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Improving efficacy and reducing adverse effects of immunosuppression after liver transplantation

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CHAPTER 6

PRIMARY SCLEROSING CHOLANGITIS AND OTHER RISK FACTORS FOR POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE AFTER LIVER TRANSPLANTATION IN ADULTS

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Abstract

Post-transplant lymphoproliferative disease (PTLD) is a rare but serious complication of liver transplantation (LT) with morbidity and mortality. The risk factors for PTLD in adults are ill-defined. The current study aimed to assess the risk factors for PTLD after LT in adults. All adult LT recipients between 1986 and 2016 from two centers in the Netherlands were included, with follow-up until 2020. PTLD was diagnosed according to the WHO classification. Potential risk factors for PTLD were assessed using multivariate Cox regression analysis. 1281 patients were included, of whom 29 (2.3%) developed PTLD. Independent risk factors for PTLD after LT in adults were no Epstein-Barr virus (EBV) load monitoring strategy, primary sclerosing cholangitis (PSC) as an indication for LT, era (historic era linked to more intense long-term immunosuppression), EBV seronegative recipient, and -trend- higher age. No other risk factors were identified in this study. Of 207 patients with PSC as an indication for LT, 13 (6.3%) developed PTLD versus 16 out of 1074 (1.5%) patients with other underlying liver diseases (log-rank p <0.001). The yearly PTLD incidence was higher in the first year than in the later years after LT (2.4%/year vs. 0.6%/year) for PSC but not for other indications (0.16%/year). In EBV seronegative recipients, PTLD occurred earlier after LT, while in the 97% seropositive recipients it could occur very late after LT.

Introduction

Post-transplant lymphoproliferative disease (PTLD) is a rare but serious complication after liver transplantation (LT), with reported incidence of 1-3% of adults and 9% of children during 3-20 years[1-3]. Over two-thirds of PTLDs are related to Epstein-Barr virus (EBV): immuno-suppression allows EBV-induced B-lymphocyte proliferation, which can evolve into PTLD[1]. The higher incidence and earlier occurrence of PTLD in pediatric LT is due to more primary EBV infections, since half of children and less than 10% of adults are EBV-negative at LT[1]. We recently reported that not only in pediatric LT, but also in adult LT recipients -who have latent EBV in 97%- an EBV monitoring strategy, with reduction of immunosuppression in case of a detectable viral load, reduces the incidence of PTLD[4]. In pediatric LT, risk factors for PTLD are EBV-negative serostatus, first year after transplantation and more intense immunosuppression[1]. However, risk factors for PTLD in adult organ recipients are ill-defined. Therefore, we assessed possible independent risk factors for PTLD after LT in adults.

Materials and methods

Patients

A two-center cohort study was performed as described recently[4]. All first deceased-donor LT recipients with >2 weeks survival between 1992-2016 in Leiden and 1986-2016 in Rotterdam, Netherlands, were included. The baseline and follow-up data were retrieved. Follow-up was conducted until 1/2020, death, or loss to follow-up. In Leiden, but not Rotterdam, an EBV viral load (VL) monitoring strategy has been used since 2003, the 'contemporary era'; before 2003 was the 'historic era.' EBV VL monitoring was weekly in the first month after LT and then monthly until 1 year after LT. Thereafter, VL samples were taken at least biannually. In case of detectable EBV VL in two consecutive samples or in one sample at the discretion of the treating physician immunosuppression was lowered[4].

During 1999-2007 immunosuppression gradually changed from prednisolone and cyclosporine to prednisolone and tacrolimus, and, if used, from azathioprine to mycophenolate mofetil. Since 1999, basiliximab was added to methylprednisolone as induction in both centers, in 94% of the patients. Over this 1999-2007 period immunosuppression became less intense, especially long-term, with lower trough levels of calcineurin inhibitors adhered to and with cessation of prednisolone in most patients around 6 months after transplantation. Therefore we chose 2003 as separation between contemporary and historic eras. Since 2009, sirolimus or everolimus has been used more often, usually in combination with low-dose

tacrolimus (trough levels 4-10 ng/ml or -in the case of combination therapy- 3-5 ng/ml).

Diagnosis and potential risk factors for PTLD
PTLD diagnosis was based on the WHO 2016 classification, including lymphocytic or plasmatic proliferation arising in a recipient of solid organ or bone marrow allogeneic transplantation with enlarged lymph nodes and/or organ involvement. PTLD can be early benign lesions, polyclonal polymorphic PTLD (P-PTLD), or monomorphic PTLD (M-PTLD), which often fulfill the criteria of non-Hodgkin lymphoma (NHL) or classic Hodgkin lymphoma-type PTLD (CHL-PTLD)[5].

Because of known risk factors for PTLD in children and possible risk factors in adults mentioned earlier in the literature the potential risk factors for PTLD assessed were: age, sex, hospital, era (with less intense immunosuppression in 'contemporary' versus 'historic' cohorts), EBV VL monitoring strategy, etiology of liver disease -especially autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), EBV IgG negative recipient serostatus, type of immunosuppression, rejection and re-transplantation.

Statistical analysis
Continuous variables (covariates) are reported as medians with interquartile ranges (IQR) and binary categorical variables as percentages or proportions. The Mann-Whitney U test was used to test the significance of differences in continuous variables, and the chi-square test was used for categorical variables.

Multivariate Cox regression analysis of the risk factors for PTLD was performed with a significance level of $p<0.05$. By including an interaction term in the Cox model (hospital*era), the ratio of the two within-hospital ratios (contemporary cohort/historic cohort) was directly calculated, representing the effect of the EBV VL monitoring strategy in one hospital (but not in the other hospital) in the contemporary era. Rejection and re-transplantation were analyzed as time-dependent variables. Additional analysis with Kaplan-Meier (KM) survival analysis with the log-rank test and Chi^2 with Yates correction was performed. IBM SPSS Statistics for Windows (version 24.0, Chicago, IL, USA) was used for analyses.

For primary sclerosing cholangitis (PSC) as a risk factor for PTLD, additional univariate analyses were performed for age, sex, and group (based on hospital and era) and the occurrence of PTLD. Proportional hazards regression was used to assess the effect of PSC with adjustment for potential confounders. Furthermore, the effect of the first re-transplantation and rejection treatment on the occurrence of PTLD was analyzed in a proportional hazards model with re-transplantation or rejection treatment as a time-dependent covariate. For these additional analyses,

SAS University 9.4, SAS Institute Inc. 2015. Cary, NC, was used for additional analyses.

Data and funding
Because of the retrospective nature of the study with existing data and the consent of patients to use the data, CME waived the need for further consent. This study complied with the latest version of the Declaration of Helsinki. The data will be made available upon request. This study was not funded by any grants.

Results

A total of 1281 consecutive LT recipients (of which 97% IgG-EBV-positive and 3% IgG-EBV-negative) were included in the historic and contemporary groups from both centers (Table 1). Despite some differences in baseline characteristics between the two centers and the above-mentioned changes in immunosuppression between contemporary and historic groups, the groups were largely similar. In the combined cohorts 29 of 1281 (2.3%) patients developed PTLD. Details of the 29 cases are described in the supplement to the previous report[4].

Risk factors for PTLD
As shown in Table 2, independent risk factors for PTLD in Cox multivariate analysis were PSC as indication for LT, era, no EBV VL monitoring, IgG anti-EBV negative recipient, and -trend- higher recipient age at transplant. The effect of monitoring was significant (significance for the interaction term of hospital with era, as shown in Table 2). No other significant independent risk factors of PTLD were identified; AIH and PBC were not risk factors. No single immunosuppressive agent or the use of double immunosuppression (always with the lowering of the concurrent calcineurin inhibitor) was a risk factor for PTLD, and short-term intensified immunosuppression during rejection or after re-transplantation was not observed to be a risk factor for PTLD.

PTLD developed during follow-up in 3/38 (7.8%) IgG-EBV-negative and 26/1243 (2.1%) IgG-EBV-positive recipients (log-rank p=0.14). In the three EBV seronegative recipients in whom PTLD developed this occurred at 3, 6, and 28 months after LT, while this occurred later in EBV seropositive patients.

Table 1. Baseline characteristics

Group	Leiden Contemporary (n=302)	Rotterdam Contemporary (n=579)	Leiden Historic era (n=116)	Rotterdam Historic era (n=284)
Age in years: median (IQR)	55 (15)	52 (18)	49 (13)	48 (16)
Gender male	217 (71.9%)	369 (63.7%)	82 (70.7%)	151 (53.2%)
Underlying liver disease				
Cirrhosis, post-hepatitis #	131 (43.4%)	200 (34.5%)	48 (41.4%)	122 (43.0%)
ALD	97	65	29	30
HBV	32	17	13	46
HCV	44	30	20	30
AIH	10	21	4	10
MASLD	18	16	0	0
Cholestatic liver disease *	47 (15.6%)	158 (27.3%)	31 (26.7%)	81 (28.5%)
PSC	33	115	20	38
PBC	14	43	11	43
HCC as primary indication	103 (34.1%)	129 (22.3%)	21 (18.1%)	23 (8.1%)
Acute liver failure	5 (1.7%)	61 (10.5%)	5 (4.3%)	50 (17.6%)
Other	16 (5.3%)	31 (5.4%)	11 (9.5%)	8 (2.8%)
EBV-IgG positive recipient	290 (96.0%)	560 (96.7%)	115 (99.1%)	278 (97.9%)
Initial immunosuppression				
Cyclosporin	34 (11.3%)	65 (11.2%)	104 (89.7%)	148 (52.1%)
Tacrolimus	267 (88.4%)	508 (87.7%)	12 (10.3%)	98 (34.5%)
Azathioprine	2 (0.7%)	3 (0.5%)	42 (36.2%)	68 (23.9%)
Mycophenolate mofetil	39 (12,9%)	164 (28.3%)	30 (25.9%)	2 (0.7%)
Basiliximab	301 (99.7%)	562 (97.1%)	66 (56.9%)	86 (30.3%)

IQR= interquartile range. Ad #) due to ALD= alcoholic liver disease, HBV= hepatitis B virus, HCV=hepatitis C virus, AIH=auto-immune hepatitis, MASLD= metabolic dysfunction associated steatotic liver disease (formerly NAFLD= non-alcoholic fatty liver disease). There were several patients with multiple etiologies (like HBV and HCV or HCV and ALD), and in the historic cohort the diagnosis of MASLD was not registered. Ad #) due to PSC= primary sclerosing cholangitis or PBC= primary biliary cholangitis.

Table 2. Multivariate Cox regression analysis of possible risk factors for PTLD after LT in adults

Factor	HR	95% CI for HR		p-value
		Lower limit	Higher limit	
Age	**1.034**	**0.977**	**1.072**	**0.072**
Sex (male)	1.749	0.716	4.274	0.220
Era (contemporary)	**0.055**	**0.006**	**0.514**	**0.011**
Hospital †	0.536	0.195	1.571	0.226
EBV VL monitoring †	**10.887**	**1.672**	**189.612**	**0.045**
AIH as LT indication	1.874	0.220	15.953	0.565
PBC as LT indication	0.483	0.061	3.848	0.492
PSC as LT indication	**4.116**	**1.867**	**9.071**	**<0.001**
EBV-IgG negative recipient	**5.664**	**1.199**	**26.767**	**0.029**
Ciclosporine	0.624	0.065	5.991	0.682
Tacrolimus	0.462	0.053	3.990	0.482
Azathioprine	0.783	0.266	2.306	0.657
Mycophenolate mofetil	0.711	0.222	2.274	0.565
Everolimus or sirolimus	0.817	0.092	7.290	0.857
Rejection *	1.902	0.861	4.204	0.112
First retransplantation *	1.135	0.369	3.492	0.826

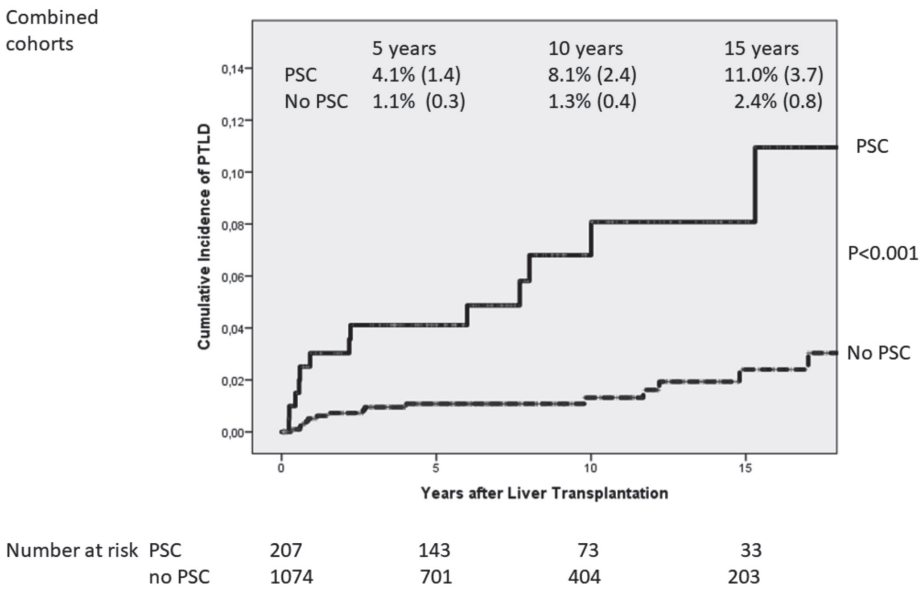
Immunosuppression mentioned was initial immunosuppression. Ad *) Rejection and first retransplantation were analyzed as time-dependent covariates, since these were not baseline factors. AIH: autoimmune hepatitis, PBC: primary biliary cholangitis, PSC: primary sclerosing cholangitis. Ad †) EBV monitoring in the contemporary era in one of the two hospitals for all patients was assessed using the interaction term 'era*hospital'. These findings show that Hospital overall is not significant, but that in the reference historic era there was less PTLD in Rotterdam than in Leiden, but in the contemporary era the hazard ration Rotterdam/Leiden of this reference historic era was multiplied 17.806 times in the second era due to the effect of EBV monitoring in Leiden.

PSC as risk factor for PTLD

In 13 out of 207 (6.3%) of the patients with PSC as an indication for LT PTLD developed, a significantly higher proportion than the 16/1074 (1.5%) cases of PTLD in patients with LT for other underlying liver diseases (log rank p<0.001) (Figure 1). The 1-, 5-, and 10-year post-LT cumulative incidence for PTLD were 4.1%, 8.1%, and 11.0% for PSC, and 1.1%, 1.3%, and 2.4%, respectively for other indications of LT. PSC was an independent risk factor in each center separately, and a similar difference in cumulative incidence of PTLD between patients with LT for PSC versus for other indications was found in both centers separately, as shown in the

Supplement. In our dataset, patients with PSC were on average 4.2 years younger than patients without PSC. Regarding sex, 14.1% of women and 17.3% of men were diagnosed with PSC. Univariate proportional hazards regression did not show an association between age, sex, and the occurrence of PTLD. We decided to include group (the two contemporary and two historic groups) and age and sex (both based on subject matter considerations) in the proportional hazards model next to PSC, where the interest is in the effect of PSC adjusted for potential confounders. Univariate analysis of PSC on PTLD showed an HR of 4.3 with a 95%CI (2.1 9.0), p<0.001. Adjusted for the above-mentioned potential confounders, this changed only slightly to an HR of 4.2 with 95%CI (2.0 9.0); p<0.001 (Supplementary data, Figure S2).

Figure 1. Kaplan-Meier 1-survival curves for cumulative incidence of PTLD after LT for PSC versus other indications for LT.



In the first year after LT for PSC, the PTLD incidence was 5/207 (2.4%), which was higher than the annual incidence of 0.6% after the first year. This difference in yearly incidence between the first and later years after LT was not observed for other LT indications, where the yearly incidence of PTLD was 0.2%. There was no difference in rejection rate between PSC and non-PSC patients (29% versus 28% in the first year after LT) (logrank p=0.93).

Of the patients who developed PTLD after LT for PSC, 9/13 (69%) had inflammatory bowel disease (IBD), all quiescent, none used biologicals, and immunosuppression use after LT did not differ from that in patients who did not develop PTLD, while none of these patients underwent a colectomy or used immunosuppression before LT. PTLD included abdominal lesions in 12/13 PSC and 10/16 non-PSC patients (Chi2 p<0.01): abdominal lymph nodes in 9/13 PSC and 3/16 non-PSC patients (Chi2 p=0.02), colon in 2/13 PSC and 1/16 non-PSC patients (Chi2 p=0.85), liver or liver hilum in 4/13 PSC and 6/16 non-PSC patients (Chi2 p=0.70). From the patients developing PTLD, 9/13 of those with PSC and 9/16 of non-PSC transplant recipients survived the PTLD episode, which was not different.

Discussion

In this long-term follow-up cohort study regarding PTLD after LT in adults, the independent risk factors for PTLD were PSC as indication for LT, historic era (associated with more intense -maintenance- immunosuppression), no EBV VL monitoring strategy, IgG anti-EBV negative recipient and a trend for higher recipient age at transplantation. No other independent risk factors of PTLD were identified.

The finding that higher recipient age tended to be an independent risk factor for PTLD after LT in adults is in agreement with previous findings that showed an increase in the incidence of malignant lymphoma with age in the general population. Immunosuppression increases this risk. A European registry including 15631 LT patients (1985-2001), reported a relative risk of malignant lymphoma compared to the general population of 24.6 in the first year and 7.3-11.2 per year during the following 9 years[6]. A Canadian study found a 21-fold increased risk of non-Hodgkin lymphoma among LT recipients with respect to the general population, in line with the European numbers[7]. In the current cohort of adults after LT it appears that except for PSC, where the risk is higher in the first year, the risk for PTLD is stably increased over many years.

Second, the protective effect of an EBV VL monitoring strategy after LT in adults regarding the risk of developing PTLD has been described recently by our group and is confirmed in the current multivariate Cox model[4]. EBV is involved in more than two-thirds of PTLD cases after transplantation. This is partially due to the inhibition of apoptosis of B-lymphocytes by EBV, but is also due to the inhibition of immune control of lymphocyte replication by immunosuppression[8]. A detectable EBV VL is seen as a marker for over-immunosuppression. In the contemporary era with EBV VL monitoring in 40% of these patients EBV VL was detectable, and in three-quarters of these patients (30% of all patients in the contemporary cohort

with EBV VL monitoring strategy) immunosuppression was reduced for a detectable EBV VL, while this lower immunosuppression could be maintained long-term in 85% of cases, which was associated with a reduced incidence of PTLD[4].

Third, the data show that even in adults, negative IgG anti-EBV serostatus is an independent risk factor for the development of PTLD after LT. In our cohort, only 3% of adults were IgG anti-EBV negative at the time of transplantation, limiting the possibility of further strong conclusions for seronegative recipients. However, in contrast to the vast majority of adults with latent EBV infection, IgG anti-EBV negative adult recipients usually acquire EBV from the donor, very much like transplanted EBV seronegative children. Compatible with this, it was remarkable that all three PTLDs in EBV seronegative recipients occurred early (3, 6, and 28 months after LT), while on average, PTLD in EBV seropositive recipients occurred later. In addition, all PTLDs in IgG anti-EBV negative recipients occurred in the center without an EBV monitoring strategy, suggesting that such a strategy might also help in the prevention of PTLD in EBV-negative recipients.

Fourth: the contemporary era carried a lower risk for PTLD than the historic era. This era effect most likely should be attributed to a change towards less intensive immunosuppression around 2003 (between 1999 and 2007) in our centers. This involved stopping prednisolone between 3 and 6 months in most patients, a change from ciclosporin to tacrolimus, and acceptance of lower trough levels. This allows for better immunity against EBV, which likely is a reason for less PTLD in the contemporary era.

No association was detected between the risk of developing PTLD and any of the oral immunosuppressive drugs. However, there was no very large group without calcineurin inhibitors for comparison. In addition, the use of double immunosuppression was not a risk factor for PTLD, probably because the combination of a calcineurin inhibitor with azathioprine or mycophenolate mofetil, sirolimus, or everolimus is usually administered to reduce the dose of the calcineurin inhibitor in order to spare kidney function, so that total immunosuppression is not different from monotherapy with a calcineurin inhibitor.

In adults, it appears to be more the long-term and not short-term, high-dose immunosuppression that appears to be associated with the development of PTLD. This idea is supported by several findings in this cohort study: first, in adults PTLD usually does not develop in the first weeks after LT, when immunosuppression is strongest and since 1999 basiliximab is given, while PTLD incidence is lower in the contemporary era. Secondly, the protective effect against PTLD of long-term reduction of immunosuppression in cases of a detectable EBV viral load, supports this idea. Furthermore, rejection and re-transplantation with their temporary short-

term increase in immunosuppression, as time-dependent risk factors, were not associated with PTLD.

The most remarkable, novel finding of this study is that PSC as an indication for LT in adults is a strong and independent risk factor for PTLD. This was also the case in both centers separately. While PSC patients were younger than average and more often male, these factors hardly influenced this risk. Although PTLD is a rare event after LT in adults, the fact that PSC is a frequent indication for LT makes it clinically relevant. In two previous reports, autoimmune hepatitis and a combined group of autoimmune liver diseases, including AIH, primary biliary cholangitis (PBC), and PSC, were risk factors for PTLD after LT[9,10]. We could only confirm this for PSC. In a recent report from the Mayo Clinic regarding malignancy after LT for PSC, a remarkable 7.5% of patients developed a hematologic malignancy (18 PTLD, 2 Hodgkin disease, 2 myelodysplastic syndrome)[11]. PTLD accounted for 24% of de novo cancers after LT for PSC, and cumulative incidences of PTLD at 1, 5, and 10 years after LT for PSC were 0.7%, 2.9%, and 6.0% respectively[11]. Incidence of PTLD after LT for non-PSC indications was not described in that report. These numbers are in line with the incidence of PTLD after LT for PSC in adults in the current report: the 1-, 5-, and 10-year post-LT cumulative PTLD incidence was 4.1%, 8.1%, and 11.0% after LT for PSC. An earlier study from the Mayo Clinic suggested that PSC might be involved in the development of PTLD, but in contrast to our current findings, in that study, PSC could not be identified as a statistically significant risk factor[12]. In the current study, PSC was a strong and independent risk factor for PTLD.

This raises the question of why PSC is a risk factor for PTLD. In the current cohort of patients with LT, almost 70% of those with PSC who developed PTLD had IBD. Although all patients had a colonoscopy before LT, not all had undergone colonic biopsies at that time; therefore, the incidence of IBD in patients with PSC might be even higher than 70%. In patients with PSC as an indication for LT developing PTLD, no IBD drug other than 5-aminosalicylic acid (5-ASA) was given before LT. Immunosuppression after LT, including trough levels of cyclosporin and tacrolimus, was not significantly different from that in patients without PSC, although some patients with PSC used thiopurine after LT and an unaccounted course of prednisolone in a referring hospital could not be completely excluded. None of the patients who developed PTLD after LT for PSC received biologicals -like anti-TNF- for IBD. There was no difference in rejection rate between PSC and non-PSC patients. It is unlikely that the increased colonic surveillance in patients with PSC, as an indication for LT as compared to the other indications, explains this higher cumulative incidence of PTLD in LT for PSC, since most PTLD in both groups was advanced-stage PTLD, not detected at the time of surveillance colonoscopy, and the majority was located outside the colon. Interestingly, patients with PSC developing PTLD had significantly more abdominal PTLD -combined

lymph nodes, bowel, and liver hilum- than those with other LT indications than who developed PTLD. An increased inflammatory state in PSC might play a role: although much is still unclear regarding pathophysiology of PSC, the gut-liver axis with increased antigen load from gut to mesenteric lymph nodes and liver with concordant inflammation appears important[13-15]. Colonic dysbiosis, increased colonic permeability a FUT2 mutation and immunological activity in mesenteric lymph nodes and liver are described in PSC, and are probably related to IBD[16,17]. Therefore it is very well possible that in PSC immunological changes in gut, abdominal lymph nodes and liver contribute to the increased risk for PTLD after LT for PSC. The increased PTLD risk in LT for PSC may also indicate that EBV VL monitoring is even more important after LT for PSC compared to other LT indications.

This study has several strengths and limitations. Strengths include a well-defined relatively large cohort with LT with long-term follow-up and almost complete data. A weakness is that the subgroup of EBV-negative adult LT recipients is relatively small, but this results from 97% seropositivity in adults. Also, not all changes in immunosuppression during the follow-up period could be included in the analysis. Another limitation is lack of diversity -most patients were Caucasian-, which may limit generalizability.

The current cohort study with long-term follow-up from two centers showed that in adult patients after LT, PSC as an indication for LT is a strong and independent risk factor for PTLD. Other independent risk factors in adults after LT were EBV-negative recipient serostatus, the historic era (linked to more intense long-term maintenance immunosuppression), no EBV VL monitoring strategy, and a trend towards higher recipient age as risk factor. Further studies on the relationship between PSC and PTLD risk after liver transplantation are warranted. This study needs to be repeated in large cohorts of LT recipients with long-term follow-up from different parts of the world before generalizability can be assumed.

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Abbreviations

AIH	Auto-immune hepatitis
EBV	Epstein-Barr virus
LT	Liver transplantation
PTLD	Post-transplant lymphoproliferative disease
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
VL	Viral load

Supplementary Files