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Systematic review and meta-analysis of post-transplant lymphoproliferative disorder in lung transplant recipients

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Abstract

A systematic review of papers in English on Post-transplant lymphoproliferative disorder (PTLD) in lung transplant recipients (LTR) using MEDLINE, EMBASE, SCOPUS, and Cochrane databases was performed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were strictly adhered to. Pooled odds ratios (pOR) were calculated from a random-effects model and heterogeneity among studies was quantitated using I^2 values. 14 studies published from 2005 to 2015 were included in the meta-analysis. 164 lung transplant recipients were included. LTRs who received single versus bilateral were associated with a 7.67-fold risk of death after PTLD (6 studies with 64 LTRs; pOR 7.67 95% CI 1.98–29.70; $p = 0.003$). pOR of death for early onset PTLD (<1 year post-LT) versus late onset (>1 year post-LT) was not different (3 studies with 72 LTRs; pOR 0.62, 95% CI 0.20–1.86, $p = 0.39$). Standardized mean difference (SMD) in time from transplant to PTLD onset between LTRs who died versus alive was not different (9 studies with 109 LTRs; SMD 0.03, 95% CI –0.48–0.53, $p = 0.92$). Survival in polymorphic versus monomorphic PTLD and extranodal versus nodal disease were similar (4 studies with 31 LTRs; pOR 0.44, 95% CI 0.08–2.51; $p = 0.36$. 6 studies with 81 LTRs; pOR 1.05 95% CI 0.31–3.52, $p = 0.94$). This meta-analysis demonstrates that single LTRs are at a higher risk of death versus bilateral LTRs after the development of PTLD.

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Keywords

post-transplant lymphoproliferative disorder (PTLD); lung transplant; malignancy; meta-analysis

Introduction

Lung transplantation is a life-saving treatment option for patients suffering from end-stage lung disease. The International Society for Heart and Lung Transplantation (ISHLT) reports unadjusted analysis of posttransplant survival 82% for bilateral and 78% for unilateral at 1-year, and 69% and 61%, respectively at 3-years [1]. Life-threatening complications such as posttransplant lymphoproliferative disease (PTLD) contributes to even worse survival outcomes. PTLD affects up to 10% [2] of all transplant recipients and between 1.8–20% of all lung transplant recipients (LTRs), with a mortality range of 20–50% in LTRs [3,4,16,17]. This wide range may be attributed to variability in patient sample size of studies conducted [2–9]. Additionally, PTLD is one of the most common forms of transplant associated malignancies, with an incidence rate of 20.8% in all posttransplant malignancies [9].

Positive in more than 80% of PTLD biopsies, the Epstein-Barr virus (EBV) [10–12,15] is acquired by 95% of the world's population during childhood or early adolescence [13]. EBV is often asymptomatic, with naïve EBV infected B cells either differentiating into memory B cells or are regulated and killed by EBV-specific cytotoxic T lymphocytes (CTL). However, in the immunosuppressed transplant recipient, naïve EBV infected B cells are allowed unregulated proliferation as the result of calcineurin inhibitors diminishing CTL function. This proliferation of lymphocytes results in the development of PTLD. If seronegative LTRs become infected with the lytic form of the virus, immunosuppression allows for a massive amplification of the virus and infection of B-cells that can lead to the development of PTLD [15]. T cell lineage is estimated to account for around 10–15% of PTLD cases, with 30% of cases being EBV positive [15,36]. Of note, the prevalence of human T-cell lymphotropic viruses in some parts of the world may contribute to a higher instance of T lymphocyte PTLD, with one publication reporting an incidence rate as high as 40% [36]. Lastly, PTLD of the natural killer cell lineage has only been reported in occasional cases [15,38].

There remains no unified treatment approach for PTLD due to the heterogeneous and unpredictable nature of the disease, with treatments ranging from reduction in immunosuppression (RI) to the use of rituximab and/or chemotherapy. Initial RI remains the first step in treatment of all types of PTLD to control EBV-induced B-cell proliferation and regain appropriate CTL function, while also preventing allograft rejection [18]. RI treatment alone is common in the minority of PTLD patients who develop early lesions, localized polyclonal PTLD [19], and carries a response rate lower than 50% [18–22]. For malignant polyclonal or monoclonal PTLD with CD20 expression, the anti-CD20 monoclonal antibody rituximab is often utilized [20]. Use of rituximab alone has been shown to achieve 44.2% effectiveness in one clinical trial [23]. Further treatment of malignant PTLD includes the use of chemotherapy agents with steroids, cyclophosphamide, doxorubicin or daunorubicin, vincristine, prednisone (CHOP), with the addition of rituximab for CD20+ PTLD (R-CHOP) [17, 20], which has reported to achieve complete remission in 40–60% of patients [20, 22, 24].

Less commonly used chemotherapy regimens for malignant T-Cell PTLD include separate courses of cyclophosphamide, vincristine, doxorubicin, and dexamethasone, followed by methotrexate and cytarabine (HyperCVAD) or the use of etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydaunorubicin (EPOCH) chemotherapy [39, 40].

Given the wide range of characteristics of PTLD and treatment regimens presented here, it is suggestive that investigation of specific PTLD characteristics will be beneficial. With relatively higher incidence rates higher than other solid organ transplants, studies assessing survival after PTLD onset in lung transplant recipients appear warranted. The primary objective of this study was to identify disease and patient characteristics associated with PTLD survival in LTRs.

Methods

Data source and search strategy

Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a literature search was performed in consultation with a medical reference librarian in July 2016 through MEDLINE, EMBASE, SCOPUS, and Cochrane databases for English, human studies, with no other filters set. The search terms “(ptld AND post transplant lymphoproliferative disease) AND (lung transplant)” were applied to all four databases to search for the primary outcome of death associated to PTLD in lung transplant recipients. This search term includes both “lymphoproliferative disease” and lymphoproliferative disorder” in the MeSH terms.

Study selection criteria

All studies were included from the initial search and were evaluated for exclusion. Four researchers (J.C., C. M., C. I., C. E.) convened to determine exclusion of studies if they (1) were duplicates of each other, (2) were non-lung studies, (3) abstracts, (4) were individual case studies, (5) did not present primary outcome data of interest, (6) were a Meta-Analysis or Literature Review, (7) did not have PTLD patients, or (8) did not provide useable clinical variables.

Data extraction

Data was extracted from the studies by one researcher (J.C.) and reviewed by three other researchers (C. M., C. I., C. E.) for accuracy and consistency. Extracted data included year and author name of publication, number of patients, age group (Adult or Pediatric), death, type of PTLD (Early or Late), PTLD morphology, histology, treatment, nodal involvement (Nodal or Extranodal), type of lung transplant, time to PTLD, antecedents, age, gender, and race of patients.

Statistical analysis

Categorical characteristics were analyzed for odds ratio using a 2x2 contingency table. Characteristics were only analyzed if they had non-zero binary values for each category presented. Studies with categorical characteristics that had at least 1 zero value were discarded, as these were not useable for calculation. Pooled odds ratio estimates and

corresponding 95% confidence intervals for type of PTLT (early or late), type of lung transplant, morphology, and nodal involvement were computed, along with its corresponding p-statistic.

Continuous characteristics were first analyzed if a standard deviation could be calculated. If a standard deviation could not be calculated, that study's characteristic was discarded. A pooled standardized mean difference for time to PTLT was then calculated with its 95% confidence interval and p-statistic.

For both categorical and continuous characteristics, the degree of heterogeneity was evaluated with the I^2 statistic and analyzed by the random effects model. Using the suggestion of identifying and measuring heterogeneity for systematic reviews by Cochrane reviews [36], chi-squared tests were analyzed by forest plot, with a p-value cut off set to 0.10 to determine significance. Calculated I^2 values were also interpreted as recommended by Cochrane reviews [47] as follows—0%–40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity; 75%–100%: considerable heterogeneity.

Results

Figure 1 details a flow-chart of the basis that studies were excluded. Of the 14 studies [3, 16, 17, 25–36], a total of 164 PTLT lung transplant patients were analyzed for outcomes and characteristics data. Table 1 shows studies that provided treatments and treatment outcomes for PTLT in LTR. Of the data extracted and compiled from the studies, characteristics of early and late onset PTLT, time from transplant to PTLT onset, morphology, nodal involvement, age, and type of lung transplant were analyzable.

Thirteen studies were retrospective cohort studies that analyzed patient charts from hospital records [3, 16, 17, 25–31, 33–36] and 1 study was a prospective cohort study that analyzed the use of rituximab as first line treatment [32]. One study was a multi-center study over 3 centers in 3 countries [33], while the remaining 13 were single studies. 8 of the studies were international [25–27, 30–35], conducted in 11 different countries, with 3 of the studies conducted in the US. Characteristics of data extracted from each study are summarized in Table 1.

A total of 6 studies analyzed lung transplant (LT) type (Single or Bilateral). The analysis included a total of 64 patients with a pOR of 7.674 (95%CI: 1.983, 29.698; $p = 0.003$; $I^2 = 0.0\%$) that showed greater odds of death from PTLT for single LT patients than Bilateral LT patients (Figure 2). Whether patients experienced early or late PTLT accounted for 3 studies, no statistical difference was found (Table 2). Twelve studies included time to PTLT in their results, no statistical difference was found (Table 2). PTLT morphologies was reported in 6 studies, no statistical difference was found (Table 2). Nodal involvement was reported in 10 of the studies analyzed, no statistical difference was found (Table 2). Age was analyzed in 14 studies, however, 4 studies were not included in the analysis due to small sample size (Lucioni et al., Knoop et al., and Baldanti et al.) and aggregated data that was unable to be incorporated (Wudhikarn et al.). No statistical difference for age was found

(Table 2). Of the 14 studies included in the analysis, 5 studies included individualized treatment data as well as outcomes of those treatments for 55 patients [3, 30–33], which are presented in table 3.

Discussion

Current literature lacks data to support the construct of prognostic factors for the management of patients who develop PTLN after lung transplantation. As these patients are subjected to an aggressive clinical course and poor outcomes, there is a need for a better understanding of characteristics that may be contributing to morbidity and mortality.

In 2011, Engels et al. [41] determined that recipients of kidney, liver, heart, or lung transplants had a doubling of risk for development of diverse infection-related and unrelated cancers compared to the general population, with LTRs having the highest incidence of all malignancies. Non-Hodgkin lymphoma was the most common malignancy in US transplant recipients, with the highest incidence occurring in LTRs. Most recipients were younger and older (age 0–34 years or 50 years old) than middle-aged recipients (age 35–49 years), a difference that we did not detect with PTLN patients. The authors recognized that the disparity for higher incidence of malignancies for LTRs may be the result of the higher intensity of immunosuppression and the large amount of lymphoid tissue within the lung graft, compared to other organs.

To our knowledge, this is the first meta-analysis of lung transplant PTLN patient characteristics and death. Our main finding was that single lung transplant recipients who developed PTLN, were at a statistically significant increased risk of death. This finding is in line with current literature supporting bilateral lung transplantation's association with better outcomes [42–45]. No study to our knowledge has directly analyzed the characteristics of bilateral or single LT and the outcomes associated with PTLN. The several studies that we analyzed here have attempted to identify patient demographics, risk factors, disease characteristics and treatments to tailor strategies for the treatment and management of PTLN, but none have established definitive conclusions for better outcomes. Kumarasinghe et al. in 2010 published their findings at one single center for heart and lung transplantation that identified overall survival prognostic factors of bone marrow involvement (HR 6.75, $p < 0.001$), hypoalbuminemia (HR 3.18, $p = 0.006$), and complete response within 1 to 3 months (HR 0.08, $p < 0.001$) [49]. The ISHLT has also reported that patients who receive bilateral lung transplants tend to be younger (<65) and are less subjected to comorbidities and posttransplant complications, since releasing registry reports in 1998 [45]. This suggests that age may have a correlation to PTLN outcomes in LTRs, however, our analysis did not show this, which may be attributed to our older patient cohort (Mean = 46 years; Median 52 years).

Several studies have concluded that patients who undergo bilateral transplant have more favorable outcomes than single lung transplant recipients [42–45]. There remains debate regarding whether bilateral transplantation has better outcomes in general, as studies have been published supporting the fact that single lung transplantation may have comparable outcomes to bilateral lung transplantation [43, 47]. As a result, our findings further suggest

the fact that larger controlled studies are needed to determine specific factors for favoring the outcomes of single or bilateral lung transplantation.

Our study had several limitations. Given the relatively rare occurrence of PTLD in lung transplant patients, there simply aren't many studies analyzing characteristics of this small and specific patient population. As a result, instead of calculating a minimum patient population to give trial power to detect a difference, we assumed our small sample size was limited in power and ability to detect a difference in all but one of our outcomes. However, although this outcome did have an I^2 statistic of 0.0% suggestive of complete homogeneity, as with 3 other outcomes studied, the large confidence interval suspects that some level of bias is taking place and the credibility of the I^2 statistic is decreased. The exclusion of 50 single case studies is notable as collectively, the inclusion of these studies may have a significant contribution to our findings. The degree of inconsistencies of characteristics reported for these single case studies made their inclusion very challenging and would have added significant heterogeneity to the findings. Furthermore, given that all but one of our studies were retrospective analyses, selection bias and the quality of evidence is questionable, as suggested by Cochrane's GRADE assessment of quality evidence [50]. Although we did not detect a difference in patient characteristics, this is in line with the studies that we presented, as none have presented a significant difference in outcomes, except Paranjothi et al. in 2001, who were able to associate allograft involvement with shorter survival than without (median 0.2 year vs. 2.6 years, $p = 0.007$) [3]. However, we were unable to analyze this any further, as this was the only study that reported allograft involvement. Although the treatments and outcomes of 55 patients were reported, we were unable to statistically analyze any of the treatment patterns or outcomes as death was reported in 89% of the patients at the end of the studies. This higher mortality rate than the earlier reported 20–50% may be attributed to the selection of our studies that included varied treatment regimens, small sample sizes, and one prospective trial with rituximab [3, 30–33]. Of the total 14 studies that were included in this meta-analysis, 13 were retrospective cohort studies, with only 1 being a prospective cohort study.

All studies, apart from the rituximab prospective trial, utilized RI as their main treatment regimen backbone. Although this has been the standard of care, the exact amount of reduction is still unknown and is tailored to patient tolerability, tumor response, and graft function [51]. A retrospective cohort analysis by Tsai et al. in 2011 was able to generalize that RI alone in transplant patients across all allograft types is effective for treatment response and was associated with improved mortality, even in EBV-negative PTLD [52]. Furthermore, they were able to identify risk factors of bulky disease (> 7 cm mass or lymph node), advanced stage, and older age as risk factors for failure to respond to therapy, as patients who lacked these factors had a 77% chance of response to RI alone [52]. This suggests that our findings from this analysis may be possibly confounded by other factors described by Tsai et al. It is difficult, however, to associate these factors in LTRs, as our analysis did not find a significant difference in any factors, except type of LT. Furthermore, of the 148 patients analyzed, only 27 were LTRs with the majority (40%) being kidney transplants, making it difficult to definitively translate these findings specifically to lung transplantation.

In conclusion, our findings that bilateral lung transplantation is associated with a significantly lower risk of death from PTLT complications than single lung transplantation adds to the body of literature that perceives bilateral lung transplantation to be associated with more favorable outcomes. Further conclusions are difficult to draw given the current state of the PTLT literature in LTRs. Accordingly, we call on our colleagues to report their single and multicenter findings of PTLT in LTRs as more research is required to define risk and treatment outcomes in a robust way.

Acknowledgments

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Abbreviations List

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTLT	posttransplant lymphoproliferative disease
LTRs	lung transplant recipients
pOR	pooled odds ratio
EBV	Epstein-Barr virus
CTL	cytotoxic T lymphocytes
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
HyperCVAD	cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine
LT	Lung transplant

References

1. Chambers DC, Yusen RD, Cherikh WS, et al. 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(10):1047–59. [PubMed: 28784324]
2. Burns DM, Crawford DH. Epstein-Barr virus-specific cytotoxic T-lymphocytes for adoptive immunotherapy of post-transplant lymphoproliferative disease. *Blood Rev*. 2004; 18(3):193–209. [PubMed: 15183903]
3. Paranjothi SM, Yusen RD, Krause MD, Lynch JP, Patterson GA, Trulock EP. Lymphoproliferative disease after lung transplantation: comparison of early and late cases. *J Heart Lung Transplant*. 2001; 20(10):1054–63. [PubMed: 11595560]
4. Levine SM, Angel L, Anzueto A, et al. A low incidence of posttransplant lymphoproliferative disorder in 109 lung transplant recipients. *Chest*. 1999; 116:1273–77. [PubMed: 10559086]
5. Walker RC, Paya CV, Marshall WF, et al. Pretransplantation seronegative Epstein-Barr virus status is the primary risk factor to posttransplantation lymphoproliferative disorder in adult heart, lung, and other solid organ transplantations. *J Heart Lung Transplant*. 1995; 14:214–21. [PubMed: 7779838]

6. Armitage JM, Kormos RL, Stuart RS, et al. Posttransplant lymphoproliferative disease in thoracic organ transplant patients: ten years of cyclosporine-based immunosuppression. *J Heart Lung Transplant.* 1991; 10:877–87. [PubMed: 1661607]
7. Aris RM, Maia DM, Neuringer IP, et al. Post-transplant lymphoproliferative disorder in Epstein-Barr virus-naïve lung transplant recipient. *Am J Respir Crit Care Med.* 1996; 154:1712–17. [PubMed: 8970360]
8. Montone KT, Litzky LA, Wurster A, et al. Analysis of Epstein-Barr virus-associated posttransplantation lymphoproliferative disorder after lung transplantation. *Surgery.* 1996; 119:544–51. [PubMed: 8619211]
9. Sampaio MS, Cho YW, Qazi Y, Bunnapradist S, Hutchinson IV, Shah T. Posttransplant malignancies in solid organ adult recipients: an analysis of the National Transplant Database. *Transplantation.* 2012; 94(10):990–8. [PubMed: 23085553]
10. Nourse JP, Jones K, Gandhi MK. Epstein-Barr Virus-related post-transplant lymphoproliferative disorders: pathogenetic insights for targeted therapy. *Am J Transplant.* 2011; 11(5):888–95. [PubMed: 21521464]
11. Johnson LR, Nalesnik MA, Swerdlow SH. Impact of Epstein-Barr virus in monomorphic B cell posttransplant lymphoproliferative disorders: a histogenetic study. *Am J Surg Pathol.* 2006; 30(12):1604–12. [PubMed: 17122518]
12. Jagadeesh D, Woda BA, Draper J, Evens AM. Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. *Curr Treat Options in Oncol.* 2012; 13(1):122–36.
13. Cohen JL. Epstein-Barr virus infection. *N Engl J Med.* 2000; 323(7):481–92.
14. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. *CR Rev Oncol-Hem.* 2005; 56:155–167.
15. Allen UD, Preiksaitis JK. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. *Am J Transplant.* 2013; 13:107–120. [PubMed: 23465004]
16. Reams BD, McAdams HP, Howell DN, Steel MP, Davis RD, Palmer SM. Posttransplant lymphoproliferative disorder: incidence, presentation, and response to treatment in lung transplant recipients. *Chest.* 2003; 124:1242–1249. [PubMed: 14555552]
17. Cohen AH, Sweet SC, Mendeloff E, et al. High incidence of posttransplant lymphoproliferative disease in pediatric patients with cystic fibrosis. *Am J Respir Crit Care Med.* 2000; 161:1252. [PubMed: 10764320]
18. Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. *Curr Hematol Malig Rep.* 2013; 8(3):173–183. [PubMed: 23737188]
19. Orjuela MA, Alobeid B, Liu X, et al. CD20 expression predicts survival in paediatric post-transplant lymphoproliferative disease (PTLD) following solid organ transplantation. *Br J Haematol.* 2011; 152(6):733–42. [PubMed: 21275950]
20. Elstrom RL, Andreadis C, Aqui NA, et al. Treatment of PTLD with rituximab or chemotherapy. *Am J Transplant.* 2006; 6(3):569–76. [PubMed: 16468968]
21. Maecker B, Jack T, Zimmermann M, et al. CNS or bone marrow involvement as risk factors for poor survival in post-transplantation lymphoproliferative disorders in children after solid organ transplantation. *J Clin Oncol.* 2007; 31:4902–4908.
22. Zimmermann H, Trappe RU. Therapeutic options in post-transplant lymphoproliferative disorders. *Ther Adv Hematol.* 2001; 2(6):393–407.
23. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. *Blood.* 2006; 107(8):3053–7. [PubMed: 16254143]
24. Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicenter phase 2 PTLD-1 trial. *Lancet Oncol.* 2012; 13(2):196–206. [PubMed: 22173060]

25. Wong JY, Trait BM, Bronwyn L, et al. Epstein-barr virus primary mismatching and HLA matching: key risk factors for post lung transplant lymphoproliferative disease. *Transplantation*. 2004; 78(2):205–2010. [PubMed: 15280679]
26. Wigle DA, Chaparro C, Humar A, Hutcheon MA, Chan CK, Keshavjee S. Epstein-barr virus serology and posttransplant lymphoproliferative disease in lung transplant. *Transplantation*. 2001; 72(11):1783–1786. [PubMed: 11740388]
27. Saueressig MG, Boussaud V, Amrein C, Guillmemain R, Souilamas J, Souilamas R. Risk factors for post-transplant lymphoproliferative disease in patients with cystic fibrosis. *Clin Transplant*. 2011; 25:E430–E436. [PubMed: 21518001]
28. Reams BD, McAdams P, Howell N, Steele MP, Davis D, Palmer SM. Posttransplant lymphoproliferative disorder. *Chest*. 2003; 124(4):1242–1249. [PubMed: 14555552]
29. Ramalingam R, Rybicki L, Smith MD, et al. Posttransplant lymphoproliferative disorders in lung transplant patients: The Cleveland clinic experience. *Mod Pathol*. 2002; 15(6):647–656. [PubMed: 12065779]
30. Muchtar E, Kramer MR, Vidal L, et al. Posttransplantation lymphoproliferative disorder in lung transplant recipients: A 15-year single institution experience. *Transplantation*. 2013; 96(7):657–663. [PubMed: 23823652]
31. Lucioni M, Capello D, Riboni R, et al. B-cell posttransplant lymphoproliferative disorders in heart and/or lung recipients: clinical and molecular-histogenetic study of 17 cases from a single institution. *Transplantation*. 2006; 82(8):1013–1023. [PubMed: 17060848]
32. Knoop C, Kentos A, Remmelink M, Garbar C, Goldman S, Feremans W, Estenne M. Post-transplant lymphoproliferative disorders after lung transplantation: first-line treatment with rituximab may induce complete remission. *Clin Transplant*. 2006; 20:179–187. [PubMed: 16640524]
33. Oertel S, Verschuuren E, Reinke P, Zeidler K, et al. Effect of anti-CD20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). *Am J Transplant*. 2005; 5:2901–2906. [PubMed: 16303003]
34. de Montpreville VT, Le Pavec J, Ladurie F, et al. Lymphoproliferative disorders after lung transplantation: clinicopathological characterization of 16 cases with identification of very-late-onset forms. *Respiration*. 2015; 90:451–459. [PubMed: 26506523]
35. Baldanti F, Rognoni V, Cascina A, Oggionni T, Tinelli C, Meloni F. Post-transplant lymphoproliferative disorders and Epstein-barr virus DNAemia in a cohort of lung transplant recipients. *Viol J*. 2011; 8:421.
36. Wudhikarn K, Holman CJ, Linan M, et al. Post-transplant lymphoproliferative disorders in lung transplant recipients: 20-year experience at the University of Minnesota. *Clin Transplant*. 2011; 25:705–713. [PubMed: 21077949]
37. Hoshida Y, Li T, Dong Z, et al. Lymphoproliferative disorders in renal transplant patients in Japan. *Int J Cancer*. 2001; 91(6):869–875. [PubMed: 11275994]
38. Kwong YL, Lam CC, Chan TM. Post-transplantation lymphoproliferative disease of natural killer cell lineage: a clinicopathological and molecular analysis. *Br J Haematol*. 2000; 110(1):197–202.
39. Williams KM, Higman MA, Chen AR, et al. Successful treatment of a child with late onset T-cell post-transplant lymphoproliferative disorder/lymphoma. *Pediatr Blood Cancer*. 2008; 50(3):667–670. [PubMed: 17318876]
40. Law MF, Chan HN, Leung C, et al. Burkitt-like post-transplant lymphoproliferative disorder (PTLD) presenting with breast mass in a renal transplant recipient: a report of a rare case. *Ann Hematol*. 2014; 93(12):2083–2085. [PubMed: 24782123]
41. Engles EA, Pfeiffer RM, Fraumeni JF. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*. 2011; 306(17):1891–1901. [PubMed: 22045767]
42. Force SD, Kilgo P, Neujahr DC, et al. Bilateral lung transplantation offers better long-term survival, compared with single-lung transplantation, for younger patients with idiopathic pulmonary fibrosis. *Ann Thorac Surg*. 2011; 91(1):244–249. [PubMed: 21172522]
43. Meyer DM, Bennett LE, Novick RJ, Hosenpud JD. Single vs bilateral, sequential lung transplantation for end-stage emphysema: influence of recipient age on survival and secondary end-points. *J Heart Lung Transplant*. 2001; 20(9):935–941. [PubMed: 11557187]

44. Weiss ES, Allen JG, Merlo CA, Conte JV, Shah AS. Survival after single versus bilateral lung transplantation for high-risk patients with pulmonary fibrosis. *Ann Thorac Surg.* 2009; 88:1616–1626. [PubMed: 19853121]
45. Thabut G, Christie JD, Ravaud P, Castier Y, et al. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. *Lancet.* 2008; 371:744–751. [PubMed: 18313503]
46. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014—An update from the pulmonary transplantation council of the international society for heart and lung transplantation. *J Heart Lung Transplant.* 2015; 34(1):1–15. [PubMed: 25085497]
47. Minambres E, Llorca J, Suberviola B, Naranjo S, Zurbano F, Gonzalez-Castro A. Early outcomes after single vs bilateral lung transplantation in older recipients. *Transplant Proc.* 2008; 40:3088–3089. [PubMed: 19010203]
48. Higgins, JPT., Green, S., editors. *Cochrane Handbook for Systematic Reviews of Interventions.* Versions 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available from www.handbook.cochrane.org
49. Kumarasinghe G, Lavee O, Parker A, et al. Post-transplant lymphoproliferative disease in heart and lung transplantation: Defining risk and prognostic factors. *J Heart Lung Transplant.* 2015; 34(11): 1406–14. [PubMed: 26279197]
50. Ryan, R., Hill, S. How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group; 2016. Dec. available at <http://cccr.org/author-resources>. Version 3.0
51. Parker A, Bowles K, Bradley JA, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients—BCSH and BTS guidelines. *Br J Haematol.* 2010; 149(5):693. [PubMed: 20408848]
52. Reshef R, Vardhanabhuti S, Luskin MR, et al. Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder. *Am J Transplant.* 2011; 11(2):336–347. [PubMed: 21219573]

Figure 1.
Study Selection

Figure 2.
Single vs. Bilateral Lung Transplant

Table 1

Reported Characteristics of Individual Data

		Characteristics										
Authors, Year	Patients , n	Age, Median; Mean years (range)	Early Onset, n	Late Onset, n	Time to PTLT, Months (range)	Monomorphic, n	Polymorphic, n	Nodal, n	Extranodal, n	Single LTX, n	Bilateral LTx, n	Heart LTx, n
Wong et al, 2004	5	41.0; 36.2 (22–49)	--	--	116 (81–734)	3	1	3	2	2	3	0
Wigle et al, 2007	12	45.5; 43.3 (15–61)	--	--	8.5 (2–48)	--	--	0	12	--	--	--
Saueressig et al, 2011	8	19.5; 17.4 (7–22)	--	--	6 (3–19)	4	3	--	--	--	--	--
Reams et al, 2003	10	58.5; 53.8 (16–65)	--	--	11.09 (3.65–25.80)	3	4	0	5	6	3	1
Ramalingam et al, 2002	8	53.5; 50.9 (31–62)	--	--	--	5	2	0	8	--	--	--
Paranjothi et al, 2001	30	52.0; 48.6 (22–61)	14	16	14.03 (1.96–112.58)	--	--	2	28	14	16	0
Muchtar et al, 2013	10	50.5; 40.3 (11–63)	4	6	41 (3–128)	--	--	2	8	7	1	2
Lucioni et al, 2006	4	excluded	--	--	25.5 (9–85)	--	--	1	3	1	3	0
Knoop et al, 2005	6	excluded	--	--	54 (7–154)	--	--	3	3	0	3	3
Cohen et al, 2000	13	12.0; 12.6 (9.3–17.6)	--	--	4.37 (1.93–72.90)	--	--	--	--	--	--	--
Oertel et al, 2005	5	57.0; 55.2 (34–73)	--	--	19.4 (3–84.4)	0	2	0	5	--	--	--
de Montpreville et al, 2015	16	47.5; 46.5 (15–63)	--	--	13 (3–276)	--	--	3	13	0	7	9
Baldanti et al, 2011	5	excluded	--	--	8 (4–42)	--	--	--	--	1	4	0
Wudhikarn et al, 2011	32	excluded	8	24	--	31	1	0	32	16	13	3
Totals	164		26	46		46	13	14	120	47	53	18

Table 2**Analysis of Characteristics**

pOR: pooled odds ratio, SMD: standard mean difference, WMD: weighted mean difference, LTx: Lung Transplant

Characteristic	Patients, n	pOR, SMD, or WMD	95% CI, p-value, I ² -value
Single or Bilateral LTx	64	pOR = 7.674	95% CI: 1.983, 29.698; p = 0.003; I ² = 0.0%
Early or Late PTLT	72	pOR = 0.62	95% CI: 0.203, 1.865; p = 0.39; I ² = 0.0%
Time to PTLT	124	SMD = 0.03	95% CI: -0.481, 0.534; p = 0.92; I ² = 23.3%
PTLT Morphologies	68	pOR = 0.44	95% CI: 0.078, 2.513; p = 0.36; I ² = 0.0%
Nodal or Extranodal	138	pOR = 1.05	95% CI: 0.311, 3.522; p = 0.536; I ² = 0.0%
Age	117	WMD = 2.476	95% CI: 2.662, 7.61; p = 0.021; I ² = 53.8%

Table 3

Treatment Outcomes

LT: Lung Transplant; SL: Single Lung; BL: Bilateral Lung; HL: Heart and Lung; RI: Reduction in immunosuppression; CHOP: cyclophosphamide, hydroxyrubicin, vincristine, prednisone; R-CHOP: rixtuximab, cyclophosphamide, hydroxyrubicin, vincristine, prednisone; M: Male; F: Female

Age	Sex	Type of LT	Treatment	Response at end of Treatment	Outcome at End of Study
22	-	BL	RI	Remission	Dead
47	-	BL	RI	Remission	Dead
61	-	SL	None	-	Dead
24	-	BL	RI	Remission	Dead
55	-	BL	RI + Chemotherapy	No response	Dead
51	-	HL	RI	Remission	Dead
46	-	BL	RI + Chemotherapy	No response	Dead
58	-	SL	RI + Chemotherapy	No response	Dead
46	-	BL	None	-	Dead
28	-	BL	RI	Remission	Dead
61	-	BL	RI	No Response	Dead
52	-	BL	RI + Chemotherapy	Remission	Dead
57	-	SL	RI	Remission	Dead
60	-	BL	RI	Regression	Dead
36	-	BL	RI + Interferon Alpha	Remission	Dead
52	-	BSL	RI + Chemotherapy	Remission	Dead
49	-	BL	RI	Remission	Dead
32	-	SL	RI + Chemotherapy	No Response	Dead
58	-	SL	RI	Remission	Dead
32	-	SL	RI + Complete Resection + Chemotherapy	Remission	Dead
60	-	SL	RI	No Response	Dead
40	-	BL	RI + Chemotherapy	No Response	Dead
52	-	SL	RI + Incomplete Resection	No Response	Dead
52	-	SL	None	No Response	Dead
52	-	SL	RI + Incomplete Resection	No Response	Dead

Age	Sex	Type of LT	Treatment	Response at end of Treatment	Outcome at End of Study
54	-	SL	RI + Complete Resection	Remission	Dead
59	-	SL	RI	-	Dead
51	-	BL	RI	Remission	Dead
52	-	BL	RI	Remission	Dead
60	-	SL	RI + Incomplete Resection	No Response	Dead
11	F	HL	RI + Ritux	Remission	Dead
21	F	BL	RI + Ritux	Progressive Disease	Alive
	M	SL	RI + Surgery	Remission	Dead
63	M	SL	RI + Acyclovir	Remission	Dead
60	F	SL	RI + R-CHOP	Remission	Dead
53	F	SL	RI + R-CHOP	Remission	Dead
26	F	SL	RI + CHOP	Progressive Disease	Dead
53	M	SL	RI + GMALL 2002+Ritux	Remission	Dead
52	M	SL	RI + R-CHOP	Remission	Alive
15	M	HL	RI + CHOP	Remission	Dead
39	M	BL	RI+ CHOP + rituximab	Progressive Disease	Dead
24	F	BL	RI + CHOP + rituximab	No Response	Dead
52	M	SL	RIS + CHOP + rituximab	No Response	Dead
26	M	BL	Interferon + rituximab	No Response	Alive
29	M	BL	RI+ rituximab + Chemotherapy	Remission	Alive
44	F	BL	RI + rituximab	Remission	Dead
30	M	BL	RI + rituximab	Remission	Dead
51	M	HL	RI + rituximab	Remission	Dead
32	M	HL	RI + rituximab	Remission	Dead
56	M	HL	rituximab Clinical Trial	No Response	Dead
60	F	-	rituximab	Remission	Dead
52	F	-	rituximab	Relapse	Alive
57	F	-	rituximab	Remission	Dead
73	M	-	rituximab	Progressive Disease	Dead

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Age	34	Sex	F	Type of LT	-	Treatment	rituximab	Response at end of Treatment	Remission	Outcome at End of Study	Alive
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