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Incidence and outcomes of post-transplant lymphoproliferative disease after 5365 solid organ transplants over a 20 year period at 2 UK transplant centres

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Abstract

Post-transplant lymphoproliferative disease (PTLD) is a life-threatening complication of solid organ transplantation (SOT). We present the incidence and outcomes of PTLD in a cohort of 5365 SOT recipients over a 20-year period at two UK transplant centres. With a median follow-up of 7.7 years, 142 of 5365 patients have developed PTLD. Cumulative incidence was 18% at 5 years post-multivisceral transplant and 1-3% at 5 years following the other SOT types. 20-year cumulative incidence was 2-3% following liver and heart transplantation and 10% following kidney transplantation. Median overall survival (OS) following SOT was 16 years which is significantly reduced compared with the age-adjusted UK population. There is relatively high early mortality following diagnosis of PTLD and only patients surviving two years regained a longer-term survival approaching the non-PTLD SOT cohort. Of 90 patients with monomorphic PTLD, diffuse large B-cell lymphoma, 66 were treated with first-line Rituximab monotherapy and 24 received first-line R-Chemotherapy. Upfront Rituximab monotherapy does not appear to compromise OS, but the number of patients dying from non-lymphoma causes pre- and post-treatment remains high with both treatment approaches. Multivariate analysis of all 90 monomorphic PTLD patients identified IPI3+ as the strongest pre-treatment variable associating with inferior 1 year OS.

Introduction

Post-transplant lymphoproliferative disease (PTLD) is a complication of solid organ transplantation (SOT) that confers a high morbidity and mortality in a vulnerable population. PTLD is driven by immunosuppression and reactivation of Epstein-Barr virus (EBV); and incidence varies according to transplant type, age of recipient and type and duration of immunosuppression. Historically, PTLD has been known to have worse outcomes than other non-Hodgkin lymphoma subtypes in response to conventional chemotherapy. In recent years, treatment algorithms have changed based on the landmark PTLD-1 trial[(1)], and upfront anti-CD20 monoclonal antibody (Rituximab, R) is now used to treat the more common CD20-positive PTLD subtypes to reduce the treatment-related mortality (TRM) that is associated with conventional chemotherapy.

The incidence of PTLD has been previously described in cohort studies. A Collaborative Transplant Study Report, published in 2003, presented cumulative 10-year incidence of PTLD in a large multinational cohort of almost 200,000 SOT recipients transplanted between 1985 and 2001[(2)],

however this was before multivisceral transplantation (MVT, defined as transplant of intestines with or without simultaneous abdominal organs), and simultaneous pancreas-kidney (SPK) transplantation became established. A French registry study[3] and the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) [4] have presented cumulative incidence at 10 years and 25 years, respectively, but only in kidney and SPK recipients. A recent Swiss cohort study found a low 5-year cumulative incidence (0.96%) of PTLD in a variety of transplant types[5]. However, there has not been a real-world dataset to describe the cumulative incidence and outcomes of PTLD in a range of transplant types in the United Kingdom (UK). The Cambridge Biomedical Campus hosts the largest and the only comprehensive adult solid organ transplant programme in the UK. We set out to utilise this large SOT recipient dataset over a period of two decades to calculate the long-term incidence of PTLD in the diversity of transplant types at our institution (kidney, pancreas, liver, intestine and multi-organ transplants at Addenbrooke's Hospital and heart and lung transplants at Royal Papworth Hospital).

We have also examined PTLD outcomes over the same 20-year period during which first-line treatment with conventional chemotherapy was superseded by a risk-stratified approach based on the findings of the PTLD-1 trial[1]. This prospective Phase II trial demonstrated that using response to Rituximab induction to stratify subsequent treatment into Rituximab or R-CHOP consolidation is as effective as sequential treatment (Rituximab x4, then CHOP x4) in terms of overall response rate and 3-year OS[6]. The risk-stratified approach has become the standard of care in the front-line management of B-cell PTLD[7] and has been in use at our institution since 2009.

In the PTLD-1 trial where patients were treated with upfront Rituximab, TRM was reduced compared with previous retrospective studies of first-line CHOP chemotherapy[8]. A recent multicentre UK real-world study by Burns et al[9] compared outcomes in 101 patients with B-cell PTLD treated with upfront Rituximab monotherapy or R-CHOP chemotherapy. Among patients with high-risk PTLD (International Prognostic Index, IPI≥3), R-mono was associated with an inferior complete response rate compared with R-CHOP. However, there was no significant difference in progression-free survival (PFS) or OS between the R-mono and R-CHOP cohorts and no difference in non-PTLD and all-cause mortality. We have set out to perform a similar real-world comparison between frontline Rituximab versus R-Chemotherapy in patients with a single histological PLTD subtype (monomorphic PTLD, diffuse large B-cell lymphoma, DLBCL) and a wider range of transplanted organs.

Methods

Solid organ transplant recipient dataset

This is a retrospective study of 5365 SOT recipients who had their first transplant between 2000 and 2021 at two UK transplant centres (Addenbrooke's Hospital and Royal Papworth Hospital). We created this SOT patient dataset by searching the electronic medical records (EPIC) at Addenbrooke's Hospital and the transplant database at Royal Papworth Hospital to identify all patients who had their first transplant during this period. To find patients within this cohort who have since developed PTLD we used a pre-existing PTLD database[10], the Addenbrooke's Clinical Informatics Repository and we checked the medical records of all 5365 SOT recipients for a diagnosis of PTLD. In total we found 142 cases of PTLD, some of whom were treated in other centres. We documented

dates of SOT, age at first transplant, organ transplanted, date of PTLD diagnosis and date of last follow-up or death. Immunosuppression is included in Supplementary Table I.

Survival after SOT was compared with the age-adjusted life expectancy of the UK population using the National life tables. A landmark analysis was performed to compare overall survival (OS) of PTLD patients with the background survival of the SOT patient population.

PTLD patient dataset

In parallel we collated a separate PTLD dataset of 225 patients who had been diagnosed with PTLD at Addenbrooke's during the same period (2000-2021). The 142 PTLD patients from the SOT recipient dataset were included and the additional 83 PTLD patients were either transplanted at other centres, or had a transplant pre-2000, and included 20 patients who received haematopoietic stem cell transplants (HSCT). The diagnosis of PTLD was verified by assessment of tissue biopsies as reported by expert haematopathologists. Data were collected on recipient characteristics (sex, age at transplant, organ transplanted, age at PTLD diagnosis, Eastern Cooperative Oncology Group (ECOG) performance score), disease characteristics (histology, CD20 status, EBV association, Ann Arbor stage, lactate dehydrogenase, number of extranodal sites of disease, IPI, treatment regimens, response to treatment, date of death or last follow-up and cause of death. PTLD was classified according to the 2016 World Health Organisation's Classification of Tumours of Haematopoietic and Lymphoid Tissues[11] using the histopathology reports. Cases were considered to be EBV-associated if EBV-encoded small RNAs (EBER) in situ hybridisation was positive in the biopsy. 4 MVT patients had no biopsy but were treated empirically for PTLD and their disease was considered EBV-associated as they had an EBV viraemia. Disease staging was determined using the available clinical and radiological information, in accordance with the Ann Arbor staging system.

A subset of 90 patients with monomorphic PTLD, DLBCL, was used to compare survival outcomes between first-line Rituximab monotherapy (R-Mono, n=66) and first-line R-Chemotherapy (R-Chemo, n=24). Patients were treated according to physician preference. Most R-Chemo patients were treated prior to adoption of the risk-stratified approach in 2009. R-Mono patients were treated with four cycles of weekly Rituximab (375mg/m^2) induction followed by assessment of disease response. Patients who had progressive disease during Rituximab induction and those who had stable or progressive disease after induction went on to receive second-line treatment (25/66). Patients achieving partial or complete remission after Rituximab induction (33/66) were managed with observation alone or additional Rituximab (21 patients, typically 4 cycles of monthly Rituximab). Response was reviewed retrospectively on PET/CT (positron emission tomography/computed tomography, in 37/90) or CT.

Statistical analysis

We used the SOT recipient dataset to estimate the cumulative incidence of PTLD for each organ transplant type, adjusted for the competing risk of death. We also modelled the PTLD incidence rate in the years following SOT. Median follow-up was calculated using known function time (KFT).

Survival after SOT was calculated from the date of first transplant to the date of death or last follow-up. Survival after PTLD was calculated from the date of PTLD diagnosis to the date of death or last follow-up. Survival analyses were performed using the Kaplan-Meier method and patients were included regardless of the amount of therapy received.

We compared patient and disease characteristics of the patients in the R-Mono and R-Chemo groups using the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.

Univariate analyses were performed using the Cox proportional hazards model. Covariates were tested for association with survival to 12 months post-PTLD diagnosis in the monomorphic PTLD, DLBCL subset. The covariates tested were sex, age at transplant, age at PTLD diagnosis, type of transplant, time from transplant to PTLD diagnosis, IPI, EBV status and first-line treatment. Variables with $p < 0.05$ on univariate analysis were entered into the multivariate Cox proportional hazards model. All analyses were performed using the survival package and bshazard package in the R software environment. The study was conducted with Health Research Authority approval and was registered with the Research and Development department at Cambridge University Hospitals.

TABLE I. SOT recipient dataset (n=5365) – Cumulative incidence of PTLD according to SOT type

Organ transplanted	No. patients transplanted	No. patients with PTLD	Median time to PTLD (years)	Median follow-up time of SOT recipients (years)	Cumulative incidence of PTLD			
					5-year	10-year	15-year	20-year
Bilateral lung	503	15	0.93	8.66	0.0277	0.0315	-	-
Single lung	148	3	0.65	9.05	0.0211	0.0211	-	-
Heart	768	10	5.19	9.14	0.00748	0.0139	0.017	0.0227
Heart-Lung	85	3	0.60	18.22	0.0235	0.0235	-	-
Kidney	1965	56	5.36	6.68	0.0168	0.030	0.0556	0.104
Kidney and pancreas	327	12	6.13	7.23	0.0119	0.0493	0.0851	-
Liver	1428	22	4.24	8.07	0.00941	0.0136	0.0266	0.0303
Multivisceral	113	21	0.36	6.40	0.184	-	-	-
Other	28	0	NA	NA	NA	NA	NA	NA
TOTAL	**5365**	**142**	**3.44**	**7.7**	**0.0178**	**0.0273**	**0.0416**	**0.0587**
TOTAL (minus MVT)	5252	121	5.36	7.7	0.0142	0.0235	0.0381	0.0553

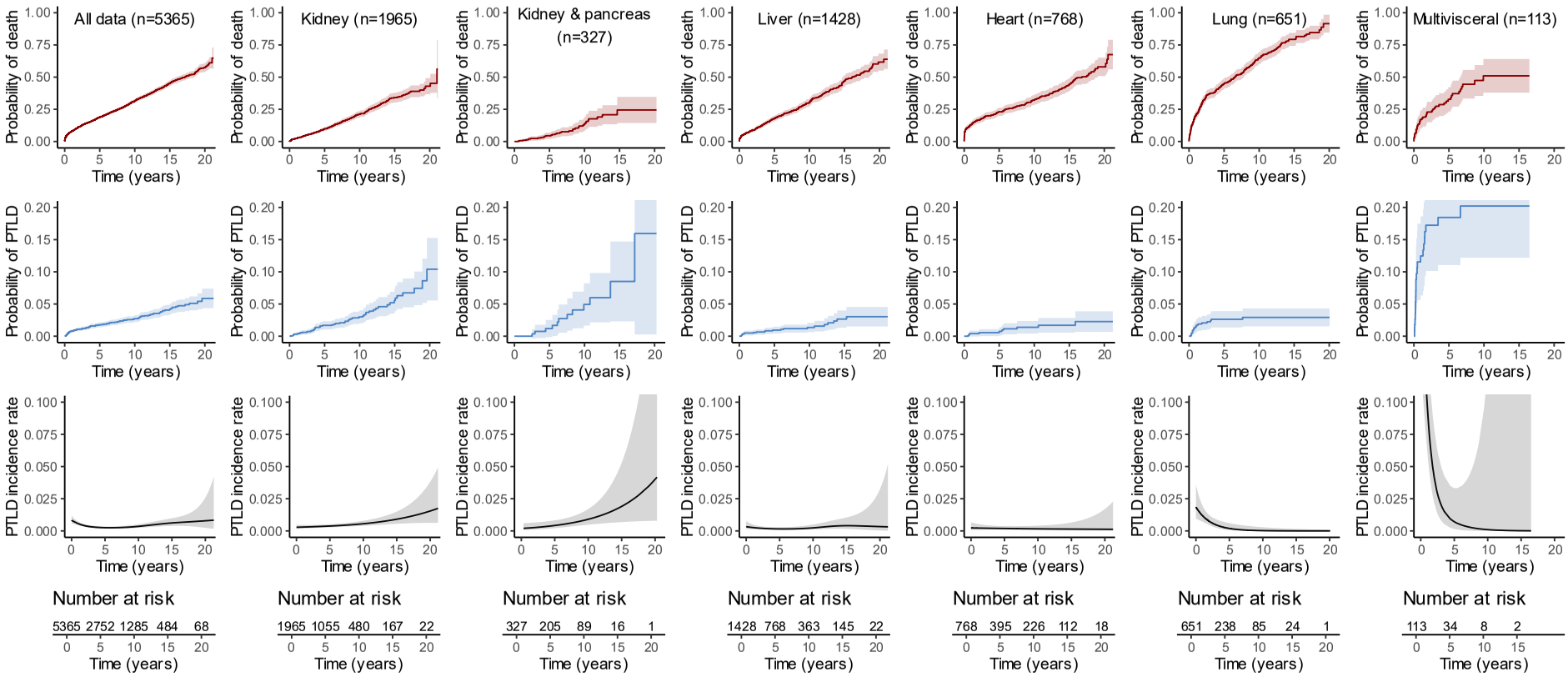


FIGURE 1. Cumulative incidence of PTLD (second row) adjusted for competing risk of death (first row) according to solid organ transplant type. Third row shows annulaised PTLD incidence rate. Bands show 95% confidence interval.

Results

From 01/01/2000 to 07/04/2021, 1504 patients received their first solid organ transplant at Royal Papworth Hospital. 768 were heart transplant recipients (including 1 heart-liver and 8 heart-kidney recipients), 503 bilateral lung transplant recipients (including 1 lung-kidney and 2 lung-liver recipients), 148 single lung transplant recipients and 85 heart-lung transplant recipients (including 1 heart-lung-liver recipient).

From 01/01/2000 to 31/12/2020, 3861 patients received their first solid organ transplant at Addenbrooke's Hospital. 1965 were kidney transplant recipients, 1428 liver transplant recipients, 327 SPK transplant recipients, 113 MVT recipients, 24 kidney-liver recipients, 2 liver-pancreas recipients and 2 pancreas recipients. SPK transplants started to be performed at Addenbrooke's from 2001 and MVT from 2004, gradually becoming more established. Consequently, MVT recipients had the shortest follow-up time and we have only been able to estimate their 5-year risk of PTLD, whereas we have included 10-year, 15-year and 20-year risk of PTLD in other transplant types where possible (Table I). Heart-lung recipients had the longest median follow-up time as this procedure has been in decline since the start of the 21st century.

Baseline characteristics

The median age at transplant was 52.0 years (range 0.8 -79.5 years). There were 88 paediatric transplants (<18 years, median age 15 years). The median age at PTLD diagnosis was 53.2 years (range 6.6 - 81.3 years). There was a slight male predominance in both the SOT recipient dataset (63%) and the PTLD dataset (60%). The median time from transplant to PTLD diagnosis was 5.4 years in the PTLD patient dataset (Table II). However, there is a bimodal distribution with MVT and lung recipients having the earliest onset (median 0.78 years) of predominantly EBV-associated disease (82%), and liver, kidney and heart recipients experiencing much later onset (median 8.71 years, $p<0.001$) and less EBV-associated disease (46%, $p<0.001$).

Incidence of PTLD

With a median follow-up of 7.7 years (KFT), 142 of 5365 SOT recipients (2.6%) transplanted between 2000 and 2021 have developed PTLD, including 56 of 1965 (3.0%) kidney transplant recipients, 22 of 1428 (1.5%) liver transplant recipients, 12 of 327 (3.7%) SPK recipients, 21 of 113 (18.6%) MVT recipients, 10 of 768 (1.3%) heart transplant recipients, 15 of 503 (3.0%) bilateral lung transplant recipients, 3 of 148 (2.0%) single lung transplant recipients and 3 of 85 (3.5%) heart-lung transplant recipients.

The 5-year cumulative incidence of PTLD (shown in Table I and Figure 1) was 18% post-MVT and 1-3% following the other SOT types. With longer-term follow-up, cumulative incidence of PTLD at 20 years post-transplant was lowest in liver and heart transplant recipients (3% and 2%, respectively); and as high as 8.5% at 15 years post-SPK transplantation and 10% at 20 years post-kidney transplantation.

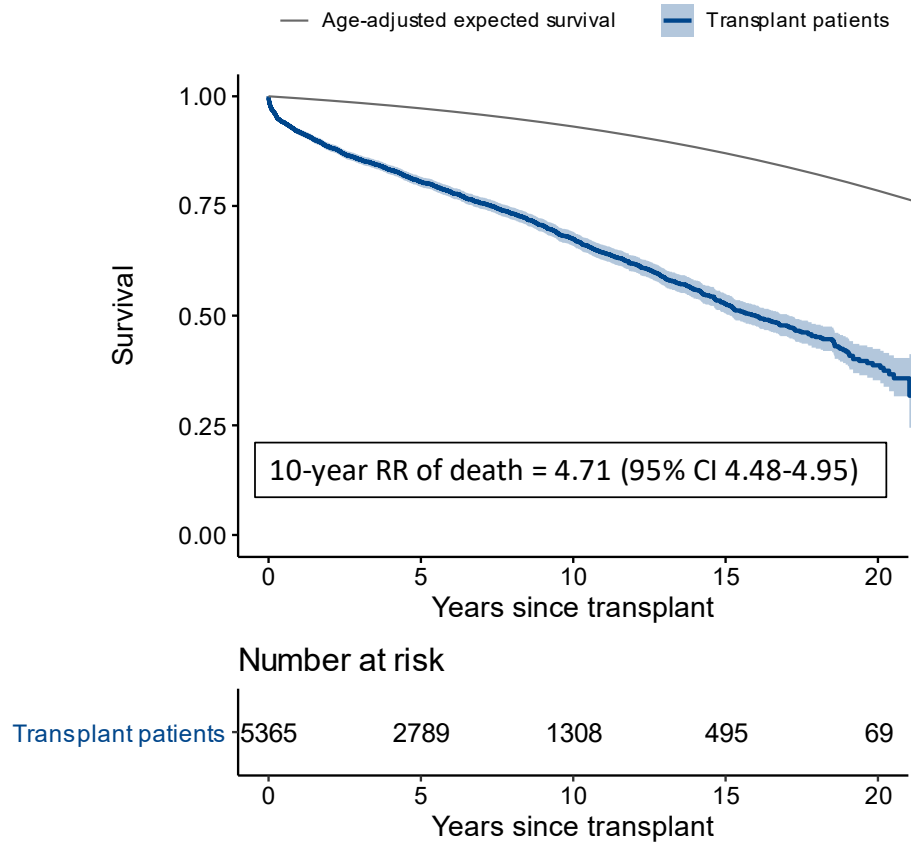
The incidence rate of PTLD (Figure 1) was highest in the first year post-transplant in lung (2% per year) and MVT recipients (15% per year). The incidence rate remained persistently low (<0.5% per

year) in liver and heart transplant recipients while the incidence rate rose gradually in kidney recipients over time.

TABLE II. PTLD patient dataset (n=225) - Histological subtypes and EBV association

Organ transplanted	No. patients with PTLD	Median time to PTLD (years)	EBV-associated PTLD	Monomorphic PTLD				Classical Hodgkin lymphoma type PTLD	Polymorphic PTLD	Low grade lymphoma	Early lesions	No biopsy	Unknown
				DLBCL	Burkitt	Plasma cell	T-cell						
Lung	20	1.06	**10/14 (71%)**	11/16 (69%)	1/16 (6%)	1/16 (6%)	1/16 (6%)	1/16 (6%)	0	1/16 (6%)	0	0	4/20
Heart	19	11.9	**7/13 (54%)**	7/19 (37%)	3/19 (16%)	1/19 (5%)	2/19 (11%)	1/19 (5%)	2/19 (11%)	3/19 (16%)	0	0	0
Heart-Lung	3	7.90	**1/2 (50%)**	2/3 (67%)	0	0	0	0	1/3 (33%)	0	0	0	0
HSCT	20	0.43	**19/20 (95%)**	13/20 (65%)	0	2/20 (10%)	1/20 (5%)	3/20 (15%)	1/20 (5%)	0	0	0	0
Kidney	90	8.42	**37/79 (47%)**	45/84 (54%)	6/84 (7%)	8/84 (10%)	7/84 (8%)	8/84 (10%)	4/84 (5%)	6/84 (7%)	0	1/90	5/90
Kidney and pancreas	16	8.79	**7/14 (50%)**	7/16 (44%)	0	5/16 (31%)	0	0	4/16 (25%)	0	0	0	0
Liver	36	8.61	**13/32 (41%)**	26/35 (74%)	1/35 (3%)	1/35 (3%)	0	2/35 (6%)	3/35 (9%)	1/35 (3%)	1/35 (3%)	0	1/36
Multivisceral	21	0.33	**18/20 (90%)**	10/16 (63%)	0	2/16 (13%)	0	0	4/16 (25%)	0	0	4/21	1/21
TOTAL	**225**	**5.42**	**126/194 (65%)**	**121/209 (58%)**	**11/209 (5%)**	**20/209 (10%)**	**11/209 (5%)**	**15/209 (7%)**	**19/209 (9%)**	**11/209 (5%)**	**1/209 (0.4%)**	**5/225**	**11/225**
All organs, EBV-associated PTLD				61/107 (57%)	6/11 (55%)	10/16 (63%)	2/9 (22%)	11/13 (85%)	16/19 (84%)	2/10 (20%)	0	4/4	NA
All organs, EBV-negative PTLD				46/107 (42%)	5/11 (45%)	6/16 (38%)	7/9 (78%)	2/13 (15%)	3/19 (16%)	8/10 (80%)	1/1	0	NA
All organs, EBV status unknown				14	0	4	2	2	0	1	0	1	NA
Median follow-up time (years)				5.9	8.7	4.7	6.4	6.4	5.0	5.0	NA	NA	NA
Median overall survival (years)				5.2	4.4	3.2	0.5	4.4	Not reached	Not reached	NA	NA	NA

HSCT, Haematopoietic stem cell transplantation; EBV, Epstein-Barr virus; DLBCL, Diffuse large B-cell lymphoma



Survival in SOT recipients

Median OS following SOT was 16 years which is significantly reduced compared with the life expectancy of the age-adjusted UK population (Relative risk of death at 10 years 4.71, Figure 2). We performed landmark analyses to compare OS from date of PTLD diagnosis with the background survival of the transplant population from corresponding time points post SOT (Figure 3). There is a relatively high early mortality rate following diagnosis of PTLD and the data suggest that in patients surviving two years, long-term survival approaches that of the non-PTLD SOT cohort (p=0.08).

FIGURE 2. Survival of all solid organ transplant recipients versus age-adjusted life expectancy of UK population (National life tables: UK (2011-2013) – Office for National Statistics)

RR, Relative risk; CI, Confidence interval

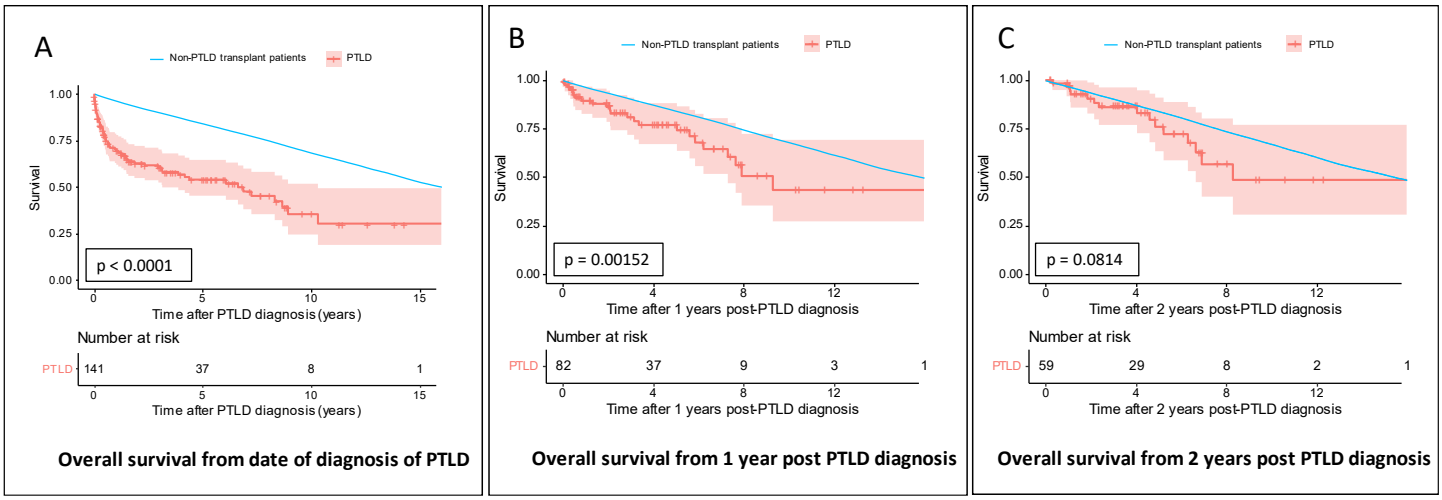


FIGURE 3. Overall survival of PTLD patients from time of PTLD diagnosis compared with survival of non-PTLD transplant patients from an equivalent time point post solid organ transplantation. **A:** Overall survival from date of diagnosis of PTLD. **B:** Overall survival from one year post-PTLD diagnosis. **C:** Overall survival from two years post-PTLD diagnosis. p values shown are for a one-sample log rank test.

Survival following upfront R monotherapy versus R-Chemotherapy

From the PTLD patient dataset we identified 90 patients with monomorphic PTLD, DLBCL subtype, who were either treated with reduction in immunosuppression (RIS) and first-line R-Mono (n=66) or RIS and R-Chemo (n=24). The patient and disease characteristics are shown in Table III. The two groups were well-matched for age and IPI. The R-Mono group had proportionately fewer males than the R-Chemo group (47% vs 71%, p=0.06) and more transplant types as MVT and SPK transplants became established around the time that upfront Rituximab monotherapy became standard of care. R-Chemotherapy was the preceding standard treatment and consequently there are no MVT and SPK recipients in the R-Chemo group and the follow-up time is longer. There was a tendency to earlier, EBV-associated PTLD in the R-Mono group, which likely reflects the relatively high proportion of MVT and HSCT recipients.

11/24 (46%) R-Chemo and 40/66 (61%) R-Mono patients are alive, with a median follow-up of 13.6 years and 5.1 years respectively. 22/24 R-Chemo patients received R-CHOP and 2/24 received R-CVP. 8/24 (33%) patients are alive and in remission after first-line treatment. 5/24 (21%) patients relapsed and 3/5 remain alive and in remission after second-line treatment.

22/66 R-Mono patients remain in remission having required no further treatment. 25/66 patients required second-line treatment with R-Chemotherapy (n=23), surgery (n=1) or cytotoxic T lymphocytes (n=1) and 18/25 achieved remission. The remaining 19/66 patients died during treatment or post-remission.

TABLE III. Characteristics of patients treated with Rituximab monotherapy or R-Chemotherapy

Patient Characteristics	R-Monotherapy (n=66)	R-Chemotherapy (n=24)	p value
Median age at PTLD diagnosis (range), years	54.0 (19.0-77.8)	54.6 (22.1-75.6)	U=798, p=0.960
Male	31 (47%)	17 (71%)	Fisher, p=0.0572
Transplant type			
Kidney	27 (41%)	8 (33%)	
Liver	9 (14%)	10 (42%)	
Kidney and Pancreas	4 (6%)	0	Fisher, p=0.0160
Multivisceral	9 (14%)	0	
HSCT	9 (14%)	1 (4%)	
Heart	1 (2%)	2 (8%)	
Lung	7 (11%)	3 (13%)	
Median time from transplantation to PTLD (range), years	1.63 (0.15-32.9)	5.41 (0.22-20)	U=648.5, p=0.192
Epstein-Barr virus (EBV) association			
EBV associated	40 (62%)	6 (40%)	Fisher, p=0.155
Non-EBV associated	25 (38%)	9 (60%)	
Unknown	1	9	
Ann Arbor stage			
Early stage (I-II)	30 (46%)	6 (32%)	Fisher, p=0.302
Advanced stage (III-IV)	35 (54%)	13 (68%)	
Unknown	1	5	
Lactate dehydrogenase			
Within normal range	19 (36%)	4 (33%)	Fisher, p=1
Elevated	34 (64%)	8 (67%)	
Unknown	13	12	
ECOG performance status			
0-2	53 (83%)	20 (95%)	Fisher, p=0.279
3-4	11 (17%)	1 (5%)	
Unknown	2	3	
Nodal disease	39 (60%)	16 (80%)	
No nodal disease	26 (40%)	4 (20%)	Fisher, p=0.117
Unknown	1	4	
Extranodal disease	56 (88%)	20 (91%)	
No extranodal disease	8 (13%)	2 (9%)	Fisher, p=1
Unknown	2	2	
International prognostic index, IPI			
<3	41 (66%)	12 (67%)	Fisher, p=1
≥3	21 (34%)	6 (33%)	
Unknown	4	6	
First-line treatment received	Rituximab, n=66	R-CHOP, n=21 R-CVP, n=2 CHOP (MINT study), n=1	NA
Number of cycles			
1	2 (3%)	2 (10%)	NA
2	8 (13%)	0	
3	4 (6%)	2 (10%)	
4	27 (43%)	2 (10%)	
5	2 (3%)	1 (5%)	
6	1 (2%)	10 (50%)	
7	1 (2%)	0	
8	18 (29%)	3 (15%)	
Unknown	3	4	
Median follow-up time, KFT (range), years	**5.05** (0-11.5)	**13.6** (0-18.3)	U=294, p=5.52×10^{-6}

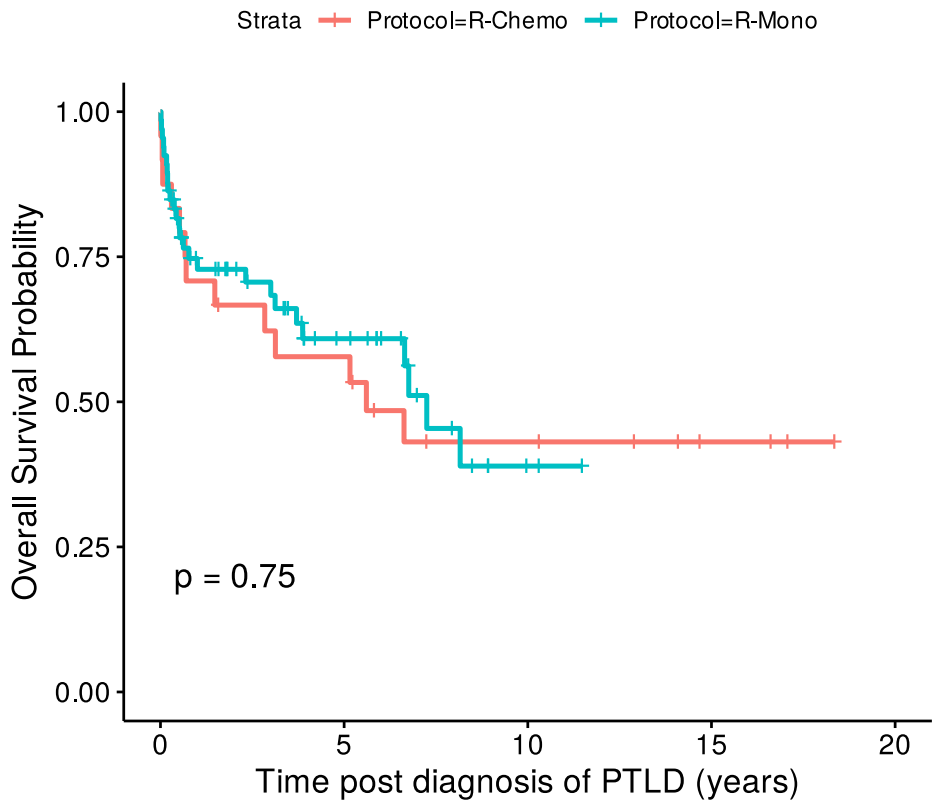


FIGURE 4. Overall survival in the upfront Rituximab monotherapy cohort (n=66) and the R-Chemotherapy cohort (n=24) among patients with monomorphic PTLD, DLBCL subtype.

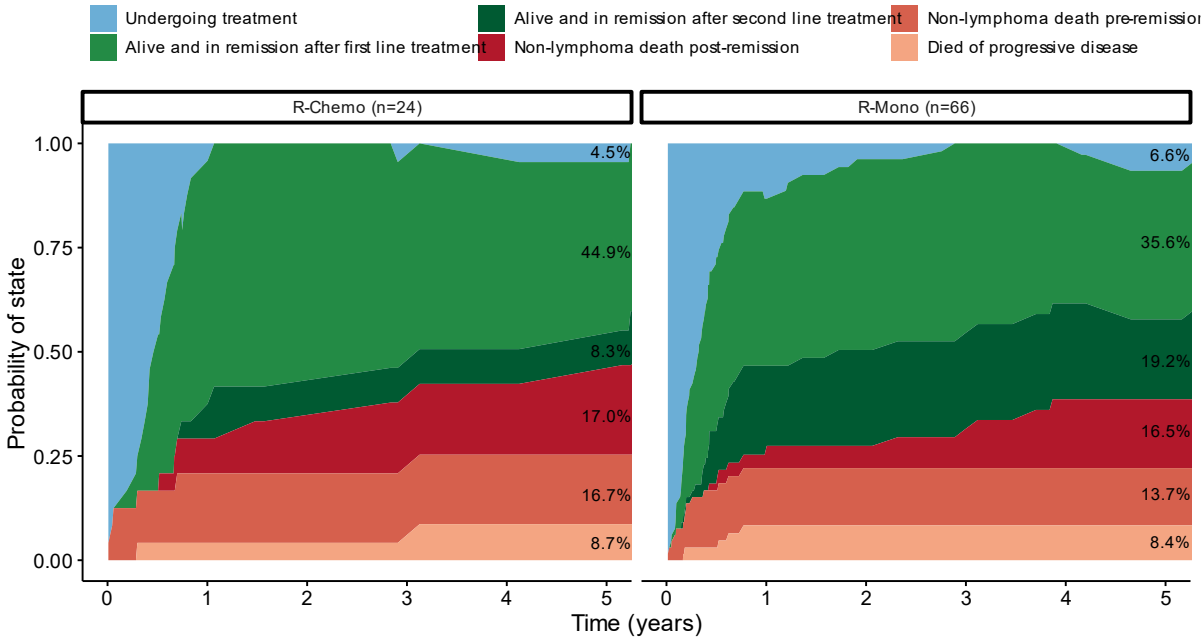


FIGURE 5. Outcomes of patients with monomorphic PTLD, DLBCL, treated with first-line Rituximab monotherapy versus R-Chemotherapy. Probability in state shown at 5 years post-diagnosis of PTLD.

TABLE IV. Univariate and Multivariate analysis of factors associated with overall survival in the first year after diagnosis of monomorphic PTLD, DLBCL

All monomorphic PTLD, DLBCL patients (n=90) Univariate analysis			
Variable	**Hazard ratio**	**95% CI**	**p-value**
Sex (ref=F)	1.21	0.530 – 2.759	0.651
IPI (ref=<3)	5.474	2.075 – 14.44	0.000591***
EBV status (ref=neg)	2.702	0.996 – 7.325	0.0508
Age at PTLD diagnosis (per year)	1.035	1.002 – 1.069	0.0385*
Age at transplant (per year)	1.050	1.011-1.091	0.0109*
Time since transplant	0.976	0.926-1.025	0.366
Time to PTLD diagnosis (per month)	0.998	0.992 – 1.003	0.388
Organ transplanted (ref=Kidney)			
Bilateral lung	1.668	0.4312 – 6.452	0.459
Heart	NA	0.000 – Inf	1
HSCT	1.920	0.5618 – 6.561	0.298
Kidney and pancreas	NA	0.000 – Inf	1
Liver	1.181	0.3744 – 3.725	0.777
Multivisceral	1.692	0.4370 – 6.549	0.446
Single lung	2.949	0.3621 – 24.016	0.312
First-line treatment (ref=R-Chemo)	0.8633	0.3549-2.1	0.746
All DLBCL patients (n=90) Multivariate analysis with backward stepwise elimination			
IPI (ref=<3)	8.820	2.859-27.2019	0.000152***
EBV status (ref=neg)	3.691	1.0034-13.185	0.0444*
First-line treatment (ref=R-Chemo)	0.235	0.0679-0.8099	0.0218*

CI, confidence interval; EBV, Epstein Barr virus; IPI, international prognostic index

Causes of death were broadly subcategorised into (i) death due to progressive PTLD, (ii) non-lymphoma death pre-remission and (iii) non-lymphoma death post-remission; and are represented graphically in Figure 5. TRM, broadly classified as non-lymphoma death pre-remission, was similar between the two groups (14% vs 17%, p=0.740) as was death due to progressive disease (9% vs 8%, p=1). Non-lymphoma death post-remission was similar at 5 years (17% in both groups).

Median PFS was 6.8 years and 5.1 years (p=0.98), and median OS was 6.8 years and 5.6 years (p=0.79) in the R-Mono and R-Chemo cohorts respectively. We have no evidence of a difference in survival between the R-Mono and R-Chemo cohorts (Figure 4), but the datasets are small and there are potential confounding factors (e.g. other changes in practice over time).

Univariate and multivariate analyses of all 90 monomorphic PTLD, DLBCL patients were performed to identify the covariates associated with death in the first 12 months following PTLD diagnosis (Table IV). Multivariate analysis of the DLBCL patients identified IPI3+ as the strongest pre-treatment variable associating with inferior 1 year OS. EBV positive status and treatment with R-Chemo also showed some association with inferior OS but with a small dataset and broad confidence intervals it is hard to be conclusive.

OS of patients with other PTLD subtypes are in Supplementary Table II. Five patients developed PTLD of the central nervous system and were treated with high-dose methotrexate regimens. Median overall survival was 1.6 months.

Discussion

In this large UK cohort of SOT recipients, the cumulative incidence of PTLD was 5.9% at 20 years after transplantation.

The strikingly high early incidence of PTLD in MVT recipients is consistent with the large volume of lymphoid tissue in the graft as well as the high immunosuppressive burden, including Alemtuzumab induction. SPK transplant recipients received similar immunosuppression to MVT recipients but experienced lower rates of early EBV-associated PTLD. PTLD occurred early after lung transplantation where transplanted lymphoid tissue is abundant, however antibody induction was not used in this group and the incidence rate was not as high as after MVT. The high long-term cumulative incidence of PTLD in kidney transplant recipients is likely due to longer duration of triple therapy (tacrolimus, azathioprine and prednisolone in low immunological risk patients and tacrolimus, mycophenolate mofetil and prednisolone in high immunological risk patients). Liver transplant recipients have a lower long-term cumulative incidence of PTLD likely reflecting lower immunosuppressive burden with earlier weaning of triple therapy and lower target trough tacrolimus levels (3-8 ng/L compared with 6-10 ng/L in kidney transplant recipients). Heart transplants involve no transfer of native lymphoid tissue and immunosuppression consists of low-dose antithymocyte globulin induction and mycophenolate mofetil maintenance, likely contributing to the low cumulative incidence of PTLD.

Our data suggest that a risk-stratified approach with first-line Rituximab monotherapy is effective and safe in the real world as well as in clinical trials. Median OS in our upfront R-Mono group was 6.8 years which is comparable to the median OS of 6.6 years in the risk-stratified sequential treatment cohort of the PTLD-1 trial.[1] A third of R-Mono patients required no further therapy and remain alive and in remission with a median follow-up of 3.85 years. A further 27% remain alive and in remission after second line treatment. There is no increase in death from progressive disease in the R-Mono group suggesting that patients have not been undertreated. Although this is a retrospective study, and we must be cautious interpreting outcomes between different treatment modalities, it is clear that there remain a high proportion of patients dying from non-PTLD causes pre- and post-remission in both the R-Mono and R-Chemo groups. Registry data documenting cause of death were incomplete however the top three causes of death in both groups were infection, PTLD and graft failure.

A recent ANZDATA study[12] showed an excess risk of death in kidney transplant recipients with PTLD particularly in the first two years after diagnosis which fits with our landmark analysis. The number of deaths in our study (39/90, 43%, median follow-up 5.9 years) is in keeping with a Canadian study restricted to DLBCL-type PTLD treated with Rituximab/R-CHOP (82/168, 48%, median follow-up 2.4 years [13]. However, a larger proportion of patients died due to non-lymphoma causes in our study (34% compared with 22% in the Canadian Study). Burns et al reported a 12-month non-PTLD

mortality of 7%[9], compared to 25% and 17% in our R-Chemo and R-Mono groups, respectively. However one of the challenges of comparing cohorts is the difference in distribution of organ transplant types.

In conclusion, we have described PTLD incidence in a range of transplant types and shown a high early incidence post-MVT and an ongoing risk of disease for many years post-SOT. Our real-world outcomes support the use of first-line Rituximab monotherapy.

There is a need for other low-toxicity PTLD treatments and for safe and effective pre-emptive strategies. The predominance of EBV-associated PTLD gives potential for the future use of EBV-directed therapies.

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Supplementary Table I: Immunosuppression strategy by organ transplanted (2000-2021)

Organ transplanted	Immunosuppression
Heart	**2000 onwards** **Time of Transplant** Rabbit anti-thymocyte globulin 2mg/kg (divided into 3 doses and administered at intervals of 48 hours) Mycophenolate Mofetil , 1g BD Corticosteroid **First year post-transplant** Tacrolimus; started once renal function recovers, target trough level 8-12 ug/L Mycophenolate Mofetil Corticosteroid; tapering dose during year one **Long-term post-transplant** Tacrolimus; target trough level 6-8 ug/L Mycophenolate Mofetil
Single lung/ Bilateral lung/ Heart and lung	**2000-2007** Induction with anti-thymocyte globulin Prednisolone, Mycophenolate mofetil and Ciclosporin/Tacrolimus **2008 onwards** Prednisolone, Mycophenolate mofetil and Ciclosporin/Tacrolimus
Kidney	**2000-2001** Standard triple therapy from day 1: Ciclosporin, Azathioprine, Prednisolone Highly sensitised patients from day 1: anti-thymocyte globulin (10 days), Azathioprine, Prednisolone; and from day 7: Ciclosporin **2001-2016** High risk: Tacrolimus, Mycophenolate mofetil, Prednisolone from day 1 Medium risk: Tacrolimus, Azathioprine, Prednisolone from day 1 Low risk: Ciclosporin, Azathioprine, Prednisolone from day 1 **2002-2016** As above + Basiliximab on D0 (pre-transplant and D4) **2003-2016** As above + Ciclosporin/Tacrolimus as pre-medication prior to transplant **2017 onwards** Standard immunological risk: Basiliximab induction (Day 0 and Day 3) Tacrolimus (target level 6-10 μg/L) Azathioprine 2mg/kg Prednisolone High immunological risk: Basiliximab induction (Day 0 and Day 3)

	Tacrolimus (target level 6-10 μg/L) Mycophenolate mofetil 750mg bd Prednisolone Steroid-free induction for special circumstances: Alemtuzumab induction Tacrolimus (target level 6-10 μg/L) Mycophenolate mofetil 500mg bd
Simultaneous pancreas and kidney	**2001-2003** Basiliximab induction with maintenance triple therapy comprising tacrolimus, mycophenolate mofetil and prednisolone **2004 onwards** Alemtuzumab induction (given subcutaneously to avoid a first dose reaction), with tacrolimus and mycophenolate mofetil maintenance without steroids
Liver	**2000 onwards** Calcineurin inhibitor, prednisolone and antimetabolite (azathioprine or mycophenolate mofetil) for the first 6-12 weeks Calcineurin inhibitor, antimetabolite thereafter Calcineurin inhibitor single agent from year one if there are no risk factors for rejection Most common renal sparing regiments include low dose calcineurin inhibitor with antimetabolite or sirolimus based immune suppression. **Additional note** There has been a broad move to lighten immune suppression over the last 20 years.
Multivisceral	**2004 onwards** Induction with Alemtuzumab 30mg subcut (one or two doses depending on individual immunological risk) and methylprednisolone Maintenance is with reducing prednisolone, Tacrolimus and mycophenolate mofetil

Supplementary Table II: Survival outcomes by histological subtype of PTLD

PTLD Histology	Number of patients	First-line treatment	Median overall survival
Monomorphic Diffuse large B cell lymphoma	121	69 Rituximab monotherapy 23 R-CHOP 2 R-CVP 1 CHOP 2 R-Ibrutinib (TIDAL study) 1 R-GemCis 1 R-IELSG 1 De Angelis 1 R-IVE 1 R-CYVE 1 PMitCEBO 1 CHOD-BVAM 2 Reduction in Immunosuppression alone 2 died before treatment 2 palliative care 11 treatment unknown	5.2 years
Monomorphic Burkitt lymphoma	11	4 R-DA-EPOCH 2 R-CODOX-M-IVAC 2 Rituximab monotherapy 2 R-CHOP 1 R-CP	4.4 years
Monomorphic plasma cell myeloma and plasmacytoma-like lesions	20	6 Rituximab monotherapy 2 Rituximab + VTD 2 R-DA-EPOCH + Bortezomib 1 Bortezomib + Dexamethasone 1 CTD 1 VCD 1 Radiotherapy 1 Surgery 4 Reduction in immunosuppression alone 1 treatment unknown	3.2 years
Monomorphic T-cell neoplasms	11	1 Methotrexate/Epo/GCSF 1 Brentuximab 2 CHOP 1 CVP 1 Fludarabine Cyclophosphamide 1 PMitCEBO 1 Gem-Etoposide 1 Radiotherapy 2 treatment unknown	0.5 years
Classical Hodgkin lymphoma type PTLD	15	5 ABVD 3 AVD 4 Rituximab monotherapy 1 Vinblastine + Brentuximab	4.4 years

		1 ChlVPP PABIOE 1 Reduction in immunosuppression alone	
Polymorphic PTLD	19	11 Rituximab monotherapy 1 R-CHOP 1 Rituximab + CTL 1 R-PMitCEBO 3 Reduction in immunosuppression alone 1 Radiotherapy 1 treatment unknown	Median OS not reached Median follow-up time (KFT)=5.0 years
Low grade lymphoma	11	7 Rituximab monotherapy 2 R-Bendamustine 1 Cytotoxic T lymphocytes 1 R-DHAOx	Median OS not reached Median follow-up time (KFT)=5.0 years)

Excluded 17 patients from PTLD dataset who had no biopsy (n=5), biopsy result unknown (n=11) or who had early lesions (n=1)