**Name of Journal:** *World Journal of Transplantation*

**Manuscript NO:** 65395

**Manuscript Type:** REVIEW

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

Sekulovski M *et al*. Complications after single lung transplant

Metodija Sekulovski, Bilyana Simonska, Milena Peruhova, Boris Krastev, Monika Peshevska-Sekulovska, Lubomir Spassov, Tsvetelina Velikova

**Metodija Sekulovski, Bilyana Simonska,** Department of Anesthesiology and Intensive care, University Hospital Lozenetz, Sofia 1407, Bulgaria

**Metodija Sekulovski,** Medical Faculty, Sofia University St. Kliment Ohridski, Sofia 1407, Bulgaria

**Milena Peruhova, Monika Peshevska-Sekulovska,** Department of Gastroenterology, University Hospital Lozenetz, Sofia 1407, Bulgaria

**Boris Krastev,** Department of Clinical Oncology, MHAT Hospital for Women Health Nadezhda, Sofia 1330, Bulgaria

**Lubomir Spassov,** Department of Cardiothoracic Surgery, University Hospital Lozenetz, Sofia 1431, Bulgaria

**Tsvetelina Velikova,** Department of Clinical Immunology, University Hospital Lozenetz, Sofia 1407, Bulgaria

**Author contributions:** Sekulovski M, Simonska B, Peruhova M, Peshevska-Sekulovska M, and Krastev B wrote the draft; Spassov L and Velikova T added additional sections and proofread the final version; All authors revised and approved the final version of the manuscript.

**Corresponding author: Tsvetelina Velikova, MD, PhD, Assistant Professor,** Department of Clinical Immunology, University Hospital Lozenetz, Kozyak 1, Sofia 1407, Bulgaria. tsvelikova@medfac.mu-sofia.bg

**Received:** March 5, 2021

**Revised:** April 15, 2021

**Accepted:** June 28, 2021

**Published online:** August 18, 2021

**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.

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

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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

**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.

**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 explanation 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 transbronchial 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 allograph 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 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 commonpost-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]. Gastropareses, 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-naive 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.

**REFERENCES**

1 **Mulligan MS**, Weill D, Davis RD, Christie JD, Farjah F, Singer JP, Hartwig M, Sanchez PG, Kreisel D, Ware LB, Bermudez C, Hachem RR, Weyant MJ, Gries C, Awori Hayanga JW, Griffith BP, Snyder LD, Odim J, Craig JM, Aggarwal NR, Reineck LA. National Heart, Lung, and Blood Institute and American Association for Thoracic Surgery Workshop Report: Identifying collaborative clinical research priorities in lung transplantation. *J Thorac Cardiovasc Surg* 2018; **156**: 2355-2365 [PMID: 30244865 DOI: 10.1016/j.jtcvs.2018.08.010]

2 **Reitz BA**, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, Stinson EB, Shumway NE. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. *N Engl J Med* 1982; **306**: 557-564 [PMID: 6799824 DOI: 10.1056/NEJM198203113061001]

3 **Venuta F**, Van Raemdonck D. History of lung transplantation. *J Thorac Dis* 2017; **9**: 5458-5471 [PMID: 29312756 DOI: 10.21037/jtd.2017.11.84]

4 **Wilson-Smith AR**, Kim YS, Evans GE, Yan TD. Single *vs* double lung transplantation for fibrotic disease-systematic review. *Ann Cardiothorac Surg* 2020; **9**: 10-19 [PMID: 32175235 DOI: 10.21037/acs.2019.12.04]

5 **Meyer DM**, Edwards LB, Torres F, Jessen ME, Novick RJ. Impact of recipient age and procedure type on survival after lung transplantation for pulmonary fibrosis. *Ann Thorac Surg* 2005; **79**: 950-957; discussion 957-958 [PMID: 15734411 DOI: 10.1016/j.athoracsur.2004.08.076]

6 **Chambers DC**, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Lung And Heart-Lung Transplantation Report-2017; Focus Theme: Allograft ischemic time. *J Heart Lung Transplant* 2017; **36**: 1047-1059 [PMID: 28784324 DOI: 10.1016/j.healun.2017.07.016]

7 **Jaksch P**, Koinig H, Klepetko W. Critical care management. In: Lung Transplantation. Vigneswaran WT, Garrity ER. Lung Biology in Health and Disease. London, 2010: 224-236

8 **Meyer KC**. Lung transplantation: chronic complications and management. In: Lung Transplantation. Eds Vigneswaran WT, Garrity ER. Lung Biology in Health and Disease. London, 2010: 357-374

9 **Studer SM**, Levy RD, McNeil K, Orens JB. Lung transplant outcomes: a review of survival, graft function, physiology, health-related quality of life and costeffectiveness. *Eur Respir J* 2004; **24:** 674-85 [PMID: 15459149 DOI: 10.1183/09031936.04.00065004]

10 **de Perrot M**, Liu M, Waddell TK, Keshavjee S. Ischemia-reperfusion-induced lung injury. *Am J Respir Crit Care Med* 2003; **167**: 490-511 [PMID: 12588712 DOI: 10.1164/rccm.200207-670SO]

11 **Kao CC**, Parulekar AD. Postoperative management of lung transplant recipients. *J Thorac Dis* 2019; **11**: S1782-S1788 [PMID: 31632755 DOI: 10.21037/jtd.2019.05.60]

12 **Christie JD**, Kotloff RM, Ahya VN, Tino G, Pochettino A, Gaughan C, DeMissie E, Kimmel SE. The effect of primary graft dysfunction on survival after lung transplantation. *Am J Respir Crit Care Med* 2005; **171**: 1312-1316 [PMID: 15764726 DOI: 10.1164/rccm.200409-1243OC]

13 **Liu Y**, Liu Y, Su L, Jiang SJ. Recipient-related clinical risk factors for primary graft dysfunction after lung transplantation: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e92773 [PMID: 24658073 DOI: 10.1371/journal.pone.0092773]

14 **Sato M**, Hwang DM, Ohmori-Matsuda K, Chaparro C, Waddell TK, Singer LG, Hutcheon MA, Keshavjee S. Revisiting the pathologic finding of diffuse alveolar damage after lung transplantation. *J Heart Lung Transplant* 2012; **31**: 354-363 [PMID: 22330935 DOI: 10.1016/j.healun.2011.12.015]

15 **Snell GI**, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, Pelaez A, Whelan TP, Perch M, Bag R, Budev M, Corris PA, Crespo MM, Witt C, Cantu E, Christie JD. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2017; **36**: 1097-1103 [PMID: 28942784 DOI: 10.1016/j.healun.2017.07.021]

16 **Christie JD**, Carby M, Bag R, Corris P, Hertz M, Weill D; ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2005; **24**: 1454-1459 [PMID: 16210116 DOI: 10.1016/j.healun.2004.11.049]

17 **Whitson BA**, Nath DS, Johnson AC, Walker AR, Prekker ME, Radosevich DM, Herrington CS, Dahlberg PS. Risk factors for primary graft dysfunction after lung transplantation. *J Thorac Cardiovasc Surg* 2006; **131**: 73-80 [PMID: 16399297 DOI: 10.1016/j.jtcvs.2005.08.039]

18 **Diamond JM**, Lee JC, Kawut SM, Shah RJ, Localio AR, Bellamy SL, Lederer DJ, Cantu E, Kohl BA, Lama VN, Bhorade SM, Crespo M, Demissie E, Sonett J, Wille K, Orens J, Shah AS, Weinacker A, Arcasoy S, Shah PD, Wilkes DS, Ware LB, Palmer SM, Christie JD; Lung Transplant Outcomes Group. Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2013; **187**: 527-534 [PMID: 23306540 DOI: 10.1164/rccm.201210-1865OC]

19 **Barr ML**, Kawut SM, Whelan TP, Girgis R, Böttcher H, Sonett J, Vigneswaran W, Follette DM, Corris PA; ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part IV: recipient-related risk factors and markers. *J Heart Lung Transplant* 2005; **24**: 1468-1482 [PMID: 16210118 DOI: 10.1016/j.healun.2005.02.019]

20 **Kuntz CL**, Hadjiliadis D, Ahya VN, Kotloff RM, Pochettino A, Lewis J, Christie JD. Risk factors for early primary graft dysfunction after lung transplantation: a registry study. *Clin Transplant* 2009; **23**: 819-830 [PMID: 19239481 DOI: 10.1111/j.1399-0012.2008.00951.x]

21 **Samano MN**, Fernandes LM, Baranauskas JC, Correia AT, Afonso JE Jr, Teixeira RH, Caramori ML, Pêgo-Fernandes PM, Jatene FB. Risk factors and survival impact of primary graft dysfunction after lung transplantation in a single institution. *Transplant Proc* 2012; **44**: 2462-2468 [PMID: 23026621 DOI: 10.1016/j.transproceed.2012.07.134]

22 **Christie JD**, Bellamy S, Ware LB, Lederer D, Hadjiliadis D, Lee J, Robinson N, Localio AR, Wille K, Lama V, Palmer S, Orens J, Weinacker A, Crespo M, Demissie E, Kimmel SE, Kawut SM. Construct validity of the definition of primary graft dysfunction after lung transplantation. *J Heart Lung Transplant* 2010; **29**: 1231-1239 [PMID: 20655249 DOI: 10.1016/j.healun.2010.05.013]

23 **Lee JC**, Christie JD. Primary graft dysfunction. *Clin Chest Med* 2011; **32**: 279-293 [PMID: 21511090 DOI: 10.1016/j.ccm.2011.02.007]

24 **Whitson BA**, Prekker ME, Herrington CS, Whelan TP, Radosevich DM, Hertz MI, Dahlberg PS. Primary graft dysfunction and long-term pulmonary function after lung transplantation. *J Heart Lung Transplant* 2007; **26**: 1004-1011 [PMID: 17919620 DOI: 10.1016/j.healun.2007.07.018]

25 **Daud SA**, Yusen RD, Meyers BF, Chakinala MM, Walter MJ, Aloush AA, Patterson GA, Trulock EP, Hachem RR. Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2007; **175**: 507-513 [PMID: 17158279 DOI: 10.1164/rccm.200608-1079OC]

26 **Fiser SM**, Tribble CG, Long SM, Kaza AK, Kern JA, Jones DR, Robbins MK, Kron IL. Ischemia-reperfusion injury after lung transplantation increases risk of late bronchiolitis obliterans syndrome. *Ann Thorac Surg* 2002; **73**: 1041-1047; discussion 1047-1048 [PMID: 11996238 DOI: 10.1016/s0003-4975(01)03606-2]

27 **Suzuki Y**, Cantu E, Christie JD. Primary graft dysfunction. *Semin Respir Crit Care Med* 2013; **34**: 305-319 [PMID: 23821506 DOI: 10.1055/s-0033-1348474]

28 **Bermudez CA**, Adusumilli PS, McCurry KR, Zaldonis D, Crespo MM, Pilewski JM, Toyoda Y. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: long-term survival. *Ann Thorac Surg* 2009; **87**: 854-860 [PMID: 19231405 DOI: 10.1016/j.athoracsur.2008.11.036]

29 **Morrison MI**, Pither TL, Fisher AJ. Pathophysiology and classification of primary graft dysfunction after lung transplantation. *J Thorac Dis* 2017; **9**: 4084-4097 [PMID: 29268419 DOI: 10.21037/jtd.2017.09.09]

30 **Hachem RR**. The role of the immune system in lung transplantation: towards improved long-term results. *J Thorac Dis* 2019; **11**: S1721-S1731 [PMID: 31632749 DOI: 10.21037/jtd.2019.04.25]

31 **Fernandez R**, Chiu S, Raparia K, Garcha P, Farver C, Budev M, Tambur AR, DeCamp MM, Budinger S, Perlman H, Mohanakumar T, Bharat A. Humoral Human Lung Allograft Rejection by Tissue-Restricted Non-HLA Antibodies. *Ann Thorac Surg* 2016; **102**: e339-e341 [PMID: 27645977 DOI: 10.1016/j.athoracsur.2016.03.042]

32 **Glanville AR**, Aboyoun C, Klepetko W, Reichenspurner H, Treede H, Verschuuren EA, Boehler A, Benden C, Hopkins P, Corris PA; European and Australian Investigators in Lung Transplantation. Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. *J Heart Lung Transplant* 2015; **34**: 16-25 [PMID: 25049068 DOI: 10.1016/j.healun.2014.06.001]

33 **Levine DJ**, Glanville AR, Aboyoun C, Belperio J, Benden C, Berry GJ, Hachem R, Hayes D Jr, Neil D, Reinsmoen NL, Snyder LD, Sweet S, Tyan D, Verleden G, Westall G, Yusen RD, Zamora M, Zeevi A. Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2016; **35**: 397-406 [PMID: 27044531 DOI: 10.1016/j.healun.2016.01.1223]

34 **Roux A**, Bendib Le Lan I, Holifanjaniaina S, Thomas KA, Hamid AM, Picard C, Grenet D, De Miranda S, Douvry B, Beaumont-Azuar L, Sage E, Devaquet J, Cuquemelle E, Le Guen M, Spreafico R, Suberbielle-Boissel C, Stern M, Parquin F; Foch Lung Transplantation Group. Antibody-Mediated Rejection in Lung Transplantation: Clinical Outcomes and Donor-Specific Antibody Characteristics. *Am J Transplant* 2016; **16**: 1216-1228 [PMID: 26845386 DOI: 10.1111/ajt.13589]

35 **Yusen RD**, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Lung and Heart-Lung Transplantation Report--2015; Focus Theme: Early Graft Failure. *J Heart Lung Transplant* 2015; **34**: 1264-1277 [PMID: 26454740 DOI: 10.1016/j.healun.2015.08.014]

36 **Verleden GM**, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant* 2014; **33**: 127-133 [PMID: 24374027 DOI: 10.1016/j.healun.2013.10.022]

37 **Gauthier JM**, Hachem RR, Kreisel D. Update on Chronic Lung Allograft Dysfunction. *Curr Transplant Rep* 2016; **3**: 185-191 [PMID: 28090432 DOI: 10.1007/s40472-016-0112-y]

38 **Verleden SE**, Ruttens D, Vos R, Vandermeulen E, Moelants E, Mortier A, Van Raemdonck DE, Proost P, Schols D, Verleden GM, Vanaudenaerde BM. Differential cytokine, chemokine and growth factor expression in phenotypes of chronic lung allograft dysfunction. *Transplantation* 2015; **99**: 86-93 [PMID: 25050473 DOI: 10.1097/TP.0000000000000269]

39 **Verleden GM**, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, Ensor CR, Gottlieb J, Hachem RR, Lama V, Martinu T, Neil DAH, Singer LG, Snell G, Vos R. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant* 2019; **38**: 493-503 [PMID: 30962148 DOI: 10.1016/j.healun.2019.03.009]

40 **Sato M**. Bronchiolitis obliterans syndrome and restrictive allograft syndrome after lung transplantation: why are there two distinct forms of chronic lung allograft dysfunction? *Ann Transl Med* 2020; **8**: 418 [PMID: 32355862 DOI: 10.21037/atm.2020.02.159]

41 **Todd JL**, Palmer SM. Bronchiolitis obliterans syndrome: the final frontier for lung transplantation. *Chest* 2011; **140**: 502-508 [PMID: 21813529 DOI: 10.1378/chest.10-2838]

42 **Verleden SE**, Vandermeulen E, Ruttens D, Vos R, Vaneylen A, Dupont LJ, Van Raemdonck DE, Vanaudenaerde BM, Verleden GM. Neutrophilic reversible allograft dysfunction (NRAD) and restrictive allograft syndrome (RAS). *Semin Respir Crit Care Med* 2013; **34**: 352-360 [PMID: 23821509 DOI: 10.1055/s-0033-1348463]

43 **Verleden SE**, Ruttens D, Vandermeulen E, Bellon H, Van Raemdonck DE, Dupont LJ, Vanaudenaerde BM, Verleden G, Vos R. Restrictive chronic lung allograft dysfunction: Where are we now? *J Heart Lung Transplant* 2015; **34**: 625-630 [PMID: 25577564 DOI: 10.1016/j.healun.2014.11.007]

44 **Beeckmans H**, Saez B, Van Herck A, Sacreas A, Kaes J, Heigl T, Vanstapel A, Ordies S, Frick AE, Verleden SE, Verleden GM, Vos R, Vanaudenaerde BM. Lung Transplantation and Precision Medicine. Precision in Pulmonary, Critical Care, and Sleep Medicine, 2019: 335–53 [DOI: 10.1007/978-3-030-31507-8\_22]

45 **Scheffert JL**, Raza K. Immunosuppression in lung transplantation. *J Thorac Dis* 2014; **6**: 1039-1053 [PMID: 25132971 DOI: 10.3978/j.issn.2072-1439.2014.04.23]

46 **Yates B**, Murphy DM, Forrest IA, Ward C, Rutherford RM, Fisher AJ, Lordan JL, Dark JH, Corris PA. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2005; **172**: 772-775 [PMID: 15976371 DOI: 10.1164/rccm.200411-1537OC]

47 **Murphy DM**, Forrest IA, Corris PA, Johnson GE, Small T, Jones D, Fisher AJ, Egan JJ, Cawston TE, Lordan JL, Ward C. Azithromycin attenuates effects of lipopolysaccharide on lung allograft bronchial epithelial cells. *J Heart Lung Transplant* 2008; **27**: 1210-1216 [PMID: 18971093 DOI: 10.1016/j.healun.2008.07.026]

48 **Machuzak M**, Santacruz JF, Gildea T, Murthy SC. Airway complications after lung transplantation. *Thorac Surg Clin* 2015; **25**: 55-75 [PMID: 25430430 DOI: 10.1016/j.thorsurg.2014.09.008]

49 **Murthy SC**, Gildea TR, Machuzak MS. Anastomotic airway complications after lung transplantation. *Curr Opin Organ Transplant* 2010; **15**: 582-587 [PMID: 20733486 DOI: 10.1097/MOT.0b013e32833e3e6e]

50 **Eberlein M**, Reed RM, Bolukbas S, Diamond JM, Wille KM, Orens JB, Brower RG, Christie JD; Lung Transplant Outcomes Group. Lung size mismatch and primary graft dysfunction after bilateral lung transplantation. *J Heart Lung Transplant* 2015; **34**: 233-240 [PMID: 25447586 DOI: 10.1016/j.healun.2014.09.030]

51 **Anile M**, Diso D, Rendina EA, Venuta F. Airway anastomosis for lung transplantation. *J Thorac Dis* 2016; **8**: S197-S203 [PMID: 26981271 DOI: 10.3978/j.issn.2072-1439.2016.01.67]

52 **Yserbyt J**, Dooms C, Vos R, Dupont LJ, Van Raemdonck DE, Verleden GM. Anastomotic airway complications after lung transplantation: risk factors, treatment modalities and outcome-a single-centre experience. *Eur J Cardiothorac Surg* 2016; **49**: e1-e8 [PMID: 26464447 DOI: 10.1093/ejcts/ezv363]

53 **Benvenuto LJ**, Costa J, Piloni D, Aversa M, Anderson MR, Shah L, Robbins HY, Stanifer B, Sonett JR, Arcasoy SM, D'Ovidio F. Right single lung transplantation or double lung transplantation compared with left single lung transplantation in chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2020; **39**: 870-877 [PMID: 32693937 DOI: 10.1016/j.healun.2020.06.009]

54 **Garrido G**, Dhillon GS. Medical Course and Complications After Lung Transplantation. Psychosocial Care of End-Stage Organ Disease and Transplant Patients, 2018: 279-288 [DOI: 10.1007/978-3-319-94914-7\_26]

55 **Parsa SA**, Khaheshi I, Dousti A, Naghashzadeh F, Ataeinia B. ST-Elevation Myocardial Infarction 33 Days after Lung Transplant in a Patient with Non-Significant CAD before Transplantation: A Case Report. *J Clin Diagn Res* 2016; **10**: OD23-OD24 [PMID: 27437285 DOI: 10.7860/JCDR/2016/18830.7800]

56 **D'Angelo AM**, Chan EG, Hayanga JW, Odell DD, Pilewski J, Crespo M, Morrell M, Shigemura N, Luketich J, Bermudez C, Althouse AD, D'Cunha J. Atrial arrhythmias after lung transplantation: Incidence and risk factors in 652 lung transplant recipients. *J Thorac Cardiovasc Surg* 2016; **152**: 901-909 [PMID: 27234020 DOI: 10.1016/j.jtcvs.2016.04.070]

57 **Fan L**, Wu B, Wang HM, Yang H, Liu D, Zhang J, Wei D, Zhou M, Zhai ZG, Chen JY. [Incidence and influencing factors of venous thromboembolism after lung transplantation]. *Zhonghua Yi Xue Za Zhi* 2019; **99**: 1848-1852 [PMID: 31269578 DOI: 10.3760/cma.j.issn.0376-2491.2019.24.003]

58 **King CS**, Khandhar S, Burton N, Shlobin OA, Ahmad S, Lefrak E, Barnett SD, Nathan SD. Native lung complications in single-lung transplant recipients and the role of pneumonectomy. *J Heart Lung Transplant* 2009; **28**: 851-856 [PMID: 19632585 DOI: 10.1016/j.healun.2009.04.023]

59 **Shehata IM**, Elhassan A, Urits I, Viswanath O, Seoane L, Shappley C, Kaye AD. Postoperative Management of Hyperinflated Native Lung in Single-Lung Transplant Recipients with Chronic Obstructive Pulmonary Disease: A Review Article. *Pulm Ther* 2021; **7**: 37-46 [PMID: 33263926 DOI: 10.1007/s41030-020-00141-6]

60 **Tsagkaropoulos S**, Belmans A, Verleden GM, Coosemans W, Decaluwe H, De Leyn P, Nafteux P, Van Raemdonck D. Single-lung transplantation: does side matter? *Eur J Cardiothorac Surg* 2011; **40**: e83-e92 [PMID: 21497108 DOI: 10.1016/j.ejcts.2011.03.011]

61 **Venuta F**, Boehler A, Rendina EA, De Giacomo T, Speich R, Schmid R, Coloni GF, Weder W. Complications in the native lung after single lung transplantation. *Eur J Cardiothorac Surg* 1999; **16**: 54-58 [PMID: 10456403 DOI: 10.1016/s1010-7940(99)00141-4]

62 **Colquhoun IW**, Gascoigne AD, Gould K, Corris PA, Dark JH. Native pulmonary sepsis after single-lung transplantation. *Transplantation* 1991; **52**: 931-933 [PMID: 1949183 DOI: 10.1097/00007890-199111000-00039]

63 **Qiao W,** Zou J, Ping F, Han Z, Li L, Wang X. Fungal infection in lung transplant recipients in perioperative period from one lung transplant center. *J Thorac Dis* 2019; **11:** 1554-1561 [PMID: 31179099 DOI: 10.21037/jtd.2019.03.18]

64 **Yonan NA**, el-Gamel A, Egan J, Kakadellis J, Rahman A, Deiraniya AK. Single lung transplantation for emphysema: predictors for native lung hyperinflation. *J Heart Lung Transplant* 1998; **17**: 192-201 [PMID: 9513858]

65 **Park SJ**. Acute native lung hyperinflation. *J Heart Lung Transplant* 2000; **19**: 510 [PMID: 10877544 DOI: 10.1016/s1053-2498(00)00086-3]

66 **Criée CP**, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, Berdel D, Köhler D, Magnussen H, Marek W, Mitfessel H, Rasche K, Rolke M, Worth H, Jörres RA; Working Group for Body Plethysmography of the German Society for Pneumology and Respiratory Care. Body plethysmography--its principles and clinical use. *Respir Med* 2011; **105**: 959-971 [PMID: 21356587 DOI: 10.1016/j.rmed.2011.02.006]

67 **Tang Y**, Zhang M, Feng Y, Liang B. The measurement of lung volumes using body plethysmography and helium dilution methods in COPD patients: a correlation and diagnosis analysis. *Sci Rep* 2016; **6**: 37550 [PMID: 27876834 DOI: 10.1038/srep37550]

68 **Hansen LN,** Ravn JB, Yndgaard S. Early extubation after single-lung transplantation: analysis of the first 106 cases. *J Cardiothorac Vasc Anesth* 2003; **17:** 36-39 [PMID: 12635058 DOI: 10.1053/jcan.2003.7]

69 **Wang TH**, Wu CP, Wang LY. Chest physiotherapy with early mobilization may improve extubation outcome in critically ill patients in the intensive care units. *Clin Respir J* 2018; **12**: 2613-2621 [PMID: 30264933 DOI: 10.1111/crj.12965]

70 **Roca O**, de Acilu MG, Caralt B, Sacanell J, Masclans JR; ICU collaborators. Humidified high flow nasal cannula supportive therapy improves outcomes in lung transplant recipients readmitted to the intensive care unit because of acute respiratory failure. *Transplantation* 2015; **99**: 1092-1098 [PMID: 25340596 DOI: 10.1097/TP.0000000000000460]

71 **Belmaati EO,** Iversen M, Kofoed KF, Nielsen MB, Mortensen J. Scintigraphy at 3 months after single lung transplantation and observations of primary graft dysfunction and lung function. *Interact Cardiovasc Thorac Surg* 2012; **14:** 792-796 [PMID: 22407739 DOI: 10.1093/icvts/ivs066]

72 **de la Torre M**, Fernández R, Fieira E, González D, Delgado M, Méndez L, Borro JM. Postoperative surgical complications after lung transplantation. *Rev Port Pneumol* *(2006)* 2015; **21**: 36-40 [PMID: 25854134 DOI: 10.1016/j.rppnen.2014.09.007]

73 **Aramini** **B**, D’Ovidio F. Gastroesophageal reflux disease and the lung transplant recipient. *Curr Respir Care Rep* 2014; **3:** 206-213 [DOI: 10.1007/s13665-014-0092-2]

74 **Paul S**, Escareno CE, Clancy K, Jaklitsch MT, Bueno R, Lautz DB. Gastrointestinal complications after lung transplantation. *J Heart Lung Transplant* 2009; **28**: 475-479 [PMID: 19416776 DOI: 10.1016/j.healun.2009.02.011]

75 **Grass F**, Schäfer M, Cristaudi A, Berutto C, Aubert JD, Gonzalez M, Demartines N, Ris HB, Soccal PM, Krueger T. Incidence and Risk Factors of Abdominal Complications After Lung Transplantation. *World J Surg* 2015; **39**: 2274-2281 [PMID: 26013207 DOI: 10.1007/s00268-015-3098-1]

76 **Lahon B**, Mordant P, Thabut G, Georger JF, Dauriat G, Mal H, Lesèche G, Castier Y. Early severe digestive complications after lung transplantation. *Eur J Cardiothorac Surg* 2011; **40**: 1419-1424 [PMID: 21497510 DOI: 10.1016/j.ejcts.2011.02.069]

77 **Davis CS**, Shankaran V, Kovacs EJ, Gagermeier J, Dilling D, Alex CG, Love RB, Sinacore J, Fisichella PM. Gastroesophageal reflux disease after lung transplantation: pathophysiology and implications for treatment. *Surgery* 2010; **148**: 737-744; discussion 744-745 [PMID: 20727564 DOI: 10.1016/j.surg.2010.07.011]

78 **Kayawake H**, Chen-Yoshikawa TF, Motoyama H, Hamaji M, Nakajima D, Aoyama A, Date H. Gastrointestinal complications after lung transplantation in Japanese patients. *Surg Today* 2018; **48**: 883-890 [PMID: 29713813 DOI: 10.1007/s00595-018-1666-3]

79 **Bhama JK**, Rayappa S, Zaldonis D, Adusumilli PS, Bansal A, Genovese EA, Teuteberg JJ, Toyoda Y, Siegenthaler MP, Bermudez CA, McCurry KR, Kormos RL. Impact of abdominal complications on outcome after mechanical circulatory support. *Ann Thorac Surg* 2010; **89**: 522-528; discussion 528-529 [PMID: 20103336 DOI: 10.1016/j.athoracsur.2009.11.016]

80 **Ishani A**, Erturk S, Hertz MI, Matas AJ, Savik K, Rosenberg ME. Predictors of renal function following lung or heart-lung transplantation. *Kidney Int* 2002; **61:** 2228-2234 [PMID: 12028464 DOI: 10.1046/j.1523-1755.2002.00361.x]

81 **Ojo AO,** Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; **349:** 931-940 [PMID: 12954741 DOI: 10.1056/NEJMoa021744]

82 **Solé A**, Zurbano F, Borro JM, Monforte V, Ussetti P, Santos F. Prevalence and Diagnosis of Chronic Kidney Disease in Maintenance Lung Transplant Patients: ICEBERG Study. *Transplant Proc* 2015; **47**: 1966-1971 [PMID: 26293082 DOI: 10.1016/j.transproceed.2015.04.097]

83 **Bloom RD**, Doyle AM. Kidney disease after heart and lung transplantation. *Am J Transplant* 2006; **6**: 671-679 [PMID: 16539623 DOI: 10.1111/j.1600-6143.2006.01248.x]

84 **Wilkinson AH**, Cohen DJ. Renal failure in the recipients of nonrenal solid organ transplants. *J Am Soc Nephrol* 1999; **10**: 1136-1144 [PMID: 10232701 DOI: 10.1681/ASN.V1051136]

85 **Ojo AO**. Renal disease in recipients of nonrenal solid organ transplantation. *Semin Nephrol* 2007; **27**: 498-507 [PMID: 17616280 DOI: 10.1016/j.semnephrol.2007.03.010]

86 **Health Resources and Services Administration**. Scientific Registry of Transplant Recipients [cited 20 March 2021]. Available from: https://srtr.transplant.hrsa.gov/

87 **Högerle BA**, Kohli N, Habibi-Parker K, Lyster H, Reed A, Carby M, Zeriouh M, Weymann A, Simon AR, Sabashnikov A, Popov AF, Soresi S. Challenging immunosuppression treatment in lung transplant recipients with kidney failure. *Transpl Immunol* 2016; **35**: 18-22 [PMID: 26892232 DOI: 10.1016/j.trim.2016.02.002]

88 **Lichtenstein GR**, Kaiser LR, Tuchman M, Palevsky HI, Kotloff RM, O'Brien CB, Furth EE, Raps EC, Berry GT. Fatal hyperammonemia following orthotopic lung transplantation. *Gastroenterology* 1997; **112**: 236-240 [PMID: 8978364 DOI: 10.1016/s0016-5085(97)70240-3]

89 **Chen C**, Bain KB, Iuppa JA, Yusen RD, Byers DE, Patterson GA, Trulock EP, Hachem RR, Witt CA. Hyperammonemia Syndrome After Lung Transplantation: A Single Center Experience. *Transplantation* 2016; **100**: 678-684 [PMID: 26335916 DOI: 10.1097/TP.0000000000000868]

90 **Robbins HY**, Arcasoy SM. Malignancies following lung transplantation. *Clin Chest Med* 2011; **32**: 343-355 [PMID: 21511094 DOI: 10.1016/j.ccm.2011.02.011]

91 **Hanto DW**, Frizzera G, Gajl-Peczalska KJ, Sakamoto K, Purtilo DT, Balfour HH Jr, Simmons RL, Najarian JS. Epstein-Barr virus-induced B-cell lymphoma after renal transplantation: acyclovir therapy and transition from polyclonal to monoclonal B-cell proliferation. *N Engl J Med* 1982; **306**: 913-918 [PMID: 6278307 DOI: 10.1056/NEJM198204153061506]

92 **Wigle DA**, Chaparro C, Humar A, Hutcheon MA, Chan CK, Keshavjee S. Epstein-Barr virus serology and posttransplant lymphoproliferative disease in lung transplantation. *Transplantation* 2001; **72**: 1783-1786 [PMID: 11740388 DOI: 10.1097/00007890-200112150-00012]

93 **Ramsay HM**, Fryer AA, Hawley CM, Smith AG, Nicol DL, Harden PN. Factors associated with nonmelanoma skin cancer following renal transplantation in Queensland, Australia. *J Am Acad Dermatol* 2003; **49**: 397-406 [PMID: 12963901 DOI: 10.1067/s0190-9622(03)00902-2]

94 **de Perrot M**, Wigle DA, Pierre AF, Tsao MS, Waddell TK, Todd TR, Keshavjee SH. Bronchogenic carcinoma after solid organ transplantation. *Ann Thorac Surg* 2003; **75**: 367-371 [PMID: 12607641 DOI: 10.1016/s0003-4975(02)04379-5]

95 **Penn I**. Post-transplant malignancy: the role of immunosuppression. *Drug Saf* 2000; **23**: 101-113 [PMID: 10945373 DOI: 10.2165/00002018-200023020-00002]

96 **Trulock EP**, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult lung and heart-lung transplant report--2004. *J Heart Lung Transplant* 2004; **23**: 804-815 [PMID: 15285066 DOI: 10.1016/j.healun.2004.05.013]

97 **Collett D**, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. *Am J Transplant* 2010; **10**: 1889-1896 [PMID: 20659094 DOI: 10.1111/j.1600-6143.2010.03181.x]

98 **De Rosa N**, Paddon VL, Liu Z, Glanville AR, Parsi K. Nonmelanoma Skin Cancer Frequency and Risk Factors in Australian Heart and Lung Transplant Recipients. *JAMA Dermatol* 2019; **155**: 716-719 [PMID: 30865218 DOI: 10.1001/jamadermatol.2018.4789]

99 **Gordon LG**, Rodriguez-Acevedo AJ, Papier K, Khosrotehrani K, Isbel N, Campbell S, Griffin A, Green AC. The effects of a multidisciplinary high-throughput skin clinic on healthcare costs of organ transplant recipients. *J Eur Acad Dermatol Venereol* 2019; **33**: 1290-1296 [PMID: 30706970 DOI: 10.1111/jdv.15458]

100 **Reams BD**, McAdams HP, Howell DN, Steele MP, Davis RD, Palmer SM. Posttransplant lymphoproliferative disorder: incidence, presentation, and response to treatment in lung transplant recipients. *Chest* 2003; **124**: 1242-1249 [PMID: 14555552 DOI: 10.1378/chest.124.4.1242]

101 **Montone KT,** Litzky LA, Wurster A, Kaiser L, Bavaria J, Kotloff R, Palevsky H, Pietra GG, Tomaszewski JE. Analysis of Epstein-Barr virus-associated posttransplantation lymphoproliferative disorder after lung transplantation. *Surgery* 1996; **119:** 544-551 [PMID: 8619211 DOI: 10.1016/s0039-6060(96)80265-0]

102 **Courtwright AM**, Burkett P, Divo M, Keller S, Rosas IO, Trindade A, Mody GN, Singh SK, El-Chemaly S, Camp PC, Goldberg HJ, Mallidi HR. Posttransplant Lymphoproliferative Disorders in Epstein-Barr Virus Donor Positive/Recipient Negative Lung Transplant Recipients. *Ann Thorac Surg* 2018; **105**: 441-447 [PMID: 29223419 DOI: 10.1016/j.athoracsur.2017.09.033]

103 **Amital A**, Shitrit D, Raviv Y, Bendayan D, Sahar G, Bakal I, Kramer MR. Development of malignancy following lung transplantation. *Transplantation* 2006; **81**: 547-551 [PMID: 16495802 DOI: 10.1097/01.tp.0000195774.26382.34]

104 **Gherzi L**, Carillo C, Diso D, Mantovani S, de Giacomo T, Venuta F, Anile M. Devastating fast-growing lung cancer after single lung transplantation. *J Thorac Dis* 2017; **9**: E1071-E1073 [PMID: 29312768 DOI: 10.21037/jtd.2017.11.57]

**Footnotes**

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

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

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

**First decision:** March 31, 2021

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

**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

**P-Reviewer:** Bos S, Meng FZ **S-Editor:** Zhang L **L-Editor:** Filipodia **P-Editor:** Yuan YY

**Figure Legends**



**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.

**Table 1 Primary graft dysfunction classification**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PGD** **grade** | **Chest radiography** | | **PaO2/FiO2 ratio in** **mmHg** | **SaO2/FiO2 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 |

FiO2: Fraction of inspired oxygen; PaO2: Partial oxygen pressure; PGD: Primary graft dysfunction; SaO2: 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.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**