Introduction to Lung Transplantation Evaluation

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Educational Objectives:

1. Review the basic epidemiology of lung transplantation.
2. Review the system for lung allocation in the U.S, the composite allocation score (CAS)
3. Understand the difference between indications for referral for evaluation versus active listing for transplantation.
4. Describe the evaluation process for determining transplant eligibility.

Scenario:
Mrs. C is a 68-year-old female, lifelong nonsmoker, with a past medical history of idiopathic pulmonary fibrosis. She had the onset of pulmonary symptoms about 6 years ago, first with a mild non-productive cough. She had increasing dyspnea until 3 years ago when she was having more exertional dyspnea with walking, especially with stairs. She then had a lung biopsy consistent with UIP. Recently she had an acute decline with increasing dyspnea and was diagnosed with pneumonia (hospital stay ~4 days). She is able to climb one flight of stairs but occasionally has to stop on the way up. Since her discharge, she has spent most of the day in a chair, including a wheelchair. She has been told by her primary physician that she may need a lung transplant.

Question 1: A) What are the main indications for lung transplant in the United States? B) What is the expected survival for lung transplant recipients?

A) In 2021, 2,569 lung transplant procedures were performed in the United States. (Valapour et al. 2023) From 1988-present, 33,743 lung transplants were performed in this country and since 1992, over 65,000 lung transplants have been performed worldwide (Perch et al. 2022). Since 2005, fibrotic lung disease has been the most transplanted pulmonary diagnosis in the United States, followed by obstructive lung disease, predominantly COPD and alpha-1-antitrypsin deficiency, cystic fibrosis, and pulmonary hypertension. This is significantly different from prior to 2005 when COPD was the predominant indication for lung transplantation. Of note, this is likely due to the increase in number of individuals transplanted for restrictive lung disease. In addition, in 2005, the LAS (lung allocation system) was introduced, changing the scoring and distribution of organs to a score-based instead of primarily time-based allocation system.

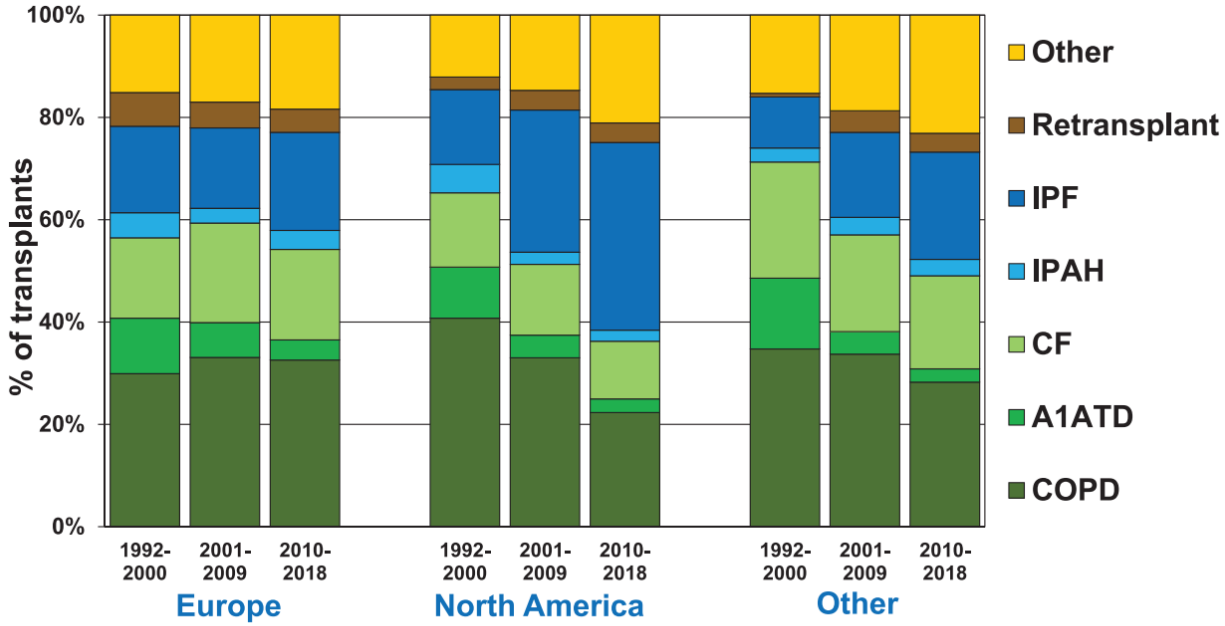
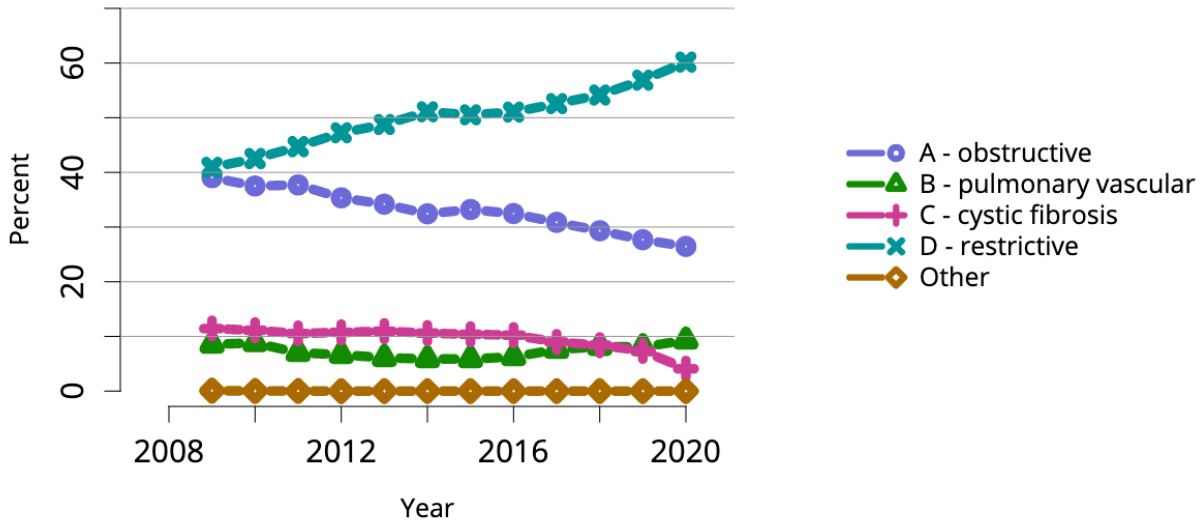


Figure 1 Diagnosis distribution by location and era (transplants: January 1992-June 2018).

Figure above borrowed from Perch, M et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-ninth adult lung transplantation report – 2022; Focus on lung transplant recipients with chronic obstructive pulmonary disease. 2022 October; 41(10): 1335-1347



Pretransplant mortality rates among candidates aged 12 years or older wait-listed for lung transplant. Figure borrowed from Valapour, M. et al. OPTN/SRTR 2020 Annual Data Report: Lung. AJT 2022; 22(S2):438-518.

B) Based on the registry data from the International Society for Heart and Lung Transplantation published in 2019, adults undergoing lung transplantation have a median survival of 6.2 years. For patients who survive the first post-transplant year, median survival increases to 8.3 years. Survival varies by type (double vs single) and indication, amongst many other factors including age, premorbid conditioning.

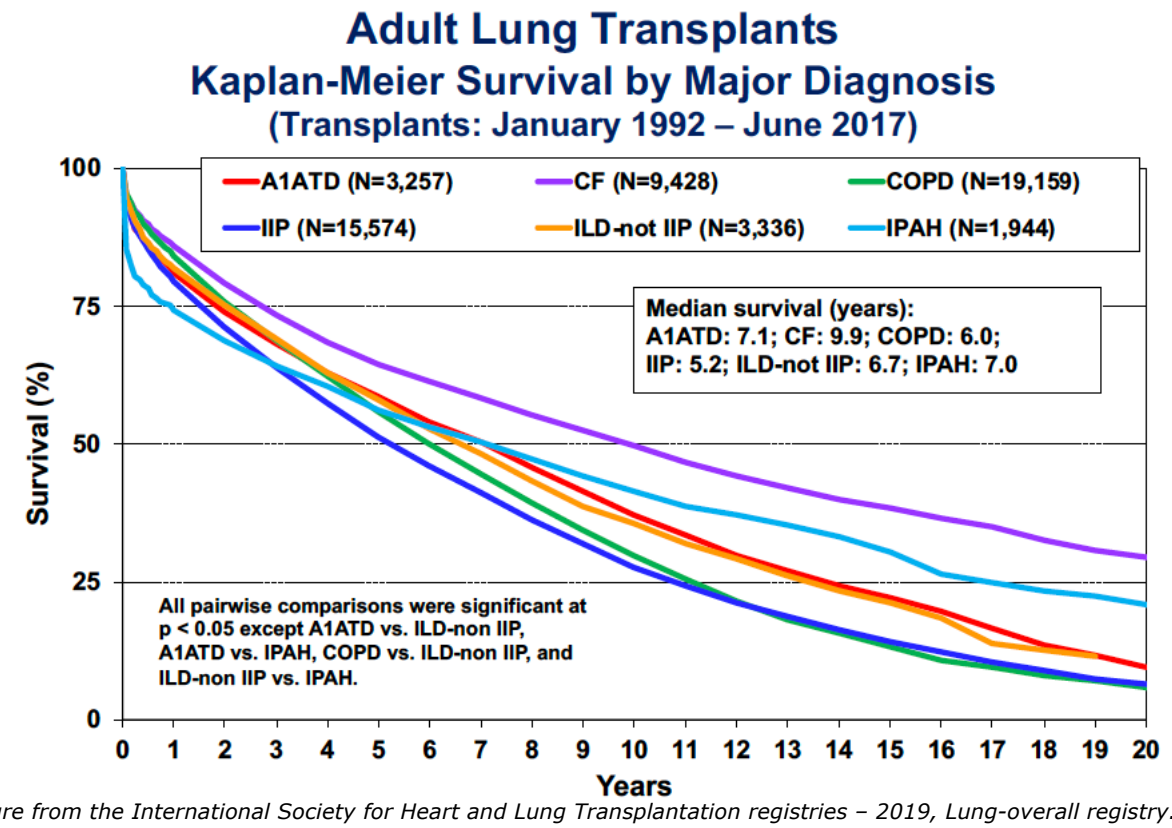


Figure from the International Society for Heart and Lung Transplantation registries – 2019, Lung-overall registry. Available at https://ishltregistries.org/registries/slides.asp and from JHLT. 2019 Oct; 38(10): 1042-1055.

Scenario continued:
Mrs. C is referred to a lung transplant clinic after being told she may benefit from a lung transplant. You have the opportunity to meet her at her first clinic visit with the lung transplant program. As you might expect, she has lots of questions.

Question 2: When should patients be referred for lung transplant evaluation?

The purpose of lung transplant evaluation is to evaluate a patient's appropriateness for listing for lung transplantation (i.e., to assess the risks and benefits of transplantation for a given patient) and to collect detailed data to calculate a lung Composite Allocation Score (CAS). This rigorous evaluation takes time, and in general, patients should be referred earlier when they can undergo extensive testing and potentially modify any factors that will improve their transplant success (i.e., weight loss for obese patients and completion of

pulmonary rehabilitation to improve deconditioning). Referral for lung transplant evaluation does not necessarily mean a patient will require or be a candidate for lung transplantation.

The decision on the appropriate timing of lung transplant referral depends on the underlying diagnosis. Lung transplant should be considered in those with end-stage lung disease with a:

- High risk of death from their underlying disease within 2 years (>50%)
- High likelihood of 5-year post-transplant survival (>80%)

In addition, there are disease-specific guidelines for referral patients for transplant consideration, updated in 2021. Please note, there are separate recommendations for listing.

Interstitial lung disease:

- At the time of diagnosis, for those with probable/definite radiographic UIP pattern or histological evidence of UIP
- Any form of pulmonary fibrosis with FVC<80% predicted or DLCO<40% predicted
- Any form of pulmonary fibrosis with the following relative decline in the past 2 years:
    - FVC 10%, DLCO 15%, FVC 5% with worsening respiratory symptoms/radiographic progression
    - Progression of inflammatory ILD on imaging or pulmonary function despite treatment
    - Supplemental oxygen therapy at rest of on exertion

Cystic Fibrosis:

- Any of the following, despite optimal medical management and trial of elaxacaftor/tezacaftor/ivacaftor if eligible:
    - FEV1<30% predicted in adults
    - FEV1<40% predicted and any of the following:
        - 6-minute walk distance <400m
        - PaCO2 >50mmHg
        - Hypoxemia at rest of with exertion
        - Pulmonary hypertension (PASP>50mmHg or right ventricular dysfunction)
        - Worsening nutritional status despite supplementation
        - 2 exacerbations per year requiring IV antibiotics
        - Massive hemoptysis (>240mL) requiring bronchial artery embolization
    - FEV1<500% predicted and rapidly declining based on PFTs/symptoms
    - Any exacerbation requiring positive pressure ventilation

COPD:

- BODE score 5-6 with additional factors suggestive of increased mortality: 1) Frequent acute exacerbations, 2) Increase in BODE score >1 over the past 24 months, 3) Pulmonary artery to aorta diameter >1 on CT scan, FEV1 20-25% predicted
- Clinical deterioration despite maximal treatment (medication, pulmonary rehabilitation, oxygen and NIPPV if indicated)
- Poor quality of life unacceptable to the patient
- Simultaneous transplant and BLVR/LVRS referral

Pulmonary Vascular Disease:

- ESC/ERS intermediate or high risk or REVEAL risk score 8 despite appropriate PAH therapy
- Significant RV dysfunction despite appropriate PAH therapy
- Need for IV or SC prostacyclin therapy

- Progressive disease despite appropriate therapy or recent hospitalization for worsening of PAH.
- Known or suspected high-risk variants, i.e. PVOD/PCH, scleroderma, large and progressive pulmonary artery aneurysms
- Signs of secondary liver or kidney dysfunction due to PAH
- Life-threatening disease complications such as recurrent hemoptysis

Scenario continued:
Mrs. C. has a 6 L resting oxygen requirement, an FVC=53% predicted, and a high-resolution chest CT consistent with a UIP pattern. She reports dyspnea with even mild activity and cannot climb a single flight of stairs. She is anxious and reports worsening depression because it is difficult to leave her home.

Question 3: What are the guidelines for the timing of listing for lung transplantation?

Similar to the timing of the initial referral, the indications for listing are also disease-specific. It is important to realize that these are overall guidelines and that program-specific and patient-specific factors affect the decision for transplant listing. Not everyone who meets these criteria should undergo lung transplantation. Some disease-specific guidelines for listing are summarized below:

Interstitial Lung Disease:
- Any form of pulmonary fibrosis with a relative decline of one of the following despite appropriate treatment:
  - FVC >10%
  - DLCO >10%
  - The absolute decline of 5% with radiographic progression
- Desaturation to <88% on a 6-minute walk test or >50m decline in 6-minute walk distance in the past 6 months
- Pulmonary hypertension on right heart catheterization or 2-dimensional echocardiogram (in the absence of diastolic dysfunction)
- Hospitalization due to respiratory decline, pneumothorax, or acute exacerbation

Cystic Fibrosis: Any of the referral criteria in combination with the following:
- FEV1<25% predicted
- A rapid decline in lung function or progressive symptoms
- Frequent hospitalization
- Any exacerbation requiring mechanical ventilation
- Chronic respiratory failure with hypoxemia or hypercapnia, especially with increasing oxygen requirements or the need for long-term NIPPV
- Pulmonary hypertension (PASP >50mmHg or evidence of right ventricular dysfunction)
- Worsening nutritional status, particularly with BMI<18kg/m2, despite interventions
- Recurrent massive hemoptysis despite bronchial artery embolization
- WHO Functional Class IV

COPD:
- BODE Score 7-10
- Additional factors that may prompt listing:
  - FEV1 <20% predicted
  - Presence of moderate to severe pulmonary hypertension
  - History of severe exacerbations
  - Chronic hypercapnia

Pulmonary Vascular Disease:

- ESC/ERS high risk or REVEAL risk score >10 on appropriate PAH therapy, including IV or SC prostacyclin analogues
- Progressive hypoxemia, especially in patients with PVOD or PCH
- Progressive, but not end-stage, liver or kidney dysfunction due to PAH
- Life-threatening hemoptysis

Question 4: Is Mrs. C an appropriate candidate for lung transplantation?

There are surprisingly few absolute contraindications for lung transplantation, although, as with the timing, there is no uniform consensus, and there is significant variation across centers. There is consensus that the following are absolute contraindications for lung transplantation:

- Malignancy with a high rate of recurrence or death (other than non-melanoma skin cancer)
- Acute coronary syndrome within 30 days (excluding demand ischemia)
- Stroke within 30 days
- Active extrapulmonary or disseminated infection
- Active tuberculosis infection
- HIV infection with detectable viral load
- Liver cirrhosis with portal hypertension/synthetic dysfunction
- Acute renal failure with rising creatinine/on hemodialysis and low likelihood of recovery OR GFR <40mL/min/1.73m2 unless considered for multi-organ transplant
- Progressive cognitive impairment
- Active substance use/dependence, including current tobacco use, vaping, marijuana smoking, or IV drug use
- Repeated episodes of non-adherence without evidence of improvement
- Lack of patient willingness or acceptance of transplant
- Limited functional status (e.g., non-ambulatory) with poor potential for post-transplant rehabilitation
- Other severe uncontrolled medical conditions are expected to limit survival after the transplant

There is no consistently agreed upon upper age cutoff, but centers become more restrictive with increasing recipient age because of the decreased survival with older recipients. Many centers have their age cutoffs.

One of the lung transplant evaluation goals is to more accurately assess the risks and benefits of a transplant for an individual potential recipient. This assessment is focused on identifying relative contraindications to lung transplantation. These relative contra-indications include:

- Obesity (associated with ↑risk of primary graft dysfunction and ↓survival, although most centers consider a BMI>35 to be an absolute contra-indication)
- Malnutrition with a BMI <16
- Significant extra-pulmonary disease
    - Untreatable hematological disorders, Hepatitis B or C with detectable viral load or liver fibrosis, LVEF <40%
- Significant deconditioning (a surrogate for frailty)

- Active extra-pulmonary collagen-vascular disease
- Significant osteoporosis, pain, or narcotic use that may impede the functional ability
- Severe esophageal dysmotility

Other factors also need to be assessed:

- Potential surgical difficulties → prior pleurodesis, median sternotomy, chest wall/spinal deformity, or surgical lung biopsy, which may make native lung extraction more challenging
- Certain infections and colonization → *Burkholderia cenocepacia* is associated with a high risk of severe, fatal infections and is considered an absolute contraindication at most transplant centers; there is an expanding body of literature regarding *Mycobacterium abscessus and lomentospora prolificans* infection and lung transplantation.
- Need for mechanical ventilation before transplant and the use of extracorporeal membrane oxygenation (ECMO) → Although there is an increased risk of short-term mortality, there has been a significant increase in the use of ECMO as a bridge to transplant for extremely ill but carefully selected recipients.
- Social support -> Critical for recovery and support following transplantation

Scenario continued:
Mrs. C. and her family proceed to lung transplant evaluation. She has normal coronaries on left heart catheterization, normal cardiac function, no pulmonary hypertension, and normal renal and hepatic function. Despite her acute decline over the last few months, she could walk 874 feet on her 6MWT, although she required 100% NRB to maintain an oxygen saturation >87%. The transplant team deemed her to be an appropriate transplant patient and is interested in being actively listed for a transplant.

Question 5: How are lungs allocated in the United States?

Before 2005, lungs were assigned within a local organ procurement organization (OPO) and then distributed based on waiting time after matching for blood type and body size. This resulted in long average wait times and a preponderance of COPD patients being transplanted. Patients with other diseases (IPF in particular) did not have the survival time to wait for a lung transplant.

In 2005, the Lung Allocation Subcommittee of the Organ Procurement and Transplantation Network (OPTN) implemented the lung allocation score (LAS). The goals of this system were: 1) reduce wait-list mortality, 2) prioritize allocation based on urgency, and 3) maximize the potential benefit of transplant. The LAS summarized the predicted risk of death on the waitlist and the one-year survival in the first year after transplant, normalized to 0-100, with higher scores indicating higher priority for lung transplantation. The institution of LAS was integral in decreasing waitlist mortality, as patients were no longer listed to accrue time on the waitlist.

In March 2023, the composite allocation score (CAS) was introduced to replace the LAS. The CAS score is calculated using patient and organ-specific factors (see table below) and uses a continuous distribution framework to allow for distribution of lungs throughout the United

States with a goal to reduce waitlist mortality. The CAS ranges from 0 to 100 points (https://optn.transplant.hrsa.gov/data/allocation-calculators/lung-cas-calculator/).

The Lung Composite Score (CAS)

Attribute	Definition	Maximum Points
Waiting list survival	**Expected 1-year waiting list survival**	**25**
Post-Transplant survival	**Expected 5-year post-transplant survival**	**25**
Candidate Biology		**15**
ABO	Based on percentage of compatible donors by blood type	5
cPRA	Based on percentage of compatible donors by cPRA	5
Height	Based on compatible donors by height	5
Patient Access	**Total of pediatric and prior living donor points**	**25**
Pediatric	For candidates under 18 years old	20
Prior living donor	For candidates who donated any organ	5
Placement efficiency	**Total of travel and proximity efficiency points**	**10**
Travel efficiency	Based on impact of distance on costs of travel	5
Proximity efficiency	Based on impact of distance on other efficiency (time, availability, etc)	5
Total		**100**

Adapted from: UNOS. Establish Continuous Distribution of Lungs. Accessed July 6, 2023. https://optn.transplant.hrsa.gov/policies-bylaws/public-comment/establish-continuous-distribution-of-lungs/?wchannelid=6r36091nxs.

Question 6: How will the CAS and LAS differ?

The lung CAS is individual for each patient with each organ offered, within a potential range of scores. A candidate receives a new CAS score with every organ offer due to fluctuating score values based on proximity and travel efficiency. cPRA (calculated panel reactive antibodies) is a new addition to the CAS. Candidates will receive a higher score for more unacceptable antigens entered. For blood type, type AB recipients are given the least points due to being a universal recipient (able to receive organs from type A, AB, and O donor), and type O the most due to having the smallest donor pool of only being able to receive organs from type O donors. Height points are the highest for recipients with very short or tall stature limiting donor opportunities.

Similar to the LAS, the patient(s) with the highest CAS will have the highest priority for an organ. The goals of the CAS and the continuous allocation framework are to significantly reduce waitlist death, decrease geographic variability in transplant rates, and increase transplant opportunities for pediatric candidates.

The CAS will weigh the expected 1-year waitlist survival equal to their expected 5-year post-transplant survival. In contrast, in the LAS, 1-year waitlist mortality was weighted twice that of 1-year post-transplant. (OPTN Policy – 10-13)

This may result in a change in potential score for some hospitalized, critically ill patients awaiting lung transplantation. These patients had some of the highest LAS scores due to the emphasis placed on waitlist mortality. Using the CAS these scores may be lower than expected due to a reduced estimated 5-year post-transplant survival, and a decreased emphasis placed on waitlist mortality.

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Pre/Post-Test Questions:

1. You see a 60-year-old male with hx of IPF, obesity (BMI 32), chronic pain, and GERD. He is a widow and never fathered any children. He has a history of depression that is well-controlled on an SSRI. He is a former smoker and quit smoking 9 months ago. You are considering referring him for lung transplant evaluation. Which of the following is (are) an absolute contra-indication(s) to transplant?

    a. Recent tobacco use within 1 year
    b. Obesity
    c. His depression
    d. Lack of adequate social support
    e. Both A and D
    f. All of the above

2. A 56-year-old female comes to your office for ongoing management of severe COPD. Her FEV1 is 40% predicted, and she requires 2L NC O2 continuously. She is currently on maximum doses of fluticasone-salmeterol, tiotropium, and PRN albuterol. Her last ABG on room air was 7.35/60/65. Her last CT scan done for lung cancer screening was negative for any lung nodules and showed only apical predominant emphysema. She continued to feel progressively short of breath over the last several years and is more limited in her daily activities. Which of the following is (are) indication(s) to refer this patient for lung transplant evaluation?

    1. Apical predominant emphysema
    2. PaO2 65
    3. Progressive dyspnea
    4. All of the above
    5. None of the above

3. A 65-year-old male with IPF comes to see you for a follow-up. His exam is remarkable for a set of 92% on 2L NC. His repeat PFTs show a decline in the FVC by 12% compared to 6 mos. Prior, his 6MWT shows a walk distance of 200 meters. His last echo from a month prior showed a normal EF of 65% and mild RV dysfunction. Which of the following are reasons to consider actively listing him for a lung transplant?

    1. His decline in FVC
    2. His six-minute walk distance
    3. Mild RV dysfunction on echo
    4. His age
    5. A & B
    6. B & C
    7. All of the above