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Comparative analysis of post-transplant lymphoproliferative disorder after kidney transplantation versus hematopoietic stem cell transplantation

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Summary

Post-transplant lymphoproliferative disorder (PTLD) is a major complication caused by immune-suppression after transplantation. Survival outcome is known to be poor and the characteristics are not fully understood because of its rare incidence. This single center retrospective study enrolled 41 adult PTLD patients after kidney-transplantation (KT, $n = 28$) and hematopoietic stem cell transplantation (HSCT, $n = 13$) from 1992 to 2012. We compared the characteristics and estimated the survival outcomes according to several factors [age-adjusted-IPI (aaIPI), pathologic subtype, viral status, extranodal manifestation] and added some significant parameters to aaIPI scoring system. Post-HSCT-PTLD patients were younger and showed earlier onset, and viral status was more frequently identified. Ten-year OS of the entire group was 44% but the 10-year OS was not significantly different between post-KT-PTLD and post-HSCT-PTLD (39% vs. 56%, $P = 0.860$). The time onset of PTLD and viral statuses were not meaningful, however, aaIPI, age > 50, extranodal manifestation and monomorphic subtype were predictive for OS. We used those factors for PTLD-specific scoring which showed intermediate-risk (HR = 7.1, $P = 0.019$) and high-risk (HR = 16.5, $P = 0.001$) presented worse OS compared to low-risk subgroup. Although the treatment strategies were heterogenous, this study showed comprehensive PTLD data between KT versus HSCT, and our PTLD-specific scoring might be validated by another larger studies.

Introduction

Post-transplantation lymphoproliferative disorder (PTLD) is a major complication with heterogenous presentation caused by immune suppression after solid organ transplantation or hematopoietic stem cell transplantation (HSCT). The heterogeneous presentation encompasses plasmacytic proliferations [1], polyclonal proliferations resembling infectious mononucleosis and monomorphic proliferations indistinguishable from diffuse large B-cell lymphoma (DLBCL) or other aggressive lymphomas [2]. The characteristic features are not fully understood due to its rare incidence and the survival outcome is known to be poor despite advances in treatment strategies including rituximab with overall survival rates ranging from 25% to 60% [2–7]. In general, the incidence of PTLD is higher in organ

transplantation than hematopoietic stem cell transplantation (HSCT), and the incidence is identified especially higher in heart, lung, and small bowel transplantation than in kidney transplantation (KT) [8–10]. The differentiation is mainly associated with the intensity of immunosuppressive protocols and post-transplant immune reconstitution according to the individual transplantations [8]. Besides, pre-transplantation serological status of Epstein-Barr Virus (EBV) and post-transplantation viral load of EBV are also related with the occurrence of PTLD [8,11].

Although several studies have attempted to determine the clinicopathological characteristics and long-term survival outcomes, retrospective data is not reliable because of the small number of patients from single-institutions and they included variable organ transplantations with heterogeneity which might disturb accurate analysis and validation of prognostic factors. Furthermore, the low incidence of PTLD also prevents further well-validated prospective studies. For analysis of prognostic factors of PTLD, many studies included transplanted organ, early- or late-onset, monomorphic or polymorphic histology, B-cell or T-cell immunohistochemistry, rituximab therapy, performance status, and extranodal involvements, some of which consists of International Prognostic Index (IPI) score [12–15].

Here we report a comparative analysis of 41 patients with PTLD after kidney transplantation (KT) and HSCT in regard of baseline characteristics and survival outcomes, and we identified somewhat distinct features according to the transplantation type. Then we tried to validate age-adjusted IPI (aaIPI) score for survival prediction of PTLD and added some PTLD-specific parameters for more definite prognostic prediction.

Patients and methods

Patients and diagnosis of PTLD

We performed 1489 kidney transplantation (KT, 694 cases between 1992 and 2002 and 795 cases between 2003 and 2012) and 2684 allogeneic-HSCT (1004 cases between 1992 and 2002 and 1680 cases between 2003 and 2012) in adult patients, and we found 41 PTLD patients. There were 28 (1.9%) post-KT PTLD patients – 8 (1.1%) cases between 1992 and 2002 and 20 (2.5%) cases between 2003 and 2012 – and 13 (0.5%) post-HSCT PTLD patients – 5 (0.5%) cases between 1992 and 2002 and 8 (0.5%) cases between 2003 and 2012 – in Catholic Medical Center in South Korea. All analyses were performed retrospectively according to the Institutional Review Board guidelines of the Catholic Medical Center (XC13RIMI0099K) with respect of Declaration of Helsinki. The diagnosis of PTLD was firstly based on the history of applying immunosuppressive agents after KT or HSCT. Then excisional biopsy for affected lesion was performed followed by pathologic review including morphological and immunohistochemical studies, with Epstein-Barr virus (EBV)-encoded-RNA (EBER) *in situ* hybridization. We recently used ISH iVIEW Blue Detection Kit and INFORM EBER Probe (Ventana Medical System, Tucson, AZ, USA; Roche, Basel, Switzerland). The final diagnosis was made according to the WHO classification [10]. The underlying renal disease treated with KT consisted of chronic glomerular nephropathy ($n = 8$), hypertensive nephropathy ($n = 7$), diabetic nephropathy ($n = 6$), IgA nephropathy ($n = 3$), and one for each of the following – amyloid kidney, renal tuberculosis, polycystic kidney, uric acid nephropathy. In the case of HSCT, there were five patients with severe aplastic anemia (SAA) and eight hematological malignancies; chronic myeloid leukemia (CML, $n = 3$), acute myeloid leukemia (AML, $n = 3$), and myelodysplastic syndrome (MDS, $n = 2$). They all underwent HSCT after pre-conditioning based on the protocol set by the Catholic Blood and Marrow Transplantation Center in Korea [16].

Immunosuppressive protocols for each transplant setting

The KT patients received initial immunosuppressive agent with a calcineurin inhibitor in combination with corticosteroids after transplantation. Both cyclosporine A (CsA) and tacrolimus (FK506) were used, and mycophenolate mofetil (MMF) was added as a primary immunosuppressant from 2001. The target trough levels of CsA were 200–400 ng/ml in the first 4 weeks and 100–200 ng/ml thereafter, and the target level of FK506 were 8–15 ng/ml in the first 3 months and 3–8 ng/ml thereafter. Methylprednisolone (1 g/day) was administered by intravenous infusion on the day of transplantation, and was then tapered to prednisone at 30 mg/day on the fourth day of transplantation. The use of FK506 was restricted to patients with more than three human leukocyte antigen (HLA) mismatches. The initial dose of MMF was 1.5 g/day, and the dose was modified to minimize adverse effects such as diarrhea and neutropenia. Acute rejection was also treated with 3–4 daily boluses of intravenous methylprednisolone (500 mg/day), followed by a 5-to7-day oral steroid tapering, and anti-thymocyte globulin (ATG) was used as a rescue regimen when methylprednisolone was not effective against acute rejection.

For HSCT patients, we used CsA when the infused stem cell was from matched sibling donor (MSD), and the target level was 200–300 ng/ml in the first 4 weeks after stem cell infusion and 100–200 ng/ml thereafter. When the infused stem cell was from unrelated donor or HLA-mismatched donor, we used FK506 with a trough level of 10–15 ng/ml in the first 4 weeks after stem cell infusion and 3–8 ng/ml thereafter. Short course of methotrexate (MTX, 5 mg/m^2 for FK506 and 10 mg/m^2 for CsA, D + 1, D + 3, D + 6, D + 11) was applied in all patients except one patient who

received T-cell depleted stem cell, and ATG was administered for patients with unrelated or HLA-mismatched transplantation at a dose of 5 mg to 10 mg/kg. Acute graft-versus-host disease (GVHD) was initially treated with steroid pulse therapy with 1 mg/kg of methylprednisolone concomitant with maintaining calcineurin inhibitors, followed by oral steroid tapering-off when the symptoms and signs resolved.

Treatment of PTLD

After diagnosis of PTLD, we actively applied immunochemotherapy for post-KT PTLD patients except one patient treated with surgery alone and two patients who were managed with reduction of immunosuppressive agent alone. Two patients received rituximab (375 mg/m^2 weekly for 4 weeks) alone [17] and eight patients received R-CHOP chemotherapy [18] and the rest 15 patients were treated with variable chemotherapies. Among 15 patients, most were treated by CHOP chemotherapy [19], and EPOCH (n = 2) [20] and ABVD (n = 2) regimens were also used. For post-HSCT PTLD, we reduced the dose of immunosuppressive agents first, unless the patients presented active sign or symptom of GVHD. Three patients were treated by reduction of immunosuppressive agents alone, and five patients additionally received donor lymphocyte infusion (DLI). In post-HSCT PTLD, four patients were treated with rituximab alone, and there were only one patient who received R-CHOP chemotherapy.

Known prognostic factors and statistical analysis

There have been several prognostic factors [i.e. IPI score, age-adjusted IPI (aaIPI) score, PTLD subtypes, extranodal manifestation, hypoalbuminemia etc.] reported for long-term survival outcome of PTLD [5,12,21]. As most of the patients were under 60 years, aaIPI score could be used for initial risk-stratification and the other factors specified for PTLD could be also evaluated. We added several significant factors and tried to modify the aaIPI scoring system to predict the long-term outcome for PTLD more precisely. Among the four parameters which consists of aaIPI, three factors were used without modification – elevated LDH level, higher stage III–IV, and Eastern Cooperation Oncology Group (ECOG) performance scale (PS) ≥2 [22]. We modified the number of extranodal involvement to ≥1, because there were many single extranodal involvement PTLDs. Other PTLD-specific parameters were evaluated for prediction of survival outcomes additionally.

The characteristics of transplantation details and the patterns of PTLD were analyzed and compared in this study, and we also tried to estimate the survival outcomes according to the transplantation type (KT vs. allo-HSCT). All categorical variables were compared using Chi-squared analysis and Fisher's exact test. Continuous variables were assessed with the Student's t-test or the Wilcoxon rank-sum test. Overall survival (OS) was calculated using Kaplan-Meier analysis, and log-rank analysis was used to evaluate differences between subgroups. Overall survival represented the proportion of people who were alive at a specified time from the date of diagnosis of PTLD. Cumulative incidence of relapse (CIR) were calculated by treating non-relapse deaths as competing risks among the patients who achieved CR, and compared using the Gray test [23]. Hazard ratio associated with survival, was calculated using Cox's proportional hazard model. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Inc., Cary, NC) and R software (version 2.15.1, R foundation for statistical Computing, 2012). A P-value <0.05 was deemed statistically significant.

Results

Baseline characteristics according to the transplantation type

We firstly identified the characteristics of transplantation details in both KT and HSCT. In both transplantation groups of PTLD patients, male gender was predominant (78%) but the age at transplantation was younger in HSCT group (32.1 vs. 40.1 years old, P = 0.071). Among 28 post-KT PTLD patients, 25 (89.3%) grafts were living-donor kidney and 3 (10.7%) grafts were from deceased donor. Human leukocyte antigen (HLA) status was haploidentical in 13 (46.4%) grafts and the other (n = 15, 53.6%) was non-identical. Most of the patients were treated with cyclosporine (n = 25, 89.3%), and ATG was applied in seven patients for treatment of graft rejection. In post-HSCT PTLD, six patients received stem cell from matched sibling donor (MSD), four patients from unrelated donor (URD) and three patients from haploidentical donor (HID). HSCT source was bone marrow (BM) in six patients and peripheral blood (PB) in seven patients. For GVHD prophylaxis, cyclosporine was used in 8 (61.5%) patients and tacrolimus was used in 4 (30.8%) patients and one patient received T-cell depleted HSCT. ATG was applied in 7 (53.8%) HLA mismatched transplantation. Among 13 post-HSCT PTLD patients, 8 (61.5%) patients suffered from acute GVHD, who were all treated with steroid pulse therapy, and there were 6 (46.2%) patients with chronic GVHD (Table 1).

Comparison of the characteristics of PTLD after KT versus HSCT

As we expected there might be some differences between post-KT versus post-HSCT PTLD, the characteristic feature of PTLD was compared between the two groups (Table 2).

Table 1. Baseline transplantation characteristics of KT and HSCT.

	KT (n = 28)	HSCT (n = 13)	P-value
Gender (Male%)	22 (78.6%)	10 (76.9%)	0.906
Age at transplantation	40.1 (22–61)	32.1 (17–62)	0.071
Transplantation donor for KT			
Vivo	25 (89.3%)	–	–
Deceased donor	3 (10.7%)	–	–
Haploidentical donor	13 (46.4%)	–	–
Non-identical donor	15 (53.6%)	–	–
Transplantation donor for HSCT			
Matched sibling donor (MSD)	–	6 (46.2%)	–
Unrelated donor (URD)	–	4 (30.8%)	–
Haploidentical donor (HID)	–	3 (23.0%)	–
Bone marrow (BM)	–	6 (46.2%)	–
Peripheral blood (PB)	–	7 (53.8%)	–
Immunosuppressive agents			
Cyclosporine (CsA)	25 (89.3%)	8 (61.5%)	0.037*
Tacrolimus (FK)	2 (7.1%)	4 (30.8%)	0.046*
Azathioprine (AZP)	1 (3.6%)	0 (0.0%)	0.490
T-cell depletion (TCD)	0 (0.0%)	1 (7.7%)	0.137
Additional use of ATG	7 (25.0%)	7 (53.8%)	0.059
Acute GVHD	–	8 (61.5%)	–
Steroid pulse treatment	–	8 (100%)	–
Chronic GVHD	–	6 (46.2%)	–
Overall grade ≥ moderate	–	2 (33.3%)	–
Acute graft rejection	9 (32.1%)	–	–
Chronic graft rejection	5 (17.8%)	–	–

KT, kidney transplantation; HSCT, Hematopoietic stem cell transplantation; ATG, Anti-thymocyte globulin; GVHD, Graft versus Host disease.
*P < 0.05.

Most of all, age at the time of diagnosis of PTLD was significantly younger in the post-HSCT group (32.4 vs. 50.5 years old, P < 0.001) which resulted from significantly shorter duration from transplantation to the diagnosis of PTLD (4.5 vs. 124.3 months, P < 0.001). We evaluated the stages of PTLD patients using Ann-Arbor system, and all of the stage I PTLD patients showed extranodal manifestations in both groups. The proportion of higher stage III–IV was 42.8% (n = 12) in post-KT and 61.5% (n = 8) in post-HSCT group (P = 0.843). In addition, calculated aaIPI and ECOG PS showed similar distributions and the proportion of elevated LDH level at diagnosis was also similar between the two groups. Extranodal manifestation involved BM, liver, stomach, intestine, lung, skin, muscle, gingival and brain. BM or skin involvement was only identified in post-KT PTLD patients. EBV *in situ* hybridization was performed in all tissue biopsies and post-HSCT PTLD showed more positive results (84.6% vs. 42.9%, P = 0.012). EBV antigenemia was performed for 12 patients in post-HSCT group and 22 patients in post-KT group. We detected EBV seropositivity in 91.6% of post-HSCT group and 36.4% of post-KT group (P = 0.006). CMV antigenemia or DNAemia was performed for 13 patients in post-HSCT group and 26 patients in post-KT group, and also, there were more proportion of positive CMV status in post-HSCT group (69.2% vs. 15.4%, P = 0.001).

Pathologic subtype of PTLD was identified in two groups. Most PTLD presented B-cell subtype in both groups (85.7% and 92.3%) and most of the post-KT PTLD presented monomorphic subtype (n = 25, 89.2%). In contrast, 7 (53.8%) patients of post-HSCT PTLD presented monomorphic subtype and almost half of the patients presented plasmacytic hyperplasia (n = 3, 23.1%) and polymorphic subtype (n = 3, 23.1%). Monomorphic subtype mostly consists of DLBCL (n = 27, 84.3%) and PTCL (n = 3, 9.3%), and two patients in post-KT group was extranodal NK-T cell lymphoma and mycosis fungoides.

Comparison of the clinical outcomes of PTLD after KT versus HSCT

With a median follow-up duration of 76.0 months (range 8.4–200.6 months), overall survival (OS) was calculated in the entire patients and in each group. Median OS was 87.6 months and 5-year and 10-year OS was 59% and 44% in the entire 41 patients. In post-KT PTLD, 5-year and 10-year OS was 55% and 39% with 85.8 months of median OS, and in post-HSCT PTLD, both 5-year and 10-year OS were 55% without reaching the median (Fig. 1a). Between the two groups, OS was not significantly different (P = 0.860).

Complete response (CR) rate after treatment was 65.9% in the entire PTLD patients (19 patients (67.9%) in post-KT PTLD and eight patients (61.5%) in post-HSCT PTLD, P = 0.691). Reduction of immunosuppressive agents with donor lymphocyte infusion (DLI) (n = 5) or without DLI (n = 5) showed CR rate of 60% in each group, and the CR rate of rituximab alone (n = 6) and R-CHOP (n = 9) was 66.7% and 77.8% respectively. CR rate of chemotherapy alone (n = 15) was 66.7%. Among the 27 patients who achieved CR, there were 6 (22.2%) relapsed patients in the post-KT PTLD group but no relapsed cases were identified in the post-HSCT PTLD group (Fig. 1b). Although all PTLD patients in this study received heterogeneous treatments and the proportion of patients treated with chemotherapy was significantly different between the two transplantation settings, response rates and survival outcomes according to the several regimens were not significantly different. Whether treatment with chemotherapy or not was concomitantly adjusted in the multivariate analysis.

Additional prognostic factors in addition to aaIPI scoring system

Early (<1 year) or late (≥1 year) diagnosis of PTLD (P = 0.556), B- or T-cell subtype PTLD (P = 0.674), EBV

Table 2. Comparison of the characteristics of PTLD between KT and HSCT.

	KT (n = 28)	HSCT (n = 13)	P-value
Age at diagnosis of PTLD	50.5 (36–68)	32.4 (17–62)	<0.001*
Time from transplantation to diagnosis of PTLD (Months)	124.3 (5.3–274.0)	4.5 (1.7–13.4)	<0.001*
Number of PTLD diagnosed < 1 year after transplantation	5 (17.9%)	12 (92.3%)	<0.001*
Stage (Extranodal)			
I/I_E	0 (0.0%)/5 (17.9%)	0 (0.0%)/3 (23.1%)	0.695
II/II_E	6 (21.4%))/5 (17.9%)	2 (15.4%)/0 (0.0%)	0.126
III/III_E	3 (10.7%)/0 (0.0%)	2 (15.4%)/0 (0.0%)	0.671
IV/IV_E	5 (17.9%)/4 (14.2%)	2 (15.4%)/4 (30.7%)	0.386
Age-adjusted IPI score (aaIPI)			
0	9 (32.1%)	4 (30.8%)	0.930
1	6 (21.4%)	4 (30.8%)	0.517
2	7 (25.0%)	2 (15.4%)	0.489
3	6 (21.4%)	3 (23.1%)	0.906
ECOG PS			
0–1	16 (57.1%)	10 (76.9%)	0.221
2	12 (42.9%)	3 (23.1%)	
Elevated LDH	16 (57.1%)	8 (61.5%)	0.790
Extranodal sites involved	14 (50.0%)	7 (53.8%)	0.819
Bone marrow	3 (10.7%)	0 (0.0%)	–
Liver	0 (0.0%)	1 (7.7%)	–
Stomach	2 (7.1%)	1 (7.7%)	–
Intestine	4 (14.3%)	3 (23.1%)	–
Lung	1 (3.6%)	2 (15.4%)	–
Skin	3 (10.7%)	0 (0.0%)	–
Etc. (Gingiva, Brain, Muscle)	3 (10.7%)	0 (0.0%)	–
Viral status			
EBV *in situ* (Tumor)	12 (42.9%)	11 (84.6%)	0.012*
EBV detected in blood	8/22 (36.4%)	11/12 (91.6%)	0.006*
CMV detected in blood	4/26 (15.4%)	9/13 (69.2%)	0.001*
Lymphoma subtype			
B-cell type	24 (85.7%)	12 (92.3%)	0.548
T-cell type	4 (14.3%)	1 (7.7%)	
Hodgkin's lymphoma	1 (3.6%)	0 (0.0%)	0.032*
Plasmacytic hyperplasia	1 (3.6%)	3 (23.1%)	
Polymorphic	1 (3.6%)	3 (23.1%)	
Monomorphic	25 (89.2%)	7 (53.8%)	
DLBCL	21 (84.0%)	6 (85.7%)	0.912
PTCL	2 (8.0%)	1 (14.3%)	0.614
ENKTL	1 (4.0%)	0 (0.0%)	0.591
Mycosis fungoides	1 (4.0%)	0 (0.0%)	0.591
Treatments			
Rituximab + CHOP	8 (28.5%)	1 (7.7%)	0.133
Rituximab alone	2 (7.2%)	4 (30.8%)	0.046*
Chemotherapy alone	15 (53.5%)	0 (0.0%)	0.001*
Surgery alone	1 (3.6%)	0 (0.0%)	0.490
IST reduction + DLI	0 (0.0%)	5 (38.5%)	0.001*
IST reduction alone	2 (7.2%)	3 (23.0%)	0.147

PTLD, Post-transplantation lympho-proliferative disease; IPI, International prognostic index; ECOG, Eastern Cooperation Oncology Group; PS, Performance scale; LDH, Lactate dehydrogenase; EBV, Ebstein-Barr virus; CMV, Cytomegalovirus; DLBCL, Diffuse large B-cell lymphoma; PTCL, Peripheral T-cell lymphoma; ENKTL, Extranodal NK/T-cell lymphoma; IST, Immunosuppressive agents; DLI, Donor Lymphocyte Infusion.
*P < 0.05.

in situ in tumor tissue (P = 0.912), and CMV antigenemia or DNAemia statuses (P = 0.340) were not significant for prediction of survival outcome. As most of the post-HSCT PTLD (92.3%) patients were early-onset (<1 year), compared to the 17.9% of the post-KT PTLD, we calculated OS according to the onset time only in post-KT group. In

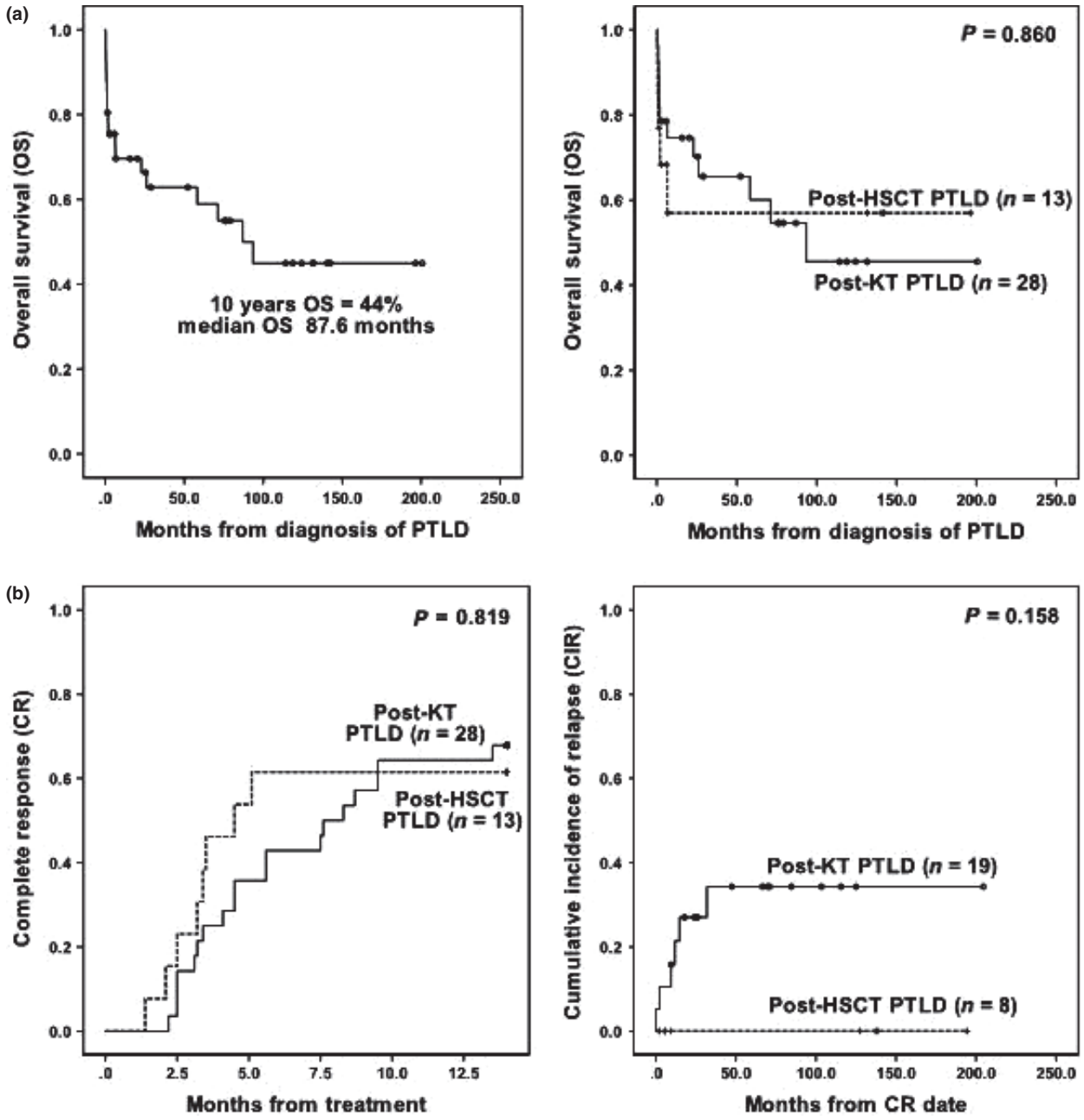

Figure 1 Clinical outcomes of Post-transplant lymphoproliferative disorder (PTLD) patients. (a) 10-year Overall survival (OS) of the entire patients was 44% with median OS of 87.6 months. There was no significant difference in OS between post-KT PTLD and post-HSCT PTLD. (b) Complete response (CR) rate was similar between the two groups [post-KT (67.9%) vs. post-HSCT 65.9%)]. After achievement of CR (n = 27), six patients were relapsed in the post-KT PTLD group but there were no relapsed patients in the post-HSCT group.

the subgroup analysis, we also identified that OS was not significantly different according to the onset time of PTLD (P = 0.846). On the contrary, higher aaIPI score ≥2 [HR=2.406 (95% CI 1.34–4.30), P = 0.003], age over 50 years [HR = 3.377 (95% CI 1.29–8.80), P = 0.013], PTLD with extranodal manifestation [HR = 2.972 (95% CI 1.05–8.43), P = 0.041], and monomorphic subtype [HR = 2.798 (95% CI 1.01–12.2), P = 0.045] showed significantly inferior OS (Fig. 2). Multivariate analysis revealed that higher-risk aaIPI and Extranodal manifestation were still significant and the other two factors – monomorphic PTLD and age ≥50 – showed marginal significance (Table 3). Finally, we added those factors and tried to modify aaIPI scoring system to a PTLD-specific scoring system. The

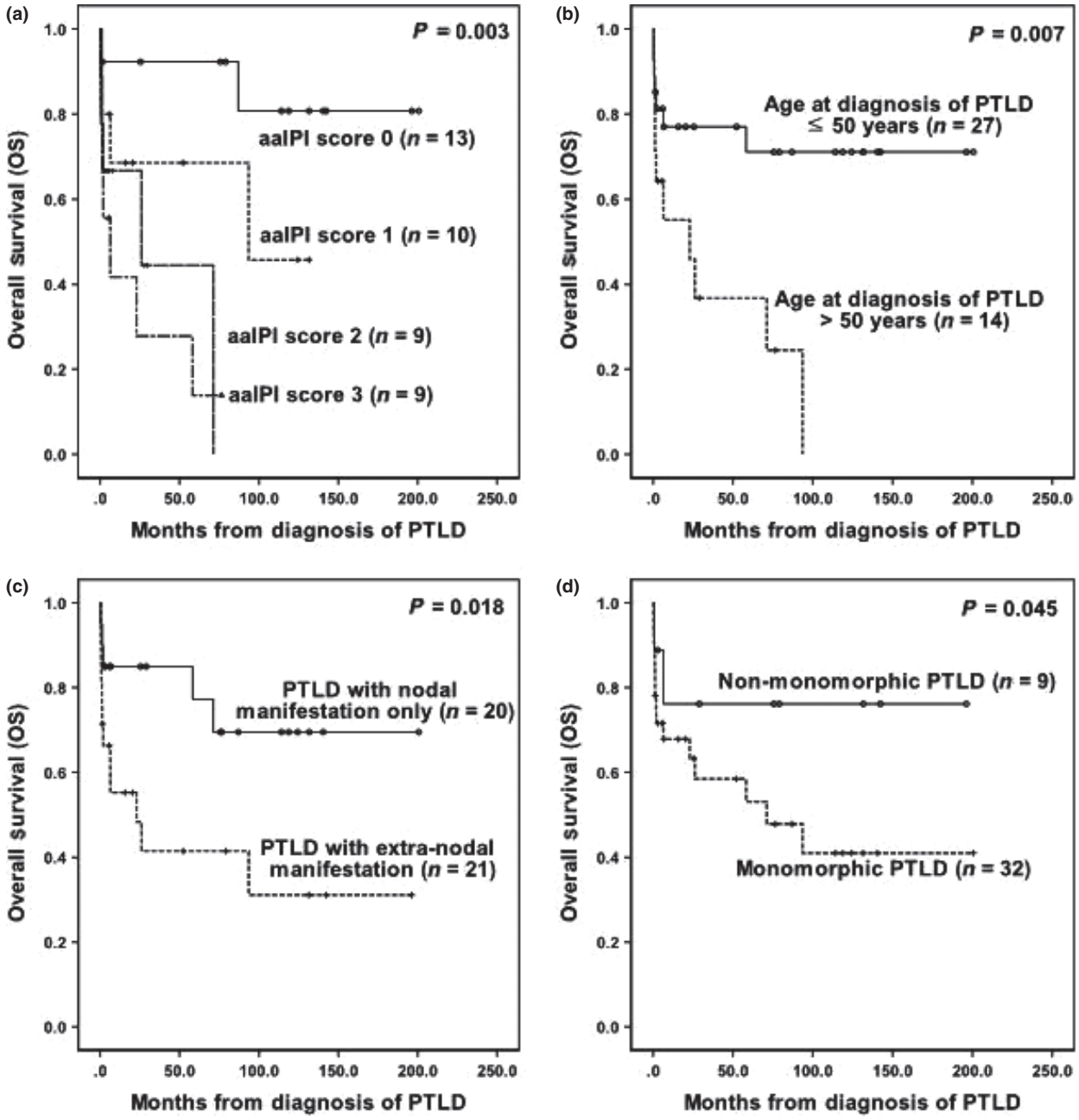

Figure 2 Factors which showed significant values for prediction of worse survival outcomes. (a) Higher age-adjusted IPI score. [aaIPI score 0 vs. score 1 ($P = 0.095$), vs. 2 ($P = 0.012$) and vs. 3 ($P = 0.002$), and aaIPI score 1 vs. score 2 ($P = 0.281$), vs. 3 ($P = 0.089$)] (b) Age over 50 years old. (c) Extranodal manifestation. (d) Monomorphic Post-transplant lymphoproliferative disorder (PTLD).

three parameters – elevated LDH level, higher stage III–IV, and higher ECOG PS ≥2 – consisting of aaIPI were used without modification (one point each). Additionally, as presented above, older age > 50 years, extranodal manifestation (at least one site), and monomorphic subtype also got one point each. With this modified PTLD-specific scoring (total score 6), we calculated OS and CIR rate according to the risk group; Low-risk (Score 0–1), Intermediate-risk (Score 2–3), High-risk (Score 4–6) group. High-risk PTLD ($n = 17$) showed worst OS [HR = 21.594 (95% CI 2.699–172.77), $P = 0.004$] and higher CIR rate compared to low-risk PTLD (Fig. 3a). We also identified that high-risk PTLD showed adverse outcome in post-KT PTLD subgroup analysis (Fig. 3b).

Table 3. Univariate and multivariate analysis of the affecting factors for Overall survival (OS) in Post-transplant lymphoproliferative disorder (PTLD).

	OS			
	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Kidney-transplantation (KT) versus Hematopoietic stem cell transplantation (HSCT)	0.988 (0.35–2.79)	0.982		
Chemotherapy	0.838 (0.32–2.17)	0.716		
aaIPI (≥High-intermediate)	2.406 (1.34–4.30)	0.003*	2.351 (1.11–4.97)	0.025*
Monomorphic PTLD	2.798 (1.01–12.2)	0.045*	5.490 (0.99–30.4)	0.051
Extranodal manifestation	2.972 (1.05–8.43)	0.041*	3.372 (1.04–10.8)	0.042*
Age ≥ 50 years	3.377 (1.29–8.80)	0.013*	2.543 (0.92–31.2)	0.058

HR indicates hazard ratio.
*$P < 0.05$.

Loss of the grafted renal function and the outcomes of the hematological malignancies

We serially checked the blood urea nitrogen and creatinine level to identify the loss of the grafted renal function after diagnosis of the post-KT PTLD (Fig. 4). We checked the time of the functional loss when the glomerular filtration rate (GFR) fell down below 50 ml/min/1.73 m^2, or when both the urea nitrogen (>50 mg/dl) and creatinine (>2.0 mg/dl) level increased for over 6 months. Cumulative incidence of the renal function loss at 1 year was 28% and the overall functional loss was estimated at 49%. Low PTLD-score group showed relatively lower rate of grafted renal function loss (14.3% vs. 38.1%, $P = 0.243$).

There were eight patients with hematological malignancies in this cohort. Among them, two AML and one MDS patients died with progression of PTLD, and one MDS patient died due to relapse even after reduction of immunosuppressive agents and DLI. The rest four patients are alive with controlled chronic GVHD.

Discussion

Current study tried to show the characteristics of PTLD after comparative analysis between KT and HSCT, but the two groups were not actually comparable due to their different characteristics. Perhaps, our data only showed the differences between the two groups. Patients who underwent HSCT were younger than KT and most of the post-HSCT PTLD (92.3%) were early-onset (<1 year). Therefore, age at diagnosis of post-HSCT PTLD was significantly younger than post-KT PTLD patients. This phenomenon might be caused by the host immunity and the trend of using immunosuppressive agents in each transplantation setting. In the case of HSCT, impaired host immunity in the early post-HSCT period and intensified immune suppression due to acute GVHD may cause early-onset of PTLD. Besides, host immune reconstitution and tapering-off of immunosuppressive agents may suppress late onset PTLD. On the contrary, preserved early host immunity and inevitable long-term use of immunosuppressive agents with aging process may cause late-onset PTLD in post-KT patients. Although significant cut-off for OS was 50 years, and there was only 1 (7.7%) patient older than 50 years in post-HSCT group and 13 (46.4%) patients in post-KT group ($P = 0.031$), OS between post-KT PTLD and post-HSCT PTLD was not significantly different both in the entire patients group (28 vs. 13, $P = 0.860$) and also in the subgroup of younger than 50 years (15 vs. 12, $P = 0.559$).

In this study, we did not try to identify the affecting factors which may increase the occurrence of PTLD specifically. According to the previous reports, the type or combination of immunosuppressive agents [8,24], and intuitively, the duration length or mean trough level might be important for inducing PTLD. But it is difficult to use pharmacokinetics practically, and the occurrence of PTLD is also affected by several factors including EBV load. Although determining the affecting factors may be useful for prevention of PTLD, we may not use them in clinical practice because of its low incidence. It is rather considered that early diagnosis followed by active treatment with identification of poor prognostic factors is more important for PTLD management at present. Despite the limitations of using one single-center based data and retrospective study with heterogeneous treatments, and long-term follow-up period during which time diagnostic techniques and treatment options changed, we precisely compared the results between different transplantation types focusing on KT versus HSCT and this data is one of a few reports of PTLD in Korea.

One recent Korean PTLD data showed male predominance and late-onset PTLD in 67.5%, extranodal manifestation in 51%, monomorphic PTLD in 51% (DLBCL in 82%), EBV *in situ* in 72.5%, which were almost similar to our current study. In the previous study, OS was 68.3% and poorer survival outcome was observed in early-onset PTLD and monomorphic PTLD. Post-KT PTLD showed

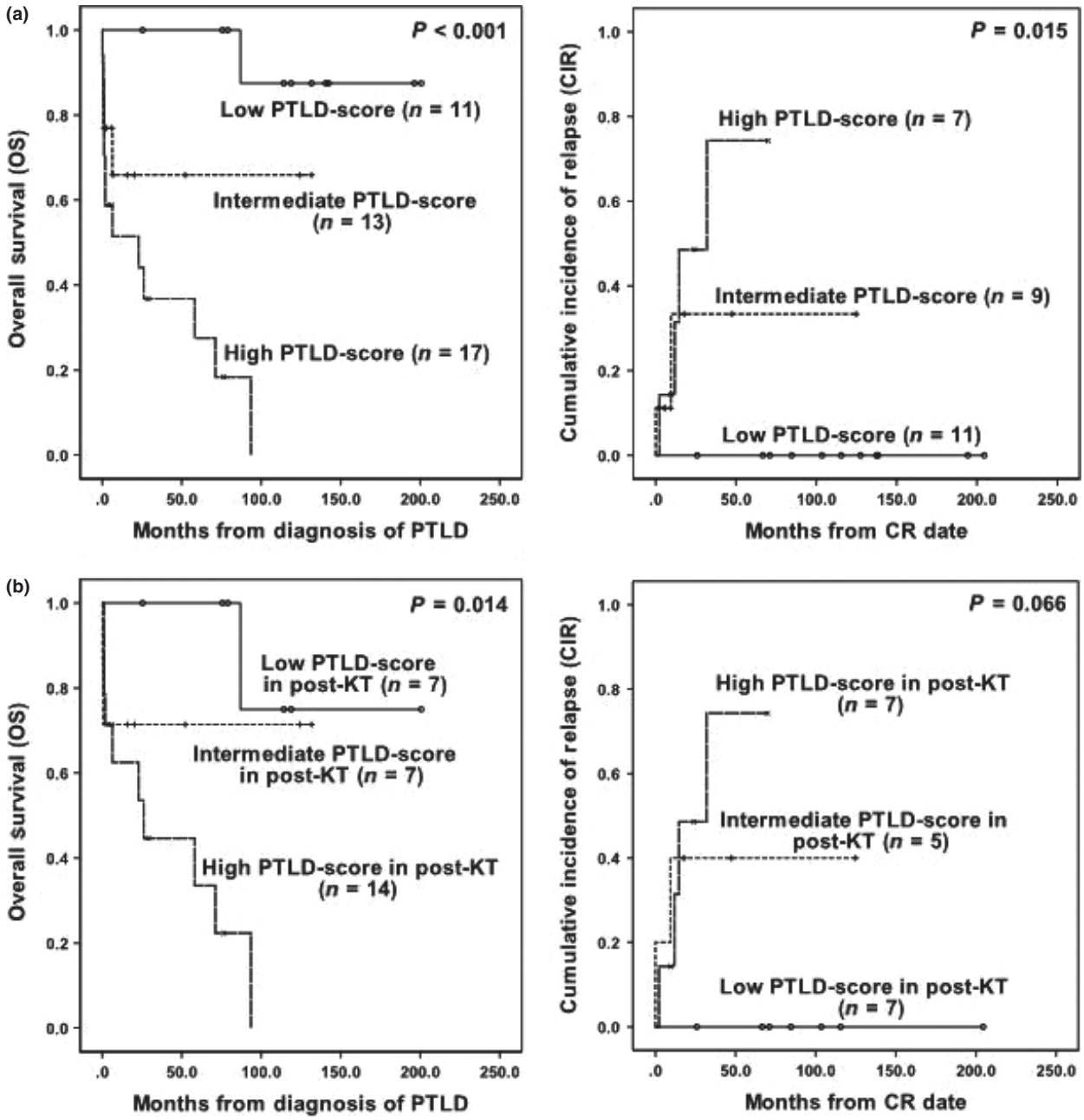

Figure 3 Post-transplant lymphoproliferative disorder (PTLD) score: Low (0–1), Intermediate (2–3), High (4–6) (a) Overall survival (OS) [Low-score vs. intermediate-score ($P = 0.058$) and vs. high-score ($P = 0.004$)] and CIR rate [Low-score vs. intermediate-score ($P = 0.054$) and vs. high-score ($P = 0.001$)] in the entire group according to the PTLD-score. (b) OS [Low-score vs. intermediate-score ($P = 0.406$) and vs. high-score ($P = 0.003$)] and CIR rate [Low-score vs. intermediate-score ($P = 0.077$) and vs. high-score ($P = 0.010$)] in the post-KT PTLD group according to the PTLD-score in post-KT PTLD.

the most favorable OS compared to other organ transplantation or hematopoietic cell transplantation [21]. In contrast, our data showed somewhat different results compared to the previous data. We identified that 10-year OS of the entire 41 patients was 44% and there were no significant differences between early-onset and late-onset PTLD, which was represented by post-HSCT PTLD (early onset) and post-KT PTLD (late onset). Only monomorphic PTLD was a consistently adverse factor for OS.

Interestingly, our data showed that post-HSCT PTLD patients were less likely to relapse after CR achievement, although the statistical significance was not definite. We

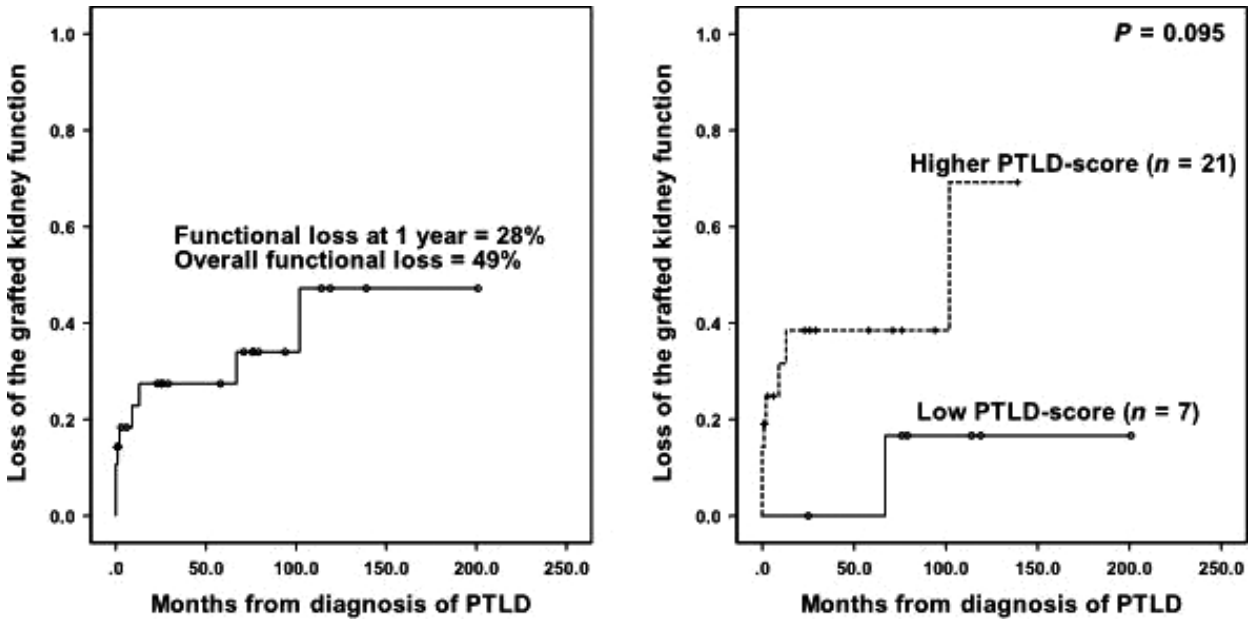

Figure 4 Failure rate of the grafted kidney. Higher Post-transplant lymphoproliferative disorder (PTLD)-score group showed earlier and more failure rate compared to low PTLD-score group.

supposed that the result might come from the distinctive post-transplant immunosuppressive management between the two groups. In the case of HSCT, we reduce the dose of immunosuppressive agents after 3–6 months from HSCT, unless moderate to severe GVHD occurs, and it is generally possible to taper off within 1 year. In this study, all of the post-HSCT PTLD patients who achieved CR rapidly tapered off and stopped immunosuppressive agent. However, relatively long-term maintenance of immunosuppressive agent was inevitable for post-KT PTLD group.

In regard of viral status, our study identified that post-HSCT PTLD which was consisted of mostly early-onset PTLD showed higher proportion of EBV *in situ* hybridization in tumor (84.6%) and EBV reactivation in blood stream (91.6%). Although large proportion of PTLD cases are associated with EBV, 20–40% are reported to be negative for EBV [10,12,25,26] and it is still unclear which threshold values of EBV in blood stream are predictive for the development of PTLD [27]. As was discussed before, prevention of PTLD according to the degree of the immune suppression is very difficult for practice. However, increased EBV viral load probably defines the patients with higher-risk of PTLD and we may prevent PTLD guided by reduction of immunosuppressive agents according to the consecutive follow-up of EBV viral load [28,29]. As post-HSCT PTLD is characterized by early-onset and large proportion of patients are associated with increased EBV viral load, we may be guided by serial follow-up of EBV DNA RQ-PCR leading to control of immunosuppressive agents for prevention of PTLD until 1-year after HSCT. In the case of post-KT PTLD, as the occurrence of PTLD requires longer duration after transplantation, routine screening or follow-up of EBV viral load may be excessive. Furthermore, based on the successful results of DLI in allogeneic HSCT setting [30] and the infusion of EBV-specific cytotoxic T-lymphocytes in solid organ transplantation setting [31], we may try immune cell-therapy in addition to the standard treatment of rituximab plus chemotherapy [6,32,33].

Although our results originated from the retrospective analysis of small number of patients treated with heterogeneous treatment modalities and only post-KT patients were analyzed on behalf of organ transplantation, this is the first paper which compared post-organ transplantation and post-HSCT PTLD. In summary, we found a discrepancy of the characteristics and future management plan for PTLD according to the transplantation type, although OS was not significantly different between them. We cautiously suggest aaIPI may be useful for prediction for prognosis of PTLD and we expected that addition of several PTLD-specific parameters – age > 50 years, monomorphic histology, extranodal manifestation – may be useful for more precise prediction of outcome, which needs validation of another study. And we recommend to check EBV viral load serially in patients with HSCT who are heavily treated with immunosuppressive agents in early period after transplantation.

Authorship

S-GC and J-HY: designed and performed this research. SL, H-JK, J-WL, W-SM, B-HC, C-WY, Y-SK, J-IK and I-SM:

collected data. E-JO, G-SP, S-GC and J-HY: analyzed data. J-HY: wrote this paper.

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References

1. Karuturi M, Shah N, Frank D, *et al.* Plasmacytic post-transplant lymphoproliferative disorder: a case series of nine patients. *Transpl Int* 2013; **26**: 616.
2. Nalesnik MA. The diverse pathology of post-transplant lymphoproliferative disorders: the importance of a standardized approach. *Transpl Infect Dis* 2001; **3**: 88.
3. Dotti G, Fiocchi R, Motta T, *et al.* Lymphomas occurring late after solid-organ transplantation: influence of treatment on the clinical outcome. *Transplantation* 2002; **74**: 1095.
4. Fohrer C, Caillard S, Koumarianou A, *et al.* Long-term survival in post-transplant lymphoproliferative disorders with a dose-adjusted ACVBP regimen. *Br J Haematol* 2006; **134**: 602.
5. Caillard S, Lelong C, Pessione F, Moulin B. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: report of 230 cases from the French Registry. *Am J Transplant* 2006; **6**: 2735.
6. Svoboda J, Kotloff R, Tsai DE. Management of patients with post-transplant lymphoproliferative disorder: the role of rituximab. *Transpl Int* 2006; **19**: 259.
7. Barnett AN, Hadjianastassiou VG, Mamode N. Rituximab in renal transplantation. *Transpl Int* 2013; **26**: 563.
8. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant* 2004; **4**: 222.
9. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. *Crit Rev Oncol Hematol* 2005; **56**: 155.
10. Swerdlow SH, Campo E, Harris NL, *et al.* (eds). *World Health Organization Classification of Tumours of Haematopietic and Lymphoid Tissue*. Lyon: IARC Press, 2008: 343.
11. Walker RC, Marshall WF, Strickler JG, *et al.* Pretransplantation assessment of the risk of lymphoproliferative disorder. *Clin Infect Dis* 1995; **20**: 1346.
12. Evens AM, David KA, Helenowski I, *et al.* Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. *J Clin Oncol* 2010; **28**: 1038.
13. Ghobrial IM, Habermann TM, Ristow KM, *et al.* Prognostic factors in patients with post-transplant lymphoproliferative disorders (PTLD) in the rituximab era. *Leuk Lymphoma* 2005; **46**: 191.
14. Ghobrial IM, Habermann TM, Maurer MJ, *et al.* Prognostic analysis for survival in adult solid organ transplant recipients with post-transplantation lymphoproliferative disorders. *J Clin Oncol* 2005; **23**: 7574.
15. Leblond V, Dhedin N, Mamzer Bruneel MF, *et al.* Identification of prognostic factors in 61 patients with posttransplantation lymphoproliferative disorders. *J Clin Oncol* 2001; **19**: 772.
16. Yoon JH, Min WS, Kim HJ, *et al.* Experiences of t-PA use in moderate-to-severe hepatic veno-occlusive disease after hematopoietic SCT: is it still reasonable to use t-PA? *Bone Marrow Transplant* 2013; **48**: 1562.
17. Gonzalez-Barca E, Domingo-Domenech E, Capote FJ, *et al.* Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. *Haematologica* 2007; **92**: 1489.
18. Miyagi S, Sekiguchi S, Kawagishi N, *et al.* Rituximab therapy and reduction of immunosuppression to rescue graft function after renal posttransplantation lymphoproliferative disorder found by macrohematuria in a pancreas and kidney transplant recipient: a case report. *Transplant Proc* 2011; **43**: 3299.
19. Choquet S, Trappe R, Leblond V, Jager U, Davi F, Oertel S. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. *Haematologica* 2007; **92**: 273.
20. Davis CL, Wood BL, Sabath DE, Joseph JS, Stehman-Breen C, Broudy VC. Interferon-alpha treatment of posttransplant lymphoproliferative disorder in recipients of solid organ transplants. *Transplantation* 1998; **66**: 1770.
21. Yoon SO, Yu E, Cho YM, *et al.* Post-transplant lymphoproliferative disorders: clinicopathological analysis of 43 cases in a single center, 1990–2009. *Clin Transplant* 2012; **26**: 67.
22. Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649.
23. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; **16**: 1141.
24. Penn I. The changing pattern of posttransplant malignancies. *Transplant Proc* 1991; **23**: 1101.
25. Norin S, Kimby E, Ericzon BG, *et al.* Posttransplant lymphoma–a single-center experience of 500 liver transplantations. *Med Oncol* 2004; **21**: 273.
26. Domingo-Domenech E, de Sanjose S, Gonzalez-Barca E, *et al.* Post-transplant lymphomas: a 20-year epidemiologic, clinical and pathologic study in a single center. *Haematologica* 2001; **86**: 715.
27. Bakker NA, van Imhoff GW, Verschuuren EA, van Son WJ. Presentation and early detection of post-transplant lympho-

proliferative disorder after solid organ transplantation. *Transpl Int* 2007; **20**: 207.
28. McDiarmid SV, Jordan S, Kim GS, *et al.* Prevention and preemptive therapy of postransplant lymphoproliferative disease in pediatric liver recipients. *Transplantation* 1998; **66**: 1604.
29. Lee TC, Savoldo B, Rooney CM, *et al.* Quantitative EBV viral loads and immunosuppression alterations can decrease PTLD incidence in pediatric liver transplant recipients. *Am J Transplant* 2005; **5**: 2222.
30. Rooney CM, Smith CA, Ng CY, *et al.* Infusion of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus-induced lymphoma in allogeneic transplant recipients. *Blood* 1998; **92**: 1549.
31. Savoldo B, Goss JA, Hammer MM, *et al.* Treatment of solid organ transplant recipients with autologous Epstein Barr virus-specific cytotoxic T lymphocytes (CTLs). *Blood* 2006; **108**: 2942.
32. Choquet S, Leblond V, Herbrecht R, *et al.* Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. *Blood* 2006; **107**: 3053.
33. Oertel SH, Verschuuren E, Reinke P, *et al.* Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). *Am J Transplant* 2005; **5**: 2901.