Retrospective Study

Post-transplant lymphoproliferative disorder after liver transplantation: Incidence, long-term survival and impact of serum tacrolimus level

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AIM

To investigate incidence and survival of post-transplant lymphoproliferative disorder (PTLD) patients after liver transplantation.

METHODS

A cross-sectional survey was conducted among patients who underwent liver transplantation at Shiraz Transplant Center (Shiraz, Iran) between August 2004 and March 2015. Clinical and laboratory data of patients were collected using a data gathering form. The study was supported by a grant from Shiraz University of Medical Sciences.

RESULTS

There were 40 cases of PTLD in the pediatric age group and 13 cases in the adult group. The incidence of PTLD was 6.25% in pediatric patients and 1.18% in adult liver transplant recipients. The post-PTLD survival of patients at 6 mo was 75.1% ± 6%, at 1 year was 68.9% ± 6.5% and at 5 years was 39.2% ± 14.2%. Higher serum tacrolimus level was associated with lower post-PTLD survival in pediatric patients.

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(OR = 1.07, 95%CI: 1.006-1.15, P = 0.032). A serum tacrolimus level over 11.1 ng/mL was predictive of post PTLD survival (sensitivity = 90%, specificity = 52%, area under the curve = 0.738, P = 0.035).

CONCLUSION
Incidence of PTLD in our liver transplant patients is comparable to other centers. Transplant physicians may consider adjustment of tacrolimus dose to maintain its serum level below this cutoff point.

Key words: Post-transplant lymphoproliferative disorder; Liver transplantation; Survival; Tacrolimus; Epstein-Barr virus

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Core tip: Post-transplant lymphoproliferative disorder (PTLD) is one of the complications that may occur after liver transplantation. The present study is a survival analysis of liver transplant patients after PTLD development. The incidence of PTLD was 6.25% in pediatric patients and 1.18% in adult liver transplant recipients. The main new finding is association of serum tacrolimus level with post-PTLD survival. Higher serum tacrolimus level was associated with lower post-PTLD survival in pediatric patients.

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INTRODUCTION
Liver transplantation is an established modality of treatment for end-stage liver diseases of various etiologies. Despite considerable improvement in outcomes of patients, complications frequently occur after transplantation that may have negative impact on survival[12]. Post-transplant lymphoproliferative disorder (PTLD) is one of the complications that may occur after liver transplantation and threatens both graft and patient survival. PTLD is generally believed to be a consequence of relative immunodeficiency state secondary to immunosuppressive regimens in these patients[23]. Immunosuppressive therapy results in depressed T-cell function that predisposes patients to lymphoid proliferation[30]. Epstein-Barr virus (EBV) infection is the other major risk factor for development of PTLD after liver transplantation and the majority of cases (60%-70%) are EBV-positive[41]. While EBV infection has minimal consequences in normal subjects, in liver transplant recipients it is associated with a spectrum of disorders, ranging from reactive monoclonal hyperplasia to aggressive malignant lymphoma[5]. In immunocompetent subjects, the EBV genome remains latent in resting memory B cells after immortalization[6]. However, after transplantation, long-term immunsuppressive therapy results in depressed T-cell function and lack of T-cell inhibition on B-cell proliferation[72]. This may lead to uncontrolled B-cell proliferation and subsequent hyperplasia, and even malignant transformation.

PTLD is more frequently encountered in pediatric patients, and younger age by itself is a known risk factor for PTLD despite controversies[8]. Another proposed risk factor for PTLD development after liver transplantation is hepatitis C virus infection[9]. With a mortality rate ranging from 12% to 60% in different studies, PTLD has imposed considerable negative impact on transplant patients until recently[10-12]. However, outcomes of patients and survival rates have been substantially improved by using new modalities for treatments, such as rituximab (a chimeric anti-CD20 monoclonal antibody) and sirolimus, in addition to reduced-dose immunosuppression[13-15].

This study aimed to investigate incidence, risk factors (including impact of immunosuppressive regimen) and survival of PTLD patients after liver transplantation in Iranian patients.

MATERIALS AND METHODS

Patients
Shiraz Organ Transplant Center (Shiraz, Iran) is a leading transplant center in Iran, with considerable annual cases of liver transplantation for both adult and pediatric patients. A cross-sectional survey was conducted among the adult and pediatric patients (< 18 years) who underwent liver transplantation at Shiraz Transplant Center between August 2004 and March 2015. Clinical and laboratory data of patients were collected using a data gathering form containing information regarding age, sex, underlying liver disease, type of allograft (deceased donor; living related donor, split liver transplantation), time of liver transplantation and time of PTLD development, survival of patients from date of liver transplantation, survival after PTLD diagnosis, immunosuppressive regimen and dosage, rejection episodes, EBV status before and after transplantation, presenting sign and symptoms, PTLD histology, multi-organ involvement, modality of treatment, response to therapy, and serum level of calcineurin inhibitors (including tacrolimus and cyclosporine). All patients received intravenous methylprednisolone as induction of immunosuppression. Patients received tacrolimus, cyclosporine, mycophenolate mofetil and prednisolone as immunosuppressive therapy during their follow-
PTLD diagnosis
Diagnosis of PTLD was confirmed by tissue biopsies reviewed by expert pathologists. World Health Organization (WHO) classification for tumors of lymphoid tissue was used for PTLD classification\(^{[16]}\). While diagnosis of PTLD was confirmed, patients underwent staging work-up, including CT scans (abdomen, chest and pelvis) and bone marrow aspiration and biopsy to detect possibility of multiple organ involvement. Frozen section or paraffin-embedded tissues were used for PTLD classification. World Health Organization (WHO) classification for tumors of lymphoid tissue was used for PTLD classification\(^{[16]}\).

PTLD characteristics and post-PTLD survival
Overall, 53 patients were diagnosed with PTLD. There were 40 cases of PTLD in the pediatric age group and 13 cases in the adult group. The incidence of PTLD was 6.25% in the pediatric patients and 1.18% in the adult patients. Thirteen patients were 40 cases of PTLD in the pediatric age group and 13 cases in the adult group. The incidence of PTLD was 6.25% in the pediatric patients and 1.18% in the adult patients. Thirteen patients were treated with ganciclovir or valganciclovir.

Post-PTLD survival of adult patients was 82.94% ± 18.58%. The post-PTLD survival of adult patients at 6 mo was 83.9% ± 10.4%, at 1 year was 74.6% ± 12.8% and at 5 years was 59.7% ± 16.8% (Figure 1B).
EBV-positive patients with PTLD had significantly higher mean survival compared to EBV-negative PTLD patients (60.58 ± 7.62 mo vs 16.72 ± 5.66 mo, \( P = 0.018 \)) (Figure 2A). Other variables including sex, CMV status, rejection episodes, time to PTLD before or after 1 year, and type of allograft had no significant effect on post-PTLD survival (Table 2).

We also analyzed the influence of different risk factors on pediatric PTLD patients separately. Multi-organ involvement and EBV negativity were significantly associated with lower mean post-PTLD survival in pediatric patients (Table 3). Higher serum tacrolimus level was associated with lower post-PTLD survival in pediatric patients (OR = 1.07, 95%CI: 1.006-1.15, \( P = 0.032 \)) (Table 4).

Impact of multi-organ involvement, and time to PTLD development

Patients were divided into those who developed PTLD in \( \leq \) 1 year and those who developed PTLD in \( \geq \) 1 year. Age, post-PTLD survival, serum tacrolimus level, tacrolimus dose and prednisolone dose were not correlated with time to PTLD development in pediatric patients (Figure 2B). EBV-positive patients with PTLD had significantly higher mean survival compared to EBV-negative PTLD patients (60.58 ± 7.62 mo vs 16.72 ± 5.66 mo, \( P = 0.018 \)) (Figure 2B). Other variables including sex, CMV status, rejection episodes, time to PTLD before or after 1 year, and type of allograft had no significant effect on post-PTLD survival (Table 2).

We also analyzed the influence of different risk factors on pediatric PTLD patients separately. Multi-organ involvement and EBV negativity were significantly associated with lower mean post-PTLD survival in pediatric patients (Table 3). Higher serum tacrolimus level was associated with lower post-PTLD survival in pediatric patients (OR = 1.07, 95%CI: 1.006-1.15, \( P = 0.032 \)) (Table 4).
patients ($P > 0.05$) (Table 5). However, multi-organ involvement was more common in patients who developed PTLD within 1 year after liver transplantation ($P = 0.007$) (Table 6). Multi-organ involvement was also more common in pediatric patients who developed PTLD within 1 year after liver transplantation ($P = 0.007$) (Table 6).

Multi-organ involvement was associated with increased mortality after PTLD development ($P < 0.05$) (Table 7). EBV-positive patients with PTLD had lower mortality when compared to EBV-negative patients ($P < 0.05$) (Table 7).

Multi-organ involvement was not associated with age, serum tacrolimus level, tacrolimus dose, prednisolone dose in univariate analysis (Table 5). EBV-positive patients were less likely to have multi-organ involvement in comparison with EBV-negative patients ($P = 0.008$) (Table 8). Pediatric patients who received liver allograft from deceased donors were more likely to develop PTLD with multi-organ involvement when compared to those receiving liver allograft from living donors ($P = 0.019$) (Table 8).

**Estimation of a cutoff value for tacrolimus level in pediatric patients**

To estimate a cutoff point value for tacrolimus level in relation to post-PTLD survival in pediatric patients, we used receiver operating characteristic (ROC) curve analysis. A serum tacrolimus of over 11.1 ng/mL was predictive of post-PTLD survival (sensitivity = 90%, specificity = 52%, area under the curve = 0.738, $P = 0.035$).

**DISCUSSION**

The present study is one of the largest series of patients with PTLD after liver transplantation. Our study showed that the incidence of PTLD following pediatric liver transplantation was much higher than for adult liver transplantation (6.25% in pediatrics and 1.18% in adults). While previous studies reported PTLD incidence of up to 20% after pediatric liver transplantation[18], recent reported incidence from different studies are lower and range from 10% to 5.5%[19,20]. Since PTLD is mainly considered as a result of interaction of immunosuppression and EBV infection, the decreased incidence in pediatric patients may be secondary to the better monitoring of patients, especially for immunosuppressive regimen and EBV infection. In pediatric patients, our reported incidence is comparable to other studies; however, due to unexplained reasons the incidence of PTLD after

### Table 2 Kaplan-Meier analysis of risk factors and post-transplant lymphoproliferative disorder survival of pediatric and adult patients

| Mean survival in mo | $P$ value |
|---------------------|-----------|
| Sex                 |           |
| Male                | 65.65 ± 13.18 | 0.902 |
| Female              | 36.06 ± 5.30  |
| Multi-organ involvement | 0.002 |
| (+)                 | 27.13 ± 6.30  |
| (-)                 | 104.25 ± 9.08 |
| CMV status          |           |
| CMV-positive        | 51.98 ± 10.50 |
| CMV-negative        | 23.29 ± 5.76  |
| EBV status          |           |
| EBV-positive        | 60.58 ± 7.62  |
| EBV-negative        | 16.72 ± 5.66  |
| Rejection episode   |           |
| (+)                 | 64.90 ± 13.78 |
| (-)                 | 65.86 ± 15.76 |
| Time to PTLD development in years | | |
| $\leq$ 1           | 62.18 ± 14.03 |
| $\geq$ 1           | 75.13 ± 12.49 |
| Type of allograft   |           |
| Living donor        | 50.56 ± 6.95  |
| Deceased donor      | 60.32 ± 14.33 |

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; PTLD: Post-transplant lymphoproliferative disorder.

### Table 3 Kaplan-Meier analysis of risk factors and post-transplant lymphoproliferative disorder survival of pediatric patients

| Mean survival in mo | $P$ value |
|---------------------|-----------|
| Sex                 |           |
| Male                | 41.41 ± 7.38 | 0.749 |
| Female              | 35.85 ± 5.76  |
| Multi-organ involvement | 0.002 |
| (+)                 | 25.82 ± 6.90  |
| (-)                 | 67.62 ± 5.56  |
| CMV status          |           |
| CMV-positive        | 58.82 ± 9.56  |
| CMV-negative        | 19.35 ± 6.21  |
| EBV status          |           |
| EBV-positive        | 60.58 ± 7.62  |
| EBV-negative        | 5.58 ± 2.72   |
| Rejection episode   |           |
| (+)                 | 43.61 ± 8.49  |
| (-)                 | 36.02 ± 5.24  |
| Time to PTLD development in years | | |
| $\leq$ 1           | 39.72 ± 6.86  |
| $\geq$ 1           | 36.45 ± 5.30  |
| Type of allograft   |           |
| Living donor        | 50.56 ± 6.95  |
| Deceased donor      | 37.37 ± 8.11  |

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; PTLD: Post-transplant lymphoproliferative disorder.
adult liver transplantation in our study was lower than previous reports from other centers[21].

Mean post-PTLD survival was higher in the adult patients than in the pediatric patients. This observation is probably due to the long-term survival (> 10 years) of 2 of our adult patients. In a recent study conducted in our center, the 1-year and 5-year overall survival of pediatric liver transplant recipients was found to be 73% and 66% respectively[22]. In this way, the 1-year post-PTLD survival in the pediatric age group is nearly equal to the overall survival of our pediatric patients. However, it should be noted that the 5-year post-PTLD survival in pediatric patients has dramatically declined to 24.1%.

Due to small numbers of adult PTLD patients, the analyses were performed on either pediatric patients or adult plus pediatric patients. We investigated the impact of different variables on post-PTLD survival. As expected, multi-organ involvement was associated with a lower post-PTLD survival and increased mortality. EBV-positive patients had higher mean post-PTLD survival in comparison with EBV-negative subjects. EBV positivity was also associated with lower

| Table 5  Influence of different continuous variables on time to post-transplant lymphoproliferative disorder development, mortality and multi-organ involvement of post-transplant lymphoproliferative disorder patients |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Mean rank PTLD development ≤ 1 yr            | Mean rank PTLD development ≥ 1 yr              | U value                                      | Z score                                      | P value                                      |
| Age                                           | 19.85                                         | 21.85                                        | 158                                          | -0.50                                        | 0.61                                         |
| Post-PTLD survival                             | 20.19                                         | 21.15                                        | 167                                          | -0.24                                        | 0.80                                         |
| Tacrolimus level                               | 16.57                                         | 14.61                                        | 86                                           | -0.54                                        | 0.58                                         |
| Tacrolimus dose                                | 19.84                                         | 18.85                                        | 154                                          | -0.27                                        | 0.78                                         |
| Prednisolone dose                              | 20.56                                         | 18.88                                        | 154                                          | -0.44                                        | 0.66                                         |
| Mean time to PTLD                              | 23.12                                         | 16.56                                        | 129                                          | -1.74                                        | 0.08                                         |
| Alive patient                                 | 23.19                                         | 16.47                                        | 127.5                                        | -1.78                                        | 0.47                                         |
| Post-PTLD survival                             | 20.19                                         | 21.15                                        | 167                                          | -0.24                                        | 0.80                                         |
| Tacrolimus level                               | 16.50                                         | 14.74                                        | 97                                           | -0.54                                        | 0.58                                         |
| Tacrolimus dose                                | 19.81                                         | 19.27                                        | 113                                          | -1.85                                        | 0.06                                         |
| Mean time to PTLD                              | 13.62                                         | 23.77                                        | 82                                           | -2.78                                        | 0.005                                        |

PTLD: Post-transplant lymphoproliferative disorder.

| Table 6  Influence of different risk factors on time to post-transplant lymphoproliferative disorder development |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| PTLD development ≤ 1 yr                       | PTLD development ≥ 1 yr                       | P value                                      | Rejection episode                             | Mortality                                    |
| Sex                                           | 0.150                                         |                                              | 0.587                                         | 0.120                                         |
| Male                                          | 17                                            | 16                                           | 13                                           | 14                                            |
| Female                                        | 14                                            | 6                                            | 6                                            | 7                                             |
| Multi-organ involvement (+)                   | 15                                            | 3                                            | 9                                            | 4                                             |
| (−)                                          | 14                                            | 18                                           | 4                                            | 1                                             |
| CMV status                                    |                                              |                                              |                                              |                                              |
| CMV-positive                                  | 9                                             | 4                                            | 1                                            | 0.296                                        |
| CMV-negative                                  | 11                                            | 1                                            | 5                                            | 0.399                                        |
| EBV status                                    |                                              |                                              |                                              |                                              |
| EBV-positive                                  | 12                                            | 5                                            | 3                                            | 13                                           |
| EBV-negative                                  | 8                                             | 1                                            | 1                                            | 3                                             |
| Rejection episode                             |                                              |                                              |                                              |                                              |
| (+)                                           | 15                                            | 9                                            | 0.324                                        |                                              |
| (−)                                           | 16                                            | 13                                           |                                              |                                              |
| Mortality                                     |                                              |                                              |                                              |                                              |
| (+)                                           | 13                                            | 7                                            | 0.118                                        |                                              |
| (−)                                           | 18                                            | 15                                           |                                              |                                              |
| Type of allograft                             |                                              |                                              |                                              |                                              |
| Living donor                                  | 19                                            | 9                                            | 0.018                                        |                                              |
| Deceased donor                                | 12                                            | 13                                           |                                              |                                              |
| Pediatric PTLD patients                       |                                              |                                              |                                              |                                              |
| Sex                                           |                                              |                                              |                                              |                                              |
| Male                                          | 15                                            | 8                                            | 0.496                                        |                                              |
| Female                                        | 12                                            | 5                                            |                                              |                                              |
| Multi-organ involvement (+)                   | 14                                            | 2                                            | 0.018                                        |                                              |
| (−)                                           | 11                                            | 11                                           |                                              |                                              |
| CMV status                                    |                                              |                                              |                                              |                                              |
| CMV-positive                                  | 9                                             | 3                                            | 0.368                                        |                                              |
| CMV-negative                                  | 9                                             | 1                                            |                                              |                                              |
| EBV status                                    |                                              |                                              |                                              |                                              |
| EBV-positive                                  | 12                                            | 5                                            | 0.184                                        |                                              |
| EBV-negative                                  | 6                                             | 0                                            |                                              |                                              |

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; PTLD: Post-transplant lymphoproliferative disorder.

Due to small numbers of adult PTLD patients, the analyses were performed on either pediatric patients or adult plus pediatric patients. We investigated the impact of different variables on post-PTLD survival. As expected, multi-organ involvement was associated with a lower post-PTLD survival and increased mortality. EBV-positive patients had higher mean post-PTLD survival in comparison with EBV-negative subjects. EBV positivity was also associated with lower
mortality, especially among the pediatric age group. These findings may be jeopardized by our other finding that EBV-positive patients had lower probability of multi-organ involvement.

Although up to 30% of PTLD patients are EBV-negative, EBV has been generally considered as responsible for most cases of PTLD. However, the influence of recipient EBV status on outcomes of PTLD patients is conflicting. Some studies have shown that EBV-negative PTLD patients have more malignant appearing disease with an aggressive course and higher mortality rate\textsuperscript{23,24}. In univariate analysis, our findings are inconsistent with these mentioned results. However, in regression analysis, EBV status was not associated with post-PTLD survival. Several other studies showed that EBV status had no significant impact on outcomes of PTLD patients, including their survival\textsuperscript{25-28}. EBV status was not associated with time of PTLD development in our study. This finding is in contrast with previous reports showing that EBV-negative PTLD occurs later after liver transplantation when compared to EBV-positive PTLD patients\textsuperscript{29,30}.

Immunosuppressive therapy has been reported to be associated with PTLD development. Treatment of rejection episodes with steroid or OKT3 were risk factors of PTLD development, especially during 1 year after treatment\textsuperscript{31,32}. Reducing dose of immunosuppressive medications is another treatment strategy used on PTLD patients in some studies\textsuperscript{33,34}. In our study, rejection episode, steroid dose and tacrolimus dose were not associated with PTLD survival, while higher serum tacrolimus level was associated with lower survival. Finally, we showed that a serum tacrolimus cutoff value of over 11.1 ng/mL is associated with post-PTLD survival, having a high sensitivity but a rather low specificity in pediatric patients. Therefore, it might be suggested that transplant physicians consider adjustment of tacrolimus dose to maintain its serum level around this cutoff point.

Although a PTLD series has been published from

### Table 7: Influence of different risk factors on mortality after post-transplant lymphoproliferative disorder

|                         | Alive patient | Deceased patient | P value |
|-------------------------|---------------|------------------|---------|
| All PTLD patients       |               |                  |         |
| Sex                     |               |                  | 0.491   |
| Male                    | 10            | 13               |         |
| Female                  | 13            | 7                |         |
| Multi-organ involvement |               |                  | 0.001   |
| (+)                     | 6             | 12               |         |
| (-)                     | 26            | 6                |         |
| CMV status              |               |                  | 0.284   |
| CMV-positive            | 9             | 4                |         |
| CMV-negative            | 6             | 6                |         |
| EBV status              |               |                  | 0.042   |
| EBV-positive            | 13            | 4                |         |
| EBV-negative            | 3             | 6                |         |
| Rejection episode       |               |                  | 0.600   |
| (+)                     | 15            | 9                |         |
| (-)                     | 18            | 11               |         |
| Type of allograft       |               |                  | 0.485   |
| Living donor            | 18            | 10               |         |
| Deceased donor          | 15            | 10               |         |
| Pediatric PTLD patients |               |                  | 0.424   |
| Sex                     |               |                  |         |
| Male                    | 13            | 10               |         |
| Female                  | 11            | 6                |         |
| Multi-organ involvement |               |                  | 0.001   |
| (+)                     | 5             | 11               |         |
| (-)                     | 19            | 3                |         |
| CMV status              |               |                  | 0.110   |
| CMV-positive            | 9             | 3                |         |
| CMV-negative            | 4             | 6                |         |
| EBV status              |               |                  | 0.018   |
| EBV-positive            | 13            | 4                |         |
| EBV-negative            | 1             | 5                |         |
| Rejection episode       |               |                  | 0.525   |
| (+)                     | 11            | 8                |         |
| (-)                     | 13            | 8                |         |
| Type of allograft       |               |                  | 0.309   |
| Living donor            | 18            | 10               |         |
| Deceased donor          | 6             | 6                |         |

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; PTLD: Post-transplant lymphoproliferative disorder.

### Table 8: Influence of different risk factors on multi-organ involvement in patients with post-transplant lymphoproliferative disorder

|                         | Multi-organ involvement (+) | Multi-organ involvement (-) | P value |
|-------------------------|----------------------------|-----------------------------|---------|
| All PTLD patients       |                           |                             |         |
| Sex                     |                           |                             | 0.421   |
| Male                    | 12                        | 19                          |         |
| Female                  | 6                         | 13                          |         |
| CMV status              |                           |                             | 0.418   |
| CMV-positive            | 6                         | 7                           |         |
| CMV-negative            | 7                         | 5                           |         |
| EBV status              |                           |                             | 0.008   |
| EBV-positive            | 5                         | 11                          |         |
| EBV-negative            | 8                         | 1                           |         |
| Rejection episode       |                           |                             | 0.448   |
| (+)                     | 9                         | 14                          |         |
| (-)                     | 9                         | 18                          |         |
| Type of allograft       |                           |                             | 0.235   |
| Living donor            | 8                         | 19                          |         |
| Deceased donor          | 10                        | 13                          |         |
| Pediatric PTLD patients |                           |                             | 0.206   |
| Sex                     |                           |                             |         |
| Male                    | 11                        | 11                          |         |
| Female                  | 5                         | 11                          |         |
| CMV status              |                           |                             | 0.335   |
| CMV-positive            | 5                         | 7                           |         |
| CMV-negative            | 6                         | 4                           |         |
| EBV status              |                           |                             | 0.006   |
| EBV-positive            | 5                         | 11                          |         |
| EBV-negative            | 6                         | 0                           |         |
| Rejection episode       |                           |                             | 0.520   |
| (+)                     | 8                         | 10                          |         |
| (-)                     | 8                         | 12                          |         |
| Type of allograft       |                           |                             | 0.019   |
| Living donor            | 8                         | 19                          |         |
| Deceased donor          | 8                         | 3                           |         |

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; PTLD: Post-transplant lymphoproliferative disorder.
our center previously\cite{26}, this study is the first that evaluates incidence, survival and associated factors influencing survival of PTLD patients after liver transplantation. This study also is the first that shows the association between serum tacrolimus level and post-PTLD survival, and suggests a serum tacrolimus cutoff point value to adjust tacrolimus dose.

**COMMENTS**

**Background**

Post-transplant lymphoproliferative disorder (PTLD) is one of the complications after liver transplantation and may threaten both graft and patient survival. This study aimed to investigate incidence and survival of PTLD patients after liver transplantation.

**Research frontiers**

Few studies with considerable number of patients have reported survival of PTLD patients after liver transplantation. This study aimed to investigate incidence, risk factors (including impact of immunosuppressive regimen) and survival of PTLD patients after liver transplantation in Iranian patients.

**Innovations and breakthroughs**

Multi-organ involvement was associated with a lower post-PTLD survival and increased mortality. Epstein-Barr virus (EBV)-positive patients had higher mean post-PTLD survival in comparison with EBV-negative subjects. EBV status was not associated with time of PTLD development in our study. This finding is in contrast with previous reports showing that EBV-negative PTLD occurs later after liver transplantation when compared to EBV-positive PTLD patients. We showed that a serum tacrolimus cutoff value of 11.1 ng/mL is associated with post-PTLD survival.

**Applications**

Adjustment of tacrolimus level to lower than 11.1 ng/mL may help improve post-PTLD survival of patients.

**Peer-review**

The reviewer has read with interest the manuscript entitled, "Post-transplant lymphoproliferative disorder after liver transplantation: incidence, long-term survival and impact of serum tacrolimus level". Eshraghian and colleagues performed a retrospective single-center study with a wide recruitment period, including 53 liver transplant patients who developed PTLD (40 pediatric and 13 adult cases). The authors evaluated the risk factors affecting post-PTLD survival of patients. They found that EBV-negative PTLD patients and multi-organ involvement are the two main risk factors of lower post-PTLD survival. They further found within a pediatric recipient cohort that higher serum tacrolimus level was associated with poor survival after PTLD development.

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