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Incidence and predictors of post-transplant lymphoproliferative disease after kidney transplantation during adulthood and childhood: a registry study

Anna Francis[1,2], David W. Johnson[3,4], Armando Teixeira-Pinto[1], Jonathan C. Craig[1] and Germaine Wong[1,5]

[1]Sydney School of Public Health, University of Sydney, Camperdown, Victoria, Australia, [2]Child and Adolescent Renal Service, Children's Health Queensland, Brisbane, Queensland, Australia, [3]Australasian Kidney Trials Network, Diamantina, Translational Research Institute, University of Queensland, Brisbane, Queensland, Australia, [4]Translational Research Institute, Brisbane, Queensland, Australia and [5]Centre for Transplant and Renal Research, Westmead Hospital, Westmead, New South Wales, Australia

Correspondence and offprint requests to: Anna Francis; E-mail: anna.francis@health.qld.gov.au

ABSTRACT

Background. Differences in the epidemiology of post-transplant lymphoproliferative disease (PTLD) between adult and paediatric kidney transplant recipients remain unclear.

Methods. Using the Australian and New Zealand Dialysis and Transplant Registry (1963–2015), the cumulative incidences of PTLD in children (age <20 years) and adults were calculated using a competing risk of death model and compared with age-matched population-based data using standardized incidence ratios (SIRs). Risk factors for PTLD were assessed using Cox proportional hazards regression.

Results. Among 23 477 patients (92% adult, 60% male), 505 developed PTLD, with 50 (10%) occurring in childhood recipients. The 25-year cumulative incidence of PTLD was 3.3% [95% confidence interval (CI) 2.9–3.6] for adult recipients and 3.6% (95% CI 2.7–4.8) for childhood recipients. Childhood recipients had a 30-fold increased risk of lymphoma compared with the age-matched general population [SIR 29.5 (95% CI 21.9–38.8)], higher than adult recipients [SIR 8.4 (95% CI 7.7–9.2)]. Epstein–Barr virus (EBV)-negative recipient serology [adjusted hazard ratio (aHR) 3.33 (95% CI 2.21–5.01), $P < 0.001$], year of transplantation [aHR 0.93 for each year after the year 2000 (95% CI 0.88–0.99), $P = 0.02$], induction with an agent other than anti-CD25 monoclonal antibody [aHR 2.07 (95% CI 1.16–3.70), $P = 0.01$] and having diabetes [aHR 3.49 (95% CI 2.26–5.38), $P < 0.001$] were independently associated with PTLD.

Conclusions. Lymphoma occurs at similar rates in adult and paediatric recipients, but has been decreasing since the year 2000. EBV-negative patients and those with diabetes or induction agent other than anti-CD25 monoclonal antibody are at substantially increased risk of PTLD.

Keywords: adult, child, kidney transplantation, lymphoproliferative disease, risk factors

INTRODUCTION

Post-transplant lymphoproliferative disease (PTLD) is a well-known complication following kidney transplantation, but differences in the epidemiology of the disease in adult and paediatric kidney transplant recipients are not well-defined. Studies of the incidence of PTLD are largely confined to single-centre and registry studies with relatively short follow-up times and not accounting for the disease trajectory over the life course of a transplant recipient from childhood to adulthood [1–5]. The cumulative incidence of PTLD in the first 10 years after transplantation is ∼1–2% in adult recipients and 3% in childhood recipients, but there is emerging evidence showing the incidence may be decreasing over time [6–9]. Few studies have reported the incidence of PTLD beyond 10 years post-transplant and the precision of these estimates is restricted by the relatively small sample sizes [6, 10–12].

The reported predictors of PTLD are also inconsistent between studies. Some have reported that thymoglobulin or Ortho Kung T3 (OKT3) therapy, transplantation during childhood, high-dose tacrolimus-based immunosuppression and male gender are associated with higher risks of PTLD [2, 13–16]. Others did not find any significant association between induction therapies, maintenance immunosuppression and subsequent risk of PTLD [3, 7, 14, 17, 18]. The only consistent risk factor observed has been pre-transplant Epstein–Barr virus (EBV) negativity [2, 3, 8, 16, 19, 20].

The aims of this study were to define the long-term incidence of PTLD in adult and paediatric renal transplant

recipients, to estimate the excess risk of lymphoma compared with the general population and to identify potential causal factors.

MATERIALS AND METHODS

Study population and setting

This cohort study included all patients (inclusive of those with first and subsequent transplants) who underwent kidney transplantation in Australia or New Zealand between 1 January 1963 and 31 December 2015. Patients who had a lymphoma prior to their first transplant and those with combined organ transplants (such as liver and kidney) were excluded. Data were collected from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry. ANZDATA collects prospective data on all patients in Australia and New Zealand who commence renal replacement therapy [21].

Covariates of interest. Data were collected on recipient characteristics [age, weight, height, self-reported race, sex, cause of end-stage kidney disease (ESKD), comorbidities (history of stroke, hypertension, peripheral vascular disease, diabetes or respiratory disease), smoking status, cytomegalovirus (CMV) serological status, EBV serological status], donor characteristics (source, age), transplant characteristics [date, human leukocyte antigen (HLA) mismatch, induction agent, immunosuppression regimen in the first month of transplantation] and transplant outcomes (graft loss, death). Childhood recipients were defined as those <20 years of age at the time of their first kidney transplant.

Outcomes. The ANZDATA registry collects information on all non-skin cancers for patients on renal replacement therapy. The treating nephrology team reports non-skin cancers to ANZDATA as they are diagnosed. Prior work has validated the concordance of cancer reporting in ANZDATA against the statutory reporting Central Cancer Registry concordance [22]. Non-Hodgkin's lymphoma (NHL), cerebral lymphoma and Hodgkin's disease occurring post-transplant were classified together with PTLD, as there was insufficient information in the registry to distinguish between the three groups. Cases of non-malignant PTLD were not recorded by the ANZDATA registry. Nodal disease was defined as disease occurring in lymph nodes, including the tonsils.

Statistical analysis

Results are expressed as mean [standard deviation (SD)] for continuous normally distributed data, median [interquartile range (IQR)] for continuous non-normally distributed data and number (percentage) for categorical data.

For survival analyses, the follow-up period was defined from the time of transplantation to the time of the first PTLD diagnosis after transplantation. Those who did not develop PTLD were censored at the time of death, loss to follow-up or 31 December 2015. The adjusted cumulative incidence of PTLD in childhood and adulthood recipients of a kidney transplant were calculated using the Fine and Gray method, allowing for the competing event of death [23]. Those who did not experience either event (death or PTLD) were censored at the end of the study or loss to follow-up.

The incidence of PTLD in the transplant population was compared with the incidence in the general population by comparing the number of cancer events and the person-years at risk for each group. Person-years for the observed were counted from the age at transplantation to the age at death, loss to follow-up, end of study (31 December 2015) or diagnosis, whichever came first. Events and person-years for the general population were taken from whole-population data from the Australian Institute of Health and Welfare (AIHW). The AIHW publishes yearly data on the incidence of lymphoma along with general population counts. The general population data were broken down into gender and 5-year age groups. The ratios of the observed to the expected incidences of PTLD were calculated using the indirect age standardization method and their 95% confidence intervals (CIs) were calculated assuming a Poisson distribution.

Risk factors for PTLD were assessed by univariable and multivariable Cox proportional hazards regression. The vast majority (87%) of PTLD occurred during the first graft period and analysis was restricted to these cases to avoid bias related to transplant non-function (and presumed reduction in immunosuppression) or bias from variables related to subsequent transplants. Those who did not develop PTLD in the first graft period were censored at death, first transplant failure date or the end of the study (31 December 2015), whichever occurred first. Variables associated with PTLD at $P < 0.25$ on univariate analysis were included in the multivariable-adjusted analyses. EBV serology, age group (child or adult at the time of first transplant), induction agent and race were specified *a priori* to enter the multivariable model, as they have been shown in previous research to be associated with PTLD [2, 3, 14–19, 24, 25]. In addition, the regression model was restricted to transplants from the year 2000, to assess the risk of PTLD in the modern era of immunosuppression. The year 2000 was chosen since widespread reporting of induction agent data has been available since then. The functional forms of continuous variables were assessed by splitting the variables into four categories and checking for ordered trend using inspection of survival curves and then applying the logrank trend test. Potential effect modification was tested between age, race, induction agent, transplant year, EBV serology and sex using two-way interaction terms, with no effect modification identified. Model suitability was tested using a stepwise backward elimination method to find the most parsimonious model. The proportional hazards assumption was tested by plotting the Schoenfeld residuals.

Records were complete for the calculation of cumulative incidence of PTLD. No imputation of missing data was performed on data analysed for the regression analysis. Missing data are quantified in Supplementary data, Figure S1.

Data were structured using Python 2.7, using the modules pandas, matplotlib and NumPy [26]. Data analysis was performed with SAS Studio (SAS Institute, Cary, NC, USA) and Python, with $P < 0.05$ considered statistically significant.

RESULTS

From 1963 to 2015, 23 700 people received a first kidney transplant in Australia and New Zealand (Supplementary data, Figure S1). There were 223 with lymphoma prior to their first transplant, leaving 23 477 included in the study. A total of 20 286 (86%) patients received only one transplant and 3191 received two or more transplants during the follow-up time. During the study period, 9947 patients died. First transplantation occurred during adulthood (age ≥20 years) in 21 629 patients and 1848 during childhood and adolescence. Baseline characteristics of the two groups are detailed in Table 1. The median follow-up time was 8.5 years (IQR 3.8–15.8), with a total follow-up of 251 269 patient-years.

Absolute and cumulative incidence of PTLD. Of the 23 477 transplant recipients, 505 [2.2% (95% CI 2.0–2.3)] developed PTLD, with 455 cases in 21 629 adult recipients [2.1% (95% CI 1.9–2.3)] and 50 cases in 1848 childhood recipients [2.7% (95% CI 2.1–3.6)]. The 25-year cumulative incidence of PTLD, adjusted for the competing risk of death, was 3.3% (95% CI 2.9–3.6) for adult recipients and 3.6% (95% CI 2.7–4.8) for child recipients (Figure 1).

Time to cancer. In adult recipients, there was a bimodal distribution of time to PTLD, with incidence peaking in the first year [62/505 (12%)] and then decreasing until the fifth year post-transplant (Figure 2). Childhood recipients were more likely than adult recipients to develop PTLD in the first year

Table 1. Characteristics of childhood and adult recipients of a first kidney transplant ($n = 23\,477$)

Variable		Childhood recipients ($n = 1848$)	Adult recipients ($n = 21\,629$)
Recipient characteristics			
Gender	Female	786 (42.5)	8153 (39.7)
Race	Caucasian	1544 (83.5)	17 329 (84.5)
	Non-Caucasian	304 (16.5)	422 (2.1)
Disease	Glomerulonephritis	606 (32.8)	9806 (45.5)
	Cystic diseases	148 (8.0)	2927 (13.6)
	Diabetes	1 (0.0)	1858 (8.6)
	Other/unknown	1089 (59.1)	6956 (32.3)
EBV serology[a]	Negative	505 (52.1)	1634 (7.6)
CMV serology[b]	Negative	671 (61.5)	4543 (31.9)
Age at transplant (years), mean (IQR)		14 (9–17)	47 (36–56)
Cigarette smoker (past or present)[c]		97 (6.4)	6858 (44.2)
Lung disease[d]		29 (0.2)	976 (5.7)
Peripheral vascular disease[e]		7 (0.0)	1191 (7.0)
Cerebrovascular disease[f]		7 (0.0)	732 (4.3)
Coronary disease[g]		1 (0.0)	2346 (13.9)
Diabetes[h]		5 (0.0)	2536 (14.3)
Donor characteristics			
Donor status	Living donor	933 (50.6)	5028 (24.5)
Transplant characteristics			
HLA mismatch[i]	0–2	648 (43.2)	6864 (37.9)
	3–4	666 (44.4)	7196 (39.6)
	5–6	184 (12.4)	4063 (22.5)
Transplant era	1963–83	396 (21.4)	3871 (17.9)
	1984–93	418 (22.6)	3957 (18.3)
	1994–2003	399 (21.6)	4931 (22.8)
	2004–15	635 (34.4)	8870 (41.0)
Baseline immunosuppression[j]	Cyc/Aza/Pred	408 (25.5)	3654 (19.5)
	Tac/MMF/Pred	482 (30.1)	5845 (31.2)
	Cyc/MMF/Pred	242 (15.1)	4424 (23.6)
	Other	471 (29.4)	4820 (25.7)
Induction agent[k]	Anti-CD25	550 (66.6)	7384 (73.7)
	ATG	155 (18.8)	1365 (13.6)
	OKT3	12 (1.4)	931 (9.3)
	Other	32 (3.9)	342 (3.4)

Data are presented as n (%) unless stated otherwise.
[a]10 174 missing data.
[b]8115 missing data.
[c]6449 missing data.
[d]4678 missing data.
[e]4747 missing data.
[f]4673 missing data.
[g]4894 missing data.
[h]4077 missing data.
[i]3851 missing data.
[j]3131 missing data.
[k]12 629 missing data.
Cyc, cyclosporin; Aza, azathioprine; Pred, prednisone; Tac, tacrolimus; MMF, mycophenolate.

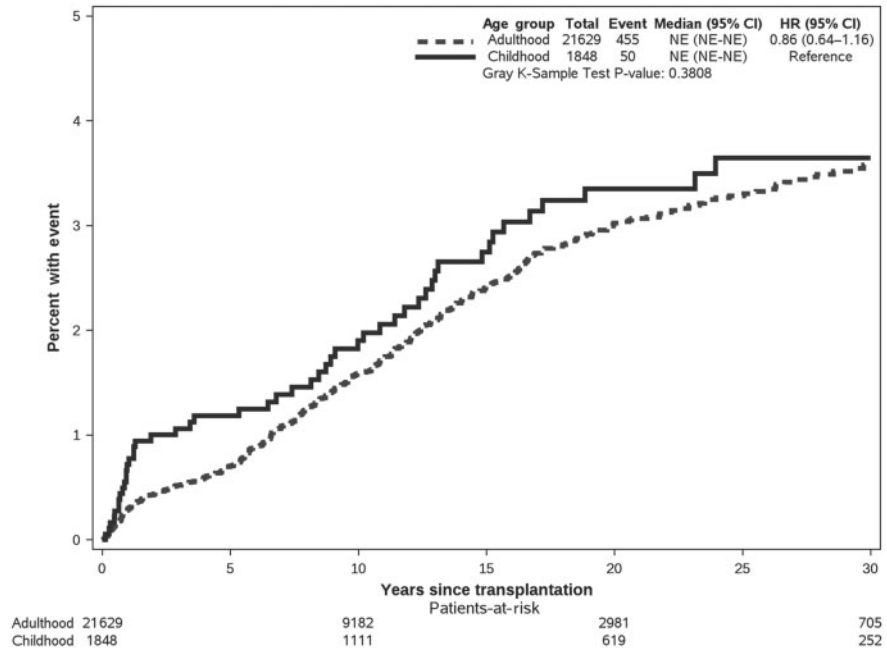


FIGURE 1: Incidence of PTLD in childhood and adult recipients of a kidney transplant, adjusted for competing risk of death.

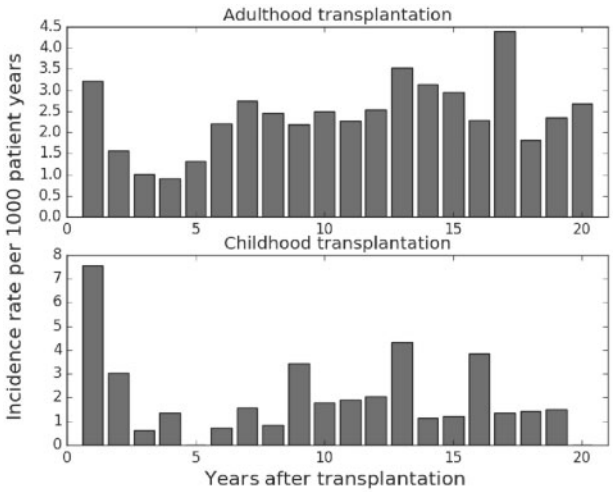


FIGURE 2: Time to PTLD for adult and childhood kidney transplant recipients.

post-transplant [13/50 (26%) compared with 62/505 (12%), $\chi^2 = 6.2$, P = 0.01). After the initial peak, the incidence remained relatively constant (Figure 2). PTLD was most likely to occur during the first graft period [440/505 (87%)], with only 22/505 (4%) of cases occurring during a dialysis period between grafts.

The median age at PTLD diagnosis for childhood recipients was 18 years (IQR 14–26) and for adult recipients was 54 years (IQR 44–63). There was no difference in median age between nodal and extranodal disease for adults (P = 0.36) or children (P = 0.18).

Site of PTLD. The site of PTLD was nodal in 147/505 (29%) and extranodal in 358/505 (71%) (Table 2). The most common extranodal sites were gastrointestinal [115/505 (22.7%)], cerebral [72/505 (14.3%)] and renal [23/453 (5.1%)]. The majority of renal PTLD was located in the donor kidney [25/26 (96%)]. There was a trend towards childhood recipients of a kidney transplant being more likely to have nodal disease than adult recipients, although this was not significant (42% versus 28%, $\chi^2 = 3.8$, P = 0.05).

In almost every year after transplantation, extranodal PTLD was more common than nodal PTLD (Figure 3), accounting for 79% (59/75) of cases in the first year and 70% (299/430) thereafter. Kidney and large bowel/anorectal PTLD occurred earlier than other locations of PTLD (Table 2). There was no significant difference in the median time to nodal or extranodal disease for children (8 years versus 3 years; P = 0.12). However, nodal disease occurred later in adults than extranodal disease (median 10 years versus 8 years; P < 0.001).

Effect of immunosuppression and transplant era on incidence of PTLD. The risk of PTLD was similar when analysed by era (Figure 4A) and by immunosuppression at the time of transplant (Figure 4B), where patients transplanted in the recent era (predominantly tacrolimus-based therapy) experienced a lower risk of PTLD compared with patients transplanted in the previous 20 years (1990–2009), which were largely cyclosporin-based regimens. During the period 1980–89, the incidence of PTLD among recipients who received azathioprine and prednisone was similar to that of the current immunosuppression era.

Standardized incidence ratios (SIRs). Recipients of a kidney transplant during childhood or adulthood were more likely to develop PTLD than their age- and gender-matched peers.

This lifetime excess risk was more marked in kidney transplant recipients during childhood and adolescence, with 50 events compared with 2 expected [SIR 29.5 (95% CI 21.9–38.8)], with males at higher risk than females. Before the age of 20 years there were 27 events for paediatric transplant recipients, compared with 0.3 expected [SIR 86.6 (95% CI 57.1–126.0)]. Those transplanted in adulthood also experienced

Table 2. Site of PTLD and time from transplant to PTLD

Site	*n* (%)	Time to PTLD (years), mean (IQR)	Age at PTLD (years), mean (IQR)
Adult recipients ($n = 455$)			
Lymph nodes	126 (27.7)	10 (5.8–14.4)	54 (41–63)
Head/face/neck/tonsils	71 (15.6)	10 (6.2–13.6)	55 (40–63)
Extranodal	329 (72.5)	8 (2.5–12.5)	54 (45–62)
Bone marrow/reticuloendothelial	32 (7.0)	8 (3.7–14.1)	60 (50–65)
Cerebral	65 (14.3)	6 (1.3–12.5)	53 (46–61)
Stomach/oesophagus	40 (8.8)	12 (7.9–14.5)	58 (50–66)
Small bowel	29 (6.4)	11 (5.4–14.4)	51 (44–61)
Large bowel/anorectal	15 (3.3)	3 (1.1–6.3)	53 (43–59)
Kidney (22 in transplant)	23 (5.0)	3 (0.3–6.6)	54 (43–57)
Childhood recipients of a kidney transplant ($n = 50$)			
Lymph nodes	21 (42.0)	8 (3.5–13.0)	17 (12–27)
Head/face/neck/tonsils	15 (30.0)	8 (3.5–15.1)	14 (12–26)
Extranodal	29 (58.0)	3 (0.9–12.3)	18 (16–26)
Cerebral	7 (14.0)	9 (1.6–16.1)	26 (18–34)
Kidney (all in transplant)	3 (6.0)	1 (0.4–1.2)	15 (13–18)

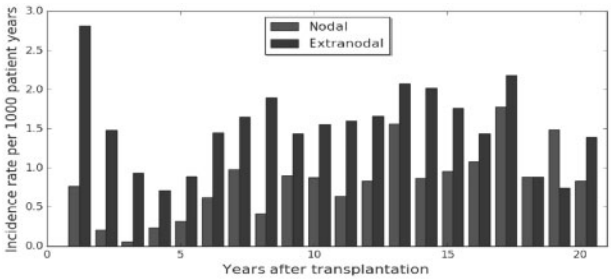


FIGURE 3: Incidence of nodal and extranodal PTLD in each year after transplantation.

higher rates of PTLD, with 54 expected cases and 455 observed [SIR 8.4 (95% CI 7.7–9.2)] (Table 3).

Predictors of PTLD. Univariate analyses for predictors of PTLD during the first graft in the modern era of immunosuppression are shown in Supplementary data, Table S1. EBV-negative recipient serology [adjusted hazard ratio (aHR) 3.33 (95% CI 2.21–5.01), $P < 0.001$], year of transplantation [aHR 0.93 for each year after the year 2000 (95% CI 0.88–0.99), $P = 0.02$], Caucasian race [aHR 1.98 (95% CI 1.10–3.57)], deceased donor [aHR 1.63 (95% CI 1.10–2.41), $P = 0.02$], induction with an agent other than monoclonal anti-CD25 antibody [aHR 2.07 (95% CI 1.16–3.70), $P = 0.01$] and having diabetes [aHR 3.49 (95% CI 2.26–5.38), $P < 0.001$] were independently associated with PTLD when adjusted for age group (Table 4).

In a time-stratified model, childhood transplant recipient, non-monoclonal anti-CD25 induction and negative EBV recipient serology were associated with increased risks of PTLD in the first 4 years, whereas diabetes contributed to increased risk after 4 years post-transplant (Supplementary data, Table S2 and Figure S2).

DISCUSSION

In this large cohort of kidney transplant recipients followed for >250 000 person-years, the cumulative incidence of PTLD for both adult and childhood recipients was ∼3% by 25 years after transplantation, after accounting for the competing risk of death. There appeared to be a bimodal distribution, with peaks in the first year and after 6 years. Extranodal disease accounted for more than two-thirds of cases, with the gastrointestinal tract and brain most frequently affected. Both children and adults were more likely to develop lymphoma than the age- and gender-matched general population, with a 20-fold higher risk in paediatric recipients and an 8-fold higher risk in adult recipients. In the modern era of immunosuppression, negative EBV serology and having type II diabetes were associated with an increased risk of PTLD by 3- to 4-fold. In Australia and New Zealand, the risk of PTLD has decreased by 8% per year over the last 15 years, to a rate of 1.5 cases per 1000 patient-years since the year 2000.

Early PTLD has been variably defined as occurring in the 1 [11] or 2 [7] years post-transplant. In this study, there was a bimodal distribution of the time to PTLD, peaking in the first year and after 6 years. This confirms an earlier report from the same database as well as French and North American studies [11, 20, 27]. The long follow-up period of this study allows a clearer picture of the timing of PTLD, showing that risk is not confined to the early period, but extends well into the post-transplant journey. In addition, the timing of PTLD appears to differ between paediatric and adult recipients, with a quarter of paediatric-recipient PTLD occurring in the first year post-transplant, compared with 10% of adult PTLD.

The incidence of PTLD also appears to vary over time. For every year since 2000 there has been an 8% reduction in the risk of developing PTLD. This finding is similar to a single study that reported a decreasing incidence of PTLD across a shorter time period from 1998 to 2005 [8]. There may be multiple reasons for this observation, including variable drug levels, changing maintenance immunosuppression and possible changes in rates of rejection over time. In addition, it could reflect changing patterns around the diagnosis of PTLD, with multiple changes in diagnostic criteria over time [28].

PTLD was more likely to be extranodal in origin and this was observed to be consistent over time since transplantation. Prior reports have suggested that early-onset disease was more likely to involve extranodal sites [8, 11]. This is the largest report with site-specific incidence and we have shown that early-onset disease

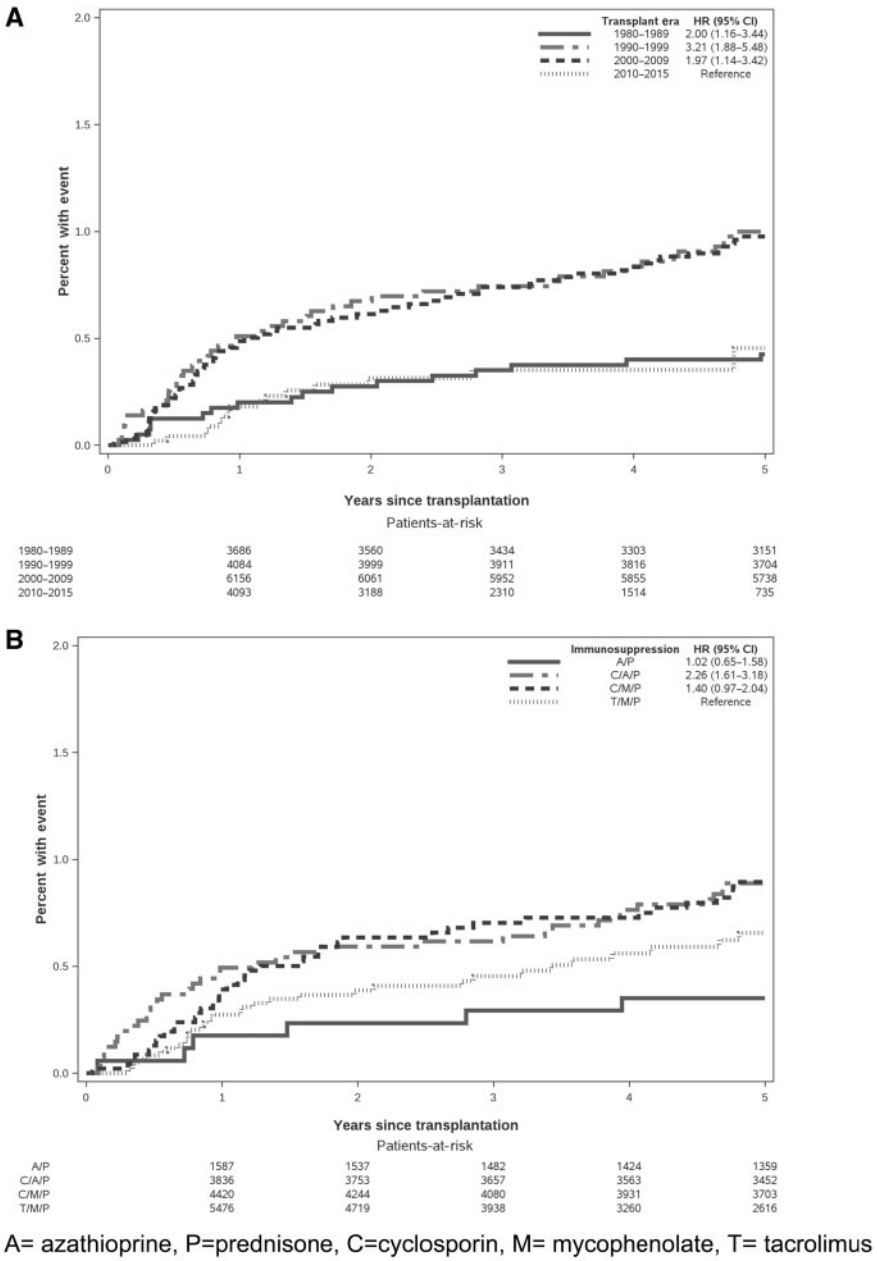


FIGURE 4: Incidence of PTLD stratified by transplant era and immunosuppression. (**A**) Incidence of PTLD by era of transplantation. (**B**) Incidence of PTLD by immunosuppressive regimen. A, azathioprine; P, prednisone; C, cyclosporin; M, mycophenolate; T, tacrolimus.

was more likely to involve extranodal sites such as the transplanted kidney, gastrointestinal tract and central nervous system.

The risk factors for PTLD were explored within the context of the modern era of immunosuppression. Childhood and adult transplant recipients appear to have different drivers of the risk of PTLD. Diabetes was much more common in adult transplant recipients (14%) than children (<1%). Having diabetes at the time of first transplant was associated with a 3.5-fold increased risk of PTLD, a finding not previously reported in kidney transplant recipients. However, similar findings were observed in a meta-analysis of observational studies, where the risk of NHL was increased by at least 20% among patients with diabetes in the absence of kidney disease compared to those without diabetes [29]. The altered immune state in diabetes may account for the additional increased risk of cancer [30]. A major driver of the increased risk for children was pre-transplant EBV seronegativity, which occurred in half of children, compared with <8% of adults. Negative recipient EBV serology was associated with a 3-fold increased risk of developing PTLD. The time-stratified regression analysis suggests that childhood transplantation, non-basiliximab induction and negative EBV serology are associated with earlier PTLD, whereas diabetes is associated with a longer-term risk of PTLD.

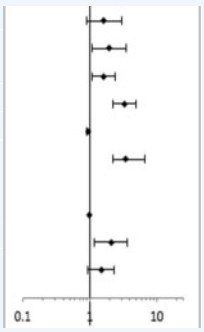
The risk of PTLD in the modern era of immunosuppression appears to be decreasing with time. This could be for multiple

Table 3. Age-standardized incidence ratio of lymphoproliferative disease

	General population observed events, *n* (person-years at risk)	Transplant population observed events, *n* (person-years at risk)	Expected events in transplant population, *n*	SIR (95% CI)
Adult at first transplant				
All	89 413 (371 977 566)	455 (210 447)	54	8.4 (7.7–9.2)
Female	39 793 (187 953 574)	154 (84 866)	19	8.0 (6.8–9.4)
Male	49 620 (184 023 992)	301 (125 581)	37	8.3 (7.4–9.3)
Child at first transplant				
All	39 850 (443 473 638)	50 (27 246)	2	29.5 (21.9–38.8)
Female	16 516 (219 028 142)	15 (11 581)	1	24.3 (13.6–40.1)
Male	23 334 (224 445 496)	35 (15 665)	1	31.3 (21.8–43.6)

Table 4. Risk factors for PTLD in the modern era (2000–15) ($n = 10\,773$)

Variable	HR (95% CI)	P-value
Childhood transplant[a]	1.63 (0.91–3.02)	0.10
Caucasian race	1.98 (1.10–3.57)	0.03
Deceased donor	1.62 (1.10–2.41)	0.73
Negative EBV serology[b]	3.33 (2.21–5.01)	<0.001
Year of transplant after 2000	0.93 (0.88–0.99)	0.02
Diabetes	3.49 (2.26–5.38)	<0.001
Induction agent		
Monoclonal T-cell (CD25)	1.0	0.04
Other agent	2.07 (1.16–3.70)	0.01
Missing data	1.47 (0.93–2.33)	0.10



[a]Age <20 years at first transplant.
[b]EBV serology in the recipient.

reasons; the decreased risk associated with monoclonal anti-CD25-based therapy (which is now the most common induction agent in Australia and New Zealand) and improved monitoring resulting in the detection of early non-malignant PTLD. Not only has the risk of PTLD been decreasing within the modern era of immunosuppression, but the risk in the era of tacrolimus-based immunosuppression appears to be lower than in earlier eras. Cyclosporin-based immunosuppression may be associated with a higher risk of PTLD. This is in contrast to earlier reports where tacrolimus was associated with a higher risk and may be due to the higher tacrolimus levels that were targeted at this time [3, 15]. In earlier transplant eras, high-dose anti-thymocyte globulin (ATG), OKT3 or muromonab CD3 and high-dose tacrolimus were associated with increased PTLD risk [2, 9, 10, 13–15, 24, 25].

Both children and adults were more likely to develop lymphoma than the age- and gender-matched general population. The lifetime relative risk of lymphoma for children with a transplant was ∼30-fold higher than for the general population, with the highest relative risk (∼90-fold) before the age of 20 years. This very high risk was lower than in a recent North American paediatric study [31]. This may reflect differing immunosuppression and induction practices between Australia/New Zealand and North America. In addition, this study has a longer follow-up time. PTLD occurs early in paediatric transplantation and thus the majority of events may have been captured within the follow-up time of both studies; however, this study was able to assess more person-years at risk, which may result in a lower overall SIR. Adult recipients of a kidney transplant were around eight times more likely to develop lymphoma than adults in the general population, similar to prior studies [11, 32].

This study has several strengths and potential limitations. It is the largest study that included adult and childhood recipients with very long-term follow-up, allowing a more comprehensive understanding of the timing of early and late PTLD. Accounting for the competing risk of death also provided a clearer understanding of the longer-term incidences of PTLD. In addition, we were able to report site-specific incidence of PTLD in both adult and paediatric kidney transplant recipients. The validity of cancer reporting in ANZDATA has been previously demonstrated [22]. This study also allowed examination of PTLD risk in the modern era of immunosuppression. EBV

data were available for the majority of cases, providing one of the largest data sets of EBV recipient data. However, EBV donor data were only available for <5% of all cases, rendering meaningful EBV mismatch analysis impossible. EBV viral loads are not commonly monitored in Australia and New Zealand, thus an analysis of the impact of post-transplant EBV infection was unable to be carried out. Histology data and tumour EBV testing were incomplete, with 47% missing, and further complicated by changing PTLD diagnostic criteria over time. The use of rituximab and valganciclovir post-transplant is also unknown. Approximately 20% of induction data were unavailable and it was unclear if the missing data were from unrecorded agents or whether no induction agents were given. Given the missing values were unlikely to be randomly distributed, imputation was not done. Instead, a category of missing induction data was created in order to allow complete case series analysis. In addition, there were limitations inherent to all registry analyses, including inability to inspect individual patient records and a lack of data on changing immunosuppression dosages over time.

In conclusion, PTLD is not uncommon and appears to occur in an early (first year post-transplant) and late manner. Childhood and adult recipients are at a similar risk of disease, but the risk in children is far higher than for their general population counterparts. Having type II diabetes and negative EBV serology at the time of transplant confer an increased risk, but the overall risk of PTLD has decreased over the last 15 years.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

A.F. participated in research design, data analysis and in writing the article. D.W.J. participated in research design and in writing the article. A.T-P. participated in data analysis and in writing the article. J.C.C. participated in research design and in writing the article. G.W. participated in research design and in writing the article.

CONFLICT OF INTEREST STATEMENT

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Transplantectomy is associated with presensitization with donor-reactive T cells and graft failure after kidney retransplantation: a cohort study

Thomas Schachtner[1,2,3,*], Natalie M. Otto[1,*], Maik Stein[2] and Petra Reinke[1,2]

[1]Department of Nephrology and Internal Intensive Care, Charité University Medicine Berlin, Campus Virchow Clinic, Berlin, Germany, [2]Berlin-Brandenburg Center of Regenerative Therapies (BCRT), Berlin, Germany and [3]Berlin Institute of Health (BIH)—Charité and Max-Delbrück Center, Berlin, Germany

Correspondence and offprint requests to: Thomas Schachtner; E-mail: thomas.schachtner@charite.de; Twitter handle: @T_Schachtner
*These authors contributed equally to this work.

ABSTRACT

Background. The number of kidney transplant recipients (KTRs) being waitlisted for a subsequent transplantation has disproportionately increased to almost 25%. Evidence for the optimal management of the failed allograft, however, remains inconsistent.

Methods. We studied 111 KTRs who underwent their second kidney transplantation from 1998 to 2015. In 51/111 KTRs (46%) the failed allograft was removed and in 60/111 (54%) the failed allograft was retained. KTRs with primary non-function and allograft loss <12 months of the first failed allograft were excluded from analysis. Samples were collected before transplantation and at 1 month posttransplantation and donor-reactive T cells were measured using an interferon-γ enzyme-linked immunosorbent spot assay.

Results. KTRs with the previous allograft removed showed significantly higher rates of acute cellular rejection compared with KTRs with the previous allograft retained [27/51 KTRs (53%) versus 18/60 KTRs (30%); P = 0.019]. KTRs with the previous allograft removed showed significantly inferior death-censored allograft survival compared with KTRs with the previous allograft retained (P = 0.022). Here, KTRs with the previous allograft removed showed significantly higher donor-reactive T cells pretransplantation compared with KTRs with the previous