Risk factors for post-transplant lymphoproliferative disorder after pediatric liver transplantation in China

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Abstract

Objectives: This study aimed to analyze the risk factors associated with post-transplant lymphoproliferative disorder (PTLD) after liver transplantation in children.

Methods: We retrospectively analyzed the clinical and laboratory data of patients treated and followed up at Shanghai Children's Medical Center between January 2012 and January 2019. Twenty-four patients with PTLD were enrolled in this study using a 1:2 pairing design. Each case was matched with two controls that had undergone liver transplantation within the same year but did not develop PTLD during the follow-up period. A total of 72 patients were included in this study.

Results: Univariate analysis demonstrated statistically significant differences in Epstein-Barr virus (EBV) infection, tacrolimus blood concentration, Platelet (PTL), Aspartate aminotransferase(AST),Alanine aminotransferase (ALT), and Cholesterol(CHOL).Multivariate logistics regression analysis revealed that EBV

infection was an independent risk factor for PTLD.

Conclusions: EBV infection is an independent risk factor for PTLD. When uncontrolled proliferation of EBV occurs after organ transplantation, the dosage of immunosuppressive agents should be appropriately reduced.

Introduction

Currently, liver transplantation is the only effective way to treat end-stage liver diseases such as intrahepatic and extrahepatic cholestasis, metabolic diseases, acute liver failure, and liver tumors in children. Advanced surgical techniques and immunosuppressants have significantly improved the overall survival rate of pediatric patients undergoing liver transplantation. The 5-year survival rate of pediatric patients undergoing liver transplantation in developed countries is as high as 80%[1]. Post-transplant lymphoproliferative disorder (PTLD) is a life-threatening complication that can occur following pediatric liver transplantation. PTLD has various clinical manifestations and is difficult to diagnose early. Most patients have a poor prognosis with a mortality rate of 30–60%. The incidence of PTLD after liver transplantation in children is 1–5%[2,3,4], with a mostly poor prognosis[5].

Epstein-Barr virus (EBV) is among the most frequently observed viral pathogens affecting pediatric patients undergoing liver transplant, and EBV infection is closely related to the incidence of PTLD[6]. Similarly, studies have identified tacrolimus as one of the risk factors for PTLD. Tacrolimus administration after transplantation is known to increase the incidence of malignant tumors and PTLD in patients[7,8,9]. Additionally, the patient's age at transplantation (between 1–10 years old) and occurrence of acute rejection after transplantation are related to the occurrence of PTLD[10,11].

The risk factors associated with PTLD after liver transplantation have not been studied in the Chinese pediatric population. Therefore, we conducted a single-center retrospective study to investigate the risk factors for PTLD after liver transplantation in China.

Methods

Patients

All patients were treated and followed up at Shanghai Children's Medical Center. The medical records of patients aged 1–2 years, who underwent liver transplantation between January 2012 and January 2019, were reviewed. All patients included in this study were diagnosed with PTLD between January 2012 and January 2019. Patients who died during the follow-up period were excluded from this analysis. Control patients were matched (1:2) according to the type of organ transplanted and period since transplantation (within one year). The control patients were recruited from a cohort of transplant recipients who did not have PTLD and underwent a transplant during the same period as the study subjects. Clinical characteristics and laboratory findings were extracted from the medical records of each patient and analyzed.

Diagnosis

EBV DNA >5,000 IU/mL in the peripheral blood was diagnosed as Epstein-Barr viremia. A workup for PTLD was initiated when indicated based on clinical symptoms, including unexplained weight loss, fever, gastrointestinal bleeding, anemia, thrombocytopenia, hypoalbuminemia, or lymphadenopathy/tonsillar hypertrophy in the absence of infection. Evaluation included cross-sectional imaging, positron emission tomography scans, and endoscopy and biopsy. Additionally, some cases of PTLD were incidentally diagnosed during endoscopic graft surveillance, allograft resection, and/or ostomy takedown. The sample obtained was examined by a pathologist and classified according to established criteria.

Data extraction

All data sources were extracted from the medical record management system of the hospital. Keywords, including “lymphocyte proliferative diseases after transplantation" and liver transplantation”, were used to search the database. The collected indicators included: the (1) basic information: gender, primary disease, age at transplantation, and weight, among others; (2)laboratory indicators: White blood cell (WBC), hemoglobin (HBG),Neutrophil(NE), PLT, ALT, AST, Total bilirubin(TBIL), Direct Bilirubin(DBIL), Albumin(ALB), Alkaline phosphatase(AKP), Gamma-glutamyl transpeptidase(γ-GGT), Creatinine(CREA), Blood urea nitrogen(BUN), blood glucose (GLU), (Prothrombin time(PT), International normalized ratio (INR), Triglyceride(TG),

CHOL), and tacrolimus concentration; (3) transplantation-related indicators: transplantation method, graft weight, graft/weight ratio, intraoperative blood loss, and blood type; (4) viral infection:preoperative EBV

and cytomegalovirus (CMV) infections, time interval between surgery, and the first EBV/CMV infection; and (5) donor information: blood type, preoperative EBV, and CMV infection, among others.

Treatment

Data were extracted from hospital medical records, and demographic, clinical, treatment, and laboratory data were obtained. All patients who underwent liver transplantation received an anti-immune rejection regimen of tacrolimus and steroids on the first postoperative day. The initial tacrolimus dose was 0.1–0.15 mg/kg/d, and the ideal blood concentrations were as follows: one month after transplantation, the serum tacrolimus concentration should be maintained within 8–12 ng/mL; 2–6 months postoperatively, the serum tacrolimus concentration should be maintained between 7 and 10 ng/mL before being reduced to 5–8 ng/mL at 7–12 months and maintained at 5 ng/mL, as appropriate, 12 months after transplantation. During this period, the drug dosage can be adjusted according to the tacrolimus blood concentration and EBV copy number. The total duration of hormone treatment was short. The first glucocorticoid dose was intravenously administered during the non-hepatic stages of surgery. The intravenous glucocorticoid dose was reduced to 4 mg/kg/d within one week postoperatively, and oral glucocorticoids (e.g. prednisone, initial dose of 0.25–1 mg/kg/d) were administered one week postoperatively. Patients with no abnormalities should stop glucocorticoid therapy at the earliest possible opportunity within 3–6 months postoperatively.

Follow-up

The outpatient follow-up plan mainly included laboratory tests and imaging examinations, which were designed to monitor graft morphology and blood flow. If the patient suffered from unexplained weight loss, fever, gastrointestinal bleeding,

anemia, thrombocytopenia, hypoproteinemia, or lymphadenopathy during follow-up, they were informed of the possibility of PTLD. Examinations, such as virological monitoring (EBV and CMV), abdominal and lymph node B-ultrasound, gastrointestinal endoscopy, and positron emission computed tomography, were selected according to the clinical manifestations. Imaging examination revealed that patients with obvious abnormal lesions could undergo surgery or gastrointestinal endoscopy to obtain biopsies, which can subsequently facilitate efficient and targeted treatment options based on different pathological manifestations.

Statistical analysis

Potential risk factors for PTLD were determined by comparing different variables between patients with PTLD and control subjects using SPSS Software. Primary analyses were conducted using a Student's t-test and chi-squared test. To eliminate confounding factors affecting the results, multivariate logistic regression analysis was conducted to further analyze the results. A P-value <0.05 was considered statistically significant.

Results

Baseline characteristics

After screening, according to the inclusion and exclusion criteria, a total of 24 patients in the PTLD group were included. Furthermore, a total of 48 control patients were enrolled.

The descriptive characteristics of the study subjects are shown in Table 1. Male and female patients comprised 33.3% and 66.7% and 37.5% and 62.5% of the PTLD and control groups, respectively. The average age at transplantation for patients with PTLD was 9.96 months (minimum age, 5 months; maximum age, 24 months). Conversely, the average age at transplantation in the control group was 8.60 months (minimum age, 5 months; maximum age, 24 months). No significant difference was observed in the distribution of transplantation age and sex between the two groups. Among the included cases, the primary disease affecting both groups was biliary atresia.

Laboratory indicators and liver transplantation characteristics

Analysis of preoperative laboratory indicators (Table 2), including blood tests (WBC, HBG, NE, PLT), liver and kidney function tests (ALT, AST, TBIL, DBIL, ALB, AKP, γ-GGT, BUN, CREA), GLU, coagulation function (PT, INR), and blood lipids (TG, CHOL) between the PTLD and control groups revealed statistically significant differences in postoperative platelets, ALT, AST, CHOL, and serum tacrolimus concentration (all $P<0.05$). Patients received tacrolimus after liver transplantation, and their serum tacrolimus concentrations were continuously monitored. The average postoperative serum tacrolimus concentrations of patients in the PTLD and control groups were 8.28±1.61 ng/mL and 7.32±1.63 ng/mL, respectively ($P<0.05$; Table 2).

Graft weight, graft body weight ratio, transplant type, intraoperative blood loss, and blood type were not related to the occurrence of PTLD (Table 2).

Viral infection

The incidences of EBV and CMV replication after post-transplantation were analyzed in patients and donors. EBV and CMV infection rates were 95.8% and 20.8% and 48.9% and 22.9% in the PTLD and control groups, respectively. A significant difference in the EBV infection rates was observed between the two groups. Statistical analysis demonstrated that EBV infection was an important risk factor for PTLD ($P<0.001$). No association was observed between CMV infection and PTLD in this study. The EBV and CMV infection statuses of donors before transplantation were classified as follows: donor-positive/recipient-negative, donor-positive/recipient-positive, donor-negative/recipient-positive, and donor-negative/recipient-negative. The viral infection status of donors and recipients before surgery were not statistically associated ($P>0.05$; Table 3).

Risk factors for PTLD after liver transplantation

Multivariate analysis identified EBV infection as an independent risk factor for PTLD (P<0.05). Tacrolimus concentration, ALT, AST, PLT, and CHOL had varying degrees of difference in the incidence of PTLD; however, no statistical differences were identified (Table 4).

Discussion

Several studies have confirmed that EBV infection is directly related to the incidence of PTLD[12,13], which was confirmed by the findings of this study. In this study, the EBV infection rate of patients with PTLD was 95.8%, suggesting that EBV infection is an important risk factor for PTLD. In the PTLD group, the time of peak EBV replication was closely related to the time of PTLD onset, indicating that PTLD is likely to occur when EBV infection undergoes rapid replication and is at or near its peak. Therefore, monitoring changes in the EBV copy number in transplant patients will allow clinicians to monitor PTLD and appropriately adjust the level of immunosuppressants administered. Immunotherapy with monoclonal antibodies, particularly anti-CD20 antibody (rituximab), is the first-line treatment for patients who do not respond to a reduction or discontinuation of immunosuppressants. In several studies, rituximab administered as treatment yielded a 40–68% response rate. In a preemptive setting, the anti-CD20 antibody can prevent EBV-associated PTLD in approximately 90% of cases. Furthermore, changes in the EBV copy number may prompt the use of rituximab therapy[14]. A recent study observed that the initial application of rituximab should be performed in patients whose EBV DNA load is > 40,000 U/mL after transplantation if they similarly exhibited at least one symptom of PTLD or demonstrated evidence of PTLD upon imaging[15].

CMV infection is common after liver transplantation in children and is associated with the following symptoms: fever of unknown origin (38.3 °C), fatigue or systemic myalgia, and leukopenia or thrombocytopenia. The relationship between CMV infection and PTLD remains unclear. Some studies believe that CMV infection is a risk factor for PTLD, although the underlying mechanism is currently unknown. Most studies consider that CMV infections are not related to the occurrence of PTLD. Kim et al.[16] analyzed 119 liver transplant patients. Among them, 66 (55.5%) patients had CMV infection, and 15 patients eventually developed PTLD. Among them, 10 patients with PTLD had a CMV infection, whereas five had no CMV infection. Statistical analysis showed that the occurrence of PTLD was not related to CMV infection (P = 0.258). In this study, the CMV infection rate was 22.2%, and the final incidence of PTLD in CMV-infected patients was 31.2%. No statistically significant relationship was observed between CMV infection and PTLD.

Studies have shown that donor EBV^+/recipient EBV^- is an important risk factor for PTLD as a high EBV infection rate can cause PTLD in younger patients. A previous study observed that in donor EBV^+/recipient EBV^- patients, 67% of patients developed postoperative EBV infection. A higher postoperative EBV infection rate increases the risk of PTLD in patients. EBV-negative patients receiving EBV-positive organs are at a high risk of developing PTLD[17]. This study assessed the viral infection status of donors. Seven of the study patients received cadaveric liver transplants; thus, in these cases, the

infection status of the donor could not be obtained. Only 65 patients who underwent liver transplants were analyzed, and the viral infection rate of donors was not high, and no statistical significance was identified, most likely due to the small sample size.

Some studies have suggested that high serum tacrolimus concentrations are a risk factor for PTLD onset[18]. Fukushima et al.[19] analyzed the changes in tacrolimus concentrations when the EBV load continued to increase and observed that the PTLD group had significantly higher tacrolimus concentrations compared to the control group. Other research has focused on the correlation between tacrolimus and EBV infection. By monitoring serum tacrolimus concentrations within two weeks of liver transplantation, Lu et al.[20] found that the EBV infection rate increased within 2–4 weeks postoperatively in patients with a high serum tacrolimus concentration. Bakker et al.[21] observed that when immunosuppressant dosages were reduced in patients suffering from uncontrolled, postoperative EBV infections, the EBV load significantly reduced.

This study evaluated the relationship between serum tacrolimus concentrations and PTLD. Univariate analysis revealed a significant difference in the serum tacrolimus concentrations (P = 0.021). At higher levels of immunosuppression, EBV is prone to uncontrolled proliferation because tacrolimus acts upon both B and T lymphocytes while suppressing humoral and cell-mediated immunity. This subsequently leaves patients susceptible to EBV infections after surgery and makes it difficult to control EBV proliferation after infection[22,23]. However, multivariate analysis demonstrated that serum tacrolimus concentrations were not a risk factor for PTLD, although the patients in the PTLD group had higher serum tacrolimus concentrations than those in the control group. In view of the fact that EBV infection is a risk factor for PTLD, it is suggested that when uncontrolled proliferation of EBV occurs after organ transplantation, the dosage of immunosuppressive agents should be appropriately reduced to prevent PTLD.

In this study, no associations were observed between baseline characteristics, laboratory indicators, and transplant-related indicators and the occurrence of PTLD. Currently, the relationship between the age at transplantation and incidence of PTLD is controversial. A study observed that younger patients undergoing organ transplantation were at a greater risk of PTLD, especially children 1–10 years old[24]. Another study concluded that the risk of postoperative PTLD was reduced by 15% with a yearly increase in age[25] and found that younger patients (at the time of transplantation) is a risk factor for postoperative EBV and CMV infections[26]. In this study, no association was observed between the age at transplantation and occurrence of PTLD, possibly because the primary disease of patients was mostly biliary atresia, and the transplantation age of patients was generally within two years. Young patients are more likely to be susceptible to PTLD because they have a higher viral infection rate than adults at the time of transplantation.

Conclusion

PTLD is a life-threatening complication that can occur in children following liver transplantation. Baseline characteristics, laboratory indicators, and transplant-related indicators are not related to the occurrence of PTLD. The results of this study suggest that EBV infection is an independent risk factor for PTLD; therefore, it is necessary to be aware of the risk of PTLD occurrence when EBV is actively replicating or the viral load is high. In addition, tacrolimus is not a direct factor leading to the occurrence of PTLD; however, the degree of immunosuppression should be reduced in children with continuously replicating EBV and a high serum concentration of tacrolimus.

Abbreviations

Abbreviations	Full-term
ALB	Albumin
ALKP	Alkaline phosphatase
ALT	Aspartate aminotransferase
AST	Aspartate aminotransferase
CHOL	Cholesterol
CMV	Cytomegalovirus
CREA	Creatinine
DBIL	Direct Bilirubin
EBV	Epstein-Barr virus
HGB	hemoglobin
INR	International normalized ratio
γ-GGT	Gamma-glutamyl transpeptidase
NE	Neutrophil
TBIL	Total bilirubin
PLT	Platelet
PT	Prothrombin time
PTLD	Post-transplant lymphoproliferative disorder
TG	Triglyceride
WBC	White blood cell

Declarations

Ethics approval and consent to participate: All analyses were based on previous blood test indicators, thus no ethical approval and patient consent are required.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article

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Tables

TABLE 1. Descriptive characteristics of the PTLD and control groups

	PTLD cases (n=24)	Control (n=48)	χ^2/t	P-value
Sex			0.120	0.799
Male	8 (33.3%)	18 (37.5%)		
Female	16 (66.7%)	30 (62.5%)		
Disease			1.565	0.476
Biliary atresia	24 (100%)	45 (93.7%)		
Alaki syndrome	0	1 (2.1%)		
Hypercholesterolemia	0	1 (2.1%)		
Methylmalonic acidemia	0	1 (2.1%)		
Age at transplantation (months) (medians, ranges)	9.96 (5-24)	8.60 (5-24)	1.230	0.223
Weight at transplantation (kg) (medians, ranges)	7.48(4.5-11)	7.21 (3.2-20)	1.130	0.648

PTLD; post-transplant lymphoproliferative disorder

TABLE 2 Analysis of laboratory indicators and liver transplantation characteristics

	PTLD cases (n=24)	Control (n=48)	χ^2/t	P-value
WBC ($\times10^9$)	11.09±4.63	11.40±7.62	-0.180	0.858
HBG (g/L)	93.69±25.47	98.19±14.49	-0.957	0.342
NE ($\times10^9$)	8.16±16.26	6.60±9.01	0.525	0.601
PLT ($\times10^9$)	168.46±77.29	237.44±115.89	-2.633	0.010
ALB (g/L)	38.04±19.50	34.68±4.82	1.134	0.260
ALT (U/L)	330.13±590.21	130.98±97.47	2.292	0.025
AST (U/L)	453.03±519.48	213.31±128.69	3.036	0.003
ALKP (U/L)	614.66±404.51	503.53±241.27	1.459	0.149
γ-GGT (U/L)	365.40±297.63	381.56±419.13	-1.169	0.851
TBIL (μmol/L)	226.63±135.87	250.76±154.15	-0.650	0.518
DBIL (μmol/L)	165.39±92.65	171.33±110.49	-0.226	0.822
CREA (μmol/L)	12.35±4.66	15.41±7.22	-1.886	0.063
BUN (mmol/L)	11.32±37.78	2.81±1.29	1.571	0.121
INR	2.67±4.02	1.56±0.80	1.854	0.068
PT(s)	16.32±4.77	17.02±8.28	-0.387	0.700
TG (mmol/L)	1.53±1.09	4.16±16.54	-0.774	0.442
CHOL (mmol/L)	3.53±1.94	6.31±1.94	-3.022	0.004
Tacrolimus concentration（ng/mL）	8.281.61	7.321.63	2.370	0.021
Graft weight (g)	256.2955.03	241.1390.45	0.864	0.391
Graft/weight ratio	3.39%0.89%	2.96%0.87%	1.976	0.643
Type of transplant			0.430	0.659
living donor	22 (91.7%)	43 (89.6%)		
cadaveric donors	2 (8.3%)	5 (10.4%)		
Intraoperative bleeding (mL)	204.35152.19	283.33162.86	1.952	0.550
blood type			0.138	0.786
matched	18 (75%)	34 (70.8%)		
mismatched	6 (25%)	14 (29.2%)		

PTLD; post-transplant lymphoproliferative disorder

TABLE 3 Viral infection in PTLD cases and controls

	PTLD cases (n=24)	Control (n=48)	X^2/t	P-values
EBV infection			19.149	<0.001
Yes	23 (95.8%)	23 (48.9%)		
No	1 (4.2%)	25 (52.1%)		
D-R EBV serostatus pretransplantation			1.819	0.403
D-R-	21 (95.5%)	37 (86.0%)		
D+R-	1 (4.5%)	3 (7.0%)		
D-R+	0	3 (7.0%)		
D+R+	0	0		
CMV infection			0.040	1.000
Yes	5 (20.8%)	11 (22.9%)		
No	19 (79.2%)	37 (77.1%)		
D-R CMV serostatus pretransplantation			4.143	0.126
D-R-	19 (86.4%)	39 (90.6%)		
D+R-	2 (9.1%)	2 (4.7%)		
D-R+	1 (4.5%)	2 (4.7%)		
D+R+	0	0		

EBV; Epstein-Barr virus; CMV; cytomegalovirus; PTLD; pediatric liver transplantation ;

D-R EBV serostatus pretransplantation; Seven of the study patients received cadaveric liver transplants, Only 65 patients who underwent liver transplants were analyzed.

TABLE 4. Multivariate analysis of factor for PTLD after liver transplantation

	B	SE	Wals	OR (95%CI)	P
Tacrolimus concentration (ng/mL)	0.405	2.223	3.292		0.070
EBV infection	3.308	1.125	8.647	27.329 (3.013-247.846)	0.003
PLT	-0.009	0.005	3.201	0.991 (0.981-1.001)	0.074
ALT	-0.015	0.008	3.656	0.985 (0.969-1.000)	0.056
AST	0.003	0.008	0.177	1.003 (0.998-1.019)	0.674
CHOL	-0.241	0.245	0.972	0.786 (0.486-1.269)	0.786