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Early- and late-onset posttransplant lymphoproliferative disorders among adult kidney and liver transplant recipients

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Abstract

Objectives: Posttransplant lymphoproliferative disorder (PTLD) in solid organ transplant recipients has a high mortality and may present early (<2 years) or late (≥2 years) posttransplantation. We investigated the clinical characteristics of early and late PTLD among kidney and liver transplant recipients.

Methods: Recipients, transplanted at Rigshospitalet, with PTLD development as adults from January 2010 to August 2020, were included. Clinical characteristics, laboratory parameters, and pathology of early and late PTLD were compared.

Results: Thirty-one PTLD cases were detected where 10 (32%) were early and 21 (68%) were late PTLD. EBV DNA in plasma was detected in 78% versus 28% in early and late PTLD ($p = .037$). None of the recipients with early PTLD and nine recipients with late PTLD (47%) had Ann Arbor stage IV at the time of their diagnosis ($p = .006$). Cyclophosphamid–Hydroxyrubicin–Oncovin–Prednisolon was used for treatment in 10 (48%) recipients with late PTLD ($p = 0.032$) only. There was no difference in mortality between the two groups.

Conclusions: Recipients with late PTLD had a lower prevalence of detectable EBV DNA in plasma, were diagnosed with more advanced disease, and were more frequently treated with chemotherapy compared to recipients with early PTLD.

KEYWORDS
kidney transplantation, liver transplantation, posttransplant lymphoproliferative disorder, solid organ transplantation

1 | INTRODUCTION

Solid organ transplant (SOT) recipients have an increased risk of infections and malignancies due to the immunosuppression they receive in order to prevent allograft rejection.[1] A well-known malignancy in SOT recipients is posttransplant lymphoproliferative disorder (PTLD),[2,3] which encompasses a broad spectrum of clinico-pathological presentations, ranging from benign neoplasms to disseminating monoclonal malignancies.[4–6]

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The incidence of PTLD in transplant recipients has increased during the last decades due to the use of more potent immunosuppressive regimens,[7] now reaching a cumulative 10-year incidence of 2% and 4% for adult kidney and liver transplant recipients, respectively.[6–10] The incidence of PTLD appears to have a bimodal distribution, with the highest incidence the first 2-year posttransplantation and a second peak approximately 5-year posttransplantation.[6,8,11] Further, there seem to be clinical and pathological differences in these early versus late PTLD cases.[12–15] Early PTLD tends to be associated with Epstein–Barr virus (EBV), the tumor cells are often CD20 positive and are often associated with graft involvement compared to late PTLD.[13,16,17] Still much is unknown and a better understanding of the differences between early and late PTLD could have clinical implications in terms of achieving more timely diagnosis and initiation of treatment. Therefore, we conducted a retrospective cohort study including all kidney and liver transplant recipients at a large tertiary transplant center who were diagnosed with PTLD as adults during the last decade to compare clinical, pathological, and treatment-related characteristics and outcomes of early and late development.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This retrospective cohort study included all PTLD, among kidney and liver recipients, diagnosed at Rigshospitalet, University of Copenhagen, between January 1, 2010 and August 31, 2020, and who were above the age of 18 years at the time of their PTLD diagnosis. The kidney and liver recipients were transplanted between January 1, 2004 and August 31, 2020.

2.2 | Material

In Denmark, each resident is provided with a unique personal civil registration (CPR) number, which allows for linkage of Danish clinical databases and registries. All data for this study were retrospectively collected from patient records, the Danish National Pathology Registry (Patobank), and the Danish National Microbiology Database (MiBA) and stored in the Knowledge Center for Transplantation (KCT) database. Patobank contains results from all Departments of Pathology in Denmark, while MiBA includes all microbiology test results from all Danish Departments of Clinical Microbiology with a complete coverage since 2010.[18,19] The KCT database contains demographics, transplant-related variables including type of transplant and immunosuppressive maintenance treatment, and outcome variables including PTLD-related mortality.

PTLD events were identified through the Centre of Excellence for Personalized Medicine in Infectious Complications in Immune Deficiency (PERSIMUNE)[20] data repository.

Retrieval of data was approved by the Centre for Regional Development (R-20051155) and permission for data storage was obtained from Pactius (P-2020-839).

2.3 | Variable and outcome definitions

Data on the immunosuppressive maintenance treatment were registered for the individual recipients 1 month before their PTLD diagnosis.

PTLD was classified according to the 2016 WHO Classification of lymphoid neoplasms and staged according to the Ann Arbor lymphoma staging system based on findings on *Positron emission tomography–computed tomography (PET/CT)*.[21,22] The recipients with PTLD were divided into two groups according to time of diagnosis relative to transplant date: early and late PTLD. Early PTLD was defined as PTLD diagnosed within the first 2 years after transplantation, while PTLD diagnosed 2 years from transplantation or thereafter was defined as late PTLD. We used a 2-year threshold based on a previous observation that the vast majority of PTLD occurred within the first 2-year posttransplant,[23] which is also supported by previous observations from other centers.[11,14,15]

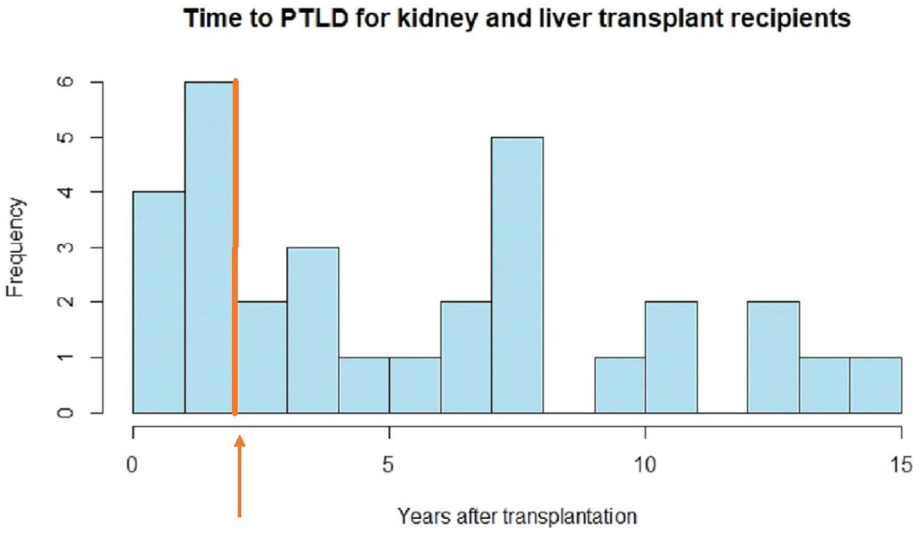

FIGURE 1 Frequency of PTLD after transplantation among kidney and liver transplant recipients. Thirty-one recipients developed PTLD. Ten of these were diagnosed within the first 2 years following transplantation (early PTLD), while 21 recipients were diagnosed with PTLD more than 2 years post-transplantation (late PTLD). The orange line marks the 2-year post-transplantation time point that distinguishes early from late PTLD. PTLD, post-transplant lymphoproliferative disorder.

TABLE 1 Demographics and clinical characteristics for kidney and liver transplant recipients with early and late PTLD

	Subsequent early PTLD ($n = 10$)	Subsequent late PTLD ($n = 21$)	p Value
Sex, male	7 (70%)	8 (38%)	$p = .135$
Age at time of transplantation in years, median (range)	**63.2 (22–70)**	**40.8 (10–72)**	**$p = .031$**
Transplanted organ			
Liver	4 (40%)	7 (33%)	$p > .999$
Kidney	6 (60%)	14 (67%)	$p > .999$
Disease leading to transplantation			
Autoimmune liver disease (LD)	1 (25%)	2 (29%)	
Cirrhosis (LD)	1 (25%)	3 (43%)	
Hepatocellular carcinoma (LD)	1 (25%)	1 (14%)	
Re-transplantation (LD)	1 (25%)	1 (14%)	
Glomerulonephritis (KD)	0	7 (50%)	
Vascular and/or hypertensive disease (KD)	2 (33%)	0	
Diabetes (KD)	2 (33%)	0	
Unknown/other kidney diseases (KD)	2 (33%)	7 (50%)	
EBV serostatus at transplantation	$n = 8$	$n = 7$	
D+/R+	7 (88%)	5 (71%)	$p = .713$
D+/R-	1 (13%)	1 (14%)	
D−/R+	0	0	
D−/R-	0	1 (14%)	
Unknown donor or recipient EBV serostatus	**2 (20%)**	**14 (67%)**	**$p = .023$**
Time from transplantation to PTLD diagnosis in years, median (IQ range)	1.3 (0.8)	7.5 (6.1)	
Status on maintenance immunosuppressive medication 1 month prior to PTLD diagnosis			
CNI, corticosteroid and MMF or AZA	7	9	
Everolimus, MMF and corticosteroid	0	2	
CNI and corticosteroid or MMF	3	6	
MMF and corticosteroid	0	2	
Everolimus or corticosteroids	0	2	
Morphological classification/histopathologic diagnosis[a] ($n = 28$)			
Nondestructive PTLD	2 (22%)	0	$p = .184$
Polymorphic PTLD	0	1 (5%)	
Monomorphic PTLD	7 (78%)	16 (84%)	
Hodgkin lymphoma-like PTLD	0	2 (11%)	
PTLD location			
Nodal	4 (40%)	9 (43%)	$p > .999$
Extra-nodal[b]	7 (70%)	17 (81%)	$p = .652$
Graft	2 (29%)	2 (12%)	$p = .552$
Liver	1 (14%)	2 (12%)	$p > .999$
Spleen	1 (14%)	0	$p = .292$
Kidney	1 (14%)	2 (12%)	$p > .999$
Gastrointestinal tract	1 (14%)	11 (65%)	$p = .069$
Pulmonary	0	2 (12%)	$p > .999$
Central nervous system	3 (43%)	2 (12%)	$p = .127$
B symptoms	4 (40%)	9 (43%)	$p > .999$

(Continues)

TABLE 1 (Continued)

	Subsequent early PTLD ($n = 10$)	Subsequent late PTLD ($n = 21$)	p Value
Ann Arbor stage ($n = 29$)			
Stage I	**8 (80%)**	**4 (21%)**	**$p = .006$**
Stage II	**1 (10%)**	**4 (21%)**	
Stage III	**1 (10%)**	**2 (11%)**	
Stage IV	**0**	**9 (47%)**	
Laboratory values at time of PTLD diagnosis			
CD20 positivity of the tumor ($n = 28$)	7 (78%)	15 (79%)	$p > .999$
Serum LDH level above normal ($n = 29$)	6 (67%)	9 (45%)	$p = .430$
EBV DNA in plasma ($n = 27$)	**7 (78%)**	**5 (28%)**	**$p = .037$**
EBV detected in PTLD tumor biopsy ($n = 23$)	5 (63%)	8 (53%)	$p > .999$
Peak EBV viral load ($n = 12$), median (IQ range)	3300 (418 400)	13 000 (629 000)	$p = .935$
Risk Groups of the International Prognostic Index[c]			
Low	4 (40%)	9 (43%)	$p = .801$
Low intermediate	4 (40%)	5 (24%)	
High intermediate	2 (20%)	5 (24%)	
High	0	0	
Treatment of PTLD			
Reduction of immunosuppression	6 (60%)	10 (48%)	$p = .704$
Rituximab[d]	8 (80%)	14 (67%)	$p = .677$
CHOP	**0**	**8 (38%)**	**$p = .032$**
ABVD	0	2 (10%)	$p > .999$
Radioimmunotherapy	1 (10%)	0	$p = .323$
Surgical removal	2 (20%)	3 (14%)	$p > .999$
Other	3 (30%)	10 (48%)	$p = .452$
Outcome			
Overall mortality, median (months), range	4 (40%)	10 (48%)	$p > .999$
	5.3 (1.7–29.8)	9.0 (0.4–107.3)	
One-year mortality	3 (30%)	6 (29%)	$p > .999$
PTLD as cause of death (1-year mortality)	3 (100%)	5 (83%)	$p > .999$
Complete remission	7 (70%)	8 (38%)	$p = .135$
Recurrence of PTLD	1 (10%)	3 (14%)	$p = .135$
Follow-up period in years, median (range)	7.56 (0.5–10.4)	4.47 (0.8–10.4)	$p = .369$

Note: IPI risk groups: Low (0–1 risk factors), low intermediate (2 risk factors), high intermediate (3 risk factors), and high (4–5 risk factors).
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AZA, azathioprine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CNI, calcineurin inhibitors; D+/R+, EBV-positive donors with graft transplanted into EBV-positive recipients; D+/R−, EBV-positive donor with graft transplanted into EBV-negative recipients; D−/R+, EBV-negative donors with graft transplanted into EBV-positive recipients and D−/R−, EBV-negative donors with graft transplanted into EBV-negative recipients, EBV, Epstein–Barr virus; KD, kidney disease; LD, liver disease; LDH, lactate dehydrogenase; MMF, mycophenolic acid; PTLD, post-transplant lymphoproliferative disorder.
[a]Three PTLD biopsies could not be classified according to the WHO 2016 Classification system of lymphoid neoplasms—two of these recipients with PTLD had multiple myeloma.
[b]Not corrected for multiple comparisons.
[c]Two unknown IPI scores due to unknown variables such as Ann Arbor stage.
[d]Nine patients were not treated with Rituximab; for example, two patients had multiple myeloma, one died shortly after the diagnosis before treatment could be initiated, while others either had CD20 negative tumors, were treated with surgical removal, or had remission due to reduction of immunosuppression.

B symptoms were present if at least one symptom (fever, weight loss, or drenching night sweats) was documented within 1 month before or after the PTLD diagnosis.

We defined EBV DNAemia at the time of PTLD diagnosis as a positive EBV PCR in plasma within 1 month before or 1 month after the date of the PTLD diagnosis.[23] According to our local reference for

s-LDH, elevated s-LDH at time of PTLD diagnosis was defined as a value above 205 U/L within 1 month before or 1 month after the date of the PTLD diagnosis.

International Prognostic Index (IPI) was calculated for each individual based on standard methods.[24]

Acute rejection of the graft was defined as either an episode of biopsy-verified acute rejection that was treated with high-dose methylprednisolone.

Underlying causes of death were classified according to *The Classification of Death Causes after Transplantation* methodology.[25]

2.4 | Statistical analyses

Comparison of the two PTLD groups at the time of transplantation, at the time of PTLD diagnosis, and at the end of follow-up was made using Fisher's exact test for categoric data, while Mann–Whitney *U*-test was used for continuous variables. Recipients with unknown results were excluded in the individual analyses. The incidence rate was calculated as the number of recipients with PTLD per Person year of follow-up (PYFU) among patients transplanted between 2010 and 2019. Estimates of the cumulative incidence of PTLD were calculated using the Aalen–Johansen estimator with death as competing risks. Data management and analysis were performed using RStudio (R version 3.6.1 [2019-07-05]). All p values were two-sided and considered statistically significant if $p \leq .05$.

3 | RESULTS

Among 1076 kidney and liver transplant recipients transplanted between January 1, 2010 and December 1, 2019, the incidence rate

FIGURE 2 Distribution of the morphological types of PTLD in recipients with early and late PTLD. The recipients with early PTLD were diagnosed with monomorphic (78%) and non-destructive (22%) PTLD. The recipients with late PTLD were diagnosed with monomorphic (84%), Hodgkin's lymphoma-like (11%) and polymorphic PTLD (5%). PTLD, post-transplant lymphoproliferative disorder.

was 2.65 (95% confidence interval [CI]: 1.52–4.33) per 1000 patient-year. The cumulative incidence of PTLD was 0.38% (95% CI: 0.008–0.747) the first year, 0.79% (95% CI: 0.24–1.33) the second year, and 1.1% (95% CI: 0.80–3.67) after 5 years. A total of 31 recipients developed PTLD in our study period, 10 recipients (32%) developed early PTLD, while the remaining 21 recipients (68%) developed late PTLD. The median time from transplantation to PTLD was 1.3 and 7.5 years in the early and late PTLD groups, respectively. The frequency of PTLD development posttransplantation is presented in Figure 1.

3.1 | Clinical characteristics of early versus late PTLD at time of transplantation and thereafter

Demographics on recipients who developed early and late PTLD are presented in Table 1. There was no significant difference between early and late PTLD with regards to gender (70% vs. 38% males in the early vs. late PTLD groups, $p = .135$) or EBV serostatus at time of transplantation (7 [88%] and 5 [71%] of the early vs. late PTLD were seropositive at time of transplantation).

Episodes of acute rejection before PTLD diagnosis occurred in both PTLD groups with no significant difference (2 [20%] and 3 [14%] recipients with acute rejections in the early vs. late PTLD groups, $p > .999$).

3.2 | Characteristics of PTLD in early versus late PTLD at time of diagnosis

Early PTLD had significantly lower Ann Arbor[22] stage at time of PTLD diagnosis compared to late PTLD, with eight (80%) of the recipients being diagnosed at Stage I and none at Stage IV. Conversely, nine recipients with late PTLD (47%) had Ann Arbor Stage IV at the time of their diagnosis. There was no difference in the IPI between the two groups, Table 1. Overall, monomorphic PTLD ($n = 23$, 82%) was the most frequent morphological PTLD type, followed by non-destructive PTLD ($n = 2$, 7%), Hodgkin's lymphoma-like PTLD ($n = 2$, 7%), and polymorphic PTLD (n = 1, 4%), as illustrated in Figure 2.

A higher proportion of recipients with early compared to late PTLD had EBV DNAemia (7 [78%] and 5 [28%], respectively, $p = .037$) at time of PTLD diagnosis, whereas there was no significant difference in EBV detection in PTLD tumors (5 [63%] and 8 [53%], respectively, $p > .999$). Further, no difference in the median peak EBV viral load among those with EBV DNAemia was found between the two groups (3300 and 13 000 copies/ml in the early and late PTLD groups, respectively, $p = .935$). EBV was not detected in neither plasma nor the tumor biopsies at time of PTLD diagnosis in one (14%) and five (36%) of the recipients with early and late PTLD, respectively.

3.3 | PTLD treatment and outcomes of early versus late PTLD

Rituximab was used as PTLD treatment in 8 (80%) and 14 (67%) recipients with early and late PTLD, respectively. Ten recipients with late PTLD were treated with chemotherapy whereas this treatment was not given to early PTLD (Table 1).

Overall mortality was 40% and 48% in the early and late PTLD groups ($p > .999$). PTLD was the cause of death in all recipients with early and five of the six recipients with late PTLD. The last recipient with late PTLD died from cardiac disease. Complete remission was achieved in seven recipients (70%) in the early PTLD group compared to eight recipients (38%) in the late PTLD group ($p = .135$). Data on PTLD treatment and outcomes are presented in Table 1.

4 | DISCUSSION

In this retrospective cohort study, we investigated the clinical, pathological, and treatment-related differences between kidney and liver transplant recipients who developed early and late PTLD as adults over a 10-year period. Recipients with early PTLD more often had EBV DNAemia detected at time of PTLD diagnosis compared to recipients with late PTLD. Furthermore, recipients with early PTLD were diagnosed at a significantly lower Ann Arbor stage compared to recipients with late PTLD. The recipients with late PTLD were more likely to receive treatment with chemotherapy. We found a 1-year mortality of 29% in the whole cohort with no difference between the two PTLD groups.

Rituximab treatment, which is considered the cornerstone of PTLD treatment, was not given to a few of the PTLD patients. This was mainly due to alternative treatments such as reduction of immunosuppression or surgical removal of tumor, which subsequently cured the patient or due to CD20 negative tumors.

Children and adolescents have previously been reported to have a higher risk of developing PTLD, and some studies have found an association between younger age and early PTLD,[8,11,12] likely due to a lack of immunity against EBV before transplantation. In this study, we included only recipients diagnosed with PTLD as adults, and thus most recipients were EBV seropositive before PTLD onset suggesting that other pathogenesis, than lack of immunity against EBV, are in play in the development of adult PTLD compared to pediatric PTLD.

EBV DNAemia occurred more often in early compared to late PTLD, whereas there was no difference between the two groups in EBV detection in the biopsies. Further, half of the recipients had no EBV detected in neither plasma nor biopsies. Gene expression analysis has suggested that EBV-positive and -negative PTLD are distinct entities, where the latter resembles lymphomas in the immunocompetent patient suggesting a different mechanism.[26] Thus, the role of EBV detected in plasma in the pathogenesis of EBV-negative PTLD tumors in the present study is uncertain and warrants further

investigations. The two PTLD groups did not differ in mortality 1 year after the PTLD diagnosis. Almost half of the recipients with PTLD died during follow-up with almost all deaths being caused by PTLD. Thus, the prognosis of this disease continues to be poor and warrants continuous attention to increase the knowledge of the pathophysiology and risk factors.

The strengths of our study include the linkage of Danish clinical databases, registries, and patient records through unique personal identification numbers which allows a complete long-term follow-up of patients. However, our study also has limitations. PTLD is a rare disease and due to the low number of PTLD among the kidney and liver transplant recipients during our 10-year study period and the single-center nature of this study, the power of our statistical analyses was limited. Further, due to the retrospective nature of this study, there were missing data as these were not performed/assessed during clinical routine due to changes in clinical practice through the years. We included adult PTLD only, potentially introducing a selection bias of lower proportion of pediatric recipients in the early PTLD group. Thus, we are not able to comment on the impact of age in early versus late PTLD.

In summary, our study provides extensive information on the clinical and pathological characteristics of early and late PTLD among kidney and liver transplant recipients. The recipients with early PTLD more often had EBV DNA in plasma at time of PTLD diagnosis. However, recipients with late PTLD more often had advanced disease, and required chemotherapy for the treatment of PTLD. The 1-year mortality for both PTLD groups combined was 29% with no significant difference in neither the overall nor the one-year mortality between the two PTLD groups.

Thus, PTLD is diverse and more studies are warranted to develop methods to better detect PTLD early.

AUTHOR CONTRIBUTIONS

Ranya Abdulovski, Susanne D. Nielsen, Dina L. Møller, Andreas D. Knudsen, Søren S. Sørensen, Allan Rasmussen, and Neval E. Wareham contributed to the research design. Ranya Abdulovski collected data, performed the research, analyzed data, and wrote the first draft with participation from Dina L. Møller, Susanne D. Nielsen, and Neval E. Wareham.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data are stored in our REDCap database under the project title "*Videnscenter for transplantation (VCT)*." The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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