CONSENSUS STATEMENT

ISHLT Consensus Statement on Short Telomere Syndrome and Lung Transplantation

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Motivated by growing evidence that the presence of critically shortened telomeres influences interstitial lung disease (ILD) trajectories and is associated with extrapulmonary conditions relevant to lung transplant candidacy and post-transplant complications, this Consensus Statement aims to address gaps in the evaluation and management of patients with short telomere syndrome (STS). These considerations reflect the work of an international Writing Committee with expertise in STS and are grounded in current literature and expert consensus. The need for this document arises from the recognition that STS is an underdiagnosed contributor to ILD, and that its presence introduces complexities that require dedicated, multidisciplinary attention in the transplant setting.

J Heart Lung Transplant

KEYWORDS:
Lung transplantation; Candidate evaluation; Short telomere syndrome; Telomere biology disorders

1. INTRODUCTION

This document represents a consensus statement to guide clinical practice and research priorities concerning short telomere syndrome (STS) in the context of lung transplant. Motivated by growing evidence that the presence of critically shortened telomeres influences interstitial lung disease (ILD) trajectories, and is associated with extrapulmonary conditions relevant to transplant candidacy and post-transplant complications, we aim to address gaps in the evaluation and management of affected patients.[1–8] We provide recommendations for screening, diagnosis, transplant risk stratification, and peri- and post-transplant care, grounded in current literature and expert

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1053-2498/
https://doi.org/10.1016/j.healun.2025.10.028

consensus. In addition, we identify research priorities in areas where substantial data are lacking. The need for this consensus statement arises from the recognition that STS is an underdiagnosed contributor to ILD, and that its presence introduces complexities that require dedicated, multidisciplinary attention in the transplant setting.

Rather than "telomere biology disorder (TBD)," we have used the term "short telomere syndrome" in our discussion of lung transplant in patients with pulmonary disease manifestations related to critically shortened telomeres.[9] Although we generally consider TBD and STS interchangeable, we have three reasons for using STS. First, patients with ILD and telomere length (TL) below the 10th age-adjusted percentile have pre- and post-lung transplant courses that characteristically differ from those with TL above the 10th percentile, regardless of the presence of pathogenic variants in telomere maintenance genes. The term STS more effectively conveys that short telomere length is the primary consideration in the transplant context as well as the syndromic nature of the associated organ dysfunction. Second, although there are rare variants in telomere maintenance genes that result in phenotypic STS without short TL, the term TBD may not sufficiently differentiate STS from diseases mediated by long telomeres.[10] While these conditions are beginning to be classified as cancer predisposition with telomere lengthening, that nomenclature is evolving. Third, the term STS best aligns with recent statements from the European Respiratory Society and the Pulmonary Fibrosis Foundation on genetic testing in idiopathic pulmonary fibrosis (IPF).[11,12]

2. METHODS

In February 2024, the International Society for Heart and Lung Transplantation (ISHLT) formed a Writing Committee to develop consensus recommendations regarding STS in lung transplant. Drawing on submissions from an open invitation to ISHLT members, the Consensus Statement Chairs selected a Writing Committee with broad representation of international practices and expertise in STS pathophysiology, epidemiology, and pre- and post-transplant pulmonary and extrapulmonary disease manifestations and management. Given limited data in children with STS-related ILD, a representative with clinical experience in the care of pediatric STS lung transplant recipients was included.

The Writing Committee was divided into three Working Groups focusing on pre-transplant, transplant evaluation, and post-transplant considerations for patients with STS. An initial literature search was performed to inform all sections of the document. Medical Literature Analysis and Retrieval System Online, Google Scholar, and Embase were reviewed for studies published through December 1st 2024. The following keywords were used in multiple combinations: short telomere syndrome, telomere biology disorder, lung transplantation, telomere maintenance genes, telomere length measurement, dyskeratosis congenita, bone marrow suppression, immunosuppression, malignancy, and hepatic disease. Case reports, case studies, case control studies, and single and multicenter retrospective and prospective studies were included. Further input was sought from all Working Group members to identify additional literature not found in the initial search and to assess the relevance of each study to the Consensus Document. A study reference library was maintained and updated during the writing and revision process.

Based on discussion and synthesis of the available literature, the Working Groups generated draft recommendations, where appropriate. A formal Delphi voting method was used to review draft recommendations, which were then revised according to input from the entire Writing Committee. There was one initial round of Delphi voting, during which all but one recommendation reached at least 80% consensus. Following a series of virtual meetings and an in person session, all recommendations reached 100% consensus. Consistent with the Standards and Guidelines requirements for ISHLT consensus documents, individual recommendations were not graded by the quality of available evidence.

3. SECTION I. SHORT TELOMERE SYNDROME PATHOPHYSIOLOGY, EPIDEMIOLOGY, AND SCREENING AND DIAGNOSIS DURING LUNG TRANSPLANT EVALUATION

This section reviews the pathophysiology, epidemiology, and clinical manifestations of STS. We describe methods for TL measurement, propose screening strategies for identifying and diagnosing STS in transplant candidates, and highlight the implication of short telomeres for ILD progression and the timing of transplant evaluation.

3.1. Introduction to short telomere syndrome

3.1.1. Telomere structure and function

Telomeres are structures found on the ends of each chromosome and are composed of a repetitive DNA sequence, GGTTAG, and a set of six proteins, termed shelterin, that coat each telomere. Telomeres carry out two essential functions. First, they suppress the DNA damage response at the linear ends of chromosomes, also known as the end protection problem.[13] The end of each chromosome is analogous to a broken piece of DNA and telomeres prevent the recognition and inappropriate repair of chromosome ends that would be catastrophic for genome integrity. This function is carried out by shelterin components that bind the telomere sequence and prevent the activation of DNA damage sensing enzymes. The second role of telomeres is to solve the end replication problem.[14,15] Each time a cell copies its DNA, a small amount of information is lost from the lagging strand. Telomeres provide a buffer that prevents the loss of essential genetic information. While these pathways have been studied for decades in the context of understanding replicative senescence and cellular immortalization, one of their largest impacts on human disease occurs with pulmonary conditions.

3.1.2. Cellular impact of telomere shortening

A unique feature of STS is that the clinical phenotype is largely driven by telomere shortening, rather than specific genetic variants. This distinction is a source of significant confusion and can contribute to the under-recognition of STS. To date, variants in *TERT, TERC, RTEL1, PARN, DKC1, NAF1, TINF2, ZCCHC8*, and *ACD* have been reported to cause pulmonary disease.[16,17] How quickly telomere shortening occurs depends on the specific process that is disrupted and can differ dramatically. For example, variants that modestly reduce telomerase activity can take generations before telomeres shorten sufficiently to cause disease.[18] In contrast, variants in the shelterin component TIN2, encoded by *TINF2*, can cause severe telomere shortening in a single generation. Although the mechanism of shortening and the pace of shortening may be distinct, all defects converge on pathologic telomere shortening. When telomeres reach a functional threshold, they are recognized as a broken piece of DNA and triggers a DNA damage response. This response can result in cellular senescence, a permanent exit from the cell cycle, or apoptosis. Thus, TL limits the number of times a cell can divide and variants that disrupt telomere maintenance can limit cell replicative potential. In general, telomeres shorten with increasing age, contributing to both senescence-related and age-related diseases.[19]

There are three components that contribute to the TL of cells from a given individual: the inherited TL, the replicative history, and the expression of telomerase. As most somatic cells do not express telomerase, TL is dependent on the inherited TL and replicative history. Thus, TL inherited at conception is the “starting point” of telomere shortening and a key determinant of the replicative potential of somatic cells. This feature of TL leads to the phenomenon of genetic anticipation, in which successive generations within a pedigree inherit progressively shorter telomeres. For example, if a variant modestly reduces telomerase activity, the first generation may not have telomeres short enough to cause clinical consequences. In later generations, shorter inherited telomeres increase the likelihood of functional consequences and clinically relevant disease. These unique genetics are often viewed as reflecting variable penetrance of a given variant but more likely result from differences in the TL of individuals. Taken together, patients with defects in telomere maintenance present a unique challenge to physicians and require an understanding of TL dynamics.

3.1.3. Manifestations of short telomere syndrome across the lifespan

Short telomeres cause a spectrum of clinical disorders that manifest differently across the lifespan.[20] In many pedigrees with variants that only moderately disrupt telomere maintenance, pulmonary fibrosis is the primary manifestation. Variants that cause significant disruption in telomere maintenance typically cause marked genetic anticipation. Early generations often present with pulmonary fibrosis, whereas subsequent generations can develop combined liver and/or bone marrow failure. As successively shorter telomeres are inherited in each generation, children can present with dyskeratosis congenita (DC), defined as a triad of nail dystrophy, reticulated skin pigmentation and oral leukoplakia, and bone marrow failure. The precise mechanism for the differing manifestations is unknown but appears to depend on the inherited TL and when telomeres reach a functional threshold.[2] This process can also be altered by exposure histories that may accelerate or alter the clinical presentation. For example, individuals with extensive smoking histories can present at earlier ages and develop

emphysema as opposed to fibrosis.[21] Taken together, the unique clinical presentation requires physicians to be aware of extrapulmonary features that may be present in individuals or their family members.

3.2. Methods of telomere length measurement

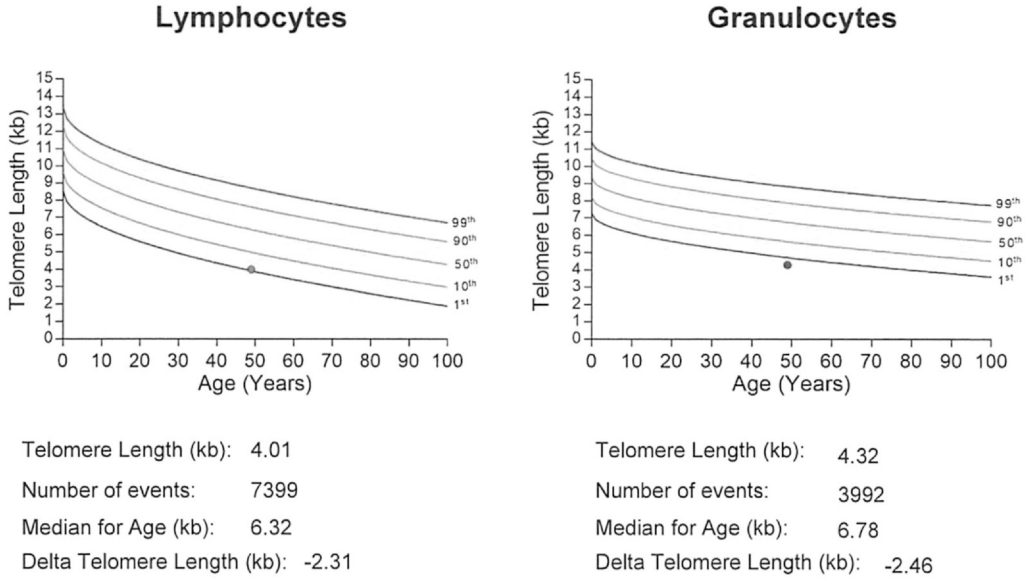
Several methods have been developed for clinical TL measurement. Unfortunately, they are not uniformly available and TL measurement according to an externally reviewed quality standard (such as Clinical Laboratory Improvement Amendments (CLIA) in the United States) is not possible in many areas of the world. Moreover, different methods for measuring TL are available from different testing sites. The lack of uniformity complicates the development of general recommendations about how to interpret TL measurements. Here, we discuss the methods most frequently used in a clinical setting and their strengths and limitations.

TL is most commonly measured in peripheral blood mononuclear cells (PBMCs) as a surrogate measure for TL across tissues. Substantial data support PBMCs as a reasonable surrogate for an individual's TL, and measurement of TL in other tissues is not common in clinical practice.[22,23] TL results used in a clinical setting should include rigorous controls and a comparison with a reference population (Figure 1). The two most widely used methods are quantitative polymerase chain reaction (qPCR) and fluorescence in situ hybridization coupled with flow cytometry (flow-FISH). A number of other methods exist, including single telomere length analysis (STELA), telomere shortest length assay (TeSLA), and short and long read sequencing.[24] Some of these methods may become relevant with assay validation in patient cohorts, but they are not widely available and there is no literature on their application to lung transplant candidates.

3.2.1. qPCR

The qPCR method for estimating TL has been available in the research setting for more than two decades and remains the fastest and least expensive technique.[25] The qPCR assay compares the relative amplification of telomere DNA sequences to a single-copy gene. Results are typically presented as an age-adjusted measurement after comparison with cohorts representing individuals across the age spectrum. Genomic DNA is generally isolated from bulk PBMCs and this method does not distinguish differences in TL between individual cell types. Like all nucleic acid tests, this method is subject to interoperator variability, particularly in less experienced

Figure 1 Sample report illustrating results of telomere length testing by flow cytometry fluorescence in situ hybridization (Flow-FISH) at a Clinical Laboratory Improvement Amendments of 1988 (CLIA) certified laboratory in the United States. The circle on each graph represents the patient's telomere length relative to the expected age-adjusted distribution of the laboratory's reference population. In this example, the 48 year old patient is at the 1st age adjusted percentile for lymphocyte telomere length and below the 1st age adjusted percentile for granulocyte telomere length.



hands.[26,27] If qPCR is the only method available, it should be performed by a laboratory that meets an externally reviewed quality standard (such as CLIA certification in the United States). Because of the potential for interoperator variability, qPCR results should be correlated with STS phenotypic manifestations and genetic testing, when available.[28] Although the absence of a pathogenic variant in a patient with TL < 10th percentile based on qPCR testing does not rule out STS, the presence of a pathogenic variant and/or multiple phenotypic manifestations can support the diagnosis (see 3.3).

3.2.2. Flow-FISH

Flow-FISH is the most clinically validated method and has been in use for more than 15 years.[2] The principle of the test relies on a fluorescently labeled probe that binds specifically to the telomere sequences. Longer telomeres bind more probe than short telomeres. Flow-FISH measures the average TL in individual cells. TL from both lymphocytes and granulocytes is routinely reported, and some testing sites offer assessments of hematologic subsets. The assay includes several internal controls that ensure the test results are reliable, but these multiple controls make the test complex. Flow-FISH requires substantial resources to perform and is not amenable to high throughput testing. Furthermore, flow-FISH requires carefully preserved, viable PBMC for test validity. This limits the assay to transplant programs that can ship fresh blood at room temperature to one of the sites that offer the flow-FISH test. The specificity of flow-FISH is also age dependent due to age-associated decline in TL.

Flow-FISH, performed by a laboratory that meets an externally reviewed quality standard (such as CLIA certification in the United States), is the preferred method for measuring TL. External review ensures rigor and reproducibility, and, as discussed in Section III, flow-FISH-based measurement of lymphocyte TL has been used to evaluate post-transplant outcomes.[28]

3.2.3. Telomere measurement summary

TL measurement assays are not uniformly available, and even where they are available, they are not uniformly applied. Each center tends to develop its own protocols and recommendations for use, often influenced by test cost. Telomere length measurements must be contextualized with other clinical factors and viewed with the limitations listed above. When available, findings should be corroborated with genetic testing in the context of genetic counseling (see 3.5).

RECOMMENDATION.

1. Telomere length should be measured in peripheral blood mononuclear cells using a validated assay that has been referenced to a percentile of a normal population. When available, flow-FISH, performed in a laboratory that meets an externally reviewed quality standard, is the preferred telomere length measurement method.

3.3. Diagnosis of a short telomere syndrome

The exact cut-off for TL that constitutes a STS is debated. STS represents a clinical spectrum, with manifestations that reflect the degree of telomere shortening (particularly TL < 1st percentile), specific organ system involvement, environmental exposures, and underlying genetics, including the presence of pathogenic variants or variants of unknown significance in individual telomere maintenance genes. STS includes patients who have ultra-short telomeres (< 1st percentile), pathogenic gene variants, and ILD, bone marrow failure, cirrhosis, and other organ system dysfunction.[29] Lymphocyte TL < 1st percentile (by flow-FISH) is 97% sensitive and 91% specific for DC, using phenotypically unaffected relatives as the control population.[30] STS, however, may also include patients with short telomeres (1–10th percentile), single organ system dysfunction with no or few other phenotypic manifestations, and no known genetic variants.[31,32]

Despite this heterogeneity, patients with STS have pre- and post-lung transplant courses and complications that characteristically differ from non-STS patients, emphasizing the need for a broad diagnostic perspective.[33] As detailed in Section III, lymphocyte TL ≤10th percentile has consistently been associated with relevant post-transplant outcomes, including cytopenias requiring adjustment in immunosuppression and CMV DNAemia, regardless of the presence of extrapulmonary STS phenotypic manifestations or pathogenic variants.[7,8] In the context of lung transplant, STS diagnosis requires, at a minimum, PBMC TL ≤10th percentile but should also consider the presence of characteristic phenotypic manifestations, and genetic testing, where available. As

reviewed in Sections II and III, the transplant-related implications of TL also depend on the degree of shortening, particularly for patients with ultra-short TL and multiple phenotypic manifestations.

Ongoing research is needed regarding STS diagnosis and characterization of patients with lymphocyte TL > 10th percentile but pathogenic variants in telomere maintenance genes, patients with discordance in lymphocyte and granulocyte TL (lymphocyte > 10th percentile, granulocyte ≤10th percentile), and the role of expanded PBMC (natural killer cells, naive T cells, memory T cells, and B cells) TL measurement.[34] There also remains uncertainty as to what age constitutes early graying, with some centers using a cutoff of less than 25 years old and others using less than 30 or 35.[35] Finally, for patients with prior allogeneic bone marrow transplant (BMT) in whom PBMC TL will reflect bone marrow donor TL, the diagnosis of STS may require genetic testing and TL measurement of non-PBMC tissue.

RECOMMENDATION.

1. The diagnosis of short telomere syndrome in patients undergoing lung transplant evaluation should consider:

- Peripheral blood mononuclear cell telomere ≤10th age-adjusted percentile
- Extrapulmonary phenotypic manifestations including but not limited to early graying of hair, unexplained macrocytosis or cytopenias, unexplained abnormal liver function tests, and family history of interstitial lung disease, cryptogenic cirrhosis, or bone marrow failure syndromes
- Genetic testing, where available

3.4. Prevalence and implications of short telomere syndrome in advanced lung disease

3.4.1. Fibrotic interstitial lung disease

IPF is the most prevalent lung disease associated with STS:[1,20] A TL ≤10th percentile of PBMCs (with no distinction of cellular subtype) is found in ~40% of familial pulmonary fibrosis kindreds.[36] In these families, genetic testing identifies a variant in 30–45% of cases, the majority being variants in telomere-related genes.[2,3] Evidence suggests that these variants increase the risk of developing pulmonary fibrosis in the presence of a second hit (such as smoking, occupational exposure, or autoimmune disease). The role of environmental exposures may account for the appearance of incomplete penetrance in families and variable ILD presentations, including hypersensitivity pneumonitis, unclassifiable fibrosis, and rheumatoid arthritis-related ILD.[37–39] Patients with a telomere-related variant are often younger than sporadic IPF patients.[40] Their chest imaging may demonstrate more diverse radiological patterns, and their clinical course often involves rapid deterioration and progression to severe disease.[41]

In non-familial IPF cohorts, short blood leukocyte TL (≤10th percentile), can be found in 26% to 62% of patients.[4,42] Telomere shortening has been described in multiple worldwide IPF populations.[4,43–47] TL also informs multiple pulmonary fibrosis characteristics. Shorter TLs are associated with more rapid disease progression. The rate of FVC decline is faster for IPF and non-IPF patients with a TL ≤10th percentile versus > 10th percentile.[48] In addition, there is an inverse association between TL and survival for patients with IPF[42,44–46] and chronic hypersensitivity pneumonitis.[49] This association remains robust when analyzing TL as a continuous or dichotomous variable. A TL ≤10th percentile has been found to be an informative cut-off with regards to patient survival.[4,42]

TL can help inform treatment decisions regarding immunosuppression use. For example, TL provides a molecular explanation for the unexpected results in the IPF-PANTHER clinical trial.[4] Worse outcomes (composite of death, lung transplant, FVC ≥10% decline, and hospitalization) were disproportionately present in the group of patients with TL ≤10th percentile who were randomized to the azathioprine/prednisone arm. There was no increase in worse outcomes for those with a TL ≥10th percentile. Subsequent studies have also shown an association between mycophenolate mofetil immunosuppression and increased risk of mortality for patients with STS and non-IPF (hypersensitivity pneumonitis and unclassifiable pulmonary fibrosis) diagnoses.[50,51] Given the risk of disease progression and reduced survival, we recommend a low threshold for referring pulmonary fibrosis patients with short telomeres—as with all patients with progressive interstitial lung disease— to a lung transplant center, absent obvious contraindications. Although most of the available literature involves adult patients, children with fibrotic lung diseases cannot be completely excluded from these recommendations until future research specifies how STS may contribute to pulmonary fibrosis in the pediatric population.

3.4.2. Emphysema

Up to 1% of patients with emphysema, even in the absence of pulmonary fibrosis, have been found to have telomere-related variants.[21,52,53] STS should be considered in patients without alpha-1-antitrypsin deficiency who display severe emphysema at a young age or with a relatively low inhalational exposure to combustible tobacco products or biomass fuel smoke.[21] The contribution of telomere shortening to the risk of more common forms of COPD remains unclear. For example, Mendelian randomization studies suggest that TL, identified from a polygenic risk score, is causally related to pulmonary fibrosis, but not COPD.[54]

RECOMMENDATION.

1. Patients with known or suspected short telomere syndrome-associated interstitial lung disease should be considered for referral for lung transplant evaluation at the time of diagnosis, noting the potential for an accelerated disease course and the added complexity of transplant evaluation.
2. Where a short telomere syndrome is suspected or confirmed during transplant evaluation, treatment with immunosuppressive therapies prior to transplant should be used with caution.

3.5. Screening for short telomere syndrome in patients referred for lung transplant

Which patients undergoing lung transplant evaluation should be screened for STS? Careful history taking and medical record review can identify STS manifestations beyond lung disease such as dystrophic nails, skin pigmentation changes, early graying of hair, isolated macrocytosis, cytopenias, liver fibrosis or cirrhosis, prior leukemia or bone marrow failure, and prior head and neck or genitourinary cancers.[55] Multiple characteristic STS phenotypic manifestations appear to have increased specificity for TL ≤10th percentile in the lung transplant referral population.[56] For example, in single center studies of ILD patients referred for lung transplant, between 24% and 33% screened positive for a familial history of lung disease or extrapulmonary STS manifestations.[35,56] However, testing TL in all patients in an ILD clinic, regardless of phenotypic manifestations, revealed a 46% prevalence of TL < 10th percentile.[28] Differences in prevalence between these investigations suggest that clinical screening based on familial history of lung disease or phenotypic features alone may not be sufficient to identify all ILD patients with TL < 10th percentile. Some patients with short TL do not have phenotypic or clinical features beyond pulmonary fibrosis.[31] Extrapulmonary disease manifestations also depend on the presence of certain underlying variants and are not always present at the time of ILD clinic evaluation or transplant referral. These features can evolve longitudinally or with additional exposures, such as anti-metabolite immunosuppression.

Measurement of TL in all patients with ILD would identify patients with critically short telomeres—those below the 1st percentile—at highest risk of developing complications related to a STS during their post-transplant course. A risk-stratified approach to post-transplant management could then be implemented to minimize potential post-transplant complications.[29] However, caution must be taken to recognize that a universal screening approach may over assign patients a STS diagnosis, thereby overestimating transplant risk. Careful understanding of the full diagnostic context for patients with TL 10th percentile is necessary to avoid unnecessarily restricting them from access to transplant (4.1).

Because TL testing may have a turnaround time of several weeks, patients who otherwise meet a center's transplant eligibility criteria should not have listing delayed solely due to pending TL results. Similarly, patients with multiple characteristic STS phenotypic manifestations (cytopenias, family history of ILD, liver disease) who are in urgent need of transplant should not wait for TL results to become available before testing for potentially risk prohibitive extrapulmonary disease.

Limitations in the availability of TL measurement include financial barriers and few testing facilities that meet externally reviewed quality standards (such as CLIA in the United States). These remain significant challenges to obtaining timely diagnostic testing. In programs or regions where barriers exist to TL testing, implementing a targeted approach to testing focused on patients at highest risk based on clinical history and clinically suggestive examination would be advisable.[56] For example, several programs recommend TL screening when one or more of the following are present: first degree relatives with ILD or bone marrow failure, early graying (with variable thresholds for the age of onset and extent of graying), macrocytosis, cytopenias or history of bone marrow failure or leukemia, unexplained elevation in liver function tests or liver fibrosis or cirrhosis, or a history of head and neck, cervical, or anal cancer.[9,35,56,57] Further data are needed regarding the sensitivity, specificity, and positive and negative predictive value of individual screening characteristics.

Consistent with recent recommendations from the European Respiratory Society, genetic testing, where available, should be offered to patients with a clinical presentation suggestive of STS.[11] Genetic testing may also be considered in patients presenting with a fibrotic ILD before the age of fifty without other signs of STS, although the yield may be lower.[12] When an individual is suspected or confirmed to have STS before or during transplant evaluation, it is also important to consider the broader implications of this diagnosis. Blood relatives may be unknowingly affected or at risk of future STS manifestations. Screening studies have demonstrated a heightened prevalence of interstitial lung abnormalities or subclinical ILD in the relatives of patients with pulmonary fibrosis, with the risk higher in those with shorter telomeres.[58,59]

Where available, genetic counseling and cascade screening, including genetic sequencing, may facilitate risk reduction and preparatory measures in blood relatives. This is particularly true for probands with pathogenic variants in telomere maintenance genes.[12] Predictive testing may help to identify individuals who would benefit from pulmonary surveillance and facilitate other considerations such as preimplantation genetic testing. Genetic counselors are also an important resource for understanding country-specific health insurance implications of a STS diagnosis.

The syndromic presentation of STS necessitates comprehensive extrapulmonary evaluation and consideration of multidisciplinary care. Patients suspected or confirmed to have STS should undergo longitudinal follow-up and monitoring for STS-specific complications, irrespective of whether they progress to lung transplant. Collaborating with non-transplant specialists with demonstrated interest or expertise in STS-related organ involvement is an important aspect of successful multidisciplinary care.

RECOMMENDATION.

1. All patients with an interstitial lung disease referred for transplant should undergo clinical screening for the possibility of a short telomere syndrome, including measurement of telomere length, where available.
2. Where a short telomere syndrome is suspected or confirmed, either by clinical features and/or confirmation of short telomere length, genetic counseling with genetic sequencing is recommended, where available.
3. Where a short telomere syndrome is suspected or confirmed, referral for multidisciplinary care, where available, should occur for longitudinal follow-up and monitoring for short telomere syndrome-specific co-morbidities.

4. SECTION II. TRANSPLANT EVALUATION AND LISTING CONSIDERATIONS FOR PATIENTS WITH SHORT TELOMERE SYNDROME

Section II outlines key considerations during lung transplant evaluation for patients with known or suspected STS, emphasizing the need for comprehensive assessment of extrapulmonary manifestations. We provide recommendations on additional testing during evaluation, multidisciplinary consultation, and risk stratification to inform transplant candidacy and anticipate post-transplant complications.

4.1. Additional testing during transplant evaluation for a patient with STS

The diagnosis of STS, by itself, should not be considered a contraindication to lung transplant evaluation. Rather, the presence of STS-related advanced lung disease warrants additional testing during the evaluation to identify and to risk stratify extrapulmonary disease manifestations. This testing may also help individualize post-transplant care (Section III).

Given the potential for bone marrow dysfunction, all patients with STS should have complete blood count (CBC) with differential measured during the transplant evaluation. While mild abnormalities such as macrocytosis are common, unexplained anemia, thrombocytopenia, and/or leukopenia should prompt expert consultation with hematology. In patients with cytopenias, we recommend further evaluation for an evolving clonal disorder, including bone marrow biopsy (BMB) with next generation sequencing (NGS), when indicated and available. This is particularly true for patients with cytopenias or pathogenic variants highly associated with bone marrow failure.[17,60] NGS of bone marrow and peripheral blood can stratify risk for subsequent myelodysplastic syndrome (MDS) and leukemic transformation.[61,62] Although a small single center study found that only patients with cytopenias had BMB findings that impacted their transplant candidacy, larger studies have not been performed investigating the role of routine BMB in all candidates with STS.[57]

Given the potential for hepatic dysfunction, all patients with STS should have liver function test (LFT) assessment. Because lung transplant candidates with STS are at risk for non-cirrhotic portal hypertension and hepatopulmonary syndrome despite normal LFTs, we also recommend cross-sectional liver imaging (abdominal computed tomography or hepatic ultrasound) as well as agitated saline echocardiography, where available, to assess for intrapulmonary shunting.[17,63,64] Patients with unexplained elevation in LFTs or radiographic, echocardiographic, or clinical evidence of hepatopulmonary syndrome, cirrhosis, or portal hypertension should undergo expert consultation with hepatology. This includes noninvasive fibrosis assessment with liver and spleen stiffness measurement and consideration of liver biopsy and portal pressure measurement, where available.

We recommend bone density testing during the transplant evaluation given increased risk for osteopenia and osteoporosis in the STS population, as well as age-appropriate cancer screening.[17] Where available, consideration should be given to obtaining baseline T cell subsets to inform early reduction in post-transplant immunosuppression.[65] Although most patients with STS have intact humoral immunity, measurement of baseline quantitative immunoglobulin levels may inform the potential need for post-transplant immunoglobulin G supplementation.[17]

Additional extrapulmonary evaluation is warranted in some specific scenarios involving patients with DC phenotypes, particularly in pediatric and young adult populations. Patients with a DC typically present with a triad of nail dystrophy, reticulated skin pigmentation and oral leukoplakia, and bone marrow failure, and tend to have earlier onset and more extensive multisystem STS-related disease.[30] For example, skin and head and neck squamous cell cancer screening should be considered in this population.[66] Patients with DC phenotype and dysphagia symptoms should also undergo evaluation for esophageal stricture.[67] Screening for gastric and small bowel arteriovenous malformations is necessary in those with previous gastrointestinal bleeding.[68] Transplant candidates with STS and prior BMT require close collaboration with oncology providers to identify and to risk stratify for BMT-related complications, such as gastrointestinal or skin graft-versus-host disease (GVHD). Similarly, early discussion with transplant pulmonology may be indicated for patients with mild ILD or interstitial lung abnormalities and bone marrow failure who are undergoing bone marrow transplant evaluation.

RECOMMENDATION.

1. All patients with short telomere syndrome should undergo complete blood count with differential, liver function tests, cross-sectional liver imaging, echocardiogram with agitated saline study (where available), bone density testing, and age-appropriate cancer screening as part of the evaluation for lung transplant.
2. Patients with short telomere syndrome and unexplained anemia, thrombocytopenia, and/or leukopenia should undergo expert consultation with hematology, including bone marrow biopsy with next generation sequencing, when indicated and where available.
3. Patients with short telomere syndrome and unexplained elevation in liver function tests or radiographic, echocardiographic, or clinical evidence of portal hypertension should undergo expert consultation with hepatology, including transient elastography and consideration of liver biopsy and/or portal pressure measurement, when indicated and where available.

4.2. Increased risk features for lung transplant for a patient with STS

Individuals with STS and MDS appear to be at particularly high risk for early graft failure and death following lung transplant. For example, the OrphaLung Network reported a 37.5% one-year survival among lung transplant recipients with MDS and germline telomere-related gene variants.[5] Because many programs now screen for MDS prior to transplant and decline to list these individuals, it is unclear whether there are some patients with STS-related MDS who have better outcomes.[57] Small numbers of longer-term survivors have been identified among those with pre-transplant MDS.[5,69,70] Certain somatic variants in telomere maintenance genes may be protective of subsequent MDS and/or marrow failure risk.[71] Given variability of trajectories, expert consultation with hematology regarding MDS risk stratification is necessary prior to lung transplant consideration. Data on post-transplant outcomes of patients with STS and hypocellular marrow with peripheral cytopenias but no morphologic evidence of MDS and normal marrow NGS are limited. As with patients with MDS, expert consultation with hematology, particularly for patients with significant hypocellularity, may be warranted.

Although there are limited data, STS patients with significant portal hypertension with or without cirrhosis are likely at increased risk for early complications and mortality following lung transplant. A multidisciplinary discussion with transplant hepatology is required for individuals with STS and advanced lung and liver involvement. In some cases, lung transplant alone, followed by liver transplant, if indicated, may be successful.[72]

In other cases, combined lung-liver transplant is necessary.[73,74] Finally, early discussion with transplant pulmonology may be indicated for patients with mild ILD and advanced cirrhosis who are undergoing liver transplant evaluation. Given the potential for accelerated pulmonary disease, concurrent "safety net" lung transplant assessment may be warranted.[75]

Other populations who require additional multidisciplinary discussion include children and adults with prior bone marrow transplant for STS-related disease. Patients with STS and advanced osteoporosis, particularly with prior fracture, may also need additional risk stratification with endocrinology. Further research is needed regarding post-transplant trajectories of patients with hypocellular bone marrow without MDS or MDS-predisposing variants as well as those with potentially MDS-protecting *TERT* promoter variants.[71]

RECOMMENDATION.

1. Patients with short telomere syndrome, advanced lung disease, and myelodysplastic syndrome or bone marrow failure syndromes are at increased risk for early post-transplant complications and mortality regardless of age. Lung transplant candidacy should be considered only in expert consultation with hematology, including myelodysplastic syndrome risk stratification.
2. Patients with short telomere syndrome, advanced lung disease, and portal hypertension with or without cirrhosis should be considered for lung transplant alone or possible lung-liver transplant only in expert consultation with hepatology.

5. SECTION III. PERI-OPERATIVE AND POST-TRANSPLANT CONSIDERATIONS FOR PATIENTS WITH SHORT TELOMERE SYNDROME

Section III addresses peri-operative and post-transplant management considerations for lung transplant recipients with STS (ST-LTRs). Variability in telomere measurement technique (qPCR vs flow-FISH) and differences in STS inclusion criteria (TL < 1st percentile versus ≤10th percentile with genetic variants versus TL ≤10th percentile regardless of genetic variants) limit comparison between studies of post-transplant outcomes among ST-LTRs.[6] Within this constraint, however, we review the impact of STS on key lung allograft outcomes, emphasizing the importance of monitoring for extrapulmonary manifestations and the role of tailored immunosuppression. We highlight areas in need of further research in the ST-LTR population.

5.1. Perioperative considerations

More than 80% of lung transplant centers utilize induction immunosuppression, most often the interleukin-2 receptor antagonist basiliximab.[76] Some centers use T cell-depleting agents such as anti-thymocyte globulin and alemtuzumab, a decision that may be based on age, hematologic reserve, prior history of malignancy, cytomegalovirus (CMV) status, and allosensitization. Although no studies to date have specifically investigated the optimal induction therapy for ST-LTRs, the potential for increased risks, including cytopenias, CMV infection, and malignancy, suggest that caution may be warranted when considering T cell-depleting induction, especially the long-acting agent, alemtuzumab.[77,78]

Primary graft dysfunction (PGD) is a form of acute lung injury related to ischemia reperfusion, affecting approximately 30% of lung transplant recipients. While some PGD risk factors have been identified from the donor, recipient, and operative course, little is known about the impact of recipient TL.[79] One single center reported an increased risk of grade 3 PGD in ST-LTRs compared to controls.[80] However, several subsequent studies evaluating PGD in LTRs with telomere gene variants found no significant difference.[81,82] In a recent systematic review of lung transplant outcomes in patients with telomere-related forms of ILD, there was insufficient evidence to suggest worsening PGD.[6] Together, the impact of recipient short TL on PGD risk remains mixed and underscores the need for further studies. Although shorter donor TL has been associated with increased risk of PGD (and increased chronic lung allograft dysfunction (CLAD), time constraints around donor offer acceptance currently limit clinical consideration of donor TL measurement.[83]

Patients with STS, particularly DC phenotypes with ultrashort TL < 1st percentile, may have mucocutaneous abnormalities and impaired wound healing.[69,84] However, the data on wound healing–including anastomotic and surgical site complications–are limited. One study compared airway complications in ST-LTRs and other LTRs,

reporting an increased incidence of dehiscence and bronchial stenosis in ST-LTRs.[85] While exploratory, this observation needs further validation as the overall number of airway complications (n=15) in the ST-LTR group was small. Further studies are also needed to assess the risk of surgical site healing complications in ST-LTRs.

RECOMMENDATION.

1. In patients with short telomere syndrome undergoing lung transplant, T-cell depleting agents should be used with caution for induction immunosuppression.
2. Vigilance is warranted for airway anastomotic and surgical site wound healing complications in lung transplant recipients with short telomere syndrome.

5.2. Hematologic complications

Hematologic complications are a major extrapulmonary manifestation in ST-LTRs. These complications were recognized in early, smaller studies.[69,82,86] Hematologic processes can range from single cell line cytopenias to the development of pancytopenia and overt bone marrow failure. The mechanism driving these cytopenias is impaired bone marrow reserve in the setting of bone marrow stressors, most often immunosuppressive therapies (e.g., anti-proliferative agents) and other post-transplant drugs (e.g., valganciclovir, trimethoprim-sulfamethoxazole) that suppress the bone marrow. In the largest study evaluating hematologic complications in ST-LTRs, 72 IPF-LTRs were compared to 72 age-matched non-IPF-LTRs.[7] In this cohort, 68% of the IPF-LTRs had TL ≤10th percentile by flow-FISH and 26% had rare variants in the telomere maintenance genes. Among ST-LTRs, 35% required discontinuation of immunosuppressive agents (predominantly mycophenolate mofetil) compared to 18% of the non-IPF cohort. Of the ST-LTRs who discontinued immunosuppression, 82% went on to require hematology consultation and BMB and 33% of these patients had dyspoietic features on BMB and/or positive NGS-based variant profiling. Finally, 41% of ST-IPF-LTR required blood product transfusion after 90 days post-transplant and 71% required granulocyte-colony stimulating factor (G-CSF) support. Need for blood transfusions and G-CSF in this group was significantly higher compared to IPF-LTRs with TL > 10th percentile and non-IPF-LTRs.

Together, these studies underscore ST-LTRs susceptibility to clinically significant post-transplant bone marrow dysfunction. Hematologic complications should also raise the possibility of telomere-mediated disease in LTRs who were not tested prior to transplant. Given this susceptibility, close monitoring of ST-LTRs for cytopenias is warranted, along with adjustments to medications that contribute to bone marrow dysfunction. Consultation with hematology is recommended, where available, for managing cytopenias and assessing for progression to MDS.[7,82] Although the synthetic sex hormone danazol has been associated with improvement in hemoglobin and neutrophil and platelet count in non-transplant patients with STS, side effects, including hepatotoxicity, myalgias, and increased risk of thromboembolism may be challenging in the lung transplant population.[87]

Although there are no universal protocols, some centers implement upfront adjustments to the immunosuppressive regimen or antiviral prophylaxis strategy for ST-LTRs to mitigate adverse events.[29] Examples include a lower than standard dose of anti-proliferative agents or long-term transition to a mammalian target of rapamycin (mTOR) inhibitor. In a recent small study, STS-LTRs were successfully transitioned to an mTOR inhibitor using the costimulation-blockade drug belatacept as an alternative immunosuppressive agent for bone-marrow-sparing in patients who developed early post-operative thrombocytopenia when challenged with mycophenolate mofetil.[88] Other strategies for bone marrow-sparing include use of letermovir for CMV prophylaxis rather than valganciclovir, transition from TMP-SMX to an alternative pneumocystis prophylaxis (atovaquone, dapsone, inhaled pentamidine), and supportive G-CSF for neutropenia, balanced against the uncertain impact of G-CSF on ACR and mortality.[89 90–92].

Research priorities in this area include data on acute and chronic rejection among STS-LTR who are treated with lower than standard doses of anti-proliferative agents or alternative therapies such as belatacept; CMV and cytopenia-related outcomes for STS-LTR on letermovir for CMV prophylaxis; and the role of mTOR inhibitors in this patient population.

RECOMMENDATION.

1. Because lung transplant recipients with short telomere syndrome have reduced bone marrow reserve and may be susceptible to cytopenias, close monitoring of blood counts are warranted, particularly with therapies that impact the bone marrow (e.g., anti-proliferative agents).

5.3. Hepatic complications

The prevalence of liver disease among patients with STS ranges from 7–15%, with variations related to the degree of TL shortening, pediatric versus adult populations, the affected genes, and secondary insults such as alcohol use or prior BMT with hepatic GVHD.[93,94] Liver disease can be clinically variable, ranging from mild LFT abnormalities to radiographic hepatic parenchymal abnormalities to non-cirrhotic portal hypertension with portosystemic shunts.[95] The most common advanced manifestation of liver disease in STS is nodular regenerative hyperplasia (NRH), which may represent a form of liver ischemia-induced injury. The pathophysiology of NRH remains incompletely understood, and it can be radiographically mistaken for hepatic steatosis. Portal hypertension can develop in the setting of NRH, representing a form of non-cirrhotic portal hypertension.

Although careful screening during the transplant evaluation should identify most STS patients with advanced liver disease, rapid worsening of mild disease or de novo impairment may occur following lung transplant. Progression from pre-transplant baseline should be monitored closely after transplant, including with routine LFTs.[96] A sustained, unexplained rise in LFTs or clinical signs of portal hypertension should prompt referral for expert hepatology consultation. Although there are no published data, because hepatic disease may develop with minimal elevations in liver biochemical tests, some centers pursue annual or semi-annual screening with abdominal ultrasound and/or noninvasive fibrosis assessment (with liver and spleen stiffness measurement).[9] ST-LTRs with portal hypertension or advanced liver disease who undergo lung transplant alone should be followed closely with expert hepatology consultation. Additional monitoring for the development of ascites, screening for gastric varices, and hepatocellular carcinoma screening should occur in these patients.

RECOMMENDATION:

1. As lung transplant recipients with short telomere syndrome may be more prone to development of liver disease, routine monitoring of liver function tests as well as hepatic imaging–as clinically indicated–are recommended, with a low threshold for expert hepatology consultation.

5.4. Malignancy and other extra-pulmonary disease

In addition to MDS and leukemia, STS patients have an increased risk of squamous cell cancers of the skin and head and neck, and anal cancer.[66] An individual's cancer susceptibility depends, in part, on underlying phenotype, with patients with DC phenotypes and/or ultrashort TL being particularly high risk.[66] In general, T-cell senescence in STS likely contributes to increased cancer susceptibility, particularly for cancers that rely on T-cell competence for suppression. This may also explain why the spectrum of cancers observed in these patients aligns with those seen in individuals with acquired T-cell immunodeficiency, as well as the increased risk for human papillomavirus positive head and neck cancers.[66] Currently, there are no data on ST-LTRs and solid malignancy susceptibility compared to LTRs with normal telomeres. Nevertheless, clinicians should remain vigilant regarding these cancers on physical exam, with regular dermatology follow-up and a low threshold for referral to other specialists such as otorhinolaryngology for suspicious head and neck lesions. In addition, it remains unknown whether ST-LTRs who receive single lung transplants are at increased risk for cancer in the native lung. Taken together, more studies are needed to fully characterize cancer risk in ST-LTRs that could impact the approach to their clinical care.

The evidence for the impact of STS in LTRs in other organ systems is limited. Early small studies in ST-LTRs reported high rates (50–80%) of renal failure requiring renal replacement therapy.[69,97] However, several subsequent larger studies did not find an increased risk of acute kidney injury.[5,80–82] Gastrointestinal complications including esophageal strictures, enteropathies, and colitis have been described in STS patients. However, substantial data in ST-LTRs are lacking with only one case report of mycophenolate mofetil-induced colitis in a ST-LTR.[69] Because drug-induced colitis is relatively common among LTRs, larger studies are needed to assess whether the risk is higher in ST-LTRs. Similarly, bone disease has been described in patients with STS, including avascular necrosis.[98,99] However, no large studies have been conducted examining osteoporosis and bone disease among ST-LTRs compared to other recipients. Finally, while the impaired T cell mediated immunity common in ST-LTRs may translate to increased susceptibility to aspergillus or other fungal pathogens, bacterial respiratory infections, and/or community associated respiratory viruses, this has not been systematically studied.

RECOMMENDATION:

1. As lung transplant recipients with short telomere syndrome may be more prone to cancer development, particularly skin cancers, regular dermatologic monitoring is warranted.

5.5. Herpesvirus infection and complications

CMV DNAemia and end-organ complications are common in LTRs and have been associated with worse post-transplant survival.[100] The first detailed study to address whether ST-LTRs have increased risk for CMV compared 42 IPF-LTRs (29 (69%) with ST as defined by ≤10th percentile by flow-FISH) to 42 age-matched non-IPF-LTRs. ST-IPF-LTRs had significantly increased incidence of CMV DNAemia episodes and other CMV complications compared to controls.[8] In addition, this study demonstrated that ST-LTRs had significantly reduced in vitro CMV-specific T cell Type-1 immune effector responses in the peripheral blood, along with impaired CMV-specific T cell proliferative responses. These data were consistent with another report in non-transplant STS patients highlighting susceptibility to herpesvirus infections and a senescent T cell compartment.[65] However, several subsequent studies either did not find an increased risk for CMV viremia in ST-LTRs or LTRs with telomere gene variants or did identify an increased risk for CMV viremia but only in mismatched patients (D+R-).[81,82,101,102]

These discordant results may be due to differences in TL measurement assay (i.e., flow-FISH versus qPCR) or to restricting the population to those with rare variants. Other confounders include differences in the type or duration of CMV prophylaxis, as ST-LTRs are not infrequently intolerant of valganciclovir due to cytopenias. The emergence of letermovir as a potential alternative for CMV prophylaxis with significantly less bone marrow suppression may alleviate this challenge, though studies in ST-LTRs are needed.[89,90] Despite mixed study results, we recommend careful monitoring for CMV DNAemia and related complications. The emergence of data for other tools, such as CMV immunity monitoring, may allow for improved stratification of ST-LTRs. Finally, in organ allocation systems where CMV negative donor offers can be preferentially directed to CMV negative STS transplant candidates, it is reasonable to pursue CMV negative status matching. In general, however, programs should avoid jeopardizing future transplant opportunities by delaying acceptance of an otherwise acceptable CMV positive offer in anticipation of a CMV negative match.

Other herpesviruses, including Epstein-Barr virus (EBV), have been implicated in post-transplant complications. For example, post-transplant lymphoproliferative disease (PTLD) is often related to loss of immunologic control of EBV in immunocompromised individuals. In a large single center study, 28 of 611 LTRs (4.6%) developed EBV-associated PTLD. EBV mismatch (D+/R-) was the largest risk factor for PTLD, while IPF was the only native lung disease associated with age- and sex-adjusted risk for PTLD.[77] Although TL was not measured in this study, a subsequent publication from the same institution reported a high prevalence of STS among that group of IPF patients.[7] While not conclusive, the potential susceptibility to PTLD among ST-LTRs would warrant increased monitoring for EBV reactivation, particularly in higher risk PTLD populations such as EBV-mismatch and pediatric patients. Research priorities in this area include conducting larger studies to evaluate STS as a risk factor for PTLD, as well as to determine whether EBV monitoring influences the frequency of cross-sectional imaging and biopsies, or alters PTLD diagnosis and management.

RECOMMENDATIONS:

1. Because lung transplant recipients with short telomere syndrome appear to have increased susceptibility to herpesvirus infections, close peripheral blood quantitative assay-based monitoring of cytomegalovirus and Epstein-Barr virus are warranted.

5.6. Allograft outcomes

The impact of TL on acute cellular rejection (ACR) and CLAD after lung transplant remains incompletely characterized. Published studies show conflicting results. Many factors contribute to this ambiguity. Foremost is the variability in short TL by underlying disease process, with IPF enriching for the shortest telomeres and the most gene variants associated with telomere disorders.[16,33,50] On average, patients with IPF patients tend to be older, with a shorter post-transplant survival, making comparisons between this group and others problematic.[103] Additionally, the immune dysfunction associated with critically short TL, which could diminish the alloreactive response, may be balanced by a decreased ability to tolerate immunosuppressant therapies and an increased incidence of infectious complications, leading to interperson variability in risk.[4,7,65]

ACR is a T cell-mediated process whereby alloreactive T cells migrate to the graft leading to injury.[104] Even in the absence of transplant, STS is associated with primary T cell dysfunction.[65] Following transplant, circulating T cells from patients with short telomeres have impaired responses to donor antigen and exhibit an accelerated shift

toward an immunosenescent phenotype.[105,106] This may account for several single center studies showing either no difference in ACR burden in ST-LTRs or a modestly reduced ACR burden with age.[33,101,106] These results underscore the need for larger, multi-center studies to fully elucidate the impact of TL on early and late ACR, controlling for transplant indication, age, bone marrow function, and immunosuppression tolerance. There are no data to suggest that transplant programs should alter their ACR surveillance practices because of STS alone. Additionally, the impact of TL on the development of de novo donor specific antibodies and antibody mediated rejection requires further investigation. Because the humoral immune response appears to be preserved in many patients with STS, transplant programs should not alter their standard DSA and AMR surveillance practices on the basis of STS alone.[17]

While the literature on ACR suggests no increased risk associated with STS, studies investigating CLAD have had discordant findings. Aside from one multi-center study investigating 14 patients with telomerase variants, these include a number of single-center studies with variable inclusion criteria.[97] One study of all lung transplant recipients, regardless of underlying diagnosis, found that shorter TL was associated with reduced CLAD-free survival.[102] Two additional single center studies, looking at all forms of pulmonary fibrosis, found that short TL or high-risk variants in *TERT*, *RTEL1*, or *PARN* were associated with increased risk of death and CLAD[81] or shorter time to CLAD and worse survival.[80] Explanted lungs from recipients with CLAD demonstrated significantly shorter tissue TL in comparison to age- and sex-matched normal lungs, suggesting increased senescence may play a role in CLAD.[107] However, in the largest study to date—including only patients with idiopathic pulmonary fibrosis—the investigators found no difference in time to CLAD or survival.[33]

These discordant findings may be due to different patient populations or in variants in TL measurement. The enrichment for patients with short TL among transplant recipients with IPF, along with overall diminished survival in IPF patients compared to others, may account for the reduced CLAD-free survival in the prior studies. However, collectively these results support the notion that ST-LTRs *are not protected from CLAD*. This presents an apparent paradox when considering ST-LTRs demonstrate impaired adaptive T cell immunity and immune senescence. Offsetting factors, including discontinuation of immunosuppression, susceptibility to CMV and other viral infections, and, as of yet, undefined risks may contribute to the persistent risk for CLAD in these patients. Larger, multi-institutional studies are needed to provide more clarity on the relationship between CLAD and TL. Until more compelling evidence exists, we do not recommend considering the potential impact of STS on either acute or chronic rejection when weighing transplant eligibility.

RECOMMENDATION:

1. The impact of short telomere syndrome on acute and chronic rejection remains unclear with conflicting evidence, and should not be a factor when considering transplant eligibility.
2. Short telomere syndrome alone does not warrant deviation from a transplant program's usual surveillance practices for acute cellular rejection, donor-specific antibodies, or antibody-mediated rejection.

6. SECTION IV. CONCLUSIONS

In the past decade, emerging evidence has suggested that patients with STS and fibrotic ILD have pre- and post-transplant clinical courses that characteristically differ from those with preserved TL. These patients are at higher risk for disease progression and mortality before transplant, may have adverse responses to immunosuppression, and may develop extrapulmonary disease manifestations such as bone marrow failure and liver disease that add additional complexity to the lung transplant evaluation. Post transplant, the weight of current evidence suggests a susceptibility to extrapulmonary manifestations including hematologic complications and CMV infection. The impact of short TL on allograft outcomes such as PGD and CLAD remains controversial, warranting further study. High quality research would start with a broader effort in the field to identify lung candidates and LTRs with short TL and rare variants in telomere maintenance genes. Longitudinal data from various consortia efforts regarding ST-LTRs will allow for the development of further evidence-based recommendations for the post-transplant care of ST-LTRs.

APPENDIX 1. — SUMMARY OF RECOMMENDATIONS

Summary of Recommendations
SECTION I. SHORT TELOMERE SYNDROME PATHOPHYSIOLOGY, EPIDEMIOLOGY, AND SCREENING AND DIAGNOSIS DURING LUNG TRANSPLANT EVALUATION
1.2 Methods of Telomere Length Measurement: Telomere length should be measured in peripheral blood mononuclear cells using a validated assay that has been referenced to a percentile of a normal population. When available, flow-FISH, performed in a laboratory that meets an externally reviewed quality standard, is the preferred telomere length measurement method.
1.3 Diagnosis of Short Telomere Syndrome: The diagnosis of short telomere syndrome in patients undergoing lung transplant evaluation should consider: • Peripheral blood mononuclear cell telomere ≤10th age-adjusted percentile • Extrapulmonary phenotypic manifestations including but not limited to early graying of hair, unexplained macrocytosis or cytopenias, unexplained abnormal liver function tests, and family history of interstitial lung disease, cryptogenic cirrhosis, or bone marrow failure syndromes • Genetic testing, where available
1.4 Prevalence and Implications of Short Telomere Syndrome in Advanced Lung Disease:Patients with known or suspected short telomere syndrome-associated interstitial lung disease should be considered for referral for lung transplant evaluation at the time of diagnosis, noting the potential for an accelerated disease course and the added complexity of transplant evaluation.Where a short telomere syndrome is suspected or confirmed during transplant evaluation, treatment with immunosuppressive therapies prior to transplant should be used with caution.
1.5 Screening for Short Telomere Syndrome in Patients Referred for Lung Transplant All patients with an interstitial lung disease referred for transplant should undergo clinical screening for the possibility of a short telomere syndrome, including measurement of telomere length, where available.Where a short telomere syndrome is suspected or confirmed, either by clinical features and/or confirmation of short telomere length, genetic counselling with genetic sequencing is recommended, where available.Where a short telomere syndrome is suspected or confirmed, referral for multidisciplinary care, where available, should occur for longitudinal follow-up and monitoring for short telomere syndrome-specific comorbidities.
SECTION II. TRANSPLANT EVALUATION AND LISTING CONSIDERATIONS FOR PATIENTS WITH SHORT TELOMERE SYNDROME
2.1 Additional Testing During Transplant Evaluation for a Patient with STS:All patients with short telomere syndrome should undergo complete blood count with differential, liver function tests, cross-sectional liver imaging, echocardiogram with agitated saline study (where available), bone density testing, and age-appropriate cancer screening as part of the evaluation for lung transplant.Patients with short telomere syndrome and unexplained anemia, thrombocytopenia, and/or leukopenia should undergo expert consultation with hematology, including bone marrow biopsy with next generation sequencing, when indicated and where available.Patients with short telomere syndrome and unexplained elevation in liver function tests or radiographic, echocardiographic, or clinical evidence of portal hypertension should undergo expert consultation with hepatology, including transient elastography and consideration of liver biopsy and/or portal pressure measurement, when indicated and where available.
2.2 Increased Risk Features for Lung Transplant for a Patient with STS:Patients with short telomere syndrome, advanced lung disease, and myelodysplastic syndrome or bone marrow failure syndromes are at increased risk for early post-transplant complications and mortality regardless of age. Lung transplant candidacy should be considered only in expert consultation with hematology, including myelodysplastic syndrome risk stratification.Patients with short telomere syndrome, advanced lung disease, and portal hypertension with or without cirrhosis should be considered for lung transplant alone or possible lung-liver transplant only in expert consultation with hepatology.
SECTION III. PERI-OPERATIVE AND POST-TRANSPLANT CONSIDERATIONS FOR PATIENTS WITH SHORT TELOMERE SYNDROME
3.1 Perioperative Considerations:In patients with short telomere syndrome undergoing lung transplant, T-cell depleting agents should be used with caution for induction immunosuppression. Vigilance is warranted for airway anastomotic and surgical site wound healing complications in lung transplant recipients with short telomere syndrome.
3.2 Hematologic Complications:Because lung transplant recipients with short telomere syndrome have reduced bone marrow reserve and may be susceptible to cytopenias, close monitoring of blood counts are warranted, particularly with therapies that impact the bone marrow (e.g., anti-proliferative agents).
3.3. **Hepatic Complications:** As lung transplant recipients with short telomere syndrome may be more prone to development of liver disease, routine monitoring of liver function tests as well as hepatic imaging–as clinically indicated–are recommended, with a low threshold for expert hepatology consultation.
3.4. **Malignancy and Other Extra-Pulmonary Disease**: As lung transplant recipients with short telomere syndrome may be more prone to cancer development, particularly skin cancers, regular dermatologic monitoring is warranted.
3.5. **Herpesvirus Infection and Complications**: Because lung transplant recipients with short telomere syndrome appear to have increased susceptibility to herpesvirus infections, close peripheral blood quantitative assay-based monitoring of cytomegalovirus and Epstein-Barr virus are warranted.

Continued

Summary of Recommendations

3.6. **Allograft Outcomes**:
The impact of short telomere syndrome on acute and chronic rejection remains unclear with conflicting evidence, and should not be a factor when considering transplant eligibility.Short telomere syndrome alone does not warrant deviation from a transplant program's usual surveillance practices for acute cellular rejection, donor-specific antibodies, or antibody-mediated rejection.

APPENDIX 2. — AUTHOR AND REVIEWER RELEVANT RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES

Committee Member Name	Employment	Consultant	Speakers Bureau	Ownership/ Partnershp/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Andrew M. Courtwright	None	None	None	None	None	Noe	None
John A Mackintosh	None	None	Speaker honoraria, Boehringer Ingelheim	None	None	None	None
Jonathan K. Alder	None	None	None	None	None	Noe	None
Garcia, Christine Kim	None	Rejuvenation Technologies Inc.	None	Rejuvenation Technologies Inc. stock options	None	AstraZeneca agreement with institution for research	None
Antoine Froidure	None	Boehringer Ingelheim, AstraZeneca	Speaker honoraria, Boehringer Ingelheim, AstraZeneca	None	None	Boehringer Ingelheim	None
Erin Lowery	None	Institute for Healthcare Improvement	None	None	None	CareDx, Cystic Fibrosis Foundation	None
Don Hayes, Jr	None	None	None	None	None	None	None
Shah Pali	None	None	None	None	None	None	None
Quentin Philippot	None	None	None	None	None	Research grants from Fondation Bettencourt Schueller, Air Liquide, and Fondation du Souffle.	None
Raphael Borie	None	Boehringer Ingelheim, Ferrer	Sanofi	None	Boehringer Ingelheim	None	Boehringer Ingelheim, Sanofi
John R Greenland	None	Arda Therapeutics	None	None	Therakos LLC, research funding to institution	None	None
Hannah Mannem	None	None	None	None	None	None	None
Mark E. Snyder	None	Graticule	None	None	AstraZeneca	None	None

Continued

Committee Member Name	Employment	Consultant	Speakers Bureau	Ownership/ Partnershp/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Merel Hellemons	None	Takeda, Pfizer	None	None	None	Chiesi, travel fee	None
Laurie D. Snyder	None	Pulmocide, Transmedics, AstraZeneca,	None	None	None	Boehringer Ingelheim, research funds to institution	None
John McDyer	None	Kamada	None	None	None	Kamada	None

There were no sources of direct funding support for this manuscript.

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