Title

Single cord blood transplantation versus HLA-haploidentical related donor transplantation using post-transplant cyclophosphamide in patients with hematological malignancies

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Authorship

F.W. and J.K. designed the research; J.K., T.K. and A.T. –K. organized the project; F.W. and J.K. performed the statistical analysis; F.W. wrote the first draft; and all other authors critically reviewed the draft and approved the final version for publication.

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Abstract

Background: Unrelated cord blood (UCB) and haploidentical related donor transplantation using post-transplant cyclophosphamide (PTCy-haplo) have become alternative options to treat patients with hematological malignancies without a human leukocyte antigen (HLA)-matched donor.

Methods: We conducted a retrospective study using registry data from the Kyoto Stem Cell Transplantation Group (KSCTG) for patients with hematological malignancies who received their first allogeneic hematopoietic cell transplantation using a single UCB unit (n=460) or PTCy-haplo (N=57) between 2013 and 2019.

Results: We found that overall survival in the UCB group was comparable to that in the PTCy-haplo group (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.66 to 1.52), although neutrophil and platelet engraftment were significantly delayed. Non-relapse mortality risk and the incidence of GVHD in the UCB group were also comparable to those in the PTCy-haplo group. Although the relapse risk was similar between the UCB group and the PTCy-haplo group regardless of the disease risk, acute myeloid leukemia patients benefit from UCB transplant with a significantly lower relapse rate (HR, 0.38; 95%CI, 0.18 to 0.76).

Conclusions: UCB transplant gives outcomes comparable to PTCy-haplo transplant, and both UCB and PTCy-haplo units are suitable as alternative donor sources for patients without an HLA-matched sibling or unrelated donor.

Introduction

Hematopoietic stem cell transplantation (HSCT) has been established as a curative therapy for patients with hematologic malignancies. In the absence of HLA-matched sibling or unrelated donors, unrelated cord blood (UCB) and haploidentical related donor transplantation have been used as alternative donor sources because of their ready availability with rapid access and tolerance to HLA mismatches.[1,2] Several studies have demonstrated comparable outcomes for the 2 donor types for hematologic malignancies.[3-5] Recently, haploidentical transplantation using post-transplant cyclophosphamide (PTCy-haplo) has been increasingly performed and has been shown to give favourable outcomes.[6-12] The Blood and Marrow Transplant Clinical Trials Network 1101 (BMT CTN 1101) trial comparing haploidentical bone marrow transplant (BMT) with PTCy versus double UCB using reduced intensity conditioning (RIC) revealed lower non relapse mortality (NRM) and higher overall survival (OS) after BMT from haploidentical relatives using PTCy.[13] Peripheral blood stem cell transplant (PBSCT) with PTCy, instead of BMT, has been increasingly used, and shows comparable survival outcomes, but with a risk of acute graft-versus-host disease (GVHD) compared to BMT with PTCy.[14,15] On the other hand, significant advances in the implementation of UCB transplant have decreased the risk of early mortality and improved long-term overall survival.[16-26] In fact, although the use of UCB has recently decreased in both Europe and the United States, the annual number of UCB transplants in Japan still exceeds 1,000.[27,28]

In the context of this background, a donor selection algorithm for these transplants has not yet been fully established. With the aim to assess the relative efficacies of UCB and PTCy-haplo transplant, we conducted a multi-center retrospective analysis to compare

the clinical outcomes in patients with hematologic malignancies. We also performed a propensity score matching analysis to minimize potential selection bias between these two transplants.

Materials and Methods

Data collection

Transplant data were obtained from the Kyoto Stem Cell Transplantation Group (KSCTG), which is a multi-center group of 18 transplantation centers in Japan. We included adult patients aged 16 years to 70 years with hematological malignancies who received a first stem cell transplantation using a single UCB unit or HLA-mismatched sibling transplantation using PTCy between 2013 and 2019. The choice of UCB or PTCy-haplo transplant depended on the decision of physicians at each center. Double-unit UCB was not used in the present study, since this is currently only under clinical trial in Japan. This study was approved by the institutional review board of each center and conducted in accordance with the Declaration of Helsinki.

Definitions

OS was measured from the day of transplant to the last date of follow-up or death. Relapse-free survival (RFS) was measured from the day of transplant to relapse, death, or the last date of follow-up. GVHD- and relapse-free survival (GRFS) was measured from the day of transplant to grade III to IV acute GVHD, extensive chronic GVHD, relapse, death, or the last date of follow-up. Relapse was defined based on morphological and clinical evidence of disease activity, and non-relapse mortality (NRM) was measured from the day of transplant to death without relapse. Neutrophil engraftment was defined as a neutrophil count of 500/μl for 3 consecutive days after transplantation. Platelet engraftment was defined as a platelet count ≥ 20,000/μl without platelet transfusion for seven consecutive days following transplantation. Acute and chronic GVHD were diagnosed and graded according to traditional criteria.[29,30] We

classified the intensity of conditioning regimens as myeloablative if either total body irradiation >8 Gy, oral busulfan ≥9 mg/kg, intravenous busulfan ≥7.2 mg/kg, melphalan >140 mg/m^2, or thiotepa ≥10 mg/kg was used, and otherwise classified it as reduced intensity.[31] We defined HLA-matching based on HLA-A, HLA-B, and HLA-DR antigen levels in UCB and PTCy-haplo donors. The refined disease risk index (rDRI) was used in risk stratification analyses.[32] Furthermore, Adult T-cell leukemia-lymphoma (ATL) in complete or partial remission ~~and myeloproliferative neoplasm~~ was defined as intermediate risk, and that in non-remission was considered very high risk.[33,34]

Endpoints

The primary endpoint of the study was to compare OS between the UCB and PTCy-haplo groups. Secondary endpoints were RFS, GRFS, relapse, NRM, neutrophil engraftment, platelet engraftment, grade II–IV acute GVHD, grade III–IV acute GVHD, chronic GVHD, and extensive chronic GVHD.

Statistical analysis

The probabilities of OS, RFS and GRFS were estimated according to the Kaplan-Meier method, and groups were compared on the basis of the log-rank test. The incidence of relapse, NRM, neutrophil engraftment, platelet engraftment and acute and chronic GVHD were estimated with the cumulative incidence curve and the groups were compared using Gray's test.[35,36] Competing events were death without relapse for relapse, relapse for NRM, and death for both neutrophil and platelet engraftment and acute and chronic GVHD. Cox proportional hazards models were used to evaluate the effects of donor source and other variables on OS and RFS, while Fine and Gray's

proportional hazards models were used for all other endpoints.[37] The incidence of chronic GVHD was evaluated in patients who survived at least 100 days. Adjusted covariates were as follows; patient sex, age (<50 or ≥50 years old), performance status (PS, 0–1 or >1), rDRI (low/intermediate or high/very high), and intensity of the conditioning regimen (reduced intensity or myeloablative). Confounding variables were selected with a variable retention criterion of $P<0.05$ in the univariate analysis of the total cohort. Significant variables, in addition to donor source, were subsequently included in the multivariate analysis of both the total cohort and the subgroup cohort. Propensity score (PS) matching was performed to minimize the selection bias between UCB and PTCy-haplo transplant.[38] Logistic regression was used for the propensity score calculation from the following variables; patient sex, age, PS, rDRI, and intensity of the conditioning regimen. A 1:1 caliper matching was performed using the nearest neighbor matching method with a fixed caliper width of 0.2 of the standard deviation of PS. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[39]

Results

Patient characteristics

The schematic workflow of inclusion and exclusion is shown in **Fig. 1**. Finally, we enrolled 517 patients who received allo-HSCT in 17 centers from 2012 to 2019. The patient characteristics are shown in **Table 1**. Among 517 patients, 460 received single UCB transplant and 57 received PTCy-haplo related donor transplant (53 peripheral blood stem cell and 4 bone marrow grafts). The median age of the UCB and PTCy-haplo groups was 55 and 52 years, respectively (P= 0.770). The performance status and rDRI were similar in the two groups (P= 0.538 and 0.180, respectively). MAC was used more often in the UCB cohort than in the PTCy-haplo cohort (P<0.001). In the PTCy-haplo cohort, the total dose of Cy was 80mg/kg (43.9%) or 100mg/kg (56.1%), and the median duration of tacrolimus and mycophenolate mofetil (MMF) use was 173 days (8 to 1115) and 34 days (4 to 76), respectively. In terms of UCB unit characteristics, the median total nucleated cells (TNCs) cryopreserved and infused ($\times 10^7$/kg) and $CD34^+$ cells infused ($\times 10^5$/kg) were 2.74 (1.40 to 5.17) and 0.73 (0.30 to 2.80), respectively. The median $CD34^+$ cells of PBSCs infused ($\times 10^6$/kg) were 3.9 (0.89 to 15.0) in PTCy-haplo units. The median follow-up periods of survivors were 2.2 and 2.4 years, respectively. Eighty-six recipients (82 UCB and 4 PTCy-haplo) had HLA antibodies and 4 patients in the UCB group and none with PTCy-haplo transplant had donor-specific HLA antibodies (DSAs). Mean fluorescence intensity (MFI) over 1,000 was set as the threshold to determine the positivity of DSAs and only 1 patient had prior treatment with bortezomib to reduce DSAs.

OS, RFS and GRFS

The 2-year OS rates in the UCB and PTCy-haplo groups were 53.7% (95%CI, 48.7% to 58.5%) and 53.6% (39.1% to 66.1%), respectively (P= 0.713, **Fig. 2a)**. The 2-year RFS rates were 48.8% (95%CI, 43.9% to 53.5%) and 47.1% (33.7% to 59.4%), respectively (P= 0.832, **Fig. 2b)**. The 2-year GRFS rates were 41.5% (95%CI, 36.8% to 46.2%) and 36.7% (24.4% to 49.0%), respectively (P= 0.853, **Fig. 2c)**. In the multivariate analysis, OS, RFS and GRFS in the UCB group were comparable to those in the PTCy-haplo group (OS; HR, 1.00, 95%CI, 0.66-1.52, P=0.99, RFS; HR, 0.91, 95% CI, 0.62-1.32, P=0.612, GRFS; HR, 0.93, 95%CI, 0.66-1.32, P= 0.69, **Table 2**).

Relapse and NRM

The 2-year relapse rates in the UCB and PTCy-haplo groups were 29.7% (95%CI, 25.4% to 34.1%) and 29.8% (95%CI,18.5% to 42.0%), respectively (P=0.885, **Fig. 3a**). The 2-year NRM rates in the UCB and PTCy-haplo groups were 21.5% (95%CI, 17.7% to 25.6%) and 21.2% (95%CI, 11.6% to 32.7%), respectively (P=0.885, **Fig. 3b**). In the multivariate analysis, relapse and NRM risk after CBT were comparable to those after PTCy-haplo (RFS; HR, 0.91, 95% CI, 0.62-1.32, P=0.612, OS; HR, 1.00, 95%CI,0.66-1.52, P=0.99, **Table 2**). The causes of death in patients who died without relapse are shown in **Supplementary Table 1**. While death from graft failure or GVHD was not observed in the PTCy-haplo group, the rates of thrombotic microangiopathy (TMA) and hemorrhage were higher in the PTCy-haplo group (TMA, 6.2% vs 13.3%, hemorrhage, 1.8% vs 13.3%). The rate of infection in the UCB group was comparable to that in PTCy-haplo group (29.2% vs 33.3%).

Acute and chronic GVHD

The rates of grade II–IV acute GVHD at 100 days after UCB and PTCy-haplo were 38.1% (95%CI, 33.6% to 42.5%) and 26.8% (15.9% to 38.9%), respectively (P=0.055, **Fig. 4a**). The rates of grade III–IV acute GVHD at 100 days after UCB and PTCy-haplo were 13.7% (95%CI, 10.8% to 17.0%) and 4.1% (0.7% to 12.5%), respectively (P=0.051, **Fig. 4b**). In the multivariable analysis, the rates of grade II–III and III–IV acute GVHD after CBT were comparable to those after PTCy-haplo transplant (grade II–III ; HR, 1.65, P=0.055, grade III–IV; HR 3.60, P=0.073, **Table 3**). The incidence of chronic GVHD at 2 years after UCB and PTCy-haplo was 25.6% (95%CI, 21.1% to 30.2%) and 25.6% (95%CI, 14.1% to 38.8%), respectively (P=0.697, **Fig. 4c**). The incidence of extensive chronic GVHD at 2 years after UCB and PTCy-haplo was 10.2% (95%CI, 7.3% to 13.5%) and 14.9% (95%CI, 6.5% to 26.6%), respectively (P=0.362, **Fig. 4d**). In the multivariate analysis, the rates of chronic or extensive chronic GVHD after UCB transplant were comparable to those after PTCy-haplo transplant (chronic GVHD; HR 0.89, P=0.68, extensive chronic GVHD; HR, 0.69, P=0.35, **Table 3**).

Neutrophil and platelet engraftment

The cumulative incidence of neutrophil recovery was 92.2% at a median of 20 days (range, 3 to 39 days) in the UCB group versus 94.7% at a median of 16 days (range, 12 to 36 days) in the PTCy-haplo group, respectively (P=0.042, **Fig. 5a**). Platelet recovery was 79.8% at a median of 40 days (range, 3 to 100 days) in the UCB group versus 82.5% at a median of 26 days (range, 4 to 76 days) in the PTCy-haplo group, respectively (P=0.003, **Fig. 5b**). UCB transplant was significantly associated with ~~a~~ delayed neutrophil and platelet engraftment in the multivariate analysis (neutrophil

engraftment, HR 0.64, 95%CI, 0.44-0.93, P=0.019; platelet engraftment, HR 0.58, 95%CI, 0.38-0.89, P=0.014; **Table 3**).

Effects of disease risk and disease according to the donor source

Since disease risk was considered the strongest prognostic factor for transplant outcomes and was clinically important, the outcomes in the standard- and high-risk groups were analyzed according to the rDRI. The 2-year OS of both risks in the UCB group were comparable to those in PTCy group (standard risk; 69.5% vs 73.6%, P=0.524, high risk; 34.3% vs 23.4%, P=0.607, **Supplementary Fig. 1**). Multivariate analysis also showed comparable OS and relapse for both risks (**Supplementary Table 2**).

Although OS after UCB and PTCy-haplo transplants was comparable regardless of disease, AML patients significantly benefit from UCB transplant with a lower risk of relapse (UBC vs PTCy-haplo; HR 0.38, 95%CI 0.18 to 0.76, P= 0.007, **Supplementary table 2**). On the other hand, ALL or lymphoma patients have comparable risk of relapse between these two donors (ALL; HR 0.80, 95%CI 0.27 to 2.34, P= 0.690, lymphoma; HR 3.43, 95%CI 0.79 to 14.97, P= 0.100, **Supplementary table 2**).

Impact of cyclophosphamide dose on PTCy-haplo transplantation

Based on the fact that NRM rates in the PTCy-haplo group were higher than previously reported, we analyzed the impact of PTCy dose (reduced dose; 80 mg/kg or standard dose; 100 mg/kg) on outcomes in the PTCy-haplo group. The decision making on the dose of cyclophosphamide was basically based on the physician decisions and the reduced dose of cyclophosphamide was more often utilized after 2018 (data not shown).

The 2-year OS in the reduced-dose group and standard-dose group was 64.8% (95%CI, 40.9% to 81.1%) and 45.0% (27.0% to 61.5%), respectively (P= 0.127, **Supplementary Fig. 2a)**. The cumulative incidence of grade Ⅱ−IV acute GVHD at 100 days in the reduced-dose and standard-dose groups was 28.0% (95%CI, 12.1% to 46.5%) and 25.8% (11.9% to 42.2%), respectively (P=0.887, **Supplementary Fig. 2b**). The 2-year NRM rate was 8.0% (95%CI, 1.3% to 22.9%) in the reduced-dose group and 31.2% (16.0% to 47.7%) in the standard dose group (P=0.037, **Supplementary Fig. 2c**). The causes of death in each of the groups revealed that death from TMA (n=2), hemorrhage (n=2), intestinal pneumonia (n=2), and acute respiratory distress syndrome (n=1) were observed only in the standard-dose group (data not shown).

Propensity Score Matching Analysis

We also performed a PS matching analysis to minimize potential selection bias, because there were significant differences in the characteristics of the patients, diseases, and transplant procedures between UCB and PTCy-haplo transplant. After PS matching, 57 patients were identified in each cohort. The patient characteristics after PS matching are shown in **Supplementary Table 3.** There were no significant differences in the characteristics of the patients, diseases, and transplant procedures, except for GVHD prophylaxis and HLA mismatch. As in the whole cohort, there were no significant differences in OS (P=0.881), RFS (P=0.858), GRFS (P=0.769), relapse (P=0.740), NRM (P=0.730), grade Ⅱ−IV acute GVHD (P=0.100), grade III–IV acute GVHD (P=0.067), chronic GVHD (P=0.560), or extensive chronic GVHD (P=0.750) between UCB and PTCy-haplo transplant (**Supplementary Table 4**). The cumulative incidences

of neutrophil (P=0.019) and platelet (P=0.006) recovery were significantly lower in UCB transplant than in PTCy-haplo transplant.

Discussion

In this retrospective multicentre analysis, we demonstrated that OS in the UCB group was comparable to that in the PTCy-haplo group, with similar risks of relapse, NRM, and GVHD. Neutrophil and platelet engraftment were significantly slower after UCB transplant. These results were consistent in the propensity score matching cohort. Both UCB and PTCy-haplo donor coordination takes much less time than unrelated BM or PBSC donor coordination. Therefore, in cases where both UCB and PTCy-haplo are available, donors should be chosen based on their advantages and disadvantages.

High rates of relapse after PTCy-haplo transplant have been a concern since it was initially developed in the setting of BMT following nonmyeloablative conditioning.[40,41] We previously demonstrated that UCB transplant showed better RFS and lower relapse rates without an increase in NRM compared to matched donor transplant for patients with high-risk hematologic diseases.[19] In this study, the risk of relapse after PTCy-haplo transplant was comparable to that after UCB transplant. Further analysis according to the disease risk classification by rDRI revealed no statistically significant differences in OS, relapse, or NRM between standard- and high-risk groups, but this may not have had sufficient power to detect any significant differences due to the heterogeneity of the diseases for which transplants were done as well as small numbers. Bashey et al. reported comparable OS and a reduced risk of relapse in PBSC recipients compared with BM recipients in the setting of PTCy-haplo transplant.[42] In addition, the MAC regimen is associated with a reduced risk of relapse, though it is associated with an increased risk of NRM compared to RIC.[43] In our PTCy-haplo transplant cohort, 93% were PBSC recipients and 36.8% received a MAC regimen, which is quite different

from the BMT CTN 1101 trial cohort, which was entirely BMT with a RIC regimen.[13] Approaches to decrease the incidence of disease relapse after PTCy-haplo transplant might consist of increasing the intensity of the conditioning regimen and the use of a stem cell source from peripheral blood rather than bone marrow. In addition, reductions in the dosage and treatment duration for MMF or calcineurin inhibitors might improve outcomes for high-risk patients after PTCy-haplo transplant. The median duration of MMF use was 34 days and only 1 patient suffered from grade III–IV acute GVHD after stopping MMF. However, an increased risk of acute and chronic GVHD should be noted.[44] These interventions might have comparable relapse rates after PTCy-haplo transplant compared to UCB transplant in this study.

A thorough disease-specific comparison of these donor sources has not been reported. In this study, AML patients had a significantly lower risk of relapse with UCB transplant. Several studies have indicated better outcomes after PTCy-haplo transplant than after UCB transplant for patients with AML, which is inconsistent with our results.[45,46] One of the reasons for this discrepancy may be differences in the population. More than 40% of the patients in our study were high-risk patients with acute leukemia. Milano et al. demonstrated favorable OS with a lower probability of relapse in a UCB group than in an HLA-match or HLA-mismatched group among acute leukemia (83.3%) and MDS (16.7%) patients with minimal residual disease, which reflects the potent graft-versus-leukemia (GVL) effect of UCB.[25] The GVL effect after UCB in AML patients may be explained by the impact of GVHD. It was previously demonstrated that grade I–II or III–IV acute GVHD after UCB transplant was significantly associated with lower relapse rates, and grade I–II acute GVHD was

associated with lower risks of non-relapse mortality and overall mortality than no acute GVHD in patients with acute leukemia.[47] This indicates that the GVL effect may be accompanied by manageable acute GVHD in patients with AML after UCB transplant. The impact of GVHD on outcomes after PTCy-haplo transplant or in lymphoma patients after both types of transplant should be analyzed in a future study.

The lower incidences of acute GVHD and GVHD-related death in the PTCy-haplo group indicate that there was enough immunosuppression to prevent GVHD, but this was associated with cyclophosphamide toxicity. Previous studies have indicated that a reduced dose of cyclophosphamide to 80 mg/m^2 is a valid option in PTCy-haplo transplantation.[44,48] In this study, transplant with a reduced dose of cyclophosphamide showed significantly lower NRM without an increase in grade Ⅱ–IV acute GVHD compared to those after standard-dose cyclophosphamide. Although the rate of NRM in the PTCy-haplo group was higher in this study than previously reported,[13] reduction of the cyclophosphamide dose may help to reduce NRM in patients with PTCy-haplo transplant, especially in older patients or those with high-risk disease.

Compared with PTCy, the use of UCB has a disadvantage with regard to neutrophil and platelet engraftment, which is consistent with previous findings.[13,32] Because the doses of nucleated cells and CD34+ cells have been major determinants of neutrophil recovery and survival, double-unit UCB has been established in Europe and the United States.[49,50] Previous studies demonstrated that alloreactivity may be enhanced after double-unit UCB transplant, leading to higher rates of severe GVHD compared to single-unit UCB.[51] In the absence of single-unit UCB with sufficient cell dose, double-

unit UCB should be selected with careful consideration about the risk of GVHD. Delayed neutrophil recovery after UCB transplant concerns the risks of early NRM. However, in this study, NRM and mortality from infections after UCB transplant were comparable to those after PTCy-haplo transplant. Better conditioning regimens and supportive care during prolonged neutropenic periods have helped to decrease NRM following UCB transplant.[52] DSA is associated with a high risk of graft failure in HLA-mismatched HSCT, particularly in UCB transplant and haploidentical transplant.[53-56] In this study, no graft failure occurred in any of the 4 DSA-positive patients after UCB transplant, but the avoidance of DSA in recipients is important to secure neutrophil and platelet recovery after UCB and PTCy-haplo transplant. In fact, the presence of DSA is one of the limitations of HLA-mismatched transplant. A randomized study comparing UCB and PTCy-haplo transplants demonstrated that 15% of patients allocated to the PTCy-haplo group did not have a suitable donor available, whereas all patients in the UCB transplant group had UCB units.[57] The avoidance of donor candidates with HLA antigens that correspond to DSA could be one reasonable strategy for donor selection between UCB and PTCy-haplo.

This study has several limitations. First, this was a retrospective study involving a small population with heterogeneous backgrounds. The heterogeneous background of the patients may have resulted in a statistical bias, although we tried to reduce this bias by adjusting the impact in multivariate analyses. Second, we only analyzed HLA-A, HLA-B, and HLA-DRB1 alleles because of the incomplete data on HLA-C. Finally, this study was based on an Asian cohort with single UCB or haploidentical-related donor units. The limited heterogeneity of the Japanese population may affect the outcomes of

transplantation.[58-61] Therefore, the findings should be externally validated in a non-Asian cohort with transplantation using double UCB units.

In conclusion, our findings suggest that UCB transplant gives outcomes comparable to PTCy-haplo transplant for patients without an HLA-matched sibling or unrelated donor. Both UCB and PTCy-haplo units are suitable as alternative donor sources and further analysis to determine a specific donor selection algorithm between these two donors is needed in a future study.

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Table 1. Patient characteristics

	Donor source (n=517)		
Characteristics	CBT (n=460)	PTCy (n=57)	P
Sex-no.(%)			0.770
Female	165(35.9)	22(38.6)	
Male	295(64.1)	35(61.4)	
Age-yr			0.614
Median	55	52	
Range	16-70	16-70	
Diagnosis-no.(%)			NA
AML	214(46.5)	15(26.3)	
ALL	63(13.7)	9(15.8)	
MDS	63(13.7)	3(5.3)	
CML	4(0.9)	3(5.3)	
NHL	75(16.3)	16(28.1)	
HL	2(0.4)	1(1.8)	
ATL	25(5.4)	7(12.3)	
MPD	14(3.0)	2(3.5)	
CLL	0(0.0)	1(1.8)	
Stem Cell Source, No. (%)			<0.001
Peripheral blood	0(0.0)	53 (93.0)	
Bone marrow	0(0.0)	4 (7.0)	
Cord Blood	460(100.0)	0 (0.0)	
ECOG PS-no.(%)			0.538
0-1	400(87.0)	48(84.2)	
>1	60(13.0)	9(15.8)	
rDRI			0.180
Low	20(4.3)	4(7.0)	
Intermediate	236(51.3)	31(54.4)	
High	150(32.6)	12(21.1)	
Very high	54(11.7)	10(17.5)	

Conditioning intensity-no.(%)			<0.001
RIC	149(32.4)	36(63.2)	
Flu/Bu/TBI	9	27	
Flu/Bu/Mel	19	0	
Flu/CY/TBI	3	0	
Flu/Mel/TBI	114	9	
CY/TBI	3	0	
BU/CY	1	0	
MAC	311(67.6)	21(36.8)	
CY/TBI	157	0	
BU/CY	11	0	
Flu/TBI	0	12	
Flu/Bu4	16	1	
Flu/Bu4/TBI	52	8	
Flu/Mel	2	0	
Flu/Mel/TBI	5	0	
Flu/Bu4/Mel	68	0	
GVHD prophylaxis-no.(%)			NA
CsA/TAC+MTX	140(30.4)	0(0.0)	
CsA/TAC+MMF	285(62.0)	54(94.7)	
CsA/TAC only	35(7.6)	3(5.3)	
CY dose			
80 mg/m^2		25(43.9)	
100 mg/m^2		32(56.1)	
HLA mismatch			<0.001
0	28(6.1)	0(0.0)	
1	79(17.1)	2(3.5)	
2	253(55.0)	21(36.8)	
3	2(0.4)	34(59.6)	
Missing	98(21.3)	0(0.0)	
Median follow-up time in survivors-yr	2.16(0.16-6.52)	2.38(0.74-5.16)	0.494

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; ATL, adult T-cell leukemia; MPD, myelodysplastic disease; CLL, chronic lymphocytic lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; rDRI, refined disease risk index; RIC, reduced-intensity conditioning; Flu, fludarabine; Bu, busulfan; TBI, total body irradiation; Mel, melphalan; CY, cyclophosphamide; MAC, myeloablative conditioning; GVHD, graft-versus-host disease; CsA, cyclosporin A;TAC, tacrolimus; MTX, methotrexate; MMF, mycophenolate mofetil; HLA, human leukocyte antigen

Table 2. Adjusted comparison of OS, RFS, GRFS, relapse, and NRM in UCB and PTCy-haplo transplant

Outcome	Donor source	HR	P
OS*	PTCy	1.00	Reference
	UCB	1.00 (0.66-1.52)	0.990
RFS**	PTCy	1.00	Reference
	UCB	0.91 (0.62-1.32)	0.612
GRFS***	PTCy	1.00	Reference
	UCB	0.93 (0.66-1.32)	0.690
Relapse†	PTCy	1.00	Reference
	UCB	0.91 (0.57-1.45)	0.690
NRM††	PTCy	1.00	Reference
	UCB	0.90 (0.49-1.66)	0.740

Abbreviations: OS, overall survival; RFS, relapse-free survival; GRFS, graft-versus-host disease-free relapse-free survival; NRM, non-relapse mortality; PTCy, post-transplant cyclophosphamide; UCB, unrelated cord blood

* Other variables included for adjustment were patient age, patient sex, performance status, and disease status.

** Other variables included for adjustment were performance status and disease status.

*** Other variables included for adjustment were performance status and disease status.

† Other variables included for adjustment were performance status and disease status.

†† Other variables included for adjustment were patient age and disease status.

Table 3. Adjusted comparison of acute/chronic GVHD and neutrophil/platelet engraftment in UCB and PTCy-haplo transplant

Outcome	Donor source	HR	P
Grade Ⅱ-Ⅳ acute GVHD*	PTCy	1.00	Reference
	UCB	1.64 (0.99-2.71)	0.055
Grade Ⅲ-Ⅳ acute GVHD*	PTCy	1.00	Reference
	UCB	3.60 (0.89-14.70)	0.073
Chronic GVHD*	PTCy	1.00	Reference
	UCB	0.89 (0.53-1.52)	0.68
Extensive chronic GVHD*	PTCy	1.00	Reference
	UCB	0.69 (0.31-1.51)	0.35
Neutrophil engraftment†	PTCy	1.00	Reference
	UCB	0.64 (0.44-0.93)	0.019
Platelet engraftment††	PTCy	1.00	Reference
	UCB	0.58 (0.38-0.89)	0.014

Abbreviations: GVHD, graft-versus-host disease; PTCy, post-transplant cyclophosphamide; UCB, unrelated cord blood

* No other variables were included for adjustment.

† Other variables included for adjustment were patient age and conditioning regimen intensity.

†† Other variables included for adjustment were patient sex, performance status, conditioning regimen intensity, and disease status.

Figure legends

Figure 1 Flowchart of inclusion and exclusion criteria

Figure 2 Kaplan-Meier estimates of OS (a), RFS (b) and GRFS (c) according to donor source.

Figure 3 Cumulative incidences of relapse (a) and NRM (b) according to donor source.

Figure 4 Cumulative incidences of grade II–IV acute GVHD (a), grade III–IV acute GVHD (b), chronic GVHD (c), and extensive chronic GVHD (d) according to donor source.

Figure 5 Cumulative incidences of neutrophil engraftment (a) and platelet engraftment (b).

Supplementary Figure 1 Kaplan-Meier estimates of OS in the standard-risk group (a) and high-risk group (b) according to donor source.

Supplementary Figure 2 Kaplan-Meier estimates of OS (a), cumulative incidence of grade II–IV acute GVHD (b), and NRM (c) according to the cyclophosphamide dose on PTCy-haplo transplantation.

Figure1

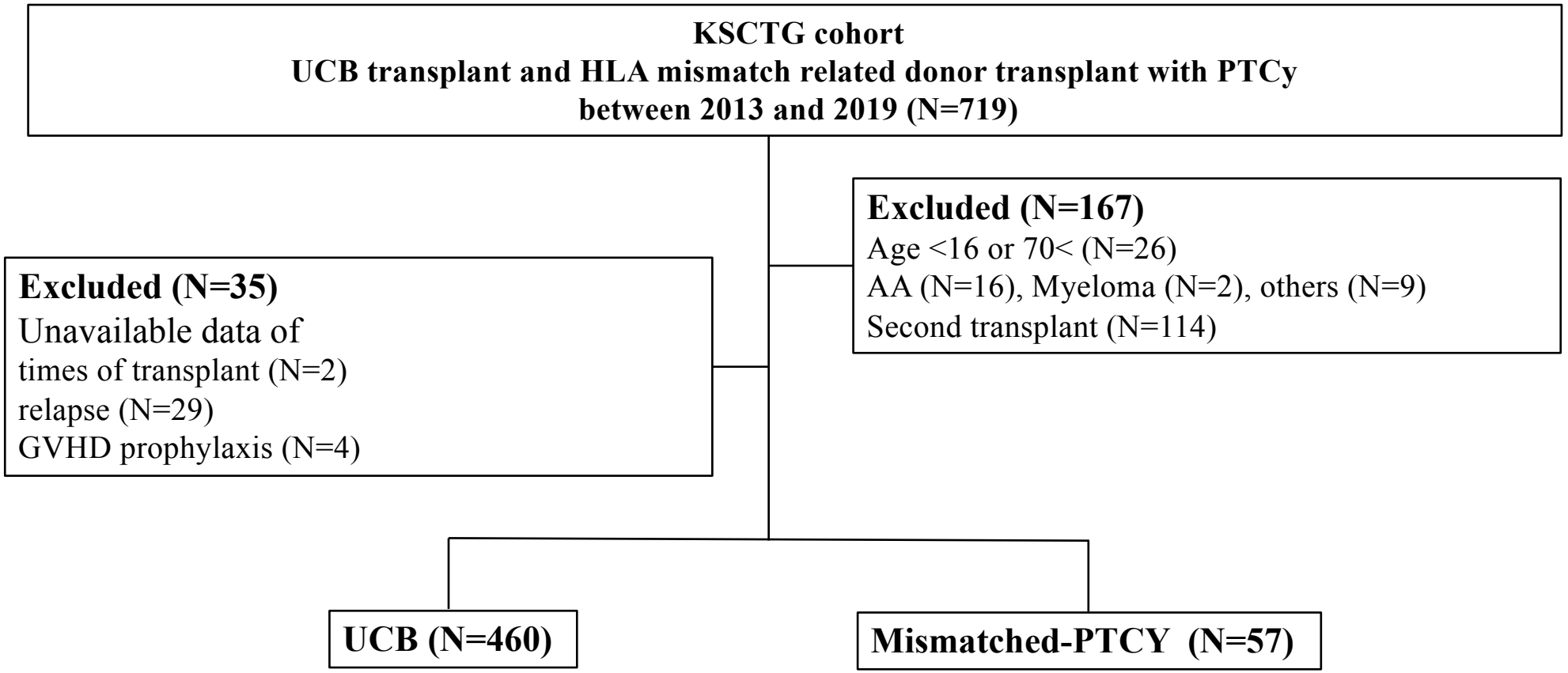
KSCTG cohort
UCB transplant and HLA mismatch related donor transplant with PTCy
between 2013 and 2019 (N=719)
Excluded (N=167)
Age <16 or 70< (N=26)
AA (N=16), Myeloma (N=2), others (N=9)
Second transplant (N=114)
Excluded (N=35)
Unavailable data of
times of transplant (N=2)
relapse (N=29)
GVHD prophylaxis (N=4)
UCB (N=460)
Mismatched-PTCY (N=57)

Figure2

Fig. 2

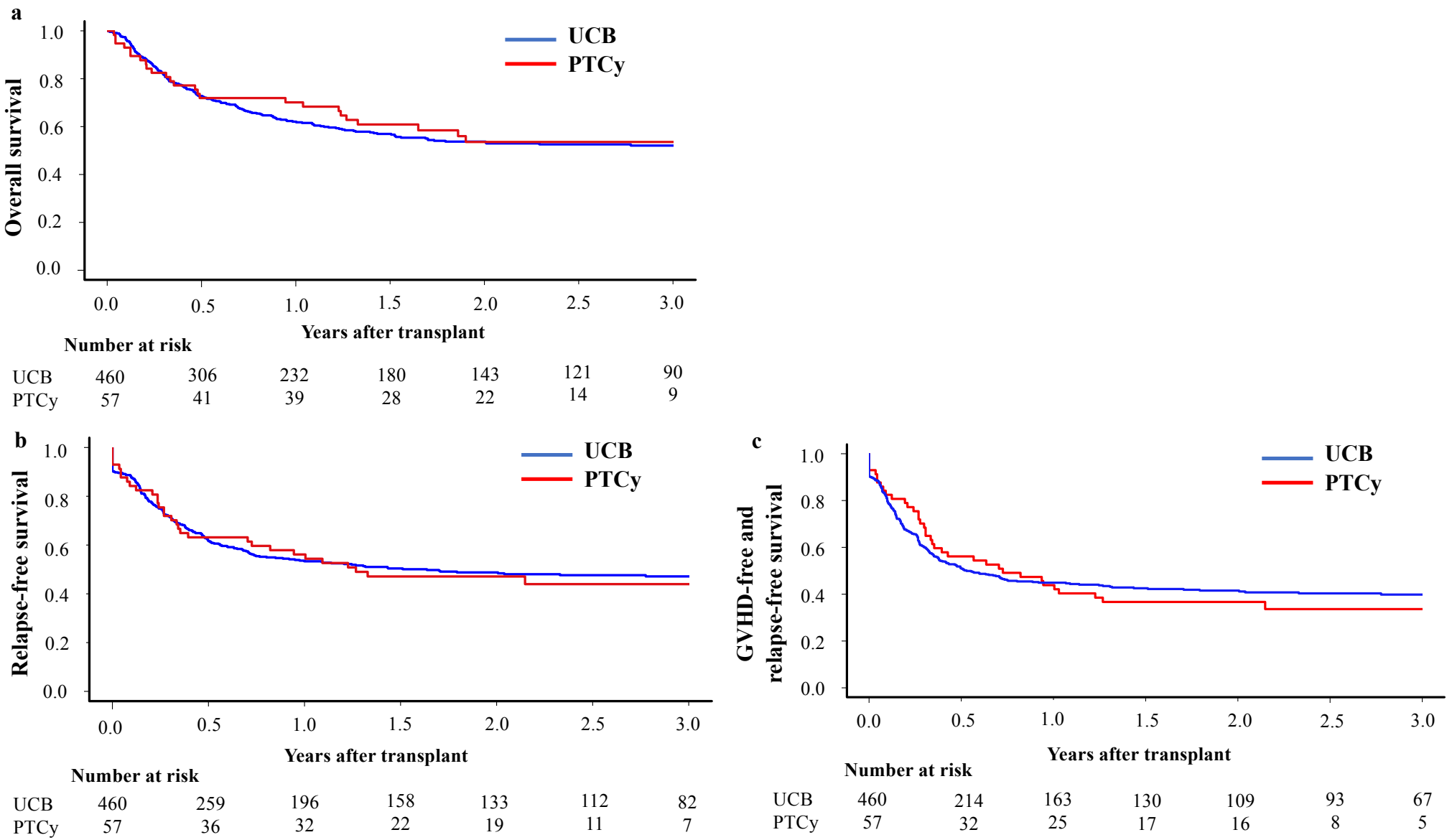

Figure3

Fig. 3

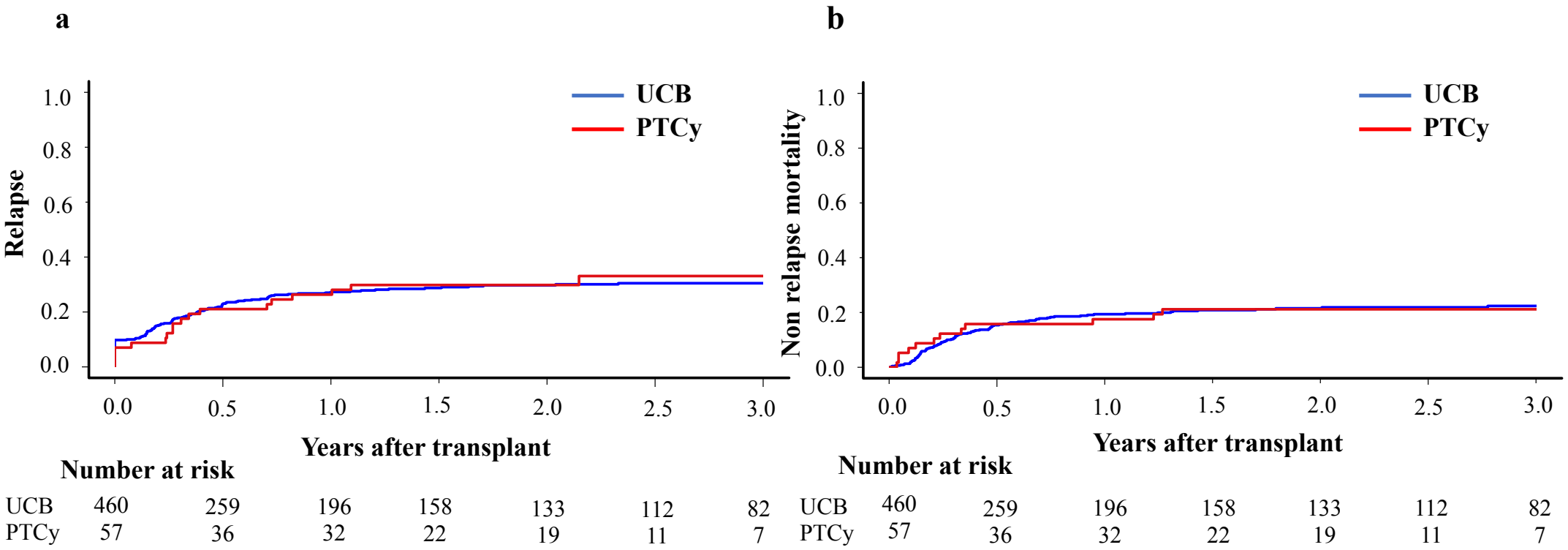

Figure4

Fig. 4

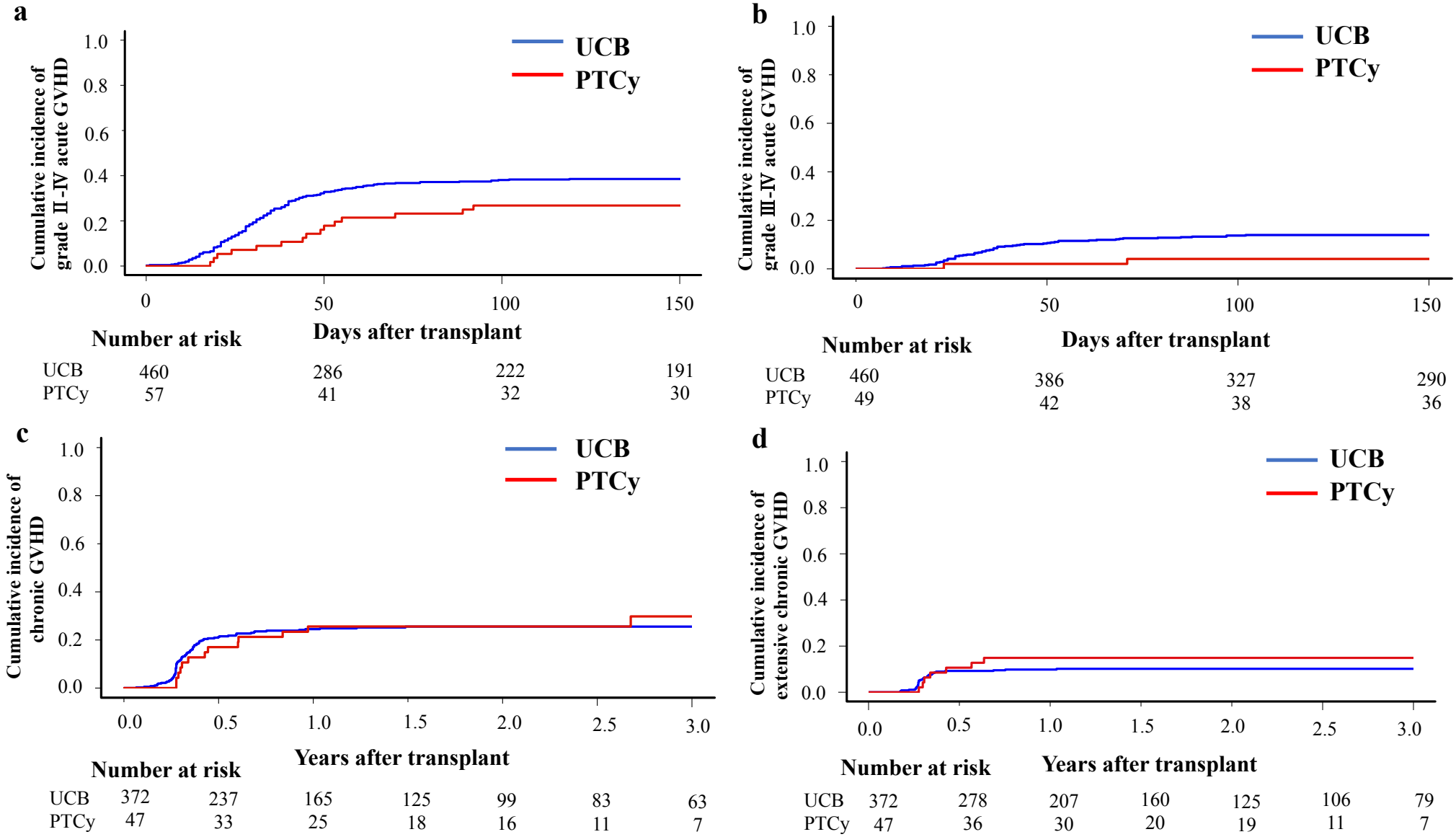

Figure5

Fig. 5