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Association of antiviral prophylaxis and rituximab use with posttransplant lymphoproliferative disorders (PTLDs): A nationwide cohort study

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Abstract

Posttransplant lymphoproliferative disorder (PTLD) is a serious complication of solid organ transplantation (SOT). Most PTLD cases are associated with Epstein–Barr virus (EBV) infection. The role of antiviral prophylaxis or rituximab therapy for prevention of PTLD in SOT recipients is controversial. In a nationwide cohort, we assessed the incidence, presentation, and outcome of histologically proven PTLD. We included 4765 patients with a follow-up duration of 23 807 person-years (py). Fifty-seven PTLD cases were identified; 39 (68%) were EBV positive (EBV+ PTLD). Incidence rates for EBV+ PTLD at 1, 2, and 3 years posttransplant were 3.51, 2.24, and 1.75/1000 py and 0.44, 0.25, and 0.29/1000 py for EBV− PTLD. We did not find an effect of antiviral prophylaxis on early and late EBV+ PTLD occurrence (early EBV+ PTLD: SHR 0.535 [95% CI 0.199–1.436], p = .264; late EBV+ PTLD: SHR 2.213, [95% CI 0.751–6.521], p = .150). However, none of the patients (0/191) who received a rituximab-containing

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; CNS, central nervous system; D, donor; EBER, EBV-encoded RNA; EBV, Epstein–Barr virus; HSCT, hematologic stem cell transplant; HSV, herpes simplex virus; IQR, interquartile range; LMP1, latent membrane protein 1; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; py, person-years; R, recipient; RMST, restricted mean survival time analysis; SHR, subdistribution hazard ratio; SOT, solid organ transplantation; STCS, Swiss Transplant Cohort Study; VZV, varicella-zoster virus; WHO, World Health Organization.

[†]The members of the Swiss Transplant Cohort Study are listed in the Appendix.

induction treatment experienced PTLD, but 57 of 4574 patients without rituximab induction developed PTLD. In an adjusted restricted mean survival time model, PTLD-free survival was significantly longer (0.104 years [95% CI 0.077–0.131]) in patients receiving rituximab as induction treatment. This study provides novel data on the association of rituximab induction and reduced risk for PTLD.

KEYWORDS
clinical research/practice, complication: infectious, hematology/oncology, immunosuppressant –fusion proteins and monoclonal antibodies: B cell specific, infection and infectious agents – viral, infection and infectious agents – viral: Epstein-Barr Virus (EBV), infectious disease, posttransplant lymphoproliferative disorder (PTLD)

1 | INTRODUCTION

Posttransplant lymphoproliferative disease (PTLD) is one of the most serious complications of solid organ transplantation (SOT). Epstein–Barr virus (EBV) is known to play a major role in the development of PTLD. However, EBV-negative PTLD accounts for 20%–30% of cases.[1] PTLD incidence ranges from 1% to 20% dependent on age,[2] allograft type,[3-5] type of induction treatment,[3,6] intensity of immunosuppressive therapy,[3] time from transplant (early <1 year, late >1 year),[7] and EBV serostatus of organ donor and recipient.[8,9] Several PTLD prevention strategies for EBV high-risk SOT recipients (donor EBV positive, recipient EBV negative; D+/R–), such as EBV DNAemia surveillance with reduction of immunosuppression when DNAemia increases or administration of the cytolytic chimeric α-CD20 monoclonal antibody rituximab[10-12] have been proposed. Even though high EBV DNAemia is a risk factor for the onset of PTLD,[13,14] the time points for monitoring, source samples, and cutoff values for intervention are not standardized.[7,15]

Antiviral prophylaxis by (val-)acyclovir or (val-)ganciclovir to prevent cytomegalovirus (CMV),[16] herpes simplex virus (HSV), and varicella-zoster virus (VZV) infection[17,18] has an inhibitory effect on lytic EBV replication and viral shedding.[19] Nevertheless, the role of antiviral prophylaxis in prevention of EBV-associated PTLD is controversial. A previous, retrospective study reported a reduced incidence of PTLD (3.9% vs. 0.5%) after introduction of antiviral prophylaxis[20] and several other retrospective studies have supported its use.[21,22] These results have been challenged by more recent studies, which did not find a significant effect of antiviral prophylaxis on PTLD incidence.[23,24] In addition, a recent meta-analysis reported no reduction in the rate of EBV-associated PTLD in SOT recipients receiving antiviral prophylaxis by (val-)acyclovir or (val-)ganciclovir.[25]

In the hematologic stem cell transplant (HSCT) setting, the use of rituximab to prevent PTLD has become an initial preemptive intervention in the context of EBV replication.[26] Moreover, rituximab used as prophylaxis pretransplant was associated with a reduction in EBV replication and EBV+ PTLD in high-risk HSCT recipients.[27] Less is known about the effect of rituximab on EBV+ PTLD occurrence in SOT recipients with EBV replication. Single center experiences have reported a reduction in PTLD rates with rituximab use in transplant recipients failing to respond to reducing immunosuppression compared with historical or contemporaneous controls.[12,28] To the best of our knowledge, the effect of rituximab, given as part of the induction regimen, on PTLD occurrence has not been studied yet.

The aim of this nationwide cohort study was to comprehensively describe the clinical characteristics of PTLD cases after SOT and to assess the effect of rituximab therapy and the use of antiviral prophylaxis on PTLD occurrence.

2 | MATERIALS AND METHODS

2.1 | Study design

We conducted a nested project based on data from the multicenter nationwide observational Swiss Transplant Cohort Study (STCS).[29] In the current study, we included all SOT recipients enrolled in the STCS from May 2008 to June 2019. Only the first transplantation was analyzed. All six Swiss transplant centers participate in the STCS, and for the analyzed period, around 95% of all recipients of SOT performed in Switzerland consented to be included. The STCS and the current subproject were approved by the local ethics committee of each participating center (Ethics Commission of the Canton of Bern, Bern, Switzerland, Nr. 2019–00858).

2.2 | Data collection

Clinical data on demographic characteristics, type of transplant, immunosuppressive regimen (induction and maintenance drugs, including rituximab), number of rejection episodes and rejection treatment (including rituximab), pretransplant donor and recipient CMV and EBV serostatus, administration and duration of antiviral prophylaxis (ganciclovir, valganciclovir, acyclovir, valacyclovir), occurrence of HSV, VZV, or CMV infection (number of episode per patient, use of antiviral therapy), and the occurrence of PTLD were prospectively collected and extracted from the STCS database. Additional data on PTLD (including localization, histopathological classification, and management) not captured in the STCS

database were retrieved through a standardized data collection sheet from electronic medical records. Patient outcome (graft loss, death, death related to PTLD) were available from the STCS database. Treating physicians report systematically the most likely causes of death to the STCS using standardized data collection forms.

2.3 | Clinical definitions

Histological confirmation was required for PTLD diagnosis. PTLD classification was based on World Health Organization criteria.[30] EBV-positive PTLD was identified by EBV-encoded RNA (EBER) *in situ* hybridization or latent membrane protein 1 (LMP1) histochemical stains. PTLD localization was categorized as nodal and extra-nodal or both. Early PTLD occurred in the first year after transplantation, late PTLD thereafter.

Viral infections are defined according to standard definitions generated by the Infectious Diseases Study Group of the STCS, as previously described.[31] Each infection episode was validated by a Transplant Infectious Diseases specialist at each center. Furthermore, CMV infection and disease were classified according the definitions published by the American Society of Transplantation guidelines.[32] We categorized SOT recipients to have rituximab-containing induction regiments if rituximab was part of the induction treatment irrespective of the co-administration of additional agents. Antiviral prophylaxis was initiated at the discretion of the treating physician in accordance with local protocols. For this study, antiviral prophylaxis was defined as the use of (val-)ganciclovir or (val-)acyclovir started within the first 2 weeks after transplantation.[18] Acute rejection was defined for each organ following the standard international criteria.[33]

2.4 | Statistical analyses

A descriptive analysis was performed to determine patients' baseline characteristics, transplant outcome variables (acute rejection, graft loss, death), and episodes of CMV, HSV, and VZV (median number of episodes per patient). Cumulative PTLD incidence was calculated overall and by organ group. The impact of antiviral prophylaxis on EBV+ PTLD was analyzed using competing risk regression models (with death and graft loss as competing risk factors for EBV+ PTLD), adjusting for predefined confounding factors such as type of organ,[3] EBV serostatus at transplantation,[8] type of induction therapy,[3] sex, and age.[34] This was done separately for early and late EBV+ PTLD, since universal prophylaxis is given directly after transplantation and the treatment effect might be different for the two time periods.[15] The impact of rituximab induction therapy on PTLD incidence was analyzed using restricted mean survival time analysis (RMST) adjusting for sex, age, transplanted organ, antithymocyte globulin (ATG) use, and EBV serostatus at transplantation. Since no development of PTLD occurred in patients with rituximab induction, competing-risk regression models could not be used (violation of the proportional hazard assumption) for this analysis. RMST is a well-established measure (based on differences in areas under Kaplan–Meier curves of two groups) that can be interpreted as the average event-free survival time up to a prespecified time point.[35] RMST is not dependent on the proportional hazards assumption.[36] For this analysis, patients were censored at a maximum follow-up duration of 9 years, death, graft loss or lost to follow-up. The statistical analysis was conducted using STATA version 15.

3 | RESULTS

3.1 | Study population

A total of 4765 SOT recipients (57% kidney, 22% liver, 9% lung, 8% heart, 5% combined) were included. Median age at transplantation was 54 years (interquartile range [IQR] 42–62 years), and 36% (1711/4765) of patients were female. Median follow-up time was 4.61 years (IQR 2.22–7.62). EBV high-risk serostatus (D+/R–) was present in 6% (266/4765) of SOT recipients. Patient characteristics are detailed in Table 1.

3.2 | Characteristics, treatment, and outcome of PTLD

Among 57 PTLD cases identified, 68% (39/57) were EBV+. Clinical characteristics, treatment, and outcome of PTLD cases are shown in Table 2.

The overall PTLD incidence was 2.39 per 1000 person-years (py) and the highest incidence was found among lung transplant recipients (5.77/1000 py; Table 2). The incidence of EBV+ PTLD was highest in the first-year posttransplant (3.51/1000 py), this was not the case for EBV– PTLD cases (Figure 1).

Histopathological classification revealed early lesions in 11% (6/57), polymorphic in 23% (13/57), and monomorphic PTLD in 67% (38/57) of cases. Most PTLDs were of B cell origin (95%; 54/57). Extra-nodal involvement was common (in 87% of EBV+ PTLD and 78% of EBV– PTLD; Figure 2) and central nervous system (CNS) involvement was exclusively found in EBV+ PTLD (21%; 8/39). PTLD lesions of the transplanted organ were detected in 29% (14/49) of patients with extra-nodal involvement and most of these lesions were EBV+ (79%; 11/14).

SOT recipients with EBV+ PTLD were younger compared to patients with EBV– PTLD (39 [IQR 20–59] vs. 61 years [IQR 54–63]; $p < .01$) and the median time from transplantation to PTLD diagnosis was shorter; 14.33 months (IQR 7.82–32.91) for EBV+ PTLD vs. 56.84 months (IQR 40.93–80.87; $p < .001$) for EBV– PTLD. EBV high-risk serostatus (D+/R–) was more frequent in EBV+ PTLD (33%; 13/39) than in EBV– PTLD (0%; 0/18; $p < .01$).

Reducing immunosuppression alone was the treatment for 18% (7/39) of EBV+ PTLD cases while none of the EBV– PTLD cases were

TABLE 1 Patient characteristics of recipients included in the analysis according to whether they developed PTLD, EBV associated or not

Characteristics	No PTLD *n* = 4708	PTLD *n* = 57	EBV+ PTLD *n* = 39	EBV− PTLD *n* = 18
Female, sex, *n* (%)	1689 (36)	22 (39)	19 (49)	3 (17)
Age at transplant, years, median (IQR)	54 (42–62)	47 (29–61)	39 (20–59)	61 (54–63)
Follow-up, years, median (IQR)	4.64 (2.22–7.64)	2.09 (0.75–4.04)	1.19 (0.65–2.74)	4.74 (3.41–6.74)
EBV serostatus, *n* (%)				
EBV low-risk (D−/R−)	58 (1)	1 (2)	1 (3)	0 (0)
EBV intermediate-risk (R+)	4326 (92)	42 (74)	24 (62)	18 (100)
EBV high-risk (D+/R−)	253 (5)	13 (23)	13 (33)	0 (0)
Missing	71 (2)	1 (2)	1 (3)	0 (0)
CMV serostatus, n (%)				
CMV low-risk (D−/R−)	925 (20)	15 (26)	12 (31)	3 (17)
CMV intermediate-risk (R+)	2827 (60)	31 (54)	20 (51)	11 (61)
CMV high-risk (D+/R−)	927 (20)	10 (18)	6 (15)	4 (22)
Missing	29 (1)	1 (2)	1 (3)	0 (0)
Transplant, *n* (%)				
Kidney	2674 (57)	23 (40)	16 (41)	7 (39)
Liver	1018 (22)	16 (28)	8 (21)	8 (44)
Heart	358 (8)	4 (7)	3 (8)	1 (6)
Lung	431 (9)	11 (19)	10 (26)	1 (6)
Combined	227 (5)	3 (5)	2 (5)	1 (6)
Antiviral prophylaxis, *n* (%)				
	2097 (45)	30 (53)	25 (64)	5 (28)
(Val-)ganciclovir, *n* (%)	1872 (40)	23 (40)	18 (46)	5 (28)
(Val-)acyclovir, *n* (%)	225 (5)	7 (12)	7 (18)	0 (0)
Duration of acyclovir prophylaxis, days, median (IQR)	94.5 (84.0–179.0)	931.0 (8.0–1606.0)	931.0 (8.0–1606.0)	0
Duration of ganciclovir prophylaxis, days, median (IQR)	98.0 (79.0–173.0)	61.0 (10.0–125.0)	93.0 (10.0–170.0)	27.0 (15.0–61.0)
Any CMV infection, *n* (%)	1358 (29)	16 (28)	10 (26)	6 (33)
Any VZV infection, *n* (%)	158 (3)	2 (4)	0 (0)	2 (11)
Any HSV infection, *n* (%)	288 (6)	4 (7)	3 (8)	1 (6)
Induction regiment contained, *n* (%)				
Basiliximab/Other	3075 (65)	41 (72)	28 (72)	13 (72)
ATG	1016 (22)	12 (21)	9 (23)	3 (17)
Rituximab	191 (4)	0 (0)	0 (0)	0 (0)
Unknown	426 (9)	4 (7)	2 (5)	2 (11)
Maintenance immunosuppression, *n* (%)				
Glucocorticosteroids	4513 (97)	55 (96)	38 (97)	17 (94)
MMF	4054 (87)	48 (84)	32 (82)	16 (89)
Azathioprin	126 (3)	3 (5)	2 (5)	1 (6)
Cyclosporin	1047 (23)	17 (30)	14 (36)	3 (17)
Tacrolimus	3305 (71)	38 (67)	25 (64)	13 (72)
Everolimus	53 (1)	1 (2)	1 (3)	0 (0)
Sirolimus	23 (0)	0 (0)	0 (0)	0 (0)
Unknown	58 (1)	0 (0)	0 (0)	0 (0)

(Continues)

Table 1 (Continued)

Characteristics	No PTLD *n* = 4708	PTLD *n* = 57	EBV+ PTLD *n* = 39	EBV− PTLD *n* = 18
Any rejection episode, *n* (%)	1794 (38)	21 (37)	13 (33)	8 (44)
Rejection episodes, *n*, median (IQR)	1 (1–3)	2 (1–2)	2 (1–2)	2 (2–2)
Treated rejection episodes, *n*, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	2 (1–2)

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; D, donor; HSV, herpes simplex virus; IQR, interquartile range; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; R, recipient; VZV, varicella-zoster virus.

managed by reducing immunosuppression alone. Rituximab monotherapy was given in 35% (20/57) of patients.

Forty-four percent (25/57) of patients diagnosed with PTLD died during follow-up, with most deaths attributed to PTLD (64%; 16/25). PTLD-related mortality was similar among EBV+ PTLD and EBV− PTLD cases (33% vs. 26%; $p = .55$, overall 28%) and the median time to PTLD-related death did not differ among EBV+ PTLD (4.1 months [IQR 0.3–8.6]) and EBV− PTLD (7.3 months [IQR 1.6–13.5]; $p = .28$).

3.3 | EBV+ PTLD and antiviral prophylaxis

Overall, 44.6% (2127/4765) of patients received antiviral prophylaxis with (val-) ganciclovir ($n = 1895$) or with (val-)acyclovir ($n = 232$) for a median duration of 97 days (IQR 79–173). The rate of recipients receiving antiviral prophylaxis was dependent on the type of transplant. Antiviral prophylaxis was more frequently given to lung transplant recipients (94% [414/442]) compared to kidney (45%; 1206/2697) heart (44%; 161/364), liver (22%; 230/1034), or combined transplant recipients (50%; 116/230). SOT recipients receiving antiviral prophylaxis were younger (median age: 53 [IQR 39–61] vs. 55 [IQR 43–62] years; $p < .001$) and more likely to have received ATG as part of the induction treatment (30% vs. 13%; $p < .001$) (Table S1). These patients also had a higher incidence of treatment requiring rejection episodes (221/1000 py [95% CI 209.4–233.9] vs. 268.5/1000 py [95% CI 254.1–283.8]). The crude EBV+ PTLD incidence rate in the first-year posttransplant was 3.87 of 1000 py (95% CI 1.94–7.73) for patients receiving antiviral prophylaxis versus 3.21 of 1000 py (95% CI 1.61–6.41) for patients without antiviral prophylaxis ($p = .35$). A trend for a higher incidence rate was found for patients receiving (val-)acyclovir (8.89/1000 py [95% CI 2.22–35.58]) compared to (val-)ganciclovir (3.26/1000 py [95% CI 1.46–7.25]; $p = .13$) in the first-year after transplant.

Crude incidence of EBV+ PTLD for the entire follow-up duration was higher for patients receiving antiviral prophylaxis (2.31/1000 py [95% CI 0.64–1.82]) compared to patients not receiving prophylaxis (1.08/1000 py [95% CI 1.56–3.42]). In the adjusted risk regression model, we did not find an effect of antiviral prophylaxis on EBV+ PTLD incidence in the first-year posttransplant or beyond this period (early EBV+ PTLD: SHR 0.535 [95% CI 0.199–1.436]; $p = .264$; late EBV+ PTLD: SHR 2.213 [95% CI 0.751–6.521]; Table 3). The results remained unchanged when comparing (val-)ganciclovir, which is believed to be more active against EBV than (val-) acyclovir,[37] versus no antiviral prophylaxis (data not shown).

Variables significantly associated with a higher risk of EBV+ PTLD occurrence differed in early EBV+ PTLD (<1 year) compared to late (>1 year) EBV+ PTLD (Table 3).

3.4 | PTLD and rituximab therapy

None of the 191 patients receiving rituximab as part of the induction treatment developed PTLD (Figure 3). Patients with rituximab induction therapy were younger (median age: 51 [IQR 41–61] vs. 54 [IQR 42–62] years; $p < .001$). The EBV serostatus distribution among both groups was similar. Most SOT recipients receiving rituximab as induction treatment were renal transplant recipients (95%; 182/191). The majority of these renal transplant recipients (88%; 161/182) received rituximab as part of their induction therapy for AB0 incompatible renal transplantation (Table S2). In the adjusted restricted mean survival time model (RMST), the mean PTLD-free survival time at 9 years of follow-up was significantly shorter (0.104 years [95% CI 0.077–0.131]) in patients not receiving rituximab as induction treatment (competing-risk models were inappropriate due to violation of proportional hazard assumption; no PTLD occurred in patients receiving rituximab). Meaning that the average loss of PTLD-free survival time at 9 years was 0.104 years in the group not receiving rituximab (Figure S1). In addition, none of the recipients receiving rituximab for treatment of rejection ($n = 121$) experienced PTLD during follow-up.

We performed a subanalysis restricted to renal transplant recipients to analyze if the effect of rituximab on PTLD occurrence is also verifiable in this subgroup. This analysis (adjusted RMST) confirmed the findings seen in the overall cohort that, patients not receiving rituximab induction had a significant shorter mean PTLD-free survival time at 9 years follow-up (0.067 years [95% CI 0.039–0.096]).

4 | DISCUSSION

We assessed the clinical characteristics, incidence, and outcome of PTLD in a nationwide cohort (STCS). In addition, we explored the association of antiviral prophylaxis and rituximab induction therapy on PTLD occurrence. The major findings of our study are

TABLE 2 PTLD incidence, classification, management, and outcome

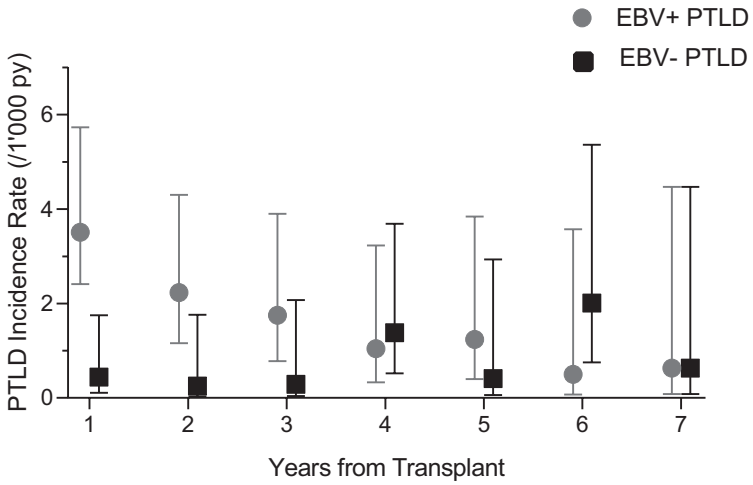
	Total	EBV+ PTLD	EVB− PTLD
	n = 57	*n* = 39	*n* = 18
Overall PTLD incidence rate /1000 py (IQR) according to organ transplant (IQR)	2.39 (1.84–3.11)	1.63 (1.19–2.24)	0.75 (0.47–1.2)
Kidney	1.59 (1.06–2.39)	1.01 (0.68–1.81)	0.48 (0.23–1.02)
Liver	3.41 (2.09–5.57)	1.71 (0.85–3.41)	1.71 (0.85–3.41)
Heart	2.41 (0.91–0.42)	1.81 (0.58–5.61)	0.60 (0.08–4.28)
Lung	5.77 (3.19–10.42)	5.24 (2.28–9.75)	0.52 (0.07–3.72)
Combined	2.68 (0.86–8.32)	1.79 (0.44–7.16)	0.89 (0.12–6.35)
PTLD WHO classification, *n* (%)			
Early lesions	6 (11)	5 (13)	1 (6)
Polymorphic PTLD	13 (23)	12 (31)	1 (6)
Monomorphic PTLD	38 (67)	22 (56)	16 (89)
B cell PTLD, *n* (%)	54 (95)	38 (97)	16 (89)
T cell PTLD, *n* (%)	3 (5)	1 (3)	2 (11)
CD20 status, *n* (%)			
Positive	43 (75)	31 (79)	12 (67)
Negative	7 (12)	5 (13)	2 (11)
Unknown	7 (12)	3 (8)	4 (22)
PTLD localization, *n* (%)			
CNS	8 (14)	8 (21)	0 (0)
Extra-nodal	48 (84)	34 (87)	14 (78)
Nodal	8 (14)	4 (10)	4 (22)
Unknown	1 (2)	1 (3)	0 (0)
PTLD management, *n* (%)			
Reduction of immunosuppression alone	7 (12)	7 (18)	0 (0)
Rituximab alone	20 (35)	14 (36)	6 (33)
Chemotherapy alone	5 (9)	1 (3)	4 (22)
Rituximab and chemotherapy	19 (33)	13 (33)	6 (33)
Other	6 (11)	4 (10)	2 (11)
PTLD outcome, *n* (%)			
Died during follow-up	25 (44)	16 (41)	9 (50)
PTLD-related death	16 (28)	10 (26)	6 (33)
Time to PTLD-related death, month (IQR)	6.8 (1.3–12.9)	7.3 (1.6–13.5)	4.1 (0.3–8.6)

Abbreviations: CNS, central nervous system; IQR, interquartile range; PTLD, posttransplant lymphoproliferative disorder; py; person-years; WHO, World Health Organization.

as follows: (1) the PTLD incidence rate among Swiss SOT recipients was low and depended on the type of transplant; (2) extra-nodal involvement was common; (3) the mortality among SOT recipients with PTLD was high; (4) antiviral prophylaxis was not associated with a reduction of EBV+ PTLD occurrence; and (5) in contrast, rituximab induction therapy was associated with a reduced risk of PTLD occurrence.

The incidence rate of PTLD ranged from 1.59/1000 py to 5.77/1000 py dependent on type of transplant which is lower than previously reported in other cohorts.[24,38] This might be due to the effects of continuous improvement in prevention, such as screening for EBV DNAemia and preemptive reduction in immunosuppression, in the current era of transplant medicine.[15] Incidence rates of EBV+ PTLD and EBV− PTLD differed over time. EBV+ PTLD incidence was highest in the first-year posttransplant (3.51/1000 py [95% CI 2.14–5.72]) and decreased thereafter; this was not the case for EBV− PTLD (0.43/1000 py [95% CI 0.11–1.75]). The distinct temporal occurrence of EBV+ and EBV− PTLD potentially reflects the different biological entity of these two malignancies[15,39,40] and may also explain the biphasic pattern of PTLD occurrence described in previous studies.[41-43]

In our study, most PTLDs had extra-nodal localization. Nodal involvement was only found in about one third of cases. Interestingly, extra-nodal involvement of lymphomas in the general population



IR/1000 py EBV+ PTLD	3.51	2.23	1.75	1.04	1.24	0.5	0.63
IR/1000 py EBV- PTLD	0.44	0.25	0.29	1.38	0.41	2.01	0.63

FIGURE 1 EBV+ and EBV− PTLD incidence per 1000 person-years. Symbols represent point-estimates, whiskers 95% confidence intervals. EBV, Epstein–Barr virus; IR, incidence rate; PTLD, posttransplant lymphoproliferative disorder; py, person-years

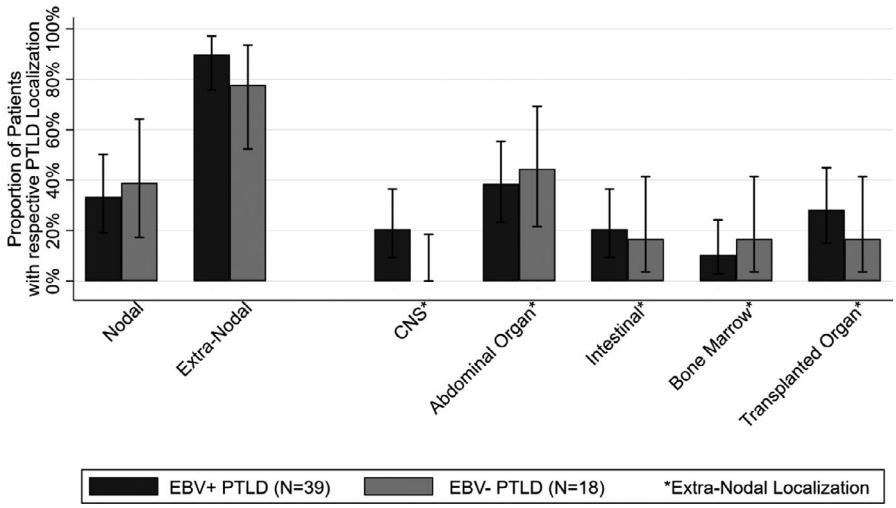


FIGURE 2 Localization of PTLD according to EBV association. Each extra-nodal localization is counted separately (exceeds number of cases). CNS, central nervous system; EBV, Epstein–Barr virus; PTLD; posttransplant lymphoproliferative disorder

is less common[44] and is associated with poor outcome.[45] PTLD localization in the transplanted organ was mainly present in lung and liver recipients and more often found in EBV+ PTLD compared to EBV− PTLD (28% vs. 16%). Similar to our findings, previous studies also reported high rates of extra-nodal PTLD.[46] In our cohort, PTLD-related mortality was around 30%. This is in line with findings of contemporary reports in pediatric[47] and adult[48] SOT PTLD patients. Present outcomes of patients, especially those with CD20+ PTLD, improved compared to historic reports, most likely as a result of the availability of rituximab and improved management of immunosuppression.[15]

Similar to previous reports, we identified different risk factors for early and late EBV+ PTLD.[7] In our analysis, early EBV+ PTLD was associated with EBV high-risk (D+/R−) serostatus (SHR 18.586 [95% CI 5.54–62.35]) and lung transplantation (SHR 5.98 [95% CI 1.54–23.17]). We did not find an association between young age or induction therapy with ATG and the risk for early EBV+ PTLD as reported by others.[38] Most likely, this is due to the underrepresentation of pediatric patients in our cohort and the lower ATG doses used in the recent era compared to historical studies.[15] Occurrence of late EBV+ PTLD was associated with young age at transplantation. However, this rather reflects an immortal person-time bias than a real finding.[49] In cohorts with an exclusively adult population, higher age is associated with occurrence of late PTLD.[7]

When correcting for known risk factors, EBV+ PTLD incidence rates were similar with or without antiviral prophylaxis. This is in line with the findings of the most recent meta-analysis.[25] There is a biologically plausible explanation for our findings. EBV-active antiviral substances ((val-)ganciclovir, (val-)acyclovir)) are pro-drugs and need to undergo phosphorylation by a viral thymidine kinase (TK), but

TABLE 3 Risk factors of EBV+ PTLD early (<1 year) and late (>1 year) after transplantation

Variable	Multivariable analysis SHR (95% CI)	*p*-value
Early EBV+ PTLD (<1 year after transplant)		
Sex		
Female	Reference	
Male	1.030 (0.379–2.798)	.953
Age	0.992 (0.967–1.017)	.525
Antiviral prophylaxis		
No prophylaxis	Reference	
Antiviral prophylaxis	0.535 (0.199–1.436)	.264
EBV serostatus		
Non high-risk (D−/R−)/(R+)	Reference	
High-risk (D+/R−)	18.586 (5.540–62.355)	<.001
Induction therapy		
No ATG	Reference	
ATG	1.284 (0.444–3.717)	.645
Organ transplant		
Kidney	Reference	
Liver	1.256 (0.269–5.851)	.771
Heart	2.055 (0.476–8.881)	.334
Lung	5.979 (1.542–23.176)	.010
Combined	3.333 (0.470–23.604)	.228
Late EBV+ PTLD (>1 year after transplant)		
Sex		
Female	Reference	
Male	0.0543 (0.229–1.283)	.164
Age	0.965 (0.943–0.988)	.003
Antiviral prophylaxis		
No prophylaxis	Reference	
Antiviral prophylaxis	2.213 (0.751–6.521)	.150
EBV serostatus		
Non high-risk (D−/R−)/(R+)	Reference	
High-risk (D+/R−)	1.760 (0.605–5.120)	.178
Induction therapy		
No ATG	Reference	
ATG	1.847 (0.519–6.571)	.343
Organ transplant		
Kidney	Reference	
Liver	1.420 (0.502–4.015)	.508
Heart	0.421 (0.045–3.927)	.448
Lung	2.083 (0.650–6.669)	.217
Combined	0.893 (0.094–8.497)	.922

Abbreviations: ATG, antithymocyte globulin; EBV, Epstein–Barr virus; D, donor; IQR, interquartile range; PTLD, posttransplant lymphoproliferative disorder; R, recipient; SHR, subdistribution hazard ratio.

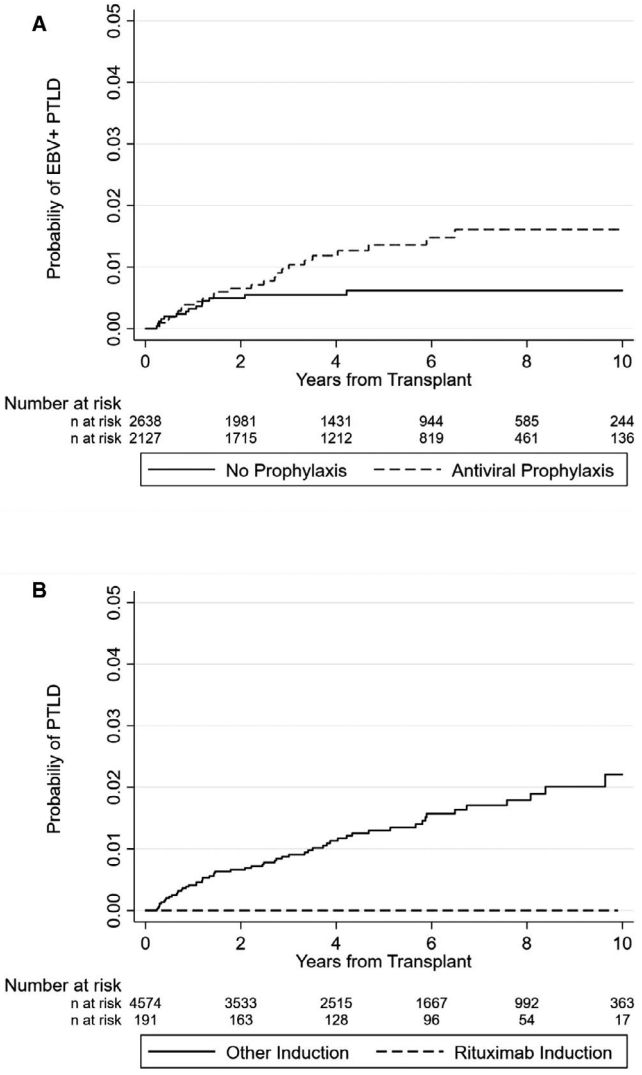


FIGURE 3 (A,B) Probability of EBV+ PTLD (A) or PTLD (B) occurrence according to antiviral prophylaxis (A) or rituximab therapy (B). EBV, Epstein–Barr virus; PTLD; posttransplant lymphoproliferative disorder

EBV-transformed proliferating B cells are latently infected and do not express EBV TK proteins.[50,51] Therefore, none of these antiviral agents can act on EBV-driven cell proliferation of B cells.

In our cohort, rituximab given as part of the induction regimen was associated with a reduced risk for PTLD. The difference in average loss of PTLD-free survival time at 9 years posttransplant (0.104 years [95% CI 0.077–0.131]) might appear small but the rarity of events and the large cohort have to be taken in to account when interpreting the data. The use of rituximab has become a common preemptive intervention strategy in EBV viremic HSCT recipients to reduce the risk of PTLD.[26] Moreover, rituximab given prophylactically before or directly after HSCT was shown to reduce EBV replication[52,53] and EBV+ PTLD in high-risk HSCT recipients.[27] In SOT, reduced PTLD rates have been reported if rituximab was used preemptively in heart[12] and renal[28] transplant recipients, who failed

to control EBV DNAemia despite reduction in immunosuppression. Rituximab is already used in the context of desensitization before AB0-incompatible renal transplantation[54] and has been given as sole induction therapy for renal transplantation.[55] Side effects associated with rituximab mainly include an increased risk for infection[56] and concerns about the emergence of CD20-negative PTLD after receiving rituximab were previously expressed.[57] The potential effect of rituximab on subsequent PTLD occurrence might be attributable to the depletion of $CD20^+$ B cells[58] which represent the major reservoir for latent EBV infection. The reduced abundance of these cells at risk for malignant transformation might be linked to a lower risk for PTLD.

Our study has several limitations. The relatively small number of PTLD cases potentially affects the power to identify factors associated with increased or reduced risk for development of PTLD. We cannot exclude underreporting of PTLD in our cohort, in particular late posttransplant, when patients were not exclusively followed at the transplant center. However, SOT recipients are to be expected to be referred to a tertiary transplant center upon PTLD diagnosis and all referral centers participate in the STCS. The duration of antiviral prophylaxis was not available for a relevant proportion of SOT recipients. In consequence, the effect of the duration of antiviral prophylaxis could not be adequately assessed. In addition, data on antiviral treatment duration for patients not receiving primary antiviral prophylaxis were not available. The majority of SOT recipients receiving rituximab as induction therapy were renal transplant recipients (95%). Therefore, the association of rituximab therapy and a reduction of PTLD incidence might not apply for other SOT recipients. Our findings regarding the effect of rituximab on PTLD occurrence are based on an observational study design, therefore we cannot exclude that this association is caused by confounding factors. However, we tried to address this by adjusting our multivariate model (restricted mean survival time model for rituximab use and development of PTLD) for confounding factors associated with PTLD including the type of transplanted organ, use of ATG, and EBV serostatus. To exclude that the effect of rituximab is solely caused by confounding due to a comparison of renal transplant patients with other transplant types which are associated with a higher PTLD risk, we performed a subgroup analysis restricted to renal transplant recipients. The association of a reduced PTLD incidence in patients with rituximab induction was also confirmed in this subgroup analysis. We therefore think that the reduced risk for PTLD development is rather associated with the use of rituximab and not by confounding factors.

In our study we did not address the potentially negative impact of rituximab induction. Therefore, we cannot provide an elaborated risk–benefit analysis of rituximab induction.

In summary, in this nationwide SOT cohort, PTLD incidence rate was low, but still associated with notable mortality. The incidence of EBV+ PTLD declined over time and was highest in the first-year posttransplant, while EBV− PTLD incidence did not decline. There was no association between antiviral prophylaxis and PTLD incidence. We provide novel information that rituximab given as part of the induction regimen was associated with a decreased risk for PTLD occurrence. This finding needs to be confirmed in independent cohorts.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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