

## Haploidentical stem cell donor choice for patients with acute myeloid leukemia: A study from the ALWP of the EBMT

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### Abstract:

There is a paucity of information to guide selection of the most suitable stem cell donor in haploidentical (Haplo) hematopoietic stem cell transplantation (HSCT). For this reason, we conducted a retrospective analysis in order to evaluate the impact of Haplo family donors characteristics on HSCT outcomes in patients with acute myeloid leukemia (AML) who received graft-versus-host disease prophylaxis with post-transplant cyclophosphamide (PTCy). The primary endpoint was GvHD-free and relapse-free survival (GRFS). Overall, 2200 patients were included. The median age of donors was 37 years (range, 8-71), 820 (37%) were females, including 458 (21%) who were used for male recipients. Additionally, 1631 (74%) donated peripheral blood (PB). Multivariable analysis identified certain donor-related risk factors with a detrimental impact on transplant outcomes. The use of PB, older donor's age and female donors to male recipients negatively affected GRFS. Donor's age and female donor to male recipient combination also affected non-relapse mortality, leukemia-free survival and overall survival. In conclusion, donor-related variables significantly influence AML patient outcomes following Haplo-HSCT with PTCy. When possible, younger donors and male donors for male recipients should be prioritized. The use of BM can additionally prevent GVHD.

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**Running Title:** Haploidentical donor selection for HSCT in AML

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1. Older donors and female donor to male recipient had a negative impact on GVHD, non-relapse mortality and survival in PTCy Haplo-HSCT.
2. The use of PB was associated with higher risk of severe acute GVHD and decreased GRFS.

## ABSTRACT

There is a paucity of information to guide selection of the most suitable donor in haploidentical (Haplo) hematopoietic stem cell transplantation (HSCT). For this reason, from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT), we conducted a retrospective analysis to evaluate the impact of Haplo donor characteristics on outcomes in patients with acute myeloid leukemia (AML) who received graft-versus-host disease prophylaxis with post-transplant cyclophosphamide (PTCy). The primary endpoint was GvHD-free and relapse-free survival (GRFS). Overall, 2200 patients were included. The median age of donors was 37 years (range, 8-71), 820 (37%) were females, including 458 (21%) who were used for male recipients. Additionally, 1631 (74%) donated peripheral blood (PB). Multivariable analysis identified certain donor-related risk factors with a detrimental impact on transplant outcomes. The use of PB, older donor's age (>37yrs) and female donors to male recipients negatively affected GRFS. Donor's age and female donor to male recipient combination also affected non-relapse mortality, leukemia-free survival and overall survival. In conclusion, donor-related variables significantly influence AML patient outcomes following Haplo-HSCT with PTCy. When possible, younger donors and male donors for male recipients should be prioritized. The use of BM can additionally prevent GVHD.

**Keywords:** Haploidentical transplant, stem cell donors, post-transplant cyclophosphamide, acute myeloid leukemia.

## INTRODUCTION

The availability of stem cell donors is no longer a limitation for patients in need of allogeneic hematopoietic stem cell transplantation (HSCT). This progress has been greatly facilitated by the successful implementation of *in vivo* T-lymphocyte depletion strategies, such as post-transplant cyclophosphamide (PTCy), which has led to a dramatic increase in HSCT from haploidentical (Haplo) donors.<sup>1</sup> In fact, in most cases, several suitable Haplo donors are available within the family, making selection of the optimal stem cell donor a common and relevant decision for transplant teams in clinical practice.

Several recommendations have been published to guide donor selection.<sup>2-4</sup> However, these recommendations are often not fully supported by good quality scientific evidence. In addition, several issues have complicated the interpretation of the available information. First, the influence of donor characteristics on transplant outcomes may differ depending on the specific transplant procedure. For instance, while a maternal donor may prove advantageous in an ex-vivo T-cell depleted graft setting,<sup>5</sup> the same donor might have deleterious effects in an unmanipulated antithymocyte globulin-based scenario.<sup>4</sup> Furthermore, focusing on PTCy platforms, different studies have reported conflicting results.<sup>6</sup> This inconsistency could be due, at least in part, to the heterogeneity of patient characteristics, encompassing different diseases and stages at transplantation.

The aim of our study was to investigate the key characteristics of Haplo family donors that could have an impact on transplant outcomes in patients with AML receiving GvHD prophylaxis with PTCy and registered in the European Society for Blood and Marrow Transplantation (EBMT) database. Our goal was to improve the criteria to guide donor selection in this setting.

## PATIENTS AND METHODS

### Study design and data source

This is a retrospective registry-based analysis on behalf of the Acute Leukemia Working Party (ALWP) of the EBMT. The EBMT is a voluntary working group of more than 650 transplantation centers that are required to report all consecutive

stem cell transplantations and follow ups once a year. In the EBMT registry, there is an internal quality control program regarding accuracy and consistency of entered data and audits are regularly performed using queries on missing/incorrect data and follow-up requests. All transplantation centers are required to obtain written informed consent before data registration with the EBMT in accordance with the 1975 Declaration of Helsinki. The ALWP of the EBMT group approved this study.

### **Patient Eligibility**

Included were all adults (age  $\geq 18$  years) with AML reported via the ProMise data entry system to the EBMT database, who underwent a first allogeneic HSCT from a Haplo family donor between 2010 and 2022, with an unmanipulated graft and PTCy, with reported data on number of human leucocyte antigen (HLA) mismatches, cytogenetics, donor age and donor/recipient CMV serostatus. Haplo was defined as recipient-donor number of HLA mismatches  $\geq 2$ .

### **Endpoints and definitions**

The primary end points were graft-*versus*-host disease (GvHD)-free and relapse-free survival (GRFS). Secondary endpoints included acute and chronic GvHD, disease relapse, non-relapse mortality (NRM), leukemia-free survival (LFS) and overall survival (OS). GRFS was defined as survival without disease relapse and severe acute or chronic extensive GvHD. OS was defined as the time between the date of transplant and death. LFS was defined as survival without relapse or progression, and was calculated until the date of first relapse, death from any cause, or the last follow-up. Relapse was defined as disease recurrence and appearance of blasts in the peripheral blood (PB) or bone marrow ( $>5\%$ ) after complete remission (CR). NRM was defined as death from any cause other than relapse.

### **Statistical Analysis**

GRFS, LFS, and OS were estimated using the Kaplan-Meier method.<sup>7</sup> Survival probabilities are given at 2 years as percentages and 95% confidence intervals (CIs). Cumulative incidence functions were used to estimate acute GvHD, chronic GvHD, relapse incidence, and NRM.<sup>8,9</sup> Competing risks were death for relapse incidence and relapse for NRM, relapse or death for acute GvHD and chronic GvHD. Univariate analyses were done using the log-rank test for LFS, GRFS, and OS and Gray's test for cumulative incidence. Multivariate analyses were performed using the Cox proportional hazard.<sup>10</sup> The following patient, disease and transplant characteristics were included in the final model: age at transplantation, cytogenetic risk group according to the Medical Research Council,<sup>11</sup> first CR (CR1) or CR2, transplantation year, CMV serostatus, conditioning regimen, hematopoietic cell transplant-specific comorbidity index (HCT-CI).<sup>12</sup> In addition, the following donor and graft characteristics were also included in the final model: donor age below or above the median, number of HLA mismatches, stem cell source, donor CMV serostatus and donor-recipient gender mismatch. To test for a center effect, we introduced a random effect or frailty for each center into the model.<sup>13</sup> The significance level was fixed at 0.05, and P values were two-sided. Statistical analyses were performed using the R statistical software version 4.2.3 (R Foundation for Statistical Computing, Austria, Vienna; available online at <http://www.R-project.org>).

## RESULTS

### Patient and Transplantation Characteristics

Patient and transplant characteristics are summarized in Table 1. Briefly, a total of 2200 patients were included with a median age of 56 years (range, 18-75). Distribution of cytogenetic risk was as follows: 161 (7%), 1451 (66%) and 588 (27%) patients had standard, intermediate and adverse-risk cytogenetics, respectively. Most patients were in CR (80%), with 1331 (61%) in CR1 and 411 (19%) in CR $\geq$  2. Regarding conditioning regimen, 1801 (82%) patients underwent chemotherapy-based conditioning and 1246 (57%) patients received a reduced-intensity conditioning (RIC) regimen. GvHD prophylaxis consisted of a triple combination with PTCy, mycophenolate-mofetil and a calcineurin inhibitor in 1924 (87%) patients.



## Donor Characteristics

Donor characteristics are summarized in Table 2. The median age was 37 years (range, 8-71). Among the 820 (37%) female donors, 458 (21%) were used for male recipients. CMV serostatus was positive in 1252 (57%) donors. PB and bone marrow was used in 74% and 26%, respectively. Donor/recipient HLA mismatch was  $\geq 4/8$  in 1638 (75%) transplants.

## Transplant Outcomes

Patient outcomes after HSCT are shown in Table 3. For the overall cohort, the 180-day cumulative incidence of acute GvHD grade II-IV and III-IV was 28% (95% CI 26-30) and 11% (95% CI 10-12), respectively. The 2-year cumulative incidence of chronic and chronic extensive GvHD was 33% (95% CI 31-35) and 14% (95% CI 12-15), respectively. The 2-year cumulative incidence of relapse and NRM was 26% (95% CI 24-28) and 22% (95% CI 20-24), respectively. The LFS, OS, and GRFS at 2 years was 52% (95% CI 50-55), 57% (95% CI 55-60), and 41% (95% CI 39-43), respectively.

## Analysis of Risk Factors

The comprehensive multivariable analysis of transplant outcomes is shown in Table 4.

### Patient, disease, and transplant factors

We found that no specific patient, disease, or transplant characteristic was significantly associated with an increased risk of severe acute GvHD, except for a lower incidence of acute GVHD grade III-IV in more recent years. However, the analysis did reveal that patients in active disease phase at time of HSCT showed a higher risk of chronic extensive GvHD. Additionally, older recipient age and high HCT-CI score had an adverse impact on NRM, LFS, and OS. Furthermore, disease stage CR >1, adverse-risk cytogenetics, and RIC were associated with a higher risk of relapse and a lower LFS and OS.

### Donor-related factors

When considering the stem cell source, patients receiving peripheral blood had higher risk of severe acute GVHD (HR=1.74; 95% CI=1.2-2.52; p=0.003), and worse GRFS (HR=1.19; 95% CI=1.02-1.39; p=0.003) compared to bone marrow (Figure 1).

Donor age significantly influenced outcomes. Patients transplanted with donors older than 37 years of age had higher risk of severe acute GVHD (HR=2.05; 95% CI=1.55-2.71; p<0.001), chronic extensive GVHD (HR=1.65; 95% CI=1.26-2.16; p<0.001), and NRM (HR=1.36; 95% CI=1.12-1.65; p=0.002) that translated into decreased LFS (HR=1.22; 95% CI=1.07-1.39; p=0.002), OS (HR=1.29; 95% CI=1.12-1.48; p<0.001), and GRFS (HR=1.32; 95% CI=1.17-1.48; p<0.001) (Figure 2).

Regarding donor gender, female donor to male recipient combination had a deleterious effect on chronic extensive GVHD (HR=1.95; 95% CI=1.46-2.61; p<0.001), NRM (HR=1.56; 95% CI=1.09-1.69; p=0.007), as well as on LFS (HR=1.18; 95% CI=1-1.38; p=0.03), OS (HR=1.25; 95% CI=1.06-1.47; p=0.007), and GRFS (HR=1.29; 95% CI=1.12-1.48; p<0.001) (Figure 3).

No specific variable was significantly associated with the risk of relapse. The degree of HLA and donor CMV serostatus did not significantly impact any transplant outcomes. The impact of stem cell source and donor gender on transplant outcomes did not significantly change when age was introduced as a continuous variable in the multivariable model.

## **DISCUSSION**

This study shows that certain donor characteristics such as age, gender and stem cell source can have a significant impact on Haplo-HSCT outcomes using PTCy in AML patients. Notably, the use of PB as the source of stem cells was associated with an increased the risk of GvHD, while older donor age and the use of female donor to male recipient were also associated with higher GvHD but also worse survival.

Our study included a large cohort of AML patients from the EBMT registry who underwent Haplo-HSCT in the last decade using PTCy as GvHD prophylaxis. This dataset represents the prevailing Haplo-HSCT practice in Europe, marked by a predominant use of PB as the stem cell source (74%), a majority of patients in CR, and a well-balanced distribution of RIC and myeloablative conditioning (MAC) chemotherapy-based conditioning regimens. This stands in contrast to previous studies,<sup>6,14,15</sup> highlighting the importance of our contribution. It should be emphasized that, in order to minimize heterogeneity and mitigate potential confounding factors, the analysis was restricted to patients with AML. However, it is imperative to acknowledge the inherent limitations of our study due to its retrospective and registry-based nature. Certain information regarding graft and donor characteristics, which could be relevant for donor selection, was either incomplete or unavailable, such as kinship, the presence of anti-HLA antibodies, cell dose, specific HLA mismatches, or natural killer alloreactivity, all of which could not be evaluated in our analysis.

Regarding transplant outcomes, our study confirms the efficacy of Haplo-HSCT in a high-risk AML population. Not surprisingly, patient-related features such as older age and the presence of comorbidities were associated with an increased NRM, while disease-related variables such as adverse-risk cytogenetics and advanced disease status at HSCT increased the risk of relapse. In contrast to these inherent and therefore unmodifiable patient and disease characteristics, the intensification of the conditioning regimen demonstrated clear benefits. The use of MAC decreased relapse without compromising NRM, ultimately resulting in superior survival compared to RIC. It is worth noting that this finding remains somewhat controversial. While a prospective randomized trial<sup>18</sup> reported improved outcomes with MAC, other retrospective studies have suggested similar survival rates.<sup>19–21</sup> In the context of PTCy, a retrospective study of the ALWP of the EBMT described a significant reduction of relapse with MAC that translated into improved survival when compared with RIC,<sup>22</sup> suggesting that increasing conditioning intensity in transplant platforms with effective GvHD control such as with the use of PTCy may be particularly relevant.

This analysis confirmed that degree of HLA match, as long as at least haploidentical, did not influence outcomes when using PTCy. This important finding, potentially relevant in clinical practice, aligns with PTCy ability to mitigate HLA-related negative impacts observed in previous studies.<sup>22–25</sup>

As expected, donor age was an important determinant of transplant outcomes. Younger donor age has long been recognized as a factor that reduces the incidence of GvHD and improves survival in HLA-matched HSCT.<sup>26,27</sup> In the Haplo-HSCT setting, donor age has consistently been highlighted as a pivotal criterion for donor selection.<sup>15,28,29</sup> While one study suggested that increasing donor age was associated with a lower incidence of disease relapse,<sup>30</sup> this finding has not been consistently validated. Furthermore, transplants from female donors to male recipients were associated with adverse outcomes. In HLA-matched HSCT, an increased risk of GvHD with female donors for male recipients has been well documented.<sup>16,31</sup> However, information regarding donor gender of Haplo donors is less clear. While maternal donors were preferred in the *ex vivo* T-cell depleted setting,<sup>5</sup> they were associated with higher NRM for male recipients in unmanipulated Haplo-HSCT without PTCy.<sup>4</sup> To our knowledge, this association has not been previously described in the context of PTCy-based Haplo-HSCT. The precise mechanism underlying the heightened predisposition to GvHD of male recipients of female grafts remains unknown, although alloreactivity to male-specific Y antigens has been speculated as a potential explanation.

The use of PB as the source of stem cells was also associated with a higher risk of acute and chronic GvHD compared to bone marrow, consequently reducing GRFS. However, this choice of stem cell source did not impact the risk of relapse, NRM, LFS or OS. This consistent finding aligns with observations from two randomized trials in matched sibling<sup>32</sup> and matched unrelated donor HSCT.<sup>33</sup> In PTCy Haplo-HSCT, several retrospective studies have reported a similar effect.<sup>22,34–36</sup>

In conclusion, donor age, gender, and stem cell source are important variables to consider when selecting an optimal donor for Haplo-HSCT using PTCy.

**When possible, younger donors and male donors for male recipients should be prioritized. The use of BM can also prevent GVHD.**

## **LIST OF ABBREVIATION**

ALWP: Acute Leukaemia Working Party

AML: acute myeloid leukemia

BM: bone marrow

CMV: cytomegalovirus

CR: complete remission

EBMT: European Society for Blood and Marrow Transplantation

GRFS: GVHD- free and relapse-free survival

GVHD: graft-versus-host disease

Haplo: haploidentical

HLA: human leukocyte antigen

HSCT: hematopoietic stem cell transplantation

LFS: leukemia-free survival

MAC: Myeloablative conditioning

NRM: nonrelapse mortality

PB: peripheral blood

PTCy: post-transplant cyclophosphamide

RIC: reduced intensity conditioning

OS: overall survival

## **DECLARATIONS**

### **Ethics approval and consent to participate**

The scientific board of the ALWP of EBMT approved this study. All patients gave written informed consent for the use of their data.

### **Consent for publication**

Not applicable for individual patient data. This is a pooled analysis.

### **Availability of data and material**

The dataset supporting the conclusions of this article are available in the ALWP of EBMT in Paris, Saint Antoine Hospital: myriam.labopin@upmc.fr

### **Competing interests**

The authors declare no competing interests.

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### **Authors' contributions**

JS, ML, MM, SP and FC: designed the study. ML: performed statistical analysis and helped with the interpretation of the results. JS: wrote the manuscript. SB, AMR, AB, JV, JT, PC, SB, RF, GS, EF, NK, YK, MIR, MZ: provided cases for the study. All authors reviewed and approved the manuscript.

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**Table 1. Patient, disease and transplant characteristics**

	<b>Haplo-HSCT</b>
<b>No. of patients</b>	2200
<b>Follow-up in months, median (IQR)</b>	24 (23-25)
<b>Age in years, median (range)</b>	56 (18-75)
<b>Gender, n (%)</b>	
Male	1314 (60)
Female	886 (40)
<b>CMV serologic status, n (%)</b>	
Negative	1656 (75)
Positive	544 (25)
<b>Karnofsky score at transplant, n (%)</b>	
< 90	611 (29)
≥ 90	1489 (71)
Missing	100
<b>HCT-CI, n (%)</b>	
0	1090 (50)
1-2	545 (25)
≥ 3	565 (25)
<b>Cytogenetic risk, n (%)</b>	
Standard	161 (7)
Intermediate	1451 (66)
Adverse	588 (27)
<b>FLT3-ITD, n (%)</b>	
Absent	871 (66)
Present	417 (32)
Missing	912
<b>NPM1, n (%)</b>	
Absent	772 (61)
Present	487 (39)
Missing	941
<b>Disease status at transplant, n (%)</b>	
CR1	1331 (61)
CR2	393 (18)
CR≥ 3	18 (1)
Relapsed/refractory disease	458 (21)
<b>Conditioning intensity, n (%)</b>	
Myeloablative	954 (43)
Reduced intensity	1246 (57)
<b>Conditioning regimen, n (%)</b>	
Chemotherapy-based	1801 (82)
TBI-based	399 (18)
<b>In-vivo T cell depletion, n (%)</b>	
No	2012 (92)
Yes	188 (9)
<b>Graft-versus-host disease prophylaxis, n (%)</b>	
PTCy + calcineurin inhibitor + MMF	1927 (86)
PTCy + Sirolimus + MMF	77 (3.5)
PTCy + calcineurin inhibitor	72 (3.3)
PTCy + calcineurin inhibitor + MTX	53 (2.6)
PTCy + MMF	45 (2)

Other	26 (1.2)
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Abbreviations: CMV, cytomegalovirus; HCT-CI, hematopoietic cell transplant specific comorbidity index; CR, complete remission; TBI, total body irradiation; PTCy, post-transplant cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate.

**Table 2. Donor characteristics**

	<b>Haplo donors</b>
<b>Age in years, median (range)</b>	37 (8-71)
<b>Group of age, n (%)</b>	
<40	1304 (59.3)
≥ 40	896 (40.7)
<b>Gender, n (%)</b>	
Male	1380 (62.7)
Female	820 (37.3)
<b>Donor/recipient gender combination, n (%)</b>	
Donor female to male recipient	458 (20.8)
Other	1742 (79.2)
<b>CMV serologic status, n (%)</b>	
Negative	948 (43.1)
Positive	1252 (56.9)
<b>Stem cell source, n (%)</b>	
Peripheral blood	1631 (74.1)
Bone marrow	569 (25.9)
<b>Donor/recipient HLA mismatch, n (%)</b>	
2-3/8	562 (25.5)
≥ 4/8	1638 (74.5)

Haplo; haploidentical; CMV, cytomegalovirus; HLA, human leucocyte antigen

**Table 3. Transplant outcomes of the entire cohort and according to the number of donor-related risk factors**

<b>Outcome*</b>	<b>Overall % (95% CI)</b>
Acute GvHD	
Grade II-IV	28 (26-30)
Grade III-IV	11 (10-12)
Chronic GvHD	
Overall	33 (31-35)
Extensive	14 (12-15)
NRM	22 (20-24)
RI	26 (24-28)
LFS	52 (50-55)
OS	57 (55-60)
GRFS	41 (39-43)

\*Acute GvHD: 180-day cumulative incidence; cGvHD, NRM and RI: cumulative incidence at 2 years; LFS, OS and GRFS: survival probability at 2 years.

Abbreviations: GvHD, graft-versus-host disease; CI, confidence interval; NRM, non-relapse mortality; RI, relapse incidence; LFS, leukemia-free survival; OS, overall survival; GRFS, graft-versus-host disease-free and relapse-free survival

Table 4. Multivariate analysis of transplants outcomes

	aGvHD III-IV		cextGvHD		NRM		RI		LFS		OS		GRFS	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
<b>Patient, disease and transplant-related variables</b>														
Patient's age per 10 years <sup>1</sup>	0.98 (0.88-1.09)	0.65	1.05 (0.94-1.16)	0.39	<b>1.29</b> <b>(1.18-1.41)</b>	<b>&lt;0.001</b>	0.94 (0.88-1.01)	0.10	<b>1.08</b> <b>(1.02-1.13)</b>	<b>0.009</b>	<b>1.14</b> <b>(1.07-1.21)</b>	<b>&lt;0.001</b>	1.04 (0.99-1.09)	0.09
Patient's CMV serostatus														
Negative	1		1		1		1		1		1		1	
Positive	1.0 (0.72-1.39)	0.99	1.26 (0.91-1.76)	0.17	1.2 (0.94-1.53)	0.14	1.07 (0.86-1.34)	0.53	1.13 (0.96-1.33)	0.14	1.17 (0.98-1.39)	0.08	1.13 (0.98-1.31)	0.10
HCT-CI														
0	1		1		1		1		1		1		1	
1-2	0.96 (0.69-1.34)	0.81	0.63 (0.44-0.89)	0.01	<b>1.32</b> <b>(1.04-1.67)</b>	<b>0.03</b>	0.86 (0.68-1.09)	0.22	1.05 (0.89-1.24)	0.55	1.12 (0.94-1.33)	0.20	1.0 (0.86-1.16)	0.97
≥3	1 (0.71-1.4)	0.99	<b>1.11</b> <b>(0.79-1.55)</b>	<b>0.54</b>	<b>1.46</b> <b>(1.14-1.86)</b>	<b>0.002</b>	1.08 (0.87-1.35)	0.49	<b>1.21</b> <b>(1.03-1.42)</b>	<b>0.02</b>	<b>1.25</b> <b>(1.05-1.48)</b>	<b>0.01</b>	<b>1.16</b> <b>(1.01-1.35)</b>	<b>0.05</b>
Disease status														
CR1	1		1		1		1		1		1		1	
CR≥2	1.21 (0.84-1.74)	0.31	0.88 (0.61-1.27)	0.49	1.28 (0.98-1.65)	0.06	<b>1.39</b> <b>(1.06-1.82)</b>	<b>0.02</b>	<b>1.33</b> <b>(1.1-1.60)</b>	<b>0.003</b>	<b>1.28</b> <b>(1.05-1.57)</b>	<b>0.02</b>	<b>1.24</b> <b>(1.05-1.46)</b>	<b>0.01</b>
Relapsed/refractory	1.37 (0.98-1.91)	0.06	<b>1.67</b> <b>(1.2-2.32)</b>	<b>0.003</b>	<b>1.6</b> <b>(1.26-2.04)</b>	<b>&lt;0.001</b>	<b>3.48</b> <b>(2.84-4.26)</b>	<b>&lt;0.001</b>	<b>2.45</b> <b>(2.11-2.85)</b>	<b>&lt;0.001</b>	<b>2.52</b> <b>(2.15-2.95)</b>	<b>&lt;0.001</b>	<b>2.13</b> <b>(1.84-2.45)</b>	<b>&lt;0.001</b>
Cytogenetic risk														
Standard	1		1		1		1		1		1		1	
Intermediate	0.88 (0.88-1.09)	0.60	0.76 (0.48-1.22)	0.26	0.92 (0.63-1.34)	0.65	1.52 (0.99-2.35)	0.06	1.18 (0.89-1.57)	0.26	1.13 (0.83-1.53)	0.45	1.01 (0.79-1.29)	0.93
High	0.99 (0.58-1.68)	0.96	0.96 (0.57-1.6)	0.86	1.18 (0.78-1.79)	0.42	<b>3.03</b> <b>(1.93-4.75)</b>	<b>&lt;0.001</b>	<b>1.94</b> <b>(1.44-2.62)</b>	<b>&lt;0.001</b>	<b>1.94</b> <b>(1.41-2.67)</b>	<b>&lt;0.001</b>	<b>1.53</b> <b>(1.18-1.97)</b>	<b>&lt;0.001</b>
Conditioning intensity														
MAC	1		1		1		1		1		1		1	
RIC	1.07 (0.78-1.47)	0.68	1.14 (0.82-1.58)	0.43	1.17 (0.93-1.48)	0.18	<b>1.32</b> <b>(1.07-1.63)</b>	<b>0.01</b>	<b>1.25</b> <b>(1.08-1.46)</b>	<b>0.004</b>	<b>1.29</b> <b>(1.1-1.53)</b>	<b>0.002</b>	<b>1.2</b> <b>(1.04-1.38)</b>	<b>0.013</b>
In-vivo T cell depletion														
No	1		1		1		1		1		1		1	
Yes	0.73	0.25	0.88	0.65	1.07	0.72	1.05	0.80	1.09	0.5	1.05	0.7	1.04	0.74

	(0.43-1.25)		(0.5-1.54)		(0.73-1.56)		(0.74-1.47)		(0.85-1.39)		(0.81-1.38)		(0.82-1.31)	
<b>Year of transplant<sup>1</sup></b>	0.93 (0.88-0.99)	0.02	0.99 (0.93-1.06)	0.77	0.99 (0.94-1.04)	0.62	1 (0.96-1.04)	0.96	1 (0.97-1.03)	0.97	1 (0.97-1.04)	0.78	0.99 (0.96-1.02)	0.59
<b>Donor-related variables</b>														
<b>Donor's age <math>\geq 37y^2</math></b>	<b>2.05</b> <b>(1.55-2.71)</b>	<b>&lt;0.001</b>	<b>1.65</b> <b>(1.26-2.16)</b>	<b>&lt;0.001</b>	<b>1.36</b> <b>(1.12-1.65)</b>	<b>0.002</b>	1.12 (0.94-1.34)	0.21	<b>1.22</b> <b>(1.07-1.39)</b>	<b>0.002</b>	<b>1.29</b> <b>(1.12-1.48)</b>	<b>&lt;0.001</b>	<b>1.32</b> <b>(1.17-1.48)</b>	<b>&lt;0.001</b>
<b>Donor's CMV serostatus</b>														
Negative	1		1		1		1		1		1		1	
Positive	1.06 (0.88-1.27)	0.57	1 (0.75-1.34)	0.98	0.91 (0.74-1.12)	0.36	0.96 (0.79-1.17)	0.71	0.94 (0.81-1.08)	0.37	0.95 (0.82-1.1)	0.51	0.95 (0.84-1.09)	0.48
<b>Donor/recipient gender</b>														
Other	1		1		1		1		1		1		1	
Female donor/male recipient	1.0 (0.72-1.38)	0.98	<b>1.95</b> <b>(1.46-2.61)</b>	<b>&lt;0.001</b>	<b>1.35</b> <b>(1.09-1.69)</b>	<b>0.007</b>	1.04 (0.84-1.29)	0.72	<b>1.18</b> <b>(1.01-1.38)</b>	<b>0.03</b>	<b>1.25</b> <b>(1.06-1.47)</b>	<b>0.007</b>	<b>1.29</b> <b>(1.12-1.48)</b>	<b>&lt;0.001</b>
<b>Donor/recipient HLA mismatch</b>														
2-3/8	1		1		1		1		1		1		1	
$\geq 4/8$	1.35 (0.98-1.87)	0.07	0.95 (0.71-1.28)	0.74	1.04 (0.84-1.30)	0.71	0.96 (0.78-1.18)	0.71	0.99 (0.85-1.15)	0.87	1.02 (0.87-1.19)	0.82	1.03 (0.9-1.18)	0.62
<b>Stem cell source</b>														
Bone marrow	1		1		1		1		1		1		1	
Peripheral blood	<b>1.74</b> <b>(1.20-2.51)</b>	<b>0.003</b>	1.38 (0.97-1.97)	0.08	1.15 (0.90-1.48)	0.26	1.06 (0.85-1.32)	0.62	1.09 (0.93-1.28)	0.30	1.04 (0.87-1.23)	0.69	<b>1.19</b> <b>(1.02-1.39)</b>	<b>0.03</b>

Abbreviations: GvHD, graft-versus-host disease; aGvHD, acute GvHD; cextGvHD, chronic extensive GvHD; CI, confidence interval; NRM, non-relapse mortality; RI, relapse incidence; LFS, leukemia-free survival; OS, overall survival; GRFS, graft-versus-host disease and relapse-free survival; HR, hazard ratio; TBI, total body irradiation; HCT-CI, hematopoietic cell transplant-specific comorbidity index; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; CR, complete remission; CMV, cytomegalovirus; HLA, human leucocyte antigen

1. Continuous variable

2. Median

## Figure legends

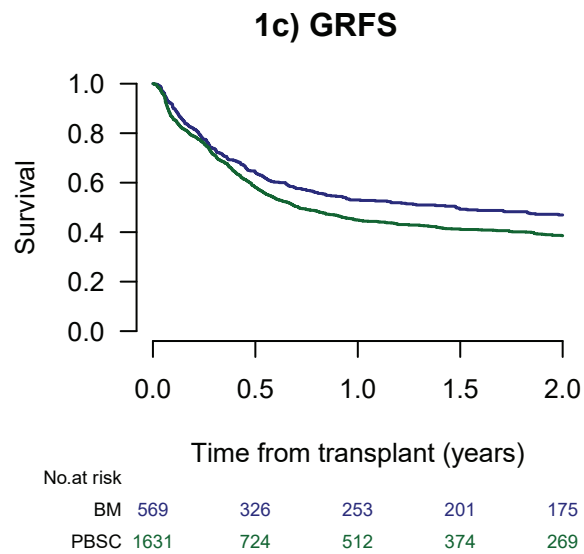
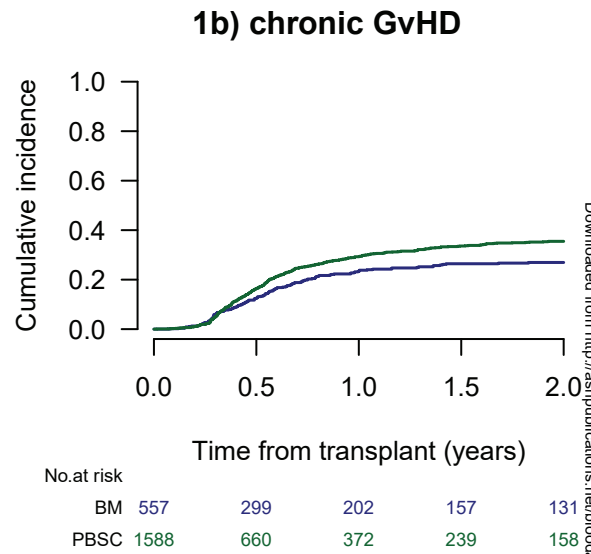
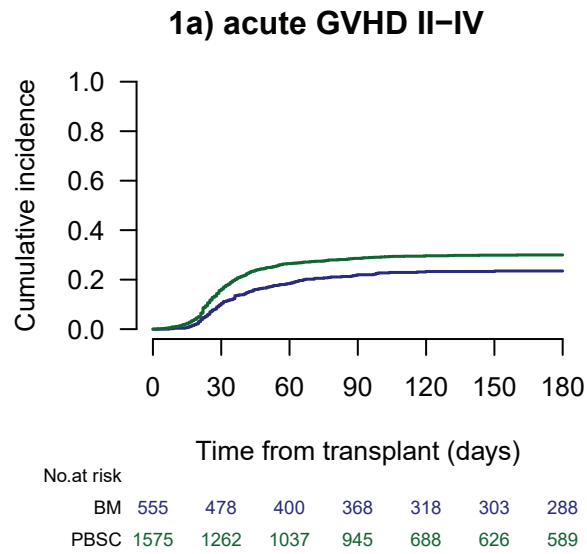
**Figure 1.** Acute and chronic graft-versus-host disease (GVHD), and graft-versus-host disease and relapse-free survival (GRFS) according to the stem cell source.

**Figure 2.** Probability of leukemia-free survival (LFS), overall survival (OS) and graft-versus-host disease and relapse-free survival (GRFS) according to donor age.

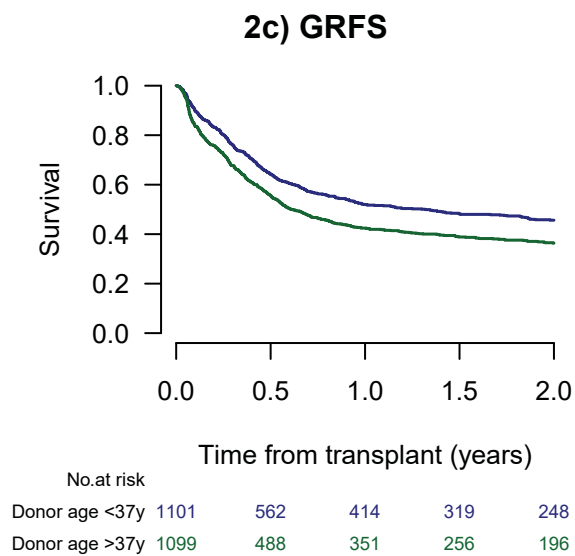
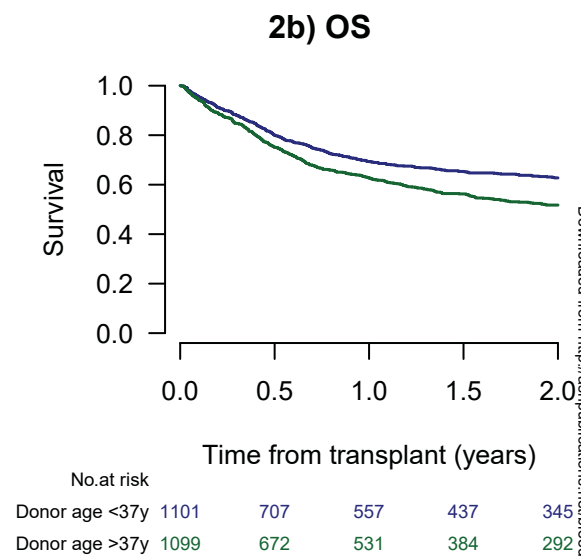
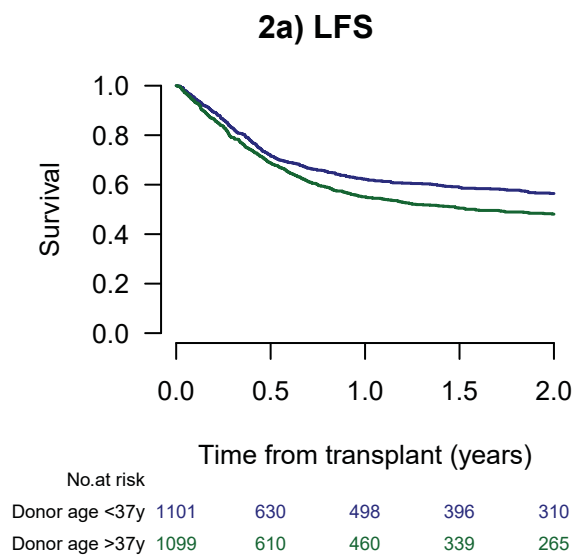
**Figure 3.** Probability of leukemia-free survival (LFS), overall survival (OS) and graft-versus-host disease and relapse-free survival (GRFS) according to donor gender.



# Figure 1



# Figure 2



# Figure 3

