blood advances

Combined effect of unrelated donor age and HLA peptide-binding motif match status on HCT outcomes

Rohtesh S. Mehta,[1] Effie W. Petersdorf,[1,3] Stephen R. Spellman,[2] and Stephanie J. Lee[1,2]

[1]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA; [2]Center for International Blood and Marrow Transplant Research, National Marrow Donor Program, Minneapolis, MN; and [3]Division of Translational Science and Therapeutics, Fred Hutchinson Cancer Center, Seattle, WA

Key Points

- Older unrelated donor age and PBM mismatching confer similarly adverse effects on OS and the impacts are additive.

- Younger donors appear to negate the detrimental effect of PBM mismatching in the unrelated-donor HCT setting.

An HLA-mismatched unrelated donor who is class I peptide-binding motif (PBM)-matched is preferred over a PBM-mismatched donor. We hypothesized that using a younger donor (aged ≤35 years vs >35 years) could compensate for the inferior overall survival (OS) associated with PBM mismatches. We compared 6 groups: HLA-matched/younger donor (n = 10 531), HLA-matched/older donor (n = 3572), PBM-matched/younger donor (n = 357), PBM-matched/older donor (n = 257), PBM-mismatched/younger donor (n = 616), and PBM-mismatched/older donor (n = 339) in patients undergoing transplantation with conventional graft-versus-host disease prophylaxis. In multivariate analysis, HLA-matched/younger donors were associated with superior OS relative to any other group. Pairwise comparisons showed that donor age significantly impacted OS in both HLA-matched and HLA-mismatched groups. Moreover, younger donors appeared to negate the detrimental effect of PBM mismatching: the PBM-matched/younger donor group had similar OS as the HLA-matched/older donor group and the PBM-mismatched/younger donor group had similar OS as the PBM-matched/older donor group. Our study suggests that older unrelated donor age and PBM mismatching confer similarly adverse effects on OS and the impacts are additive, a finding which may widen the "acceptable" donor pool. The best OS is observed with HLA-matched/younger donors and the worst with PBM-mismatched/older donors. These findings should be validated with other data sets and with posttransplantation cyclophosphamide-based prophylaxis.

Introduction

A novel donor selection algorithm based on HLA class I peptide-binding motif (PBM) matching was recently proposed for the mismatched unrelated donor (MMUD) selection for hematopoietic cell transplantation (HCT).[1] A study using the Center for International Blood and Marrow Transplant Research data found that as compared with the 10/10 HLA matched unrelated donor group, there was no statistically significant difference in overall survival (OS) of patients that were either PBM matched with their donors or had unidirectional PBM mismatches in the host-versus-graft direction, whereas PBM mismatches in the graft-versus-host (GVH) direction appeared to be associated with significantly worse OS.[1]

The full-text version of this article contains a data supplement.

Although these observations suggest that PBM-matches or the host-versus-graft PBM mismatches are better tolerated than GVH PBM mismatches, consideration for donor age is also clinically relevant[2-7], and frequently the choice of donors is not optimal for both HLA and donor age concurrently. To expand on this, we analyzed the impact of donor age on outcomes in both HLA matched and mismatched groups Specifically, we tested 2 hypotheses: (a) OS with younger donors would be superior to that with older donors in HLA-matched, HLA-mismatched/PBM-matched, and HLA-mismatched/PBM-mismatched groups; and (b) using a younger donor could compensate for the inferior OS associated with HLA/PBM mismatches; that is, OS with PBM-matched/younger donors would be similar to that with HLA-matched/older donors, and OS with PBM-mismatched/younger donors would be similar to PBM-matched/older donors.

Methods

We performed a secondary analysis of the data previously published by Crivello et al[1] using the publicly available Center for International Blood and Marrow Transplant Research data set.[8] Our study population includes patients aged ≥18 years with acute myeloid leukemia, acute lymphoblastic leukemia, or myelodysplastic neoplasm who underwent a 10/10 HLA–matched unrelated donor or 9/10 HLA–MMUD HCT (mismatched at HLA-A, -B, or -C) between 2008 and 2018. All patients received calcineurin inhibitor–based prophylaxis. Posttransplant cyclophosphamide–based prophylaxis was excluded.

The assignment of the PBM groups and HLA-DPB1 matching was defined as previously published.[1] The local Institutional Review Board (FHIRB0020181) granted the study permission, which was conducted in accordance with the Declaration of Helsinki. We defined donors aged >35 years as "older" and those aged ≤35 years as "younger" based on summary statistics of the receiver operating characteristic curve, which revealed a cutoff of 35.5 years as a predictor of mortality. This is also consistent with several previous publications that showed a survival advantage with donors aged <30 to 36 years vs older donors.[2-7] The statistical methods are elaborated in the supplemental Material.

First, we assessed the independent effects of HLA match and donor age on OS. In multivariate analysis, older donors (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.15-1.27; $P < .001$ vs younger donors) and the HLA match (PBM matched: HR, 1.21; 95% CI, 1.09-1.35; $P = .001$; and PBM mismatched: HR, 1.49; 95% CI, 1.37-1.62; $P < .001$ vs HLA matched) were both noted to be significant predictors of OS. No interaction was found between the HLA match and donor age. Similarly, older donors (HR, 1.27; 95% CI, 1.17-1.38; $P < .001$ vs younger donors) and the HLA match (PBM matched: HR, 1.31; 95% CI, 1.09-1.57; $P = .003$; and PBM mismatched: HR, 1.63; 95% CI, 1.41-1.88; $P < .001$ vs HLA matched) were both noted to be significant independent predictors of nonrelapse mortality (NRM).

Next, using a combination of HLA/PBM matching and donor age, 6 groups were created: HLA-matched/younger donor (n = 10 531), HLA-matched/older donor (n = 3572), PBM-matched/younger donor (n = 357), PBM-matched/older donor (n = 257), PBM-mismatched/younger donor (n = 616), and PBM-mismatched/older donor (n = 339). All statistical analyses were performed using STATA/MP 18 (College Station, TX; StataCorp LLC).

Results and discussion

Baseline characteristics of the comparison groups are shown in Table 1 and univariate analyses are shown in supplemental Table 1. The best-estimated 4-year OS was noted in the HLA-matched/younger donor group (49.9%; 95% CI, 48.8-50.9) and the worst in the PBM-mismatched/older donor group (29.0%; 95% CI, 24.1-34.1). In multivariate analysis, the hazards of overall mortality increased in a stepwise fashion from the HLA-matched/younger donor (reference group) to HLA-matched/older donor and the PBM-matched/younger donor (HR, 1.18 in both groups), to PBM-matched/older donor and the PBM-mismatched/younger donor (HR, 1.48 and 1.42, respectively), and finally to the PBM-mismatched/older donor group (HR, 1.91; Figure 1A; Table 2). The notable findings of the pairwise comparisons were as follows: first, donor age significantly affected OS in both HLA-matched and HLA-mismatched groups, and the negative impact of older donors relative to younger donors appeared to be the highest in the worst HLA category (PBM-mismatched: HR, 1.35) and the lowest in the best HLA category (HLA-matched: HR, 1.18; supplemental Table 2; pairwise comparison group 1). Secondly, younger donors appeared to negate the detrimental effect of HLA/PBM mismatching. Specifically, the PBM-matched/younger donor group had a similar OS (HR, 1.00) as that of the HLA-matched/older donor group, and the PBM-mismatched/younger donor group had a similar OS (HR, 0.96) as that of the PBM-matched/older donor group (pairwise comparison group 2).

The differences in OS were not explained by relapse, which did not differ significantly between the groups, but by NRM. We observed similar patterns for NRM as for OS, that is, the lowest 4-year NRM was noted in the HLA-matched/younger donor group (21.6%; 95% CI, 20.8-22.4) and the highest in the PBM-mismatched/older donor group (41.3%; 95% CI, 36-46.5). In multivariate analysis, the hazards of NRM increased in an almost stepwise fashion from the HLA-matched/younger donor (reference group) to the HLA-matched/older donor and PBM-matched/younger donor (HR, 1.18 in both groups), to the PBM-matched/older donor and PBM-mismatched/younger donor (HR, 1.48 and 1.42, respectively), and the PBM-mismatched/older donor group (HR, 1.91; Figure 1B; Table 2). In the direct pairwise comparisons, the risk of NRM was numerically higher with older donors than with younger donors in all HLA/PBM groups, although it did not reach statistical significance in the HLA-mismatched groups. Younger donors appeared to negate the higher risk of NRM with HLA/PBM mismatching. Specifically, the PBM-matched/younger donor group had a similar risk of NRM (HR, 1.00) as that of the HLA-matched/older donor group; and the PBM-mismatched/younger donor had a similar risk of NRM (HR, 0.92) as that of the PBM-matched/older donor group (supplemental Table 2).

The reason for differences in the NRM between the groups could not be determined because of the lack of data on cause of death but it may be related to infections or other causes and less likely because of GVH disease (GVHD). Among bone marrow graft recipients, older donors were associated with a significantly higher risk of chronic GVHD in the HLA-matched (HR, 1.23) and the PBM-matched (HR, 1.83) groups as than in the HLA-matched/younger donor group, and a numerically higher risk but without statistical significance in the PBM-mismatched group (HR, 1.44). The risk of chronic GVHD did not differ significantly between the

Table 1. Baseline characteristics

	HLA-matched/ younger donor		HLA-matched/ older donor		PBM matched/ younger donor		PBM matched/older donor		PBM mismatched/ younger donor		PBM mismatched/ older donor	
	10 531		**3 572**		**357**		**257**		**616**		**339**	
Donor age in y, median (IQR)	25.4 (22.4-28.9)		41.9 (38.2-47.3)		26.6 (23.1-30)		43.8 (39.6-48.4)		26.7 (23.2-29.7)		42.9 (39.0-48.4)	
Patient age in y, median (IQR)	56.2 (38.9-64.8)		54.7 (38.6-64.0)		52.1 (33.4-61.4)		50.7 (35.4-60.0)		50.3 (30.1-61.0)		51.7 (31.4-61.2)	
Patient age, y												
<40	2 741	26%	951	27%	107	30%	75	29%	212	34%	113	33%
40-55	2 505	24%	953	27%	96	27%	89	35%	165	27%	93	27%
55.1-65	3 100	29%	1 006	28%	115	32%	62	24%	165	27%	94	28%
>65	2 214	21%	677	19%	39	11%	31	12%	76	12%	40	12%
Disease												
AML	6 057	57%	2 033	57%	201	56%	136	53%	372	60%	199	59%
ALL	2 052	19%	750	21%	77	22%	66	26%	137	22%	74	22%
MDS	2 451	23%	804	22%	79	22%	55	21%	109	18%	67	20%
Stage												
Early-intermediate	6 991	66%	2 366	66%	230	64%	168	65%	408	66%	239	70%
Advanced	3 569	34%	1 221	34%	127	36%	89	35%	210	34%	101	30%
Graft source												
BM	2 061	20%	664	19%	76	21%	54	21%	148	24%	71	21%
PB	8 499	80%	2 923	81%	281	79%	203	79%	470	76%	269	79%
Conditioning												
MAC	6 310	60%	2 263	63%	221	62%	177	69%	410	66%	208	61%
NMA/RIC	4 250	40%	1 324	37%	136	38%	80	31%	208	34%	132	39%
GVHD prophylaxis												
Tac based	8 892	84%	2 954	82%	280	78%	193	75%	457	74%	269	79%
CsA based	1 668	16%	633	18%	77	22%	64	25%	161	26%	71	21%
In vivo TCD												
No	6 612	63%	2 245	63%	166	46%	142	55%	269	44%	171	50%
Yes	3 948	37%	1 342	37%	191	54%	115	45%	349	56%	169	50%
Sex mismatch												
F-to-M	1 272	12%	599	17%	80	22%	56	22%	109	18%	67	20%
Others	9 288	88%	2 988	83%	277	78%	201	78%	509	82%	273	80%
KPS												
<90	4 327	41%	1 441	40%	129	36%	105	41%	219	35%	132	39%
90-100	6 233	59%	2 146	60%	228	64%	152	59%	399	65%	208	61%
HCT-CI												
0-1	3 964	38%	1 467	41%	154	43%	112	44%	275	45%	148	44%
≥2	6 596	62%	2 120	59%	203	57%	145	56%	343	55%	192	56%
D/R CMV status												
+/+	2 762	26%	1 159	32%	110	31%	83	32%	185	30%	102	30%
+/−	985	9%	419	12%	32	9%	30	12%	79	13%	45	13%
−/+	3 847	36%	1 187	33%	122	34%	81	32%	214	35%	118	35%
−/−	2 966	28%	822	23%	93	26%	63	25%	140	23%	75	22%
HLA-DPB1 mismatch												
GVH nonpermissive mismatch	1 461	18%	510	19%	46	19%	39	22%	99	23%	57	23%
No GVH nonpermissive mismatch	6 634	82%	2 178	81%	200	81%	139	78%	341	78%	196	77%

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; CsA, cyclosporine; D/R CMV, donor/recipient cytomegalovirus; F-to-M, female donor to male recipient; HCT-CI, HCT-specific comorbidity index; HLA, human leukocyte antigen; IQR, interquartile range; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MDS, myelodysplastic neoplasms; NMA nonmyeloablative conditioning; PB, peripheral blood; RIC, reduced intensity conditioning; Tac, tacrolimus; TCD, T-cell depletion.

Table 1 (continued)

	HLA-matched/ younger donor		HLA-matched/ older donor		PBM matched/ younger donor		PBM matched/older donor		PBM mismatched/ younger donor		PBM mismatched/ older donor	
	10 531		3 572		357		257		616		339	
Time to HCT, mo												
<6	6 007	57%	1 949	54%	165	46%	112	44%	287	46%	157	46%
6-12	2 058	19%	785	22%	79	22%	52	20%	134	22%	74	22%
12-24	1 283	12%	418	12%	58	16%	44	17%	108	17%	62	18%
>24		11%	434	12%	55	15%	48	19%	89	14%	47	14%
Year of HCT												
≤2014	5 258	50%	2 122	59%	236	66%	185	72%	374	61%	239	70%
>2014	5 302	50%	1 465	41%	121	34%	72	28%	244	39%	101	30%
Follow-up in mo, median (IQR)	48.0 (25.29-71.6)		52.9 (31.4-73.7)		59.6 (36.1-89.6)		60.7 (34.6-92.7)		49.9 (32.0-72.2)		60.5 (36.2-89.7)	

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; CsA, cyclosporine; D/R CMV, donor/recipient cytomegalovirus; F-to-M, female donor to male recipient; HCT-CI, HCT-specific comorbidity index; HLA, human leukocyte antigen; IQR, interquartile range; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MDS, myelodysplastic neoplasms; NMA nonmyeloablative conditioning; PB, peripheral blood; RIC, reduced intensity conditioning; Tac, tacrolimus; TCD, T-cell depletion.

groups among peripheral blood graft recipients. The reason for this unexpected finding could not be explained; however, it may suggest that the unfavorable impact of peripheral blood grafts on chronic GVHD is greater than the potential protective effects of donor age. The risk of grade 3/4 acute GVHD did not differ significantly by donor age in the HLA-matched group with either graft source, whereas both PBM-mismatched groups had a significantly higher risk irrespective of donor age than the HLA-matched donor groups. The impact of our main variable (donor age/HLA matching) on all outcomes was independent of other predictors (supplemental Table 3). Although in vivo T-cell depletion was associated with a significantly lower risk of GVHD and NRM, it was also associated with a significantly higher risk of relapse, which translated to no significant impact on OS.

Because NRM was the primary driver for worse outcomes, we performed exploratory analyses to study the relative impact of older vs younger donors based on patient characteristics that were significant predictors of NRM in the multivariate analysis. For these analyses, we dichotomized patient age as ≤40 vs >40 years because the risk of NRM increased in patients aged >40 years in the multivariate analysis. The goal of these analyses was to assess the effect of donor age in patients with the lowest risk features (eg, age of <40 years, HCT-specific comorbidity index score of 0-1, and Karnofsky performance status of ≥90) and in those with the highest risk features (eg, age of ≥40 years, HCT-specific comorbidity index score of >2, and Karnofsky performance scale score of <90), after fitting the multivariate model adjusted for covariates. We found that the older donor group had an increased hazard of NRM as compared with the younger donor group in both the patients at lowest risk (HR, 1.28; 95% CI, 1.15-1.42) and those at highest risk (HR, 1.94; 95% CI, 1.46-2.56), but the effect appeared to be more pronounced in patients at highest risk. These findings suggest that although selecting a younger donor, in general, is important whenever possible, the need becomes even more critical in patients with baseline increased risk of NRM because of older patient age, high comorbidity index, and low performance status. The risk of NRM was higher in the older donor group than the younger donor group irrespective of whether in vivo T-cell depletion

was used (HR, 1.57; 95% CI, 1.28-1.92; P < .001) or not (HR, 1.68; 95% CI, 1.34-2.09; P < .001).

Our study findings apply to patients undergoing HCT who received calcineurin inhibitor–based prophylaxis. Whether similar findings would be seen with posttransplant cyclophosphamide–based or other novel GVHD prophylaxis regimens remains unknown. In addition to the shortcomings mentioned above and biases inherent to retrospective analysis, other limitations of our study are the lack of data on the molecular classification of disease and female-donor parity. Also, because of a lack of data on systemic therapy–requiring chronic GVHD, we were unable to compute GVHD-free relapse-free survival. Lastly, our study population predominantly comprised HLA-matched donor groups, whereas the number of patients in the HLA-MMUD groups was relatively small. The rationale for adverse outcomes with older donors may be because of several factors. These include changes in the DNA methylation patterns leading to an alteration of immune function[9] or epigenetic aging,[10,11] which is correlated with a higher risk of GVHD, infection-related deaths,[10,12] and inferior survival.[12] Other reasons could be age-related thymic involution[13] or clonal hematopoiesis, which is associated with dysregulated cytokine signaling causing an inflammatory milieu in HCT recipients.[14]

Donor age, categorized by decades, was also shown to be an independent predictor of OS in the original analysis.[1] It also showed no statistically significant differences in OS between the HLA-matched and the PBM-matched groups. Our study adds further granularity by showing that the HLA-matched and the PBM-matched groups may or may not differ in OS depending on the donor age and that younger donors can overcome the adverse effects of HLA/PBM mismatching. These findings should be validated with other independent data sets.

To summarize, older donor age and HLA/PBM mismatching result in similar independent adverse effects on OS after HCT, and the impacts are additive. Unrelated donor preference related to donor age and PBM matching should be HLA matched, followed by HLA mismatched/PBM matched, and finally HLA mismatched/PBM
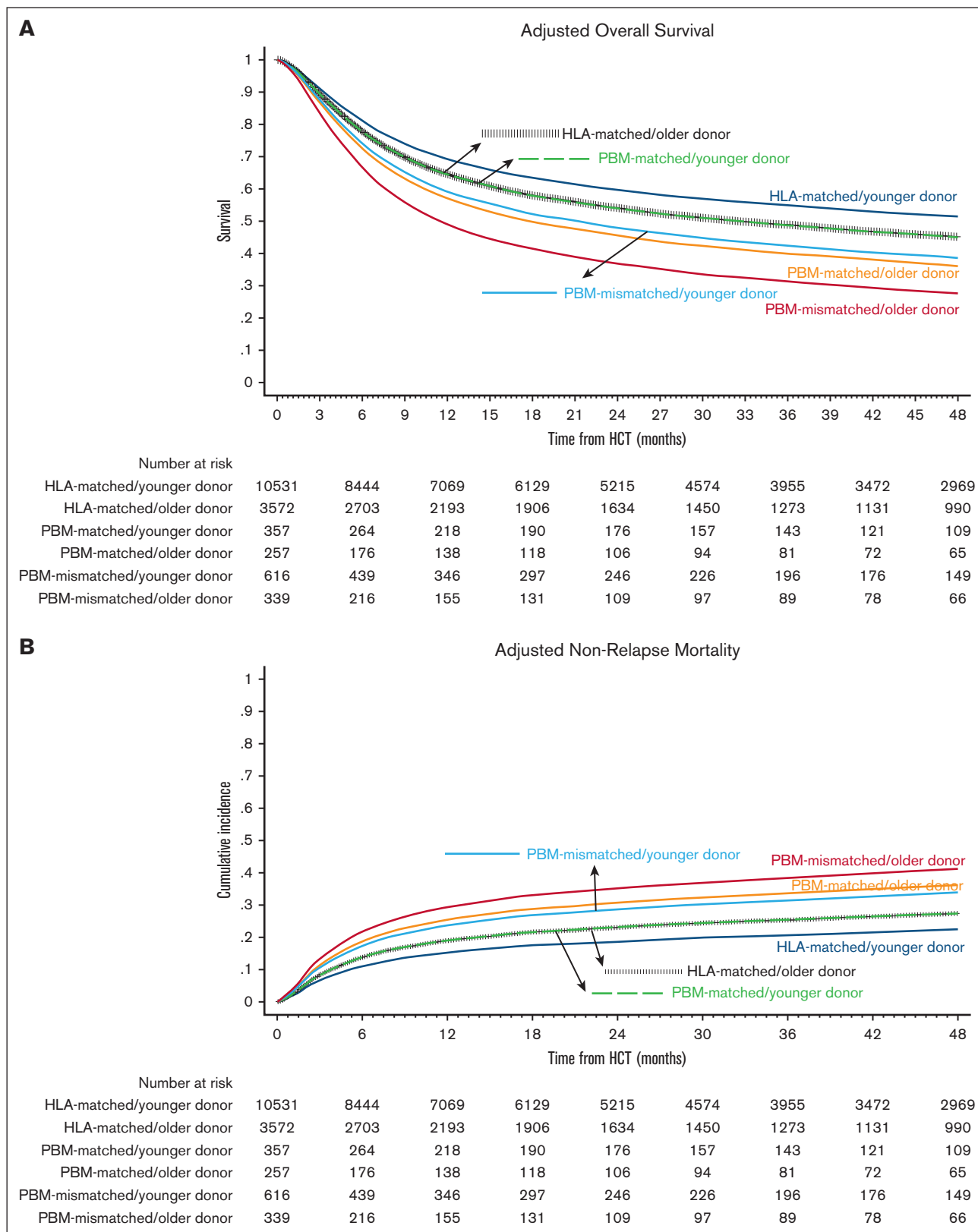
Figure 1. Overall Survival and Nonrelapse Mortality. Outcomes of HLA-matched/younger donor (navy blue), HLA-matched/older donor (vertical dashed black); PBM-matched/younger donor (dashed green); PBM-matched/older donor (dark orange); PBM-mismatched/younger donor (light blue), and PBM-mismatched/older donor (maroon). (A) Adjusted OS, and (B) adjusted NRM.

Table 2. Outcomes

	Total, n	Events	Cumulative incidence (95% CI)*	Multivariate analysis†		
				HR	95% CI	*P* value
OS						
HLA-matched/younger donor	10 531	4 908	49.9 (48.8-50.9)	Ref		
HLA-matched/older donor	3 572	1 899	44.0 (42.2-45.7)	1.18	1.12-1.25	<.001
PBM matched/younger donor	357	186	45.4 (39.9-50.7)	1.18	1.02-1.37	.026
PBM matched/older donor	257	160	35.6 (29.6-41.7)	1.48	1.26-1.73	<.001
PBM mismatched/younger donor	616	356	39.4 (35.4-43.5)	1.42	1.27-1.58	<.001
PBM mismatched/older donor	339	234	29.0 (24.1-34.1)	1.91	1.67-2.18	<.001
NRM						
HLA-matched/younger donor	10 531	2 138	21.6 (20.8-22.4)	Ref		
HLA-matched/older donor	3 572	893	26.1 (24.6-27.6)	1.27	1.16-1.39	<.001
PBM matched/younger donor	357	91	26.3 (21.8-31.1)	1.27	0.98-1.65	.072
PBM matched/older donor	257	96	38.3 (32.2-44.3)	1.77	1.39-2.26	<.001
PBM mismatched/younger donor	616	176	29.7 (26.0-33.5)	1.63	1.36-1.96	<.001
PBM mismatched/older donor	339	138	41.3 (36.0-46.5)	2.10	1.69-2.62	<.001
Relapse (early/intermediate disease)						
HLA-matched/younger donor	6 898	1 866	28.3 (27.2-29.4)	Ref		
HLA-matched/older donor	2 329	673	30.0 (28.1-32.0)	1.08	0.98-1.2	.13
PBM matched/younger donor	229	68	30.3 (24.4-36.4)	1.09	0.82-1.46	.55
PBM matched/older donor	168	43	26.3 (19.7-33.2)	1.17	0.83-1.64	.37
PBM mismatched/younger donor	405	117	29.9 (25.4-34.5)	0.96	0.76-1.22	.76
PBM mismatched/older donor	236	69	30.1 (24.3-36.1)	1.20	0.92-1.56	.19
Relapse (advanced disease)						
HLA-matched/younger donor	3 523	1 433	41.9 (40.2-43.5)	Ref		
HLA-matched/older donor	1 205	496	42.0 (39.1-44.8)	1.01	0.9-1.14	.87
PBM matched/younger donor	126	45	37.0 (28.4-45.6)	0.90	0.64-1.26	.55
PBM matched/older donor	89	29	33.8 (23.9-44)	0.78	0.52-1.18	.24
PBM mismatched/younger donor	206	88	43.7 (36.7-50.5)	0.88	0.69-1.13	.32
PBM mismatched/older donor	101	32	31.7 (22.9-40.9)	0.75	0.48-1.17	.21

Other significant predictors were: OS: disease (MDS [HR, 0.76; 95% CI, 0.71-0.81; *P* < .001]); advanced stage disease (HR, 1.71; 95% CI, 1.62-1.80; *P* < .001) recipient age (40-55 years [HR, 1.20; 95% CI, 1.13-1.29; *P* < .001], 55.1-65 years [HR, 1.46; 95% CI, 1.37-1.56; *P* < .001], and >65 years [HR, 1.62; 95% CI, 1.50-1.73; *P* < .001]), KPS score of 90-100 (HR, 0.81; 95% CI, 0.77-0.84; *P* < .001), HCT-CI of ≥2 (HR, 1.27; 95% CI, 1.21-1.33; *P* < .001), female donor to male recipient (HR, 1.08; 95% CI, 1.01-1.15; *P* = .02), donor/recipient CMV⁻/CMV⁺ status (HR, 1.11; 95% CI, 1.06-1.16; *P* < .001), time to HCT from diagnosis (6-12 months [HR, 1.16; 95% CI, 1.10-1.22; *P* < .001]), year of HCT (2010-2012 [HR, 0.84; 95% CI, 0.78-0.91; *P* < .001], 2013-2015 [HR, 0.74; 95% CI, 0.68-0.79; *P* < .001], and 2016-2018 [HR, 0.64; 95% CI, 0.59-0.69; *P* < .001]). NRM: disease (ALL [HR, 1.35; 95% CI, 1.21-1.51; *P* < .001], and MDS [HR, 1.56; 95% CI, 1.42-1.71; *P* < .001]), recipient age (40-55 years [HR, 1.50; 95% CI, 1.33-1.70; *P* < .001], 55.1-65 years [HR, 1.61; 95% CI, 1.42-1.82; *P* < .001], and >65 years [HR, 1.67; 95% CI, 1.46-1.91; *P* < .001]), CsA-based GVHD prophylaxis (HR, 1.22; 95% CI, 1.09-1.36; *P* < .001), in vivo TCD (HR, 0.87; 95% CI, 0.80-0.94; *P* = .001), KPS score of 90 to 100 (HR, 0.82; 95% CI, 0.75-0.88; *P* < .001), HCT-CI score of ≥2 (HR, 1.37; 95% CI, 1.26-1.49; *P* < .001), time to HCT from diagnosis (6-12 months [HR, 1.14; 95% CI, 1.04-1.26; *P* = .008], 12-24 months [HR, 1.23; 95% CI, 1.09-1.38; *P* = .001], and >24 months [HR, 1.28; 95% CI, 1.14-1.44; *P* < .001]), year of HCT (2013-2015 [HR, 0.85; 95% CI, 0.77-0.93; *P* < .001], and 2016-2018 [HR, 0.71; 95% CI, 0.64-0.78; *P* < .001]), DPB1 nonpermissive GVH mismatch (HR, 1.14; 95% CI, 1.03-1.25; *P* = .008). Relapse (early/intermediate risk disease): disease (ALL [HR, 0.82; 95% CI, 0.74-0.91; *P* < .001], and MDS [HR, 0.78; 95% CI, 0.66-0.92; *P* = .004]), recipient age (55.1-65 years [HR, 1.20; 95% CI, 1.08-1.34; *P* = .001], and >65 years [HR, 1.28; 95% CI, 1.11-1.46; *P* < .001]), NMA/RIC (HR, 1.27; 95% CI, 1.14-1.41; *P* < .001), in vivo TCD (HR, 1.15; 95% CI, 1.05-1.25; *P* = .002), KPS score of 90 to 100 (HR, 0.89; 95% CI, 0.82-0.97; *P* = .011), time to HCT from diagnosis (>24 months [HR, 0.86; 95% CI, 0.74-1.00; *P* = .047]), year of HCT (2016-2018 [HR, 0.82; 95% CI, 0.74-0.90; *P* < .001]), DPB1 nonpermissive GVH mismatch (HR, 0.84; 95% CI, 0.75-0.94; *P* = .003). Relapse (advanced risk disease): disease (MDS [HR, 0.41; 95% CI, 0.37-0.45; *P* < .001]), recipient age of >65 years (HR, 1.23; 95% CI, 1.10-1.38; *P* < .001), in vivo TCD (HR, 1.18; 95% CI, 1.07-1.30; *P* = .001); PB graft (HR, 1.18; 95% CI, 1.02-1.35; *P* = .02), HCT-CI of ≥2 (HR, 1.17; 95% CI, 1.05-1.30; *P* = .004), time to HCT from diagnosis (12-24 months [HR, 0.79; 95% CI, 0.69-0.91; *P* = .001], and >24 months [HR, 0.60; 95% CI, 0.51-0.70; *P* < .001]), year of HCT (2010-2012 [HR, 0.73; 95% CI, 0.61-0.87; *P* < .001], 2013-2015 [HR, 0.81; 95% CI, 0.68-0.96; *P* = .013], 2016-2018 [HR, 0.76; 95% CI, 0.64-0.91; *P* = .002]), DPB1 nonpermissive GVH mismatch (HR, 0.85, 95%0.74-0.96; *P* = .011). Chronic GVHD (PB graft): disease (ALL [HR, 0.91, 95% CI, 10.84-0.99; *P* = .02], MDS [HR, 1.26; 95% CI, 1.16-1.36; *P* < .001]), advanced disease stage (HR, 0.80; 95% CI, 0.74-0.86; *P* < .001), recipient age (40-55 years [HR, 0.90; 95% CI, 0.83-0.98; *P* = .02], 55.1-65 years [HR, 0.86; 95% CI, 0.79-0.94; *P* < .001], and >65 years (HR, 0.78; 95% CI, 0.71-0.86; *P* < .001]), in vivo TCD (HR, 0.61; 95% CI, 0.57-0.65; *P* < .001), KPS score of 90 to 100 (HR, 1.20; 95% CI, 1.13-1.27; *P* < .001), HCT-CI of ≥2 (HR, 0.93; 95% CI, 0.88-0.99; *P* = .02), time from diagnosis to HCT of 6 to12 months (HR, 0.88; 95% CI, 0.82-0.95; *P* < .001). Chronic GVHD (BM graft): MDS (HR, 1.36; 95% CI, 1.14-1.63; *P* = .001), advanced disease stage (HR, 0.77; 95% CI, 0.66-0.91; *P* = .002), recipient age of >65 years (HR, 0.65; 95% CI, 0.51-0.84; *P* = .001), in vivo TCD (HR, 0.68; 95% CI, 0.59-0.78; *P* < .001), female donor to male recipient (HR, 1.40; 95% CI, 1.18-1.67; *P* < .001). Acute GVHD, grade 3/4 (PB graft): disease (ALL [HR, 1.42; 95 % CI 1.24-1.62; *P* < .001], and MDS [HR, 1.39; 95% CI, 1.21-1.59; *P* < .001]), advanced disease stage (HR, 1.23; 95% CI, 1.09-1.39; *P* = .002), NMA/RIC conditioning (HR, 0.79; 95% CI, 0.71-0.88; *P* < .001), in vivo TCD (HR, 0.80; 95% CI, 0.72-0.89; *P* < .001), year of HCT 2016-2018 (HR, 0.76; 95% CI, 0.68-0.85; *P* < .001). Acute GVHD, grade 3/4 (BM graft): disease (MDS [HR, 1.36; 95% CI, 1.06-1.75; *P* = .02]), recipient age (40-55 years [HR, 0.75; 95% CI, 0.57-0.99; *P* = .04], and 55.1-65 years [HR, 0.72; 95% CI, 0.54-0.97; *P* = .03]), NMA/RIC conditioning (HR, 1.37; 95% CI, 1.06-1.78; *P* = .02), DPB1 nonpermissive GVHD mismatch (HR, 1.30; 95% CI, 1.01-1.66; *P* = .04).

ALL, acute lymphoblastic leukemia; BM, bone marrow; CsA, cyclosporine; KPS, Karnofsky performance status; MDS, myelodysplastic neoplasms; NMA, nonmyeloablative conditioning; PB, peripheral blood; Ref, reference group; RIC, reduced intensity conditioning; TCD, T-cell depletion.

*All outcomes are at 4 years, except acute GVHD (day 100).

†Full models shown in supplemental Table 3.

Table 2 (continued)

	Total, n	Events	Cumulative incidence (95% CI)*	Multivariate analysis†		
				HR	95% CI	P value
Chronic GVHD (peripheral blood)						
HLA-matched/younger donor	8 249	4 413	55.0 (35.2-39.5)	Ref		
HLA-matched/older donor	2 845	1 454	52.2 (39.0-46.7)	0.96	0.89-1.03	.21
PBM matched/younger donor	277	145	53.7 (26.2-48.2)	1.05	0.86-1.28	.65
PBM matched/older donor	197	92	47.6 (35.1-61.6)	0.92	0.72-1.18	.52
PBM mismatched/younger donor	457	226	50.3 (35.1-51.4)	1.11	0.95-1.29	.21
PBM mismatched/older donor	261	112	43.5 (37.8-61.0)	0.91	0.73-1.12	.36
Chronic GVHD (bone marrow)						
HLA-matched/younger donor	2 013	730	37.3 (53.9-56.1)	Ref		
HLA-matched/older donor	652	275	42.8 (50.3-54.1)	1.23	1.05-1.43	.009
PBM matched/younger donor	74	27	37.2 (47.5-59.5)	1.01	0.64-1.58	.972
PBM matched/older donor	53	26	49.1 (40.4-54.4)	1.83	1.19-2.8	.005
PBM mismatched/younger donor	143	61	43.4 (45.5-54.8)	1.17	0.86-1.59	.318
PBM mismatched/older donor	70	35	50.0 (37.4-49.5)	1.44	0.96-2.15	.08
Grade 3/4 acute GVHD, day 100 (peripheral blood)						
HLA-matched/younger donor	8 108	1 253	15.5 (14.68-16.25)	Ref		
HLA-matched/older donor	2 749	496	18.0 (16.63-19.5)	1.10	0.98-1.24	.123
PBM matched/younger donor	268	58	21.6 (16.93-26.74)	1.52	1.12-2.05	.007
PBM matched/older donor	190	38	20.0 (14.65-25.96)	1.22	0.83-1.79	.306
PBM mismatched/younger donor	455	103	22.6 (18.91-26.58)	1.41	1.11-1.8	.005
PBM mismatched/older donor	256	73	28.5 (23.12-34.13)	1.59	1.19-2.13	.002
Grade 3/4 acute GVHD, day 100 (bone marrow)						
HLA-matched/younger donor	1 981	278	14.0 (12.55-15.6)	Ref		
HLA-matched/older donor	641	83	13.0 (10.49-15.68)	1.00	0.77-1.31	.998
PBM matched/younger donor	75	14	18.7(10.82-28.18)	1.12	0.55-2.26	.761
PBM matched/older donor	54	20	37.0 (24.42-49.67)	3.00	1.74-5.16	<.001
PBM mismatched/younger donor	144	42	29.2 (21.98-36.71)	2.00	1.36-2.95	<.001
PBM mismatched/older donor	71	23	32.4 (21.9-43.32)	2.67	1.65-4.32	<.001

Other significant predictors were: OS: disease (MDS [HR, 0.76; 95% CI, 0.71-0.81; P < .001]); advanced stage disease (HR, 1.71; 95% CI, 1.62-1.80; P < .001) recipient age (40-55 years [HR, 1.20; 95% CI, 1.13-1.29; P < .001], 55.1-65 years [HR, 1.46; 95% CI, 1.37-1.56; P < .001], and >65 years [HR, 1.62; 95% CI, 1.50-1.73; P < .001]), KPS score of 90-100 (HR, 0.81; 95% CI, 0.77-0.84; P < .001), HCT-CI of ≥2 (HR, 1.27; 95% CI, 1.21-1.33; P < .001), female donor to male recipient (HR, 1.08; 95% CI, 1.01-1.15; P = .02), donor/recipient CMV⁻/CMV⁺ status (HR, 1.11; 95% CI, 1.06-1.16; P < .001), time to HCT from diagnosis (6-12 months [HR, 1.16; 95% CI, 1.10-1.22; P < .001], year of HCT (2010-2012 [HR, 0.84; 95% CI, 0.78-0.91; P < .001], 2013-2015 [HR, 0.74; 95% CI, 0.68-0.79; P < .001], and 2016-2018 [HR, 0.64; 95% CI, 0.59-0.69; P < .001]). NRM: disease (ALL [HR, 1.35; 95% CI, 1.21-1.51; P < .001], and MDS [HR, 1.56; 95% CI, 1.42-1.71; P < .001]), recipient age (40-55 years [HR, 1.50; 95% CI, 1.33-1.70; P < .001], 55.1-65 years [HR, 1.61; 95% CI, 1.42-1.82; P < .001], and >65 years [HR, 1.67; 95% CI, 1.46-1.91; P < .001]), CsA-based GVHD prophylaxis (HR, 1.22; 95% CI, 1.09-1.36; P < .001), in vivo TCD (HR, 0.87; 95% CI, 0.80-0.94; P = .001), KPS score of 90 to 100 (HR, 0.82; 95% CI, 0.75-0.88; P < .001), HCT-CI score of ≥2 (HR, 1.37; 95% CI, 1.26-1.49; P < .001), time to HCT from diagnosis (6-12 months [HR, 1.14; 95% CI, 1.04-1.26; P = .008], 12-24 months [HR, 1.23; 95% CI, 1.09-1.38; P = .001], and >24 months [HR, 1.28; 95% CI, 1.14-1.44; P < .001]), year of HCT (2013-2015 [HR, 0.85; 95% CI, 0.77-0.93; P < .001], and 2016-2018 [HR, 0.71; 95% CI, 0.64-0.78; P < .001]), DPB1 nonpermissive GVH mismatch (HR, 1.14; 95% CI, 1.03-1.25; P = .008). Relapse (early/intermediate risk disease): disease (ALL [HR, 0.82; 95% CI, 0.74-0.91; P < .001], and MDS [HR, 0.78; 95% CI, 0.66-0.92; P = .004]), recipient age (55.1-65 years [HR, 1.20; 95% CI, 1.08-1.34; P = .001], and >65 years [HR, 1.28; 95% CI, 1.11-1.46; P < .001]), NMA/RIC (HR, 1.27; 95% CI, 1.14-1.41; P < .001), in vivo TCD (HR, 1.15; 95% CI, 1.05-1.25; P = .002), KPS score of 90 to 100 (HR, 0.89; 95% CI, 0.82-0.97; P = .011), time to HCT from diagnosis (>24 months [HR, 0.86; 95% CI, 0.74-1.00; P = .047]), year of HCT (2016-2018 [HR, 0.82; 95% CI, 0.74-0.90; P < .001]), DPB1 nonpermissive GVH mismatch (HR, 0.84; 95% CI, 0.75-0.94; P = .003). Relapse (advanced risk disease): disease (MDS [HR, 0.41; 95% CI, 0.37-0.45; P < .001]), recipient age of >65 years (HR, 1.23; 95% CI, 1.10-1.38; P < .001), in vivo TCD (HR, 1.18; 95% CI, 1.07-1.30; P = .001); PB graft (HR, 1.18; 95% CI, 1.02-1.35; P = .02), HCT-CI of ≥2 (HR, 1.17; 95% CI, 1.05-1.30; P = .004), time to HCT from diagnosis (12-24 months [HR, 0.79; 95% CI, 0.69-0.91; P = .001], and >24 months [HR, 0.60; 95% CI, 0.51-0.70; P < .001]), year of HCT (2010-2012 [HR, 0.73; 95% CI, 0.61-0.87; P < .001], 2013-2015 [HR, 0.81; 95% CI, 0.68-0.96; P = .013], 2016-2018 [HR, 0.76; 95% CI, 0.64-0.91; P = .002]), DPB1 nonpermissive GVH mismatch (HR, 0.85, 95% CI 0.74-0.96; P = .011). Chronic GVHD (PB graft): disease (ALL [HR, 0.91, 95% CI, 10.84-0.99; P = .02], MDS [HR, 1.26; 95% CI, 1.16-1.36; P < .001], advanced disease stage (HR, 0.80; 95% CI, 0.74-0.86; P < .001), recipient age (40-55 years [HR, 0.90; 95% CI, 0.83-0.98; P = .02], 55.1-65 years [HR, 0.86; 95% CI, 0.79-0.94; P < .001], and >65 years (HR, 0.78; 95% CI, 0.71-0.86; P < .001]), in vivo TCD (HR, 0.61; 95% CI, 0.57-0.65; P < .001), KPS score of 90 to 100 (HR, 1.20; 95% CI, 1.13-1.27; P < .001), HCT-CI of ≥2 (HR, 0.93; 95% CI, 0.88-0.99; P = .02), time from diagnosis to HCT of 6 to12 months (HR, 0.88; 95% CI, 0.82-0.95; P < .001). Chronic GVHD (BM graft): MDS (HR, 1.36; 95% CI, 1.14-1.63; P = .001), advanced disease stage (HR, 0.77; 95% CI, 0.66-0.91; P = .002), recipient age of >65 years (HR, 0.65; 95% CI, 0.51-0.84; P = .001), in vivo TCD (HR, 0.68; 95% CI, 0.59-0.78; P < .001), female donor to male recipient (HR, 1.40; 95% CI, 1.18-1.67; P < .001). Acute GVHD, grade 3/4 (PB graft): disease (ALL [HR, 1.42; 95 % CI 1.24-1.62; P < .001], and MDS [HR, 1.39; 95% CI, 1.21-1.59; P < .001]), advanced disease stage (HR, 1.23; 95% CI, 1.09-1.39; P = .002), NMA/RIC conditioning (HR, 0.79; 95% CI, 0.71-0.88; P < .001), in vivo TCD (HR, 0.80; 95% CI, 0.72-0.89; P < .001), year of HCT 2016-2018 (HR, 0.76; 95% CI, 0.68-0.85; P < .001). Acute GVHD, grade 3/4 (BM graft): disease (MDS [HR, 1.36; 95% CI, 1.06-1.75; P = .02], recipient age (40-55 years [HR, 0.75; 95% CI, 0.57-0.99; P = .04], and 55.1-65 years [HR, 0.72; 95% CI, 0.54-0.97; P = .03], NMA/RIC conditioning (HR, 1.37; 95% CI, 1.06-1.78; P = .02), DPB1 nonpermissive GVHD mismatch (HR, 1.30; 95% CI, 1.01-1.66; P = .04).

ALL, acute lymphoblastic leukemia; BM, bone marrow; CsA, cyclosporine; KPS, Karnofsky performance status; MDS, myelodysplastic neoplasms; NMA, nonmyeloablative conditioning; PB, peripheral blood; Ref, reference group; RIC, reduced intensity conditioning; TCD, T-cell depletion.

*All outcomes are at 4 years, except acute GVHD (day 100).

†Full models shown in supplemental Table 3.

mismatched. Our data show that younger donors with inferior matching led to comparable survival as older donors with better matching, a finding that may widen the "acceptable" donor pool. The best OS is noted with HLA-matched/younger donors and the worst with HLA mismatched/PBM-mismatched/older donors. Further studies are needed to decipher the causes of worse outcomes with older donors and whether the use of novel GVHD prophylaxis regimens can alter these conclusions.

Authorship

Contribution: R.S.M. conceptualized the study, performed the statistical analysis, interpreted data, and wrote the manuscript; E.W.P., S.R.S., and S.J.L. reviewed and interpreted the data, reviewed the manuscript, and provided critical feedback; R.S.M. had full access to the raw data, which are publicly available; all authors approved the manuscript; and the corresponding author had the final responsibility to submit for publication.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: R.S.M., 0000-0002-8532-544X; S.J.L., 0000-0003-2600-6390.

Correspondence: Rohtesh S. Mehta, Clinical Research Division, Fred Hutchinson Cancer Center, University of Washington School of Medicine, 1100 Fairview Ave N, D5-280, Seattle, WA 98109; email: rmehta@fredhutch.org.

References

1. Crivello P, Arrieta-Bolanos E, He M, et al. Impact of the HLA immunopeptidome on survival of leukemia patients after unrelated donor transplantation. *J Clin Oncol.* 2023;41(13):2416-2427.

2. Guru Murthy GS, Kim S, Hu ZH, et al. Relapse and disease-free survival in patients with myelodysplastic syndrome undergoing allogeneic hematopoietic cell transplantation using older matched sibling donors vs younger matched unrelated donors. *JAMA Oncol.* 2022;8(3):404-411.

3. Shaw BE, Logan BR, Spellman SR, et al. Development of an unrelated donor selection score predictive of survival after HCT: donor age matters most. *Biol Blood Marrow Transplant.* 2018;24(5):1049-1056.

4. Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. *Blood.* 2016;127(2):260-267.

5. Kroger N, Zabelina T, de Wreede L, et al. Allogeneic stem cell transplantation for older advanced MDS patients: improved survival with young unrelated donor in comparison with HLA-identical siblings. *Leukemia.* 2013;27(3):604-609.

6. Carreras E, Jimenez M, Gomez-Garcia V, et al. Donor age and degree of HLA matching have a major impact on the outcome of unrelated donor haematopoietic cell transplantation for chronic myeloid leukaemia. *Bone Marrow Transplant.* 2006;37(1):33-40.

7. Kollman C, Howe CW, Anasetti C, et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. *Blood.* 2001;98(7):2043-2051.

8. Center for International Blood and Marrow Transplant Research. Publicly Available Datasets. Accessed 24 May 2023. https://cibmtr.org/CIBMTR/Resources/Publicly-Available-Datasets

9. Marioni RE, Shah S, McRae AF, et al. DNA methylation age of blood predicts all-cause mortality in later life. *Genome Biol.* 2015;16(1):1-12.

10. Stolzel F, Brosch M, Horvath S, et al. Dynamics of epigenetic age following hematopoietic stem cell transplantation. *Haematologica.* 2017;102(8):e321-e323.

11. Weidner CI, Ziegler P, Hahn M, et al. Epigenetic aging upon allogeneic transplantation: the hematopoietic niche does not affect age-associated DNA methylation. *Leukemia.* 2015;29(4):985-988.

12. Alsaggaf R, Katta S, Wang T, et al. Epigenetic aging and hematopoietic cell transplantation in patients with severe aplastic anemia. *Transplant Cell Ther.* 2021;27(4):313.e1-313.e8.

13. Liang Z, Dong X, Zhang Z, Zhang Q, Zhao Y. Age-related thymic involution: mechanisms and functional impact. *Aging Cell.* 2022;21(8):e13671.

14. Gibson CJ, Kim HT, Zhao L, et al. Donor clonal hematopoiesis and recipient outcomes after transplantation. *J Clin Oncol.* 2022;40(2):189-201.