Pre-transplant prognostic factors of long-term survival after allogeneic peripheral blood stem cell transplantation with matched related/unrelated donors

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ABSTRACT

Mobilized peripheral blood has become the predominant stem cell source for allogeneic hematopoietic cell transplantation. In this retrospective single center study of 442 patients with hematologic malignancies, we analyzed prognostic factors for long-term survival after peripheral blood stem cell transplantation from HLA-matched related or unrelated donors. To account for disease/status heterogeneity, patients were risk-stratified according to the Disease Risk Index. Five-year overall survival was similar after transplants with matched related and unrelated donors (45% and 46%, respectively; *P*=0.49). Because donor age ≥60 years impacted outcome during model building, we further considered 3 groups of donors: matched unrelated (aged <60 years by definition), matched related aged <60 years and matched related aged ≥60 years. In multivariate analysis, the donor type/age group and the graft $CD34^+$ and $CD3^+$ cell doses impacted long-term survival. Compared with matched unrelated donor transplant, transplant from matched related donor <60 years resulted in similar long-term survival (*P*=0.67) while transplant from matched related donor ≥60 years was associated with higher risks for late mortality (hazard ratio (HR) 4.41; *P*=0.006) and treatment failure (HR: 6.33; *P*=0.009). Lower mortality risks were observed after transplant with $CD34^+$ cell dose more than $4.5x10^6$/kg (HR: 0.56; *P*=0.002) and $CD3^+$ cell dose more than $3x10^8$/kg (HR: 0.61; *P*=0.01). The Disease Risk Index failed to predict survival. We built an "adapted Disease Risk Index" by modifying risks for myeloproliferative neoplasms and multiple myeloma that improved stratification ability for progression-free survival (*P*=0.04) but not for overall survival (*P*=0.82).

Introduction

Over the past decade, mobilized peripheral blood (PB) has progressively overtaken bone marrow as source of stem cells for allogeneic hematopoietic stem cell transplantation (HSCT).[1] This was supported by evidence of faster engraftment,[2-5] decreased relapse in high-risk patients[6] and, for some authors, better survival after PB-HSCT. However, higher risks for chronic graft-*versus*-host disease (GVHD) associated with PB-HSCT are of particular concern. Despite this, the number of PB-HSCT is still increasing.[7]

Human leukocyte antigen (HLA)-matched unrelated donor (MUD) is now a widely accepted alternative donor source when no suitable HLA-matched related donor (MRD) is available. Outcome after MUD-HSCT has dramatically improved over the past 20 years, mainly due to the advent of high resolution allelic level HLA typing techniques.[8] Most US centers consider donor/recipient allelic matching at HLA-A, -B, -C and -DRB1 loci for MUD selection (8/8 MUD) while many European centers also further search for allelic identity at the HLA-DQB1 locus (10/10 MUD). Several prospective and large retrospective studies have reported current similar survival after MUD-HSCT compared to MRD-HSCT for patients with hematologic malignancies.[9-13] However, few studies have considered PB as the sole stem cell source and 10/10 allelic level HLA-matched donor/recipient pairs for MUD-HSCT.

Regardless of donor type, other pre-transplant factors may impact survival after PB-HSCT. Identification of clinical predictors of long-term success of PB-HSCT is important for patient counseling and clinical trial design. Recently, Armand *et al.* have proposed a new tool for risk-stratifying patients with respect to overall survival (OS) and progression-free survival (PFS) on the basis of disease diagnoses and stages at the time of HSCT: the Disease Risk Index (DRI).[14] This index was applicable regardless of conditioning intensity. Although Armand *et al.* validated this index in an independent cohort, DRI needs to be further tested in other independent populations.

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Here, we report a large single center retrospective study of PB-HSCT with MRD or 10/10 MUD in patients with hematologic malignancies. To account for disease/status heterogeneity, patients were stratified for disease risk according to the DRI. The aims of this study were: 1) to evaluate how donor type (MRD vs. MUD) and other pre-transplant factors may predict for long-term OS and PFS after PB-HSCT; and 2) to evaluate DRI as a predictor for OS and PFS.

Methods

Patients

We performed a retrospective analysis of all consecutive patients with hematologic malignancies who underwent a first PB-HSCT from either MRD or MUD at Saint-Louis Hospital (Paris, France) between January 2000 and December 2010. According to institutional guidelines, MRD was considered as the first donor choice and search for MUD was only undertaken if no suitable MRD was identified. For MUD PB-HSCT, only donor/recipient pairs matched at the allelic level at HLA-A, -B, -C, -DRB1 and -DQB1 loci (10/10 HLA-matched) were included. Data concerning pre-transplant characteristics and transplant outcomes were extracted from our transplantation database. To assess for pre-transplant comorbidities, the hematopoietic cell transplantation-specific comorbidity index (HCT-CI)[15] was retrospectively calculated for patients transplanted between 2006 and 2010 (*Online Supplementary Methods*). All patients provided written informed consent for use of protected health data for research, in accordance with the Declaration of Helsinki.

Disease risk at transplant

Disease risk was retrospectively assessed according to disease diagnosis and disease stage at the time of HSCT, using the DRI.[14] In the original paper, diseases underrepresented in the training cohort were randomly assigned into the intermediate disease type risk category (first step of DRI building). These included myeloproliferative neoplasms (MPN) and multiple myeloma (MM). We, therefore, built an adapted DRI in which both of these diseases were assigned risks according to their observed outcomes and we compared it with the original DRI.

Definitions and study end points

Definitions for transplant modalities and outcomes are available in the *Online Supplementary Methods*. End points of the study were OS and PFS. To assess long-term outcome after HSCT, we also studied relapse, non-relapse mortality (NRM) and chronic GVHD.

Statistical methods

Characteristics of patients transplanted from MRD or MUD were compared using Wilcoxon rank sum tests and Fisher exact tests. Outcomes were censored at 60 months, given the study follow up. Relapse and NRM were considered to be mutually competing risks. OS was estimated using the Kaplan-Meier product-limit estimator. For competing risks analyses, cumulative incidence functions were estimated using the usual methodology.[16]

Factors associated with outcomes were analyzed using proportional hazards models for the cause-specific hazard (chronic GVHD, relapse and NRM)[17] and Cox proportional hazards models (PFS and OS). Tested variables (only pre-transplant parameters) are listed in the *Online Supplementary Methods*. The proportional hazards assumption was checked by examination of Schoenfeld residuals and the Grambsch and Therneau lack-of-fit test.[18] For multivariate analysis, all variables achieving $P<0.25$ in univariate analysis were considered. No backward variable elimination procedure was used. The usual 'rule of thumb' of 10 events per variable was not enforced but we ensured the models had no less than 5 events per variable as this has been shown to yield similar properties.[19] All tests were two-sided and $P\leq0.05$ was considered significant.

Stratification ability of DRIs was evaluated by the C-statistic. Comparison of DRIs involved testing of null differences between C-indexes, integrated discrimination improvement index (IDI) and continuous net reclassification index (NRI).[22-25]

Analyses were performed using the R-statistical software version 2.15.0.[26]

Results

Study patients

A total of 442 patients were included. Base-line characteristics are summarized in Table 1. Overall, 278 patients were transplanted from MRD and 164 from MUD. MUD and MRD cohorts were balanced for patient age, disease distribution, DRI and intensity of the conditioning regimen.

Median follow-up time after transplant was 36 months with 25% of patients being followed for at least 60 months. The 5-year OS was 45% (95% confidence interval (CI): 35-57) and 46% (95%CI: 39-54) (P=0.49); PFS was 43% (95%CI: 34-54) and 39% (95%CI: 32-46) (P=0.72); and NRM was 33% (95%CI: 24-42) and 22% (95%CI: 17-27) (P=0.071) after MUD and MRD PB-HSCT, respectively. In the MUD cohort, the most frequent primary cause of death was HSCT-related (65%) while relapse accounted for 31%. In the MRD cohort, relapse accounted for 50% of primary cause of death. The 5-year cumulative incidence (CIf) of relapse was lower after MUD transplant (24%, 95%CI: 17-32%) than after MRD transplant (39%, 95%CI: 32-46%) (P=0.038). The 5-year CIf of chronic GVHD was 59% (95% CI: 50-67%) and 58% (95%CI: 51-64%) after MUD and MRD PB-HSCT, respectively (P=0.26).

Impact of pre-transplant factors on overall and progression-free survival

Univariate analysis (Online Supplementary Table S1). Donor type (MRD *vs.* MUD) was not associated with survival. Factors that impacted survival were older donor age (≥60 years), graft $CD34^+$ and $CD3^+$ cell doses, DRI and recipient age. As almost all donors ≥60 years old were MRD (except 1 MUD aged 60 years), 3 groups of donors according to type and age (MUD, MRD<60y and MRD≥60y) were further defined. Patients transplanted with MRD≥60y experienced low 5-year OS (6%, standard error 6%) (Figure 1A) and relapse accounted for 68% of their cause of death. Characteristics of patients transplanted with MRD≥60y are provided in the *Online Supplementary Table S2*. DRI did not fully stratify patients for OS and PFS as no significant difference was observed for patients with low, intermediate and high DRI (Figure 2A and B).

Multivariate analysis. Variables significantly impacting OS and PFS were the donor type/age group and graft $CD34^+$ and $CD3^+$ cell doses (Table 2). Compared with MUD-PB-HSCT, PB-HSCT with MRD<60y resulted in similar risks for late mortality and treatment failure while PB-HSCT with MRD≥60y was associated with higher risks for late overall mortality and treatment failure (from

18 and 9 months post-transplant, respectively). Regardless of donor source, high graft CD34+ and CD3+ cell doses significantly predicted lower risks for mortality and treatment failure. DRI only predicted survival for patients within the very high risk category. Higher recipient age was associated with increased hazard ratio for mortality risks, but the correlation did not remain significant.

Relapse, non-relapse mortality and chronic graft-versus-host disease

We further evaluated how these pre-transplant predictors of OS and PFS impacted other long-term outcomes (Table 2 and *Online Supplementary Table S1*).

Donor type and age. When considering donor type/age groups, we observed that patients transplanted with MRD≥60y experienced a high relapse rate (Figure 1B). In multivariate analysis, PB-HSCT with MRD≥60y resulted in higher risks for relapse, lower risks for chronic GVHD and a trend of lower NRM as compared with MUD PB-HSCT.

Graft cell doses. In both univariate and multivariate analyses, high CD34+ and CD3+ cell doses predicted lower NRM.

DRI. DRI stratified relapse for patients with low and very high DRI (Figure 2C) in univariate analysis but only for patients with low DRI in multivariate analysis.

Subgroups analyses

Comorbidity. The HCT-CI[15] was calculated for 258 patients (86% of the patients transplanted after January 2006). We built a multivariate model for OS and PFS adjusted for HCT-CI in this subgroup (*Online Supplementary Table S3*). The donor type/age group remained significant for survival prediction. High CD34+ and CD3+ cell doses were associated with a trend of higher OS and PFS. The DRI only predicted survival for patients with very high DRI. The HCT-CI was not associated with survival in this subpopulation.

Older patients. The majority of patients transplanted

Table 1. Base-line patients', disease and transplant characteristics

Pre-transplant variable	Entire cohort (442) n. (%)*	MRD cohort (278) n. (%)*	MUD cohort (164) n. (%)*	P
Recipient age, median (range) years	48 (7-68)	49 (7-67)	46 (7-68)	0.23
<20	22 (5)	4 (1)	18 (11)	
20-29	52 (12)	32 (12)	20 (12)	
30-39	56 (13)	38 (14)	18 (11)	
40-49	113 (26)	76 (27)	37 (23)	
50-59	155 (35)	105 (38)	50 (30)	
≥ 60	44 (10)	23 (8)	21 (13)	
Male gender	277 (63)	170 (61)	107 (65)	0.42
Disease				0.23
AML	122 (27)	77 (28)	45 (27)	
MDS	60 (14)	39 (14)	21 (13)	
CML	18 (4)	11 (4)	7 (4)	
MPN	36 (8)	25 (9)	11 (7)	
ALL	40 (9)	20 (7)	20 (12)	
CLL	18 (4)	10 (4)	8 (5)	
NHL	62 (14)	40 (14)	22 (13)	
HD	29 (7)	18 (6)	11 (7)	
MM	57 (13)	38 (14)	19 (12)	
DRI§¥				0.48
Low	59 (13)	35 (13)	24 (15)	
Intermediate	279 (63)	174 (63)	105 (64)	
High	91 (21)	59 (21)	32 (20)	
Very high	12 (3)	10 (4)	2 (1)	
aDRI¥				0.33
Low	73 (17)	44 (16)	29 (18)	
Intermediate	236 (54)	148 (53)	88 (54)	
High	114 (26)	71 (26)	43 (26)	
Very high	18 (4)	15 (5)	3 (2)	
Conditioning regimen				0.60
MAC	138 (31)	84 (30)	54 (33)	
RIC	304 (69)	194 (70)	110 (67)	
GVHD prophylaxis				0.41
CyA + MTX	139 (31)	83 (30)	56 (34)	
CyA + MMF	220 (50)	138 (50)	82 (50)	
Other	83 (19)	57 (21)	26 (16)	
ATG‡	85 (19)	38 (14)	47 (29)	0.0002
Graft CD34+ cell dose, x10⁶/kg				
Median, range	7.2 (1.1-30)	7.0 (1.1-21.8)	7.4 (2.0-30.0)	0.025
< 4.5	78 (18)	54 (19)	24 (15)	
≥ 4.5	364 (82)	224 (81)	140 (85)	
Graft CD3+ cell dose, x10⁸/kg				
Median, range	2.5 (0.3-9.7)	2.4 (0.4-7.7)	2.7 (0.3-9.7)	0.021
Donor age, median (range) years	40 (18-72)	47 (18-72)	30 (18-61)	<0.0001
<30	117 (26)	35 (13)	82 (50)	
30-39	108 (24)	57 (21)	51 (31)	
40-49	100 (23)	72 (26)	28 (17)	
50-60	79 (18)	78 (28)	1 (1)	
≥60 #	37 (8)	36 (13)	1 (1)	
Donor/recipient gender				0.001
Female/male	113 (26)	82 (29)	31 (19)	
Other combinations	329 (74)	196 (71)	133 (81)	
Donor/recipient CMV status				<0.0001
Negative/Negative	118 (27)	62 (22)	56 (34)	
Negative/Positive	105 (24)	46 (17)	59 (36)	
Positive/Negative	64 (15)	47 (17)	17 (10)	
Positive/Positive	155 (35)	123 (44)	32 (20)	
Donor/recipient ABO match				0.003
Compatibility	253 (57)	176 (63)	77 (47)	
Major incompatibility¶	105 (24)	56 (20)	49 (30)	
Minor incompatibility	84 (19)	46 (17)	38 (23)	
HCT-CI†				0.14
0	37 (14)†	15 (10)†	22 (19)†	
1-2	70 (27)†	41 (28)†	29 (25)†	
≥3	151 (59)†	88 (61)†	63 (55)†	
FU, median (range) months	36 (2-133)	37 (2-133)	25 (3-105)	0.009

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*aDR: adapted Disease Risk Index; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ATG: antithymocyte globulin; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; CMV: cytomegalovirus; CyA: cyclosporine A; DRI: Disease Risk Index ; FU: follow up; GVHD: graft-versus-host disease; HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index; HD: Hodgkin disease; MAC: myeloablative conditioning; MDS: myelodysplastic syndrome; MM: multiple myeloma; MMF: mycophenolatemofetil; MPN: myeloproliferative neoplasm; MRD: matched related donor; MTX: methotrexate; MUD: matched unrelated donor; NHL: non-Hodgkin lymphoma; PB HSCT: peripheral blood stem cell transplantation; RIC: reduced-intensity conditioning. *Percentages may not add to 100 because of rounding. §Classified according to Armand et al.,[14]. ¥Not evaluable for 1 patient, in the MUD group (disease stage not reported). ‡Pre-transplant use of ATG, as part of conditioning regimen or for GVHD prophylaxis. #One MUD was aged of 60 years at the time of stem cell donation. ¶As they were rare in our cohort, bidirectional ABO incompatibility states were referred as major ABO incompatibility states. †As pre-transplant pulmonary function tests were not systematically performed before 2006 in our institution, the HCT-CI was only assessable for patients who underwent PB-HSCT after January 2006 (258 patients in the entire cohort: 144 in the MRD and 114 in the MUD cohorts, respectively).*

with MRD≥60 were ≥50 years old (30 of 36 patients) and were older than those transplanted from MUD or MRD<60y. We built a multivariate model for survival in a selected subgroup of 199 patients aged ≥50 years (71 patients transplanted with MUD, 98 with MRD<60 and 30 with MRD≥60) (*Online Supplementary Table S3*). As compared with MUD transplant, PB-HSCT with MRD≥60y was still associated with significantly higher risks for late treatment failure and a trend of higher risks for late overall mortality.

Adapted Disease Risk Index

In our study, Disease Risk Index was not fully predictive of either OS or PFS (Table 2, Figure 2A and B and *Online Supplementary Table S3*). In the original DRI publication, MPN and MM were randomly assigned into the intermediate disease type risk category.[14] When assessing both diseases, we observed that MPN and MM patients had respectively better and worse outcomes than patients assigned to the intermediate disease type risk category (*Online Supplementary Figure S1*). Therefore, we constructed an "adapted DRI (aDRI)" in which MPN and MM were respectively assigned to the low-risk category and to the high-risk category for disease type (first step of DRI assessment).

OS, PFS and cumulative incidence of relapse stratified by aDRI are shown in Figure 2 D-F. In our multivariate model, aDRI successfully stratified patients for relapse (P<0.05), correlated with PFS for patients with intermediate, high and very high aDRI (P<0.05), but was not predictive for OS (*Online Supplementary Table S4*). Stratification ability of DRI and aDRI for OS, PFS and relapse were finally assessed (Table 3). Compared with DRI, aDRI better stratified relapse and PFS but not OS.

Based on these results, previous multivariate analyses were verified using aDRI instead of DRI as candidate effects for adjustment. Similar correlations between risk factors and outcomes were observed as those reported above (*data not shown*).

Discussion

Identification of clinical predictors of long-term survival after HLA-matched PB-HSCT is a current major concern. Here, we reported a 10-year single center retrospective analysis of long-term OS and PFS after PB-HSCT from MRD or 10/10 MUD in patients with hematologic malignancies.

In accordance with previous studies reporting various graft sources,[9-13] we observed similar 5-year OS after transplant from MUD and MRD with PB as the unique stem cell source. By further considering MRD age, we observed that PB-HSCT from MUD and MRD<60y indeed resulted in similar long-term survival, whereas PB-HSCT with MRD≥60y was associated with notably poor long-term OS and PFS.

Though it has to be interpreted with caution due to small sample size, the poor long-term survival we observed for patients transplanted with MRD≥60y is intriguing. Several factors may have contributed to their lower survival as compared with patients transplanted from MUD. 1) Patients transplanted from MRD≥60y were older and we could not formally exclude that their older age might not have contributed to their lower OS and PFS. However, in a subgroup analysis of selected older recipients (≥50 years old), PB-HSCT from MRD≥60y remained associated with lower long-term survival. 2) Because they were older, patients transplanted with MRD≥60y might also have heavier comorbidities. However, transplant from MRD≥60y remained associated with lower survival after adjustment for HCT-CI in a sub-analysis of patients for whom this index was assessable. 3) A significant proportion of patients transplanted with MRD≥60y fell into the high or very high (a)DRI categories. However, higher risks for mortality were still observed after MRD≥60y-transplant after adjustment for DRI or aDRI in multivariate analysis. 4) Lower CD34$^+$ cell doses were collected

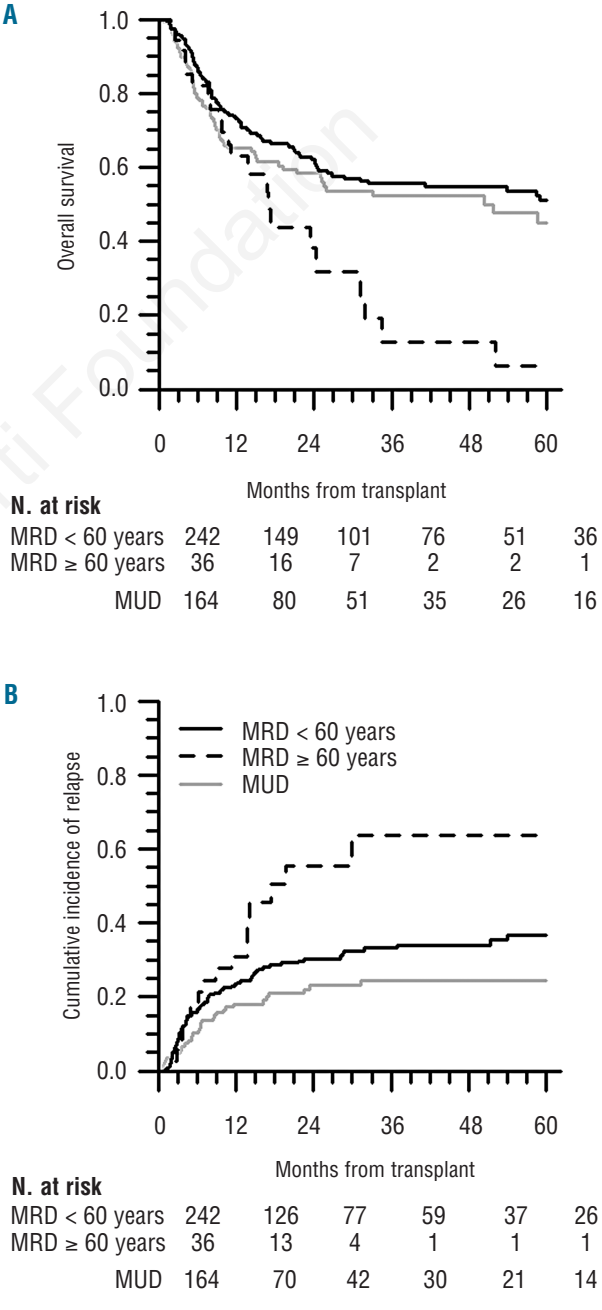

Figure 1. Outcomes according to donor type/age groups. OS (A) and cumulative incidence of relapse (B). For relapse, patients at risk were patients alive and relapse-free at each time.

from MRD≥60y. As CD34+ graft cell dose was associated with survival, this might have contributed to the lower OS and PFS observed after transplant with MRD≥60y.

The main cause of death of MRD≥60y recipients was relapse and relapse incidence was higher for these patients compared with MUD recipients. Lower risks for chronic GVHD were also observed after MRD≥60y-transplant compared with MUD-transplant. These results could not be explained by an ATG effect as MRD≥60y recipients did not receive ATG more frequently than MUD recipients, nor by the frequent use of RIC for patients transplanted with MRD≥60y as the intensity of the conditioning was not associated with these outcomes. Because of its potential anti-tumoral effect, the low chronic GVHD incidence experienced by MRD≥60y recipients might have contributed to the high relapse rate. Moreover, the high relapse rate and the low incidence of chronic GVHD after transplant with MRD≥60y may also suggest lower alloreactivity of grafts from older MRD. This can be supported by some experimental data having shown a decline of T-cell allogeneic reactivity[27] and an increase in the number of circulating tolerogenic regulatory T cells with advanced age.

Several studies have reported adverse impact of older donor age on OS after HSCT.[30-36] However, few studies have assessed the combined effect of donor age and type on outcome. Some studies have suggested more favorable outcome after transplant with young MUD as compared with older MRD. In contrast, in a large registry trial of elderly patients, Alousi *et al*. recently reported better survival after MRD≥50y-HSCT in comparison with MUD-HSCT, particularly for fit patients at the time of transplant.[39] Compared to our study, only 38% of MRD were older than 60 years in their study. By further exploring for a donor age cut off among MRD, they observed that patients who received grafts from MRD aged ≥67 years experienced higher relapse and mortality risks compared to those transplanted from younger MRD. Which donor source is preferable between an old MRD and a younger MUD and what is the MRD age cut off, if any, above which MUD may be preferred, remain controversial and have to be investigated in further studies.

Graft CD34+and CD3+ cell doses also impacted long-term survival in our study. High CD34+ cell dose was associated with better OS and PFS and lower NRM, as previously reported.[40] Faster engraftment, earlier lymphocyte recovery and lower rate of infections have been reported with higher CD34+ infused cell dose[41-43] and might have contributed to our results. Some authors have, however, suggested inferior outcome after transplant with very high CD34+ cell dose (>8-10x10^6 cells/kg).[44] We did not observe such a negative impact of very high dose (*data not shown*). As previously reported,[45] we also observed a significant advantage of high graft CD3+ cell dose with respect to OS, PFS and NRM, even after adjustment for pre-transplant ATG use. Interestingly, patients transplanted with high graft CD34+ or CD3+ cell doses did not experience higher risks for chronic GVHD.

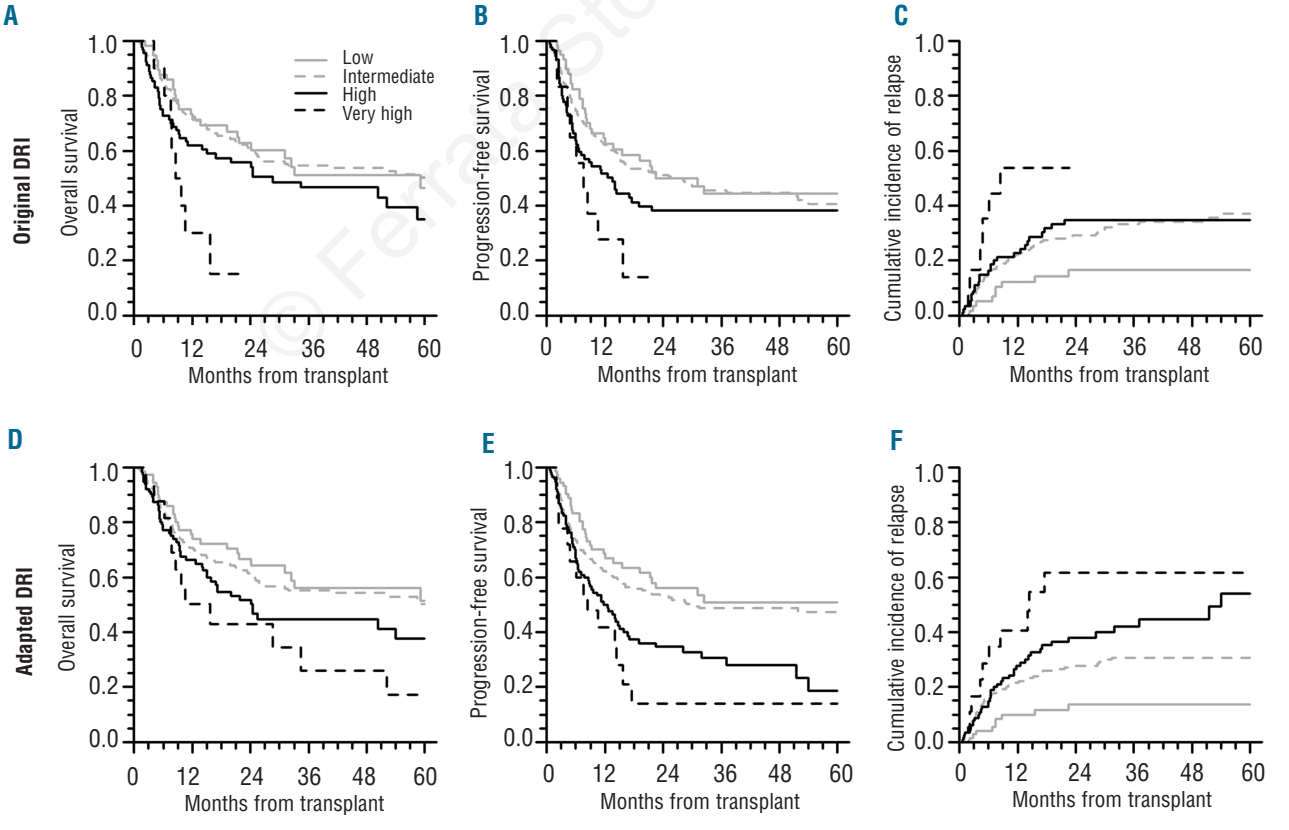

Figure 2. Outcomes according to DRI (A, B, C) and aDRI (D, E, F). OS (A, D), PFS (B, E) and cumulative incidence of relapse (C, F).

We failed to fully validate DRI[14] for survival prediction as only patients with very high DRI (representing only 3% of patients) had significant worse OS and PFS. Our cohort differed from the training and validation cohorts originally reported by Armand *et al*. First, children were included in our study. Whether DRI is applicable for a pediatric population has to be evaluated. Secondly, disease distribution was different. Due to the specific recruitment of our cen-

Table 2. Multivariate analysis of pre-transplant factors associated with outcomes after PB-HSCT.

Pre-transplant variable	Overall mortality (inverse of OS)			Treatment failure (inverse of PFS)			Relapse			NRM			Chronic GVHD		
	HR	(95%CI)	P	HR	(95%CI)	P	HR	(95%CI)	P	HR	(95%CI)	P	HR	(95%CI)	P
Donor type/age†															
MUD	1			1			1			1			1		
MRD<60y§							1.51	(0.97 - 2.36)	0.070	0.58	(0.37 - 0.90)	0.015	0.82	(0.62 - 1.09)	0.17
<6 mo	0.55	(0.33 - 0.91)	0.019	0.95	(0.64 - 1.42)	0.82	–			–			–		
6-9 mo	0.93	(0.44 - 2.00)	0.86	0.71	(0.36 - 1.41)	0.33	–			–			–		
9-18 mo	1.03	(0.49 - 2.17)	0.93	1.46	(0.72 - 2.95)	0.29	–			–			–		
≥ 18 mo	1.18	(0.55 - 2.55)	0.67	1.16	(0.46 - 2.94)	0.75	–			–			–		
MRD≥60y§							2.43	(1.28 - 4.63)	0.007	0.49	(0.21 - 1.13)	0.095	0.48	(0.25 - 0.94)	0.031
<6 mo	0.48	(0.19 - 1.21)	0.12	0.88	(0.43 - 1.78)	0.71	–			–			–		
6-9 mo	0.45	(0.10 - 2.08)	0.31	0.74	(0.21 - 2.57)	0.63	–			–			–		
9-18 mo	2.41	(0.93 - 6.24)	0.069	3.20	(1.23 - 8.34)	0.018	–			–			–		
≥18 mo	4.41	(1.52 - 12.8)	0.006	6.33	(1.60 - 25.0)	0.009	–			–			–		
Recipient age, years															
< 20	0.71	(0.29 - 1.73)	0.45	N/C*			N/C*			0.68	(0.17 - 2.67)	0.58	N/C*		
20-29	1			N/C*			N/C*			1			N/C*		
30-39	1.27	(0.68 - 2.39)	0.46	N/C*			N/C*			1.35	(0.52 - 3.54)	0.54	N/C*		
40-49	1.30	(0.74 - 2.28)	0.36	N/C*			N/C*			2.55	(1.09 - 5.99)	0.031	N/C*		
50-59	1.21	(0.70 - 2.07)	0.50	N/C*			N/C*			2.42	(0.99 - 5.88)	0.052	N/C*		
≥ 60	1.63	(0.85 - 3.11)	0.14	N/C*			N/C*			2.82	(1.01 - 7.91)	0.048	N/C*		
DRI															
Low	0.90	(0.57 - 1.41)	0.64	0.90	(0.60 - 1.37)	0.63	0.42	(0.20 - 0.89)	0.023	1.69	(0.98 - 2.91)	0.057	N/C*		
Intermediate	1			1			1			1			N/C*		
High	1.13	(0.78 - 1.64)	0.51	1.32	(0.94 - 1.83)	0.11	1.40	(0.87 - 2.24)	0.16	1.19	(0.71 - 2.01)	0.50	N/C*		
Very high	2.46	(1.15 - 5.24)	0.020	2.24	(1.12 - 4.48)	0.023	2.38	(0.99 - 5.71)	0.052	1.44	(0.43 - 4.81)	0.55	N/C*		
Conditioning regimen															
MAC	N/C*			N/C*			1			1			N/C*		
RIC	N/C*			N/C*			0.97	(0.62 - 1.52)	0.90	0.54	(0.31 - 0.93)	0.026	N/C*		
ATG															
No	N/C*			1			1			N/C*			1		
Yes	N/C*			1.25	(0.88 - 1.79)	0.21	1.78	(1.10 - 2.90)	0.020	N/C*			0.71	(0.49 - 1.05)	0.085
CD34+ cell dose, x10⁶/kg															
<4.5	1			1			N/C*			1			N/C*		
≥4.5-10	0.56	(0.39 - 0.81)	0.002	0.70	(0.50 - 0.98)	0.039	N/C*			0.50	(0.31 - 0.81)	0.005	N/C*		
CD3+ cell dose, x10⁸/kg															
< 2	1			1			1			1			N/C*		
2-3	0.68	(0.48 - 0.97)	0.035¶	0.76	(0.55 - 1.05)	0.093	0.90	(0.59 - 1.38)	0.63	0.55	(0.34 - 0.91)	0.019¶	N/C*		
> 3	0.61	(0.42 - 0.89)	0.010¶	0.65	(0.46 - 0.91)	0.011	0.69	(0.43 - 1.10)	0.12	0.54	(0.33 - 0.89)	0.016¶	N/C*		
Female/male D/R															
No	N/C*			N/C*			N/C*			N/C*			1		
Yes	N/C*			N/C*			N/C*			N/C*			1.40	(1.05 - 1.86)	0.024
D/R CMV status															
Negative/Negative	1			N/C*			N/C*			N/C*			N/C*		
Negative/Positive	0.97	(0.64 - 1.47)	0.87	N/C*			N/C*			N/C*			N/C*		
Positive/Negative	0.67	(0.39 - 1.14)	0.14	N/C*			N/C*			N/C*			N/C*		
Positive/Positive	1.03	(0.70 - 1.52)	0.88	N/C*			N/C*			N/C*			N/C*		
D/R ABO match															
Compatibility	N/C*			N/C*			1			N/C*			N/C*		
Major incompatibility	N/C*			N/C*			1.03	(0.65 - 1.61)	0.91	N/C*			N/C*		
Minor incompatibility	N/C*			N/C*			0.66	(0.38 - 1.15)	0.15	N/C*			N/C*		

*ATG: antithymocyte globulin; CI: confidence interval; CMV: cytomegalovirus; D/R: donor/recipient; DRI: Disease Risk Index; HR: hazard ratio; mo: months after transplant; MAC: myeloablative conditioning; MRD: matched related donor; MUD: matched unrelated donor; N/C: not considered; OS: overall survival; PFS, progression-free survival; RIC, reduced-intensity conditioning. *Not considered because only variable achieving a P-value < 0.25 in the univariable analysis were considered in the model. †For donor type and donor age, we used the new variable (donor type/age group) for adjustment in the multivariate setting, to minimize bias. §Concerning OS and PFS, because evidence of non-proportional hazards according to time from HSCT for donor type/age groups (MRD≥60y: P=0.003 and P=0.014 for OS and PFS, respectively), we performed a time-dependent effects analysis for this variable by assessing hazards during four successive quartiles of time, each corresponding to a period during which 25% of deaths had occurred within the entire cohort (0 to 6, 6 to 9, 9 to 18 and ≥18 months after PB-HSCT). ¶These results were not altered by additionally adjusting for pre-transplant ATG use.*

Table 3. *C*-statistics for DRI and aDRI, and reclassification indexes comparing the stratification ability of aDRI to DRI.

Outcome	Relapse	Progression-free survival	Overall survival
C-index (95% CI)			
DRI	0.563 (0.501 to 0.624)	0.540 (0.497 to 0.583)	0.543 (0.500 to 0.586)
aDRI	0.631 (0.579 to 0.682)	0.572 (0.533 to 0.611)	0.550 (0.501 to 0.600)
Difference	0.068 (0.021 to 0.115)	0.032 (0.001 to 0.063)	0.007 (-0.054 to 0.068)
P	0.005	0.040	0.82
IDI (95% CI)	0.060 (0.014 to 0.145)	0.039 (0.003 to 0.079)	-0.002 (-0.032 to 0.026)
NRI (95% CI)	0.317 (0.058 to 0.569)	0.246 (-0.055 to 0.357)	-0.094 (-0.229 to 0.230)

aDRI: adapted Disease Risk Index; DRI: Disease Risk Index ; IDI: integrated discrimination improvement index; NRI: net reclassification index.

ter, there was a relative greater representation of MM and MPN (mainly myelofibrosis) in our cohort. Low relapse rate and high long-term PFS and OS were noted for patients transplanted for MPN, as previously reported.[46,47] Conversely, high relapse incidence and low long-term PFS and OS were observed after PB-HSCT for MM patients, as reported by others.[48,49] Thus, assignment of MPN and MM within the intermediate disease type risk category as originally suggested might have altered the stratification ability of DRI for survival in our cohort. Using an adapted index (aDRI) by reclassifying MPN and MM to the low and high disease type risk categories, respectively, we observed that aDRI better discriminated relapse and PFS than DRI. However, aDRI did not improve stratification ability for OS. Further comparisons of DRI and aDRI are needed.

As the aim of this study was to identify pre-transplant factors impacting outcome after PB-HSCT, we did not consider post-transplant events (such as acute or chronic GVHD) as covariates in our multivariate model. However, they might have influenced the results we observed.

Because HLA-matched PB-HSCT currently accounts for the majority of HSCT in adult patients with hematologic malignancies, the multivariate risk factor analysis presented here can be useful for defining clinical pre-transplant predictors of its long-term success.

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