CONSENSUS PERSPECTIVE

ISHLT Consensus Statement on Short Telomere Syndrome and Lung Transplantation: Authors' Perspective

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1. INTRODUCTION

Telomeres are repetitive DNA sequences bound by a six-protein shelterin complex that cap the ends of chromosomes to maintain genetic stability. When telomere length (TL) falls below a functional threshold, uncapped telomeres drive a DNA damage response, leading to senescence or apoptosis.[1] Consequently, TL limits the number of times a cell can divide. Genetic variations in telomere maintenance genes are implicated in short telomere syndrome (STS), although patients with STS may not have known genetic variants.[2] In either case, telomere dysfunction can lead to multisystem clinical manifestations—collectively termed STS—that may develop across the lifespan.[3] STS-related conditions include bone marrow failure, interstitial lung disease (ILD), and cirrhosis, among others.[4]

Motivated by growing evidence that the presence of critically shortened telomeres influences ILD trajectories and is associated with extrapulmonary conditions relevant to transplant candidacy and post-transplant complications, this Consensus Statement aims to address gaps in the evaluation and management of patients

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with 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.

2. TOP TAKEAWAYS

- As extrapulmonary STS manifestations may be absent during initial clinical evaluation and can evolve longitudinally or with subsequent exposures, all patients with ILD referred for lung transplant evaluation should be screened for STS.[5,6] Where available, this should include measurement of TL in peripheral blood mononuclear cells (PBMC). Flow-fluorescent in situ hybridization is the preferred assay, when performed in laboratories meeting externally reviewed quality standards.[4,5]
- In the context of lung transplant, STS diagnosis minimally requires PBMC TL ≤10th percentile but should also consider the presence of characteristic phenotypic manifestations, and genetic testing, where available.
- 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 risk-stratify extrapulmonary disease manifestations, particularly among patients with ultrashort TL (< 1st percentile).[2,7]
- To identify and risk stratify individuals with STS and underlying bone marrow failure, patients with STS and unexplained anemia, thrombocytopenia, and/or leukopenia identified during the transplant evaluation should undergo expert consultation with hematology. This should include bone marrow biopsy with next generation sequencing, when indicated and where available.
- Patients with STS and unexplained elevation in liver function tests or radiographic evidence of portal hypertension identified during the transplant evaluation should undergo expert consultation with hepatology, including transient elastography and consideration of liver biopsy and/or portal pressure measurement, when indicated and where available.
- Patients with STS who undergo lung transplant require vigilant monitoring for complications unique to their condition.[8] This includes close surveillance of blood counts, particularly following exposure to anti-proliferative agents or other marrow suppressing medication.[9–11]
- Lung transplant recipients with STS appear to have increased susceptibility to herpesvirus infections, with particular risk for CMV infection.[12,13] Additional monitoring considerations include vigilance for airway anastomotic complications and for the development of STS-related liver disease as well as skin cancers[14,15]
- The impact of TL on acute cellular rejection (ACR) and chronic lung allograft dysfunction (CLAD) after lung transplant remains incompletely characterized. While literature on ACR suggests no increased risk associated with STS, STS alone does not warrant deviation from a transplant program's usual surveillance practices for ACR, donor-specific antibodies, or antibody-mediated rejection.[16,17] Collectively, the current literature does not suggest that lung transplant recipients with STS are protected from acute rejection or CLAD.

3. CONCLUSION

STS represents a clinical spectrum with manifestations that reflect the degree of telomere shortening, specific organ system involvement, environmental exposures, and underlying genetics.[18–20] Despite this heterogeneity,

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patients with STS and ILD have pre- and post-lung transplant courses and complications that characteristically differ from non-STS patients. They may also develop extrapulmonary diseases such as bone marrow failure and hepatic dysfunction that add complexity to the lung transplant evaluation. Following transplant, the weight of current evidence suggests increased susceptibility to extrapulmonary manifestations including hematologic complications and CMV DNAemia. However, the impact of short TL on allograft outcomes, including CLAD, is not fully defined and remains controversial, underscoring the need for further research.

We hope that this document improves patient access to appropriate TL screening, informs the development of STS diagnostic and management pathways within transplant programs, encourages collaborative, multidisciplinary care for patients with STS, and facilitates their access to lung transplantation. We also support high-quality, multicenter research aimed at identifying lung transplants candidates and recipients with STS, including those with rare variants in telomere maintenance genes. We anticipate that longitudinal data built on these efforts will drive further refinements in evidence-based recommendations to optimize post-transplant care for lung transplant recipients with STS.

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