Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinico-pathological characteristics and prognostic factors

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Abstract

Hematopoietic stem cell and solid organ transplant recipients diagnosed with biopsy-confirmed posttransplant lymphoproliferative disorder (PTLD) at our institution from 1989 to 2010 were identified. Patient-, transplantation- and disease-related characteristics, prognostic factors and outcome were collected and analyzed. One hundred-forty biopsy-proven PTLD cases were included. Overall incidence in the transplant population was 2.12% with heart transplant recipients carrying the highest risk. Most PTLDs were monomorphic (83.6%) with diffuse large B cell lymphoma being the most frequent subtype. The majority of cases (70.7%) occurred > 1 year posttransplantation, whereas 66% were Epstein Barr virus positive. Following initial therapy overall response rate was 68.5%. Three-year relapse-free and overall survival were 59% and 49%, respectively. At last follow-up 44% of the patients were alive. Multivariable analysis identified several classical lymphoma-specific poor prognostic factors for the different outcome measures. The value of the International Prognostic Index was confirmed in our analysis.

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Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinico-pathological characteristics and prognostic factors

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Short title: Posttransplant lymphoma monocenter analysis

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Abstract

Hematopoietic stem cell and solid organ transplant recipients diagnosed with biopsy-confirmed posttransplant lymphoproliferative disorder (PTLD) at our institution from 1989 to 2010 were identified. Patient-, transplantation- and disease-related characteristics, prognostic factors and outcome were collected

and analyzed. One hundred-forty biopsy-proven PTLD cases were included. Overall incidence in the transplant population was 2.12% with heart transplant recipients carrying the highest risk. Most PTLDs were monomorphic (83.6%) with diffuse large B cell lymphoma being the most frequent subtype. The majority of cases (70.7%) occurred > 1 year posttransplantation, whereas 66% were Epstein Barr virus positive. Following initial therapy overall response rate was 68.5%. Three-year relapse-free and overall survival were 59% and 49%, respectively. At last follow-up 44% of the patients were alive. Multivariable analysis identified several classical lymphoma-specific poor prognostic factors for the different outcome measures. The value of the International Prognostic Index was confirmed in our analysis.

Keywords: immunosuppression, posttransplant lymphoproliferative disorder, PTLD, transplantation

Introduction

Posttransplant lymphoproliferative disorder (PTLD) is a rare complication of solid organ (SOT) and hematopoietic stem cell transplantation (HSCT), caused by drug-induced reduced immune surveillance. Pathologically, PTLD exhibits a heterogeneous spectrum of appearance, ranging from a benign condition to real lymphoma with Epstein Barr virus (EBV) playing an essential role in the pathogenesis of the majority of PTLDs [1]. Similar to its heterogeneous presentation, treatment options are diverse [2].

Several single or multicenter reports have been published, of which the largest comprised 170 patients [3]. Important limitations of these studies are the heterogeneous populations and the relative small absolute numbers of patients, especially when compared with large transplant registry analyses which contain many more patient index cases but often lack detailed information.

The primary aim of this analysis was to obtain detailed information on incidence, clinico-pathological characteristics, risk factors and outcome of biopsy-proven PTLD derived from a large population of SOT and HSCT recipients. The results of this retrospective cohort study should enable clinicians, at least in part, to base their clinical management strategies for PTLD on systemically acquired evidence recovered from a representative large study population, in the absence of prospective studies.

Material and methods

Data collection

We conducted a monocentric retrospective analysis of all patients diagnosed with biopsy-confirmed PTLD at the University Hospitals Leuven, Belgium between January 1989 and December 2010. The clinical and pathological institutional databases were used to identify patients. All tissue biopsies were reviewed by three expert hematopathologists (C.DWP./X.S./ T.T.) and classified according to the WHO 2008 classification [1]. EBV-status was determined by Epstein Barr-encoded RNA (EBER) *in situ* hybridization (ISH) if possible. Patient-related characteristics including age, gender, EBV-status pre-transplantation and Eastern Cooperative Oncology Group (ECOG) performance state were reported. Transplantation-related characteristics included time between transplantation and PTLD onset and immunosuppressive therapy. PTLD-related characteristics included presence of B-symptoms, biochemical data (hemoglobin, lactate dehydrogenase-LDH-, albumin), Ann Arbor stage at diagnosis, number of extranodal sites and involvement of different organ systems. We also collected data on EBV polymerase chain reaction (PCR) in peripheral blood, if available. However, EBV-status of the tumor was based solely on the ISH data. International Prognostic Index (IPI) scores were calculated retrospectively, according to previous defined criteria [4]. For statistical reasons combined kidney-pancreas (n=3), heart-lung (n=3) and liver-pancreas (n=1) transplant patients were classified as kidney, lung and liver transplant recipients respectively. Monomorphic diffuse large B-cell lymphoma

(DLBCL) was compared to all other PTLD subtypes. Patients were treated by physicians of the Divisions of Hematology, Medical Oncology and Pediatric Hemato-oncology. Data on treatment, treatment response and outcome were collected. This study was approved by the Ethical Committee of the University Hospitals Leuven and was conducted according to the Declaration of Helsinki.

Statistical analysis

Kaplan-Meier estimates are used to create survival curves for Overall Survival (OS) and Relapse-free Survival (RFS). Cumulative incidence estimates are used to construct curves for the % free from PLTD death and from relapse. Deaths due to other causes and deaths without preceding relapse are considered as a competing risk in these curves, respectively. Cox regression models are used to verify the relation between various predictors and the (cause-specific) hazard function. The proportional hazards assumption and the functional form of the continuous predictors have been verified by applying graphical and numerical methods. To study the relation with complete and/or partial response, Fisher's Exact tests, trend tests and logistic regression models are used.

The following list of variables is considered in the multivariable models: age at diagnosis, sex, time between transplantation and diagnosis, performance state (score 0-4), transplanted organ, monomorphic subtype, CD20-positivity, EBER-positivity, graft organ involvement, extranodal disease, advanced stage (Ann Arbor III/IV), elevated LDH and hypoalbuminemia. A backward variable selection method is used to obtain a parsimonious multivariable model. To avoid identification of noise variables as independent predictors and to take into account the uncertainty in the model selection process, a bootstrap resampling procedure is applied [5]. More specifically, 100 datasets of the same size as the original one are drawn with replacement from the original dataset and in each sample the backward selection method is applied. The significance level for removing a variable from the model is set at 0.157. For each predictor, the percentage of samples is reported where the predictor is retained (the so-called bootstrap importance frequency (BIF)). A significant variable retained in the final model on the original sample but with a low BIF is likely to be a noise variable. All analyses have been performed using SAS software, version 9.2 of the SAS System for Windows. Copyright © 2002 SAS Institute Inc.

Results

Baseline characteristics (Table I)

Between January 1989 and December 2010, 6607 transplantations (60% men) were performed at the University Hospitals Leuven, Belgium. These included 3566 kidney, 853 liver, 568 lung, 519 heart, 9 intestinal/multivisceral and 1092 allogeneic HSC transplantations. Of these, 140 patients with biopsy-confirmed PTLD were identified and treated at the same center. In two cases diagnosis was made by flow cytometry analysis (on bone marrow and ascites).

Patient-related characteristics

The median age at time of PTLD diagnosis was 54 years (range, 2 to 83 years), 86 patients (61%) were younger than 61 years. There was a male predominance (75%).

Transplant-related characteristics

The most commonly transplanted organ was kidney (38.5%), followed by heart (18.5%), liver (17%), HSC (13%) and lung (13%). The organ specific PTLD incidence however was the highest in heart (5.0%), followed by lung (3.2%), liver (2.8%), HSC (1.7%) and kidney (1.5%), with an overall incidence in the whole transplant population of 2.12%. In the 18 HSC patients the type of donor was matched unrelated in 10, haplo-identical in 5 and umbilical cord blood in 3 cases. The median interval between transplantation and diagnosis of PTLD was 4.0 years (range 0.1-35.4), with 41 (29%) patients experiencing early (<1 year posttransplantation) PTLD. Immunosuppressive maintenance therapy at PTLD diagnosis included calcineurin inhibitors in 128 (89%) patients (cyclosporin/tacrolimus 63/65), antimetabolites in 95 (68%) patients (azathioprine/mycophenolate 48/46, 1 combination) and low dose corticosteroids in 94 (67%) patients. Sixty (49%) of the SOT patients with PTLD received classical triple therapy (combination of calcineurin inhibitor, antimetabolite and low dose steroids). Eighty-seven (62%) of the patients received induction (SOT) or conditioning (HSCT) with depleting or non-depleting therapy.

Disease-related characteristics

Pathological examination showed early lesions (13 cases), polymorphic PTLD (8 cases), monomorphic PTLD (115 cases) and classical Hodgkin lymphoma type PTLD (4 cases). The majority of monomorphic subtypes were DLBCL (72%). Other monomorphic subtypes included T-cell NHL (n=10), plasmablastic NHL (n=8), plasmacytoma (n=4), IG/c-MYC-rearranged Burkitt lymphoma (n=3), small cell B-NHL (n=2) and unspecified cases (n=5). For statistical analysis monomorphic PTLD was separated in DLBCL type and non-DLBCL. EBER ISH was positive in 86 (66%) of the 130 evaluable biopsies. In early PTLD more cases (76%) were EBV positive compared to late PTLD (62%). Hundred and five (78%) of 133 evaluable cases were CD20 positive. At time of diagnosis B-symptoms were present in 51 (36%) patients, whereas ECOG performance state was ≥ 2 in 59 (42%) patients. Hundred-one (72%) patients presented with advanced stage, LDH elevation and hypoalbuminemia were observed in 65 (46% and 47% respectively) evaluable patients. The gastrointestinal tract was the organ system most commonly involved (29%). Pulmonary, bone marrow, graft and central nervous system (CNS) involvement were reported in 23, 15, 15 and 5% respectively. Of seven patients presenting with CNS abnormalities, 6 were diagnosed with primary CNS lymphoma. Patients belonged to IPI score low risk in 29%, low-intermediate risk in 21%, high intermediate risk in 29% and high risk in 21%.

Plasma EBV DNA loads were measured at diagnosis in 88 (63%) patients. Of these 67 (76%) had detectable EBV viral load.

Therapy and outcome

The median follow up for all patients after diagnosis of PTLD was 3.9 years (95% CI, 2.9-6.3). Initial therapy included reduction of immunosuppression (RIS; 89%), rituximab (53%), chemotherapy (28%), surgery (12%), antiviral therapy (8%), radiotherapy (7%) and high dose steroids (7%). Only 19 (14%) patients were treated with RIS alone as initial therapy. Following initial therapy the rates of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were 53%, 16%, 5% and 17%, respectively. Three patients were treated with palliative support only whereas 10 patients (7%) died during induction therapy and hence were not evaluated for treatment response (Figure 1).

Overall survival rates for the whole cohort at 1, 3 and 5 years were 62, 49 and 40% respectively (Figure 2). At last follow-up 62 (44%) patients were alive, 45 (32%) had died due to PTLD and 33 (24%) had died of other causes (mostly infections). In 74 patients reaching complete remission following initial therapy 9 (12%) relapsed. RFS at 1, 3 and 5 years were 80%, 59% and 47%, respectively (Figure 2).

As shown in Figure 3, different OS was observed according to the different IPI risk groups ($p < 0.0001$, log rank test). Complete response rates in the different IPI risk groups were 80.5%, 58.6%, 31.7% and 37.9% for the low, low intermediate, high intermediate and high risk scores, respectively ($p < 0.0001$, trend test).

Univariable and multivariable analysis

Univariable analysis identified a number of factors significantly associated with the different outcome variables, as shown in Table II and III. In multivariable analysis however, only a few of these factors maintained prognostic significance. Higher age at PTLD diagnosis, female gender, liver (as compared to kidney) transplantation, extranodal disease, elevated LDH and hypoalbuminemia emerged as independent prognostic factors for reduced overall survival, whereas higher age at PTLD diagnosis, transplanted organ (lung and HSC as compared to kidney), monomorphic DLBCL type, advanced stage and hypoalbuminemia were poor prognostic factors for PTLD-related death. Female gender, monomorphic DLBCL type, elevated LDH, and CD20 positivity were independently associated with treatment failure (no complete or partial response). Finally higher age at PTLD diagnosis, late onset PTLD, transplanted organ (liver and HSC as compared to kidney), extranodal involvement and hypoalbuminemia were associated with poor RFS. All significant predictors in the final multivariable models had a BIF > 60%.

Because one of the primary aims of this study was to identify predictive prognostic factors at PTLD diagnosis, initial therapy and treatment response were not included in the multivariable analysis. None of the different therapeutic regimens were significantly associated with better outcome in univariable analysis. However, reaching complete or partial response to initial therapy was associated with superior survival outcomes in univariable analysis (results not shown).

Discussion

PTLD comprises a broad and heterogeneous spectrum of morphological conditions, ranging from a benign pathological condition to frank lymphoma [1]. Among 140 patients diagnosed with PTLD during the last twenty years in our institution, the monomorphic subtype was observed most frequently, with DLBCL being the most common histology (60%). In agreement with data from the literature, other subtypes including early lesions (9%), polymorphic PTLD (6%), other monomorphic PTLD subtypes (22%) and classical Hodgkin lymphoma type PTLD (3%) were less common [4,7]. In the non-DLBCL monomorphic subtype (31 cases) we found a rather large number of different subtypes of T-cell NHL (32%) and plasmablastic NHL (26%), whereas Burkitt NHL was rare (9.4%). As expected the occurrence of plasmablastic NHL was associated with an inferior outcome with 50% of the patients dying in the first three months following diagnosis. On the other hand three patients with plasmacytoma showed long term survival with RIS with or without local radiotherapy, whereas the fourth patient died rapidly, due to concomitant cutaneous squamous cell carcinoma with diffuse metastases. Of note, the excellent prognosis of plasmacytoma type PTLD was recently shown in a series of eight patients [8].

As during this 20-year period no pre-emptive strategies were implemented based on EBV PCR monitoring following SOT, the incidences of PTLD seem to represent a reliable estimation of the true incidence. In HSCT however EBV-driven pre-emptive reduction of immunosuppression with or without administration of rituximab was not uncommon. Together with the fact that obtaining a biopsy is often considered a risk because of the presence of profound thrombocytopenia, PTLD incidence in this specific population may have been underestimated in our analysis.

During the last decade the incidence of PTLD seems to be increasing. This is illustrated by the finding that during the period 1989-1999 21 cases of PTLD were diagnosed in our center, whereas this number raised to 119 cases from 2000 to 2010. This more than 5-fold increase can only partially be explained by the expansion of transplant activities. Other possible contributing factors include the use of more potent induction therapy (especially in kidney transplantation), the increased number of haplo-identical HSCTs, higher recipient age, increased clinical awareness and perhaps a longer observation time [9,10]. Although PTLD was initially reported to occur early (less than one year) following transplantation, recent data have shown a shift towards later occurrence, except for HSCT [7,10]. In our analysis median time from transplantation to PTLD diagnosis was 4 years, with 71% diagnosed more than one year after transplantation. In a recent multi-institutional analysis, Evens et al observed 15% very late (more than ten years) PTLDs, a number which was even higher in our study (25.7%) [7]. The longest interval we observed between transplantation and diagnosis of PTLD was 23 years. Early onset PTLD is associated with EBV positivity and younger age, whereas late PTLD is associated with older age, raising the question whether these lymphomas can be considered true PTLD or only reflect an older population [11]. When looking at the different organs HSC (94%) and lung (53%) transplantation were

associated with a higher incidence of early PTLD whereas in heart (81%), kidney (84%) and especially liver (96%) transplantation a clear predominance for late PTLDs was observed. The reason for this absence of early PTLDs in liver transplant recipients is not clear. In the largest single center experience published until today, Jain et al reported on 170 PTLD cases following liver transplantation. In this series median time between transplantation and PTLD diagnosis was 10 months, with almost 70% of the cases diagnosed in the first year following transplantation [4]. The reason for this discrepancy may be the use of less intensive immunosuppressive regimens following liver transplantation in Europe compared to the United States.

Up to 80-85% of the PTLD cases are associated with EBV primary infection or reactivation [2,12]. The pathogenesis of the remaining cases is less clear. These EBV negative cases have the tendency to occur late following transplantation. Possible explanations include involvement of other infectious agents or loss of EBV during PTLD evolution ('hit and run' hypothesis). This hypothesis is supported by the description of Burkitt and Hodgkin lymphoma cases who seem to lack expression of EBV genes, but still have fragments of EBV DNA [13]. Different viruses have been identified as important contributors of lymphomagenesis, both in immunocompetent and immunosuppressed patients but currently there is no hard evidence to support their role in PTLD [14,15]. In accordance with the above described shift in favor of late PTLD, we found EBV positivity (defined as positive EBER ISH) in 66% of the evaluable cases with 76% and 62% of early and late PTLDs being positive respectively.

In contrast to the very heterogeneous presentation of most classical lymphomas PTLD tends to occur with advanced disease and frequent extranodal involvement. In our population 72% of the patients showed Ann Arbor stage III/IV with 78% displaying one or more extranodal localization. The gastrointestinal tract was the organ system most commonly involved (29%). Compared to other studies the incidence of CNS disease was rather low with only 6 patients presenting with primary CNS lymphoma and 1 patient showing disseminated disease with CNS involvement [7].

Current treatment of PTLD is mainly based on retrospective data, and only few prospective trials with rituximab therapy have been performed [16-21]. As a consequence there is no consensus on treatment strategy. RIS is considered the cornerstone of PTLD treatment, especially but not exclusively in EBV positive cases. However, its role in monotherapy is not clear, which is illustrated by the results of two recent prospective trials, showing conflicting ORR (6% in the Baltimore study and 45% in the Pennsylvania experience) [22,23]. In case of insufficient response, chemotherapy and rituximab, alone or in combination, are most frequently initiated showing response rates of approximately 70% [24]. Although 89% of the initial treatment regimens included RIS in our population, only a minority (14%) were treated with RIS alone. However, overall response rate (ORR) in this latter population was 80% with 70% CR. Interestingly, eight patients (50%) responding to RIS only were diagnosed with late onset PTLD. Of the patients with CR following RIS only, two relapsed. One patient, a lung transplant recipient, relapsed ten years following RIS. Based on the promising results with rituximab in smaller prospective trials

and due to its superior safety profile compared to chemotherapy, rituximab monotherapy is considered treatment of choice by many physicians in patients with CD20-positive B-PTLD failing initial treatment with RIS, although a recent phase 2 trial showed that the use of sequential therapy with rituximab and chemotherapy improved response rates [21]. In our analysis, treatment with rituximab was not associated with superior outcome, even when we re-analyzed the data excluding T-cell NHL and Hodgkin lymphoma cases. However, this finding might be attributed to the retrospective character of the analysis with different time points and schedules for rituximab administration. In addition, no differences were found for patients treated in the pre-rituximab compared to those treated in the rituximab era. Interestingly, CD20 positivity was an adverse prognostic factor for ORR. Importantly, only 62% of the CD20 positive cases were initially treated with a rituximab-containing regimen.

Although several prognostic scores have been proposed by different authors, validation of these scores in different transplant populations have not been done or have shown conflicting results, partially due to heterogeneity in patient population and treatment. However, poor prognostic factors in immunocompetent lymphoma patients, including higher age, advanced disease, poor performance status, elevated LDH and hypoalbuminemia, have also shown to be predictive for outcome in PTLD patients [7,20,25-27]. In our analysis hypoalbuminemia, higher age at PTLD diagnosis and elevated LDH were the most important independent prognostic factors for the different outcome parameters, whereas PTLD in heart transplant recipients –although at higher risk for development of PTLD- was associated with better outcome compared with other organs. The prognostic role of the IPI score has been shown in some PTLD series, whereas others could not confirm this finding. In our study the IPI score remained a significant predictor for survival in patients with PTLD.

In a large registry report of the United Network for Organ Sharing (UNOS), male gender was an independent risk factor for PTLD development [28]. This finding however was not confirmed in other registry studies. The high male/female ratio of 3/1 in our analysis can only partially be explained by the higher number of transplantations in male recipients (60%). On the other hand male gender was an adverse prognostic factor in two recent trials in immunocompetent patients with DLBCL or follicular lymphoma, treated with rituximab-containing therapy [29,30]. In our analysis however, female gender was an independent poor prognostic factor for OS and ORR, but not for RFS and PTLD-related death. The reason for this finding is not clear, but may be explained by different pharmacokinetics of chemotherapeutics between women and men.

Currently serial monitoring of Epstein-Barr viral load has become common practice in many transplant centers, leading in some of them to pre-emptive therapy including reduction of immunosuppression or anti-CD20 immunotherapy, especially following HSCT and pediatric SOT [31,32]. Because measuring EBV viral load became common practice only in the beginning of this century, plasma EBV DNA loads were measured at diagnosis in only 63% of the patients. Detectable EBV viral load, present in 76% of these patients, correlated well with positive tissue EBER ISH. However, prospective and serial monitoring

data are necessary to determine its real predictive role in the development of PTLD.

This study carries the typical limitations of a single center retrospective cohort study, including heterogeneity in treatment by different physicians, no uniformity in timing of staging and missing data. However, in contrast to large registry studies, single institution databases provide more detailed information with less missing data and less reporting bias. In our analysis the only variables with > 10% missing data were bone marrow examination, EBV status at the moment of transplantation and peripheral blood EBV viral load data, which is due to the fact that this test was only routinely introduced in our center eight years ago. Additionally our results reflect daily clinical practice in a large European university transplant center. The intention of this study was not to create a new prognostic model, but to assess the utility of well known prognostic factors and scores.

In summary, this analysis represents the largest European single center study on PTLD after SOT and HSCT. Although not randomized or prospective, the patient cohort is representative of the general PTLD population, providing a real life picture of the incidence, the clinic-pathological features, the therapeutic changes over the last decade and the outcome of patients diagnosed with PTLD. Classical prognostic factors, including the IPI risk score, for poor outcome in immune competent patients remain independent predictors in transplant patients with biopsy confirmed PTLD.

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Conflict of interest statements

The authors declare no competing financial interests.

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Figure Legends

Figure 1

Outcome by histological subtype and Epstein Barr virus (EBV) status.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; EBV, Epstein Barr virus, defined by biopsy EBV-encoded RNA; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; DDI, death during induction; NT, not treated; AWD, alive without disease; AWD, alive with disease; DWOD, dead without disease; DWD, dead with disease.

Figure 2

Overall survival, PTLD-related death, relapse-free survival and freedom from relapse.

Figure 2. Overall survival, PTLD-related death, relapse-free survival and freedom from relapse.

Figure 3

Overall survival for the survival for the different IPI (International Prognostic Index) risk scores.

Figure 3. Overall survival for the survival for the different IPI (International Prognostic Index) risk scores.

Table Legends

Table I

Baseline characteristics

Age at diagnosis(years)	
Median	54
Range	2-83
Gender	
Female	35(25%)
Male	105(75%)
Transplanted organ	
HSC	18(13%)
Heart	26(19%)
Heart-lung	3(2%)
Kidney	51(36%)
Kidney-pancreas	3(2%)
Liver	23(16%)
Liver-pancreas	1(1%)
Lung	15(11%)
Time transplantation-PTLD	
Median (years)	4
Range (years)	0-35
Histology	
Early lesions	13(9%)
Polymorphic	8(6%)
Monomorphic	115(82%)
Classical Hodgkin type	4(3%)
CD20	
Positive	105(75%)
Negative	28(20%)

EBV status blood	
Negative	21(15%)
Positive	25(18%)
Strong positive	29(21%)
Positive without quantification	13(9%)
NA	52(37%)
EBV-status patient pre-transplantation	
Negative	15(11%)
Positive	39(28%)
NA	86(61%)
ECOG performance state	
0-1	81(58%)
2	54(38%)
3-4	5(4%)
LDH	
Normal	75(54%)
Elevated	65(46%)
Hemoglobin(g/dL)	
Median	11.0
Range	6.40-16.20
Albumin	
Normal	71(51%)
Low	65(46%)
NA	4(3%)
Number of extranodal sites	
0	31(22%)

NA	7(5%)
EBV-status tumor	
Negative	44(31.5%)
Positive	86(61.5%)
NA	10(7%)

1	43(31%)
>1	66(47%)
Ann Arbor classification	
I	25(18%)
II	14(10%)
III	25(18%)
IV	76(54%)

Abbreviations: HSC, hematopoietic stem cell; EBV, Epstein Barr virus; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NA, not available.

Table II

Prognostic factors for overall survival and PTLT related death. Hazard ratios and p-values are only given for the variables in the final model; bootstrap importance frequencies are reported for all considered variables.

Predictor	Overall survival					PTLT related death				
	Univariable analysis		Multivariable analysis			Univariable analysis		Multivariable analysis		
	HR (95% CI)	p	HR(95% CI)	p	BIF	HR (95% CI)	p	HR (95% CI)	p	BIF
Age at diagnosis (yrs)	1.03 (1.01-1.04)	<0.0001	1.04 (1.02-1.05)	<0.0001	98	1.02 (1.00-1.04)	0.0178	1.03 (1.01-1.06)	0.0059	68
Male gender	0.73 (0.44-1.21)	0.2218	0.52 (0.28-0.98)	0.0429	74	0.80 (0.41-1.55)	0.5077			59
Time Tx-PTLT (yrs)	1.00 (0.97-1.03)	0.9775			43	0.99 (0.95-1.04)	0.7950	1.04 (0.99-1.10)	0.1258	50
Performance state		<0.0001			24		<0.0001			36
2 ^a	1.33 (0.81-2.21)	0.2639				1.70 (0.86-3.36)	0.1281			
3 ^a	6.25 (2.79-13.99)	<0.0001				7.23 (2.94-17.76)	<0.0001			
4 ^a	4.08 (1.43-11.64)	0.0086				5.89 (1.98-17.53)	0.0015			
Transplanted organ		0.5793		0.0498	90		0.3837		0.0303	84
HSC ^b	1.84 (0.88-3.84)	0.1038	1.82 (0.65-5.11)	0.2544		2.39 (0.99-5.47)	0.0514	8.82 (1.73-44.99)	0.0089	
Heart ^b	1.32 (0.72-2.41)	0.3663	0.82 (0.38-1.76)	0.6071		1.12 (0.47-2.68)	0.7946	0.89 (0.28-2.87)	0.8459	
Liver ^b	1.34 (0.70-2.57)	0.3810	3.11 (1.41-6.85)	0.0048		1.33 (0.55-3.17)	0.5272	3.23 (0.99-10.51)	0.0518	
Lung ^b	1.28 (0.61-2.65)	0.5136	1.56 (0.67-3.61)	0.3003		1.52 (0.61-3.77)	0.3649	5.76 (1.59-20.88)	0.0078	
Monomorphic subtype	2.41 (1.16-5.02)	0.0188			43	3.80 (1.17-12.29)	0.0258	5.17 (1.31-20.36)	0.0190	60

CD20-positivity	0.63 (0.38-1.06)	0.0829	48	0.47 (0.25-0.90)	0.0230	0.48 (0.20-1.13)	0.0915	55		
EBER-positivity	1.25 (0.75-2.08)	0.3856	27	1.16 (0.60-2.24)	0.6641			34		
Graft organ involved	1.07 (0.58-1.95)	0.8311	27	1.01 (0.45-2.28)	9841			38		
Extranodal disease	2.02 (0.19-3.76)	0.0261	3.67 (1.61-8.36)	0.0020	83	2.07 (0.87-4.90)	0.0977	48		
Advanced stage	2.14 (1.22-3.78)	0.0085			33	4.61 (1.65-12.88)	0.0036	3.66 (1.09-12.20)	0.0350	62
Elevated LDH	3.00 (1.87-4.81)	<0.0001	2.19 (1.22-3.91)	0.0085	63	6.79 (3.14-14.70)	<0.0001			66
Hypoalbuminemia	3.29 (2.03-5.34)	<0.0001	3.55 (1.99-6.35)	<0.0001	99	3.70 (1.89-7.22)	0.0001	4.77 (1.86-12.21)	0.0011	93
PCNSL ^d	2.04 (0.50-8.37)	0.319				3.18 (0.77-13.21)	0.1112			
IPI ^d		<0.0001					0.0026			
LI ^c	1.79 (0.81-3.95)	0.1504				13.49 (1.68-108.30)	0.0143			
HI ^c	3.37 (1.75-6.50)	0.0003				29.74 (4.01-220.80)	0.0009			
high ^c	4.94 (2.45-9.95)	<0.0001				28.92 (3.78-221.26)	0.0012			

Abbreviations: HR, hazard ratio; CI, confidence interval; BIF, bootstrap importance frequency); yrs ,years; Tx, transplantation; HSC, hematopoietic stem cell; EBER EBV-encoded RNA; LDH, lactate dehydrogenase;

PCNSL, primary central nervous system lymphoma; IPI, International Prognostic Index; LI: low intermediate; HI: high intermediate; high: high risk score.

^a Compared with performance state score 0/1

^b Compared with kidney transplantation

^c Compared with IPI low risk score

^d Not considered in the multivariable model

Table III

Prognostic factors for overall response rate and relapse free survival. Odds ratios and p-values are only given for the variables in the final model; bootstrap importance frequencies are reported for all considered variables.

Predictor	overall response rate					relapse free survival				
	Univariable analysis		Multivariable analysis			Univariable analysis		Multivariable analysis		
	OR (95% CI)	p	OR (95% CI)	p	BIF	OR (95%CI)	p	OR (95% CI)	p	BIF
Age at diagnosis(yrs)	0.98 (0.96-1.00)	0.0646			37	1.04 (1.02-1.06)	0.0003	1.04 (1.00-1.07)	0.0185	81
Male gender	1.97 (0.89-4.35)	0.0955	3.54 (1.13-11.11)	0.0304	75	0.75 (0.35-1.59)	0.4472	0.45 (0.15-1.30)	0.1388	40
Time Tx-PTLD(yrs)	1.00 (0.96-1.06)	0.8389			22	1.04 (1.00-1.08)	0.0281	1.08 (1.00-1.15)	0.0363	80
Performance state		0.0180	0.51 (0.26-1.03)	0.0599	67		0.1458			49
2 ^a	0.48 (0.21-1.08)	0.0777				1.32 (0.65-2.68)	0.4500			
3 ^a	0.24 (0.06-0.87)	0.0301				7.40 (0.92-59.40)	0.0597			
4 ^a	0.07 (0.01-0.68)	0.0217								
Transplanted organ		0.9593			34		0.7243		0.0026	96
HSC ^b	1.00 (0.32-3.13)	10.000				1.37 (0.31-6.09)	0.6797	9.89 (1.59-61.72)	0.0141	
Heart ^b	1.36 (0.48-3.85)	0.5665				1.06 (0.48-2.35)	0.8786	0.56 (0.19-1.69)	0.3074	
Liver ^b	0.94 (0.33-2.64)	0.9029				1.70 (0.70-4.08)	0.2390	7.80 (2.19-27.80)	0.0015	
Lung ^b	1.37 (0.38-4.96)	0.6269				0.80 (0.26-2.45)	0.6995	1.62 (0.42-6.21)	0.4834	
Monomorphic subtype	0.24 (0.07-0.85)	0.0269	0.09 (0.01-0.70)	0.0204	73	1.75 (0.73-4.20)	0.2131			46
CD20-positivity	3.33 (1.41-7.89)	0.0062	6.75 (1.87-24.33)	0.0035	96	1.25 (0.48-3.28)	0.6441			45
EBER-positivity	0.91 (0.41-2.02)	0.8288			32	1.23 (0.59-2.58)	0.5757			48
Graft organ involved	1.44 (0.49-4.27)	0.5091			23	0.89 (0.39-2.04)	0.7844			46
Extranodal disease	0.57 (0.22-1.44)	0.2329			27	1.34 (0.63-2.84)	0.4460	4.17 (1.14-15.21)	0.0304	65
Advanced stage	0.30 (0.12-0.79)	0.0142	0.36 (0.09-1.46)	0.1535	61	1.46 (0.74-2.86)	0.2759			38
Elevated LDH	0.14 (0.06-0.32)	<0.0001	0.25 (0.09-0.72)	0.0102	90	1.74 (0.89-3.39)	0.1049			59
Hypoalbuminemia	0.40 (0.19-0.85)	0.0180			25	2.80 (1.47-5.36)	0.0018	4.46 (1.76-11.34)	0.0017	88
PCNSL ^d	0.22 (0.02-2.50)	0.2230								
IPI ^d		0.0009					0.0017			

LI ^c	0.13 (0.03-0.69)	0.0164	0.91 (0.32-2.53)	0.8523
HI ^c	0.05 (0.01-0.23)	0.0001	1.47 (0.62-3.48)	0.3815
high ^c	0.06 (0.01-0.31)	0.0007	4.72 (2.02-11.05)	0.0003

Abbreviations: OR, Odds ratio; CI, confidence interval; BIF, bootstrap importance frequency); yrs ,years; Tx, transplantation; HSC, hematopoietic stem cell; EBER EBV-encoded RNA; LDH, lactate dehydrogenase;
PCNSL, primary central nervous system lymphoma; IPI, International Prognostic Index; LI: low intermediate; HI: high intermediate; high: high risk score.

^a Compared with performance state score 0/1

^b Compared with kidney transplantation

^c Compared with IPI low risk score

^d Not considered in the multivariable model