LETTER TO THE EDITOR

Integrating biological HLA-DPB1 mismatch models to predict survival after unrelated hematopoietic cell transplantation

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An appendix with all contributing EBMT centers can be found at the end of the manuscript.

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Supplementary Data

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Supplementary Tables S1 and S2

Supplementary Figure Legend

Supplementary Figure S1

Supplementary Table S1: Association of non-HLA-DPB1 variables with clinical endpoints.

Variable[a,b]	**OS**			**RFS**			**GRFS**			**Relapse**			**NRM**			**aGvHD 2-4**		
	HR	CI	*P*	HR	CI	*P*	HR	CI	*P*	HR	CI	*P*	HR	CI	*P*	HR	CI	*P*
Patient Age[c]	1.16	1.10 – 1.22	***<.001***	1.11	1.07 – 1.17	***<.001***	1.08	1.03 – 1.12	***<.001***	1.06	1.00 – 1.12	*.06*	1.24	1.15 – 1.34	***<.001***	0.93	0.89 – 0.98	***.01***
Donor Age[c]	1.08	1.02 – 1.14	***.01***	1.05	1.00 – 1.11	*.07*	1.08	1.03 – 1.14	***.002***	0.99	0.92 – 1.06	*.76*	1.16	1.07 – 1.26	***<.001***	1.12	1.05 – 1.20	***<.001***
Donor Sex Male vs Female	0.98	0.87 – 1.10	*.70*	0.99	0.89 – 1.11	*.91*	0.91	0.82 – 1.01	*.08*	1.06	0.92 – 1.23	*.41*	0.91	0.76 – 1.08	*.28*	0.88	0.77 – 1.01	.08
CMV status others vs neg/neg	1.00	0.89 – 1.11	*.94*	0.99	0.89 – 1.09	*.78*	1.01	0.92 – 1.12	*.82*	0.92	0.81 – 1.05	*.23*	1.09	0.92 – 1.29	*.33*	0.89	0.78 – 1.01	.07
Diagnosis: MDS+MPN vs AML+ALL	0.94	0.82 – 1.09	*.41*	0.91	0.79 – 1.04	*.16*	1.06	0.94 – 1.21	*.34*	0.63	0.52 – 0.76	***<.001***	1.48	1.20 – 1.82	***<.001***	1.34	1.14 – 1.59	***<.001***
Diagnosis: others vs AML+ALL	0.70	0.59 – 0.81	***<.001***	0.90	0.78 – 1.04	*.15*	1.02	0.90 – 1.17	*.72*	0.8	0.67 – 0.96	***.02***	1.12	0.89 – 1.41	*.35*	1.12	0.94 – 1.34	.19
Disease Stage: intermediate vs Early	1.32	1.15 – 1.51	***<.001***	1.26	1.11 – 1.44	***<.001***	1.19	1.04 – 1.33	***.008***	1.39	1.18 – 1.65	***<.001***	1.07	0.87 – 1.31	*.53*	1.01	0.86 – 1.18	.94
Disease Stage: advanced vs Early	1.63	1.40 – 1.89	***<.001***	1.65	1.44 – 1.90	***<.001***	1.38	1.21 – 1.57	***<.001***	2.03	1.69 – 2.44	***<.001***	1.24	0.99 – 1.55	*.06*	1.10	0.92 – 1.31	.28
Year of HCT: 2012-2017 vs 2005-2011	0.95	0.84 – 1.08	*.42*	0.94	0.84 – 1.06	*.30*	0.99	0.88 – 1.10	*.81*	1.01	0.86 – 1.18	*.92*	0.86	0.72 – 1.03	*.11*	1.14	0.97 – 1.34	.11

Stem Cell Source PBSC vs BM	1.08	0.91 – 1.28	*.39*	0.98	0.84 – 1.15	*.84*	1.14	0.98 – 1.32	*.08*	1.0	0.81 – 1.22	*.97*	1.00	0.78 – 1.28	*.99*	1.14	0.94 – 1.38	.18
Conditioning Reduced vs Standard	1.00	0.88 – 1.15	*.95*	1.04	0.92 – 1.17	*.56*	0.92	0.82 – 1.04	*.18*	1.16	0.99 – 1.36	*.07*	0.84	0.69 – 1.03	*.09*	0.72	0.62 – 0.84	***<.001***
TCD Yes vs No	0.93	0.83 – 1.05	*.25*	1.04	0.93 – 1.16	*.52*	0.75	0.67 – 0.83	***<.001***	1.24	1.06 – 1.44	***.006***	0.80	0.67 – 0.95	***.01***	0.67	0.59 – 0.77	***<.001***
Karnofsky <=90 vs >90	1.59	1.28 – 1.98	***<.001***	1.52	1.23 – 1.88	***<.001***	1.39	1.11 – 1.73	***.004***	1.36	1.01 – 1.82	***.04***	1.74	1.27 – 2.38	***<.001***	1.16	0.85 – 1.58	.36
Mismatch HLA-DQB1 Yes vs No	0.86	0.67 – 1.12	*.27*	0.94	0.74 – 1.18	*.58*	1.03	0.83 – 1.27	*.81*	0.82	0.59 – 1.13	*.22*	1.12	0.80 – 1.57	*.52*	1.20	0.91 – 1.58	.21
GvHD regimen CSA/MMF vs CSA/MTX	1.13	1.00 – 1.28	***.04***	1.06	0.95 – 1.19	*.32*	1.30	1.17 – 1.45	***<.001***	0.83	0.71 – 0.96	***.01***	1.47	1.23 – 1.76	***<.001***	1.31	1.14 – 1.51	***<.001***
GvHD regimen other vs CSA/MTX	1.69	1.24 - 2.30	***<.001***	1.46	1.08 – 1.96	***.01***	1.44	1.06 – 1.94	***.02***	1.18	0.80 – 1.76	*.41*	1.88	1.18 – 3.01	***.008***	1.38	0.92 – 2.09	.12
GvHD regimen TAC-based vs CSA/MTX	1.05	0.86 – 1.28	*.64*	1.05	0.88 – 1.26	*.59*	0.94	0.79 – 1.11	*.45*	0.91	0.71 – 1.15	*.42*	1.30	0.98 – 1.72	*.07*	0.83	0.66 – 1.05	.12

[a] Median follow-up was 36.7 months (interquartile range 19.15 to 64.43). At 5-years, RFS, OS and GRFS were 42% (95% CI 41-44%), 49% (95% CI 47-51%) and 33% (95% CI 31-35%) respectively. The cumulative incidences of relapse, NRM and cGVHD at 5-years were 34% (95% CI 32-36%), 23% (95% CI 21-24%) and 42% (95% CI 41-44%) respectively. The cumulative incidences of aGVHD 2-4 and aGVHD 3-4 at 100 days were 30% (95% CI 29-31%) and 11% (95% CI 10-12%), respectively.

[b] Abbreviations: TCD, T-cell depletion; CMV, cytomegalovirus; BM, bone marrow; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; Year of transplantation: first period 2005-2011, second period 2012-2017; AL, acute leukemia (myeloid or lymphatic); MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm. Disease stage was defined as in the legend to **Table 1** in the main text. Donor and patient age was analyzed as continuous variable by decades.

[c] Patient and donor age was considered as linear variable, with higher age associated with worse outcome.

Supplementary Table S2. Multivariable associations between HLA-DPB1 mismatching models and HCT outcomes.

HLA-DPB1 Status[a]	**RFS**[b]			**Relapse**[b]			**aGvHD grade 2-4**[b]			**NRM**[b]		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Allele-matched	1			1			1			1		
Allele-mismatched[c]	0.95	0.87 to 1.05	.31	0.78	0.69 to 0.88	**<.001**	1.25	1.11 to 1.41	**<.001**	1.26	1.07 to 1.47	**.005**
TCE-permissive[c]	0.94	0.85 to 1.03	.20	0.81	0.71 to 0.92	**.001**	1.18	1.04 to 1.35	**.01**	1.16	0.98 to 1.38	.09
TCE-nonpermissive[c]	0.98	0.88 to 1.08	.64	0.75	0.65 to 0.86	**<.001**	1.35	1.18 to 1.54	**<.001**	1.38	1.16 to 1.65	**<.001**
Low-expression[d]	0.98	0.87 to 1.1	.74	0.87	0.75 to 1.01	.07	1.09	0.94 to 1.27	.27	1.16	0.96 to 1.41	.13
High-expression[d]	0.91	0.81 to 1.03	.14	0.69	0.59 to 0.81	**<.001**	1.3	1.12 to 1.52	**<.001**	1.33	1.09 to 1.61	**.005**
TPHE[d,e]	0.81	0.69 to 0.95	**.01**	0.68	0.55 to 0.84	**<.001**	1.5	1.25 to 1.8	**<.001**	1.1	0.85 to 1.41	.47
Other[d,e]	0.99	0.89 to 1.1	.84	0.82	0.71 to 0.94	**.004**	1.11	0.96 to 1.27	.16	1.28	1.07 to 1.53	**.006**

[a] No associations were observed for any of the models with the endpoints aGvHD grade 3-4, cGvHD, GRFS and OS. [b] Adjustment was made for non-HLA-DPB1 variables as in *Online Supplementary Table S1*. [c] tested in the overall cohort. [d] tested in the single HLA-DPB1 GvH mismatched cohort. [e] TPHE: TCE-permissive and high-expression single HLA-DPB1 GvH mismatches; Other: Non-TPHE single HLA-DPB1 GvH mismatches.

Legend to Supplementary Figure S1.

Study design and RFS according to combined HLA-DPB1 TCE and Expression mismatches A) Flow chart of patient stratification according to HLA-DPB1 matching status. Shown is the absolute number of patients in each group, followed by (in parenthesis) the respective percentage referred to the entire study cohort. B) 5-year probability of RFS after HCT from donors with a single HLA-DPB1 GvH mismatch that is TCE-permissive and high expression (TPHE; 49%), TCE-permissive and low expression (42%), TCE-nonpermissive and high expression (44%) or TCE-nonpermissive and low expression (42%), or DPB1 allele matched (39%).

Supplementary Figure S1.