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Survival and Prognostic Factors of 215 Post-Transplant Lymphoproliferative Disorders After Solid Organ Transplantations in a Finnish Nationwide Population-Based Study Over 30 Years

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ABSTRACT

Post-transplant lymphoproliferative disorder (PTLD) is a rare, dreaded complication of organ transplantation with major clinical challenges. We conducted a nationwide population-based study of all solid organ transplant (SOT) recipients ($n = 6555$), both adults and children, over a 30-year period in Finland. Altogether, 215 patients developed PTLD, including 146 aggressive B-cell lymphomas, in a median of 7.8 years after SOT. The incidence of PTLD was 322 per 100,000 patient-years. In median follow-up of 11.5 years after PTLD diagnoses, 155 patients deceased, 119 (55%) of them PTLD related. The median overall survival (OS) was 1.7 years for all. After curatively intended therapy ($n = 165$), the median OS was 6.1 years, 5-year OS rate 52%, and 5-year disease-specific survival (DSS) 58%. In all, 120 patients (56%) achieved complete remission (CR); 69% receiving first-line rituximab and 73% with chemotherapy, and their 5-year DSS rate was 79%. Relapses or second PTLD was recorded in 55 patients (36%) in a median of 1.5 years, and ten cases occurred over five years after the original PTLD diagnosis. International Prognostic Index (IPI) and age over 45 years at PTLD diagnosis were associated with inferior outcomes. Early deaths (< 100 days; $n = 60$; 28%) were related to progressive PTLD or treatment-related complications. However, a decreasing trend in 100-day mortality was observed, with improved DSS over the study period (1988–2002 compared with 2003–2017, $p = 0.011$), despite increased median age at PTLD diagnosis. In conclusion, early mortality remained high throughout the study period. In a long follow-up, the relapses were a major problem even after 5 years. PTLD related mortality rate was remarkably lower in more recent years.

Abbreviations: DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; M-PTLD, monomorphic PTLD; PT-ABCL, post-transplant aggressive B cell lymphoma; PTLD, post-transplant lymphoproliferative disorder; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RIS, reduction of immunosuppression; SOT, solid organ transplantation.

1 | Introduction

Post-transplant lymphoproliferative disorder (PTLD) is an aggressive immunosuppression-related complication of organ transplantation affecting up to 2%–20% of transplant recipients [1–7]. PTLD is frequently related to Epstein-Barr virus (EBV) infection or reactivation in immunocompromised patient [7–9]. Prognosis of PTLD is highly variable, and there are no good prognostic markers to guide risk-adapted therapy. Frontline treatment of CD20+ PTLD is well established [10, 11]. However, there is a lack of data on other PTLD subgroups and on the treatment of relapsed and refractory (R/R) PTLDs, especially in the era of novel therapies for diffuse large B-cell lymphoma (DLBCL) [12]. Optimal treatment is unclear [13–15]. Some organ recipients may be too fragile for chemotherapy. However, reduction of immunosuppression can be effective for selected patients, although it carries a risk of transplant rejection [16].

A better understanding of the risk and prognostic factors of PTLD is needed, as the survival of solid organ transplantation (SOT) recipients has improved over time, and the number of SOT recipients has increased over the last decades. Real-world data can provide important insights, given the limited feasibility of prospective studies in extremely rare diseases like PTLD [10, 11, 16–18]. The aim of this population-based study was to characterize demographic features and outcomes in relation to host- and tumor-specific factors and to evaluate whether PTLD prognosis has improved over a 30-year period.

2 | Materials and Methods

2.1 | Study Cohort

This nationwide retrospective study identified patients diagnosed with PTLD after SOT primarily from the registry of transplant center, and by combining data with the Finnish Cancer Registry [19, 20]. Total of 6555 first SOTs (including 7.5% childhood SOTs) were performed in Finland at the Helsinki University Hospital, the only transplant center in the country, between January 1, 1987, and December 31, 2016 [21]. All 215 patients with PTLD (14% after childhood SOTs) diagnosed before December 31, 2017, were included. The median follow-up time after transplantation was 8.9 years for all SOT recipients, 9.6 years for kidney recipients ($n = 4514$), 8.3 years for heart ($n = 599$), 8.1 years for liver ($n = 1078$), 4.5 years for lung ($n = 280$), 4.3 years for intestine ($n = 7$), and 2.9 years for pancreas–kidney recipients ($n = 77$). All PTLD subtypes were included, following the latest WHO classification (WHO HAEM5, 2022) [22]. Follow-up for the PTLD study cohort ended on April 26, 2024.

Detailed clinical data, including laboratory test results, treatments, responses, and outcomes, were collected from patient records at hospitals where patients were followed up after transplantation. For nine PTLD patients (including four diagnosed at autopsy), only registry data were available. Performance status according to the Eastern Cooperative Oncology Group (ECOG), staging according to the Ann Arbor, and the International Prognostic Index (IPI) were registered retrospectively, when possible, if not documented in the medical records.

The association of EBV with PTLD was determined based on the detection of EBV-encoded RNAs (EBER) by in situ hybridization, the presence of Latent Membrane Protein 1 (LMP-1) in biopsy samples, or the detection of EBV nucleic acid in blood.

The original histological tissue samples were re-evaluated for pathological diagnoses by a specialized hematopathologist. If re-evaluation of the original tissue sample was not possible (40%), the original pathology report was re-analyzed. PTLD was classified according to the 2017 World Health Organization's Classification of Tumors of Hematopoietic and Lymphoid Tissues.

2.2 | Statistical Analysis

Cumulative incidence (CI) was calculated as the proportion of all organ recipients who developed PTLD during the follow-up period after transplantation. The incidence rate was computed as the number of PTLD cases divided by the total person-time at risk (cases per 100,000 person-years), accounting for varying lengths of follow-up after transplantation.

Follow-up time for the PTLD patients was measured from the day of the diagnostic tissue sample to the date of death, loss to follow-up, or the last recorded contact, whichever occurred first.

The Kaplan-Meier method was used to estimate survival times. Overall survival (OS) was defined as the time from the date of PTLD diagnosis until death from any cause. Disease-specific survival (DSS) was defined as the time from diagnosis to death attributable to PTLD. Patients who were alive at the end of follow-up were censored for OS and DSS, as were patients with death unrelated to PTLD for DSS. Three patients were censored due to loss to follow-up. Survival times were calculated for all patients and for patients intended to be treated curatively.

The univariable and multivariable analyses of prognostic factors for DSS were performed using Cox proportional hazards regression. The log rank test was used for survival comparisons. A p-value of less than 0.05 was considered statistically significant. The statistical analyses were conducted by SPSS version 29.0 (SPSS Inc., Chicago Illinois, USA), and with R version 4.4.1. (R Core Team).

3 | Results

3.1 | Incidence

Altogether, 215 (3.4%) SOT recipients developed PTLD in 66,771 person-years after transplantation. PTLD incidence was 322 per 100,000 person-years. Median time after SOT to PTLD was 7.8 (interquartile range [IQR] 2.5–13.2) years. The cumulative incidence was highest among thoracic organ (heart 7.9% and lung 6.6% in 20 years) and small intestine recipients (2 PTLDs among 7 recipients), and lowest among kidney and liver recipients (2.4% and 3.5% in 20 years, respectively). Early PTLDs (< 1 year after SOT) accounted for 15% ($n = 32$) of the cases and very late PTLDs (> 10 years) for 39% ($n = 83$) (Table 1 and S1).

TABLE 1 | Characteristics of the study cohort.

Characteristics	PTLD patients, *N* (%) or median years (range)
Gender of PTLD patients	215 (100.0)
Female	60 (27.9)
Male	155 (72.1)
Age at SOT, PTLD patients	47.9 (0.6–74.1)
Female	41.8 (1.1–68.2)
Male	48.9 (0.6–74.1)
< 18 years	31 (14.4)
> 18 years	184 (86.6)
≥ 60 years	35 (16.3)
Transplant type, PTLDs (all SOTs, $n = 6555$)	215 (100.0)
Kidney, incl. 2 re-Tx with liver ($n = 4514$)	116 (54.0)
Heart ($n = 599$)	43 (20.0)
Liver, incl. 1 liver-kidney ($n = 1078$)	37 (17.2)
Lung, incl. 2 heart-lung blocks ($n = 280$)	17 (7.9)
Pancreas-kidney ($n = 77$)	0 (0.0)
Small intestine ($n = 7$)	2 (0.9)
Calendar year of transplantation, all SOTs	
1987–1999 ($n = 2374$)	113 (52.6)
2000–2016 ($n = 4181$)	102 (47.4)
Calendar year of PTLD diagnosis	
1988–2002	43 (20.0)
2003–2017	172 (80.0)
Time from SOT to PTLD diagnosis	7.8 (0.1–27.5)
During the 1st year after SOT	32 (14.9)
1–5 years after SOT	46 (21.4)
> 5 years after SOT	137 (63.7)
> 10 years after SOT	83 (38.6)
Follow-up after SOT[a], PTLD patients	13.1 (0.3–35.8)
Deceased at the end of follow-up ($n = 165$)[b]	11.4 (0.3–33.7)
Alive at the end of follow-up ($n = 50$)	21.2 (8.8–35.8)
Other malignancies, PTLD patients	
Pre-transplant[c]	8 (3.7)
Post-transplant before PTLD[d]	34 (15.8)
Post-transplant after PTLD	24 (11.1)
NMSC only after PTLD	8
Solid tumor	15
Myelodysplastic syndrome	1
Died of other malignancy after PTLD	7 (3.3)
Immunosuppressive regimen	
Corticosteroids	215 (100)
Cyclosporine A	196 (91.1)
Azathioprine	135 (62.8)
Mycophenolate mofetil	80 (37.2)

(Continues)

TABLE 1 | (Continued)

Characteristics	PTLD patients, *N* (%) or median years (range)
Tacrolimus	38 (17.7)
Anti CD-3	0 (0.0)
mTOR inhibitors (sirolimus, everolimus)	3 (1.4)
IL2-receptor antibody (basiliximab/daclizumab)	17 (7.9)
Antithymocyte globulin (ATG)[e]	51 (23.7)
Rejection episodes, PTLD patients	
Acute or chronic before PTLD	72 (33.4)
Acute or chronic after PTLD	25 (11.6)
Graft failure, PTLD patients	
Ever	50
Before PTLD	18
After PTLD	32
Retransplantation	18
Before PTLD	11
After PTLD	8
Kidney donor type, living (all, $n = 253$)	8 (6.9)
Autoimmune disease, any	70 (34.0)

Abbreviations: CI, confidential interval; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NMSC, non-melanoma skin cancer; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation; Tx, transplantation.
[a]From the first solid organ transplantation to death or last clinical control, study period for PTLDs ended April 26, 2024.
[b]45% (96/215) died during the first and 60% (128/215) during 5 years.
[c]NHL 25 years pre kidney Tx, NHL 6.5 years pre liver Tx, HL 16 years pre heart Tx, HL relapse 28 years pre heart Tx, kidney ca 5 years pre kidney Tx, cervix ca 6 years pre heart Tx, cholangio ca in explanted liver and HCC in explanted liver.
[d]21 NMCSs only, 2 melanomas, 2 lip, 2 kidney, 1 bladder, 1 lung, 1 prostata, 1 sigma, and 1 tongue cancers, 1 Kaposi sarcoma and 1 polycytaemia vera.
[e]40 heart, 6 lung, 3 kidney, 2 liver transplantations; early onset (< 1v) PTLDs 6% (3/51).

3.2 | Characteristics of the PTLD Patients

The median age of patients at the time of PTLD diagnosis was 55 (IQR 40–66) years, and 72% of cases were males. Immunosuppressive medications included mainly cyclosporine (91%), azathioprine (63%), mycophenolate mofetil (37%), and tacrolimus (19%) in addition to corticosteroids. Induction therapy with antithymocyte globulin at the time of SOT was given to 24% of PTLD patients (78% heart transplant recipients). History of pretransplant cancer was recorded in 3.7%, autoimmune disease in 34%, and graft rejection (acute or chronic) in 33% of the patients before the diagnosis of PTLD (Table 1).

3.3 | Histological Subtypes and Characteristics of PTLDs

PTLD subtypes were distributed as follows: 80% were monomorphic (M-PTLD, including 68% aggressive B cell, 7% plasma cell, and 6% T-cell lymphomas), 6% polymorphic, 2% classical Hodgkin lymphoma, and 2% nondestructive PTLDs. In addition, 11 cases were indolent B-cell lymphomas (5%) and 10 unspecified non-Hodgkin lymphomas (5%). EBV positivity was detected in all early-onset PTLDs and in 60% of all cases analyzed ($n = 148$) (Table 2).

The histological subtype varied highly according to the onset of PTLD. Polymorphic PTLDs appeared earliest with a median time of 1.4 years after transplantation, followed by Burkitt lymphomas (3.4 years), DLBCLs (8.8 years), and indolent B-cell lymphomas (12.3 years).

Ann Arbor stage III - IV disease was observed in 59% of patients, including bone marrow (14%), liver (15%), or central nervous system (7%) involvement. Altogether, extranodal involvement was common, occurring in 82% of all PTLD cases. The allograft was involved in 14% ($n = 30$) of the cases, of which 60% were diagnosed within the first year after transplantation.

3.4 | Differences in PTLDs Among SOT Groups

The proportion of M-PTLDs was highest in the heart (93%) and lowest in the lung (77%) recipients (Table S2A). EBV association and early onset of PTLD along with allograft involvement were more frequent among intestine, lung, and liver recipients, as compared with heart and kidney recipients, who, in contrast, presented more often with bone marrow involvement. IPI scores were similar between the SOT subgroups. (Table S2B).

3.5 | Overall Outcomes

3.5.1 | Follow-Up, Early Mortality, and Survival

The median follow-up time after PTLD diagnosis was 1.7 years (IQR 0.2–9.4). Patients who were alive at the end of follow-up

TABLE 2 | Distribution of PTLD subtypes with outcomes. The table shows differences in onset of PTLD, age at diagnosis, association with Ebstein-Barr virus, and proportion of treated patients between PTLD subtypes.

PTLD characteristics and outcome in subtypes	All *n* (%)	Time to PTLD, median years (interquartile range, IQR)	Age at PTLD diagnosis, median years (range)	EBV + *n* (% of analyzed)[a]	Treatment for PTLD, ever *n* (%)	Treatment related deaths *n* (% of treated)	PTLD related deaths *n* (% of subgroup)	Follow-up post PTLD, median years (IQR)[b]	K-M estimate for median OS, years (IQR)	2 years OS rate	5 years OS rate
Subtypes, all	**215 (100)**	**7.8 (2.5–13.2)**	**55 (0–86)**	**89 (60)**	**180 (84)**	**43 (24)**	**119 (55)**	**1.7 (0.2–9.4)**	**1.7 (0.8–11.8)**	48%	40%
Nondestructive (early lesion) PTLD	4 (1.9)	9.2 (2.6–12.9)	41 (9–60)	3 (75)	3 (75)	0	0	13.8 (8.8–19.7)	NR	100%	100%
Polymorphic PTLD	**12 (5.6)**	**1.4 (0.4–6.8)**	**24 (6–71)**	**11 (92)**	**11 (92)**	**4 (36)**	**6 (50)**	**4.3 (0.4–13.0)**	**1.0 (0.3–12.2)**	50%	50%
Monomorphic PTLD (indolent lymphomas excluded)	**173 (80)**	**8.3 (2.6–13.5)**	57 (0–86)	69 (58)	148 (86)	37 (25)	37 (22)	**1.5 (0.2–8.5)**	**1.5 (0.2–10.3)**	46%	36%
Aggressive large B-cell lymphomas (PT-ABCL)	**146 (68)**	**8.2 (2.2–13.8)**	**57 (40–67)**	**63 (59)**	**129 (88)**	**33 (26)**	**84 (58)**	**1.4 (0.2–8.7)**	**1.3 (0.2–11.7)**	45%	38%
Diffuse large B-cell lymphoma (DLBCL)	132 (61)	8.8 (2.5–13.9)	58 (0–86)	56 (57)	116 (88)	29 (25)	69 (58)	1.5 (0.2–8.4)	1.0 (0.2–9.6)	43%	36%
Germinal center type	22/65 (34)	11.8 (4.3–14.8)	60 (16–86)	9 (45)	na	na	na	5.6 (0.5–10.6)	5.0 (0.6–10.3)	59%	55%
Non-germinal center type	43/65 (66)	9.5 (1.3–15.5)	61 (16–77)	20 (56)	na	na	na	1.3 (0.3–7.7)	1.3 (0.3–8.8)	49%	37%
Primary CNS lymphoma (PCNSL)[c]	14	9.8 (1.9–11.9)	62 (14–77)	7 (88)	9 (64)	2 (22)	9 (64)	0.4 (0.1–4.1)	0.2 (0.1–1.8)	21%	21%
Burkitt lymphoma/ Burkitt cell leukemia	10	3.4 (2.5–4.9)	44 (16–57)	6 (75)	10 (100)	2 (20)	3 (30)	10.7 (2.8–13.6)	11.2 (3.6–13.3)	80%	70%
Aggressive B-cell lymphoma, other[d]	3	na	na	1	3	0	3 (100)	na	na		

(Continues)

TABLE 2 | (Continued)

PTLD characteristics and outcome in subtypes	All *n* (%)	Time to PTLD, median years (interquartile range, IQR)	Age at PTLD diagnosis, median years (range)	EBV + *n* (% of analyzed)[a]	Treatment for PTLD, ever *n* (%)	Treatment related deaths *n* (% of treated)	PTLD related deaths *n* (% of subgroup)	Follow-up post PTLD, median years (IQR)[b]	K-M estimate for median OS, years (IQR)	2 years OS rate	5 years OS rate
T/NK-cell lymphoma type PTLD	**12 (5.6)**	**6.7 (3.4–18.2)**	52 (36–73)	**5 (50)**	**9 (75)**	2 (22)	**9 (75)**	**0.7 (0.2–5.8)**	**0.5 (0.1–1.6)**	25%	25%
Anaplastic large cell lymphoma	4 (1.9)										
Peripheral T-cell lymphoma, unspecified	4 (1.9)										
Primary cutaneous CD30+ ALK negative lymphoma	2 (0.9)										
Hepatospenic gamma delta T-cell lymphoma	1(0.5)										
T-cell lymphoma, unspecified	1(0.5)										
Plasma cell type PTLD	**15 (7.0)**	**9.5 (1.1–13.8)**	54 (23–65)	1	**10 (67)**	2 (20)	**7 (47)**	**3.3 (0.5–6.6)**	**3.3 (0.4–6.6)**	67%	33%
Plasma cell myeloma, bone marrow involvement	10										
Extramedullary plasmacytoma	5										
Classical hodgkin lymphoma type PTLD	**5 (2.3)**	**6.3 (4.5–11.8)**	24 (11–53)	**3 (100)**	**5 (100)**	2 (40)	**2 (40)**	**6.6 (0.5–16.0)**	**6.6 (0.8–15.3)**	60%	60%
Indolent B-cell lymphomas	**11 (5.1)**	**12.3 (8.6–13.9)**	57 (46–75)	**1 (14)**	**11 (100)**	0	**2 (18)**	**10.3 (7.2–13.0)**	**12.7 (7.1–16.1)**	100%	91%

(Continues)

TABLE 2 | (Continued)

PTLD characteristics and outcome in subtypes	All *n* (%)	Time to PTLD, median years (interquartile range, IQR)	Age at PTLD diagnosis, median years (range)	EBV + *n* (% of analyzed)[a]	Treatment for PTLD, ever *n* (%)	Treatment related deaths *n* (% of treated)	PTLD related deaths *n* (% of subgroup)	Follow-up post PTLD, median years (IQR)[b]	K-M estimate for median OS, years (IQR)	2 years OS rate	5 years OS rate
NHL, unspecified[e]	10 (4.7)	5.4 (2.3–6.5)	53 (48–66)	2	2	na	9 (90)	0.1 (0.0–1.5)	na	10%	10%
Early/late PTLD											
Onset < 1 year post transplant	32 (15)			**29 (100)**				**1.5 (0.2–10.3)**	1.5 (0.2–12.8)		
Onset > 1 year post transplant	183 (85)			**60 (50)**				**1.8 (0.2–9.4)**	1.8 (0.2–11.8)		
Onset > 10 years post transplant	83 (39)			**21 (40)**				**1.5 (0.4–8.4)**	1.6 (0.4–11.6)		

Note: The bold values indicate when the result is intended to be highlighted.
[a]Eber in situ hybridization or LMP-1 positive in 74 of 139 analyzed PTLD samples. If negative or not analyzed, but Epstein-Barr viremia in blood detected (15 patients [analyzed in 120 PTLD patients]), PTLD was cathegorized as EBV associated (EBV+). Analysis available from Dec 1999 on in Helsinki (HUSLab).
[b]real follow-up times for all; median follow-up time was 11.5 (IQR 8.6–14.5) years for the patients alive at the end of the study follow-up.
[c]includes 13 DLBCLs and one CNS PTLD with B cell lymphoma diagnosis in neuropathological autopsy.
[d]mediastinal B cell lymphoma, intestinal B cell lymphoma and B cell lymphoma diagnosed from cervical lymph node (stage III, official cause of death DLBCL).
[e]8 with diagnosis of non- Hodgkin lymphoma, unspecified (4 without the treatment data). Two not biopsy proven, both died for PTLD.

were observed for at least 6.2 years and median 11.5 (IQR 8.6–14.5) years. Figure 1 illustrates patient survival, PTLD relapses, and causes of death at different time points throughout the follow-up.

Early mortality was relatively high, as 60 patients (28%) died within 100 days after PTLD diagnosis, and 33 of them within the first 30 days. However, a decreasing trend in the 100-day mortality rate was observed over recent years (26% during 2003–2017, compared with 37% during 1988–2002, $p = 0.133$). Early deaths were related to progressive disease ($n = 51$) and/or complications related to PTLD treatment (23 infections, 3 intestinal perforations or strangulations, 1 bleeding complication, and 1 hemolytic uremic syndrome).

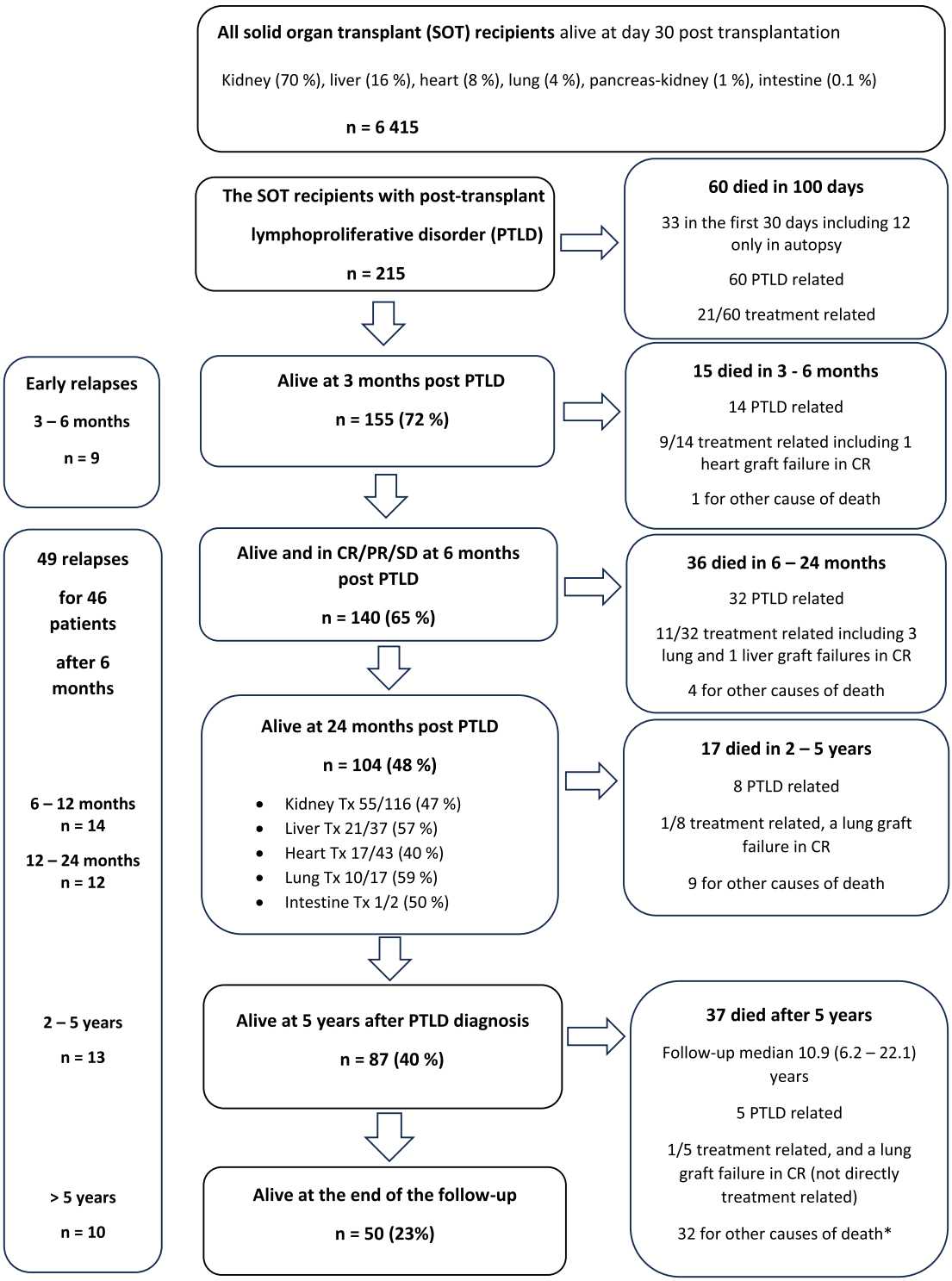

FIGURE 1 | Flowchart of the study cohort. The flowchart shows patient survival, PTLD relapses, and causes of death at different time points throughout the follow-up. *Causes of death after 5 years were (number of patients): cardiac and vascular complications (14), infections (8), PTLD (5), non-PTLD malignancies (4), pulmonary complications (2), degenerative brain disease (1), diabetic ketoacidosis (1), and undefined (2).

The 1-year, 2-year, and 5-year OS rates were 55%, 48% and 40%, respectively, for all patients (n = 215), whereas for patients treated with curative intent (n = 165), the OS rates were 68%, 61% and 52%, respectively. Additionally, DSS rates differed from OS by only 2%–3% during the first 5 years (Figure 2).

A temporal trend toward a longer median OS was detected for patients diagnosed in more recent years, 2003–2017 (2.4 years, n = 172), compared with earlier years, 1988–2002 (0.4 years, n = 43; p = 0.072). However, DSS had improved from median of 0.4–5.0 years (p = 0.011), despite older age at PTLD diagnoses in the later years (median age 57 compared with 49 years, p = 0.008).

3.5.2 | Patient-Related Factors and Outcome

Good performance status (ECOG 0–1), younger age (as a continuous variable and < 45 years), normal lactate dehydrogenase level, and lower IPI were associated with favorable outcome. Outcomes were not significantly associated with EBV positivity, presence of autoimmune disease, or the interval from transplantation to PTLD diagnosis.

M-PTLD, male gender, B symptoms, and heart transplant showed inferior prognostic value for DSS in univariable, but not in multivariable analysis (Table S3).

The least favorable OS was observed among heart recipients, while the most favorable OS was among liver recipients (median OS of 0.8 and 7.2 years, respectively), but the difference was not statistically significant, p = 0.52 (Figure S1).

3.6 | Treatment and Response

3.6.1 | Firstline Therapy

PTLD-specific treatment was initiated in 176 patients (82%), with curative intent in 91% of cases (Table 3 and Figure S2). Altogether, 143 patients received rituximab (R) and/or chemotherapy (combination in 63%). Twenty-five patients were treated with localized therapy (surgery/radiotherapy), and eight with only reduction of immunosuppression (RIS). Overall response (ORR) and complete response (CR) rates after first line therapy were 85% and 68% for the patients treated with a curative intent (RIS in 75%; no prognostic difference with or without RIS, data not shown), and 87% and 74% for the patients treated with a combination of rituximab and chemotherapy. The OS estimate was a median of 6.3 years for the patients treated with rituximab-based first-line treatments (19% received only rituximab) (Table 3 and Table S4).

No benefit in outcome was seen in patients with CD20-positive M-PTLDs and polymorphic PTLDs treated first with rituximab monotherapy (n = 26) compared with the combination of rituximab and chemotherapy (R-chemo; n = 77). There were more polymorphic, EBV-associated, and earlier PTLDs in the monotherapy group as compared with the R-chemo group. The

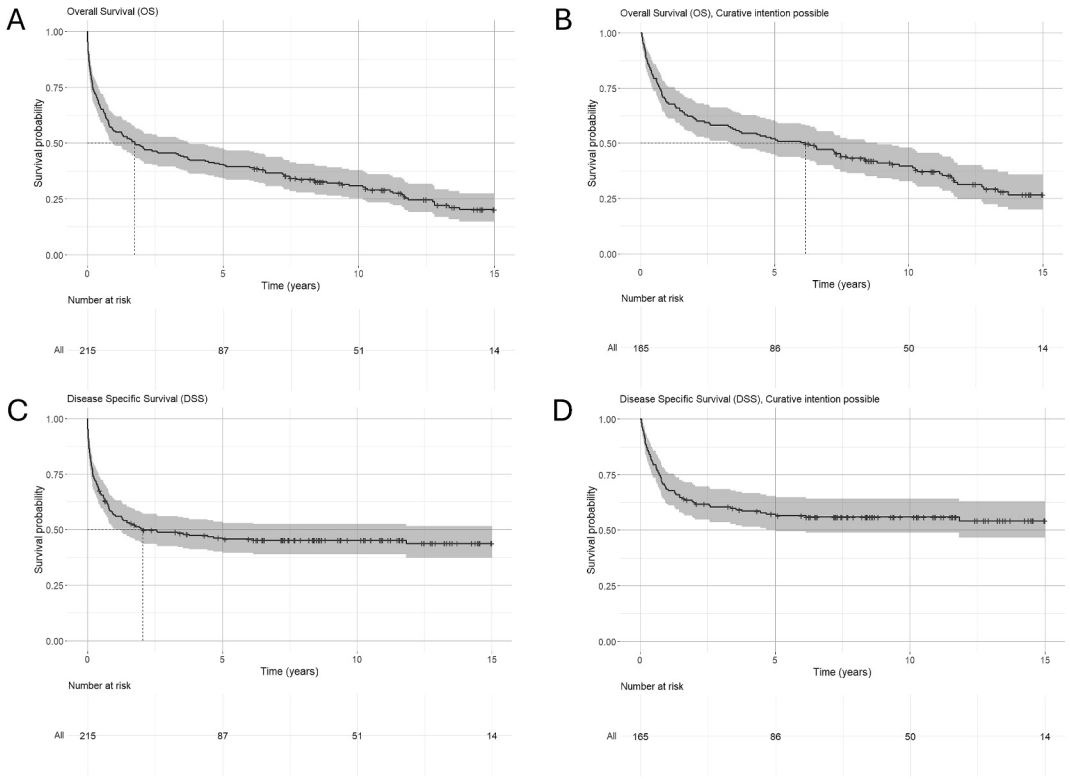

FIGURE 2 | Kaplan-Meier survival curves demonstrate differences between median overall survival (OS) and disease specific survival (DSS) with 95% confidential intervals (CI). For all 215 PTLD patients, median OS was 1.7 (0.3–3.2) years (A), and DSS was 2.0 (0.0–8.3) years (C). For the 165 PTLD patients treated with curative intention, median OS was 6.1 (3.4–8.8) years (B), and DSS was 16.1 (5.5–26.7) years (D).

TABLE 3 | PTLD treatments with outcomes. Reduction of immunosuppression (RIS) was combined with 75% of curative intention treatments. No difference in survival was observed between the groups with RIS and without RIS, data not shown.

Initial therapy	All PTLDs, number	Aggressive B cell lymphomas	Curative intention	RIS in combination therapy	ORR/CR number of patients	Deceased in 100 days	All PTLDs median OS, years (95% CI)	3 years OS rate	5 years OS rate	5 years DSS rate
All treatments in first line	176	128	160	134	142/109	32	3.6 (0.7–6.5)			
Curative intention (watch and wait included)	**165**	**116**	**165**	**124**	**141/112**	**23**	**6.1 (3.4–8.9)**	**58%**	**52%**	**58%**
Rituximab (R), total	**111**	**92**	**110**	**94**	**95/77**	**14**	**6.3 (2.3–10.3)**	**58%**	**53%**	**60%**
Sequential therapy starting with R mono	31	18	30	na	16/10	7	1.6 (0.7–2.4)			
Monotherapy	21	11	20	na	14/10	5	1.7 (0.8–2.7)	43%	43%	52%
With surgery	3	2	3	na	3/1	na	na			
Chemotherapy, total	**122**	**100**	**121**	**97**	**104/85**	**18**	**4.9 (1.7–8.0)**	**57%**	**50%**	**53%**
CHOP[a] or EPOCH like	94	82	94	na	79/65	12	4.6 (0.2–8.7)	54%	48%	46%
CHOP[a]	57	48	57	na	49/42	5	7.3 (3.2–11.3)	63%	56%	
CHOEP or DA-EPOCH	23	22	23	na	18/17	4	3.4 (0.0–7.2)	52%	43%	
Chemo with rituximab	**90**	**81**	**90**	**75**	**78/67**	**9**	**6.0 (2.3–9.6)**	**61%**	**54%**	**61%**
Chemo without rituximab	32	19	31	na	25/17	9	na			
With surgery	17	16	17	na	17/16	na	na			
With radiotherapy	22	17	21	na	17/14	na	na			
Surgery, total	**31**	**24**	**27**	**21**	**28/24**	**4**	**10.2 (4.5–16.0)**	**71%**	**65%**	**71%**
Alone	7	4	6	na	5/5	2	na			
With radiotherapy	3	2	1	na	3/2	na	na			
Radiotherapy (adjuvant not included)	18	8	10	5	15/8	2	0.78 (0.0–3.09)	39%	28%	50%
Alone	15	6	8	na	12/6	2	na			
Reduction of immunosuppression (RIS) alone	8	5	3	8	3/2	5	na			
Watch and wait (4 spontaneus remissions)	8	0	5	0	4/4	1	na			

(Continues)

TABLE 3 | (Continued)

Initial therapy	All PTLDs, number	Aggressive B cell lymphomas	Curative intention	RIS in combination therapy	ORR/CR number of patients	Deceased in 100 days	All PTLDs median OS, years (95% CI)	3 years OS rate	5 years OS rate	5 years DSS rate
Total (first line)	**184**	**128**	**165**	**134**	**146/113**	**33**	**3.7 (0.9–6.4)**	**53%**	**47%**	**54%**
Palliative corticosteroid only	22	17	0	na	0	22	na	0%	0%	
No treatment data[b]	9	0	na	na	na	6	na	11%	11%	
Second or further line therapy	56	33	55	na	23[c]	0	3.8 (0.0–7.9)	55%	48%	
Chemotherapy in second line	40	23	39	na	19[c]	0	3.3 (0.1–6.6)	55%	45%	
ASCT[d]	9	5	9	6	9/6	0	3.8 (2.3–5.2)	67%	44%	56%
Complete remission (best response)	**120**	**84**	**119**	**92**	**120/120**	**1**	**11.2 (8.8–13.5)**	**79%**	**71%**	**79%**
TOTAL	215	146	165	134	151/120	60	1.7 (0.3–3.2)	46%	40%	45%

Note: The bold values indicate when the result is intended to be highlighted.

Abbreviations: ASCT, autologous stem cell transplantation; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone; CR, complete response; DA-EPOCH, dose adjusted, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DSS, disease spesific survival; na, not analyzed; ORR, overall response rate; OS, overall survival; RIS, reduction of immunosuppression.

[a]CHOP or CHOP like (cyclophosphamide and doxorubicin containing) regimen.

[b]Finnish Cancer Registry data only (n = 9): diagnosed in autopsy (n = 4), neuropatholocical autopsy report available (n = 1).

[c]overall response for second line treatment.

[d]1 heart, 1 liver, and 7 kidney recipients (between 2003 and 2018).

distribution of age, IPI and performance status were balanced between the groups (Table S5).

3.6.2 | Relapses

In total, 55 patients experienced PTLD recurrence after achieving a response to first-line treatment, with a median time of 1.5 years (IQR 0.6–3.2) after the initial PTLD diagnosis. Among patients who survived longer than 1 year after PTLD diagnosis, 26% developed a subsequent PTLD. Altogether, 14 relapses were different PTLD subtypes from the original one. Ten of all 55 relapses (18%) occurred later than five years after the first PTLD. Altogether 31% of all PTLD related deaths were due to relapses (Table 4, Figure 1).

3.6.3 | Second-Line and Subsequent Therapies

In total, 56 patients received second-line treatment for refractory ($n = 20$) or relapsed ($n = 36$) disease. Altogether 40 patients received chemotherapy, and salvage therapy of 10 patients contained high- or intermediate-dose methotrexate. For five patients with DLBCL and four patients with plasma cell PTLD, autologous stem cell transplantation (ASCT) was given as consolidation therapy with a 67% CR rate. The 5-year survival rates for all patients with second line treatments and after ASCT were 48% and 44%, respectively.

3.7 | Outcomes According to the Histological Subtype

Outcomes differed by histological subtype and site of PTLD. Primary CNS PTLDs (all PT-ABCLs) and T-cell lymphomas were associated with the poorest outcome (median OS 0.2 and 0.5 years, $p = 0.002$), and nondestructive PTLD and indolent B cell lymphomas with the most favorable outcome (Table 2).

3.7.1 | DLBCL and Other Aggressive B-Cell Lymphoma Type PTLDs (PT-ABCLs)

A total of 128 patients (88%) with PT-ABCLs started treatments, 81 patients (63%) received chemotherapy with rituximab (R) (ORR 88%/CR 75%), 19 patients (15%) only chemotherapy (ORR 74%/CR 53%), and 11 patients (11%) R-monotherapy (ORR 75%/CR 45%). Operation and/or radiation therapy alone were administered to 8% (ORR 67%/CR 25%). The median OS was 9.4 years (95% CI 5.9–12.8) for those who achieved CR after first-line treatments ($n = 81$), with a 5-year DSS rate of 78%.

All 10 patients with Burkitt lymphoma were treatment eligible. Seven of them had durable responses (R-DA-EPOCH (3), R-CVAD + MTX + ARA-C, BFM with rituximab, Magrath (2), combined with it MTX, and adjuvant radiotherapy), whereas one patient died due to early CNS relapse (after six cycles of R-CHOP), and two due to transplant rejections (heart and lung recipients) in CR (after RIS and R-cyclophosphamide or chemotherapy before rituximab era).

Only five of the 14 patients with primary CNS PTLD were eligible for curative intended treatment, four patients received palliative brain irradiation whereas five died early without any treatment. Two patients received rituximab and temozolomide. Three patients received combination chemotherapy with rituximab according to CNS treatment protocols, two with high dose methotrexate. Three patients achieved CR. Treatment was discontinued in two patients due to complications.

3.7.2 | Other M-PTLD Subtypes

Plasma cell type PTLDs accounted for 7% ($n = 15$; five local extramedullary diseases) of all PTLDs. Six patients (40%) achieved CR, but three of them relapsed, one presented later with DLBCL, and another with T-cell lymphoma. The median OS was 3.3 years.

T-cell type PTLDs were rare ($n = 12$, 6%) and associated with a very poor outcome as 75% of patients died from lymphoma with median OS of 0.5 years. Of note, one of the patients relapsed with nodular lymphocyte predominant Hodgkin lymphoma (after 1.8 years of remission).

3.7.3 | Non-Aggressive Subtypes

Indolent CD20-positive B-cell lymphomas (36% also CD38/138+) were diagnosed in 11 patients, mostly as a localized disease (73%). Along with local therapy (radiotherapy/surgery), three patients were treated with R-monotherapy and two with R-CHOP. Transformation to DLBCL occurred in four patients: 2.8 years after diagnosis of follicular lymphoma and 3.4–10.0 years after MALT lymphoma. Median OS for all was 12.7 years.

Polymorphic PTLDs were diagnosed in 12 patients, of which 83% were CD20 positive. Nine patients started with R-monotherapy, and 4 later received R-CHOP (3) or DA-EPOCH-R (1) at disease progression. One patient received CHOP (before the rituximab era). Altogether, 58% of the polymorphic PTLDs progressed to lymphomas: DLBCL ($n = 5$), T-cell lymphoma ($n = 1$), and MALT ($n = 1$) (Table 4). CR was achieved in 50% of the patients, whereas others died due to aggressive lymphoma progression.

4 | Discussion

This large, nationwide, population-based cohort describes the demographic features and prognosis of PTLD after SOTs over a 30-year period. Cumulative incidence was highest among thoracic (7.6%) and lowest among kidney (2.5%) SOTs. Median onset was 7.8 years after SOT. The median OS was only 1.7 years with a high (28%) 100-day mortality in line with Spanish renal and Swedish all SOT cohorts [1, 23]. The clinical outcome was favorable in 56% of patients who achieved CR, with median OS of 11.2 years. The 5-year OS rate after rituximab-based treatments was 53%, in line with other large cohorts [1, 18, 23–25].

TABLE 4 | PTLD relapses with histological subtypes.

PTLD subtypes	PTLD patients, number	Survival < 100 days[a]	Relapse patients, number	All progressions, relapses or transformations	Early relapses (< 1 year from dg or < 1 year after ASCT)	Later relapses, number of patients/number at risk (alive > 1 year)	Late relapses (1–5 years from dg)	Very late relapses (> 5 years)	Relapse related deaths
Nondestructive	4	0	1	1 DLBCL	0	1/4	1 DLBCL	0	0
Polymorphic	12	2	5	5 DLBCL[b], 1 T cell, 1 indolent, 1 non-destructive	1 DLBCL, 1 CNS, 1 T cell, 1 indolent	1/7	1 nondestructive	0	3
Monomorphic DLBCL[c]	122	37	27	25 DLBCL, 1 PEL, 1 polymorphic	13 DLBCL	14/63	9 DLBCL, 1 CNS relapse, 1 polymorphic	2 DLBCL, 1 PEL	21
Monomorphic PCNSL	14	7	1	1 CNS relapse	1 CNS relapse	0/4	0	0	1
Monomorphic burkitt	10	0	1	1 CNS relapse	1 CNS relapse	0/8	0	0	1
Monomorphic plasma cell	15	3	5	3 plasma cell, 1 DLBCL, 1 ALCL	0	5/11	3 plasma cell, 1 DLBCL	1 ALCL	3
Monomorphic T-cell	12	3	4	3 T-cell, 1 NLPHL	3 T-cell	1/5	1 NLPHL	0	3
Indolent B cell lymphomas	11	0	8	4 DLBCL, 7 indolent	0	8/11	2 DLBCL, 3 indolent	2 DLBCL, 4 indolent	2
Classical hodgkin lymphoma	5	1	1	1 DLBCL	1 DLBCL	0/3	0	0	1
NHL, unclassifiable	8	6	1	1 NHL	1 NHL	0/2	0	0	1
PTLD nos (no PAD)	2	1	1	1 PTLD nos	0	1/1	1 PTLD nos	0	1
All PTLDs	215	60	55			31/119			
All relapses[d]	55	0	**55**	61[b]	**24**	**31**	24	10	37

(Continues)

TABLE 4 | (Continued)

PTLD subtypes	PTLD patients, number	Survival < 100 days[a]	Relapse patients, number	All progressions, relapses or transformations	Early relapses (< 1 year from dg or < 1 year after ASCT)	Later relapses, number of patients/number at risk (alive > 1 year)	Late relapses (1–5 years from dg)	Very late relapses (> 5 years)	Relapse related deaths
Median time to relapse, years (IQR)				1.5 (0.6–3.2)	0.5 (0.4–0.8)	2.7 (1.7–6.8)			
Median OS after relapse, years (95% CI)				0.6 (0.1–1.1)	0.1 (0.0–0.4)	2.2 (0.2–4.2)			

Note: The bold values indicate when the result is intended to be highlighted.
Abbreviations: ALCL, anaplastic large cell lymphoma; ASCT, autologous stem cell transplantation; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PEL, primary effusion lymphoma.
[a]no relapses < 100 days.
[b]three polymorphic PTLDs progressed to DLBCL in 3 months, and 3 patients with multiple relapses.
[c]includes three other or unspecified aggressive B cell lymphomas.
[d]Relapses distributed as follows: 34 in kidney, 12 in heart, 8 in liver, and 1 in intestine recipients.

Relapses and late transformations to DLBCL occurred frequently affecting 36% of patients, even after 5 years from original PTLD, with high mortality (67%). Intensive chemotherapy followed by ASCT was a rare option for eligible R/R PTLD patients (six of total nine patients achieved CR), with high (22%) treatment related mortality as was shown also in EBMT analysis [26]. Overall, 55% died due to PTLD, but mortality was shown to be significantly (31%) lower in more recent years (2003–2017 compared with 1988–2002, $p = 0.013$), and DSS improved from median 0.4 years to 5.0 years ($p = 0.011$), in line with a Belgian and Australian study cohorts [27, 28].

However, although survival for rituximab-based treatments was comparable with other studies [18, 25, 29], we couldn't show superior outcome for rituximab monotherapy in first line. Similar findings have been observed in some other retrospective PTLD cohorts [1, 25, 29–31].

Prognostic factors for inferior DSS were poor performance status, high IPI, older age, elevated lactate dehydrogenase, and advanced Ann Arbor stage, in line with earlier reports [31–33]. The age limit of 45 years for the differences in outcomes was consistent with findings from the Swedish cohort [1], but lower than in some previous studies [24, 34]. In addition, an existing autoimmune disease, a known risk factor for developing lymphoma [35], was not prognostic for outcomes in PTLD.

Polymorphic PTLD warrants close attention, as aggressive progression was common. The 2-year OS in polymorphic PTLDs was only 50%, comparable to DLBCL, and lower than reported in most other cohorts [29, 31], but similar OS has been reported in a large SEER database cohort in US [34]. However, all patients with aggressive Burkitt lymphoma responded to chemotherapy, and only one patient had a relapse. The non-inferior outcomes among Burkitt lymphomas were found also in a pediatric PTLD cohort [36].

The usual limitations of retrospective studies apply to this study, as the data are based on administrative records from clinical practice. Therefore, some early PTLDs (diagnosed or treated only after suspicion of PTLD) may not be included. However, the strengths of this study include large nationwide population-based cohort, comprehensive data collection, and long follow-up after PTLD diagnosis.

We showed that relapse treatment results were poor, and better treatments are needed.

Several novel therapies have recently been approved for R/R DLBCL [12]. Novel therapeutic agents, which are recommended in recent PTLD guidelines like CAR-T cells, tabelecleucel [37], or daratumumab, were not available during the study period [13, 37, 38]. Brentuximab vedotin was used only for one patient for PTLD relapse [17].

5 | Conclusions

Our population-based, nationwide study demonstrated the aggressiveness of PTLD and treatment challenges in frail SOT patients. Rituximab in combination with chemotherapy was the

best treatment option for most of the patients. Late onset PTLDs and risk of relapses are increasing. PTLD must be considered even years after transplantation.

Author Contributions

T.K.F., S.L., R.R., and B.S. designed the study. T.K.F. collected the data, made the statistical analyses, and wrote the manuscript with assistance of R.R. and B.S., M.H. collected the data on lung transplant patients. The histopathological diagnoses were reviewed and confirmed by expert hematopathologists P.E.K. and S.V. All authors reviewed the results and the manuscript and contributed to improvement of the manuscript. All authors approved the final version of the manuscript.

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Ethics Statement

The study protocol was approved both by the Ethics Committee of the Helsinki University Hospital (194/13/03/00/16) and by the National Institution for Health and Welfare (THL/1001/5.05.00/2016) with an update considering the new legislation (FINLEX 552/2019) for secondary use of health and social data (Findata THL/2081/14.06.00/2022). Written informed consent was not obtained as patient consent is not a requirement in registry studies according to Finnish regulations. The study was performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Peer Review

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: hon70177-sup-0001-suppl-data.pdf.