Shiraz E-Med J. 2022 March; 23(3):e110017. doi: 10.5812/semj.110017.

Published online 2021 December 6. **Research Article**

Post-transplant Lymphoproliferative Disorder in Pediatric Liver Transplantation: A Population-based Study from Shiraz, Iran

Mohammad Hadi Imanieh [1, 2], Zahra Jalali [1], Negar Azarpira [3], Seyed Mohsen Dehghani [1, 2], Heidar Safarpour [4, *], Seyed Ali Malekhosseini [3] and Yasaman Mansoori [5]

[1] Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, Iran
[2] Gastroenterology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[3] Transplant Research Center, Transplant Center, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran
[5] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

[*] *Corresponding author*: Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran. Tel: +98-7136281506, Email: heidar.safarpour@yahoo.com

Received 2020 December 28; **Revised** 2021 October 23; **Accepted** 2021 October 28.

Abstract

Background: This study aimed to determine the prevalence of post-transplant lymphoproliferative disorder (PTLD) based on the clinical and epidemiological characteristics of donors and pediatric transplant recipients.

Methods: This cross-sectional study was conducted on the patients who had experienced liver transplantation at Shiraz Transplant Center, Shiraz, Iran, from April 2007 to March 2017. Data on the epidemiological characteristics, underlying diseases, dosage of immunosuppressive drugs, and duration of drug consumption from the time of liver transplantation until the onset of PTLD for transplant recipients, and donors' age, sex, and family relationship with recipients were collected using a data-gathering form. Log rank test was employed to determine the variations in the distribution of survival in different sex and age groups.

Results: The study findings indicated that 49 out of the 1207 children who had undergone liver transplantation developed PTLD, revealing a prevalence of 4%. The results showed no significant relationship between gender and the incidence of PTLD (P = 0.13). However, the mean age of the cases with PTLD was 4.93 ± 1.07 years at the time of transplantation, while non-PTLD patients showed a higher mean age at that time (7.80 ± 5.54). The mean dose of the immunosuppressive drugs (dose/kg) consumed by the recipients was as follows: Tacrolimus = 0.2753 ± 0.23435, prednisolone = 0.6761 ± 0.62218, cellcept = 0.0724 ± 0.12963, and sirolimus = 0.1078 ± 0.08813. The average consumption period of the above-mentioned drugs from the time of transplantation until the onset of PTLD was 14.7 ± 14.409 months. Based on the results, the five-year survival rate was much lower in the patients with PTLD compared to the non-PTLD patients (31% Vs. 72.7%). The survival distribution was significantly different based on sex and age groups (P = 0.59 and P = 0.06, respectively).

Conclusions: The prevalence of the clinical and epidemiological features of the PTLD in the patients under the present investigation was similar to those of the patients in other hospitals. Recognizing the clinical and epidemiological characteristics of transplant recipients with and without PTLD and donors can provide a basis for managing these patients.

Keywords: PTLD, Liver Transplant, Immunosuppressive Drugs, Survival

1. Background

Liver transplantation is a proven therapeutic modality for end-stage liver diseases with distinct etiologies. Despite the significant improvements in patients' conditions, problems that frequently happen following transplantation can have adverse effects on their lives (1). One of the complications of liver transplantation is post-Transplant lymphoproliferative disorder (PTLD), which affects patient survival and graft function. Moreover, children who undergo organ transplantation are at risk of developing lymphoproliferative disorders, with Non-Hodgkin lymphoma (NHL) being the most serious disease (2) whose definitive diagnosis requires histopathological examination. In these patients, PTLD is commonly considered a result of immunodeficiency caused by the consumption of immunosuppressive medications, eventually leading to depressed T cell activity and lymphoid proliferation (3, 4). Also, PTLD is usually an Epstein-Barr virus (EBV)-associated condition; approximately 60 - 70% of the patients are EBV-positive, with the lack of a cytotoxic T cell response due to the suppression of the immune system (5-8).

Copyright © 2021, Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, provided the original work is properly cited.

Advances in biology as well as the promotion of knowledge about the epidemiology and diverse clinical presentations of PTLD have led to the identification of patients at risk of PTLD after solid organ transplantation (9). Young age is one of the known risk factors that lead to PTLD. In fact, this disorder is more common amongst pediatric patients (10). Support for infants is partly provided by mothers' immune system, while their endogenous responses to puberty continue until childhood and adolescence. This period is accompanied by most physical and hormonal changes, except for pregnancy, causing differences in the risk of PTLD and the related risk factors in different pediatric age groups (11-14). Furthermore, PTLD is more common in recipients undergoing long-term treatment with immunosuppressive drugs after transplantation. These treatments are varied, but they basically include immunosuppression reduction, anti-CD20 antibody, surgery, radiotherapy, and chemotherapy (15). The use of effective treatment methods such as rituximab (RTX) and Sirolimus, as well as decreasing the dosage of immunosuppressive drugs, has resulted in a significant improvement in health conditions and the overall survival (16, 17). For instance, preventive therapy using RTX has been found to lead to a temporary decrease in the EBV level (18).

2. Objectives

Based on what was mentioned above, the present study aimed to investigate the demographic and clinical features of PTLD among Iranian patients after liver transplantation.

3. Methods

Shiraz Transplant Hospital (Shiraz, Iran) is Iran's main center, with significant pediatric liver transplant cases annually. This cross-sectional study was conducted on the patients aged < 18 years who had undergone liver transplantation at this center from April 2007 to March 2017. The inclusion criteria of the study were aging < 18 years and having undergone liver transplantation. The exclusion criteria were incomplete demographic information in hospital files and death due to transplant complications in the first week after transplantation.

The donors' and recipients' epidemiological and clinical features were obtained using a form including information about age, gender, underlying liver disease, type of graft (partial, split, and whole organ), age at liver transplantation, time of PTLD development, multi-organ involvement, immunosuppressive regimen (tacrolimus, sirolimus, cellcept), and dosage and period of consumption of immunosuppressive drugs prior to PTLD. Here, PTLD was diagnosed by histopathological biopsy specimens and was confirmed by pathologists according to the World Health Organization (WHO) classification (19). After that, screening work-ups such as computed tomography (chest, pelvis, and abdomen), bone marrow aspiration, and biopsy were done to assess the likelihood of multi-organ damage. The patients' survival rate after PTLD was also recorded. The cumulative survival proportion was compared between males and females as well as between the patients aged below and above six years. The differences between different sex and age groups in terms of survival were evaluated via the log rank test. The data were analyzed using the SPSS software, version 22.

4. Results

Out of the 1207 pediatric patients who had undergone liver transplantation in Shiraz Organ Transplant Center, Shiraz, Iran, from April 2007 to March 2017, 49 were diagnosed with PTLD following liver transplantation, representing a prevalence of 4%. The mean age of the transplant recipients who developed PTLD at the time of transplantation was 4.93 $\pm$ 1.07 years, ranging from 11 months to 9 years. The mean age at transplantation was 7.80 $\pm$ 5.54 years in the non-PTLD cases. In addition, the female-to-male ratio was 51.49% in the PTLD group and 44.56% in the non-PTLD group. The recipients' mean weight was 14.828 $\pm$ 0.96 kg at the time of PTLD. Biliary atresia was the most common underlying disease in both PTLD and non-PTLD patients, with 12 and 148 cases per 1,000 patients, respectively. The second most common underlying diseases were Crigler-Najjar disease in the patients with PTLD (9 cases per 1000 patients) and Wilson disease in the non-PTLD patients (168 cases per 1,000 patients). Of the 49 patients with PTLD, 28 (57%) had received a partial graft, while 11 (23%) had received a whole organ transplant (Table 1). Organ involvement was also assessed in the 49 patients with PTLD. The results indicated that the liver (8%), bowel (8%), and cervical (8%), and submandibular lymph nodes (8%) were the most affected sites (Table 2).

The results of the comparison of the two groups regarding the mean dose/kg of immunosuppressive drugs have been presented in Table 2. Accordingly, the highest dose was related to prednisolone with the mean value of 0.67 $\pm$ 0.62 mg/kg. Additionally, the immunosuppressive drugs were used for 14.79 $\pm$ 14.40 months from the time of transplantation until the date of PTLD diagnosis. The five-year survival rate was 31% in the patients diagnosed with PTLD compared to 72.7% in the non-PTLD patients.

The epidemiological characteristics of the donors (n = 49) of the recipients who developed PTLD were evaluated in

Table 1. Demographic Data and Underlying Causes of Transplantation in the Recipients [a]

Demographic Data	PTLD	Non-PTLD
Mean age at the time of liver transplantation (y)	4.93 ± 1.07	7.80 ± 5.54
Sex, female	25 (51)	508 (44)
Underlying disease		
Autoimmune hepatitis	1 (2)	92 (7.9)
Biliary atresia	15 (30.7)	179 (15.5)
Budd-Chiari	1 (2)	-
Crigler-Najjar	11 (22.5)	83 (7.2)
Hepatocellular carcinoma	1 (2)	11 (0.9)
Progressive familial intrahepatic cholestasis	8 (16.4)	152 (13.1)
Tyrosinemia	8 (16.4)	106 (9.1)
Tyrosinemia superimposed with hepatocellular carcinoma	1 (2)	-
Wilson disease	1 (2)	168 (14.5)
Hyperoxalouria	-	17 (1.5)
Acute liver failure	-	32 (2.8)
Primary sclerosing cholangitis	-	20 (1.7)
Hypercholesterolemia	-	50 (4.3)
Neonatal hepatitis	-	37 (3.2)
Cryptogenic cirrhosis	-	113 (9.8)
Missing cases	2 (4)	98 (8.5)
Allograft		
Living donor	32 (65)	470 (40)
Cadaver	17 (35)	688 (60)
The graft types in the recipients		
Partial	28 (57)	463 (40)
Split	10 (20)	139 (12)
Whole organ	11 (23)	556 (48)

[a] Values are expressed as mean ± SD or No. (%).

Table 2. The Mean Immunosuppressive Drug Consumption (Dose/kg) and Organ Involvement in the PTLD Patients [a]

Variables	Values
Mean immunosuppressive drug consumption (mg/kg)	
Tacrolimus	0.27 ± 0.23
Sirolimus	0.10 ± 0.08
Prednisolone	0.67 ± 0.62
Cellcept	0.07 ± 0.12
Organ involvement	
Liver	4 (8)
Multi organ involvement	1 (2)
Mass in abdomen	4 (8)
Axillary	1 (2)
Bowel	4 (8)
Cervical lymph node	4 (8)
Inguinal lymph node	1 (2)
CNS	2 (4)
Colon	1 (2)
Duodenum	2 (4)
Heart	1 (2)
Kidney	1 (2)
Para aortic mass	1 (2)
Submandibular lymph node	4 (8)

[a] Values are expressed as mean ± SD or No. (%).

this study. Based on the results, the mean age of the donors was 25.28 ± 1.2 years (range = 3 - 45 years). Besides, most of them had a familial relationship with the recipients (Table 3). Comparison of the cumulative survival proportion in male and female patients with PTLD is depicted in Figure 1 (P = 0.59). Additionally, comparison of this proportion in < 6 and 6 - 12 age groups has been shown in Figure 2 (P = 0.06). Accordingly, the cumulative survival proportion was higher in males as well as in the patients aged under six years compared to females and the patients over six years old. The significance of these differences was evaluated using a log rank test. The results revealed no significant difference in the distribution of the survival proportion on the basis of these two factors (sex and age groups) (P = 0.59 and P = 0.06, respectively).

5. Discussion

This study was conducted on the epidemiological characteristics of the pediatric graft recipients with PTLD and their donors following liver transplantation. The results demonstrated that the mean age at transplantation was lower in the patients with PTLD than in the non-PTLD children (4.93 vs. 7.80 years). Haung et al. (20) reported a mean age of 4.1 years at the time of transplantation. In another study by Barış et al., the mean age at transplantation was 2.71 ± 3.21 years, and low age at transplantation, especially ages < 2.5 years, was considered a risk factor for the occurrence of PTLD (21). These results were consistent with those of the present investigation.

In the current study, the most common underlying disease was biliary atresia (30.7%). High rate of biliary atresia in patients with PTLD has been reported in other studies,

Table 3. Characteristics of the Donors of the Recipients with and Without PTLD [a]

Donors' Characteristics	PTLD	Non-PTLD
Mean age (y)	25.28 ± 1.2 (3 - 45)	21.71 ± 13.40 (1 - 83)
Relationship with the recipient		
First-degree relative	31 (63.4)	444 (38.4)
Second-degree relative	1 (2)	26 (2.2)
Cadaver	17 (34.6)	688 (59.4)

[a] Values are expressed as mean ± SD or No. (%).

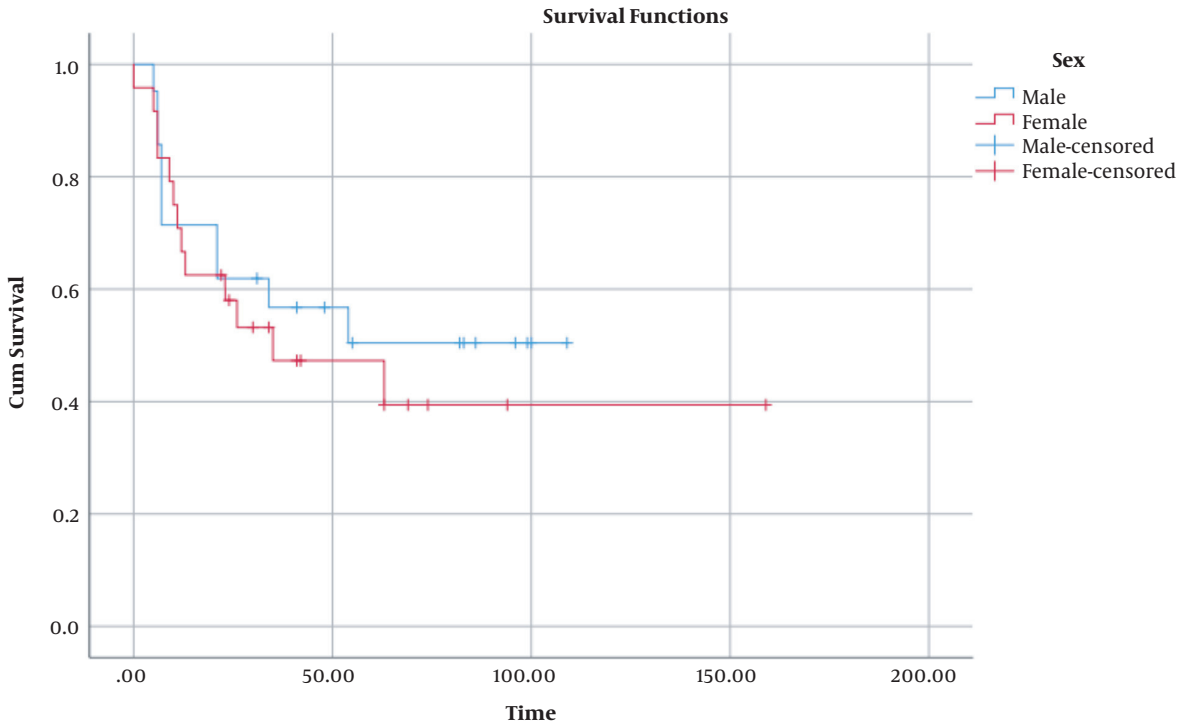

Figure 1. Comparison of the male and female patients with PTLD regarding the cumulative survival proportion (Log rank (Mantel-Cox): Chi-square = 0.285, df = 1, P = 0.594)

as well. For instance, Wiederkehr et al. disclosed that 57.1% of the patients were diagnosed with biliary atresia prior to PTLD, which accounted for the majority of the cases (22). In the study carried out by Haung et al., biliary atresia was also detected in 66.7% of the patients (20).

In the present research, 57% of the cases had received partial transplants, and 23% had received whole organ grafts. In addition, first-degree relatives (parents and siblings) comprised 63.4% of the donors. Borenstein et al. also performed a study on 13 patients in need of transplantation and indicated that all the 13 donors were selected from living individuals, 12 of whom were the first-degree relatives of the recipients. Additionally, all the patients received partial transplants, and only 23% showed PTLD complications (23). Lozano et al. revealed better results in whole organ transplant recipients in terms of transplant maintenance and post-transplant complications (24), which was in agreement with the current study results. In the present study, the mean age of the graft donors was 25.28 ± 1.2 years. According to Tiao et al., donor's age < 6 months or > 50 years was found to be a risk factor for a decrease in the lifespan of the recipients and transplants (25).

The current study findings demonstrated that the abdomen, liver, cervical lymph nodes, and submandibular lymph nodes were the most common locations affected

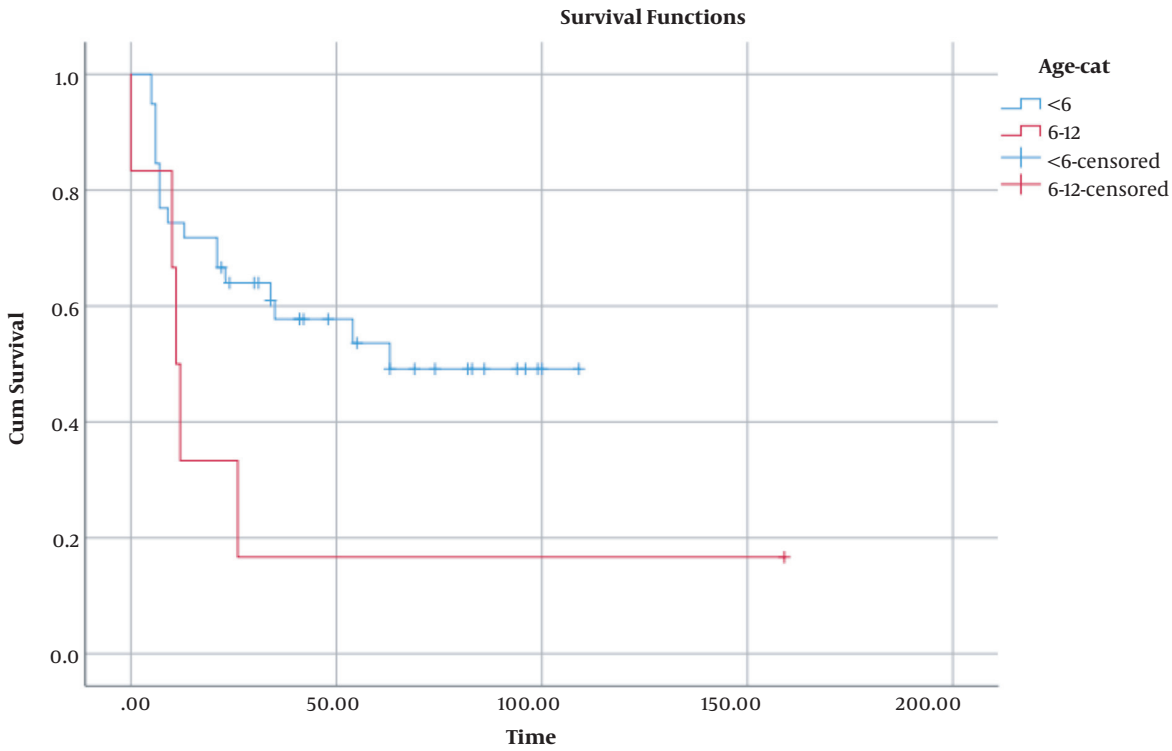

Figure 2. Comparison of < 6- and 6-12-year-old patients with PTLD regarding the cumulative survival proportion (Log rank (Mantel-Cox): Chi-square = 3.551, df = 1, P = 0.060)

by PTLD. A previous study by Barış et al. also revealed the liver, peripheral lymph nodes, and gastrointestinal system as the most common sites of involvement (21).

In the present research, the mean dose of tacrolimus consumption was 0.27 mg/kg from the date of transplantation until the occurrence of PTLD. The mean consumption doses of prednisolone, cellcept, and sirolimus were also 0.67, 0.07, and 0.10 mg/kg, respectively. However, Jeong et al. conducted a study on 20 patients over 20 years of age and measured the mean dose of tacrolimus as 0.15 - 0.22 mg/kg. Moreover, the duration of drug use from the time of transplantation until PTLD occurrence was 14.79 ± 0.96 months in the present study. This measure was found to be 15.63 months in another research (26), which was close to the current study results. It should be noted that the two groups under the current investigation could not be compared in terms of the cumulative immunosuppressive drug dose, weight, and age at transplantation (missing data).

In the current study, the survival rate of the patients was an average of 63% after transplantation. The findings of a similar study conducted in Shiraz between 2004 and 2015 revealed a six-month survival of 75.1 ± 6%, a one-year survival of 68.9 ± 6.5%, and five-year survival of 39.2 ± 14.2% after transplantation (10). In research conducted on 54 patients with PTLD at Florida University from 1994 to 2017, the mean follow-up was 28.8 months, and the average five-year survival rate was 87.6% for all age groups (95% CI: 74.3 - 94.2) (27). The differences were also assessed between different sex and age groups regarding the survival rate in the present research. The results revealed no significant difference between different sex and age groups concerning the survival distribution (P = 0.59 and P = 0.06, respectively).

Liver transplant recipients acquire immunodeficiency due to drug consumption. Immunocompromised patients are prone to complications, particularly opportunistic infection and oncogenic virus-associated malignancy. EBV-associated PTLD is also one of the catastrophes that may happen in transplant recipients. In a study conducted by Weisert et al. on heart transplant recipients, EBV was considered a risk factor, but the frequency of EBV screening varied among patients (28). Seo et al. assessed patients under 18 years old who had received liver transplants by a detailed analysis of the EBV blood level from January 2006 to March 2015. In children, the prevalence of PTLD was 10% after transplantation. Besides, the results of the multivariate

analysis indicated that primary cytomegalovirus (CMV) infections and high-level EBV DNAemia after transplantation were linked to a higher risk of PTLD. Increased EBV viral load with the cut-off value of 44,000 copies/mL/week was associated with an increased risk of PTLD with a sensitivity of 64.3% and a specificity of 70.9% (29). Another study carried out in China also suggested that close monitoring of EBV DNA loads and checking the tacrolimus concentration might be useful in preventing the occurrence of PTLD amongst children after liver transplantation (30). Similarly, Chen et al. recommended the tapering of immunosuppressants in case of high EBV viral load in children (31). The above-mentioned studies revealed the importance of routine screening of EBV and CMV infections. However, EBV screening and viral load monitoring were not routinely performed for the recipients in the present study, which was the major limitation of the research. Therefore, routine viral monitoring is recommended for better evaluation and treatment of pediatric patients with PTLD.

5.1. Conclusions

The prevalence of the clinical and epidemiological features of PTLD in the patients with liver transplants was similar to that of the patients in other hospitals. Monitoring of EBV viral load in transplant recipients can provide a basis for managing patients and increasing their life expectancy.

Acknowledgments

The authors would like to thank Ms. A. Keivanshekouh at the Research Consultation Center (RCC) of Shiraz University of Medical Sciences for revising the manuscript.

Footnotes

Authors' Contribution: All authors are involved in study designee and article writing.

Conflict of Interests: No conflict of interest was reported by the authors.

Ethical Approval: This project was approved by Shiraz University of Medical Sciences, and had ethical code: IR.SUMS.MED.REC 1398-285.

Funding/Support: This study was funded by Shiraz University of Medical Sciences with code number of 17193.

Informed Consent: The informed consent was received from participants' relatives (Mother and/or father of children).

References

1. Starzl TE, Fung JJ. Themes of liver transplantation. *Hepatology*. 2010;**51**(6):1869–84. doi: 10.1002/hep.23595. [PubMed: 20235333]. [PubMed Central: PMC4507423].
2. Dembowska-Baginska B, Wakulinska A, Daniluk I, Teisseyre J, Jankowska I, Czubkowski P, et al. Non-Hodgkin lymphoma after liver and kidney transplantation in children. Experience from one center. *Adv Clin Exp Med*. 2020;**29**(2):197–202. doi: 10.17219/acem/112605. [PubMed: 32154678].
3. Penn I. Posttransplantation de novo tumors in liver allograft recipients. *Liver Transpl Surg*. 1996;**2**(1):52–9. doi: 10.1002/lt.500020109. [PubMed: 9346628].
4. Vaysberg M, Lambert SL, Krams SM, Martinez OM. Activation of the JAK/STAT pathway in Epstein Barr virus+-associated posttransplant lymphoproliferative disease: role of interferon-gamma. *Am J Transplant*. 2009;**9**(10):2292–302. doi: 10.1111/j.1600-6143.2009.02781.x. [PubMed: 19656130]. [PubMed Central: PMC2774223].
5. Loren AW, Porter DL, Stadtmauer EA, Tsai DE. Post-transplant lymphoproliferative disorder: a review. *Bone Marrow Transplant*. 2003;**31**(3):145–55. doi: 10.1038/sj.bmt.1703806. [PubMed: 12621474].
6. Malatack J, Gartner J, Urbach AH, Zitelli BJ. Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lymphoproliferative disease: A growing concern. *J Pediatr*. 1991;**118**(5):667–75. doi: 10.1016/s0022-3476(05)80024-1.
7. Ho M, Jaffe R, Miller G, Breinig MK, Dummer JS, Makowka L, et al. The frequency of Epstein-Barr virus infection and associated lymphoproliferative syndrome after transplantation and its manifestations in children. *Transplantation*. 1988;**45**(4):719–27. doi: 10.1097/00007890-198804000-00011. [PubMed: 2833828]. [PubMed Central: PMC2993427].
8. Schubert S, Abdul-Khaliq H, Lehmkuhl HB, Yegitbasi M, Reinke P, Kebelmann-Betzig C, et al. Diagnosis and treatment of post-transplantation lymphoproliferative disorder in pediatric heart transplant patients. *Pediatr Transplant*. 2009;**13**(1):54–62. doi: 10.1111/j.1399-3046.2008.00969.x. [PubMed: 18518912].
9. Absalon MJ, Khoury RA, Phillips CL. Post-transplant lymphoproliferative disorder after solid-organ transplant in children. *Semin Pediatr Surg*. 2017;**26**(4):257–66. doi: 10.1053/j.sempedsurg.2017.07.002. [PubMed: 28964482].
10. Eshraghian A, Imanieh MH, Dehghani SM, Nikeghbalian S, Shamsaeefar A, Barshans F, et al. Post-transplant lymphoproliferative disorder after liver transplantation: Incidence, long-term survival and impact of serum tacrolimus level. *World J Gastroenterol*. 2017;**23**(7):1224–32. doi: 10.3748/wjg.v23.i7.1224. [PubMed: 28275302]. [PubMed Central: PMC5323447].
11. Zangwill SD, Hsu DT, Kichuk MR, Garvin JH, Stolar CJ, Haddad JJ, et al. Incidence and outcome of primary Epstein-Barr virus infection and lymphoproliferative disease in pediatric heart transplant recipients. *J Heart Lung Transplant*. 1998;**17**(12):1161–6. [PubMed: 9883755].
12. Katz BZ, Pahl E, Crawford SE, Kostyk MC, Rodgers S, Seshadri R, et al. Case-control study of risk factors for the development of post-transplant lymphoproliferative disease in a pediatric heart transplant cohort. *Pediatr Transplant*. 2007;**11**(1):58–65. doi: 10.1111/j.1399-3046.2006.00609.x. [PubMed: 17239124].
13. Hsu CT, Chang MH, Ho MC, Chang HH, Lu MY, Jou ST, et al. Post-transplantation lymphoproliferative disease in pediatric liver recipients in Taiwan. *J Formos Med Assoc*. 2019;**118**(11):1537–45. doi: 10.1016/j.jfma.2018.12.023. [PubMed: 30630698].
14. Webber SA, Naftel DC, Fricker FJ, Olesnevich P, Blume ED, Addonizio L, et al. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. *Lancet*. 2006;**367**(9506):233–9. doi: 10.1016/S0140-6736(06)67933-6. [PubMed: 16427492].
15. Liu Y, Sun LY, Zhu ZJ, Wei L, Qu W, Wang L, et al. Post-transplant lymphoproliferative disorder after paediatric liver transplantation. *Int J Clin Pract*. 2021;**75**(4). e13843. doi: 10.1111/ijcp.13843. [PubMed: 33222369].

16. Gonzalez-Barca E, Domingo-Domenech E, Capote FJ, Gomez-Codina J, Salar A, Bailen A, et al. Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. *Haematologica*. 2007;**92**(11):1489–94. doi: 10.3324/haematol.11360. [PubMed: 18024397].
17. Majewski M, Korecka M, Kossev P, Li S, Goldman J, Moore J, et al. The immunosuppressive macrolide RAD inhibits growth of human Epstein-Barr virus-transformed B lymphocytes in vitro and in vivo: A potential approach to prevention and treatment of posttransplant lymphoproliferative disorders. *Proc Natl Acad Sci U S A*. 2000;**97**(8):4285–90. doi: 10.1073/pnas.080068597. [PubMed: 10759564]. [PubMed Central: PMC18230].
18. Hyun H, Park E, Cho M, Min SI, Ha J, Kang HJ, et al. Post-Transplant Lymphoproliferative Diseases in Pediatric Kidney Allograft Recipients with Epstein-Barr Virus Viremia. *J Korean Med Sci*. 2019;**34**(30). e203. doi: 10.3346/jkms.2019.34.e203. [PubMed: 31373185]. [PubMed Central: PMC6676002].
19. Harris N, Swerdlow S, Frizzera G, Jaffe E, Harris N, Stein H, et al. Post-transplant lymphoproliferative disorders. *World Health Organization classification of tumours: Pathology and genetics of tumours of hematopoietic and lymphoid tissues*. Lyon: IARC Press; 2001.
20. Huang JG, Tan MYQ, Quak SH, Aw MM. Risk factors and clinical outcomes of pediatric liver transplant recipients with post-transplant lymphoproliferative disease in a multi-ethnic Asian cohort. *Transpl Infect Dis*. 2018;**20**(1). doi: 10.1111/tid.12798. [PubMed: 29071779].
21. Baris Z, Ozcay F, Yilmaz Ozbek O, Haberal N, Sarialioglu F, Haberal M. A single-center experience of post-transplant lymphoproliferative disorder (PTLD) cases after pediatric liver transplantation: Incidence, outcomes, and association with food allergy. *Turk J Gastroenterol*. 2018;**29**(3):354–60. doi: 10.5152/tjg.2018.17731. [PubMed: 29755021]. [PubMed Central: PMC6284654].
22. Wiederkehr JC, Coelho IM, Avilla SG, e Silva EM, Schuller S, Ouno DD, et al. Prevalence of posttransplantation lymphoproliferative disease in pediatric liver transplant recipients. *Transplant Proc*. 2010;**42**(2):521–2. doi: 10.1016/j.transproceed.2010.01.013. [PubMed: 20304183].
23. Borenstein S, Diamond IR, Grant DR, Greig PD, Jones N, Ng V, et al. Outcome of pediatric live-donor liver transplantation-the Toronto experience. *J Pediatr Surg*. 2003;**38**(5):668–71. doi: 10.1016/jpsu.2003.50179. [PubMed: 12720166].
24. Lozanov J, Millis J, Anand R. Surgical outcomes inprimary pediatric liver transplantation:SPLIT database report - Ab-stract #1453. *American Transplant Congress*. Seattle, WA. American Journal of Transplantation Supplement; 2005.
25. Tiao GM, Alonso MH, Ryckman FC. Pediatric liver transplantation. *Semin Pediatr Surg*. 2006;**15**(3):218–27. doi: 10.1053/j.sempedsurg.2006.03.008. [PubMed: 16818143].
26. Jeong HJ, Ahn YH, Park E, Choi Y, Yi NJ, Ko JS, et al. Posttransplantation lymphoproliferative disorder after pediatric solid organ transplantation: experiences of 20 years in a single center. *Korean J Pediatr*. 2017;**60**(3):86–93. doi: 10.3345/kjp.2017.60.3.86. [PubMed: 28392824]. [PubMed Central: PMC5383637].
27. Bosse RC, Franke AJ, Paul Skelton W, Woody LE, Bishnoi R, Wang Y, et al. Post Transplant Lymphoproliferative Disorder risk factors in children: Analysis of a 23-year single-institutional experience. *Pediatr Transplant*. 2020;**24**(5). e13747. doi: 10.1111/petr.13747. [PubMed: 32497335].
28. Weisert M, Harake D, Hede S, Russell M, Alejos J, Menteer J. A multicenter survey on post-transplant lymphoproliferative disorders in pediatric heart transplant recipients: A case for development of consensus guidelines for screening, surveillance, and treatment? *Pediatr Transplant*. 2020;**24**(5). e13730. doi: 10.1111/petr.13730. [PubMed: 32416037].
29. Seo E, Kim J, Oh SH, Kim KM, Kim DY, Lee J. Epstein-Barr viral load monitoring for diagnosing post-transplant lymphoproliferative disorder in pediatric liver transplant recipients. *Pediatr Transplant*. 2020;**24**(4). e13666. doi: 10.1111/petr.13666. [PubMed: 32067332].
30. Qin T, Gu XQ, Jeong SS, Song YY, Liu JC, Zheng JX, et al. Impact of EBV infection and immune function assay for lymphoproliferative disorder in pediatric patients after liver transplantation: A single-center experience. *Hepatobiliary Pancreat Dis Int*. 2020;**19**(1):3–11. doi: 10.1016/j.hbpd.2019.12.005. [PubMed: 31932195].
31. Chen HS, Ho MC, Hu RH, Wu JF, Chen HL, Ni YH, et al. Roles of Epstein-Barr virus viral load monitoring in the prediction of posttransplant lymphoproliferative disorder in pediatric liver transplantation. *J Formos Med Assoc*. 2019;**118**(9):1362–8. doi: 10.1016/j.jfma.2018.12.007. [PubMed: 30612881].