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ORIGINAL ARTICLE

Delayed platelet recovery after allogeneic transplantation: a predictor of increased treatment-related mortality and poorer survival

P Ramírez, CG Brunstein, B Miller, T DeFor and D Weisdorf

Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, MN, USA

Delayed platelet recovery (DPR) is common after allo-SCT. Insufficient data on risk factors and association with OS and TRM are available. We conducted a retrospective analysis of all allografts at the University of Minnesota between 2000 and 2005 to characterize the frequency of DPR (platelets $<50\,000/\mu L$ by day 60), risk factors and related complications. A total of 850 patients with hematological malignancies and benign disorders were included. Myeloablative (MA) conditioning was used in 65% of the patients and 45% received umbilical cord blood (UCB) grafts. The 60-day cumulative incidence of platelet recovery was 40% in UCB, 57% in unrelated donor (URD) and 74% in sibling donor. Multivariate analysis confirmed that the variables associated with DPR were MA (versus reduced intensity) conditioning, graft source other than sibling donor, ABO major mismatch, recipient CMV-positive serostatus, the presence of grade II–IV acute GVHD and slower neutrophil recovery. These data demonstrate that DPR is frequent after allogeneic hematopoietic cell transplantation, especially after UCB. DPR is a significant independent risk factor for increased TRM and poorer OS along with HLA-mismatched URD, but not UCB, grade II–IV acute GVHD, old age and advanced disease stage.
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Introduction

Thrombocytopenia after hematopoietic cell transplantation (HCT) is a common complication, described in 5–37% of the recipients.[1] The main causes are (a) decreased BM production due to low numbers of infused cells, relapsed disease, marrow fibrosis, graft-vs-stroma effect and drug-induced marrow inhibition, and (b) increased platelet destruction associated with GVHD, sinusoidal obstructive syndrome and infections.[2]

HCT has become a standard treatment for a number of malignant and non-malignant diseases.[3–7] In spite of prompt neutrophil recovery after allogeneic HCT, studies reporting delayed platelet recovery (DPR) have suggested that the source and dose of stem cells,[8,9] CMV serostatus,[10] diagnosis[2] and HLA disparity[11] are risk factors for DPR, but the biological reasons for this dichotomy are still unclear. Moreover, it has been suggested that those patients with DPR have inferior outcomes.[11,12]

We analyzed the incidence of DPR in a cohort of patients undergoing allogeneic HCT using either related or unrelated adult donor (URD) and unrelated umbilical cord blood (UCB) grafts to identify risk factors and to determine if the time-to-platelet recovery was associated with OS and TRM.

Patients and methods

Patients

In this retrospective study, 850 consecutive patients who underwent allogeneic HCT at the University of Minnesota between 2000 and 2005 for malignant and non-malignant diseases were included. Patient demographics, laboratory data and clinical outcomes were obtained from the University of Minnesota Bone Marrow Transplant Database. In order to estimate the impact of DPR on OS and TRM (beyond day 60) after allografting, patients with primary or secondary graft failure ($n=62$), patients who died before platelet recovery ($n=87$) and patients who underwent second transplant without previous platelet recovery ($n=1$) were excluded.

Definitions

Platelet recovery was defined as the first of three untransfused platelet counts greater than $50\,000/\mu L$ over 7 days with rising counts during the week. DPR was defined as patients who did not have platelet counts $>50\,000/\mu L$ by day 60 to avoid confounding by early death or graft failure. Patients who died before day 60 or had graft failure without platelet recovery were scored as having no platelet recovery, but were excluded from correlations with later events to focus our analysis on the impact of engraftment,

Correspondence: Dr D Weisdorf, Blood and Marrow Transplant Program, University of Minnesota, Mayo Mail Code 480, 420 Delaware Street SE, Minneapolis, MN, USA.
E-mail: weisd001@umn.edu
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but with impaired thrombopoiesis on later outcomes. Secondary graft failure was also excluded ($n=4$).

Hematological malignancies were stratified into early, intermediate and advanced disease groups. Early group included chronic myeloid leukemia in chronic phase, CLL Rai 0-II or Binet A and B, lymphomas, and acute leukemias in first and second CR. Intermediate group included chronic myeloid leukemia in accelerated phase, CLL Rai stage III and IV, or Binet stage C, lymphomas, acute leukemias and other malignancies with primary induction failure yet chemotherapy sensitive, and those with partial response or myelodysplasia. Advanced group included diseases resistant to chemotherapy and progressive disease.

Statistical analysis

The major end point of this study was early platelet recovery by day 60. Other end points included OS and TRM. Cumulative incidence was used to estimate the probability of platelet recovery by day 60, treating relapse, subsequent transplants or early mortality as competing risks. Cumulative incidence was also used to estimate TRM treating relapse as a competing risk.[13] Kaplan–Meier curves were used to estimate the probabilities of OS.[14]

Fine and Gray competing hazards regression analysis was used to assess the independent effect of factors on platelet recovery as well as TRM.[15] Cox regression analysis was used to assess the effect of factors on OS,[16] along with a complementary analysis including platelet recovery as a time-dependent variable. Factors evaluated in the regression models included donor type (matched sibling versus URD matched versus URD mismatched versus single UCB versus double UCB), recipient CMV serostatus, time to neutrophil recovery, age (<35 versus $\geqslant 35$), disease stage (non-malignant versus early versus intermediate versus advanced), conditioning (myeloablative (MA) versus reduced intensity conditioning (RIC), acute GVHD (0–I versus II–IV), ABO match (match versus minor mismatch versus major mismatch) and gender match (match versus mismatch). GVHD prophylaxis, which was confounded by its assignment by graft source, was not analyzed separately. For TRM and OS beyond day 60, platelet status (early versus late recovery) was also considered. Patient and transplant characteristics were compared across donor type. Statistical comparison of continuous factors was performed by the Kruskal–Wallis test. Differences in categorical factors between subgroups were tested using the chi-square or Fisher's exact test.[17]

Table 1 Patients and transplant characteristics

Factors	*Sibling* n *(%)*	*URD* n *(%)*	*UCB* n *(%)*	P
Total	312	145	393	
Age at transplant				
Median (range)	42 (0.4–69)	14 (0.8–62)	24 (0.2–69)	<0.01
Graft type				
BM	76 (24%)	137 (94%)	0	
PBSC	236 (76%)	8 (6%)	0	
Cord	0	0	393 (100%)	
Single			187	
Double			206	
Cell dose infused ($\times 10^8$/kg)				<0.01
Median (range)	7.4 (0.04–27.2)	1.4 (0.01–86.8)	Single 0.4 (0.1–2.7) Double 0.2 (0.1–2.5)	
Diagnosis				<0.01
Aplastic anemia/FA	20 (6%)	44 (30%)	25 (6%)	
Non-malignancies	23 (8%)	40 (28%)	64 (16%)	
Leukemia	166 (53%)	46 (32%)	236 (60%)	
Lymphoma	78 (25%)	12 (8%)	59 (15%)	
Other malignancies	25 (8%)	3 (2%)	9 (2%)	
Preparative regimen				<0.01
Myeloablative	204 (65%)	117 (81%)	234 (60%)	
Reduced intensity	108 (35%)	28 (19%)	159 (40%)	
GVHD prophylaxis				<0.01
CSA/MMF	109 (35%)	31 (21%)	268 (68%)	
CSA/MPD ± ATG	3 (1%)	1 (1%)	108 (27%)	
MTX/CSA	173 (55%)	28 (19%)	1 (<1%)	
T cell deplete	14 (5)	79 (55%)	0	
Other	13 (4%)	6 (4%)	16 (4%)	
ABO match				<0.01
Match	209 (67%)	54 (37%)	106 (27%)	
Minor mismatch	37 (12%)	39 (27%)	116 (30%)	
Major mismatch	64 (21%)	51 (35%)	169 (43%)	
Unknown	2 (1%)	1 (1%)	2 (1%)	
Recipient CMV serostatus				0.08
Negative	156 (50%)	86 (59%)	201 (51%)	
Positive	152 (49%)	55 (38%)	190 (48%)	
Unknown	4 (1%)	4 (3%)	2 (1%)	
Disease stage				<0.01
Non-malignant	43 (14%)	84 (58%)	89 (23%)	
Early	123 (39%)	25 (17%)	170 (43%)	
Intermediate	89 (29%)	28 (19%)	78 (20%)	
Advanced	57 (18%)	8 (6%)	56 (14%)	

Abbreviations: ATG = anti-thymocyte globulin; CI = confidence interval; FA = Fanconi anemia; MPD = methylprednisolone; MMF = mycophenolate mofetil.

Results

Patient, graft and transplant characteristics

Between January 2000 and December 2005, 850 patients underwent allogeneic HCT at the University of Minnesota. Patient, graft and transplant characteristics are summarized in Table 1.

Most commonly used regimens included MA: CY/1320 cGy TBI ± anti-thymocyte globulin (Cy/TBI ± ATG) ($n=259$, 30%), BU/CY ± ATG (Bu/Cy ± ATG) ($n=104$, 12%) and RIC: CY/Fludarabine/200 cGy TBR ± ATG (Cy/Flu/TBI ± ATG) ($n=207$, 24%).

Platelet engraftment

Of 850 patients, 475 had platelet recovery over 50 000/μL by day 60 for a cumulative incidence of 56% (CI 53–59%). In this early-recovery group, the median time to platelet

recovery was 45 days for UCB (range 1–59), 32 days for URD marrow (range 17–55), 17 days for URD peripheral blood mobilized stem cells (PBSCs) (range 13–45), 32 days for sibling marrow (range 19–45) and 20 days for sibling PBSCs (range 1–50). The T-depletion group had a 51% platelet recovery rate (CI 39–63%). The T-replete group had a 60% platelet recovery rate (CI 46–74%), $P = 0.08$.

In univariate analysis, platelet recovery was found to be influenced by age, diagnosis, conditioning regimen intensity, donor type and HLA match, CMV serostatus of the recipient, gender match between donor and recipient, presence of grade II–IV acute GVHD and ABO match between donor and recipient (Table 2). In multivariate analysis, MA conditioning, unrelated grafts (both UCB and volunteer URD donors), CMV-seropositive recipients, presence of major ABO mismatch and development of acute grade II–IV GVHD were all significant predictors of DPR (Table 3). Among patients with neutrophil engraftment, quicker neutrophil recovery (before 15 days) was associated with a greater likelihood of platelet recovery by day 60 (72% (CI 66–78%)) versus slower neutrophil recovery (after day 15) (47% (CI 42–52%), $P < 0.01$). Other potential confounders such as infection with human herpesvirus 6 were not included in the model as it is generally tested only in cases of delayed engraftment after UCB transplantation and thus its analysis would be confounded by ascertainment bias.

Platelet recovery was influenced by both the conditioning intensity and the graft source. We observed a 60-day cumulative incidence of platelet recovery for sibling RIC of 86% (CI 76–96%), sibling MA of 69% (CI 61–77%), URD RIC of 64% (CI 44–84%), URD MA of 55% (CI 46–65%), UCB RIC of 47% (CI 39–55%) and UCB MA of 35% (CI 29–47%) (Figure 1a). In addition, analysis by donor type and graft source showed that sibling donor recipients had the most frequent platelet recovery (75% at 60 days), with no observed differences between BM 75% (CI 62–88%) and PBSC 75% (CI 67–83%). Within the PBSC subgroup, RIC was still associated with a significantly better platelet recovery (88% (CI 78–97%)) compared with MA conditioning (67% (CI 57–77%), $P < 0.01$). URD had 55% (CI 46–64%) platelet recovery by day 60 after BM and 88% (CI 59–100%) after PBSC. In contrast, UCB had the lowest platelet recovery by day 60 with a cumulative incidence of 40% (CI 35–45%) (Figure 1b), which did not differ between UCB grafts containing either one or two UCB units (39% (CI 31–47%) versus 40% (CI 32–48%), respectively, $P = 0.89$).

Table 2 Platelet recovery by day 60, based on univariate analysis

Factor	n	*No. recovered*	*Platelet recovery at 60 days (95% CI)*	P
Overall	850	475	56% (53–59%)	
Age				<0.01
<35	462	231	50% (45–55%)	
⩾35	388	244	63% (37–70%)	
Diagnosis				<0.01
AA	89	54	61% (51–71%)	
Non-Malignant	127	58	46% (38–54%)	
Leukemia	448	240	54% (50–58%)	
Lymphoma	149	97	65% (58–72%)	
Other Malignancy	37	26	70% (55–85%)	
Conditioning				<0.01
Reduced intensity	295	185	63% (58–68%)	
Myeloablative	555	290	52% (48–56%)	
Graft type				<0.01
UCB single	180	71	39% (31–47%)	
UCB double	206	83	40% (32–48%)	
URD marrow	137	75	55% (46–64%)	
URD PBSC	8	7	88% (59–100%)	
Sibling Marrow	76	57	75% (62–88%)	
Sibling PBSC	236	178	75% (67–83%)	
Graft type and HLA match				<0.01
UCB	386	154	40% (35–45%)	
URD HLA match	117	66	56% (51–61%)	
URD mismatch	28	16	57% (36–78%)	
Sibling	319	239	75% (62–88%)	
Days to neutrophil recovery[a]				<0.01
⩽15 days	412	297	72% (66–78%)	
>15 days	382	178	47% (42–52%)	
Gender match				<0.01
Match	366	232	63% (59–67%)	
Mismatch	484	243	50% (46–54%)	
Recipient CMV serostatus				0.03
Negative	443	264	59% (55–63%)	
Positive	397	206	52% (48–56%)	
ABO match				<0.01
Match	369	241	65% (61–69%)	
Minor mismatch	192	96	50% (43–57%)	
Major mismatch	284	134	47% (41–53%)	
Grade II–IV acute GVHD				<0.01
No	622	378	61% (57–65%)	
Yes	228	97	43% (37–49%)	

Abbreviation: AA = aplastic anemia.
[a]Among patients with neutrophil engraftment.

Impact of DPR on survival and TRM

DPR adversely impacted both TRM and OS. One-year OS for the 475 patients who achieved platelet recovery by day 60 was 77% (CI 73–81%) as compared with 59% (CI 53–65%) for those who did not ($P < 0.01$) (Figure 2a). TRM at 1 year was 11% (CI 8–14%) in patients who achieved early platelet recovery versus 30% (CI 24–36%) for those who did not ($P < 0.01$) (Figure 2b). The most frequent causes of death in the early-recovery group were disease recurrence ($n = 67$, 61%), GVHD ($n = 12$, 11%), infections ($n = 11$, 10%) and organ failure ($n = 4$, 4%). In the delayed-recovery group, causes of death were more often due to non-relapse causes and included disease recurrence ($n = 32$, 31%), GVHD ($n = 19$, 20%), infections ($n = 22$, 23%) and organ failure ($n = 18$, 19%). Neither thrombocytopenia nor bleeding was the cause of death in either group.

Multivariate analysis for survival identified DPR, URD mismatch (but not URD match or UCB), disease stage and grade II–IV acute GVHD, each as significant predictors of decreased survival (Table 4). A complementary

multivariate analysis considering platelet recovery as a time-dependent covariate confirmed the significant adverse impact of DPR on OS (RR 3.7, CI 2.8–4.9, $P<0.01$). Multivariate analysis of TRM identified DPR, URD mismatch, recipient age >35 and grade II–IV acute GVHD as significant predictors of increased TRM (Table 4). Time to neutrophil recovery or conditioning intensity did not significantly influence 12-month TRM.

Table 3 Multivariate analysis of platelet recovery

Factor	*Relative risk of delayed platelet recovery (95% CI)*	P
Conditioning		
Myeloablative*	1.0	
Reduced intensity	0.5 (1.6–3.3)	<0.01
Donor type		
Sibling*	1.0	
UCB: single	3.3 (2.8–5.0)	<0.01
UCB: double	3.3 (2.5–5.0)	<0.01
URD match	2.0 (1.4–2.5)	<0.01
URD mismatch	2.0 (1.1–3.3)	0.02
CMV Serostatus		
Negative*	1.0	
Positive	1.3 (1.0–1.6)	0.03
ABO match		
Match*	1.0	
Minor mismatch	1.1 (0.8–1.4)	0.37
Major mismatch	1.3 (1.1–1.6)	0.04
Acute GVHD		
Grade 0–I	1.0	
Grade II–IV	1.6 (1.2–2.0)	<0.01

Abbreviation: CI = confidence interval.
*Reference group.

Discussion

This study demonstrates that DPR is a frequent problem after allogeneic HCT and is somewhat more common after UCB transplantation. Overall, 32% of all patients, but 60% of UCB recipients had DPR. This complication is clinically relevant and is associated with increased TRM and decreased OS. Interestingly, none of the patients with DPR died due to hemorrhagic complications.

In examining the confounding influences of donor type and graft source, we observed that similarly to other series comparing sibling and URD PBSC with BM,[8,18,19] in both sibling and URD, PBSC was associated with a faster median time to platelet recovery compared with BM. Interestingly, despite the faster median recovery time, we did not observe differences in the 60-day cumulative incidence of platelet recovery between sibling PBSC and BM. In URD, more complete platelet recovery after PBSC over BM grafts was possibly related to the small number of patients receiving PBSC ($n=8$) compared with BM ($n=137$). In the UCB setting, several small case series and registry data have also documented DPR, but the specific reasons for this finding are still unclear.[20–25] Platelet recovery was similar in recipients of single versus double UCB HCT. Our data suggest that two UCB grafts do not compromise stem cell homing and engraftment as shown by similar rates of platelet recovery and neutrophil engraftment. Double UCB transplantation is associated with prompt hematologic recovery,[25] and more recently we have reported its association with improved leukemia control.[26]

Factors influencing platelet recovery found in the multivariate model included conditioning intensity, CMV serostatus, major ABO incompatibility and the presence of grade II–IV acute GVHD. These factors have been previously described in adult donors and UCB transplant series.[10,11,27–30] Another finding was the direct correlation

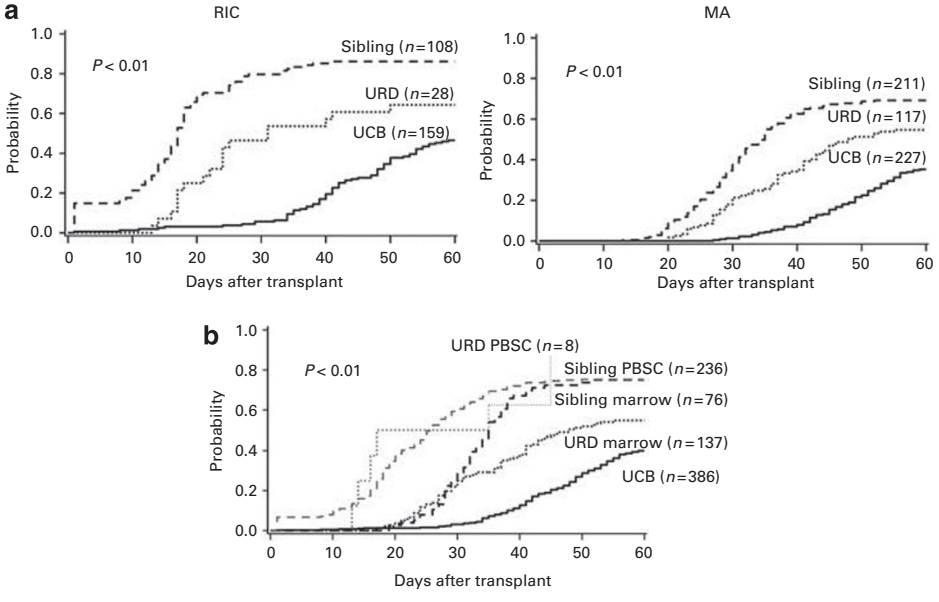

Figure 1 Platelet recovery by (**a**) conditioning regimen intensity and graft source and by (**b**) donor and graft source. (**a**) Engraftment probability of sibling donors (dashed line), URD (dotted line) and UCB (solid line). (**b**) Engraftment probability of UCB (continuous line), URD marrow (dotted black line), URD PBSCs (gray dotted line), sibling marrow (black dashed line) and sibling PBSC (gray dashed line).

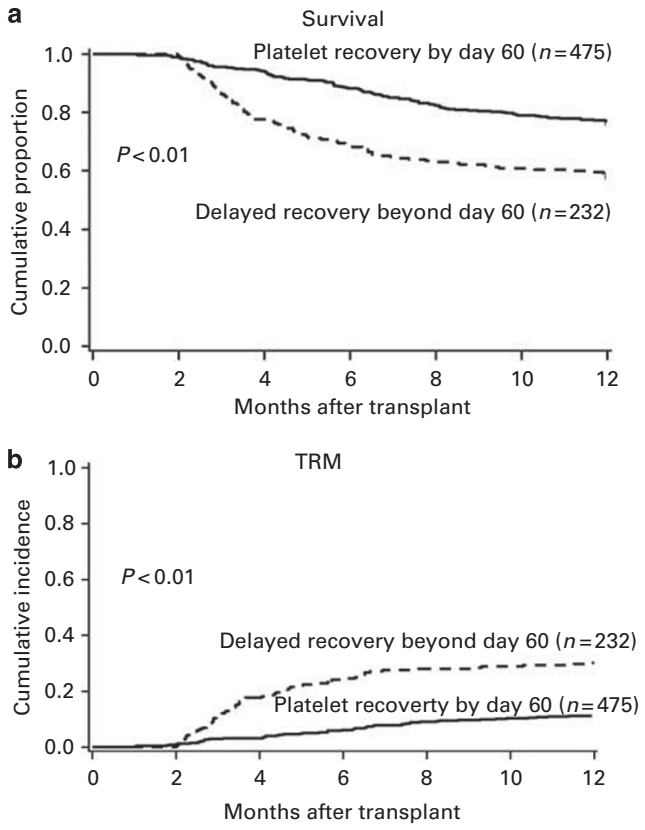

Figure 2 (**a**) Survival and (**b**) TRM by platelet recovery status. Probability of outcome in the early-recovery group (solid line) and delayed-recovery group (dashed line).

between the speed of neutrophil and platelet recovery, which suggests biological dependence between these two variables.

Multivariate analysis confirmed that DPR led to higher TRM and poorer survival. Despite the somewhat lower platelet recovery by day 60 after UCB compared with sibling donors, UCB was not independently associated with either inferior OS or increased TRM. Survival and TRM after UCB HCT were slightly better than even sibling donor grafts. The reasons for this finding are unclear, but the lower risk of chronic GVHD following UCB grafts in comparison with other hematopoietic stem cell sources may explain, at least in part, these encouraging outcomes.[25,31,32] Cox regression analysis including platelet recovery as a time-dependent variable confirmed the adverse impact on OS although when using this modeling approach, early death is included in failure of platelet recovery.

The analysis also showed that the conditioning intensity was directly correlated with platelet recovery independent of the stem cell source. MA conditioning was associated with slower recovery compared with RIC.[33,34] The reasons for this finding are uncertain, but could be related to persistent recipient hematopoiesis after RIC that subsequently is displaced by the donor HSC. Additionally, a lower incidence of acute GVHD after RIC compared with MA conditioning could partially explain the observed superior platelet recovery.[35]

Table 4 Multivariate analysis of survival and TRM

Factor	*Relative risk of death (95% CI)*	P
Survival at 1 year		
Platelet recovery		
By day 60*	1.0	<0.01
Delayed beyond day 60	2.7 (1.9–3.7)	
Conditioning		
Myeloablative*	1.0	
Reduced intensity	1.0 (0.9–1.1)	0.26
Donor type		
Sibling*	1.0	
UCB	0.8 (0.5–1.1)	0.12
URD match	0.9 (0.6–1.5)	0.74
URD mismatch	2.5 (1.3–4.8)	<0.01
Disease stage		
Non-malignant*	1.0	
Early	1.1 (0.8–1.7)	0.54
Intermediate	1.7 (1.1–2.6)	0.02
Advanced	1.7 (1.0–2.8)	0.04
Acute GVHD		
Grade 0–I	1.0	
Grade II–IV	1.4 (1.0–1.9)	0.03
TRM at 1 year		
Platelet recovery		
By day 60*	1.0	
Delayed beyond day 60	2.7 (2.0–3.8)	<0.01
Conditioning		
Myeloablative*	1.0	
Reduced intensity	1.1 (0.8–1.6)	0.57
Donor type		
Sibling*	1.0	
UCB	0.7 (0.5–1.1)	0.11
URD match	1.0 (0.6–1.5)	0.87
URD mismatch	2.6 (1.4–4.9)	<0.01
Recipient age		
<35 years	1.0	
⩾35 years	1.6 (1.0–2.3)	<0.01
Acute GVHD		
Grade 0–I	1.0	
Grade II–IV	1.4 (1.1–1.9)	0.02

Abbreviation: CI = confidence interval.
*Reference group.

Ongoing evaluation for the consequences of DPR needs further investigation and perhaps greater recognition as a marker for late adverse complications of HCT.

Conflict of interest

The authors declare no conflict of interest.

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