

# Frequency, Characteristics, Management, and Outcomes of Posttransplant Lymphoproliferative Disorder After Allogeneic Hematopoietic Stem Cell Transplantation in Children: A Multicenter Retrospective Study of the Turkish Pediatric BMT Study Group

Çocuklarda Allojenik Hematopoetik Kök Hücre Nakli Sonrası Posttransplant Lenfoproliferatif Hastalığın Sıklığı, Özellikleri, Yönetimi ve Sonuçları: Türk Pediatrik Kemik İliği Nakli Çalışma Grubu'nun Çok Merkezli Retrospektif Çalışması

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## Abstract

**Objective:** Posttransplant lymphoproliferative disorder (PTLD) is a rare yet potentially life-threatening complication following allogeneic hematopoietic stem cell transplantation (HSCT). This study aimed to determine the incidence, clinical features, management strategies, and prognostic factors influencing outcomes of PTLD after allogeneic HSCT in children.

## Öz

**Amaç:** Posttransplant lenfoproliferatif hastalık (PTLH), allojenik hematopoetik kök hücre nakli (HKHN) sonrası nadir görülen ancak yaşamı tehdit edebilen bir komplikasyondur. Bu çalışma, çocuklarda allojenik HKHN sonrası PTLH'nin insidansını, klinik özelliklerini, tedavi stratejilerini ve sonuçlarını etkileyen prognostik faktörleri belirlemeyi amaçlamıştır.



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## Abstract

**Materials and Methods:** Data were retrospectively collected from 15 pediatric centers performing allogeneic HSCT between June 2010 and May 2025. Clinical features, treatment approaches, and outcomes of the cases were analyzed.

**Results:** During the study period, 6129 children underwent allogeneic HSCT and 34 (0.56%) developed PTLD. The median interval between HSCT and PTLD diagnosis was 197 days, with the majority of cases occurring within the first posttransplant year. At diagnosis, gastrointestinal involvement was observed in 22 patients (64.7%), cytopenia in 17 (50%), central nervous system (CNS) involvement in 7 (20.5%), pulmonary involvement in 6 (17.6%), and macrophage activation syndrome in 4 (11.7%). Rituximab-based therapy was administered to 29 patients (85.3%) and immunosuppression was reduced in 25 (73.5%). Mortality was significantly higher among patients presenting with CNS involvement (4 of 7, 57.1%;  $p<0.05$ ). Treatment response also affected the prognosis; among 27 patients who achieved remission, 25 survived (92.6%) compared to only 1 of 7 (14.3%) non-responders ( $p<0.05$ ). The overall PTLD-related mortality rate was 17.6% (6 patients). Median follow-up among survivors was 43 months, with a 5-year overall survival (OS) rate of 76.5%.

**Conclusion:** PTLD occurred infrequently among pediatric allogeneic HSCT recipients. CNS involvement and failure to achieve remission were strongly associated with poorer OS.

**Keywords:** Posttransplant lymphoproliferative disorder, Hematopoietic stem cell transplantation, Epstein-Barr virus

## Öz

**Gereç ve Yöntemler:** Veriler, Haziran 2010 ile Mayıs 2025 tarihleri arasında allojenik HKHN uygulayan 15 pediatrik merkezden retrospektif olarak toplanmıştır. Pediatrik PTLH olgularının klinik özellikleri, tedavi yaklaşımları ve sonuçları analiz edilmiştir.

**Bulgular:** Çalışma süresince 6129 çocuğa allojenik HKHN uygulandı ve 34 (%0,56) hastada PTLH geliştiği saptandı. HKHN ile PTLH tanısı arasındaki ortalama süre 197 gün olup, olguların çoğu nakil sonrası ilk yıl içinde tanı aldı. Tanı anında 22 hastada (%64,7) gastrointestinal tutulum, 17 hastada (%50) sitopeni, 7 hastada (%20,5) merkezi sinir sistemi (MSS) tutulumu, 6 hastada (%17,6) pulmoner tutulum ve 4 hastada (%11,7) makrofaj aktivasyon sendromu gözlemlendi. Rituximab bazlı tedavi 29 hastaya (%85,3) uygulandı ve 25 hastada (%73,5) immünosüpresyon azaltıldı. MSS tutulumu olan hastalarda mortalite anlamlı derecede daha yüksekti (7 hastanın 4'ü, %57,1;  $p<0,05$ ). Tedavi yanıtı da prognozu etkiledi; remisyona ulaşan 27 hastadan 25'i (%92,6) hayatta kalırken, yanıt vermeyen 7 hastanın sadece 1'i (%14,3) hayatta kaldı ( $p<0,05$ ). PTLH ile ilişkili genel mortalite oranı %17,6 idi (6 hasta). Sağ kalanlar arasında ortalama takip süresi 43 ay olup, 5 yıllık genel sağkalım (OS) oranı %76,5 olarak saptandı.

**Sonuç:** PTLH, pediatrik allojenik HKHN alıcıları arasında nadiren görülmüştür. MSS tutulumu ve remisyon sağlanamaması, daha düşük OS ile ilişkili bulunmuştur.

**Anahtar Sözcükler:** Posttransplant lenfoproliferatif hastalık, Hematopoetik kök hücre nakli, Epstein-Barr virüs

## Introduction

Posttransplant lymphoproliferative disorder (PTLD) constitutes a heterogeneous group of lymphoid proliferations that arise as a consequence of immunosuppression following hematopoietic stem cell transplantation (HSCT). The disease spectrum ranges from benign polyclonal lymphoid hyperplasia to aggressive monoclonal lymphoid malignancies. In most cases, PTLD is associated with Epstein-Barr virus (EBV) infection and characterized by B-cell proliferation expressing CD20-positive lymphocytes [1,2].

Several risk factors have been implicated in the development of PTLD, including T-cell depletion of the graft, use of in vivo serotherapy, mismatched or unrelated donors, and umbilical cord blood transplantation [3,4,5]. Despite advances in transplantation techniques and posttransplant monitoring, PTLD remains a major cause of morbidity and mortality after HSCT. Before the year 2000, mortality following HSCT-related PTLD was as high as 84.6% [6]. The introduction of EBV monitoring via polymerase chain reaction (PCR), preemptive antiviral or immunomodulatory strategies, and timely initiation of rituximab-based therapy have markedly improved outcomes. Nevertheless, PTLD continues to be associated with substantial mortality, with approximately one-third of affected patients dying from the disease [4,6].

Although PTLD is a well-recognized and serious complication after allogeneic HSCT, national data on its epidemiology, clinical characteristics, and prognostic factors remain scarce. In Türkiye, previously published evidence has been limited to isolated pediatric case reports [7]. Consequently, there is a lack of comprehensive multicenter data regarding the incidence, clinical presentation, management approaches, and outcome determinants of pediatric PTLD following allogeneic HSCT at the national level.

To address this gap, we conducted a large-scale multicenter retrospective study spanning a 15-year period. The primary objective of this investigation was to systematically characterize the incidence, clinical features, therapeutic interventions, and prognostic factors associated with PTLD development after allogeneic HSCT in the pediatric population in Türkiye.

## Materials and Methods

### Study Design and Setting

This multicenter retrospective study included pediatric patients diagnosed with PTLD following allogeneic HSCT between 1 June 2010 and 1 June 2025. Data were obtained from 15 pediatric HSCT centers across Türkiye that routinely perform allogeneic transplantations. The study was approved by the Koç University Ethics Committee (protocol no: 2025.491.IRB2.224, date: 04.11.2025).

## Case Definitions

PTLD cases were classified using a comprehensive, tiered system based on established international criteria. “Proven PTLD” included diagnoses confirmed by histopathological examination of biopsy specimens, while “probable PTLD” included cases identified based on clinical and/or radiological findings accompanied by significant EBV-DNAemia.

Histopathological classification of biopsy-proven PTLD followed the fifth edition of the World Health Organization’s Classification of Haematolymphoid Tumours [8]. The diagnostic definitions for probable PTLD and proven PTLD were applied in accordance with the recommendations of the Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines [6].

Additionally, specific to our study, patients with isolated EBV-DNAemia receiving rituximab were defined as a separate group (asymptomatic group) from PTLD patients to observe the spectrum of posttransplant EBV reactivation and the outcomes of preventive approaches.

Quantitative EBV-DNAemia levels were measured using PCR analysis of plasma samples. Clinical data including patient demographics, transplant characteristics, PTLD presentation, treatment modalities, and outcomes were obtained retrospectively through the review of medical records. A detailed summary of patient and HSCT characteristics is provided in Table 1, including patients in the asymptomatic group.

## Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Overall survival (OS) was defined as the time from PTLD diagnosis (for probable and asymptomatic patients, defined as the date of the first documented positive EBV viral load) to death or last follow-up. Survival curves were generated using the Kaplan-Meier method. Associations between categorical variables and mortality were analyzed using the chi-square test or Fisher exact test as appropriate. A two-tailed p value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics 28.0 for Windows (IBM Corp., Armonk, NY, USA).

## Results

### Incidence and Timing of Posttransplant Lymphoproliferative Disorder

During the study period, 34 cases of PTLD were identified among 6129 pediatric allogeneic HSCT recipients, corresponding to an overall incidence of 0.56%. The median time from transplantation to PTLD diagnosis was 197 days (range: 31-3285 days). Most cases (n=29; 85.3%) occurred within the first posttransplant year (i.e.,

**Table 1. Characteristics of patients and hematopoietic stem cell transplantations. This table contains a total of 42 cases, including 34 PTLD cases in addition to 8 asymptomatic cases.**

Characteristics	n	%
Median age, years (range)		7 (4 months to 18 years)
<b>Sex, female/male</b>	18/24	42.9/57.1
<b>Underlying diseases</b>		
Acute leukemia	13	30.9
Primary immunodeficiency	12	28.6
Thalassemia major	6	14.3
Hemophagocytic lymphohistiocytosis	2	4.8
Juvenile myelomonocytic leukemia	2	4.8
Aplastic anemia	2	4.8
Fanconi aplastic anemia	3	7.2
Congenital dyserythropoietic anemia	1	2.3
Diamond-Blackfan anemia	1	2.3
<b>Number of transplants</b>		
1	37	88.1
>1	4	9.6
Liver transplant + HSCT	1	2.3
<b>Donor types</b>		
Matched unrelated donor	25	59.5
Haploidentical ( $\alpha/\beta$ T-cell-depleted & post-Cy)	10 (7 & 3)	23.8
Matched sibling donor	5	11.9
Matched family donor	2	4.8
<b>Conditioning regimens</b>		
MAC	31	73.9
NMA	10	23.8
None	1	2.3
<b>ATG in the conditioning regimen</b>		
Yes	36	85.7
No	6	14.3
<b>Graft sources</b>		
Peripheral blood	23	54.7
Bone marrow	14	33.3
Peripheral blood + bone marrow	3	7.2
Cord blood	2	4.8
<b>GVHD prophylaxis</b>		
Cyclosporin A-based	34	81.0
Other	7	16.7
None	1	2.3
<b>EBV serostatus (patient/donor)</b>		
(-)/(+)	4	9.6
(+)/(+)	3	7.2
(+)/(+)	35	83.2
<b>Acute GVHD</b>		
Yes	18	42.9
No	24	57.1
<b>Chronic GVHD</b>		
Yes	8	19.0
No	34	81.0
<b>Accompanying cytomegalovirus PCR positivity</b>		
Yes	10	23.8
No	32	76.2

PTLD: Posttransplant lymphoproliferative disorder; HSCT: hematopoietic stem cell transplantation; post-Cy: posttransplant cyclophosphamide; MAC: myeloablative conditioning; NMA: non-myeloablative conditioning; ATG: antithymocyte globulin; GVHD: graft-versus-host disease; EBV: Epstein-Barr virus; PCR: polymerase chain reaction.

early-onset cases), whereas 5 patients (14.7%) developed PTLD after 1 year (late-onset cases) and 1 patient (2.9%) presented as a very late-onset case 9 years after HSCT. All 5 patients with late-onset PTLD had monomorphic PTLD. Three were not receiving immunosuppression at diagnosis. The very late-onset case was histopathologically diagnosed as marginal zone B-cell lymphoma. This patient was not receiving immunosuppression therapy at the time of diagnosis. Remission was achieved with 6 cycles of R-CHOP chemotherapy and the patient has been alive for over 5 years.

In addition to these 34 patients, 8 patients were in the asymptomatic group.

### Pretransplant Epstein-Barr Virus Serostatus

Before transplantation, both donors and recipients were EBV-seropositive in 35 transplants. Four recipients were EBV-seronegative with seropositive donors, including the very late-onset case, and 3 were seropositive with seronegative donors.

### Clinical Presentation and Organ Involvement

At diagnosis, the most frequent presenting symptoms were fever, lymphadenopathy, malaise, abdominal pain, and weight loss. Organ involvement included the gastrointestinal tract in 22 patients (64.7%), bone marrow (cytopenia) in 17 (50%), the central nervous system (CNS) in 7 (20.5%), and the lungs in 6 (17.6%). Macrophage activation syndrome (MAS) was observed in 4 (11.7%) patients.

EBV viremia was detectable in all but 1 case. The single EBV-negative patient presented with a retrovesical mass encasing the right ureter, and biopsy revealed B-cell non-Hodgkin lymphoma.

### Diagnostic Classification and Histopathology

Fifteen patients (44.1%) were diagnosed by biopsy, while 19 (55.9%) were diagnosed based on clinical and/or radiological findings with EBV-DNAemia. Among the biopsy-confirmed cases, 3 patients had polymorphic PTLD and 12 had monomorphic PTLD, including 5 diffuse large B-cell lymphomas, 5 Burkitt lymphomas, 1 marginal zone lymphoma, and 1 Hodgkin lymphoma subtype.

### Treatment Modalities

Immunosuppression therapy was reduced or modified for 25 patients (73.5%) and rituximab was administered for 29 (85.3%).

Among the 19 probable PTLD cases, 14 patients received both rituximab and immunosuppression reduction, 3 received rituximab alone, 1 received immunosuppression reduction plus intravenous immunoglobulin, and 1 received rituximab combined with chemotherapy.

Two patients with polymorphic PTLD achieved complete remission with immunosuppression reduction alone. One patient underwent surgery for ileus and subsequently received 8 doses of rituximab with full remission.

Among the 12 monomorphic PTLD cases, 1 patient died before treatment initiation. Four were treated with rituximab monotherapy; 3 were treated with rituximab plus chemotherapy; 1 was treated with rituximab, chemotherapy, and surgery; 1 was treated with rituximab, chemotherapy, and radiotherapy; and 2 were treated with chemotherapy alone.

Two of 7 patients with CNS involvement received intrathecal rituximab (20 mg per dose). One achieved remission and the other died.

Eight asymptomatic patients received rituximab, and 5 of them also underwent immunosuppression reduction (Table 2).

### Outcomes and Survival

Eight patients died during follow-up, 6 of whom died from PTLD-related causes, corresponding to a PTLD-attributable mortality rate of 17.6%. Among these deaths, 5 occurred among the monomorphic PTLD cases (4 PTLD-related and 1 due to relapse of underlying acute myeloid leukemia during PTLD remission). Three deaths occurred among the probable PTLD cases (2 PTLD-related and 1 due to relapsed acute lymphoblastic leukemia). Additionally, one patient in the asymptomatic EBV-DNAemia group died due to graft-versus-host disease (GVHD) (Table 2).

The median follow-up for PTLD patients was 43 months and the 5-year OS rate was 76.5% (Figure 1a). The median follow-up period was 46 months in the proven PTLD group and 42 months in the probable PTLD group, with 5-year OS rates of 66.7% and 84.2%, respectively (Figure 1b).

Among survivors, 2 developed hypogammaglobulinemia, 1 developed immune hemolytic anemia, and 1 experienced EBV-associated graft failure necessitating a second transplantation.

### Prognostic Factors

No statistically significant association was found between mortality and sex, underlying disease, transplant type, donor source, conditioning regimen, antithymocyte globulin (ATG) or steroid use, presence of acute or chronic GVHD, concurrent cytomegalovirus reactivation, cytopenia, or gastrointestinal or pulmonary involvement at diagnosis ( $p > 0.05$  for all; Table 3). However, CNS involvement at the time of PTLD diagnosis was significantly associated with mortality (4 of 7 deaths;  $p = 0.012$ ).

Treatment response strongly influenced prognosis: 25 of 27 patients achieving remission survived (92.6%), compared to only 1 of 7 patients (14.3%) who failed to achieve remission ( $p = 0.001$ ) (Table 3).

Table 2. Treatments and outcomes of all groups.			
n	Asymptomatic group (preemptively treated patients)	PTLD	
		Probable PTLD	Proven PTLD
8	8	19	3
Treatment	- All 8 patients were treated with rituximab - 5 patients had their immunosuppression reduced and/or changed in addition to rituximab therapy	- 14 patients received immunosuppression reduction and rituximab - 3 received rituximab alone - 1 received immunosuppression reduction and IVig - 1 received immunosuppression reduction and rituximab plus chemotherapy	- 2 patients were successfully treated with immunosuppression reduction alone - 1 patient underwent surgery for ileus and was successfully treated with 8 doses of rituximab  - 1 patient died before receiving treatment - 4 patients were treated with only rituximab - 3 patients were treated with rituximab + chemotherapy - 1 patient was treated with rituximab + chemotherapy + surgery - 1 patient was treated with rituximab + chemotherapy + radiotherapy - 2 patients were treated with only chemotherapy
Deaths (n)	1	3	5
PTLD-related death	0	2	4
Deaths from other causes	1 death was due to GVHD while EBV-DNAemia was under control	1 death was due to relapse of underlying ALL while PTLD was in remission	1 death was due to relapse of underlying AML while PTLD was in remission

PTLD: Posttransplant lymphoproliferative disorder; IVig: intravenous immunoglobulin; EBV: Epstein-Barr virus; GVHD: graft-versus-host disease; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia.

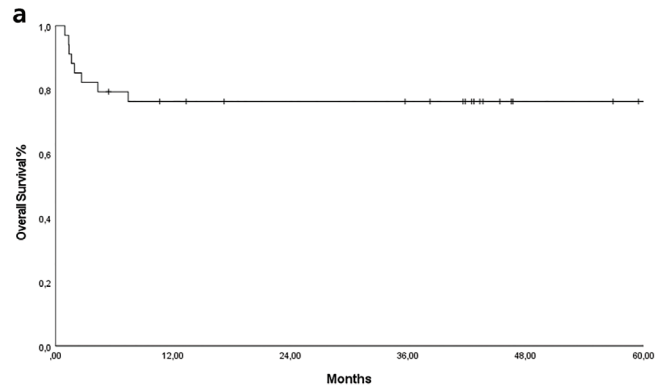


Figure 1a. Five-year overall survival for all patients with posttransplant lymphoproliferative disorder.

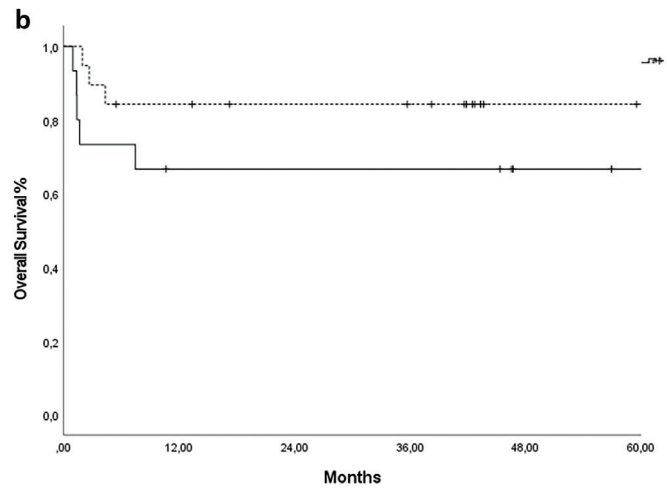


Figure 1b. Five-year overall survival for patients with probable (dotted line) and proven (solid line) posttransplant lymphoproliferative disorder.

### Discussion

In this multicenter cohort, 34 of 6129 pediatric allogeneic HSCT recipients in Türkiye developed PTLD, yielding an overall incidence of 0.56%. This rate falls within the pediatric range reported in the literature (0%-3.5%) [9], but it is below the 3.5% incidence reported by the European Society for Blood and Marrow Transplantation in a pediatric analysis [10]. Differences in reported incidence rates likely reflect variability in patient characteristics, donor/recipient serostatus distributions, the intensity and composition of immunosuppression, and ATG exposure [5,11]. Additionally, center-level practices such as specific early diagnostic pathways, routine EBV-DNA monitoring, and initiation of preemptive therapy at lower thresholds may contribute to lower observed rates. The relatively low number

**Table 3. Factors affecting patient survival. This table contains the data of 34 patients with posttransplant lymphoproliferative disorder.**

	Alive, n (%)	Died, n (%)	p
<b>Sex</b>			
Female	11 (42.3)	4 (50)	>0.05
Male	15 (57.7)	4 (50)	
<b>Primary diseases</b>			
Malignant	10 (38.5)	4 (50)	>0.05
Non-malignant	16 (61.5)	4 (50)	
<b>Donor types</b>			
Matched donor	21 (80.7)	5 (62.5)	>0.05
Haploidentical donor	5 (19.3)	3 (37.5)	
<b>Conditioning regimens</b>			
MAC	21 (80.7)	5 (62.5)	>0.05
NMA	5 (19.3)	3 (37.5)	
<b>ATG use</b>			
Yes	22 (84.6)	7 (87.5)	>0.05
No	4 (15.4)	1 (12.5)	
<b>Acute GVHD</b>			
Yes	9 (34.6)	4 (50)	>0.05
No	17 (65.4)	4 (50)	
<b>Chronic GVHD</b>			
Yes	3 (11.5)	-	>0.05
No	23 (88.5)	8 (100)	
<b>Steroid use</b>			
Yes	9 (34.6)	4 (50)	>0.05
No	17 (65.4)	4 (50)	
<b>Cytomegalovirus reactivation</b>			
Yes	6 (23.1)	4 (50)	>0.05
No	20 (76.9)	4 (50)	
<b>GIS involvement</b>			
Yes	17 (65.4)	5 (62.5)	>0.05
No	9 (34.6)	3 (37.5)	
<b>Lung involvement</b>			
Yes	5 (19.3)	1 (12.5)	>0.05
No	21 (80.7)	7 (87.5)	
<b>CNS involvement</b>			
Yes	3 (11.5)	4 (50)	<b>&lt;0.05 (0.012)</b>
No	23 (88.5)	4 (50)	
<b>Cytopenia</b>			
Yes	12 (46.1)	5 (62.5)	>0.05
No	14 (53.9)	3 (37.5)	
<b>MAS</b>			
Yes	4 (15.4)	-	>0.05
No	22 (84.6)	8 (100)	
<b>Immunosuppression modulation</b>			
Yes	20 (76.9)	6 (75)	>0.05
No	6 (23.1)	2 (25)	
<b>Rituximab treatment</b>			
Yes	22 (84.6)	6 (75)	>0.05
No	4 (15.4)	2 (25)	
<b>PTLD in remission</b>	25 (96.2)	2 (25)	<b>&lt;0.05 (0.001)</b>
<b>PTLD not in remission</b>	1 (3.8)	6 (75)	

MAC: Myeloablative conditioning; NMA: non-myeloablative conditioning; ATG: antithymocyte globulin; GVHD: graft-versus-host disease; GIS: gastrointestinal system; CNS: central nervous system; MAS: macrophage activation syndrome; PTLD: posttransplant lymphoproliferative disorder.

of asymptomatic EBV-DNAemia events in our dataset may also reflect retrospective data capture and heterogeneity in posttransplant surveillance protocols across centers.

The median time to PTLD was 197 days in our cohort, with 85.3% of patients presenting within the first posttransplant year, consistent with reports that most PTLD arises within 6-12 months in both pediatric and adult patients [2,12]. While PTLD beyond 1 year is uncommon (~4%) and occurrences beyond 5 years are rare [4], our cohort included 14.7% late-onset cases ( $\geq 1$  year) and a single very late-onset case that occurred 9 years after HSCT, underscoring the need for continued clinical vigilance.

The most frequent presenting features were fever, lymphadenopathy, malaise, abdominal pain, and weight loss. Extranodal involvement was dominated by the gastrointestinal tract (64.7%), followed by bone marrow/cytopenia (50%), CNS involvement (20.5%), and pulmonary sites (17.6%); MAS was observed in 11.7% of cases. These patterns mirror those of multicenter series in which gastrointestinal disease was the most common extranodal manifestation at rates of approximately 40%-60%, with CNS and pulmonary involvement affecting approximately 10%-20% and 10%-15% of cases, respectively [5,10,12]. Notably, MAS has been reported infrequently in pediatric PTLD (~2%) [13,14]. The higher MAS rate in our cohort may reflect cohort-specific clinical characteristics or differences in recognition and reporting; this finding warrants prospective evaluation of surveillance, diagnostic triggers, and immunologic status.

Pediatric EBV reactivation rates after HSCT vary widely, ranging in the literature from approximately 30% to 60% [15,16,17,18,19]. We identified only 8 asymptomatic EBV-DNAemia cases, a low figure that likely underestimates the true burden, because we included only asymptomatic patients who received preemptive therapy; centers may not have submitted all EBV-DNAemia-only cases. We therefore suspect that EBV-DNAemia is more common nationally than our retrospective capture suggests, highlighting the need for harmonized surveillance policies.

Consistent with the ECIL-6 recommendations, preemptive rituximab (with immunosuppression reduction when feasible) is advised for high-risk EBV-DNAemia [6]. Pediatric series report high rates of EBV clearance with preemptive strategies (approximately 89%-100%) [20,21]. In our cohort, all patients with asymptomatic EBV-DNAemia received rituximab and over half also underwent immunosuppression reduction, aligning with the ECIL-6 guidelines [6] and the favorable prognostic impact of rapid viral control reported by Kania et al. [15]. Across HSCT recipients, pooled data suggest favorable outcomes in ~90% of cases with preemptive rituximab and ~65% with PTLD treated with rituximab [3,4,6,22]. Combining immunosuppression reduction with rituximab improves outcomes (>80%), whereas

reduction alone yields success rates of approximately 68% [4,6,22,23]. EBV-specific cytotoxic T cells achieve >90% favorable outcomes in preemptive settings and ~75% in overt PTLD [6,22,24,25]; however, this modality is not currently accessible in Türkiye, representing a therapeutic gap.

CNS disease remains a key adverse feature. Systemic rituximab exhibits limited CNS penetration, with cerebrospinal fluid concentrations reported at <5% of serum levels [26], constraining efficacy in isolated CNS PTLD. Pediatric series have yielded encouraging results with intrathecal/intraventricular rituximab, though optimal dosing and schedules remain undefined [7,27]. In a pediatric report [27], 169 intrathecal or intraventricular doses were administered to 23 patients (median of 6 doses; 10-40 mg per dose) and were generally well tolerated. Transient grade 1-2 neurotoxicity, headache, and allergic symptoms were the most common adverse events, and approximately 82.6% of patients achieved CNS remission with or without adjunctive CNS-directed therapy. In our cohort, 2 patients with CNS involvement received 20 mg of intrathecal rituximab; 1 achieved remission and 1 died. When this result is evaluated together with the existing literature, this approach has both potential and limitations.

Prognostically, prior studies associate poorer outcomes with malignant primary disease, advanced stage, female sex, multifocal/extranodal involvement, CNS and bone marrow disease, B symptoms, elevated lactate dehydrogenase, high baseline EBV-DNAemia, CD20- or EBV-negative tumors, and monomorphic or late-onset PTLD [5,6,9,12]. In our cohort, remission status was the dominant determinant of survival; 92.6% of patients achieving remission survived versus 14.3% among non-responders, reinforcing studies in the literature that underscore response as a principal prognostic marker [2,12]. Mortality was also significantly higher with CNS involvement, consistent with the therapeutic challenges noted above. Other candidate factors did not reach statistical significance in our sample, likely owing to limited power.

The reported 5-year OS in pediatric PTLD ranges from 50% to 88% [12], with heterogeneity driven by the inclusion of solid-organ recipients, mixed adult/pediatric populations, treatment era (pre- vs. post-rituximab), and histological subtypes in the analyses. An Austrian pediatric series reported a 5-year OS rate of ~64% [12], while some single-center cohorts have approached rates of 80% [4,28]. Our 5-year OS of 76.5% aligns with outcomes in the rituximab era. Historically, PTLD-attributable mortality after HSCT approached 84.6% before 2000 [1,6]; despite substantial improvements with EBV-PCR monitoring, prophylaxis/preemptive therapy, and rituximab, contemporary mortality generally remains near one-third of the previous rate [4,6]. In contrast, our PTLD-attributable mortality rate of 14.3% compares favorably with prior reports, potentially reflecting timely recognition and standardized first-line management.

## Study Limitations

This study is limited by its retrospective design, multicenter data collection with variability in surveillance and management practices, and small subgroup sizes, which reduced the power to detect modest effect sizes. Due to the limited sample size, multivariate analyses could not be performed. Most importantly, the absence of a national EBV surveillance policy likely introduced heterogeneity in case ascertainment, particularly for asymptomatic EBV-DNAemia, potentially underestimating the true frequency of EBV events.

## Conclusion

Given that PTLD remains a significant cause of morbidity and mortality following pediatric allogeneic HSCT, national-level consensus guidelines and standardized EBV surveillance/management policies are urgently needed to harmonize monitoring thresholds, the timing of preemptive intervention, and access to advanced therapies including EBV-specific cytotoxic T cells. Such alignment is likely to further improve early detection, treatment response, and long-term survival.

## Ethics

**Ethics Committee Approval:** The study was approved by the Koç University Ethics Committee (protocol no: 2025.491.IRB2.224, date: 04.11.2025).

**Informed Consent:** Retrospective study.

## Footnotes

## Authorship Contributions

Surgical and Medical Practices: F.E., M.K., E.Y., A.Ö., G.Ö., S.A., Ü.K., Z.K., V.U., B.M., Av.A., S.S.Ç., Ar.A., F.T.K., S.Ö., K.Y., N.Y.Ö., Ö.D., B.Ş.K., A.B.A., F.A., B.A.A., D.A., S.K., M.E.; Concept: F.E.; Design: F.E.; Data Collection or Processing: F.E., M.K., E.Y., A.Ö., G.Ö., S.A., Ü.K., Z.K., V.U., B.M., Av.A., S.S.Ç., Ar.A., F.T.K., S.Ö., K.Y., N.Y.Ö., Ö.D., B.Ş.K., A.B.A., F.A., B.A.A., D.A., S.K., M.E.; Analysis or Interpretation: F.E.; Literature Search: F.E.; Writing: F.E.

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