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Risk Factors for Early-onset and Late-onset Post-transplant Lymphoproliferative Disorder in U.S. Kidney Recipients

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Summary

Incidence of post-transplant lymphoproliferative disorder (PTLD) is bimodal, suggesting distinct early-onset and late-onset subtypes. We evaluated differences in risk factors for early-onset and late-onset PTLD in a retrospective cohort study of U.S. kidney transplant recipients using data from the Scientific Registry of Transplant Recipients (N=156,740, 1999–2007). Multivariate hazard ratios (HRs) for risk factors were estimated using proportional hazards models. For early-onset PTLD, significantly increased risk was associated with young age at transplantation (HR 3.97 for <20 vs. 20–50 years), non-Hispanic white race/ethnicity (HR 1.82), and seronegativity for Epstein Barr virus (EBV) and cytomegalovirus at transplantation (HRs 3.13 and 1.49, respectively). By comparison, younger and older age (HRs 2.68 and 1.28 for <20 and >50, respectively, vs. 20–50 years) and non-Hispanic white race/ethnicity (HR 1.77) increased late-onset PTLD risk. The association with young age was weaker for late-onset than early-onset PTLD ($p=0.06$), and EBV and cytomegalovirus serostatus were not associated with late-onset PTLD risk. These results support somewhat different etiologies for early-onset and late-onset PTLD. For early-onset PTLD, associations with young age and EBV seronegativity highlight the etiologic role of primary EBV infection. For late-onset PTLD, higher risk with older age is consistent with lymphoma patterns in the general population.

Keywords

kidney transplant; United States; Epstein-Barr Virus; post-transplant lymphoproliferative disorder

Solid organ transplant recipients have an elevated risk for some malignancies, due to the requirement for immunosuppression (1). In particular, non-Hodgkin lymphoma (NHL) is common and comprises one end of a spectrum of post-transplant lymphoproliferative disorder (PTLD) ranging from benign hyperplasia to lymphoid malignancy (2). PTLD risk is influenced by the type of organ transplanted, the age and Epstein Barr virus (EBV) serostatus of the transplant recipient, and the intensity of immunosuppression (3–9). PTLD incidence is high immediately after transplantation, decreases subsequently, then rises again 4–5 years from transplantation (10;11). This incidence pattern suggests the presence of separate early-onset and late-onset PTLD subtypes. Early-onset PTLDs tend to be EBV-positive and, when extranodal, are more likely than late-onset PTLDs to be localized to the transplanted organ (12;13). Late-onset PTLD is less likely to be associated with EBV, and overall is more likely than early-onset PTLD to be extranodal (13;14). The Scientific Registry of Transplant Recipients (SRTR) includes data on a large number of U.S. solid organ transplant recipients and information on malignancies diagnosed post-transplant. We

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used these data to conduct a retrospective cohort study among kidney transplant recipients to examine differences in risk factors between early-onset PTLD and late-onset PTLD.

The study included 156,740 kidney transplant recipients (Table 1). During follow-up, 762 cases of PTLD were diagnosed. Cumulative incidence of PTLD at 5 and 10 years after transplantation was 0.7% and 1.4%, respectively. As shown in Figure 1, a “U-shaped” pattern of incidence with time since transplantation was observed, with high PTLD incidence shortly after transplantation, decreasing until approximately 4 years from transplantation, and rising thereafter. Early-onset PTLD (i.e., within the first two years after transplant, N=361) was more likely to be monomorphic than polymorphic (48.2% vs. 41.6%, with 10.2% of unknown pathology), and late-onset PTLD (more than two years after transplant, N=401) was even more likely to be of monomorphic pathology (55.9% vs. 31.4%, 12.7% unknown). Early-onset PTLD was predominantly of B-cell origin (72.3% B-cell versus 4.2% T-cell, 23.6% unknown). Late-onset PTLD showed a slightly higher proportion of T-cell PTLD (64.3% B-cell versus 9.7% T-cell, 25.9% unknown).

We examined PTLD risk factors stratified by onset time (Table 2). Gender was not associated with early-onset PTLD risk, but males had significantly higher late-onset PTLD risk than females (hazard ratio [HR] 1.23). Young age was more strongly associated with risk of early-onset PTLD than late-onset PTLD (HRs 6.59 and 2.98, respectively, compared to age 20–50 years at transplant; $p<0.0001$ for difference in HRs), while older age (>50 years) was significantly associated only with late-onset PTLD risk (HR 1.29). Non-Hispanic whites were at significantly higher risk of early-onset and late-onset PTLD than other racial/ethnic groups (HRs 2.09 and 1.76, respectively). EBV seronegativity was associated with significantly increased risk of both early-onset and late-onset PTLD, although the association was much stronger for early-onset PTLD (HRs 4.76 vs. 1.52, $p<0.0001$). CMV seronegativity was also associated with increased early-onset PTLD risk more strongly than late-onset PTLD risk (HRs 2.44 vs. 1.25, $p=0.0001$).

Steroid maintenance therapy did not impact early-onset PTLD risk, but significantly decreased the risk of late-onset PTLD (HR 0.64). Use of antibody induction or anti-rejection therapies was not associated with PTLD risk, even when restricted to T-cell based therapies (Table 2). The degree of HLA mismatch was also not associated with PTLD risk, regardless of the timing of PTLD onset.

Results of separate multivariate models for early-onset and late-onset PTLD are shown in Table 3. When EBV and CMV serostatus were not included (model 1), young age was significantly associated with both early-onset and late-onset PTLD risk (HRs 6.47 and 2.92, respectively, compared to age 20–50 years), and non-Hispanic whites were at significantly increased risk of both early-onset PTLD and late-onset PTLD, compared to other racial/ethnic groups (HRs 2.11 and 1.73, respectively). The association with young age was stronger for early-onset than for late-onset PTLD ($p<0.0001$).

With addition of information for EBV and CMV serostatus (model 2), young age remained significantly associated with both early-onset and late-onset PTLD risk (HRs 3.97 and 2.68, respectively, compared to age 20–50 years), although the association was attenuated for early-onset PTLD compared to the results of model 1. Non-Hispanic whites continued to be at significantly increased risk of both early-onset PTLD and late-onset PTLD compared to other racial/ethnic groups (HRs 1.82 and 1.77, respectively). EBV and CMV seronegativity were significantly associated with increased risk of early-onset PTLD only (HRs 3.13 and 1.49, respectively). In both multivariate models, gender was no longer associated with risk of either early-onset or late-onset PTLD. When added to model 2, steroid maintenance therapy remained a significant predictor of decreased late-onset PTLD risk (HR 0.66).

This large retrospective cohort study of kidney transplant recipients showed a clear bimodal pattern in onset for PTLD, and there were distinct differences in pathology and risk factors between early-onset PTLD and late-onset PTLD. Independent risk factors for early-onset PTLD included young age at transplantation, and EBV and CMV seronegativity. By comparison, independent risk factors for late-onset PTLD included older age at transplantation, and non-Hispanic white race/ethnicity. Although the differences in risk factors were not large, the results suggest that early-onset and late-onset PTLD comprise different entities with somewhat different etiologies.

The cumulative incidence of PTLD in our study was similar to that reported previously (9;10;15;16). As in prior studies (10;11), we also observed a “U-shaped” pattern of PTLD incidence with time since transplantation. This pattern identifies early-onset PTLD, occurring in the 1–2-year period immediately following transplantation, and late-onset PTLD, occurring some years later. In our study, a greater proportion of late-onset PTLDs than early-onset PTLDs were of monomorphic pathology and of T-cell origin. Other studies have found similar biological differences between early-onset PTLD and late-onset PTLD (13;17). While early-onset PTLD is more likely than late-onset PTLD to be localized in the transplanted organ (12;13), we were unable to examine this pattern in our study due to insufficient data on tumor location.

The increased risk of PTLD seen in young recipients (9;18) is likely due to the high percentage who are EBV naive at transplantation, leaving them susceptible to primary infection immediately following transplantation. Supporting this interpretation, we found that the association of young age at transplant with early-onset PTLD became weaker when we included EBV serostatus in a multivariate model (model 2 vs. model 1, Table 3). Primary infection during the period of intense immunosuppression immediately following transplantation allows for uncontrolled EBV-driven lymphoproliferation (4;7;19). The vast majority of early-onset PTLDs express EBV proteins (13). The role of CMV infection is less well understood. An earlier study pointed to a possible synergistic role of CMV disease with primary EBV infection in causing PTLD (20). Nonetheless, the association that we observed between CMV serostatus and risk of early-onset PTLD could be the result of uncontrolled confounding, since CMV serostatus is related to age, EBV serostatus, and perhaps other unmeasured factors. In our study EBV seronegativity was not an independent risk factor for late-onset PTLD, although this has been suggested in other work (21).

We did not find an association between antibody induction therapy and early-onset PTLD risk, in contrast to earlier reports (9;19;22;23). The discrepancy could relate to calendar period differences, because we focused on a later calendar period (1999–2007), well after widespread introduction of antibody induction therapy during the mid to late 1990s (24). When new therapies are introduced, the rate of PTLD has been observed to increase as transplant centers work to establish the appropriate dosing regimen to ensure a balance of efficacy and safety (“learning-curve” effect) (1). We hypothesize that transplant centers had had sufficient time by 1999 to gain experience with antibody-based induction therapies, leading to an attenuation of associated PTLD risk.

In terms of pathology and clinical features, compared to early-onset PTLDs, late-onset PTLDs more closely resemble lymphomas seen in the general population (8). In the general population, NHL incidence is higher among non-Hispanic whites than other races/ethnicities and increases monotonically with age (25;26), which may explain the observed associations of these two factors with late-onset PTLD. While the association with increasing age has been described previously (9;27), the protective effect of steroid-based maintenance therapy on late-onset PTLD risk is a new finding. Of interest, research on NHLs in the general population has yielded inconsistent results on the possible effect of steroid-based

medications, with some studies showing that they increase NHL risk and other studies showing no relationship (28).

Our study had several important strengths, including its large size and inclusion of both malignant and non-malignant PTLDs. Limitations to our study also need to be considered. We likely did not have complete ascertainment of PTLT, especially for diagnoses that occurred late after transplantation. Transplant centers are typically able to follow a very high percentage of recipients in the first 1–2 years after transplantation, but this percentage decreases with time, and by 5 years post-transplant, up to 25% of kidney transplant recipients may be lost to follow-up (29). Losses to follow-up would have led to underestimation of PTLT incidence but should not have differed across the risk factors we examined. Missing data on EBV and CMV serology for a large percentage of transplant recipients required that we impute the data using demographic and other characteristics, so that these findings need to be interpreted with some caution. In addition, our data on immunosuppressive medications were limited to baseline and did not include specific dosing information. Thus, we could not assess the effect of immunosuppressive intensity or changes in the immunosuppressive regimen on PTLT risk.

In conclusion, the bimodal timing of PTLT after transplant and the observed differences in pathology and risk factors provide evidence that early-onset PTLT and late-onset PTLT are either distinct disease entities or, perhaps more likely, are composed of a variable mixture of subtypes with different etiologies. PTLT remains an important source of morbidity associated with solid organ transplantation, and additional research on the risk factors and clinical features of PTLT, particularly late-onset PTLT, is required to better understand the role of prolonged immunosuppression and immune dysfunction in lymphomagenesis.

Methods

We conducted a retrospective cohort study of U.S. kidney transplant recipients using SRTR data. Data on all U.S. kidney transplants since 1986 are provided by transplantation centers and organ procurement organizations that together comprise the Organ Procurement and Transplantation Network (OPTN). Baseline data are collected at the time of registration and at transplantation, and follow-up data are collected 6 and 12 months after transplantation and annually thereafter. Recipients of first kidney transplants conducted between October 1, 1987, and August 31, 2007 were eligible for the present study. Included recipients had no evidence of human immunodeficiency virus infection and had at least 30 days of follow-up after transplantation.

For each transplant recipient, SRTR data included demographic characteristics, human leukocyte antigen (HLA) mismatches with the donor at the A, B, and DR loci, and serology results for EBV (EBV IgG) and cytomegalovirus (CMV IgG). Information on the initial immunosuppressive regimen prescribed prior to hospital discharge was obtained.

Transplant centers reported on the occurrence of PTLT during follow-up, which were categorized according to pathology (polymorphic including hyperplasia, monomorphic, or unknown) and cell type (B-cell, T-cell, or unknown). Cases of multiple myeloma and Hodgkin lymphoma were excluded. Reporting of PTLT to the SRTR changed over time. OPTN did not routinely collect PTLT data on kidney transplant recipients until March 1, 1997. In 1999, the SRTR transitioned from a paper-based to a web-based system for filing follow-up reports.

Statistical analysis

Recipients were followed from 30 days after transplant until the earliest of PTLT diagnosis, graft failure, re-transplantation, death, loss to follow-up, or 10 years post-transplantation. To ensure uniform reporting of PTLT, we included only follow-up time and PTLT events from January 1, 1999 onwards.

Based on the pattern of PTLT risk in relation to time since transplant, we divided cases into early-onset PTLT (within 2 years of transplantation) and late-onset PTLT (2 or more years from transplantation). Risk factors for these two periods were evaluated using separate proportional hazards regression models. In these analyses, recipients contributed to each model during their person-time within the window of interest. To determine if the strength of association differed for each risk factor between early-onset and late-onset PTLT, we tested the significance of an interaction term between the variable of interest and a time-dependent indicator variable that distinguished early and late follow-up periods. In multivariate models, we included variables that were significant in univariate models or seemed relevant based on earlier work.

Baseline EBV and CMV data were missing for 62.1% and 41.9% of recipients, respectively. We therefore used a multiple imputation approach to assign EBV and CMV baseline serostatus based on demographic and transplant characteristics for recipients initially missing this information. This full dataset including the imputed values was used to estimate hazard ratios associated with EBV and CMV serostatus. The imputation and estimation was repeated 10 times and the results were combined using the Rubin method in the MIANALYZE procedure (SAS, Version 9.1, Cary, NC) (30).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Incidence of post-transplant lymphoproliferative disorder (PTLD) among kidney recipients during 1999–2007. Incidence and 95% confidence intervals are shown as a function of time since transplantation. PTLD incidence is displayed as PTLD events per 100,000 person-years. Follow-up for all recipients began 30 days (0.083 years) after transplantation.

Table 1

Demographic and transplant characteristics of kidney recipients followed during 1999–2007 in the United States (N=156,740)

Characteristic	Recipients, n (%)
Gender	
Male	93,830 (59.9%)
Female	62,910 (40.1%)
Age at transplant, years	
0–19	10,711 (6.8%)
20–50	82,186 (52.4%)
>50	63,843 (40.7%)
Median age	47.0
Race/ethnicity	
Non-Hispanic white	91,867 (58.6%)
Other	64,873 (41.4%)
Calendar year of transplant	
1987–1995	29,081 (18.6%)
1996–1998	25,902 (16.5%)
1999–2007	101,757 (64.9%)
EBV serostatus	
Positive	49,790 (31.8%)
Negative	9,666 (6.2%)
Missing/not done	97,284 (62.1%)
CMV serostatus	
Positive	56,877 (36.3%)
Negative	34,250 (21.8%)
Missing/not done	65,613 (41.9%)
Antibody induction *	
Yes	84,458 (54.5%)
No	70,373 (45.5%)
T-cell antibody induction *	
Yes	45,984 (29.7%)
No	108,847 (70.3%)
Steroid maintenance *	
Yes	135,635 (87.6%)
No	19,196 (12.4%)
Anti-rejection therapy *	
Yes	12,780 (8.3%)
No	142,051 (91.7%)
T-cell anti-rejection therapy **	
Yes	5,729 (3.7%)
No	149,102 (96.3%)

Characteristic	Recipients, n (%)
HLA mismatch , number of alleles	
0–2	46,838 (30.1%)
3–4	66,269 (42.6%)
5–6	42,300 (27.2%)

Notes

Abbreviations: EBV Epstein Barr virus, CMV cytomegalovirus, HLA human leukocyte antigen Recipients accrued a total of 532,342 person-years of follow-up (mean 3.4 years per recipient).

* Medication information was missing for 1,909 kidney recipients.

[†] HLA mismatch information was missing for 1,333 kidney recipients.

[§] Reason for transplant was missing for 355 kidney recipients.

** T-cell directed therapies included thymoglobulin, anti-thymocyte globulin (ATG), Campath, OKT3, OKT4, NRATG, and anti-lymphocyte globulin (ALG).

Table 2

PTLD risk factors among U.S. kidney transplant recipients during 1999–2007

Characteristic	Early-onset PTLD HR(95% CI)*	Late-onset PTLD HR (95% CI)*	P-value [†]
Gender			
Male	1.00 (0.81–1.24)	1.23 (1.01–1.51)	0.16
Female	1.0 (ref)	1.0 (ref)	
Age at transplant, years			
0–19	6.59 (5.12–8.48)	2.98 (2.26–3.92)	<0.0001
20–50	1.0 (ref)	1.0 (ref)	
>50	1.04 (0.81–1.33)	1.29 (1.04–1.61)	0.19
Race/ethnicity			
Non-Hispanic white	2.09 (1.66–2.64)	1.76 (1.41–2.21)	0.30
Other	1.0 (ref)	1.0 (ref)	
EBV serostatus			
Positive	1.0 (ref)	1.0 (ref)	
Negative	4.76 (3.70–5.88)	1.52 (1.12–2.08)	<0.0001
CMV serostatus			
Positive	1.0 (ref)	1.0 (ref)	
Negative	2.44 (1.89–3.13)	1.25 (0.97–1.61)	0.0001
Antibody induction			
Yes	1.08 (0.87–1.34)	1.23 (1.00–1.50)	0.39
No	1.0 (ref)	1.0 (ref)	
T-cell antibody induction			
Yes	1.19 (0.95–1.49)	1.22 (0.99–1.51)	0.86
No	1.0 (ref)	1.0 (ref)	
Steroid maintenance			
Yes	1.33 (0.96–1.84)	0.64 (0.44–0.95)	0.005
No	1.0 (ref)	1.0 (ref)	
Anti-rejection therapy			
Yes	0.68 (0.40–1.14)	1.15 (0.84–1.57)	0.09
No	1.0 (ref)	1.0 (ref)	
T-cell anti-rejection therapy**			
Yes	0.62 (0.26–1.51)	1.08 (0.67–1.74)	0.29
No	1.0 (ref)	1.0 (ref)	
HLA mismatch, number of alleles			
0–2	1.0 (ref)	1.0 (ref)	
3–4	1.12 (0.88–1.44)	1.02 (0.82–1.28)	0.56
5–6	0.85 (0.64–1.13)	1.02 (0.78–1.34)	0.36

Notes

Abbreviations: PTLD post-transplant lymphoproliferative disorder, HR hazard ratio, CI confidence interval, EBV Epstein-Barr virus, CMV cytomegalovirus, HLA human leukocyte antigen

* Early-onset PTLT is defined as occurring less than 2 years after transplantation; late-onset PTLT is defined as occurring 2 or more years after transplantation. Hazard ratio is based on a univariate proportional hazards regression model.

[†] P-value compares hazard ratios for early-onset and late-onset PTLT and is based on the significance of an interaction term between the variable of interest and an indicator variable that distinguished early and late follow-up periods.

** T-cell directed therapies included thymoglobulin, anti-thymocyte globulin (ATG), Campath, OKT3, OKT4, NRATG, and anti-lymphocyte globulin (ALG).

Table 3
Multivariate analysis of risk factors for PTLTD among U.S. kidney transplant recipients during 1999–2007

Characteristic	Model 1			Model 2		
	Early-onset PTLTD HR (95% CI)*	Late-onset PTLTD HR (95% CI)*	P-value†	Early-onset PTLTD HR (95% CI)*	Late-onset PTLTD HR (95% CI)*	P-value†
Gender						
Male	1.00 (0.81–1.23)	1.20 (0.98–1.47)	0.21	0.93 (0.75–1.15)	1.19 (0.97–1.47)	0.10
Female	1.0 (ref)	1.0 (ref)		1.0 (ref)	1.0 (ref)	
Age at transplant, years						
<20	6.47 (5.02–8.33)	2.92 (2.21–3.84)	<0.0001	3.97 (3.02–5.22)	2.68 (1.97–3.64)	0.06
20–50	1.0 (ref)	1.0 (ref)		1.0 (ref)	1.0 (ref)	
>50	0.98 (0.77–1.26)	1.26 (1.02–1.57)	0.14	1.09 (0.85–1.41)	1.28 (1.02–1.60)	0.37
Race/ethnicity						
Non-Hispanic white	2.11 (1.68–2.67)	1.73 (1.38–2.16)	0.22	1.82 (1.43–2.32)	1.77 (1.39–2.25)	0.87
Other	1.0 (ref)	1.0 (ref)		1.0 (ref)	1.0 (ref)	
EBV serostatus						
Positive	--	--		1.0 (ref)	1.0 (ref)	
Negative				3.13 (2.44–4.17)	1.26 (0.91–1.79)	<0.0001
CMV serostatus						
Positive	--	--		1.0 (ref)	1.0 (ref)	
Negative				1.49 (1.15–1.96)	0.99 (0.75–1.30)	0.02

Notes

Abbreviations: PTLTD post-transplant lymphoproliferative disorder, HR hazard ratio, CI confidence interval, EBV Epstein-Barr virus, CMV cytomegalovirus

* Early-onset PTLTD is defined as occurring less than 2 years after transplantation; late-onset PTLTD is defined as occurring 2 or more years after transplantation. Hazard ratios are based on a multivariate proportional hazards regression model controlling for gender, age at transplant, race/ethnicity, EBV status, and CMV status.

† P-value compares hazard ratios for early-onset and late-onset PTLTD and is based on the significance of an interaction term between the variable of interest and an indicator variable that distinguished early and late follow-up periods.