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# Immune aging: biological mechanisms, clinical symptoms, and management in lung transplant recipients

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While chronologic age can be precisely defined, clinical manifestations of advanced age occur in different ways and at different rates across individuals. The observed phenotype of advanced age likely reflects a superposition of several biological aging mechanisms which have gained increasing attention as the world contends with an aging population. Even within the immune system, there are multiple age-associated biological mechanisms at play, including telomere dysfunction, epigenetic dysregulation, immune senescence programs, and mitochondrial dysfunction. These biological mechanisms have associated clinical syndromes, such as telomere dysfunction leading to short telomere syndrome (STS), and optimal patient management may require recognition of biologically based aging syndromes. Within the clinical context of lung transplantation, select immune aging mechanisms are particularly pronounced. Indeed, STS is increasingly recognized as an indication for lung transplantation. At the same time, common aging phenotypes may be evoked by the stress of transplantation because lung allografts face a potent immune response, necessitating higher levels of immune suppression and associated toxicities, relative to other solid organs. Age-associated conditions exacerbated by lung transplant include bone marrow suppression, herpes viral infections, liver cirrhosis, hypogammaglobulinemia, frailty, and cancer risk. This review aims to dissect the molecular mechanisms of immune aging and describe their clinical manifestations in the context of lung transplantation. While these mechanisms are more likely to manifest in the context of lung transplantation, this mechanism-based approach to clinical syndromes of immune aging has broad relevance to geriatric medicine.

## KEYWORDS

immunosenescence, short telomere syndrome, frailty, hypogammaglobulinemia, mitochondrial dysfunction, epigenetic clock

## 1 Introduction

While human age can be simply formulated as the length of time which a person has been alive, humans change over time in programmed ways. Beyond the well-known progression from childhood to adolescence and from young to elderly adult, we recognize that some people age more slowly than others, hence leading to differences in biological vs. chronological age. Biological age is a more accurate estimate of the functional decline of cells and organs estimated by age-dependent biomarkers including

DNA methylation, telomere length, transcriptome and proteomic signatures (1, 2). Certain DNA methylation patterns are so closely linked to biological age that they can be used to define molecular clocks, measuring the organ's effective age. Telomere length is more loosely associated with chronological age, and clinical manifestations of short telomeres are relatively rare.

Not everyone ages in the same way. Whereas some individuals develop gray hair from a young age, others may develop wrinkled skin first. Such clinical findings generally reflect biological mechanisms, such as melanocyte senescence with grey hair or a loss of subcutaneous elastin leading to wrinkles, and understanding these mechanisms is key to optimal management of aging syndromes (Figure 1). For example, a clinician recognizing premature gray hair and a compatible family history, might check peripheral blood telomere length and identify a short telomere syndrome, allowing for earlier detection and treatment of pulmonary fibrosis, and helping to preserve quality and duration of life. Age-dependent biological changes may be differentially exacerbated by environmental factors, sleep loss, oncogenic stress, chronic viral infections, diet, and gut dysbiosis. Individual organs may even age at varying rates depending on their respective, genetically-determined biological clocks as well as differential effects of lifestyle and environmental factors (1, 3).

Senescent cells accumulate with age and are fundamental drivers of age-associated pathologies (4). Cellular senescence is characterized by loss of replicative capacity, resistance to apoptosis, and the development of a senescence associated secretory phenotype (SASP), defined by secretome of pro-inflammatory cytokines and chemokines, stem cell stressors, tissue damaging enzymes, and other toxic mediators. Indeed, the use of agents specifically clearing senescent cells (senolytics) or those which modulate their pro-inflammatory secretome (senostatics) have gained attention for their potential in ameliorating age-associated disorders (5). Accelerated senescence may be precipitated by stress signals including DNA damage,

telomere erosion, exposure to radiation or oncogenic stimuli, nutrient starvation, and oxidative and genotoxic stress.

The aging immune system is characterized by cellular senescence, with highly proliferative naïve lymphocytes being replaced by more quiescent effector and memory cells in older individuals. Aged T cells display reduced T cell receptor diversity, a more rigid T helper phenotype, and SASP (6). Age-dependent remodeling also significantly affects the phenotype of B cells as well as different subsets of innate cells (7, 8). The primary drivers of immunosenescence include telomere dysfunction, thymic involution, mitochondrial dysfunction and perturbed proteostasis. Cumulative exposure to infectious agents, environmental pollutants, or carcinogens leads to high replicative demands, which can accelerate senescence (9, 10). Immunosenescence compromises protective responses necessary to control microbes, viruses, and tumors, while impairing regulatory mechanisms that prevent autoimmune diseases. Thus, immune aging drives immunodeficiency and a chronic sterile low-grade inflammation referred to as inflammaging.

Distinct molecular and biological drivers of immunosenescence can be associated with specific clinical manifestations, such that recognizing molecular aging phenotypes may help personalize health care within the aging population. These phenotypes linked to defined biological mechanisms can be termed endotypes.

Immune-related endotypes are particularly relevant in lung transplant candidates and recipients. The median age of lung transplant recipients continues to increase, rising from 46 to 60 years over the past 20 years (11). Further, telomere dysfunction is a common indication for lung transplant, a surgery that addresses pulmonary but not immune sequelae of this systemic process. Finally, lung transplant is a profound physiological stress that can unmask aging biology. Table 1 summarizes biological manifestations of immune aging and corresponding treatment proposals in the lung transplant population. While this review focuses on immune aging biological mechanisms and their

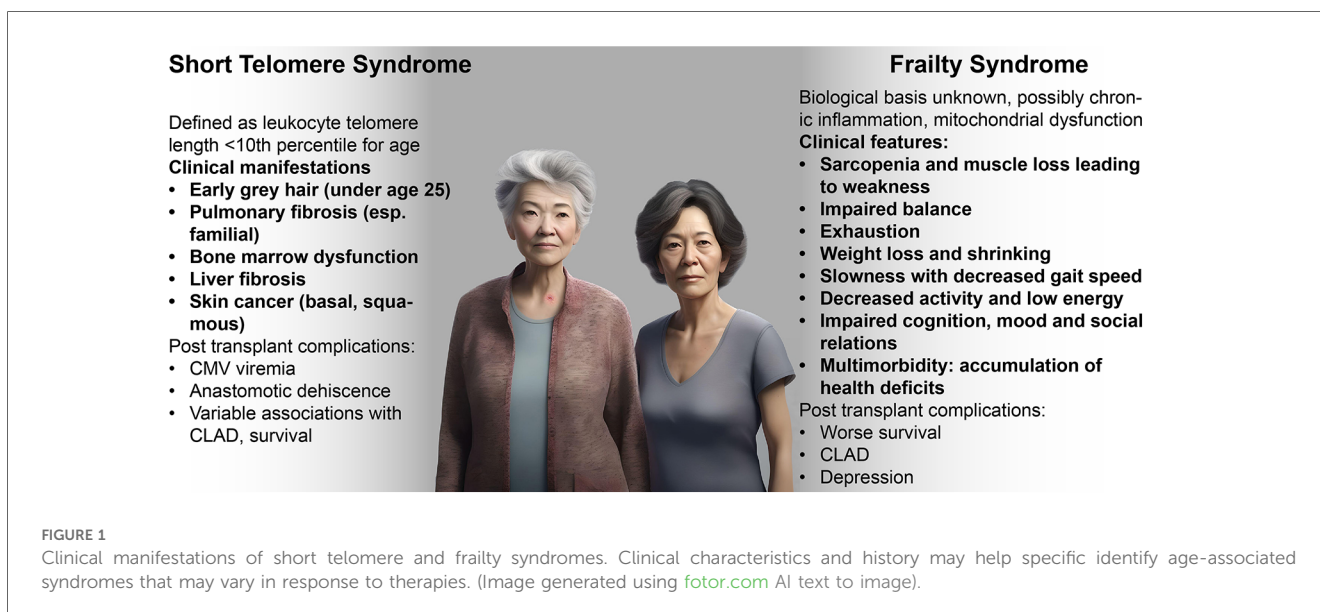


TABLE 1 Examples of possible immune aging biology-based treatment strategies.

Primary mechanism	Biological phenotype	Clinical manifestations	Treatment approaches	References
Telomere dysfunction	DNA damage response SASP Replicative senescence	Idiopathic pulmonary fibrosis Bone marrow dysfunction. CMV reactivation	Tailored immunosuppression and infection prophylaxis. Transfusion and bone-marrow stimulants	(12–18)
Preceding CMV infection	Inflation of memory T cells Impaired donor-specific responses	Infection susceptibility CMV reactivation Graft dysfunction	CMV prophylaxis and aggressive treatment	(19–21)
Thymus involution	Reduced TCR repertoire	Increased risk of cancer and infection	Vaccination and infection prophylaxis	(22–26)
Impaired bone marrow hematopoiesis	B-cell dysfunction	Hypogammaglobulinemia Impaired vaccine responses	IVIG Alternate vaccination strategies	(27–30)
Mitochondrial dysfunction	Increased ROS generation Immune activation (e.g., IL-6)	Sarcopenia Frailty	Structured exercise programs Myostatin inhibitors Protein supplementation IL-6 antagonists	(31–37)

clinical manifestations in lung transplant recipients, these observations are broadly relevant to gerontology.

## 2 Biologic mechanisms of immune aging

### 2.1 Telomere dysfunction

Telomeres are ribonucleoprotein structures at the end of chromosomes comprised of tandem repeats of TTAGGG sequences and a shelterin protein complex. During cell division, the DNA at the chromosome terminus is not entirely copied due to defects in DNA replication machinery, resulting in single-stranded DNA overhangs. The shelterin complex protects the terminal and single stranded DNA resulting from incomplete replication from being recognized by DNA repair machinery. Telomeres shorten with each round of replication. Telomerase is an enzyme recruited by the shelterin complex which drives *de novo* synthesis of TTAGGG repeats at the telomere ends, thereby maintaining telomere length (38, 39). Telomeres progressively shorten with age and defects in telomere maintenance machinery drive premature ageing phenotypes (40, 41). Short telomeres are an important risk factor for early mortality and result in predisposition to developing age-related disorders including cardiovascular diseases, cancer, and osteoporosis (42–47), whereas, long telomeres may increase the risk of certain cancers, such as melanoma and chronic lymphocytic leukemia (48). Indeed, the heterogeneity in human telomere function may reflect this balance between promoting cellular regeneration and limiting cancer risk.

While telomeres tend to become shorter with cellular replication, physiologic consequences manifest only when telomers reach a critical length. Critically short telomeres no longer bind to Shelterin complexes, leading to uncapping of single-stranded DNA and subsequent recognition by DNA damage response pathways, such as ataxia-telangiectasia mutated (ATM)-dependent activation of p53 and checkpoint kinases (49). These DNA damage responses halt cell cycle progression leading to replicative arrest and development of

SASP (50). Clinically, telomere length is generally reported as an average number of base pairs within a cell type. Notably, across cell populations and even within the same cell, telomere lengths have a broad distribution. Thus, the finding that lower mean telomere lengths drive pathology likely reflect that an increased number of cells are approaching the critical limit that will drive senescence.

Telomere shortening may be resulted by genetic factors or senescence-precipitating environmental cues. Mutations in telomere maintenance machinery or defects in DNA repair signaling result in a spectrum of inheritable diseases known as telomeropathies (51). Telomeropathies present with pulmonary fibrosis, liver cirrhosis, aplastic anemia, and sporadic acute myelogenous leukemia; and multiple pathologies may concurrently manifest in the same individual due to the common underlying etiology of telomere dysfunction (52). Telomere shortening is also accelerated by lifestyle factors including obesity, diet and exercise, and smoking. Exposure to harmful substances including pollutants, genotoxic or carcinogenic agents, and radiation also drive telomere shortening (2, 53). The clinical complications of telomere dysfunction are detailed in Section 3.1.

### 2.2 The epigenetic clock

While telomere dysfunction is a well-studied aging mechanism, particularly in the transplant population, it is only one of many biological mechanisms driving aging phenotypes. An important regulator of biological aging is epigenetic age. While there are also age-associated changes in histone modifications and chromatin accessibility, epigenetic clocks are typically defined based on patterns of DNA methylation (54). Cytosine guanine dinucleotides (CpG) in DNA sequences undergo cytosine methylation by DNA methyltransferases (DNMT), generally rendering the DNA regions less transcriptionally active. Conversely, ten-eleven transposition (TET) participate in DNA demethylation. This process of reversibly redacting DNA regions is a large part how cells retain their identities. For example, T cells have a set of specific methylation regions that have been shown to determine regulatory vs. effector functions (55).

Secondary to cell type, DNA methylation patterns play an important role in aging phenotypes.

Consistent patterns of DNA methylation changes have been observed across many cell types conserved across species. These sites, linked to long-term histone-based epigenetic silencing, are associated with development, cancer, obesity, and longevity-related genes (56). Linear combinations of these DNA methylation patterns can allow construction of epigenetic clocks that are strongly associated with cell age. These patterns likely reflect imperfections in the epigenetic maintenance system, and these clocks have meaningful age acceleration in response to environmental stressors. Epigenetic clocks include Horvath's clock, Hannum's clock, DNA PhenoAge, and DNA GrimAge (54, 57). These clocks differ in their training and tuning to target either time since birth, rate of aging, or time to death. Schizophrenia, for example, primarily accelerates mortality clocks, like GrimAge (58). Mood stabilizers and antipsychotics are associated with decreasing epigenetic age, and dietary interventions to improve longevity have been shown to decrease GrimAge (59). It remains to be seen whether therapies that selectively modify epigenetic age would have a corresponding effect on mortality (60).

Divergence between chronologic and biologic age, as measured by epigenetic clock, can be relevant in transplant recipients. In a cohort of renal transplant recipients, peripheral blood DNA methylation age was a better predictor than chronologic age of infections in the first year (61).

## 2.3 Senescence in the adaptive immune system

### 2.3.1 Thymic involution

The thymus is a bilobed organ in the anterior mediastinum that is the primary site for maturation of T cells. The cellular composition of thymus includes thymocytes (immature T cells) and thymic epithelial cells, which play a role in negative selection of alloreactive cells. T cells released by thymus are immunologically naïve until they recognize an antigen with high affinity. Antigen recognition together with costimulatory signals leads to their proliferation and differentiation into effector cells. A subset of effector cells survives long-term to provide immunological memory to the specific antigen. Thymus function declines with age, otherwise known as age-related thymus involution. Thymus involution leads to reduced proportions of thymocytes and thymic epithelial cells, increased perivascular space, and adipose tissue deposition in thymic compartments. Disruption of thymic architecture results in loss of naïve T cells and a relative increase in memory T cells, thereby leading to reduced T cell-capacity of recognizing diverse pathogen-derived antigens leading to increased susceptibility to infection (6). Thymic involution may also explain decrease in immune responses to vaccines (62).

T cell maturation requires T cell receptor rearrangement and results in the formation of T cell receptor excision circles (TRECs) (63, 64). TRECs are stable and non-replicative, and

progressively diminish with cell divisions. TRECs are therefore a useful measure of thymic output. Recent thymic emigrants are identified by elevated copy numbers of TRECs, and TREC frequency declines with aging (22, 23). Studies have correlated loss of transplant recipient thymic function, as measured by decreased TREC frequency, with poor post transplantation outcomes including cancer (24) and viral infections (25). Pre-transplant thymic function is identified as independent risk factor for viral infection post solid organ transplantation (26).

Strategies to address thymus loss could potentially have a role in transplantation. Grafting thymus lobes from an allogeneic donor into the neonatally thymectomized mice induced tolerance towards tissue antigens of the donor (65–67). Hence, concurrent thymus transplantation is a possible strategy to induce allospecific tolerance, while preserving immune function. Strategies to reverse thymus involution might also use thymostimulatory cytokines (68).

### 2.3.2 T cell dysfunction

Cumulative antigenic exposure results in accumulation of terminally differentiated pro-inflammatory T cells with aging. Aged T cells display senescence hallmarks including short telomeres, DNA damage responses, replicative arrest, resistance to apoptosis, and secretion of pro-inflammatory cytokines (6). T cell aging is accelerated by chronic viral infections such as CMV, which drives the expansion of terminally differentiated CD8+ effector memory cells ( $T_{EMRA}$ ) (69).  $T_{EMRA}$  cells exhibit markers of senescence while retaining the cytokine production and cytotoxicity potential of precursor cells (19).  $T_{EMRA}$  cells may have greater potential to drive allograft damage, as increased proportions of circulating  $T_{EMRA}$  correlate with higher risk of renal graft failure (20). In lung transplant recipients, CMV infection increases the risk of graft failure and susceptibility to infections (21). Hence, age-associated T cell defects driven by persistent viral antigenic stimulation may worsen clinical outcomes in transplantation recipients.

### 2.3.3 Regulatory T cell dysfunction

Tregs are professional anti-inflammatory cells that have a critical role in limiting allograft rejection (70). Aging correlates with a rise in inflammatory T cells at the expense of Tregs, The preponderance of data link robust Treg responses to improved outcomes, with the caveat that acute rejection drives a compensatory Treg expansion, limiting their utility as a biomarker (71). Tregs in older recipients transition to an effector phenotype in the context of IL-6 stimulation, a cytokine associated with senescent cells, Age-associated inflammation further drives dysregulation of microbiota in aged lungs perpetuating an inflammatory phenotype (72). Accordingly, therapeutic targeting IL-6, restoration of lung eubiosis by healthy diet and exercise harnessing the gut-lung axis, or directly administering *in vivo* expanded Treg have been proposed as strategies to improve graft survival. Notably, the limited proliferative capacity of Tregs from transplant recipients has proven a critical barrier to their development as a therapeutic (73).

### 2.3.4 B cell dysfunction

B-cells and plasma cells generate antibodies in concert with T cell help. Such antibodies are key to immune responses to infections, but also drive antibody-mediated rejection. B cell antigen specificity and immunoglobulin type are refined through DNA rearrangements, known as class-switch recombination, which involves exchanging the IgM or IgD heavy chain region of the antibodies to an IgA, IgG, or IgE type, resulting in improved ability to eliminate pathogens, and somatic hypermutation, involving DNA mutations that generate antibodies with high antigen affinity. However, B cell precursors derive from the bone marrow, and an age-dependent shift in bone marrow myelopoiesis leads to impaired generation of B cell precursors (74). Extrinsic and cell intrinsic factors necessary for commitment, differentiation and maintenance of mature B cells are reduced with age (75, 76). Antibodies produced by aged B cells are less potent in class switching and somatic hypermutation (77), which may manifest as poor vaccination outcomes in elderly (7). As part of age-associated inflammation, B cells displaying a hyperreactive pro-inflammatory phenotype accumulate with age (78). Aged B cells respond in a B cell receptor independent innate fashion and contribute to inflammation and disease pathogenicity in autoimmune and autoinflammatory disorders (78).

The inflammatory phenotype of aged B cells may reduce allograft tolerance, as depletion of B cells delayed allograft rejection in aged mice and adoptive transfer of aged B cells worsened graft survival in young mice in a model of skin transplantation (79). However, an understanding the role of aged B cells in regulating outcomes in lung transplantation remains nascent.

## 2.4 Aging in the myeloid lineage

### 2.4.1 Macrophages and dendritic cells

Lung-resident alveolar macrophages exhibit a dual role in modulating inflammation. At steady state, alveolar macrophages clear apoptotic debris and subdue inflammation. These anti-inflammatory macrophages play a protective role in solid organ transplantation. For example, they promote the resolution of inflammation resulting from ischemia-reperfusion injury (80, 81). However, upon sensing of pathogens or tissue debris, alveolar macrophages are activated to release proinflammatory mediators which promote tissue injury (8, 82). Aging leads to impaired apoptotic clearance and anti-inflammatory cytokine production by macrophages thereby leading to prolonged inflammation and tissue injury (8, 83). Reduced reparative functions of aged alveolar macrophages potentiates inflammation potentially impairing graft survival.

Similarly, dendritic cells display an age-associated decline in function, evidenced by reduced phagocytosis, impaired antigen processing and presentation, reduced migration potential, diminished expression of co-stimulatory molecules and impaired cytokine production, leading to a dampened adaptive response in aged individuals and altered alloimmune responses in solid organ transplantation (6, 8).

### 2.4.2 Myeloid derived suppressor cells and dendritic cells

Myeloid derived suppressor cells (MDSCs) are a heterogenous cell population of myeloid lineage with potent immunosuppressive activity. MDSCs are pathologically activated in inflammation, infection, and cancer. Aging skews the differentiation of hematopoietic progenitor cells towards myeloid lineage resulting in reduced lymphopoiesis and correspondingly increased proportions of myeloid derived suppressor cells (MDSCs). MDSCs inhibit T cell proliferation and are associated with improved graft survival in models of solid organ transplantation (84). Aged MDSCs express increased levels of cell cycle-associated senescent markers and can suppress T cells (85), potentiating their beneficial role in suppressing alloimmunity in solid organ transplantation.

## 2.5 Mitochondrial dysfunction

Mitochondria are cellular organelles responsible for the synthesis of cellular ATP and are thus considered the powerhouse of the cell. Mitochondrial dysfunction is a well-known hallmark of age-associated senescence. Deletion of genes encoding proteins involved in mitochondrial function also promotes T cell dysfunction and leads to the acquisition of a pro-inflammatory phenotype (86, 87).

Mitochondrial ATP synthesis involves the Krebs cycle and oxidative phosphorylation. The Krebs cycle utilizes the catabolic end products of sugars, fatty acids, and proteins to generate substrates for oxidative phosphorylation (88). Electrons from TCA cycle derivatives are transferred sequentially to the respiratory chain complexes and eventually to molecular oxygen. The electron transfer is coupled with the release of protons into inter membrane space leading to the formation of an electrochemical gradient which is subsequently resolved by the ATP synthase, which couples the restoration of protons back to the matrix with ATP synthesis (89). Senescent cells are less efficient in ATP generation due to reduced mitochondrial membrane potential and impaired oxidative phosphorylation (90).

Reactive oxygen species (ROS) are a major by-product of ATP synthesis. Premature leak of electrons from respiratory chain complexes results in partial reduction of O<sub>2</sub>. The O<sub>2</sub><sup>-</sup> free radical is rapidly dismutated to H<sub>2</sub>O<sub>2</sub> by enzymatic actions and enters the cytosol to convey signaling pathways involved in cell proliferation, differentiation, and apoptosis (91–93). Senescence is associated with increased ROS production (31). Conversely, mitochondrial ROS are important drivers of cellular senescence. ROS production caused by dysfunctional mitochondria can drive oxidative DNA damage leading to cell cycle arrest (94). Furthermore, ROS lead to the creation of γH2AX foci, histone triggers of the DNA damage response that drive a senescence phenotype (95). ROS are also potent inducers of telomere dysfunction and can result in replicative senescence. Experimentally, ROS promote hepatocyte damage in a model of liver ischemia reperfusion injury (96). ROS scavenging leads to

rescued telomere shortening in CD8+ T cells and extended lifespan in fibroblasts cultured *in vitro*.

### 2.5.1 Mitochondria in frailty, sarcopenia, and immunosenescence

Inherited disorders of mitochondrial function primarily manifest with myopathies, or disorders of skeletal muscle. Mitochondrial dysfunction can also manifest as encephalomyopathy, neuromuscular disorders, cardiac arrhythmias, diabetes, loss of vision and hearing, and stunted growth. The age-related loss of skeletal muscle, termed sarcopenia, is clinically defined as pathologically reduced muscle mass and strength and considered distinct from atrophy secondary to inactivity. Sarcopenia increases the risk of falls, fractures, physical disability, and death (97, 98). Sarcopenic muscle is characterized by increased mitochondrial DNA mutations, leading to the synthesis of dysfunctional respiratory chain components with reduced ATP synthesis capacity and increased ROS production (32). Physical exercise is potentially the most effective treatment strategy for sarcopenic individuals (99). Although the effect of exercise on sarcopenia is more complex than just muscle activation, exercise is associated with improved muscle mass, strength, and physical performance in older adults (33). Restoring metabolism of aged myeloid cells by targeting lipid signaling pathway may help decrease age-associated inflammation and restore mitochondrial homeostasis (100). Alternatively, controlled physical exercise promotes generation of ROS (101, 102) and simultaneous upregulation of antioxidant enzymes which counteract ROS generation (103). Exercise may help reduce the effects of oxidative stress in advanced age and thereby delay the onset of sarcopenia in physically active elderly population.

Older adults with sarcopenia have increased circulating cell-free mitochondrial DNA (104). Stressed cells release endogenous contents that are recognized by pattern recognition receptors (PRRs) present on antigen presenting cells, induce an inflammatory response. Such endogenous moieties are referred to as danger associated molecular patterns (DAMPs). Mitochondrial DNA is capable of functioning as a DAMP when released into the cytosol as well as the circulation. Cell free mitochondrial DNA induces pro-inflammatory pathways to promote IFN- $\beta$  release (105, 106). Furthermore, high levels of mitochondrial DAMPs in circulation are associated with increased severity of primary graft dysfunction, i.e., severe acute lung injury in first 72 h of transplantation which is a major cause of mortality in lung transplant recipients (107). Inhibition of receptors sensing damaged mitochondrial components rescued graft injury in a mouse orthotopic lung transplant model of primary graft dysfunction (34).

Systemic accumulation of ROS in sarcopenic patients may potentially contribute to immune activation (108). In a model of skin transplantation, mice undergoing regular exercise had improved graft survival (109). Interestingly, prolonged and exhaustive exercise promotes endotoxemia and systemic inflammation (110, 111). Thus, structured exercise interventions are worth investigating to address immune activation from mitochondrial dysfunction.

Beyond the role of systemic mitochondrial dysfunction in immune stimulation, dysfunctional mitochondria can directly drive immunosenescence through lymphocyte and myeloid cell dysregulation. Specifically, mitochondrial activities, including glycolysis and oxidative phosphorylation are implicated in T and B cell activation, differentiation, and proliferation, and mitochondrial impairment leads to a shift towards myeloid proliferation (112).

## 3 Clinical manifestations and approaches to immune aging

### 3.1 Clinical complications of short telomere syndrome post lung transplantation

As described above, telomere length is genetically determined with a defined normal range, but germline or somatic mutations in telomerase maintenance genes can increase the rate of telomere shortening that usually occurs with aging, leading to premature aging syndromes. The short telomere syndrome (STS) refers to a constellation of clinical manifestations caused by mutations in the telomerase and other telomere maintenance genes. The STS presents as degenerative clinical phenotypes of organ failure across multiple organ systems. The adult clinical presentation of the STS phenotype can include pulmonary fibrosis, with usual-interstitial pneumonia pattern pulmonary fibrosis being the most common pulmonary manifestation of STS; emphysema and other lung diseases; cryptogenic cirrhosis and hepatopulmonary syndrome; immunodeficiencies; bone marrow suppression or failure; bone marrow derived malignancies such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML); and other malignancies including squamous cell cancers (113). Clinical features and presentations that can heighten the suspicion for STS are contrasted with frailty syndrome in Figure 1 (114).

Telomere length measurement has become routine practice in some clinical Interstitial Lung Disease (ILD) programs but has not been integrated in the assessment of lung transplant candidates with IPF at most lung transplant centers in the US. Further, uniformity in standardization of testing is still not established (113). The threshold of age-adjusted lymphocyte telomere length the <10th percentile has been examined as a predictor of worse outcomes in IPF patients receiving immunosuppression. Age adjusted telomere lengths <10th percentile of normal (shortest telomere lengths) can be found in 40% of patients with familial IPF and 25% of sporadic cases without a family history of fibrosis.

The implications of telomere length in IPF lung transplant recipients have been of growing interest. STS has been reported to be twice as common in IPF lung transplant recipients compared to those with IPF who do not receive transplantation (115). In one cohort, 32% of IPF lung transplant recipients had a telomere length <10th percentile (116). Questionnaire-based screening followed by comprehensive telomere testing identified critically short (<1st percentile or known pathological variant) in 8% of

TABLE 2 Multidisciplinary team framework of care Pre or post lung transplant recipients With short telomere syndrome (113, 114).

- Consult hematology to address treatment and evaluation of cytopenias and need for bone marrow biopsy
- Consult genetic counseling to assist with familial risk for short telomere syndrome risk.
- Consult hepatology for liver parenchyma evaluation and appropriate imaging for evidence of cirrhosis, evaluation for hepatopulmonary syndrome and need for liver transplantation.
- Consult Infectious Disease for management of antimicrobial and antiviral prophylaxis in setting of cytopenias
- Routine surveillance skin checks for assessment of skin cancers
- If lung transplant candidate with STS is CMV IgG negative and stable, favor a CMV negative donor if feasible.

ILD transplant candidates (117). Its frequency may justify establishing the diagnosis of underlying STS prior to lung transplantation in effort to anticipate and prevent the post-transplant morbidities and complications described below. Identification of short telomeres may allow strategies to prevent irreversible complications of STS in lung transplant recipients (113, 115, 116). Table 2 provides a suggested multidisciplinary team evaluation of STS in the pre or post lung transplantation (114).

### 3.1.1 Graft-specific complications

Comparisons of STS lung transplant recipients and those with normal telomere lengths have shown inconsistent results in terms of survival and graft outcomes such as primary graft dysfunction (PGD), acute cellular rejection (ACR), and CLAD. Newton et al. reported that STS lung transplant recipients had an increased rate of PGD and CLAD as well as with a nearly 11-fold increased risk of death compared to non-STs referents (116). Similarly, Courtwright et al. found that pre-transplant shortened telomere length was associated with leukopenia and decreased CLAD-free survival after lung transplant (118). Faust et al. found decreased telomere length was associated with leukopenia after transplant but was not associated with worse CLAD-free survival (12). In contrast, a more recent study of IPF lung transplant recipients found that telomere mutations and length was not associated with PGD, ACR, time to CLAD, or post-transplant survival (115). One potential reason for these inconsistencies is that short telomeres were not defined in the same way across all studies.

T-cell immunosenescence may be the predominant reason for the observation of less frequent acute rejection in STS lung transplant recipients. In a cohort of STS lung transplant recipients, there was an age-dependent decrease in acute rejection associated with evidence of immune aging, which was manifest as T cell differentiation, clonal expansion, and exhaustion (119). A similar immunosenescent phenotype has been observed in older renal transplant recipients, with short telomeres, evidence of T cell exhaustion, and decreased rates of acute rejection (120). IPF lung transplant recipients have relatively suppressed donor-specific effector and regulatory T cell responses at the time of transplant. This type of immunosenescence results in a state of anergy that is readily broken with strong cytokine stimulation, such as would be seen with infections (121). Thus, while lower rates of acute graft rejection may be seen in STS transplant

recipients, these recipients are at continued risk of chronic rejection (122, 123).

### 3.1.2 Bone marrow suppression

Bone marrow reserves in STS lung transplant recipients are vulnerable. Cytopenias and bone marrow complications can emerge in the setting of antimetabolite or other immunosuppression medications, and certain antimicrobial and antiviral prophylaxis (124). Short recipient telomere length is a risk factor for clinically significant leukopenia (125). In a cohort with IPF, those who received lung transplantation were more likely to have bone marrow dysfunction requiring bone marrow biopsy (4% vs. 29%) (126). Management strategies to avert or mitigate bone marrow suppression may include dose modification of standard immunosuppression regimen by holding or decreasing antimetabolite therapies, holding viral polymerase inhibitors like valganciclovir, and using dapsone in place of trimethoprim/sulfamethoxazole for *Pneumocystis* prophylaxis (114).

Other than reduction of immunosuppression therapies and avoidance of myelosuppressive antimicrobial and antiviral prophylaxis, treatment for post-transplant cytopenia or bone marrow suppression is mainly supportive. Blood or platelet transfusions and granulocyte colony stimulating factor (G-CSF) for neutropenia have been utilized. G-CSF use has not been shown to increase risk for acute cellular rejection or CLAD when used in severely neutropenic patients (127). There is hesitation to use danazol in this population is due a lack of data and potential risk for MDS and AML (113). Bone marrow biopsy may be necessary to evaluate dyscrasias in certain cases given the risk for MDS and AML (126). Therefore, a multidisciplinary team including hematologists should be considered in the care of STS lung transplant recipients.

### 3.1.3 CMV and other herpes viral infections

STS lung transplant recipients are at higher risk for herpes virus (HSV) and cytomegalovirus (CMV) infections due to T-cell immunodeficiency. Indeed, STS lung transplant recipients have up to a 5-fold increased risk for relapsing CMV viremia (13, 114, 128). As CMV viremia is a risk factor for CLAD, this telomere-dependent impairment of T cell immunity may contribute to increased CLAD risk in STS lung transplant recipients (43, 129). At the same time, several factors can complicate the treatment of CMV viremia in the STS population. STS lung transplant recipients are susceptible to CMV drug resistance and can develop myelosuppression from antiviral medications including ganciclovir and valganciclovir. Alternative treatments with foscarnet or cidofovir have limited utility in certain situations due to renal and bone marrow suppression and poor tolerance. Letermovir, a viral terminase inhibitor, has been approved for the prophylaxis of CMV infection in allogeneic stem cell transplants. Letermovir has been studied off label for CMV prophylaxis in thoracic transplant recipients, including 37 lung transplant recipients, in whom it was well tolerated and effective. Without the side effect of bone marrow suppression, letermovir use may have facilitated antimetabolite therapy in certain

number of patients (130). While there is concern that letermovir may be susceptible to CMV mutations conferring resistance, further study is warranted to determine whether letermovir could have a role for CMV prophylaxis, specifically in STS lung transplant recipients.

Iasella *et al.* (131) reported an increased risk for Epstein-Barr virus (EBV)-associated posttransplant lymphoproliferative disorder (PTLD) in IPF lung transplant recipients, which was postulated to be secondary to STS immune dysfunction (131). When designing care protocol approaches to patients with known STS, consultation with infectious disease providers may be helpful to consider alternative agents to prevent and manage herpes viral infections (113).

### 3.1.4 Liver disease and cirrhosis

Liver abnormalities have been reported in approximately 10% of STS patients. The combination of IPF, liver disease and bone marrow failure is a classic triad associated with severe STS (132). Gorgy *et al.* demonstrated that telomere shortening can also be linked to non-cirrhotic portal hypertension manifested as hepatopulmonary syndrome (HPS). STS patients with progressive HPS can present with clinical manifestations of severe hypoxemia, development of portal hypertension and complications including gastrointestinal bleeding from varices. Liver transplantation can reverse the hypoxemia in HPS however STS patients remain at risk for the development of progressive IPF (133). Several case reports describe combination of liver and lung transplantation in STS patients with end-stage IPF and cirrhosis with acceptable early outcomes (134, 135). Early screening for liver pathologies is recommended in patients with diagnosed STS in the pre-lung transplant period with appropriate laboratory evaluation, imaging, and subsequent referral to a hepatologist if liver disease or cirrhosis is suspected. Continued surveillance and monitoring for liver disease should be continued post transplantation.

### 3.1.5 Cancer risk

Lung transplant recipients are at significantly increased risk of malignancy. Only 76% of double lung transplant recipients and 66% of single lung transplant recipients are free from non-skin malignancies by 15 years post-transplant, with a notable burden of lung cancer in single lung recipients (11). STS does not necessarily increase the risk of developing cancer in this cohort (116), but chronic immunosuppression appears to amplify the cancer risk associated with immune aging. Epigenetic dysregulation in combination with accumulation of DNA damage and senescent cells contribute to oncogenesis in the aged population, while proinflammatory cytokines can support tumor growth and metastasis (136).

Although the overall risk for cancer in STS is relatively low, IPF and STS can be associated with certain malignancies. IPF lung transplant recipients have increased risk for EBV-associated post-transplant lymphoproliferative disease, particularly after receiving alemtuzumab, in induction agent associated with immunosenescence (131). Outside of transplant, individuals with STS have increased risk for myelodysplastic syndrome (MDS)

and acute myeloid leukemia (AML). STS patients who develop MDS or AML may have concomitant lung fibrosis or liver disease or both making treatment decisions complex. The option for hematopoietic stem cell transplant and immunosuppressive regimens may be difficult due to risk for pulmonary injury and the choice for living related donor given the familial nature of STS may be limited (137). Combined bone marrow and lung transplantation has been reported with STS-associated bone marrow failure and ILD (138).

In sum, telomere length may be a potential biomarker pre-transplantation to assess the risk for various post-transplant complications, but the limited and inconsistent evidence from a series of single center studies must be approached with caution. There is insufficient evidence to exclude lung transplant candidates from listing based on the presence of STS categorically, but there may be some circumstances where the severity of liver and/or bone marrow involvement may preclude the potential benefits of lung transplantation.

## 3.2 Donor immune age and its impact on the allograft

The airway epithelium plays an essential role in detecting pathogens and initiating immune responses. However, the lung epithelium is donor derived so its age is determined by the donor date of birth. This can be demonstrated by epigenetic measurements of age, where airway epithelial cell age one-year post-transplant is strongly correlated with donor age but has no association with recipient age (139). Decreasing telomere length in donor peripheral blood cells has been associated with worse CLAD-free survival in one cohort (12). Despite a plausible mouse model demonstrating how short club cell telomeres lead to CLAD pathology (140), other studies have not replicated this finding (121, 141). Telomere dysfunction is sufficiently rare in the lung donor population that we would not recommend screening donors.

Even if the immune age of the allograft is normal at the time of transplant, post-transplant complications may accelerate biological mechanisms of lung aging, with potential clinical implications. There is a substantial turnover in epithelial cells following lung transplant, as evidenced by high levels of donor derived cell-free DNA (142) and diffuse Ki-67 positivity in some airways (14). PGD is associated with both increased airway epithelial epigenetic age (139) and accelerated telomere dysfunction (14). Epigenetic remodeling from PGD is linked to persistent activation of hypoxia signaling, while telomere dysfunction in airway epithelial cells is associated with inflammation and dysregulated remodeling. Thus acceleration of epithelial aging pathways may be a mechanism linking PGD to CLAD risk (14).

## 3.3 Hypogammaglobulinemia

Hypogammaglobulinemia is a symptom of B and plasma cell dysfunction that manifests more commonly at extremes of age.



Primary hypogammaglobulinemia can reflect inherited immunodeficiency, whereas secondary hypogammaglobulinemia may be a side effect of immunosuppressing medications. In practice, it may not be clear whether hypogammaglobulinemia is primary or secondary or a combination. Studies have reported a gradual decrease in immunoglobulin G (IgG) and IgM concentrations with aging, with IgG levels decreasing considerably between the third and sixth decade of life (27).

Hypogammaglobulinemia is a well described phenomenon in adult lung transplant recipients. In these recipients, IgG levels are inversely correlated with bacterial infections, invasive fungal infections, days in the hospital, and CLAD risk (28, 29). Severe hypogammaglobulinemia defined as IgG level <400 mg/dl was associated with CLAD, increased antibiotic use, and bacterial, fungal and CMV reactivation (30). IgA, IgM, and IgG levels may decrease post lung transplantation, and immunoglobulin level screening may be considered before and after transplant to identify patients who may need IgG replacement therapy post lung transplantation to reduce infection risk. Hypogammaglobulinemia can be accompanied by suppression of vaccine responses. Completing the recommended vaccinations prior to transplantation is important aspect of bacterial and viral prophylaxis since multiple immunosuppressive agents administered post-transplant can further attenuate vaccine responses (29). Consultation with a clinical immunologist may be helpful to design protocols and manage recipients with hypogammaglobulinemia to consider immunoglobulin replacement and vaccine protocols.

### 3.4 Impaired vaccine responses

Vaccine responses in transplant recipients may be diminished by immunosenescence, inflammaging, and comorbid disease states (62), all of which are compounded by post-transplant immune suppression. Less than 20% of transplant recipients generated expected responses to the SARS-CoV-2 mRNA vaccine in one study (143). Relative to other solid organ transplant recipients, lung transplant recipients have the most impaired/blunted vaccine responses, for instance, there were 68% patients which did not respond to vaccines in a separate study (144).

Several strategies have been proposed to address poor vaccine responsiveness in transplant recipients. Whenever possible, transplant candidates should receive necessary vaccines prior to transplantation. For recipients transplanted prior to the COVID-19 pandemic, this was not possible, and so a common strategy was to provide additional boosters until acceptable antibody titers were achieved. However, some recipients did not display evidence of immunity despite several boosters. Infusion of virus specific monoclonal antibodies has been used (145), although this strategy has not been consistently effective and can be expensive and susceptible to viral evolutionary escape. As antimetabolites are most strongly associated with poor vaccine responses, a three week pause in antimetabolites around the time of vaccination has been proposed. However, it is not known to what extent this pause could trigger initial or progressive chronic rejection (146).

Other theoretical approaches to improving vaccine doses include using higher antigen doses or novel adjuvants, although there are diminishing returns to additional antigen loads (147). Immune responses vary by vector and route of administration (148), and these approaches have not been well studied in transplant recipients. Other interesting ideas include using senolytics or immune modulatory drugs like mTOR inhibitors, or adjusting vaccine patterns based on circadian rhythms (62).

### 3.5 Immune dysregulation leading to frailty

Frailty is a clinical syndrome characterized by weakness, muscle loss, fatigue, and impaired physical activity. Frailty refers to a general depletion in physiologic reserves resulting in disproportionate decline in health status in response to an otherwise inconsequential stressor (149). Frailty is linked to delisting and death in lung transplant candidates, and predicts worse quality of life and survival post transplantation (62, 150). Intriguingly, incident frailty after lung transplantation is also associated with increased risk for CLAD, suggesting that frailty may be associated with systemic inflammation that can drive chronic rejection (151). A pro-inflammatory subtype of frailty has been identified, with increased levels of IL-6, CRP, PTX3, TNF-R1, and IL-1RA, mitochondrial stress, sarcopenia, malnutrition, and decreased exercise tolerance (152). Age-adjusted short leukocyte telomere length has also been associated with frailty in some cohorts (153). As frailty can be observed even in younger transplant candidates and recipients, there is increasing interest in quantifying frailty to stratify transplant risk and identify individuals for frailty-specific interventions. Frailty is a potentially modifiable risk factor, as exercise programs can improve at least some components of frailty (154). Exercise has been shown to impact immune function, boosting NK and T cell proliferation and cytotoxicity, in particular (155). However, the impact of structured exercise programs on immunosenescence and inflammation in transplant needs further study.

### 3.6 Immunosuppression intolerances

Immunosuppressive medications are relatively more potent in older recipients. Due to alternations in the metabolism of drugs through CYP3A5-enzyme complexes, similar doses of calcineurin inhibitors (CNI) achieve greater blood levels in older patients (156, 157). The clearance of steroids may also decline with age (156–158). Further, mouse and human studies show that tacrolimus is more potent in older immune systems, relating to suppressed calcium influx and intracellular calcineurin levels (159). There is a paucity of clinical trial evidence comparing immunosuppression approaches in older patient cohorts. In clinical practice, responses to immune aging-related side effects, such as leukopenia or infection, tends to be responsive rather than anticipatory.

As an alternative or adjunct to a CNI-based regimen, mTOR inhibitors have been considered to address CNI-based

complications, including renal dysfunction and malignancy. The 4EVERLUNG study combined low-dose CNI and mTORi at 3–18 months post-transplant for a 4-drug immune suppression regimen. At 5-year follow up, 46% of participants had discontinued the 4-drug regimen, there was a trend towards improved CLAD-free survival, but there were no significant differences in long-term outcomes. In animal studies, the mTOR inhibitor rapamycin increases longevity in invertebrates and promotes allograft survival in old mice. Further, low daily doses of a mTOR inhibitor for 6 weeks before administration of influenza vaccine to older adults was shown to increase the antibody response to the vaccine by 20% (160). Whether there is a role for mTOR inhibitors in addressing immune aging in lung transplant recipients remains to be seen, but investigating such biological mechanisms may be necessary for clinical success in such studies.

## 4 Conclusions

Multiple mechanisms drive immune aging, and immune aging phenotypes may have clinically relevant manifestations. Early identification of biological manifestations of aging is important. Because organ systems typically have impressive physiological reserve, biological aging processes begin long before they manifest as physiological phenotypes, and even further before they result functional decline.

Lung transplantation is of particular interest in aging biology for several reasons: STS is an indication for lung transplantation, such that this otherwise rare aging syndrome is highly enriched in the lung transplant population. Lung transplant candidates tend to be older than for other solid organs and they have endured physiologic stresses that may drive age acceleration. Further, potent alloimmune responses necessitate higher levels of immunosuppression, and transplantation itself is a major physiologic stressor that can unmask age-associated pathologies. Although we are gaining experience managing aging transplant recipients, some have questioned the ethics of transplanting older individuals based on the decreased utility in terms of expected survival and the principle of justly granting an “equal chance to live a full life” (161).

Accordingly, lung transplant recipients are particularly sensitive to immune aging complications. Immune aging can be driven by telomere dysfunction, CMV infection, thymus involution, impaired bone marrow hematopoiesis, and mitochondrial dysfunction, and the degree to which these mechanisms contribute may contribute to the variety of

manifestations of immune aging syndromes. While STS is the best-defined immune aging syndrome in this population, lung transplant recipients are also at risk for hypogammaglobulinemia and or immune aging from mitochondrial dysfunction. There are multiple interventions under investigation to address immune senescence mechanisms, including danazol for STS, senolytics to remove senescent immune cells, and exercise and nutrition to address mitochondrial dysfunction. There is a compelling rationale to target investigations of treatment strategies for immune aging mechanisms based on biological phenotypes. However, much work remains to define and match appropriate interventions to endotypes of immune age.

## Author contributions

BK: Writing – original draft, Writing – review & editing. MB: Writing – original draft, Writing – review & editing. JS: Writing – original draft, Writing – review & editing. JG: Conceptualization, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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