Active ongoing complicated extrapulmonary manifestations like musculoskeletal, or neuro, despite optimal therapy. • Inflammation-related fever with negative infection workup.

antibody-mediated rejection and/or for possible disease recurrence in the transplanted lung. The recommendations for standardization of pathology protocol of explanted lungs and transbronchial biopsies (TBBx) from CTD recipients are summarized in Table 14.

In summary, this protocol proposes a framework for tissue procurement/preservation and sampling to enhance pathological reliability in diagnosis and classification, in the evaluation of pretransplant treatment protocols, and research opportunities in pulmonary manifestation in CTD.[117,118]

Table 10 Contraindications for Lung Transplant Specific to SLE: Absolute Agreement Strength

Absolute Agreement strength (≥80%)		Relative	
Rheumatologic	• Active extrapulmonary manifestations of SLE like kidney, neuro, or cardiac disease despite maximal therapy. (92%)	Hematologic	• Patients with antiphospholipid syndrome (APS). • Patients with Myelodysplastic Syndrome (MDS).
Renal	• Patients who have an active diffuse or focal proliferative lupus nephritis despite maximal therapy or refractory to therapy. (92%)	Renal	• CrCl <40 ml/min unless they are considered candidates for combined lung-kidney transplant.
Cardiac	• Active myocarditis leading to refractory systolic heart failure despite maximal therapy and NOT a candidate for lung-heart transplant. (98%)		
Neurologic/ Pshychiatric	• Active neuropsychiatric complications such as: *a)* SLE cerebritis; *b)* active psychosis; *c)* advanced and/or progression of dementia while on maximal therapy; and *d)* uncontrolled neuropsychiatric lupus symptoms with high risk for non- compliance with medical regimen post-transplant. (99%)		
Musculoskeletal/Respiratory muscle	• Bilateral diaphragmatic muscle weakness and paralysis. (88%) • Evidence of active muscle disease that cannot be controlled with standard post-transplant immunosuppression, or progressive muscle weakness causing severe frailty and unable to perform pre-and post-transplant pulmonary rehabilitation. (98%)	Musculoskeletal/ Respiratory muscle	• Severe pretransplant frailty based on pretransplant assessment. • Unilateral diaphragmatic weakness or paralysis. • Patients with shrinking lung syndrome (SLS) who are considered to be at high surgical risk based on extensive diaphragmatic fibrosis and small chest cavities.

Abbreviations: CrCl= creatinine clearance; SLE, systemic lupus erythematosus.

Table 11 Contraindications for Lung Transplant Specific to PM/DM: Absolute Agreement Strength

Absolute Agreement strength (≥80%)		Relative	
Rheumatologic	• Active extrapulmonary manifestations of PM/DM like musculoskeletal or cardiac despite maximal therapy, assess by myositis disease activity index based on Rheumatologist evaluation. (86%)	Hematologic/Oncologic	• Patients with a risk for cancer associated myositis (CAM). • History of >2-year cancer-free interval combined with a low predicted risk of recurrence (e.g., nonmelanoma localized skin cancer). • History of >5-year cancer-free interval in patients with a history of hematologic malignancy, sarcoma, melanoma, or cancers of the breast, bladder, or kidney.
Gastrointestinal	• Severe oropharyngeal dysphagia with aspiration, not amenable to swallow therapy: PAS ≥ 4 on more than 1 consistency. (88%)		
Cardiac	• Active myocarditis leading to refractory systolic heart failure despite maximal therapy and not a candidate for lung-heart transplant. (99%)		
Musculoskeletal/ Respiratory muscle	• Bilateral diaphragmatic weakness and paralysis. (92%)	Musculoskeletal/ Respiratory muscle	• Severe frailty with an inability to perform pre- and post-transplant pulmonary rehabilitation.

Abbreviations: DM, dermatomyositis; PAS, Penetration Aspiration Scale; PM, polymyosytis.

Table 12 Contraindications for Lung Transplant Specific to Vasculitis: Absolute Agreement Strength

Absolute Agreement strength (≥80%)		Relative	
Rheumatologic	• Ongoing active extrapulmonary manifestations of vasculitis like kidney, skin with non-healing ulcers, or neuro, despite maximal therapy. (96%)	Rheumatologic	• ANCA-positive at the time of transplant.
Airway	• Recurrent extensive subglottic stenosis which is unresponsive to therapy. (82%) • Patients with severe and extensive proximal tracheobronchial disease, particularly multiple mass lesions and severerecurrent stenosis, who are considered high surgical risk or have increased risk for post-transplant morbidity. (94%)	Renal	• CrCl <40mL/min unless they are candidates for combined lung-kidney transplant. • Patients with a Hx AVV (e.g., GPA and MPA) related glomerulonephritis who are considered based on nephrologist evaluation, to be at high risk for relapse and early renal failure after transplantation.
Neurologic	• Active neuropsychiatric complications related to vasculitis such as: *a)* active psychosis; *b)* advance or progression of dementia while on maximal therapy with high risk for noncompliance with medical regimen post-transplant. (98%) • Acute or subacute transverse myelitis within 1 year. (84%) • Mononeuritis multiplex with severe uncontrolled symptoms of pain despite maximal therapy causing severe frailty and interferes to perform pre-and post-transplant pulmonary rehabilitation. (90%)	Neurologic	• History of transverse myelitis.

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; CrCl, creatinine clearance; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, Granulomatosis with polyangiitis; Hx, history; MPA, microscopic polyangiitis.

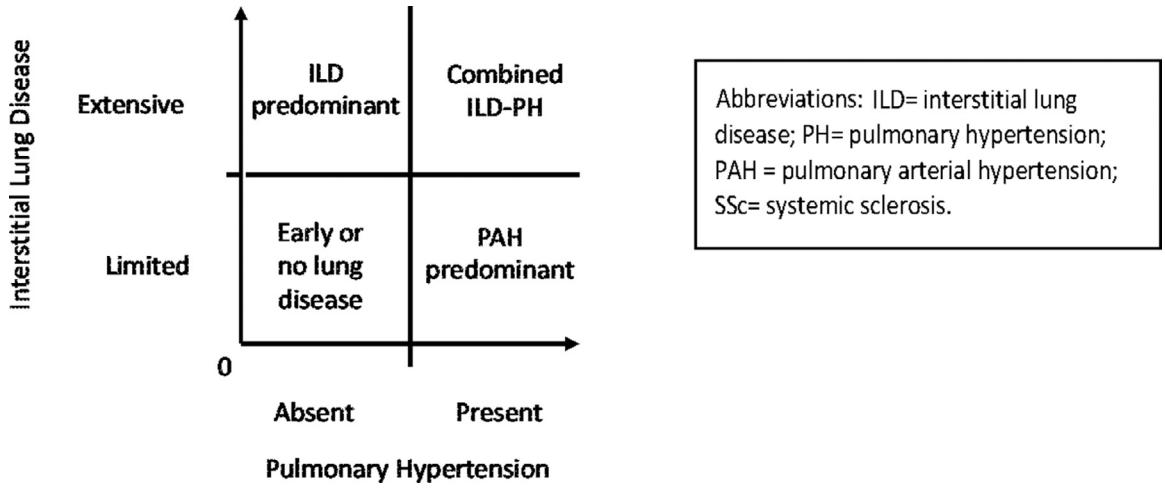

Figure 1 Systemic Sclerosis (SSc) pulmonary phenotypes: Extent of interstitial lung disease (ILD) and hemodynamic Porfiles.

Table 13 Classification of SSc Pulmonary Phenotypes in Lung Transplant Candidates : Proposal

	Predominant ILD	Combined ILD-PH	Predominant PAH
ILD extent on HRCT[a]	≤20%	>20%	≤20%
Hemodynamic Profile	mPAP≤ 20 mmHg PVR < 3 WU PAWP≤15	mPAP >20 mmHg PVR ≥ 3 WU PAWP ≤15	mPAP > 20 mmHg PVR ≥ 3 WU PAWP≤15

Abbreviations: HRCT, high resolution computed tomography; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; WU, wood units.

[a]when indeterminate, ILD predominance determined by forced vital capacity (FVC).

Table 14 Pathology Standardization Protocol of Explanted Lungs and TBBx from CTD Recipients: Recommendations

Lung Explanted Tissue Preparation	Fresh unfixed sample Fresh tissue blocks Snap frozen for molecular analysis Samples should include areas with both heavily involved and less involved pathology
Fixation of Explanted Tissue	Infuse fresh explanted lung through the airways with 10 to 15% buffered formalin at physiologic pressures Fix for a minimum of 3 hours
Macroscope Evaluation/Preparation	Evaluate lung parenchyma for nodules/masses, cavities, fibrosis, vascular disease (thrombosis, hemorrhage), airway diseases (bronchiectasis, obliterative/constrictive bronchiolitis), and pleuritis. Follow institutional protocols, we suggest cutting explant into 2 segments along sagittal plane parallel to hilus, photograph and then sequentially at 0.5 to 1.0 cm intervals along axial plane to permit correlation with CT images.
Unique Microscopic Features in CTD Explants or TBBx from Recipients with CTD	Presence of vasculitis and/or pulmonary hypertensive vasculopathology: • Elastic stains may be helpful Presence of hemosiderin: • Prussian blue or other iron stains may be helpful Presence of foreign material or a giant cell reaction as a manifestation of aspiration: • Bile acid stains remain controversial • Oil red O stain may highlight aspirated fat vacuoles Pediatric population consider BAL staining

Abbreviations: CTD, connective tissue disease; TBBx, transbronchial biopsies.

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