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Review

What Is the Current Status of Single Lung Transplantation? A Literature Review

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Abstract

Lung transplantation (LTx) is the gold standard for the surgical treatment of end-stage lung disease. Ongoing discussions persist whether single lung transplantation (SLT) or bilateral lung transplantation (BLT) lead to better patient outcomes and quality of life. This study analyzed 58 peer-reviewed articles from 1990 to 2024, comparing SLT and BLT across several parameters, including indications for transplantation, overall survival, pulmonary hypertension, complications, chronic rejection, functional status, and quality of life outcomes. The review also addressed native lung complications, the future of lung transplantation, and the outcomes of non-transplanted lungs in SLT cases. Bilateral lung transplantation (BLT) may offer a more definitive solution for bilateral lung disease. However, the choice between single

lung transplantation (SLT) and BLT should be personalized according to each patient's unique requirements. Further research is needed to elucidate each approach's specific advantages and limitations, enhance patient outcomes, and refine lung transplantation practices.

Keywords
Single lung transplant; bilateral lung transplant

1. Introduction

The challenge for transplantation is the shortage of suitable donors despite medical advances. Single lung transplantation (SLT) is a strategy aimed at maximizing donor organ usage. It has the potential to benefit two candidates from a single donor, provided recipient selection criteria are met.

Approximately 4,600 lung transplants (LTx) occur annually worldwide, with 55% of them performed in North America. Data from the Organ Procurement and Transplantation Network (OPTN) suggest that there have been about 52,621 LTx, and the number is increasing daily [1]. The major indications for LTx are end-stage pulmonary diseases such as chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, pulmonary hypertension, and cystic fibrosis, among others. However, there is no consensus on the indications, benefits, and risks of single versus bilateral lung transplantation.

The Composite Allocation Score (CAS) is currently used to provide a more comprehensive method to prioritize lung transplants and allocate donor lungs while decreasing mortality in the waitlist. Nonetheless, there are diverse survival rates between bilateral vs single lung transplant recipients during the first 5 years, according to the United Network for Organ Sharing (UNOS) [1]. This data can be attributed to the difference in recipient selection for BLT versus SLT.

Herein, we aim to provide an understanding of the differences between Single and Double lung transplants by delineating the indications/allocation, short—and long-term outcomes, and risks with each modality.

2. Lung Transplant Allocation and It's Relation with BLT vs SLT

Prior to the Lung Allocation Score (LAS), recipients were determined based on waiting times. However, this did not address the severity of the disease or prioritize the patient's clinical condition. To address this deficiency, the LAS was implemented in 2005 to reduce waitlist mortality, prioritize recipients based on medical urgency, and maximize benefits based on post-transplant survival probabilities [2-4].

The Composite allocation Score (CAS) was created in 2023 with a more comprehensive approach to lung allocation by having a broader range of variables than LAS [1, 5]. It has been proven to reduce waitlist deaths by 36-47%, improve equity and fairness, and improve post-transplant survival. It predicts that 88.5% of adults receiving a lung transplant will survive 1-year post-transplant [6, 7].

The CAS influences the decision between Single and bilateral lung transplantation by preferring BLT in patients with greater medical urgency, higher scores, and severe disease [8]. Patients with pulmonary fibrosis and higher CAS scores had significantly improved graft survival and outcomes

from BLT compared to SLT [9, 10]. The survival advantage of BLT over SLT in COPD is less pronounced. The increased waitlist mortality with a more restricted listing preference in BLT might lead the clinician to use single transplantation in certain situations [11].

3. Indications for Lung Transplant in Pulmonary Diseases

The first successful LTx was performed in 1983 by Dr. Joel Cooper in a patient with idiopathic pulmonary fibrosis (IPF) and end-stage lung disease without options for medical management [12, 13], paving the way for the surgical management of end-stage lung disease [14]. The incidence of IPF increases yearly, with a survival rate of two to five years. In 2014, the Food and Drug Administration approved two medications, pirfenidone and nintedanib, to help reduce the forced vital capacity; however, these are not curative and help relieve symptoms. LTx remains the preferred treatment for patients with end-stage lung disease secondary to IPF. Transplantation is indicated if they fail medical management along with signs and symptoms of progression to advanced disease [15].

The Indications for lung transplantation have expanded from IPF to include other pulmonary conditions such as pulmonary hypertension (PH) and COPD and restrictive diseases such as Cystic fibrosis (CF), alpha -1 antitrypsin deficiency. In PH, therapies like prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors have improved the management of the disease and delayed the need for LTx. However, once a rapid decline in clinical condition and worsening symptoms despite therapy develop, a LTx referral is indicated [16].

The role of CFT modulators (i.e. TRIKAFTA) in CF has significantly declined the need for transplantation by improving symptoms and lung volumes. Nonetheless, CF, and other fibrotic lung conditions would benefit from LTx with advanced disease and deterioration or complications from bacterial infections [17, 18].

Over a third of LTx are performed on patients with end-stage chronic obstructive pulmonary disease (COPD) [19-21]. The guidelines from the International Society for Heart and Lung Transplantation (ISHLT) in 2014 stated that patients with COPD are eligible for LTx referral once a patient's BODE index is analyzed to be less than 6 along with increasing hospitalizations due to exacerbations [21]. Mutyala et al. suggested referral for transplantation in patients with COPD if medical management failed, which included limited relief with bronchodilators, oxygen supplementation, smoking cessation, and endoscopic lung volume reduction [20].

4. Role of SLT vs BLT

Historically, the decision to perform an SLT over a BLT has been made based on surgical risks. For instance, SLTs were a less complicated procedure since they required less cardiac manipulation, which would decrease postoperative morbidity and mortality overall. However, as surgical techniques have advanced, the decision between both procedures has become less clear. Weiss et al. and Force et al. [22, 23] showed that those in a higher LAS quartile or those who were overall higher risk were more likely to receive a BLT than an SLT. High-risk patients who received a SLT had lower one-year survival rates when compared with BLT (hazard ratio 0.73, 95% confidence interval 0.60 to 0.87, P = 0.00064) [23]. Weiss et al. showed no survival difference between SLT and BLT within a 90-day postoperative period [22].

Black et al. showed that patients in lower LAS categories had comparable survival rates between SLTs and BLT [8]. Similarly, Schaffer et al. analyzed the difference between SLT and BLT due to underlying COPD or IPF. This study concluded that patients with IPF had a beneficial increase in survival when they received BLT. However, there was no five-year survival difference between either type of procedure for patients with COPD [9].

In PH, BLT is preferred due to the long-term survival outcomes. It improves survival in patients with higher allocation scores and severe Pulmonary hypertension (mean pulmonary pressure >40 mmhg). However, SLT should be considered in patients >70 years of age and less severe disease [10]. In Cystic fibrosis, BLT is ideal due to the bilateral nature of the disease and the need to remove an infected lung that can affect the transplanted lung [17, 24].

There are no guidelines to guide the decision between SLT and BLT. Center experience plays a pivotal role in the selection of patients. Patients with CF and severe PH should get BLT; however, if supply is limited, patients with less severe PH can be considered for SLT. Higher LAS/CAS scores represent higher acuity and sicker patients, and BLT is the best choice for improved outcomes [17, 24]. Conversely, older patients (>70 years) would benefit from SLT due to decreased manipulation and time spent under anesthesia and surgery. [10] SLT has shown equivalent outcomes in lower LAS scores. Therefore, patients with less severe disease could benefit from SLT [23] (See Table 1).

Table 1 Indications of Single vs Bilateral Lung Transplantation.

Single Lung Transplant	**Bilateral Lung Transplant**
Older patients with idiopathic pulmonary fibrosis (IPF)	Severe pulmonary hypertension
Age greater than 70 years	Cystic fibrosis (CF) or infectious lung disease
Lower Composite Allocation Score (CAS)	Higher CAS
Significant ventilation/perfusion (V/Q) mismatch	Younger patients with chronic obstructive pulmonary disease (COPD) or IPF
Absence of significant pulmonary hypertension	Presence of significant right ventricular dysfunction
Resource limitations (e.g., donor shortage situations)	Higher BMI

LAS = Lung Allocation Score; CAS = Composite Allocation Score; V/Q = Ventilation/Perfusion.

5. Survival Differences between SLT vs BLT

Survival depends on multiple factors, including the patient's age, the underlying pathology, the presence of pulmonary hypertension, and the LAS/CAS. Generally, a double lung transplant provides better long-term survival and improved pulmonary function [25]. However, there is no consensus across multiple studies.

Sugimoto et al. concluded that there was no statistically significant difference in the overall survival of patients who received an SLT and those who received a BLT [26]. Black et al. showed that

there can be a difference in overall survival depending on the LAS. High LAS patients who received BLT had a 1 and 2-year survival rate of 57% and 32% compared to 49% and 27% of patients who received SLT [8].

In COPD and IPF, BLT has been shown to improve survival and reduce 5-year mortality compared to SLT [10]. In COPD, there is a marked improvement in survival in patients younger than 60 years of age, with studies showing an improved survival of 6.5 years in comparison to 5.3 years in SLT. There is an increased 5-year survival in BLT (59%) vs SLT (51%) [11, 25]. However, studies like Mansour et al., showed that there was a higher survival rate in patients younger than 60 years who received SLT over their counterparts who received BLT. They theorized that this was due to the decrease in allograft ischemic times [19]. Furthermore, the study by Mutyala et al. did not show a statistically significant survival difference when analyzing patients who received SLT over BLT after 1, 3, and 5 years [20]. Similarly, Yu et al. analyzed FEV1 after SLT and BLT and found that those with more severe symptoms had survival benefits if they received a BLT as compared with SLT [25].

In IPF, BLT is associated with long-term survival; Villavicencio et al. demonstrated an improved 10-year survival for patients with BLT in all age groups, no matter the LAS, except in those older than 70 [10]. Neurohr et al., found and increased survival at 3 months to 5 years in BLT with survival of 66.8% compared to 42.7% in SLT at 5 years. In addition, SLT was associated with an increased development of Bronchiolitis Obliterans (BOS) and bacterial or cytomegalovirus (CMV) pulmonary infections [27]. Higher LAS patients evidenced an increased survival with BLT, with better graft survivals, despite having a lower postoperative survival independent of the technique [9, 10].

There is a favorable survival with BLT in patients with Alpha-1 Antitripsin (A1AT) deficiency and Systemic sclerosis at 1 year, but the mortality difference was non-significant. Those recipients of lung transplants had a similar 1–5-year survival compared with IPF patients [19].

BLT is beneficial in younger patients, and decreased mortality is related to the fact that younger patients have reduced mortality risk and on average, have better pulmonary function as compared to older patients [9].

6. Pulmonary Hypertension: Is SLT a Viable Option?

There has been an improvement in pulmonary artery (PA) pressures with lung transplantation [28]. However, BLT offers better survival and overall outcomes than SLT. Bilateral transplantation offers an improved 5-year survival rate of 84% in the BLT group in comparison to 51% survival in the SLT group [29]. SLT recipients with mean PA pressures (mPAP) >40 mmhg had an overall survival of 43.9%, whereas BLT did not show any difference based on mPAP [30].

BLT is preferred in patients with pulmonary artery hypertension. It provides better long-term survival and improves pulmonary function [29, 30]. Furthermore, it is associated with fewer complications, such as bronchiolitis obliterans, and improves exercise capacity. However, SLT is an option in selected candidates to minimize surgical insult or when donor lung availability is limited. SLT should be avoided in patients with severe Pulmonary hypertension with mPAP >40 mmhg [30, 31].

7. Complications of SLT vs BLT

Overall, Lung transplantation is associated with increased morbidity and mortality, with many factors, such as patients' baseline clinical status and underlying pathology, surgical technique, and postoperative care with immunosuppressive drugs playing an important role [32].

In categories such as COPD, IPF, and Pulmonary hypertension, BLT has been associated with fewer complications. BLT had a lower incidence of primary graft dysfunction and Bronchiolitis obliterans (BOS). However, SLTs are associated with fewer immediate postoperative complications and shorter hospital stays [9]. In IPF, BLT has the highest risk of primary graft dysfunction but provides better long–term survival and pulmonary function [25].

Lung transplants have been associated with venous thromboembolism, such as deep venous thrombosis and pulmonary embolism. These common postoperative complications are more likely to affect patients with hypercoagulability, longer intensive care unit (ICU) stays, and SLT [32]. Kristensen et al. compared the frequency of pulmonary embolisms in patients who underwent an SLT to those who received a BLT. They found that out of 35 cases of post-lung transplant pulmonary embolisms, 77% of them occurred in patients who received an SLT. The other pulmonary embolism cases occurred in patients who received a BLT (14%) or heart-lung transplant (9%). Studies have found that pulmonary embolism is more prevalent in SLT, possibly due to the vascular dysfunction in the single allograft with vasoconstriction of the native lung. The authors noted the differences in LTx indications as a significant limitation in differentiating the frequency of thromboembolic events in SLT and BLT [33].

Epstein Barr Virus (EBV) is commonly associated with transplantation. The increased risk is attributed to chronic infection before transplantation or the graft donor's transmission. In lung transplant patients who are immunosuppressed, an EBV infection can promote unregulated proliferation of lymphocytes to become post-transplant lymphoproliferative disease (PTLD). BLT patients who developed PTLD had better survival than did the SLT patients with PTLD. Preventing PTLD through post-transplant EBV monitoring, antiviral prophylaxis, and appropriate immunosuppressive regimens is pertinent [34].

Although the morbidity and mortality rate of LTx has decreased over time, the post-SLT period still poses a risk for various complications to arise. In a retrospective review by Wei et al. including 109 patients with IPF who underwent an LTx found that pulmonary bacterial infection (40.4%), grade 2-3 primary graft dysfunction (38.5%), and anastomosis complications (30.3%) were the most common complications that occurred among the cohort. Interestingly, there was no significant difference in the incidence rates of these complications between the BLT and SLT groups [15].

A retrospective study by Meyers et al found that the only statistically significant intraoperative difference was that BLTs had a 40% higher frequency of needing cardiopulmonary support. Postoperatively, there was an increased rate of death in SLT than in BLT (9.4 vs 7.7%) and causes were anastomotic dehiscence, sepsis, ischemic bowel, and primary graft failure [35].

8. Complications in the Native Lung after Transplant

The primary difference between types of complications that can arise from SLT and BLT are that one native lung remains after the SLT operation. This native lung is subject to its own set of complications such as shunting, hyperinflation, opportunistic infections, and new malignancies [32].

Hyperinflation is one of the most common postoperative complications of SLT, it is characterized by the mediastinum shift towards the contralateral side and the diaphragm flattening on the ipsilateral side of the native lung. This presents clinically as hemodynamic instability and respiratory failure that compromises the patient's recovery. Benvenuto and colleagues performed a retrospective cohort study to compare right SLT versus left SLT with regards to post-transplant outcomes in COPD patients. They found that left SLT patients had an increased mortality risk than right SLT patients. They attributed this difference in survival to the decreased hyperinflation risk in right SLT associated with a smaller, heart-limited native left lung [36]. To prevent hyperinflation in SLT recipients, it is recommended that the patient be extubated and mobilized early while utilizing noninvasive positive pressure ventilation [37].

Patients with SLT are at higher risk of lethal infections in the native lung. Post-transplant patients have been found to have changes in sputum and reduced mucociliary clearance that are possibly contributing factors to an infection's development. Some common species of opportunistic infection include Mycobacterium, Candida, and Aspergillus. On the other hand, the use of corticosteroids in LTx patients naturally increases their risk of infection through immunosuppression and would require postoperative prevention and monitoring [32].

The possibility of developing a primary malignancy in the native lung of a post-transplant patient is increased. There is an increased risk in SLT of developing bronchial carcinoma in the native lung when they have a prior history of smoking, pulmonary fibrosis, or center-acinar emphysema. The reason for this is not only because of the chronic inflammation and fibrosis that the diseased lung already had pre-transplant but also because of the immunosuppressive therapies needed post-transplant [32].

Benvenuto et al. found that 30% had issues related to their native lungs. These complications did not affect 30-day mortality but were linked to higher long-term mortality, particularly in COPD patients. Native lung issues resulted in longer ICU and hospital stays and extended intubation. Early complications included atelectasis, pneumothorax, pneumonia, and air leaks, while long-term problems were often due to COPD progression or neoplasms. Interestingly, 30-day mortality was higher in IPF patients compared to COPD patients, and those without native lung complications had higher 30-day mortality rates. For COPD patients, survival was notably worse with native lung complications, especially late ones, which significantly impacted long-term survival, unlike in IPF patients [36].

9. Chronic Rejection in SLT vs BLT

Chronic lung rejection, specifically chronic lung allograft dysfunction (CLAD), including bronchiolitis obliterans syndrome (BOS), differs in SLT and BLT. Rejection is the cause in postoperative complications in transplant patients. CLAD is a significant complication of lung transplant that is characterized by a persistent decline of lung function. It encompasses two types: BOS and restrictive allograft syndrome (RAS). BOS is markedly obstructive airway disease, and RAS involves restrictive disease with associated parenchymal fibrosis [37].

BOS is characterized by an obstructive decline in lung function secondary to inflammation and fibrosis of the small airways, leading to obliterative bronchiolitis, creating air trapping and airflow obstruction with progressive decline in forced expiratory volume in 1 second (FEV1) without radiographic findings. It is more commonly seen in SLT recipients due to the presence of a native

lung, which is a substrate for infections and complications. RAS is associated with a restrictive decline in lung functions due to fibrosis of the lung parenchyma and pleura, leading to a restrictive allograft dysfunction. It is related to a decline in total lung capacity (TLC) and forced vital capacity (FVC) with radiographic infiltrates. RAS is seen in both SLT and BLT, with increased severity due to the larger volume of transplanted tissue at risk of fibrosis. RAS is less common but more severe than BOS [37].

BLT is associated with lower rates of chronic lung rejection and better long-term outcomes in comparison with SLT in patients with COPD, IPF, and PH. In COPD, BLT has a lower incidence of BOS with freedom from it at 3- and 5-years post-transplant (57.4% vs 50.7% at 3 years and 44.5% vs 17.9% at 5 years) [25, 38]. In IPF, BLT results in better BOS-free survival, but SLT recipients have a higher risk of BOS and poorer long-term outcomes. Finally, in patients with PH, SLT is not recommended for severe stages due to the higher risk of chronic rejection and poorer survival [29, 35].

Hadjiliadis et al. indicated a higher incidence of BOS in SLT (49.3% vs 31.7%), concluding that BLT is associated with a reduced risk of chronic rejection in the form of BOS [39]. Furthermore, they identified that freedom from BOS was higher in BLT at 3 and 5 years [38]. Similarly, Yu et al., in their systematic review and meta-analysis, found a lower incidence of BOS in BLT with better long-term survival and improved pulmonary function [25] and Fakhro et al. found a superior long-term survival at ten years with a lower incidence of BOS in BLT [40].

BLT is generally associated with lower rates of chronic rejection and better long-term outcomes, including a lower incidence of BOS, potentially less severe RAS, and improved pulmonary functions.

10. Functional Status and Quality of Life Outcomes in SLT vs BLT

Functional outcomes and Quality of life are essential assessments of the long-term follow-up after interventions. It plays a role in the general sense and notion of the intervention being evaluated and is an important tool to counsel patients prior to transplantation.

In 2001, a European cross-sectional study assessed post-transplant Quality of Life using the Euro Quality of Life (EuroQoL) questionnaire. It evaluated various health dimensions, such as mobility, self-care, pain, and emotional well-being, alongside a Visual Analogue Scale (VAS) for subjective health ratings. The analysis revealed that patients undergoing a SLT experienced more challenges across all five EuroQoL domains than those undergoing a BLT. Furthermore, individuals who received BLT or combined heart-lung transplants consistently reported higher EuroQoL domains and VAS scores than their SLT. Notably, there was no significant difference between the BLT and heart-lung groups. The transplanted patients demonstrated greater EuroQoL and VAS scores compared to patients still on the transplant waiting list [41].

Gerbase et al. conducted a prospective study comparing the long-term health-related quality of life among recipients of SLTs and BLTs, regardless of the underlying disease, and among a subgroup of patients with native pulmonary emphysema. Patients who underwent either SLT or BLT experienced substantial enhancements in FEV1, 6-minute walk test results, and SGRQ scores. Despite the significantly lower FEV1 values observed in patients following an SLT compared to those following a BLT ($p < 0.01$), there were no significant differences in the 6-minute walk test and SGRQ scores between recipients of each procedure [42].

At Duke University Medical Center in Durham, a multicenter, randomized, placebo-controlled trial focused on CMV prevention enrolled 131 adult first-time LTx recipients between July 2003 and

January 2007. As a secondary outcome, they analyzed Quality of life by utilizing the Medical Outcomes Study 36-Item Short-Form Health Survey, version 2. The study revealed a substantial improvement in the Physical Component Score, notably within the initial 3 months post-transplantation. Also, both BLT and SLT exhibited comparable levels of Quality of life in terms of their Physical Component Score despite slightly higher scores among those with BLT [43, 44].

11. SLT in the United States: What Happens to the Other Donor Lung? And Ex-Vivo Lung Perfusion

As demand for LTx rises, the limited supply of donor organs becomes critical. SLT presents an opportunity to maximize donor organs, benefiting two recipients from one donor.

Speicher et al. performed a retrospective cohort analysis utilizing data from UNOS Standard Transplant Analysis and Research files. Their findings corroborate previous observations regarding the underutilization of the second lung in SLTs. It emphasizes the significance of this issue and suggests that logistical difficulties play a major role in this underutilization. Of the SLT donors only (43.3%) had both lungs utilized, resulting in over 200 second potential donor lungs unused every year [45].

Ex vivo lung perfusion (EVLP) is a technique used to assess preserve and potentially recondition donor lungs before transplantation. EVLP allows for the use of lungs that might otherwise be unsuitable for transplant. This increases the availability of the donor lung pool. Wallinder et al. reported acceptable short-term results in EVLP-treated lungs used for SLT. EVLP is a technique that has been shown to improve function, making marginal lungs suitable for both SLT and BLT [46-49].

12. Conclusion

The reduced pool of donors, increased wait-list times, and improvement in specific medical therapies have affected the landscape of lung transplantation. For end-stage lung disease, a lung transplant offers a benefit in improving survival and quality of life. However, the use of single or bilateral lungs remains controversial. Severe PH is associated with worse outcomes if a single transplantation is undertaken. However, in high-risk patients with COPD and IPF, high risk surgical candidates, disease localized to one specific lung SLT provides an alternative that gives the benefit of transplantation without the risk of a prolonged and more complex surgery.

Despite the preference for BLTs at many leading transplant centers, the choice between BLTs and SLTs remains unresolved. While BLTs are often favored for their potential to address bilateral lung disease comprehensively, many institutions continue to support SLTs, citing their ability to achieve comparable outcomes with potentially fewer complications related to the native lung.

The ongoing debate is influenced by various factors, including ethical concerns regarding organ allocation and the perceived surgical risks associated with BLTs. These considerations highlight the need to critically assess how BLTs align with contemporary transplantation practices and patient needs.

Research is clearly needed to better define the distinct advantages and disadvantages of SLT compared to BLT. Such research would provide a more robust evidence base to guide decision-making in lung transplantation. Until such evidence is available, the choice between SLT and BLT should be individualized, considering each patient's specific condition, the potential risks of native-lung complications, and their overall prognosis.

Tailoring the transplantation strategy to each patient's unique needs is crucial for optimizing outcomes and advancing the field of lung transplantation.

Author Contributions

SY and CAV were responsible for the conception of the manuscript, database search, manuscript writing, and required corrections with proofreading of the final product. SG and EM were responsible for writing the manuscript. SK was responsible for the conception, reviewing the main manuscript, and making corrections.

Competing Interests

The authors have declared that no competing interests exist.

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