# Post-transplant lymphoproliferative disorder in liver transplant recipients: Characteristics, management and outcome from a single-centre experience with >1000 liver transplantations

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**BACKGROUND:** The literature regarding post-transplant lymphoproliferative disorder (PTLD) in liver transplant recipients (LTRs) is limited.
**OBJECTIVES:** To study the incidence, predictors and outcomes of PTLD after liver transplantation in a single, large-volume centre.
**METHODS:** The charts of all LTRs (n=1372) in the authors' centre between January 2000 and June 2012 were retrospectively reviewed and those who developed PTLD were identified. Demographic, clinical and treatment data were prospectively collected. Responses to treatment, including complete response, no response, relapse and survival, were recorded.
**RESULTS:** The incidence of PTLD in LTRs was 32 in 1372 (2.3%). Overall, median survival was 37 months (range 0.5 to 195 months), with one-, three- and five-year survival rates of 81%, 74% and 60%, respectively. Epstein-Barr virus (EBV)-negative patients had a better mean (± SD) survival (95±79 months) than EBV-positive patients (41±42 months) (P=0.02). For stage I/II PTLD, one-, three- and five-year actuarial survival was 87%, 87% and 75%, compared with 50%, 30% and 0% for stage III/IV PTLD, respectively (P=0.001). In patients with complete response, median survival was 58 months (range 10 to 195 months); and one-, three- and five-year actuarial survival was 100%, 94% and 76%, respectively, after diagnosis of PTLD. Changing immunosuppression (IS) from calcineurin inhibitor to sirolimus at the time of diagnosis may have improved survival (seven of seven survivors) compared with only decreasing or stopping IS (14 of 25 survivors) (P=0.07).
**CONCLUSIONS:** This series from a single large-volume centre showed excellent short and long-term survival after PTLD in adult LTRs who were EBV negative, had early disease and showed complete response. Consistent with the known in vitro antiproliferative effect of sirolimus, switching IS from calcineurin inhibitor to sirolimus may improve survival.

**Key Words:** *Immunosuppression; Liver; Lymphoma; PTLD; Sirolimus; Transplant*

## Les troubles lymphoprolifératifs après une transplantation du foie : les caractéristiques, la prise en charge et les résultats après plus de 1 000 transplantations dans un seul centre

**HISTORIQUE :** Les publications scientifiques sur les troubles lymphoprolifératifs après une transplantation (TLAP) chez des greffés du foie (GF) sont limitées.
**OBJECTIFS :** Étudier l'incidence, les prédicteurs et les résultats des TLAP chez les GF dans un seul centre à grand volume.
**MÉTHODOLOGIE :** Les auteurs ont effectué l'examen rétrospectif du dossier de tous les GF (n=1 372) de leur centre entre janvier 2000 et juin 2012 et extrait ceux qui ont présenté un TLAP. Ils ont fait une collecte prospective des données démographiques, cliniques et thérapeutiques. Ils ont saisi les réponses au traitement, y compris la réponse complète, l'absence de réponse, la récidive et la survie.
**RÉSULTATS :** Chez les GF, l'incidence de TLAP était de 32 cas sur 1 372 (2,3 %). Dans l'ensemble, la survie médiane était de 37 mois (plage de 0,5 à 195 mois) et le taux de survie au bout de un, trois et cinq ans de 81 %, 74 % et 60 %, respectivement. Les patients négatifs au virus d'Epstein-Barr (VEB) présentaient une meilleure survie moyenne (± ÉT) (95±79 mois) que ceux qui y étaient positifs (41±42 mois) (P=0,02). En cas de TLAP de stade I/II, la survie actuarielle au bout de un, trois et cinq ans s'élevait à 87 %, 87 % et 75 %, par rapport à 50 %, 30 % et 0 %, respectivement, pour la TLAP de stade III/IV (P=0,001). Chez les patients ayant une réponse complète, la survie moyenne était de 58 mois (plage de dix à 195 mois) et la survie actuarielle au bout de un, trois et cinq ans, de 100 %, 94 % et 76 %, respectivement, après le diagnostic de TLAP. Le passage du traitement immunosuppresseur (IS) par un inhibiteur de la calcineurine à un sirolimus au diagnostic a peut-être accru la survie (sept des sept survivants) par rapport à la diminution ou à l'abandon de l'IS (14 des 25 survivants) (P=0,07).
**CONCLUSIONS :** Cette série tirée d'un seul centre à grand volume a révélé une excellente survie à court et à long terme après un TLAP chez des GF adultes négatifs au VEB atteints peu après la transplantation et ayant une réponse complète. Conformément à l'effet antiprolifératif *in vitro* connu du sirolimus, le passage IS par un inhibiteur de la calcineurine au sirolimus améliore peut-être la survie.

Post-transplant lymphoproliferative disorder (PTLD) reflects uncontrolled B cell proliferation in the post-transplant setting, with pathological features ranging from polymorphic cellular expansion of lymphocytes of any size to monomorphic large-cell non-Hodgkin lymphomas (1). Compared with lymphoma in the general population, PTLD is characterized by increased extranodal involvement, a more aggressive clinical course and poorer response to conventional treatment (2,3).

Overall, the incidence of PTLD after solid organ transplantation ranges from 1% to 10%, with a mortality rate often exceeding 50% (4,5).The incidence varies with the type of allograft transplanted (6), the highest incidence (up to 30% lifetime) being observed in recipients of small bowel, heart and lung transplants (7,8). The prevalence of PTLD in liver transplant recipients (LTRs) ranges from 2% to 4% in adults (9,10), but is as high as 20% in pediatric series (10-13). PTLD

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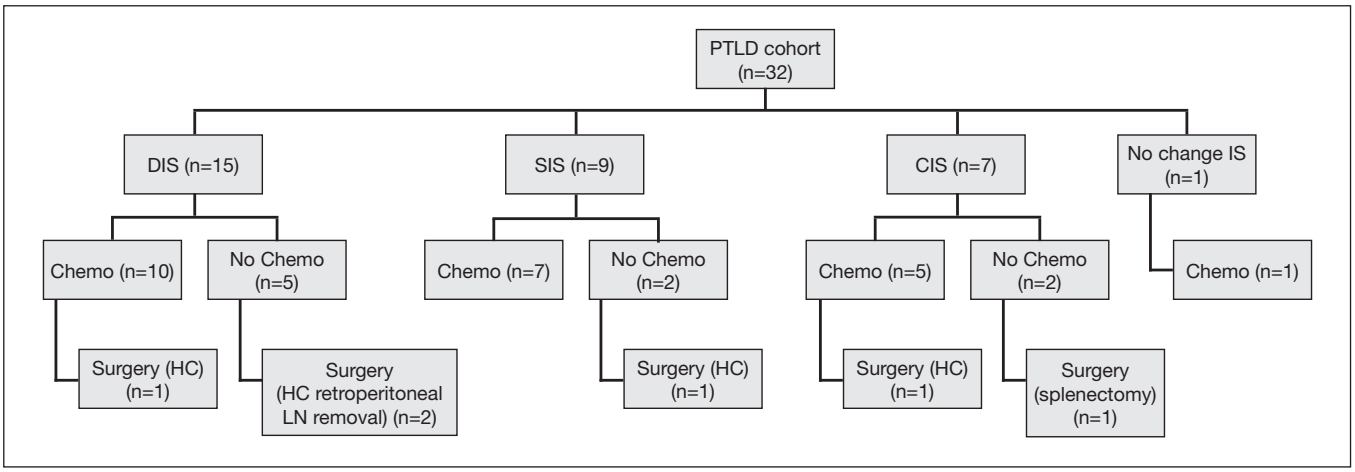


**Figure 1)** *Algorithm of various interventions used in the cohort of post-transplant lymphoproliferative disorder (PTLD) patients. Chemo Chemotherapy; CIS Changing immunosuppression to sirolimus; DIS Decrease in immunosuppression; HC Hemicolectomy; IS Immunosuppression; LN Lymph node; SIS Stopping immunosuppression*

typically manifests within the first year of liver tranplantation (LT), but may present as early as 20 days after LT and as late as several decades after the engraftment. However, the general concept is that the highest risk of PTLD development occurs in the early post-LT period, principally due to the higher doses of immunosuppression (IS) administered early. Early onset PTLD has been reported to have a more favourable outcome while late-onset disease is more likely to behave like an aggressive lymphoma (14).

Due to the limited understanding of the pathogenesis of PTLD, there is a lack of clear consensus in its management (15). Management options include reduction of IS, chemotherapy, such as combination of cyclophosphamide, hydroxy doxorubicin, vincristine (Oncovin, Eli Lilly, USA) prednisone (CHOP) and/or rituximab, as well as surgical resection in some cases (4-8,11-13).

Due to the small number of PTLD cases occurring at adult liver transplant centres, incidence, risk factors and outcomes of PTLD after adult LT remain debated. Therefore, we aimed to assess incidence, predictors and outcomes of PTLD after adult LT in our large-volume institution.

## METHODS

The present study was approved by the authors' institutional ethics committee and conducted according to the Declaration of Helsinki.

The present study was a retrospective analysis of prospectively collected data from all adult patients who underwent LT at the Toronto General Hospital (Toronto, Ontario) between January 2000 and December 2012. Data were retrieved from the Organ Transplant Tracking Record (Hickman-Kenyon Systems, USA) (16), which is an internal web-based transplantation database linked to the electronic medical record for a solid organ transplant at the University Health Network, University of Toronto (Toronto, Ontario), which was instituted at Toronto General Hospital in 2000. To maintain group homogeneity, patients who underwent a liver re-transplant (re-LT) or a combined liver/non-liver solid organ transplant were excluded.

### Diagnosis and follow-up of PTLD

Cytomegalovirus and Epstein-Barr virus (EBV) serology of the recipients before LT were recorded. Diagnosis and staging of PTLD was based on histological examination of biopsies or surgical specimens of tumours supplemented by computed tomography (CT) scans and/or gastrointestinal endoscopy, wherever indicated. WHO classification was used for defining PTLD, and lesions were classified as polymorphic or monomorphic disease (6). Results of immunohistochemistry for light-chain restriction, flow cytometry and in situ hybridization for EBV messenger RNA (EBER-1) were collected. Patients were staged according to the Ann Arbor staging system (17).

Serial CT scans of the brain, chest, abdomen and pelvis were used to assess response to therapy in all patients with PTLD. Bone marrow biopsies and gastrointestinal endoscopy were performed for diagnosis, staging and response assessment during follow-up when indicated.

### IS

The IS protocol used in the authors' program has been reported elsewhere (18). Briefly, all patients received intravenous solumedrol (starting with 200 mg and tapered over five days), followed by oral prednisone 20 mg once daily, which was tapered and discontinued over a three-month period.

Thymoglobulin or basiliximab was used as induction per protocol in all living donor LT recipients, as well as in recipients with neurological and/or renal impairment to enable delaying calcineurin inhibitor (CNI) use. Maintenance IS (MIS) was CNI (cyclosporine A or tacrolimus) with or without an antiproliferative (mycophenolate mofetil, mycophenolate sodium or azathioprine) and was at the discretion of the responsible transplant hepatologist. Pre- or post-PTLD episodes of acute cellular rejection (ACR) were bioptically documented and graded according to the Banff system (19). Treatment typically consisted of boluses of intravenous solumedrol 500 mg daily for three (and up to five days) or of increasing MIS including oral prednisone, if the rejection was mild.

### PTLD therapy

Therapy for PTLD included stopping antiproliferatives, if applicable, along with either: reduction of CNI dose; stopping all IS including CNI; or switching from CNI to sirolimus. The next step included one of following: CHOP with or without rituximab; rituximab alone; ABVD protocol (see below); radiation, and/or surgery. The CHOP regimen was given every 21 days for up to six cycles with or without concurrent rituximab (2,3). Rituximab was administered as a slow intravenous infusion weekly for four doses (2,3). The ABVD protocol consists of adriamycin, bleomycin, vinblastine and dacarbazine given monthly for four cycles (2). Surgery was reserved for anatomically limited disease with significant symptoms such as segmental small bowel PTLD presenting as small bowel obstruction. Radiotherapy was used for PTLD nonresponsive to chemotherapy and central nervous system involvement.

### Definitions

Treatment response was assessed according to the revised International Workshop criteria (20) as follows: complete response (CR) was defined as complete disappearance of tumour (imaging, endoscopy) and absence of new lesions for at least four weeks after completing therapy; stable disease was defined as a decrease <50% or an increase <25% in tumour

**TABLE 1**
**Demographics and descriptive results of post-transplant lymphoproliferative disorder (PTLD) patients (n=32)**

| Variable | |
|---|---|
| Age at liver transplantation, years, median (range) | 44 (20–65) |
| Age at PTLD diagnosis, years, median (range) | 53 (25–75) |
| Sex, male/female, n/n | 18/14 |
| Etiology of liver disease | |
| Autoimmune liver disease(s) | 15 (47) |
| Hepatitis C virus disease | 10 (31) |
| Alpha 1 antitrypsin deficiency | 3 (9) |
| Others | 4 (13) |
| DDLT/LDLT | 27 (84)/5 (16) |
| Epstein-Barr virus recipient positive | 26 (81) |
| Cytomegalvirus recipient positive | 24 (75) |
| Thymoglobulin induction | 5 (16) |
| Basiliximab induction | 5 (16) |
| Cyclosporine | 18 (56) |
| Tacrolimus | 14 (44) |
| Mycophenolate | 9 (28) |
| Azathioprine | 9 (28) |

*Data presented as n (%) unless otherwise indicated. DDLT Deceased donor liver transplantation, LDLT Living donor liver transplantation*

size, with no evidence of new lesions; partial response (PR) was defined as >50% size reduction of detectable lesions, without evidence of new lesions; and progressive disease was defined as enlargement of lesions by >25%, the occurrence of new lesions or worsening of clinical symptoms. Because the number of cases was limited, PR and progressive disease were analyzed together as no response. Relapse was defined as recurrence of PTLD at any time after having achieved a CR. Survival was reported from the time (in months) of diagnosis of PTLD to longest follow-up. The time between LT and PTLD diagnosis was defined as the period (in months) between engraftment and histopathological diagnosis of PTLD. Patients who presented with PTLD within the first 12 months post-LT were categorized as the 'early onset PTLD' group, and liver graft recipients who re-presented the disease beyond this time period after LT were 'late-onset PTLD' patients. Death was attributed to PTLD if either the patient died within six months postdiagnosis, or the patient died due to complications classified as a complication of the PTLD treatment (21).

### Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (IBM Corporation, USA). Descriptive analysis was performed for demographic and clinical features and results were presented as median with ranges for quantitative variables, and numbers (percentages) for qualitative variables. $\chi^2$ and Fisher's exact tests were used for categorical variables, as appropriate, while the independent sample *t* test was used for numerical variables. The Kaplan-Meier method and log-rank test were used to estimate and compare cumulative survival (time from PTLD diagnosis to death from any cause). All P values were two-sided and considered to be statistically significant at P<0.05.

## RESULTS

A total of 1372 patients received LT at the authors' institution during the study period; of these, 42 (3%) developed PTLD and 32 (2.3%) were eligible for the study. Of the 10 PTLD patients excluded, four underwent re-LT and six had combined liver/non-liver solid organ transplant.

### Patient characteristics

The median age at the time of LT was 44 years (range 20 to 65 years). The most common etiology for LT was autoimmune liver disease (primary biliary cirrhosis [n=4]; autoimmune hepatitis [n=4]; primary sclerosing cholangitis [n=7]) in 15 (47%), followed by hepatitis C virus (HCV) in 10 (31%) PTLD patients. The details of EBV/cytomegalovirus serology, induction and MIS are presented in Table 1.

Before the diagnosis of PTLD, 14 (44%) patients developed ACR; three had experienced >1 episode of rejection. One patient had severe rejection, four had moderate and nine had mild ACR.

Median age at time of diagnosis of PTLD was 53 years (range 25 to 75 years). Median time between LT and diagnosis of PTLD was 60 months (range three to 240 months). The distribution of features of early and late-onset PTLD is elaborated in Table 2. PTLD was diagnosed with the help of radiological imaging in 22 (70%) patients and gastrointestinal endoscopy in 10 (30%). Abdominal viscera were involved in 42% (stomach 12%, small intestine 15%, large intestine and liver 6% each, and spleen 3%), followed by mesenteric and/or retroperitoneal lymph nodes 40%, cervical lymph nodes 9% and lungs 3%.

Diffuse large B cell lymphoma was the most common phenotype (n=21 [65%]), followed by Hodgkin disease (n=4 [13%]) and Burkitt type, diffuse large T cell type, and T and B cell mixed monoclonal lymphoma (n=2 each [6%]), and one monoclonal B cell type lymphoma.

All were tested for EBV in tissue samples and 17 (53%) were positive as determined by EBER in situ hybridization. Eight (89%) patients were EBER-positive in early onset PTLD compared with nine (39%) in late-onset PTLD (P=0.02).

**TABLE 2**
**Presentation of early and late-onset post-transplant lymphoproliferative disorder (PTLD) in adult liver transplant (LT) recipients**

| | PTLD onset | | |
|---|---|---|---|
| Variable | Early (n=9) | Late (n=23) | P |
| Age at LT, years, mean ± SD | 45±13 | 42±11 | 0.51 |
| Age at PTLD diagnosis, mean ± SD | 52±13 | 53±11 | 0.82 |
| Sex, male/female, n/n | 5/4 | 13/10 | 0.63 |
| Time to PTLD, months, mean ± SD | 20±42 | 93±56 | – |
| Autoimmune liver disease | 2 (22) | 13 (56) | 0.08 |
| Cytomegalovirus seropositive | 8 (89) | 16 (70) | 0.25 |
| Epstein-Barr virus seropositive | 6 (75) | 20 (87) | 0.18 |
| EBER seropositive | 8 (89) | 9 (39) | 0.02 |
| Tacrolimus/cyclosporine, n/n | 5/4 | 9/14 | 0.40 |
| Diffuse large B cell lymphoma | 7 (78) | 14 (61) | 0.35 |
| CD20 tissue positive | 8 (89) | 17 (72) | 0.45 |
| CD45 tissue positive | 4 (44) | 11 (48) | 0.94 |
| Multiorgan involvement | 7 (78) | 15 (65) | 0.49 |
| Disseminated PTLD | 2 (22) | 3 (13) | 0.52 |
| Hodgkin disease | 0 (0) | 4 (17) | 0.18 |
| Non-Hodgkin lymphoma type | 7 (78) | 17 (74) | 0.82 |
| Monomorphic/polymorphic, n/n | 5/3 | 12/6 | 0.83 |
| Stage I & II/stage III & IV, n/n | 6/3 | 18/5 | 0.50 |
| Chemotherapy used | 5 (56) | 18 (78) | 0.20 |
| Complete response | 7 (78) | 18 (78) | 0.97 |
| Relapse of PTLD | 1 (11) | 4 (17) | 0.90 |

*Data presented as n (%) unless otherwise indicated. EBER Epstein-Barr virus messenger RNA*

### Treatment modalities and responses

The most common early treatment strategy was decrease in IS (n=15), followed by stopping IS (n=9), changing to sirolimus (n=7) and no change in IS (n=1). Figure 1 summarizes the various treatment modalities in all 32 PTLD patients according to the treatment response. Among later interventions, chemotherapy (n=23 [72%]) was the most common followed by decrease in IS (n=5 [15%]) and surgery (n=4 [12%]). The details, in additon to outcomes of these interventions, are illustrated in Figure 2 and summarized in Table 3.

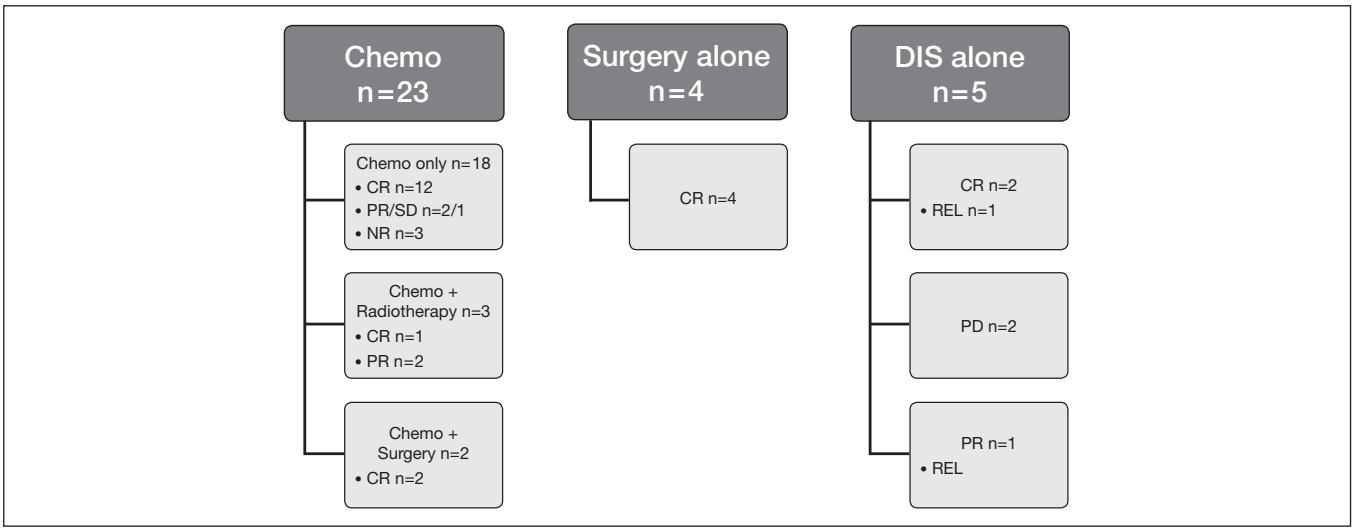


**Figure 2)** *Various interventions offered to post-tranplant lymphoproliferative disorder (PTLD) patients and their responses. Chemo Chemotherapy; CR Complete response; DIS Decrease in immunosuppression; NR No response; PD Progressive disease; PR Partial response; REL Relapse; SD Stable disease*

**TABLE 3**
**Results of chemotherapy in patients with post-transplant lymphoproliferative disorder**

| Chemotherapy | CR | Relapse | NR | Survival, months, median (range) | Still alive |
|---|---|---|---|---|---|
| R-CHOP (n=8) | 6 | 0 | 2 | 12 (1–39) | 5 |
| CHOP* (n=7) | 6 | 1 | 1 | 75 (12–149) | 5 |
| Rituximab (n=7) | 5 | 1 | 2 | 60 (4–142) | 5 |
| ABVD (n=3) | 2 | 1 | 1 | 24 (3–48) | 1 |

**Two patients were treated with cyclophosphamide, hydroxydoxorubicin, vincristine (Oncovin, Eli Lilly, USA) and prednisone (CHOP) after failure of rituximab monotherapy; ABVD Adriamycin, bleomycin, vinblastine and dacarbazine; CR Complete response; NR No response; R-CHOP Rituximab + CHOP*

### Predictors of survival

Overall, median survival in all patients with PTLD was 37 months (range 0.5 to 195), and the one-, three- and five-year actuarial survival rates after diagnosis of PTLD were 81%, 74% and 60%, respectively (Figure 3). The 25 patients who achieved CR survived median of 58 months (10 to 195) months, and one-, three- and five-year actuarial survival after diagnosis of PTLD was 100%, 94% and 76%, respectively. All seven patients who did not respond to therapy died within one year of diagnosis of PTLD, with a median survival of only three months (range 0.5 to 12) (Figure 4). A better mean (± SD) survival was observed after diagnosis of PTLD in patients who were EBV negative (95±79 months) compared with those who were EBV positive (41±42 months; P=0.02). Stage I/II PTLD patients had a better overall survival (19 of 24 [79%]) compared with stage III/IV (two of eight [25%]) (P=0.05). Moreover, one-, three- and five-year cumulative survival among stage I/II was 87%, 87% and 75%, compared with 50%, 30% and 0%, respectively, in stage III/IV patients (P=0.001) (Figure 5).

Moreover, switching from CNI to sirolimus-based IS tended to lead to an improved survival, seven of seven patients surviving compared with decreasing and stopping IS (14 of 25 [56%]) (P=0.07) (Figure 6). However, this did not reach statistical significance, possibly due to the limited sample size. Finally, there were no differences in survival based on CD20 serology, early versus late PTLD, monomorphic versus polymorphic, and type of CNI use as MIS.

### Cause of death

Eleven patients died in the present series. In nine patients, the cause of death was classified as PTLD related (among these, three experienced a relapse of PTLD before death and six had no response). One patient died from metastatic melanoma 39 months after achieving CR; another patient died a month after achieving CR with one cycle of rituximab + CHOP from graft failure and sepsis. Median survival from diagnosis of PTLD among the 11 deceased patients was 11 months (range 0.5 to 58 months) and mean survival 17±19 months, respectively.

## DISCUSSION

We report a large series of PTLD after adult LT from a single centre. The observed incidence of PTLD in our program (2.3%) compares well with that previously reported by others in adult LTRs (2% to 3%) (14,22,23). The most intriguing observation of our retrospective analysis was that switching IS from a CNI to a sirolimus-based IS regimen may have improved survival after diagnosis of PTLD.

PTLD is a well-recognized complication of solid organ transplantation, with an incidence ranging in adults from 1% to 10% (4,5,23) and is associated with a significant mortality rate.

The highest rates of lymphomas (58% to 60%) were previously reported by others in graft recipients within the first 12 months post-LT, so-called 'early onset PTLD' (19). In contrast, late PTLD (occurring >12 months after LT) was observed in our series, with 72% of cases more frequently than early onset PTLD (28%). It is suggested by various authors that early and late PTLD consists of two different clinical and pathological entities (9,11,12). Early onset PTLD is characterized by being EBER negative (24) and CD20-positive, and more commonly involving the engrafted organ than late-onset PTLD. However, all of our cases were predominantly EBER positive (89%), and CD20 was equally distributed in the two groups. Also noteworthy, and in contrast to previous reports, none of our PTLD patients had involvement of the engrafted organ.

The most common underlying etiology leading to the need for LT in our PTLD patients was autoimmune liver disease (47%), followed by HCV (31%): previous reports suggest both of them as a possible risk factors for the development of PTLD (25-28). While HCV was the underlying cause of liver disease in approximately 30% of all LTs performed at our institution during the study period, underlying autoimmune liver diseases are clearly over-represented in the PTLD cohort. This may be attributable to the often higher level of IS required by these patients. Accordingly, Zimmermann et al (29) reported autoimmune liver disease and pre-LT prolonged steroid intake as independent risk factors predicting late PTLD development.

Not unexpectedly, we observed that early compared with late-stage PTLD (stage I/II versus II/IV) has a favourable cumulative survival (P=0.001). Nevertheless, a stage effect was absent in a previous retrospective review involving 27 pediatric patients (30). However, this report included heart and small intestine transplant patients, apart from a few with LT.

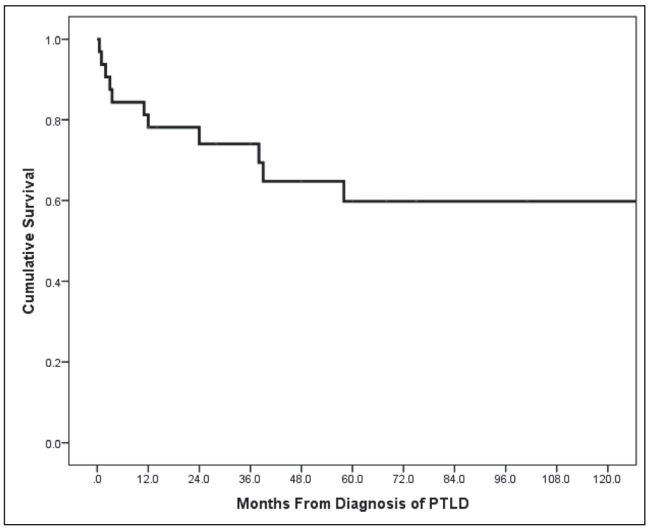


**Figure 3)** *Kaplan-Meier curve showing cumulative survival in 32 patients at one, three and five years after the diagnosis of post-transplant lymphoproliferative disorder (PTLD)*

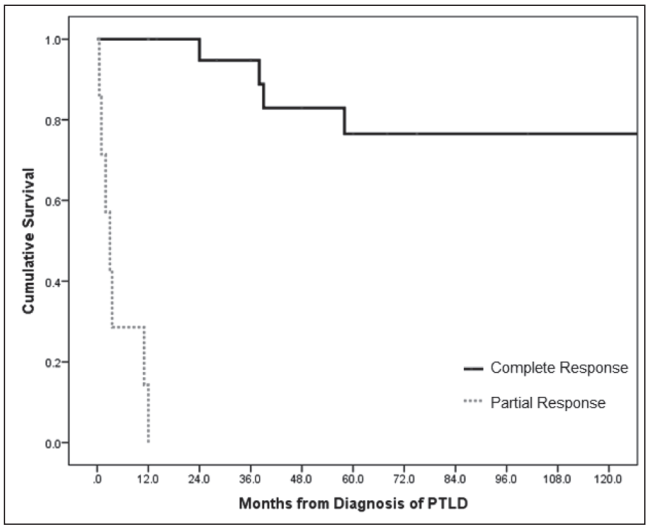


**Figure 4)** *Kaplan-Meier curve comparing survival among patients with complete response (n=25) and partial response (n=7) with post-transplant lymphoproliferative disorder (PTLD)*

There is no consensus as to the best approach to treatment of PTLD. This appears, at least in part, attributable to clinical variability of the disease, its frequent extranodal involvement and the wide spectrum of histological features. Reduction or cessation of IS is the most common initial approach, which was first reported by Starzl et al (31) in 1984, and has been practiced for several decades since (32,33). The hypothesis behind this strategy is that the recovery of the host's immune system will allow the development of cytotoxic T lymphocytes (CTL) against EBV with subsequent control of EBV-driven B cell proliferation. Another approach may be the use of mammalian target of rapamycin (mTOR) inhibitors such as rapamycin (sirolimus), which has a potent antiproliferative effect on in-vitro PTLD-derived cell lines and has been shown to inhibit the growth of solid tumours in a mouse model of PTLD without significantly compromising graft rejection (34,35). A multicentre clinical experience from European transplant centres supports the approach of using mTOR inhibitors in the management of PTLD following renal transplantation (36). While not reaching statistical significance, presumably due to the limited sample size, our observation of a trend toward improved survival with switching PTLD patients from CNI to sirolimus-based IS is entirely consistent with this renal transplant experience, and may warrant formal exploration in a controlled trial.

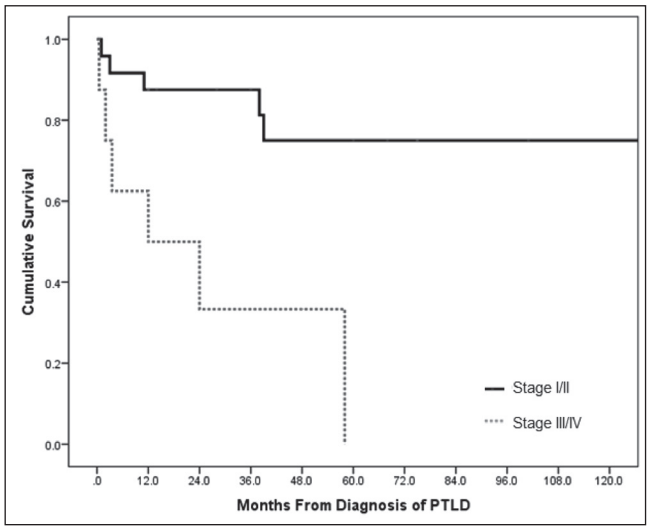


**Figure 5)** *Kaplan-Meier curve comparing the one-, three- and five-year survival in stage I/II post-transplant lymphoproliferative disorder (PTLD) compared with with stage III/IV PTLD*

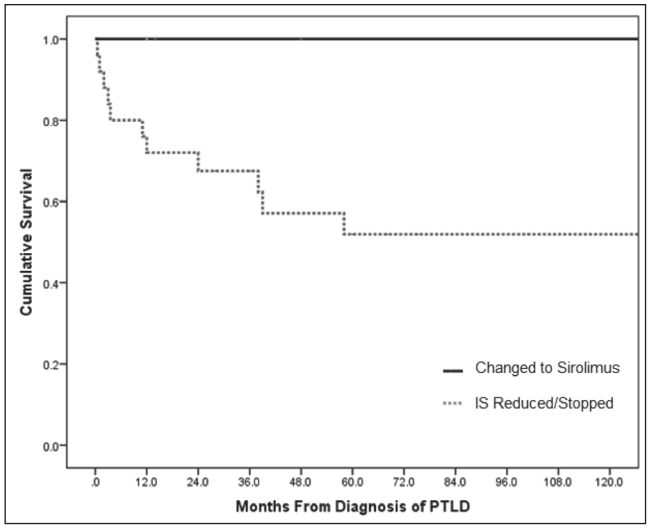


**Figure 6)** *Kaplan-Meier curve showing comparing changing immunosuppression (IS) to sirolimus approach with decrease in IS/stopping IS. PTLD Post-transplant lymphoproliferative disorder*

The present study clearly shows that short-term and long-term patient survival rates after diagnosis of PTLD are not as dismal as reported in other series (37,38). At a median follow-up of 60 months (range seven to 142 months), 19 of the 20 patients with CR were alive and without evidence of disease. The median overall survival after PTLD diagnosis was 37 months, with one-, three- and five-year cumulative survival rates of 81%, 74% and 60%, respectively. These survival rates are better than those reported in other series (25) and similar to those reported by Jain et al (15) from Pittsburgh, Pennsylvania (USA). Early onset PTLD in adults was associated with worse patient survival in one series (39), while late-onset PTLD was a poor prognostic factor in another series (11). However, we did not find any difference in terms of CR, mortality and survival at one, three and five years among early or late-onset PTLD.

A major limitation of our study was related to the rarity of the condition (ie, the limited sample size) and its retrospective nature. Moreover, we were unable to perform a logistic regression analysis due to small sample size. On the other hand, the heterogeneity of PTLD treatments makes it difficult to analyze a specific outcome of patients according to their treatment.

## CONCLUSION

The incidence of PTLD in adult LT recipients was 2.3%. Early onset PTLD was characterized by a high percentage of EBER positivity; however, the other variables were comparable in early and late onset PTLD. Younger patients transplanted for various autoimmune liver diseases, such as primary biliary cirhhosis, primary sclerosing cholangitis and autoimmune hepatitis, appear to be at higher risk for PTLD. Patients with early stage PTLD, treatment with CHOP alone or in combination with rituximab and those achieving a CR have a favourable outcome. Most intriguingly, switching from CNI to sirolimus-based IS may improve survival and appears to warrant testing in a controlled trial.

**DISCLOSURES:** None of the authors have any commercial associations or other arrangements (eg, financial compensation received, patent-licensing arrangements, potential to profit, consultancy, stock ownership, etc) that may pose a conflict of interest in connection with this article.

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