

# World Journal of *Transplantation*

*World J Transplant* 2021 August 18; 11(8): 320-355



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**INDEXING/ABSTRACTING**

The WJT is now abstracted and indexed in PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Yu-Jie Ma*, Production Department Director: *Yu-Jie Ma*, Editorial Office Director: *Jia-Ping Yan*.

**NAME OF JOURNAL**

*World Journal of Transplantation*

**ISSN**

ISSN 2220-3230 (online)

**LAUNCH DATE**

December 24, 2011

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Maurizio Salvadori, Sami Akbulut, Vassilios Papalois

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2220-3230/editorialboard.htm>

**PUBLICATION DATE**

August 18, 2021

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<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Factors affecting complications development and mortality after single lung transplant

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**Conflict-of-interest statement:** The authors declare no conflict of interests.

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### Abstract

Lung transplantation (LT) is a life-saving therapeutic procedure that prolongs survival in patients with end-stage lung disease. Furthermore, as a therapeutic option for high-risk candidates, single LT (SLT) can be feasible because the immediate morbidity and mortality after transplantation are lower compared to sequential single (double) LT (SSLTx). Still, the long-term overall survival is, in general, better for SSLTx. Despite the great success over the years, the early post-SLT period remains a perilous time for these patients. Patients who undergo SLT are predisposed to evolving early or late postoperative complications. This review emphasizes factors leading to post-SLT complications in the early and late periods including primary graft dysfunction and chronic lung allograft dysfunction, native lung complications, anastomosis complications, infections, cardiovascular, gastrointestinal, renal, and metabolite complications, and their association with morbidity and mortality in these patients. Furthermore, we discuss the incidence of malignancy after SLT and their correlation with immunosuppression therapy.

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**Manuscript source:** Invited manuscript

**Specialty type:** Transplantation

**Country/Territory of origin:** Bulgaria

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**Received:** March 5, 2021

**Peer-review started:** March 5, 2021

**First decision:** March 31, 2021

**Revised:** April 15, 2021

**Accepted:** June 28, 2021

**Article in press:** June 28, 2021

**Published online:** August 18, 2021

**P-Reviewer:** Bos S, Meng FZ

**S-Editor:** Zhang L

**L-Editor:** Filipodia

**P-Editor:** Yuan YY



**Key Words:** Lung transplantation; Single lung transplant; Primary graft dysfunction; Native lung complications; Technical transplant complications; Vascular transplant complications; Graft rejection; *De novo* malignancy

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**Core Tip:** Improvement in surgical techniques and adequate intra- and post-operative management significantly increased patients' short- and long-term survival after a single lung transplant. Conditions such as volume overload, cardiovascular complications, antibody-mediated rejection, aspiration, and/or pneumonia could mimic the lung allograft's acute dysfunction. However, events related to improved surgical techniques and post-operative control of pulmonary immunogenicity through immunosuppressive therapy are among the reasons leading to the reduction of early mortality and prolonged survival of these patients. Thus, the post-operative management after single lung transplantation has to be multidisciplinary and complex.

**Citation:** Sekulovski M, Simonska B, Peruhova M, Krastev B, Peshevska-Sekulovska M, Spassov L, Velikova T. Factors affecting complications development and mortality after single lung transplant. *World J Transplant* 2021; 11(8): 320-334

**URL:** <https://www.wjgnet.com/2220-3230/full/v11/i8/320.htm>

**DOI:** <https://dx.doi.org/10.5500/wjt.v11.i8.320>

## INTRODUCTION

Lung transplantation (LT) is a life-saving therapeutic procedure that prolongs survival in patients with end-stage lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, idiopathic pulmonary fibrosis (IPF), pulmonary arterial hypertension (PAH), and alpha-1 antitrypsin deficiency[1]. Since the first successful LT in 1981, there have been many improvements in surgical and anesthetic procedures[2]. These events lead to a significant increase in post-LT survival in these patients[3]. As a therapeutic option for high-risk candidates, single LT (SLT) could be a feasible option because the immediate morbidity and mortality after transplantation are lower compared to sequential single (double) LT (SSLTx). Still, the long-term overall survival is, in general, better for SSLTx. Patients with IPF, PAH, and COPD could be appropriate candidates for SLT because of more negligible operative trauma, shorter ischemic time, and ethical considerations-one donor helps 2 patients[4,5]. It is estimated that more than 4000 lung transplants are currently performed annually worldwide, with significantly lower morbidity and mortality rate compared to data from 20 years ago[5,6]. Despite the great success over the years, the early post-SLT period remains a perilous time for these patients. Approximately 7% of SLT recipients have a short-life expectancy (30 d), while a larger percent are expected to develop complications[6]. Patients who underwent SLT are predisposed to evolve early or late post-operative complications. Primary or chronic lung allograft dysfunction (CLAD), anastomosis complications, infections, cardiovascular disease, renal, metabolic, and gastrointestinal (GI) disorders, as well as *de novo* malignancy (DNM) are the most common[7,8]. Events related to improved surgical techniques and post-operative control of pulmonary immunogenicity through immunosuppressive therapy are among the reasons leading to the reduction of early mortality and the prolonged survival of these patients[9]. Thus, the post-operative management after SLT has to be multidisciplinary and complex.

The aim of this review is to emphasize factors leading to post-SLT complications in the early and late periods and their association with morbidity and mortality in these patients. Furthermore, we discuss the incidence of malignancy after SLT and its correlation with immunosuppression therapy.



## POST SLT COMPLICATIONS RELATED TO GRAFT FUNCTION

Improvement in surgical techniques and adequate intra- and post-operative management significantly increased short- (up to 30 post-operative days) and long-term (> 1 year) survival[6]. Due to acute worsening of pulmonary function status with a rapid increase in shortness of breath, graft failure is the leading early post-operative complication. Conditions such as volume overload, cardiovascular complications, antibody-mediated rejection (AMR), aspiration, and/or pneumonia can mimic acute lung allograft dysfunction (ALAD)[10]. Therefore, the primary focus should be on circulatory and ventilatory support in the intensive care unit (ICU). In patients without early post-operative complications, early ventilator weaning during the first 12 h is recommended. Nevertheless, the mortality rate in this period is still high[11].

### Primary graft dysfunction

Primary graft dysfunction (PGD) is one of the leading causes of mortality (42%) after SLT in the early post-operative period[12]. A study by Liu *et al*[13] reported that mortality rates in patients after SLT with PGD are eight times higher than recipients without this kind of complication. The Consensus Statement of the International Society for Heart and LT (ISHLT) defines PGD as an acute lung injury (in the first 3 post-operative days) after LT, most often caused by mechanical ventilation, immunological and inflammatory processes, and “possibly” infectious agents. In general, this injury clinically manifests as pulmonary edema, leading to reduced lung vascular compliance and ineffective graft oxygenation. In clinical practice, PGD is most often mistaken for acute respiratory distress syndrome as a consequence of increased permeability and alveolar damage to the pulmonary capillaries[14,15]. PGD is characterized by diffuse alveolar infiltrates on chest radiographs, which correlates with the degree of hypoxemia[16]. PGD severity is rated (from 0 to 3) based on the presence of radiographic lung infiltrates and the ratio of alveolar oxygenation to the fraction of inspired oxygen. The classification of PGD presented by ISHLT is presented in Table 1 [15]. An interesting study by Whitson *et al*[17] showed that patients who developed PGD1 and PGD2 had better long-term survival compared to those with PGD3. A prospective study by Diamond *et al*[18] between 2002 and 2010 registered PGD3-30.8% in the first 72 h after LT. Furthermore, Mulligan *et al*[1] reported that PGD3 correlated with a mortality rate of 23% in 3 post-operative months and 34% in 1 year, compared to 5% and 11% for those without PGD, respectively.

A large number of studies have been conducted to obtain an appropriate classification of risk factors associated with PGD. We summarized the most common possible risk factors in Table 2[18-21]. Mechanisms related to PGD3, especially in SLT, include: Diluting effect of inadequate oxygenation related to the shunting in the remaining native lung, higher cardiac output through the graft vascularization, and higher capillary tension in cases of size mismatch (*i.e.* lobar or undersized LTx)[15]. All of these complications can prolong the duration of mechanical ventilation and ICU stay. Therefore, an inappropriate treatment strategy may affect long-term survival since PGD is a risk factor for CLAD development[22-26]. Events such as ischemia-reperfusion injury, innate immunity mechanisms, oxidative and nitrosative stress, inflammatory response, and vascular dysfunction with loss of alveolar architecture are thought to be the basic pathophysiological mechanism for the development of PGD. Intensive care strategy includes careful use of sedation and muscle relaxants, lung-protective mechanical ventilation, inhaled nitric oxide or/and prostaglandin, restrictive fluid balance, and prevention of nosocomial infection and extracorporeal membrane oxygenation[23,27,28]. Proper donor selection, pre-operative optimizing matching, and improved therapies and techniques for lung preservation after explantation could prevent the development of PGD[29].

### Acute and chronic lung allograft dysfunction

Multiple lung graft rejection forms are hyperacute, acute cellular and AMR, and chronic lung allograft dysfunction[30]. Hyperacute rejection is rare due to enhanced methods for detecting pre-formed donor-specific antibodies to human leukocyte antigen (HLA) or non-HLA antigens. It is thought that these antibodies lead to endothelial cell necrosis, coagulation cascade activation, and hemorrhagic infarction due to binding to HLA molecules on endothelial cells and activate the complement cascade[31]. In contrast, acute cellular rejection is a common complication after SLT and SSLTx. Moreover, 30% of transplanted patients (SLT and SSLTx) experience at least one episode in the first year, mostly in the first 6 mo. Still, the incidence may be as high as 40%-50%[32]. The diagnosis of acute cellular rejection is still made by trans-

**Table 1 Primary graft dysfunction classification**

PGD grade	Chest radiography		PaO <sub>2</sub> /FiO <sub>2</sub> ratio in mmHg	SaO <sub>2</sub> /FiO <sub>2</sub> ratio
	Diffuse allograft infiltration	Pulmonary edema		
0	No	No	Any	Any
1	Yes	Yes	> 300	> 315
2	Yes	Yes	200-300	235-315
3	Yes	Yes	< 200	< 235

FiO<sub>2</sub>: Fraction of inspired oxygen; PaO<sub>2</sub>: Partial oxygen pressure; PGD: Primary graft dysfunction; SaO<sub>2</sub>: Oxygen saturation.

**Table 2 Possible risk factor associated with the development of primary graft dysfunction**

Risk factor for PGD		
Factors correlated with the recipient	Factors correlated with the donor	Other (Intra- and post-operative)
BMI ≥ 25	Heavy smoker	Intracellular type preservation solutions
Sarcoidosis	DCD	Prolonged warm or/and cold ischemia
IPF	Traumatic brain injury/DBD	SLT
PPH	Female gender	Poly-transfusion of blood product
Elevated mean PAP	African American ethnicity	Use of cardiopulmonary bypass
LVDD	Younger than 21 yr, older than 45	High fractional inspired oxygen upon reperfusion
	Alcoholism	Prolonged mechanical ventilation
	Aspiration	Peri-operative insults

BMI: Body mass index; DBD: Donation after brain death; DCD: Donation after circulatory death; IPF: Idiopathic pulmonary fibrosis; LVDD: Left ventricular diastolic dysfunction; PGD: Primary graft dysfunction; PPH: Primary pulmonary hypertension; SLT: Single lung transplant.

bronchial lung biopsy, where minimal (grade A1), mild (grade A2), moderate (grade A3), and severe (grade A4) forms exist. They have characteristic histologic findings in common: A mononuclear cell infiltrate circumferentially surrounding small vessels [31].

Clinical AMR is defined as the presence of all the following criteria: Allograft dysfunction, clinically proven; lung injury, histologically proven; capillary complement fragment 4d (C4d) deposition (optional); circulating donor-specific antibodies; and other causes for allograft dysfunction excluded[33]. However, to improve the SLT outcomes, AMR should be better diagnosed. However, factors such as C4d staining limitations, inter-observer variability, and the influence of non-DSA HLA genes may impact AMR diagnosis. Finally, although this form of rejection leads to reversible allograft failure, CLAD has a high incidence among survivors[34].

Patients can develop acute worsening of the condition of deteriorated pulmonary function in the years after SLT, with a sudden rise in shortness of breath-ALAD. This entity is another early complication. It is thought that capillary leak syndrome, anastomotic complications (*e.g.*, dehiscence of bronchial anastomoses), pulmonary embolism, and infection and allograft rejection are one of the main culprits for its development[35]. The mortality rate of ALAD is estimated at 3.6% for SLT recipients within the first 30 d. Therefore these data should be kept in mind by clinicians. There is a strong correlation between the number of episodes of ALAD in SLT recipients and developing CLAD. Therefore, this complication should not be underestimated[36]. However, if the reduction in pulmonary function is not returned to > 90% of the baseline 3 wk after ALAD, despite the treatment of the secondary causes such as infection, acute allograft rejection, or airway stenosis, CLAD diagnosis can be assumed [37,38]. CLAD is characterized by a reduction (≥ 20%) in measured forced expiratory volume in one second value compared to the baseline value. It could present with either an obstructive ventilatory pattern, a restrictive pattern, or a mixed pattern[38-40]. Furthermore, CLAD could be subdivided into clinical phenotypes: Bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), mixed or undefined

subphenotype[38]. BOS is a condition of intraluminal airway fibrosis, defined by progressive airflow obstruction, unexplained by acute rejection, infection, or other coexistent conditions[41].

On the other hand, RAS is characterized as pleuroparenchymal fibroelastosis, most often triggered by a variety of microorganisms isolated in sputum or bronchoalveolar lavage, which lead to an excessive fibrotic reaction[42]. However, RAS was also associated with AR development (and especially AMR) and chronic rejection, where inflammation plays a significant role. Literature data showed that within the first 5 years following SLT, approximately 50% of recipients are diagnosed with either BOS- or RAS-related CLAD. BOS-related CLAD has been more common after SLT and represents 70%, of all CLAD complications, in contrast to RAS-related CLAD, which develops in one-third of all SLT recipients[6,43]. The main three mechanisms for complications after SLT are presented in Figure 1.

As there is typically a higher chance of rejection after lung transplant, SLT recipients need life-long and intense immunosuppressive treatment to prevent graft rejection. Immunosuppressive regimen after LT most often involves a triple combination of corticosteroid, cyclosporine/tacrolimus, and azathioprine/mycophenolate mofetil[44, 45].

Despite the unclear treatment algorithm, several authors reported azithromycin's role in delaying CLAD progression because of its antibiotic, anti-inflammatory, and promotility effects. Another feasible option for the management of CLAD is switching classes of immunosuppressive drugs[46,47]. However, the last therapeutic option in treating end-stage CLAD is retransplantation.

## TECHNICAL COMPLICATIONS RELATED TO SLT

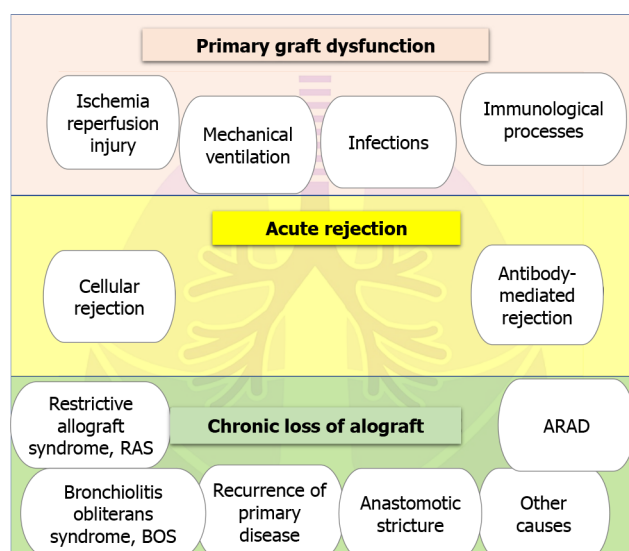
Since the early days of LT, anastomotic complications have been recognized as one of the risk factors for post-LT mortality (2%-3%)[48]. Many authors classify anastomotic complications as obstructive (persistent airway stenosis) and necrotic (including partial or full-thickness ischemia)[49]. The most common anastomotic obstructive complications are airway stenosis as a result of excessive production of granular tissue, cicatrix fibrosis, and dynamic collapse secondary to bronchomalacia. On the other hand, bronchial dehiscence (with or without pleural fistula), anastomotic ulceration, and sloughing of the eschar mucosal tissue are necrosis-related complications [49]. Technical anastomotic complications are frequently complex, influenced by different factors such as surgical, immunosuppressive treatment, mechanical ventilation, reperfusion time (ischemic injury), and donor-related factors. For example, a size mismatch between donors' or recipients' airways and blood vessels is associated with PGD3. Simultaneously, the usage of positive pressure mechanical ventilation could lead to early graft failure[50]. Besides, from a surgical perspective, absorbable suture materials and shortened bronchial cuffs decrease the risk of anastomotic complications (10.9%)[51].

Moreover, Yserbyt *et al*[52] reported that surgical anastomotic complication has right-sided predominance with a frequency of 67%. Contrariwise, Benvenuto *et al*[53] showed that compared to left SLT for patients with COPD, right SLT has decreased mortality risk. They reported that COPD recipients with right SLT had significantly higher short-term and long-term survivals compared to left SLT recipients. Benvenuto *et al*[53] considered that reduced survival in left SLT recipients resulted from intense native lung hyperinflation. Therefore, right SLT is more successful because the left lung has a smaller size and heart-limiting excessive hyperinflation. The authors also reported that post-LT infectious airway complications are lower in patients with right SLT. Another critical factor for developing anastomotic complications is the type of immunosuppressive therapy and different regimens, especially high-dose steroids, which might affect the graft function and patient's outcome[54]. High-dose corticosteroids can increase the risk of airway complications by increasing susceptibility to infection, by delaying healing[48].

## CARDIOVASCULAR COMPLICATIONS AFTER SLT

Cardiovascular complications (CVCs) are one of the major causes leading to high mortality rates after SLT. There are plenty of CVCs in the post-SLT period. Still, atrial dysrhythmias are the most common early complication with an incidence of 25%-35%. It was established that the usage of catecholamines, adverse effects of medications, and





**Figure 1 Complications after single lung transplantation.** The major complications associated with a single lung transplant: Primary graft dysfunction, as a consequence of organ procurement, cold storage, and implantation; cell- and antibody-mediated acute and chronic rejection (CLAD). CLAD phenotypes are presented mainly as bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), recurrence of primary disease, anastomotic stricture, and azithromycin-responsive allograft dysfunction, as well as other specific causes of decline in lung function.

mechanical stresses related to vascular anastomoses could be risk factors for atrial dysrhythmias[55]. A study by D'Angelo *et al*[56] that involved 652 lung transplant recipients, showed that the appearance of atrial arrhythmias is associated with prolonged hospital stay and significantly increased the mortality rate of these patients. Additionally, the authors determined that atrial arrhythmias could be a feasible independent predictor for determining mortality rate after SLT. Another important CVC that leads to a high mortality rate after SLT is developing coronary artery disease (CAD) and myocardial infarction (MI). Risk factors such as dyslipidemia, hypertension, chronic kidney disease (CKD), chronic usage of corticosteroids, and immunosuppressive medications are thought to be the significant causes for CAD and MI[55].

### **Venous thromboembolism after SLT**

Venous thromboembolic (VTE) complications, especially deep venous thrombosis (DVT) and pulmonary embolism (PE) are important and common post-operative complications after LT. The announced frequency of PE and DVT is 5%-15% and 20%-45%, respectively. Factors such as SLT, hypercoagulable status, immunosuppressive therapy, high doses of corticosteroids, and prolonged ICU stay duration are strongly associated with VTE development[54]. Moreover, a study by Fan *et al*[57], including 316 lung transplant patients, showed that 19 (6%) patients developed VTE during the follow-up period. Furthermore, the part of SLT in the VTE group was higher than that in the non-VTE group (78.9% *vs* 48.5%). The thrombotic events could dramatically deteriorate the patient's outcome; thus, efforts must be directed towards the early and adequate prophylaxis after SLT.

## **NATIVE LUNG COMPLICATIONS**

Even though SLT has several benefits over bilateral LT, it is still a double-edged sword regarding the native lung, which remains one of the major causes of post-SLT complications[58,59].

In contrast to SSLTx, SLT recipients are more likely to experience pneumothorax, hyperinflation, and opportunistic infections, especially with *Mycobacterium* species and *Aspergillus* associated with native lung. Therefore, this can potentially compromise both early and late outcomes[58,60].

Pneumothorax is often a result of post-operative mechanical ventilation in the underlying native lung disease (*e.g.*, emphysema and pulmonary fibrosis). However, it could develop later, years after the transplant, depending on the primary disease[61].

Other important complications in the native lung are opportunistic infections, which frequently had a lethal outcome in patients, despite normal preoperative sputum

examination and bronchoscopy. The persistence of bacterial colonization despite proper pharmacotherapy is one indicator that favors double LT (DLT), especially in pulmonary fibrosis patients. This assessment aims to reduce the chance of bacterial complications arising in the native lung and spread of the infection to the graft after immunosuppression onset[58]. Reduced mucociliary clearance, altered sputum characteristics, and in some cases, chronic bacterial colonization might contribute to the predisposition to infections as well as their early spreading[62].

Considering the immunosuppressive treatment, one might expect a high infection rate, especially fungal, after SLT. The prevalence of fungal infection among lung transplant recipients is estimated to be 15%–35%, with *Candida* and *Aspergillus* being the most common pathogens. In the perioperative phase, however, invasive fungal infection in lung transplant recipients was comparatively low. Antifungal prophylaxis and care should be tailored to the fungal dissemination status of each organism[63].

In the current context of native lung complications, it is well admitted that acute native lung hyperinflation (ANLH) is a post-SLT complication characterized by radiographic mediastinal shift and ipsilateral diaphragmatic flattening. This entity has an occurrence rate of 15%–30% after SLT[64]. Clinically, ANHL presents with hemodynamic instability, the necessity of catecholamine therapy, and respiratory failure due to allograft compression[65]. Body plethysmography can provide useful information about this entity, but the diagnosis is based on the aforementioned specific radiographical signs[66,67]. Several critical points prevent ANLH, such as early post-operative extubation and respiratory physiotherapy, with the patient's early mobilization[68,69].

Furthermore, Shehata *et al*[59] emphasized mechanical ventilation regimens intending to treat ANLH. They suggested that prophylactic noninvasive positive pressure ventilation was the first-choice treatment because it reduces the weaning time and risk of prolonged invasive mechanical ventilation. Also, Roca *et al*[70] have shown that high-flow nasal cannula has a significantly beneficial role in treating ANLH as well. They concluded that high-flow nasal cannula reduces the necessity of invasive ventilation in LT recipients readmitted to the ICU with acute respiratory failure. The noninvasive positive pressure ventilation or high flow nasal cannula could be a feasible option to prevent respiratory failure in ANLH.

On the other hand, in cases with ANHL indicated for endotracheal intubation, several authors recommend endoscopic suction and the application of bronchial blockers[71]. If this strategy fails, differential lung ventilation is another option for the management of ANHL. However, the last step of management is lung volume reduction surgery.

Last, but not least, recipients with pulmonary fibrosis and smoking-induced emphysema have a greater risk of developing bronchial carcinoma in the native lung after SLT. Pneumonectomy of the residual lung may then be used as a therapeutic option to help these patients live longer[58].

## GI COMPLICATIONS AFTER SLT

Many published studies have shown that in patients who have undergone LT, GI complications are common and represent a significant cause of post-operative morbidity and mortality[72]. Gastroparesis, microaspiration, diminished cough reflex, abnormal mucociliary clearance are conditions that have occurred with high frequency after LT. These entities might be associated with complications such as laryngitis, pneumonia, lung abscess, acute and chronic bronchitis after LT[73]. A correlation was established between GI complications and impaired malabsorption of medications and malnutrition after the early post-operative period, and recurrent lung allograft dysfunction[35,74,75]. GI complications may occur during the first 30 d after SLT (early complications) or if prolonged > 30 d, they are classified as late complications[71].

We found that high mortality rates after SLT are associated with early-onset (< 30 d) and severe GI complications[76]. Few studies are conducted on possible risk factors involved in the development of severe GI complications. For example, age and bilateral LT are associated with severe GI complications. Hypoxia can explain this correlation because bilateral LT is associated with longer ischemic time, more extended procedure, and reduced oxygenation, with an increased risk of primary graft failure[75]. Severe GI complications have been identified as any GI or biliary tract-related diagnosis leading to a significant repercussion for the patient that could endanger their life or involve an invasive therapeutic procedure[72].

The immunosuppressive regimen of patients after SLT plays a significant role in the development of GI complications. In patients with severe immunosuppression,

cholecystitis and diverticulosis are more common compared to the general population [77,78].

Grass *et al* [75] published a fascinating study analyzing various risk factors related to GI complications in patients after LT for a period of 17 years. They estimate a 61.5% frequency of GI complications after LT, which is higher than other studies. The authors included 205 patients; of these, 180 underwent DLT, 40 underwent SLT, and 7 underwent multiorgan transplantations. GI complications such as gastroesophageal reflux disease (GERD) (22.9%), infectious colitis (20.5%), and gastroparesis (10%) were observed with high frequency. Another important conclusion from the study was that severe GI complications were observed in 83 patients (40.5%). As risk factors, they defined DLT and early transplantation period [75]. Many authors consider GERD as one of the most common GI complications after SLT. For example, Davis *et al* [77] estimated that the prevalence of GERD is about 51%-69% in patients after LT. They showed that distal and proximal reflux depends on LT type. They demonstrated that bilateral LT or re-transplantation are associated with a higher incidence of distal and proximal reflux.

On the other hand, unilateral LT correlates with a lower percentage of GERD, regardless of the course of lung disease. Multiple factors have been involved, including intraoperative vagal nerve damage, cough reflex deficiency, impaired mucociliary clearance, and gastroparesis development. They also noted an association between calcineurin inhibitors (CNIs) and other post-transplant immunosuppression therapies in GERD development [77]. Kayawake *et al* [78] published a report about GI complications following LT among the Japanese population. They included 160 LT patients (77 Living-donor lobar lung transplant and 83 deceased donor lung transplant), 59 SLT, 101 bilateral LT. GI complications were registered in 58 of these patients. Thus, gastroparesis, followed by GERD, clostridium difficile colitis, and GI bleeding, was the most common complication. An important implication from their study is that gastroparesis and clostridium difficile colitis appeared early after LT. At the same time, cytomegalovirus gastroenteritis and pneumatosis intestinalis emerged in the late LT period [78].

Overall, the authors postulated some significant findings related to GI complications after LT. First, they established a positive correlation between gastroparesis and bilateral LT incidence with extracorporeal circulation. They also found no major disparity between higher mortality in Japanese patients with GI complications after LT than in Western countries [78].

In conclusion, GI complications after LT are more common in patients who underwent bilateral LT compared to those with SLT [79]. This correlation could be explained by longer ischemic time, more prolonged procedure, and reduced oxygenation. Careful post-operative surveillance, comprehensive monitoring, and evaluation of GI complications by a multidisciplinary team are mandatory for better outcomes after LT [80].

## KIDNEY COMPLICATIONS AFTER SLT

Nowadays, SLT patients have more prolonged survival; thus, they are more prone to clinical complications. One of the common and increasingly known is renal failure [77]. Renal failure increases the difficulty of patient care in both acute and chronic settings. It leads substantially to morbidity and mortality after transplantation. It was estimated that the mortality risk is 4- to 5-fold higher in patients with CKD after LT [81].

It is considered that recipient-related factors such as a low BMI and older age could be related to CKD development [82]. Aggravation of kidney function typically begins within the first 6 mo after transplantation and progressively deteriorates after that [83]. Approximately 3%-10% of patients who underwent LT ultimately develop end-stage renal disease [84]. The typical CKD presentation in LT recipients is characterized by a decrease in the GFR in the first 6 mo post-transplant, approximately 30% to 50% [85]. The main risk factors associated with arising of CKD after LT are kidney function immediately pre-transplant and in the early post-operative period, increasing recipient age at transplant time, female gender, presence of diabetes mellitus, hypertension as well as immunosuppressive treatment [81].

CNIs (*i.e.* cyclosporine, tacrolimus) are the cornerstone of immunosuppression after LT [86]. Many studies have reported the correlation between impaired kidney function and CNI administration among lung recipients. CNI-mediated nephrotoxicity can lead to both acute and chronic renal failure after LT.

A study by Solé *et al*[82] pointed out that CNI reduction is an optional strategy to improve renal function instead of total CNI withdrawal. A study by Högerle *et al*[87] demonstrated promising results using basiliximab as an induction immunosuppressant drug after LT patients to prevent kidney failure by delaying administration of CNI until the fourth post-operative day. It must be kept in mind that significant deterioration of renal function after LT confirms the need for new strategies to improve patients' outcomes after LT.

## HYPERAMMONEMIA SYNDROME AFTER SINGLE LUNG TRANSPLANT

Primary hyperammonemia is a sporadic condition associated with urea cycle enzyme deficiency. Secondary hyperammonemia has been linked with various etiologies such as hepatic dysfunction as a result of different entities, obstructive uropathy with overgrowth of urea-splitting organisms, and many others[88].

In the literature, there are little data related to this rare post-SLT complication. A study by Chen *et al*[89] which included 807 LT patients, focused on hyperammonemia as a fatal complication. They diagnosed hyperammonemia in 8 patients (underwent DLT); 6 (75%) died due to this syndrome. The authors contributed a rationale treatment protocol for managing patients with hyperammonemia after LT. They recommended bowel decontamination, renal replacement therapy, amino acid supplementation, and nitrogen scavenger therapy as the main therapeutic strategies for treating hyperammonemia.

## DE NOVO MALIGNANCY AFTER SLT

Considering post-transplant complications, secondary malignancies are among the most devastating ones. There are various mechanisms behind tumor initiation in transplanted patients, mainly attributed to therapeutic immunosuppression and consequent abnormalities in T-cell function, deoxyribonucleic acid repair, angiogenesis, cellular proliferation, and invasiveness[90]. Other exogenous factors such as Epstein-Barr virus (EBV), ultraviolet light, or tobacco smoking are also implicated in post-transplant tumors' etiology[91-94]. Beyond common risk factors, valid for every organ recipient, in the specific setting of SLT, one should account for an additional risk ensuing from leaving a native lung. Presumably, at the time of transplantation, the remaining organ has already suffered severe damage by preexisting chronic inflammation and fibrosis, increasing the chance for lung cancer, especially when antitumor immune surveillance is compromised by the post-transplant treatment.

The overall risk of malignancies after transplantation is several times higher than that for the general population. According to some series, nearly one-third of transplanted patients develop tumors in the first decade following transplantation[95]. The most common tumors in the post-transplant period are skin neoplasms and lymphoproliferative diseases. Still, any other kind of cancer, including those with the heaviest social burden such as colon cancer, breast carcinoma, and lung cancer, could also be encountered.

Both hematologic and solid tumors are considered among the significant reasons for death after LT, being third only to graft rejection and infections[35]. Among lung transplanted patients, cancer morbidity rises with time increasing from 3.8% in the first year to 13% in year 5[96]. Skin neoplasms account for the majority of the malignancies in the post-transplant period. A high frequency of skin cancer was demonstrated in a study by the Mayo Clinic, with an incidence of squamous cell and basal cell cancer of 28% and 12%, respectively, among lung transplant recipients, within 5 years of LT. Similar results were obtained from other LT centers (Sydney, Australia, and London, United Kingdom)[97-99].

In LT patients, their incidence is highest between years 5 and 7 after transplantation [94]. The risk of non-melanoma skin cancer is greater than that for melanoma. For specific entities like squamous cell carcinoma, it is up to 200 times higher than for the general population. These tumors tend to show more aggressive clinical behavior than those seen in non-transplant (immunocompetent) patients, with a higher tendency for local recurrence and metastatic spread. Other skin neoplasms such as basal cell carcinoma, Merkel cell carcinoma, and malignant melanoma are also found with a higher incidence among lung recipients. Of great importance for LT recipients is to receive whole-body dermatological examinations annually.

Another major group of transplant-related malignancies is post-transplant lymphoproliferative diseases (PTLD), which account for most of the neoplasms in the first year after LT[96]. EBV infection and immunosuppression plays significant role in their pathogenesis. In patients after LT, incidence varies widely (2.5%-20%) according to different reports[100,101].

A possible explanation for this is the difference in EBV infection prevalence and the type of immune suppression. Chronic EBV infection could already be present in the recipient at transplantation time. Still, it could also be transmitted from the donor with the graft. Secondary lymphoma risk is significantly higher when an EBV-naïve recipient is transplanted with an EBV-infected graft[102]. As LT is still an evolving field, finding a suitable donor is often a challenge. This often precludes a selection based on EBV status. In these situations, when a graft from an EBV+ donor is transplanted to an EBV recipient, prevention of PTLD relies on different approaches in the post-transplant period including serial EBV monitoring, cautious lowering of the immune suppression, or implementation of antiviral prophylaxis[103]. In lung-transplant patients, secondary lung cancer is an issue that deserves special attention due to the aggressive nature and poor prognosis of this malignancy. It could occur in up to 4% of lung recipients. Apart from well-known common factors, the risk also depends on the type of transplantation: Whether it is DLT or SLT. In SLT, lung cancer sometimes originates from the transplanted lung, but 20 times more often, it develops in the native one. This means that, as already discussed, not only immunosuppression but the overall condition of the organ, affected by the preexisting disease, is a strong predisposing factor to malignancy. On the other side, the graft's rigorous assessment in this direction is also mandatory to lower the chance of any early (subclinical) malignant lesions being transplanted to the recipient. An example of the aggressive nature of secondary lung cancers after SLT is provided by Gherzi *et al*[104], who reported a 62-year-old woman with fast-progressing adenocarcinoma of the native lung only 15 mo after transplantation for pulmonary fibrosis. Due to multiple graft rejection episodes, the patient was treated with intensive immunosuppression in the post-transplant period. In this case, the clinical evolution of the carcinoma lasted for only 2 wk with no radiological evidence of any chest tumors as near as 1.5 mo before the lethal outcome.

Clinicians engaged in the surveillance of lung-transplanted patients must always stay alert of the potential occurrence of secondary malignancies, and in SLT specifically, the native lung deserves additional attention. Transplant specialists should also be aware of different prophylaxis and prevention strategies, including selecting immunosuppressive regimens with lower impact on antitumor immune response, monitoring, controlling EBV infection in the post-transplant period, and educating patients on how to reduce lifestyle risk factors.

## CONCLUSION

Patients who underwent SLT are predisposed to evolving early or late post-operative complications. Primary or CLAD, anastomosis complications, infections, cardiovascular disease, renal, metabolic, GI disorder, and DNM. Events related to improved surgical techniques and post-operative control of pulmonary immunogenicity through immunosuppressive therapy are among the reasons leading to the reduction of early mortality and longer survival of these patients. Thus, the post-operative management after SLT has to be multidisciplinary and complex.

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