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REVIEW

# Elderly patients with multiple comorbidities: insights from the bedside to the bench and programmatic directions for this new challenge in lung transplantation

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## SUMMARY

In aging populations, many patients have multiple diseases characterized by acceleration of the aging process including cardiovascular diseases, metabolic diseases, and chronic kidney disease. Remarkable progress in minimally invasive, interventional therapies, such as percutaneous coronary intervention and transcatheter aortic valve replacement has enabled patients who were previously not transplant candidates because of co-existing problems to become potentially viable candidates for lung transplantation. Recently, we have observed an outstanding and steady increase in patients older 70 years of age with multiple comorbidities who are referred to our high-volume center as potential candidates for lung transplantation. However, the impact of diseases characterized by an accelerated aging process and their treatments on transplant outcomes remains unclear. This review aims to highlight these challenges in the current era of lung transplantation, review the prior literature, and discuss future directions with a multidisciplinary view including translational research, transplant medicine, and surgery, as well as from a programmatic and administrative standpoint.

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## Introduction

Since the first clinical lung transplant was successfully performed in 1983 [1], lung transplantation has evolved into a well-recognized therapy for patients with end-stage lung diseases. According to the most recent registry data from the International Society of Heart and Lung Transplantation (ISHLT) [2], the total number of lung transplants performed in the world continues to increase and is currently ~4000 transplants annually. Interestingly, whereas a recent report from Washington University School of Medicine, one of the most historic and high-volume transplant centers in the United States, demonstrated that conservative selection for the recipients' age led to excellent long-term survival [3], there has been a steadily increase in the number of lung transplant recipients who are older than 70 years of age [4]. In aging populations, however, many patients have multiple diseases characterized by acceleration of the normal aging process, such as cardiovascular disease [e.g., coronary artery


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disease (CAD), valve disease, aortic dissection], metabolic disease (e.g., diabetes mellitus, morbid obesity, chronic kidney disease), and cancer. The common underlying disease mechanisms include oxidative stress, telomere shortening, and cellular senescence [5] (Fig. 1). Given persistent and significant donor organ shortages and the current, suboptimal outcomes of lung transplantation, the best course of action in elderly patients with end-stage lung disease and multiple comorbidities remains uncertain. Herein, we learn from previous experience and address the future directions for care of elderly patients with age-related comorbidities by highlighting essential issues in a multidisciplinary fashion. Transplant surgeons should continue to take up the challenge of providing hope to these patients.

## Review of the literature

### Cardiovascular comorbidities

Historically, lung transplantation was not considered for older patients with major cardiovascular comorbidities. However, recently, thanks to remarkable progress in minimally invasive, interventional therapies, such as percutaneous coronary intervention (PCI) and transcatheter aortic valve replacement (TAVR) [6,7], physicians caring for elderly patients have the ability to treat co-existing problems, enabling some elderly patients with cardiovascular comorbidities become potentially viable candidates for lung transplant. Therefore, cardiovascular disease, a major chronic disease associated with accelerated aging, has been increasingly seen in elderly lung transplant candidates [8].

While the most recent consensus document for selection of lung transplant candidates from the 2014 working group of the ISHLT places CAD equivocally under the heading of relative contraindications [9], the majority of the lung transplant community recognizes that the negative impact of prior CAD on post-transplant outcomes can be minimized in experienced centers by effective palliation with either prior intervention, such as PCI, or concurrent coronary artery bypass grafting (CABG) surgery [10]. That said, some series also suggest that prior CAD should serve as an important risk factor in lung transplant candidates and may identify recipients who will underperform when long-term mortality metrics are examined [11]. While I agree that prior PCI or CABG alone should not preclude transplant candidacy, we should take these prior interventions into account when discussing multiple comorbidities in the elderly patients with lung transplantation. One recent largest retrospective study using the United Network for Organ Sharing Standard Transplant Analysis and Research database suggests that perhaps patients with prior CABG should be candidates only for single lung transplant [12], which is basically in line with our current strategy where the option for single lung transplant is also prioritized for those elderly patients who need concurrent CABG because of their severe CAD that precludes a PCI option with dual antiplatelet therapy because of their closing window for transplantation.

In contrast, the impact of concurrent aortic or mitral valve disease, neither pretransplant nor post-transplant, on transplant outcomes has been sufficiently discussed; although, there are case reports of successful valve repair or replacement in lung transplant recipients [13,14]. This is a long-standing question. Most of the limited evidence available supports prior heart valvular disease, in particular severe aortic or mitral diseases, as

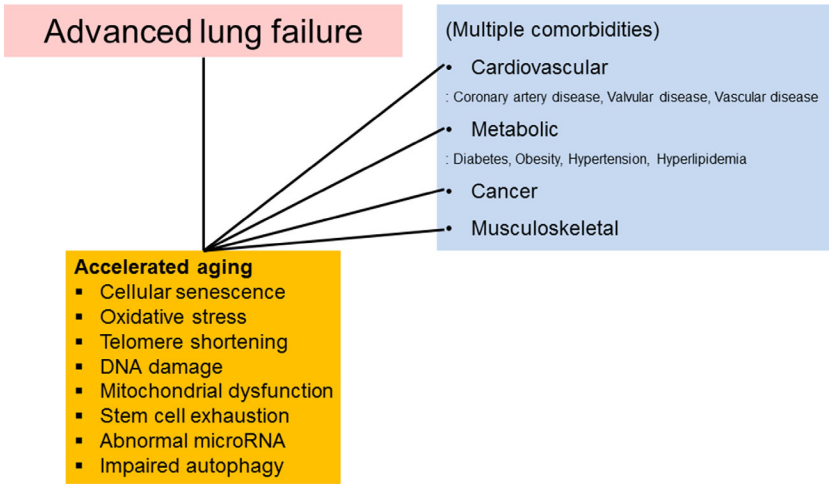


**Figure 1** An accelerated aging process, characterized by unique signaling pathways and cellular events including cellular senescence, telomere shortening, or stem-cell exhaustion, underlies most advanced lung diseases and their major comorbidities such as cardiovascular diseases, metabolic diseases, malignant diseases, or musculoskeletal diseases.



Transplant International 2020; 33: 347–355

an absolute contraindication for lung transplantation, despite three decades of successfully treating heart valvular diseases [15]. This is not attributed to technical complexity of such surgical procedures but likely because the physiological complexity and burden of concomitant heart valve surgeries with the risks inherent to lung transplantation are unanimously considered to be too excessive to be duly managed and yield acceptable transplant outcomes. In addition, while a series of cases with severe endocarditis for the patients with prior valve replacement or those who underwent concurrent valvular surgery have been addressed by the very experienced lung transplant experts (personal communication), this imminent risk should be strongly borne in mind and these exclusively high-risk patients who would be deemed to be a candidate otherwise should be referred to the high-volume centers.

However, with the recent remarkable progress in catheter-directed interventions, such as TAVR [16–18], there is currently an ongoing transformation in transplant candidacy consideration. These inventions enable patients who were not previously considered for organ transplantation to become viable candidates in the absence of other contraindications. Interestingly, in patients with end-stage liver diseases, the issue of concurrent severe aortic valve stenosis has been well addressed, and acceptable outcomes after liver transplantation in patients who have undergone TAVR have been reported [19]. Similar work is needed in patients with end-stage lung disease.

Conversely, the impact of chronic lung disease on clinical outcomes following TAVR has been well studied. The PARTNER (Placement of Aortic Transcatheter Valve) trial precisely reported that the patients with chronic lung disease who underwent TAVR had worse outcomes than those without chronic lung disease. In patients with chronic lung disease, poor mobility and oxygen-dependency were independent predictors of 1-year mortality, and in patients with chronic obstructive pulmonary disease, poor mobility predicted a lack of benefit after TAVR. Many of these patients appeared to be possible candidates for lung transplantation when assessed on other criteria [20,21].

The available literatures are very few regarding the association of other vascular diseases including peripheral vascular disease (PVD) and aortic aneurysm and lung transplantation whereas those demonstrating the impact of PVD on postheart or abdominal transplantation clinical outcomes have been well reported [22–24]. Indeed multiple reports have supported that the presence of symptomatic PVD was one of the strongest predictors of mortality after solid organ transplantation. However, as is addressed above with TAVR for the heart valvular diseases, emerging remarkable progress with endovascular aortic repair (EVAR) minimally invasive procedure has been changing the face of the therapeutic strategies for PVD and aortic diseases with success [25,26]. At our institution, we have seen increasing number of referrals of those patients with significant vascular diseases with or without prior EVAR while we remain selective at this point in time when discussing their candidacy for lung transplantation.

While the number of TAVR or EVAR programs continues to increase dramatically, this is also a cohort of patients that exclusively should undergo the evaluation and/or the procedure of lung transplantation at high-volume centers with great cardiovascular expertise.

### Metabolic comorbidities

There is a complex relationship between lung transplant and metabolic disorders including diabetes, morbid obesity, and metabolic syndrome. Diabetes is highly prevalent prior to transplantation and early post-transplantation [27,28]. In particular, up to 60% of patients with cystic fibrosis have been reported to have diabetes. More importantly, the presence of diabetes is associated with a significantly increased risk for death on the wait list before lung transplantation in patients with cystic fibrosis, but does not influence survival after transplantation [29]. However, poorly controlled diabetes prior to transplantation is associated with poorer outcomes and a higher incidence of diabetes-related complications following lung transplantation [30].

With regards the effects of obesity, several studies have demonstrated that a healthy body mass index (BMI) is a predictor of success in lung transplantation [31]. High BMI is associated with a greater incidence of post-transplant mortality [32], an increased risk of developing new-onset diabetes after transplant [33], and has a negative impact on post-transplant functional status and quality of life [34].

It is well recognized that the drugs currently used for post-transplant immunosuppression have side effects resulting in metabolic derangement [35]. Notably, both cyclosporine and tacrolimus are associated with hypertension, hyperglycemia, and dyslipidemia, which are the main features of metabolic syndrome, a term that refers to a cluster of cardiovascular risk factors [36,37]. Indeed, post-transplant metabolic syndrome (PTMS) has been well documented after abdominal organ transplantation [38,39] but few reports have discussed PTMS

following lung transplantation [40]. PTMS is an appropriate term to consolidate several existing comorbidities including diabetes, hypertension, obesity, and atherogenic dyslipidemia and understand their impact after lung transplantation. With the underlying mechanisms of the aging process, there is a complex interplay among multiple determinants affecting outcomes (Table 1). In particular, new-onset PTMS following transplantation can augment the progression of existing major cardiovascular or metabolic diseases and negatively impact the quality of the lung graft, leading progressively to very poor outcomes.

## Accelerated aging: underlying mechanisms impacting transplant outcomes

Chronic progressive lung diseases that lead to advanced lung failure, major cardiovascular diseases, metabolic diseases, cancer, and musculoskeletal disease, such as sarcopenia, share a mutual underlying disease mechanism—an accelerated aging process (Fig. 2). The accelerated aging process is characterized by multiple and complex signaling pathways and cellular events including cellular senescence, oxidative stress, telomere shortening, DNA damage, mitochondrial dysfunction, and stem-cell exhaustion, which have been well described elsewhere in particular in an excellent review by Dr. Barnes [5].

Many large series have been published to date examining the impact of the recipient's age on lung transplant outcomes [41–43], and specific risk factors with a negative impact on post-transplant outcomes have been identified in elderly patients. These risk factors include prior CAD, diabetes, age greater than 75 years, pulmonary hypertension, double lung transplantation, and the intraoperative usage of cardiopulmonary bypass [44–46]. Currently, we do not have cut-off age for a lung transplant candidate while the oldest patient ever was 81 years old and we had a couple of other octogenarian recipients who underwent lung transplantation at our institution. The recognition of these risk factors will certainly help clinically highlight patients with lower survival benefits from lung transplantation and patients who will require a higher acuity of care to yield outcomes similar to those without such risks. Outcomes research plays a pivotal role in any field of clinical medicine but is particularly needed in challenging fields like lung transplantation. However, when dealing with elderly patients with multiple comorbidities, in whom an interplay of factors contribute to their clinical condition, currently available clinical evidence does not appear sufficient to appropriately deal with the critical question that arises: to transplant or not to transplant.

**Table 1.** Common comorbidities in elderly patients with end-stage lung disease.

| Comorbidity | Transplant-associated complications that may by an augmenting factor |
|---|---|
| Cardiovascular (CAD, Valvular, PVD) | Steroid-induced vasculopathy, PTMS |
| Metabolic (DM, Obesity, HL, HT) | PTMS |
| Cancer | Immunosuppression |
| Musculoskeletal (Sarcopenia) | PTMS |

CAD, coronary artery disease; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; PTMS, post-transplant metabolic syndrome; PVD, peripheral vascular disease.

Interestingly, although there is a strong correlation between short telomeres, which is one of the major features of the accelerated aging process, and the pathogenesis of idiopathic pulmonary fibrosis, neither of two previous reports examining the effects of telomere length on lung transplant outcomes demonstrated an association between recipient telomere length and adverse outcomes [47,48]. Nonetheless, a recent paper published in the American Journal of Respiratory and Critical Care Medicine [49] demonstrated that a high-risk recipient group who had a short telomere defect had inferior transplant outcomes as compared with patients without the defect as a result of impaired cytomegalovirus (CMV) immunity leading to CMV-associated major complications including end-stage kidney disease. This suggests that accelerated aging and the associated telomere shortening impacts transplant outcomes independent of standard metrics, such as age or comorbidities.

Indeed, both telomere-length-dependent and telomere-length-independent mechanisms contribute to distinct molecular programs of T-cell apoptosis with aging [50]. Most importantly, a recent study that focused on the genetic variation in telomere-related genes suggested that these genotypic analyses could help identify patients at increased risk for early death or chronic lung allograft dysfunction (CLAD) after lung transplantation [51]. This study also suggests that such genotypic analyses, targeting alterations typical of the accelerated aging process, may better tailor or personalize post-transplant management leading to optimal post-transplant outcomes. Another very recent interesting paper focused on pediatric renal transplant recipients that suggest activation of mechanisms preserving telomere length and telomerase activity regulating factors on the quality of allografts among young recipients appears to be in line with this direction [52].



Transplant International 2020; 33: 347–355

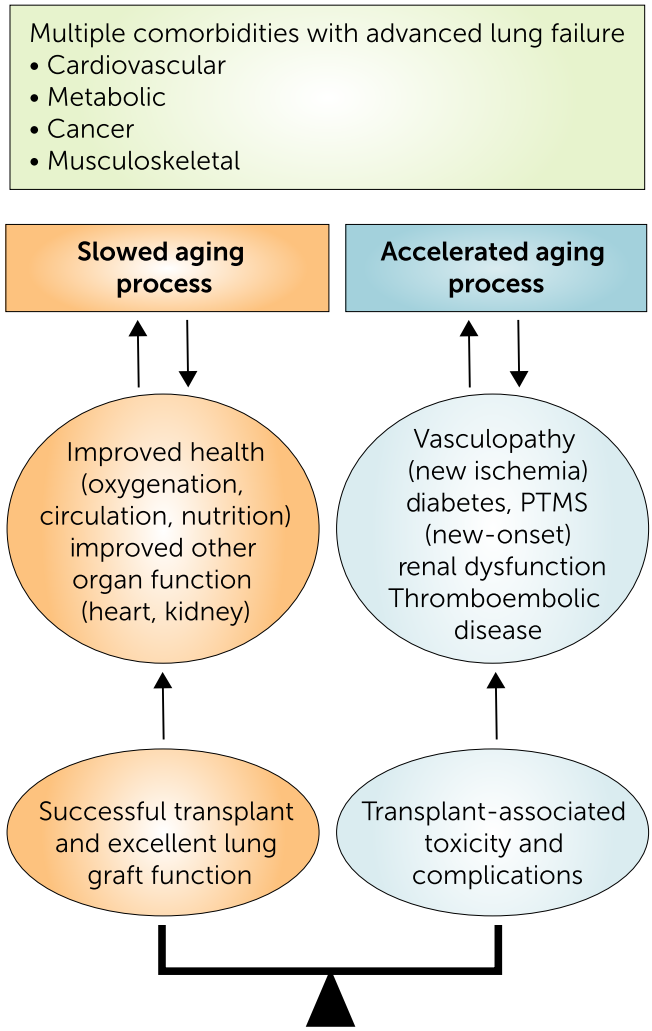


**Figure 2** The positive and negative impact of lung transplantation on the outcomes of elderly patients with multiple comorbidities. Modulation of the aging process should either accelerate (negative: BLUE) or slow down (positive: RED) this common underlying mechanism and act as a driving force toward opposite outcomes. PTMS, post-transplant metabolic syndrome.

Further studies are needed to clarify the roles of telomere length, function, and variants in lung transplantation and their prognostic value. This may also help us define realistic goals for elderly patients with comorbidities after lung transplantation by giving a basic, scientific-evidence-based expectation for transplant outcomes including the incidence of complications. In addition, clarification of these pivotal correlations may lead to further risk stratification and personalized medication management leading to improving transplant outcomes in elderly patients.

## Overall benefits of lung transplantation for patients with multiple comorbidities

Theoretically, in patients with multiple comorbidities, their comorbidities are expected to improve along with the health of their lungs after lung transplantation. Successful transplant leading to excellent lung graft function will bring normal oxygenation and "health" back to the entire body, improved circulation with better organ perfusion, and better nutrition. All of these should eventually contribute to slowing down the progression of many co-existing morbidities including CAD, metabolic syndrome, obesity, and chronic kidney disease (Fig. 2, left). However, surgical complications or organ toxicities inherent to the nature of transplantation may further accelerate the disease progression of existing major comorbidities through the common underling mechanism of the aging process and eventually outweigh the benefits obtained by transplantation (Fig. 2, right). Surgical complications and organ toxicity as a result of transplant-specific medications have been well discussed to date [53–55]; however, complications with the accelerated aging process as the "root cause," as described above, have rarely been elaborated but have

become relevant in the current era. There has been a notable increase in the number of elderly patients with comorbidities who are being considered for lung transplantation [56], and we have observed an outstanding and steady increase in patients older 70 years of age with multiple comorbidities who are referred to our high-volume center as potential candidates after being declined candidacy elsewhere.

## How to cope with this new challenge as a transplant specialist, program director, and as a scientist

Currently, it is recommended to be very selective and cautious when considering lung transplant in this unique patient cohort in whom the interplay between lung transplantation and the aging process remains unclear. From a surgical and peri-operative standpoint, the care team should be technically able to duly manage and overcome underlying cardiovascular risks. However, with regards to postoperative management, more caution should be used. All experienced specialists, in particular senior pharmacists, need to optimize the patient's treatments and avoid organ toxicity because complex underlying disease mechanisms may trigger a negative spiral and further accelerate progression of comorbidities beyond that which the care team can control (Fig. 2).

From an administrative standpoint, as a result of the nature of organ donation and the persistent and significant organ shortage affecting all solid organ transplantations, the performance of all transplant programs is closely monitored in the United States by the United Network for Organ Sharing (UNOS) through multiple metrics including wait-list mortality, organ acceptance, transplant volume and rates, and risk-adjusted graft and patient survival [57]. In addition, the Centers for Medicare and Medicaid Services (CMS) and private insurance payers currently use 1-year graft and patient survival as the primary criteria to judge transplant-center quality [58]. Generally speaking, these models of transplant-center assessment force transplant administrators and program directors to continually evaluate negative outcome events and complications and improve areas of weakness. This makes it more difficult for them to push the envelope by transplanting high-risk patients, particularly in patient cohorts with whom the transplant community has limited prior experience and for whom robust supporting evidence is lacking.

In the field of lung transplantation, this is particularly pertinent to patients older than 70 years of age with prior TAVR. TAVR is currently indicated for patients who are deemed "inoperable" because of high surgical risks including patients who are older than 80 or with other end-stage organ diseases. Frankly, few lung transplant specialists are sure if these patients can uneventfully survive for more than a year after transplant, which is the current benchmark of transplant metrics, even when comorbidities can be resolved by surgically correction. Mindful of this, program directors should decide whether to proceed to transplant or not depending on their program's scope, desired direction, activity, and outcomes achieved.

High-volume transplant centers are privileged as the leaders of the field to spearhead future directions in lung transplantation by pushing the envelope while demonstrating consistently improving transplant outcomes. For instance, recently, in high-volume centers, there has been a paradigm shift toward performing lung transplant in patients with lung allocation scores in the highest tertile and a softening of attitudes toward the use of respiratory support before lung transplantation, such as prior mechanical ventilation and extracorporeal lung support (ECLS) including extracorporeal membrane oxygenation (ECMO), as was reported elsewhere [59]. In fact, accumulating evidence supports using ECMO and ECLS to treat lung failure and support patients before and after lung transplantation, and the success of ECLS in lung transplantation sheds a new light on expanding its use toward long-term artificial respiratory support for advanced lung failure [60]. This is a good example of how high-volume transplant centers are pushing the envelope and paving the way to move forward, enabling progress in pulmonary medicine and translational science. In the future, long-term artificial respiratory support or artificial lungs might become an alternative to lung transplantation, replacing the need for donated lungs with a fully functional, man-made device incorporated into the respiratory and circulatory systems.

Because the nature of lung transplantation is complex and outcomes are currently suboptimal as compared with the outcomes of other solid organ transplantations, lung transplant specialists may feel pressured to limit transplant candidates to those proven to have the best outcomes. However, the potential impact of successful lung transplant on improving the health of very sick individuals with complex medical problems, such as elderly patients with multiple comorbidities, may also yield big advances in medicine and should be highly rewarded. As long as we continue to carefully select appropriate elderly patients with multiple comorbidities



Transplant International 2020; 33: 347–355

who would benefit completely from lung transplantation and allow them to undergo transplant when donated lungs become available, I believe this "envelope" is worth continuing to push.

We also need to strive to accumulate evidence from basic and translational science research to support the pioneering work that is being attempted in elderly patients with multiple comorbidities. For example, if we can provide data that demonstrate the stabilizing or extension of the telomeres or the slowing down cellular-senescence events after lung transplantation in elderly patients with multiple comorbidities, it will strongly support pushing the envelope for these patients to undergo transplant despite the programmatic hurdles. The evaluation of key cellular events and signaling pathways underlying the aging process as biomarkers using the evolving "-omics" technologies, including direct genome sequencing, genomics, transcriptomics, proteomics, and metabolomic analyses [61,62] may also help risk stratification among elderly patients with multiple comorbidities. Further research efforts should be strongly encouraged so that all these efforts—scientifically, surgically, programmatically, and globally—can be collated and coordinated to overcome this big challenge.

## Conclusion

Lung transplantation for the elderly patients with multiple comorbidities is becoming a timely challenge. Recent notable advances in the development of less invasive procedures to correct major comorbidities, in particular less-invasive procedures for the treatment of cardiovascular diseases, have been changing the previous definition of a "suitable" candidate for lung transplantation. Surgeons need to remain cautious in the selection of lung transplant candidates; however, given all the current conflicting and challenging issues that are present systemically, socially, administratively, and structurally. Further translational research to support transplant practices in patients with challenging conditions is strongly warranted to move the field forward.

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## Conflicts of interest

Dr. Shigemura has no conflicts of interest with this work.

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