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Non-T-Depleted Haploidentical Transplantation Compared to Allogeneic Transplantation From Matched Siblings or Unrelated Donors in Patients With Secondary AML in First Complete Remission: A Study From the ALWP/EBMT

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative option for secondary acute myeloid leukemia (sAML). This study compared haploidentical donor (Haplo), matched sibling donor (MSD), and matched unrelated donor (MUD) HSCT in patients with sAML in first complete remission (CR1). Data from 3862 patients (Haplo = 643, MSD = 715, MUD = 2504) transplanted between 2010 and 2022 were analyzed, with a median follow-up of 3.3 years. Groups differed in patient and donor age, conditioning regimen, stem cell source, and graft-versus-host disease (GVHD) prophylaxis. Multivariate analysis showed that MSD-HSCT had a higher relapse risk than Haplo-HSCT (hazard ratio [HR]: 1.64) but lower non-relapse mortality (NRM, HR: 0.32) and acute GVHD risk (HR: 0.54 for grade II–IV), leading to an overall survival (OS) benefit (HR: 0.76). MUD-HSCT had lower NRM than Haplo-HSCT (HR: 0.63) but there were no significant differences in OS or GVHD risk. Donor type did not impact leukemia-free survival (LFS) or GVHD-free and relapse-free survival (GRFS). Adverse cytogenetics and reduced-intensity conditioning were associated with increased relapse risk, while lower Karnofsky scores, older age, and adverse cytogenetics independently predicted worse NRM, LFS, OS, and GRFS outcomes. Female-to-male donor-recipient pairs had an increased risk of

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chronic GVHD. In this registry-based analysis, MSD offered the best outcomes for sAML in CR1. Haplo-HSCT was comparable to MUD-HSCT, despite a higher NRM, and achieved long-term disease control in 60% of patients due to a low relapse incidence. In the absence of an MSD, both Haplo and MUD are viable alternatives.

1 | Introduction

Secondary acute myeloid leukemia (sAML) is a distinct form of acute myeloid leukemia (AML) that arises following an antecedent hematological disorder, such as myelodysplastic syndrome (MDS) or myeloproliferative disorder (MPD), or as a consequence of prior neoplastic therapy [1–6]. It is characterized by poor response to conventional therapies, with complete remission (CR) rates ranging from 40% to 50%, a high risk of early relapse, early mortality, and an overall survival (OS) of approximately 7 months. The dismal prognosis of sAML can be attributed to several factors, including the older age of patients, the presence of adverse cytogenetic features, and the antecedent hematological disease—all of which are established poor prognostic markers in AML. Additionally, the biology of sAML is more aggressive, with a lower susceptibility to chemotherapy and a reduced ability to tolerate intensive treatment, leading to poorer quality of remission. Previous studies have demonstrated that allogeneic hematopoietic stem cell transplantation (HSCT) using either human leukocyte antigen (HLA)-matched sibling donors (MSD) or matched unrelated donors (MUD) results in inferior outcomes for patients with sAML compared to those with de novo AML [7–9]. In contrast, haploidentical donor (Haplo) transplantation combined with post-transplantation cyclophosphamide (PTCy) has shown promise, significantly reducing non-relapse mortality (NRM) and the incidence of graft-versus-host disease (GVHD), while potentially enhancing the graft-versus-leukemia (GVL) effect. Our recent work suggests that Haplo-HSCT with PTCy may rescue 30%–60% of patients with sAML, including those with relapsed/refractory disease, offering hope for improving the prognosis in this challenging patient group [10–12]. Despite these promising developments, the question of whether a particular donor type offers superior outcomes in sAML remains unanswered, as no formal comparisons have been conducted. This manuscript aims to address this gap by evaluating the comparative efficacy and safety of these three donor types in the context of sAML in first CR (CR1).

2 | Methods

2.1 | Study Design and Patient Population

This was a retrospective, multicenter analysis. Data were provided by the registry of the ALWP of the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centers, mainly located in Europe, which are required to report all consecutive stem cell transplantations and follow-ups once a year. Data are entered, managed, and maintained in a central database. Since 1990, all patients have provided informed consent authorizing the use of their personal information for research purposes. The validation and quality control program includes verification of the computer print-out of the entered data, cross-checking with the national registries, and on-site visits to selected teams. The study was approved by the ALWP of the EBMT institutional review board and conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. This study included adult patients (≥18 years) diagnosed with sAML who underwent their first T-cell-replete HSCT from either a Haplo, a MSD, or a 9–10/10 MUD between 2010 and 2022. Conditioning regimens consisted of either myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC). The graft source was either bone marrow (BM) or peripheral blood stem cells (PBSC). Patients were excluded if they had a history of prior HSCT, received both BM and PBSC, underwent cord blood transplantation, received ex vivo T-cell-depleted grafts, or had a disease status other than CR1 before transplantation. Data collected included recipient and donor characteristics (age, gender, cytomegalovirus serostatus, Karnofsky performance status [KPS], and hematopoietic cell transplantation specific comorbidity index [HCT-CI]), disease characteristics including disease type, disease status, cytogenetic risk (European LeukemiaNet [ELN] 2017 cytogenetics classification), antecedent hematological disorder, year of transplant, type of conditioning regimen, stem cell source, and GVHD prophylaxis regimen. The conditioning regimen was defined as MAC when containing total body irradiation with a dose > 6 Gray or a total dose of busulfan > 8 mg/kg or > 6.4 mg/kg when administered orally or intravenously [13], respectively. All other regimens were defined as RIC. Grading of acute GVHD was performed using established criteria [14]. Chronic GVHD was classified as limited or extensive according to published criteria [15]. For this study, all necessary data were collected according to the EBMT guidelines. The list of institutions contributing data to this study is provided in the Supporting Information Appendix.

2.2 | Study Endpoints and Statistical Analysis

The median, interquartile range (IQR), and range were used to describe quantitative variables, while frequency and percentage were used for categorical variables. The study endpoints included OS, leukemia-free survival (LFS), relapse incidence (RI), NRM, engraftment, acute GVHD, chronic GVHD, and GVHD-and relapse-free survival (GRFS). All endpoints were measured from the time of transplantation. Engraftment was defined as achieving an absolute neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days. OS was defined as the time to death from any cause. LFS was defined as survival without evidence of relapse or progression. NRM was defined as death from any cause without prior relapse or progression. Modified GRFS criteria were used for this study, with GRFS events defined as the first occurrence of grade III–IV acute GVHD, extensive chronic GVHD, relapse, or death from any cause [16]. Patient, disease, and transplant-related characteristics were compared using the Mann–Whitney U test for numerical data and the χ^2 or Fisher's exact test for categorical data. Probabilities of OS, LFS, and GRFS were estimated using the Kaplan–Meier method. Cumulative incidence functions in a competing risks framework were used to calculate RI and NRM, with death in remission treated as a competing event for relapse, and death

as a competing event for engraftment. For estimating the cumulative incidence of acute or chronic GVHD, relapse and death were considered competing events. Univariate analyses were performed using the log-rank test for OS, LFS, and GRFS, and Gray's test for cumulative incidence. Multivariate analyses were conducted using the Cox proportional-hazards regression model [17]. All variables differing significantly between the groups, and potential risk factors, were included in the model. To account for inter-center heterogeneity in the effects of characteristics or treatments, a random effect (frailty) term was included in the Cox model [18]. All potential interactions between core variables and other significant variables were evaluated. Univariate and multivariate analyses were conducted on complete cases. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All p values were two-sided, with a type I error rate of 0.05. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL) and R version 4.3.2 (R Core Team).

3 | Results

3.1 | Patient and Transplant Characteristics

A total of 3862 patients met the inclusion criteria, comprising 643 who underwent Haplo-HSCT, 715 who received HSCT from MSD, and 2504 who underwent HSCT from MUD. Patient and transplant characteristics are summarized in Table 1. The median year of transplantation was 2017 (IQR: 2014–2020), with Haplo-HSCT performed more recently compared to MSD and MUD transplants. The overall median follow-up duration was 3.3 years (IQR: 3.1–3.5), with the shortest median follow-up observed in Haplo-HSCT recipients (2.6 years), compared to a median of 4.0 years for MSD and 3.3 years for MUD. The median patient age at transplantation was 60.5 years (IQR: 53.0–65.8) and differed significantly across groups, with median ages of 61 years for Haplo, 59 years for MSD, and 61 years for MUD ($p < 0.001$). Recipients of Haplo- and MUD-HSCT were slightly older (median: 61.0 and 60.9 years, respectively) than MSD-HSCT recipients (median: 58.9 years). Similarly, donor age varied significantly ($p < 0.001$), with younger MUD (median: 29.2 years) and Haplo (median: 36.0 years) compared to MSD (median: 56.8 years). The cytogenetic classification of AML did not differ significantly between groups ($p = 0.066$), with intermediate-risk cytogenetics being the most common category overall (64%). The most frequent prior diagnosis was MDS or MPD, diagnosed in 48% of patients. A KPS of ≥ 90 was observed in 72% of the cohort, with similar distributions across groups ($p = 0.92$). However, patient and donor sex distributions differed significantly between groups ($p = 0.035$ and $p < 0.001$, respectively). Transplants from female donors to male patients were more frequent in the Haplo (21%) and MSD (27%) groups compared to MUD (11%) ($p < 0.001$). Cytomegalovirus serostatus of patients and donors differed significantly across groups ($p < 0.001$) and negative-to-positive donor–recipient pairs were more common in the Haplo (25%) and MSD (26%) than in the MUD (19%) group ($p < 0.001$). HCT-CI scores ≥ 3 were less frequent among Haplo- (29%) and MSD-HSCT (27%) recipients compared to MUD-HSCT (35%) recipients ($p < 0.001$). A greater proportion of Haplo-HSCT patients received MAC regimens (53.6%) compared to the MSD (41.4%) and MUD (44.4%) groups ($p < 0.001$). The conditioning regimens used are listed in Table S1. PBSC was the predominant graft source across all groups (93%). However, Haplo-HSCT recipients had a higher proportion of BM as the cell source (21%) compared to MSD (3.2%) and MUD-HSCT (5.1%) recipients ($p < 0.001$). PTCy was the main GVHD prophylaxis in Haplo-HSCT (90.4%), while ATG was predominantly used in MSD (88.4%) and MUD (90.3%) transplants ($p < 0.001$). Additional GVHD prevention strategies also varied across groups ($p < 0.001$) and are shown in Table S2. The median time from diagnosis to HCT was shortest for MSD (4.34 months), followed by MUD (4.76 months) and Haplo (5.06 months) ($p < 0.001$).

3.2 | Transplantation Outcomes

Table 2 summarizes the univariate analysis of transplant outcomes. At 2 years, OS rates were 56.9% (95% CI: 52.6–60.9) for Haplo, 58.3% (95% CI: 54.2–62.0) for MSD, and 58.8% (95% CI: 56.7–60.9) for MUD (Figure 1A). LFS rates were 51.6% (95% CI: 47.3–55.7) for Haplo, 48.9% (95% CI: 44.9–52.8) for MSD, and 53.0% (95% CI: 50.8–55.1) for MUD (Figure 1B). GRFS rates were 39.2% (95% CI: 35.1–43.4) for Haplo, 39.4% (95% CI: 35.5–43.3) for MSD, and 42.8% (95% CI: 40.6–44.9) for MUD (Figure 1C). RI rates at 2 years were 21.8% (95% CI: 18.4–25.4), 40.4% (95% CI: 36.6–44.2), and 26.8% (95% CI: 25.0–28.7) for Haplo, MSD, and MUD, respectively (Figure 1D). The 2-year NRM rates were 26.5% (95% CI: 23.0–30.2), 10.6% (95% CI: 8.4–13.2), and 20.2% (95% CI: 18.5–21.9) for Haplo, MSD, and MUD, respectively (Figure 1E). The incidence of acute GVHD grade ≥ II at Day 180 was 29.7% (95% CI: 26.1–33.3), 20.1% (95% CI: 17.2–23.1), and 27.0% (95% CI: 25.3–28.8) for Haplo, MSD, and MUD, respectively (Figure 2A). Acute GVHD grade ≥ III at day 180 occurred in 8.7% (95% CI: 7.9–9.7), 10.6% (95% CI: 8.3–13.2), and 5.7% (95% CI: 4.2–7.6) for Haplo, MSD, and MUD, respectively (Figure 2B). Chronic GVHD at 2 years occurred in 30.9% (95% CI: 27.0–34.9), 33.4% (95% CI: 29.7–37.2), and 32.5% (95% CI: 30.5–34.6) of patients, respectively (Figure 2C). Extensive chronic GVHD at 2 years was observed in 10.7% (95% CI: 8.2–13.6), 13.4% (95% CI: 10.8–16.2), and 12.9% (95% CI: 11.4–14.4) of patients, respectively (Figure 2D).

3.3 | Cause of Death

The causes of death are summarized in Table 3, based on data from 1626 patients (42%). Relapse of leukemia was the most common cause, accounting for 56.2% of deaths, followed by HSCT-related complications (36.2%). Other causes accounted for 7.6% of deaths. Among Haplo-HSCT recipients, transplant-related complications were the leading cause of death (52.6%), compared to 18.1% in the MSD group and 37.3% in the MUD group. Conversely, relapse of leukemia predominated in the MSD (78.7%) and MUD (53.5%) groups but was less frequent in Haplo-HSCT recipients (40.4%).

3.4 | Multivariate Analysis

Table 4 summarizes the multivariate analysis. MSD transplantation was associated with a higher risk of relapse compared

TABLE 1 | Patient and transplant characteristics.

Variable	Overall ($N=3862$)	Haplo ($N=643$)	MSD ($N=715$)	MUD ($N=2504$)	p[a]
Year of transplantation	2017 (2014, 2020)	2019 (2016, 2021)	2017 (2014, 2019)	2017 (2014, 2020)	<0.001
Median FU, y (IQR)	3.3 (3.1–3.5)	2.6 (2.3–3)	4 (3.4–4.7)	3.3 (3.1–3.7)	
Age of the patient at HCT, y (IQR)	61 (53, 66)	61 (53, 67)	59 (52, 64)	61 (53, 66)	<0.001
Age of the donor at HCT, y (IQR)	33 (26, 46)	36 (28, 45)	57 (49, 62)	29 (24, 37)	<0.001
ELN 2017 cytogenetic risk					0.066
Favorable	35 (1.2%)	5 (1.0%)	12 (2.3%)	18 (1.0%)	
Intermediate	1821 (63.9%)	318 (61.7%)	323 (61.5%)	1180 (65.2%)	
Adverse	995 (34.9%)	192 (37.3%)	190 (36.2%)	613 (33.8%)	
Missing	1011	128	190	693	
Previous diagnosis					
MDS	1290 (33.4%)	188 (29.2%)	224 (31.3%)	878 (35.1%)	
MPN	266 (6.9%)	43 (6.7%)	57 (8.0%)	166 (6.6%)	
MDS/MPN	317 (8.2%)	53 (8.2%)	52 (7.3%)	212 (8.5%)	
Unknown if MDS or combined MDS/MPN	1555 (40.3%)	301 (46.8%)	290 (40.6%)	964 (38.5%)	
AML	8 (0.2%)	2 (0.3%)	0 (0.0%)	6 (0.2%)	
ALL	11 (0.3%)	2 (0.3%)	1 (0.1%)	8 (0.3%)	
CML	18 (0.5%)	1 (0.2%)	4 (0.6%)	13 (0.5%)	
Lymphoma	9 (0.2%)	3 (0.5%)	1 (0.1%)	5 (0.2%)	
NHL	49 (1.3%)	9 (1.4%)	6 (0.8%)	34 (1.4%)	
Hodgkin	31 (0.8%)	1 (0.2%)	13 (1.8%)	17 (0.7%)	
Solid tumor not breast	145 (3.8%)	20 (3.1%)	34 (4.8%)	91 (3.6%)	
Breast cancer	139 (3.6%)	16 (2.5%)	29 (4.1%)	94 (3.8%)	
Bone marrow failure	1 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	
Bone marrow failure acquired	7 (0.2%)	2 (0.3%)	1 (0.1%)	4 (0.2%)	
Nonmalignant disease	16 (0.4%)	1 (0.2%)	3 (0.4%)	12 (0.5%)	
Type of donors					<0.001
Haplo	643 (20.4%)	643 (100.0%)	0 (NA%)	0 (0.0%)	
UD 9/10	492 (15.6%)	0 (0.0%)	0 (NA%)	492 (19.6%)	
UD 10/10	2012 (63.9%)	0 (0.0%)	0 (NA%)	2012 (80.4%)	
Missing	715	0	715	0	
Karnofsky score					0.92
≥90	2630 (71.6%)	442 (70.9%)	484 (71.5%)	1704 (71.7%)	
<90	1045 (28.4%)	181 (29.1%)	193 (28.5%)	671 (28.3%)	
Missing	187	20	38	129	
Female donor to male patient					<0.001
No	3255 (84.5%)	504 (78.5%)	522 (73.2%)	2229 (89.3%)	
Yes	595 (15.5%)	138 (21.5%)	191 (26.8%)	266 (10.7%)	

(Continues)

TABLE 1 | (Continued)

Variable	Overall ($N=3862$)	Haplo ($N=643$)	MSD ($N=715$)	MUD ($N=2504$)	p[a]
Missing	12	1	2	9	
CMV antibodies donor to patient					< 0.001
Neg to Neg	865 (22.8%)	100 (15.8%)	145 (20.7%)	620 (25.1%)	
Neg to Pos	941 (24.8%)	160 (25.3%)	132 (18.8%)	649 (26.3%)	
Pos to Neg	300 (7.9%)	37 (5.9%)	74 (10.5%)	189 (7.7%)	
Pos to Pos	1695 (44.6%)	335 (53.0%)	351 (50.0%)	1009 (40.9%)	
Missing	61	11	13	37	
HCT-CI					< 0.001
0	1320 (45.7%)	264 (49.0%)	276 (53.3%)	780 (42.6%)	
1–2	632 (21.9%)	120 (22.3%)	100 (19.3%)	412 (22.5%)	
≥ 3	938 (32.5%)	155 (28.8%)	142 (27.4%)	641 (35.0%)	
Missing	972	104	197	671	
RIC or MAC regimen					< 0.001
RIC	2087 (54.3%)	293 (46.0%)	418 (58.6%)	1376 (55.2%)	
MAC	1758 (45.7%)	344 (54.0%)	295 (41.4%)	1119 (44.8%)	
Missing	17	6	2	9	
Main GVHD prevention					< 0.001
ATG	2955 (76.5%)	62 (9.6%)	632 (88.4%)	2261 (90.3%)	
PTCY	907 (23.5%)	581 (90.4%)	83 (11.6%)	243 (9.7%)	
Cell source					< 0.001
PB	3576 (92.6%)	508 (79.0%)	692 (96.8%)	2376 (94.9%)	
BM	286 (7.4%)	135 (21.0%)	23 (3.2%)	128 (5.1%)	
Median months between diagnosis and HCT (IQR)	4.73 (3.68, 6.21)	5.06 (3.75, 6.90)	4.34 (3.48, 5.77)	4.76 (3.71, 6.24)	< 0.001

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; Chemo, chemotherapy; CMV, cytomegalovirus; FU, follow-up; Haplo, haploidentical donor; Haplo, haploidentical donor; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; MSD, matched sibling donor; MSD, matched sibling donor; MUD, matched unrelated donor; Neg, negative; PB, peripheral blood; Pos, positive; RIC, reduced intensity conditioning; TBI, total body irradiation; TCI, transplantation conditioning intensity; UD, unrelated donor; y, year.
[a]Pearson's Chi-squared test; Kruskal–Wallis rank sum test.

TABLE 2 | Univariate analysis.

Outcomes % (95% CI)	OS (2y)	LFS (2y)	GRFS (2y)	RI (2y)	NRM (2y)
Haplo	56.9 (52.6–60.9)	51.6 (47.3–55.7)	39.2 (35.1–43.4)	21.8 (18.4–25.4)	26.5 (23–30.2)
MSD	58.3 (54.2–62)	48.9 (44.9–52.8)	39.4 (35.5–43.3)	40.4 (36.6–44.2)	10.6 (8.4–13.2)
MUD	58.8 (56.7–60.9)	53 (50.8–55.1)	42.8 (40.6–44.9)	26.8 (25–28.7)	20.2 (18.5–21.9)

Outcomes % (95% CI)	aGVHD ≥ II (180d)	cGVHD (2y)	extcGVHD (2y)
Haplo	29.7 (26.1–33.3)	30.9 (27–34.9)	10.7 (8.2–13.6)
MSD	20.1 (17.2–23.1)	33.4 (29.7–37.2)	13.4 (10.8–16.2)
MUD	27 (25.3–28.8)	32.5 (30.5–34.6)	12.9 (11.4–14.4)

Abbreviations: aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; d, days; extcGVHD, extensive cGVHD; GRFS, GVHD-free, relapse-free survival; GVHD, graft-versus-host disease; Haplo, haploidentical donor; LFS, leukemia-free survival; MSD, matched sibling donor; MUD, matched unrelated donor; NRM, non-relapse mortality; OS, overall survival; RI, relapse incidence; y, years.

to Haplo (HR: 1.79, 95% CI: 1.31–2.45, $p < 0.001$), but both MSD and MUD transplants had lower NRM (HR: 0.26, 95% CI: 0.17–0.38, $p < 0.001$; HR: 0.65, 95% CI: 0.47–0.9, $p = 0.010$, respectively). Donor type was not prognostic for LFS. MSD donors were associated with improved OS and GRFS compared to Haplo (OS HR: 0.69, 95% CI: 0.53–0.9, $p = 0.005$; GRFS HR: 0.79, 95% CI: 0.63–0.98, $p = 0.036$), whereas MUD showed no significant differences.

MSD was also associated with lower risk of acute GVHD grade II–IV and III–IV compared to Haplo (HR: 0.5, 95% CI: 0.36–0.7, $p < 0.001$; HR: 0.36, 95% CI: 0.2–0.63, $p < 0.001$), with no differences for chronic GVHD.

Adverse cytogenetics was associated with increased risk of relapse (HR: 2.03, 95% CI: 1.77–2.32, $p < 0.001$). For NRM, lower KPS (< 90) and increasing patient and donor age at HSCT were associated with higher risk (KPS—HR: 1.28, 95% CI: 1.06–1.53, $p = 0.009$; patient age—HR: 1.24, 95% CI: 1.13–1.36, $p < 0.001$; donor age—HR: 1.13, 95% CI: 1.05–1.23, $p = 0.002$). For LFS, older patient age (HR: 1.11, 95% CI: 1.05–1.17, $p < 0.001$) and adverse cytogenetics (HR: 1.6, 95% CI: 1.44–1.79, $p < 0.001$) were associated with higher event probability. For OS, lower KPS (HR: 1.15, 95% CI: 1.02–1.3, $p = 0.027$), older patient age (HR: 1.17, 95% CI: 1.1–1.24, $p < 0.001$), and adverse cytogenetics (HR: 1.64, 95% CI: 1.46–1.84, $p < 0.001$) predicted worse outcomes. Similarly, older patient age (HR: 1.07, 95%

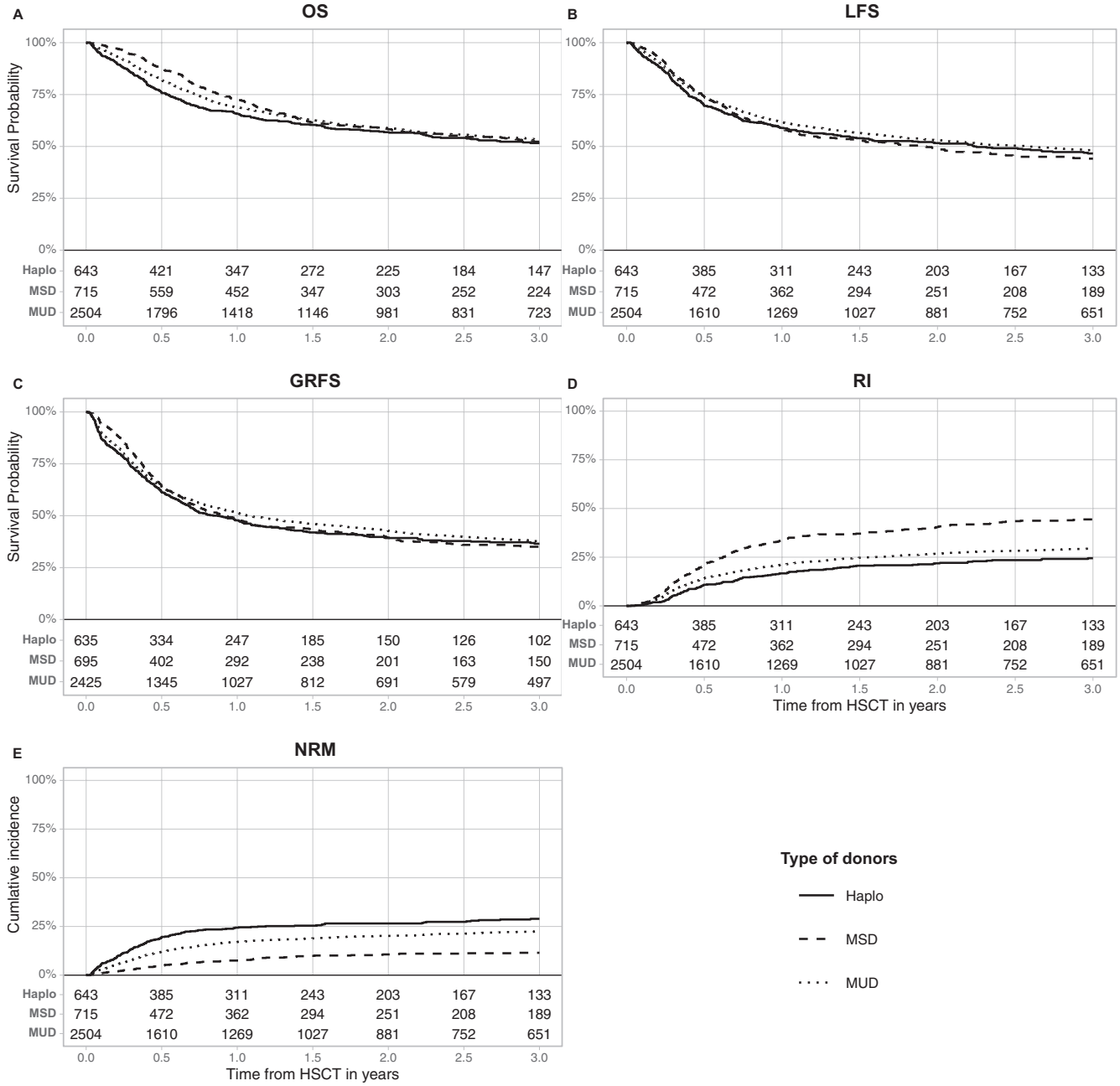

FIGURE 1 | Impact of donor type on outcomes in sAML patients undergoing allogeneic HSCT in CR1. Kaplan–Meier curves for OS (A), LFS (B), and GRFS (C) and cumulative incidence curves for RI (D) and NRM (E) comparing Haplo, MSD, and MUD transplantation are shown. Survival curves were compared using log-rank tests; Gray's test assessed cumulative incidence differences.

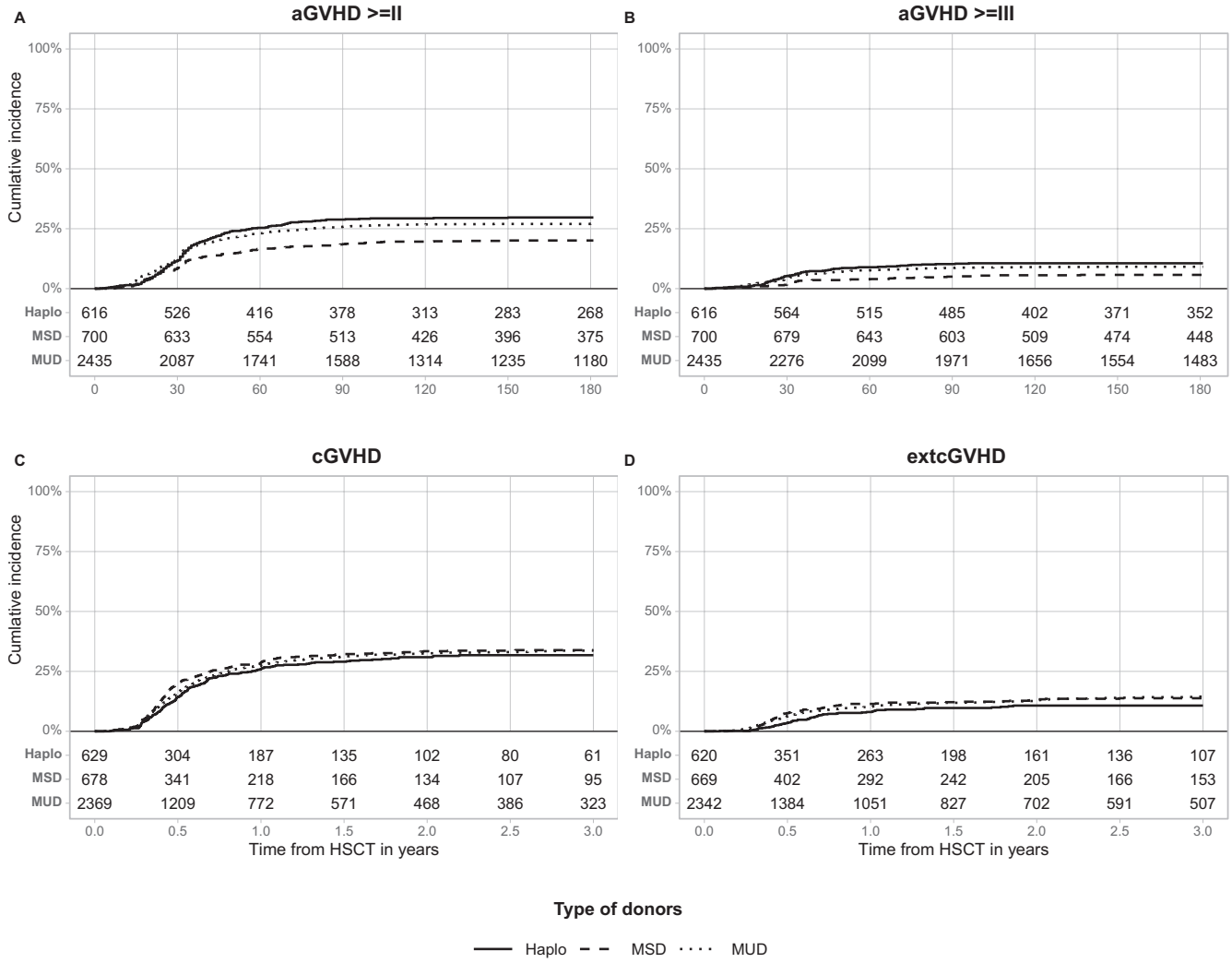

FIGURE 2 | Impact of donor type on GVHD in sAML patients undergoing allogeneic HSCT in CR1. Cumulative incidence curves for acute GVHD grade II–IV (A), acute GVHD grade III–IV (B), chronic GVHD (C), and extensive chronic GVHD (D) comparing Haplo, MSD, and MUD transplantation. Curves were compared using Gray's test.

TABLE 3 | Cause of death.

Main cause of death	Overall ($N=1633$)	MSD ($N=311$)	Haplo ($N=276$)	MUD ($N=1046$)
Relapse	913 (55.9%)	244 (78.5%)	110 (39.9%)	559 (53.4%)
HSCT related	621 (37.9%)	58 (18.8%)	151 (54.6%)	214 (40%)
Secondary malignancy	26 (1.6%)	4 (1.3%)	2 (0.7%)	20 (1.9%)
Other	73 (4.5%)	5 (1.6%)	13 (4.7%)	55 (5.3%)

Abbreviations: Haplo, haploidentical donor; HSCT, hematopoietic stem cell transplantation; MSD, matched sibling donor; MUD, matched unrelated donor.

CI: 1.02–1.13, $p=0.007$) and adverse cytogenetics (HR: 1.43, 95% CI: 1.29–1.58, $p<0.001$) were associated with higher risk for GRFS.

Longer intervals between diagnosis and HCT were associated with a lower risk of acute GVHD grade II–IV and III–IV (HR: 0.96, 95% CI: 0.93–1.00, $p=0.025$; HR: 0.93, 95% CI: 0.88–0.99, $p=0.014$, respectively). Female donor to male recipient was associated with a higher risk of chronic GVHD (HR: 1.34, 95% CI; 1.11–1.6, $p=0.002$), while no significant predictors were identified for extensive chronic GVHD.

3.5 | Subgroup Analysis

In the subgroup restricted to patients receiving PTCy (Tables S3–S5 and Figures S1 and S2), the unfavorable impact of Haplo on NRM compared with both MSD and MUD remained

TABLE 4 | Multivariate analysis.

Variable	OS		LFS		RI		NRM		GRFS	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Type of donors: Haplo vs. MSD	0.69 (0.53–0.9)	0.005	0.85 (0.66–1.08)	0.174	1.79 (1.31–2.45)	0.000	0.26 (0.17–0.38)	0.000	0.79 (0.63–0.98)	0.036
Type of donors: Haplo vs. MUD	0.82 (0.65–1.02)	0.077	0.85 (0.69–1.05)	0.124	1.11 (0.84–1.46)	0.482	0.65 (0.47–0.9)	0.010	0.85 (0.71–1.03)	0.099
Karnofsky score: ≥90 vs. <90	1.15 (1.02–1.3)	0.027	1.12 (1–1.26)	0.052	1.01 (0.87–1.17)	0.923	1.28 (1.06–1.53)	0.009	1.09 (0.98–1.22)	0.108
Age of the patient at HCT (per 10 years)	1.17 (1.1–1.24)	0.000	1.11 (1.05–1.17)	0.000	1.04 (0.97–1.12)	0.240	1.24 (1.13–1.36)	0.000	1.07 (1.02–1.13)	0.007
Age of the donor at HCT (per 10 years)	1.04 (0.98–1.1)	0.154	1.02 (0.96–1.07)	0.527	0.94 (0.88–1.01)	0.106	1.13 (1.05–1.23)	0.002	1.02 (0.97–1.07)	0.501
Female donor to male patient: No vs. Yes	0.99 (0.85–1.15)	0.883	0.97 (0.84–1.12)	0.664	0.88 (0.72–1.06)	0.179	1.12 (0.9–1.4)	0.308	1.01 (0.89–1.16)	0.850
Cytogenetic AML classification: Favorable/Int/Missing vs. Adverse	1.64 (1.46–1.84)	0.000	1.6 (1.44–1.79)	0.000	2.03 (1.77–2.32)	0.000	1.08 (0.9–1.31)	0.407	1.43 (1.29–1.58)	0.000
Months between diagnosis and HCT	1.02 (1–1.04)	0.090	1.01 (0.99–1.03)	0.352	1 (0.97–1.03)	0.987	1.03 (0.99–1.06)	0.116	1 (0.98–1.02)	0.960
RIC or MAC regimen: RIC vs. MAC	0.91 (0.8–1.04)	0.182	0.9 (0.8–1.02)	0.091	0.88 (0.75–1.02)	0.092	0.93 (0.76–1.12)	0.438	0.87 (0.78–0.98)	0.017
Main Gvh Prevention: ATG vs. PTCY	0.85 (0.7–1.05)	0.127	0.86 (0.71–1.04)	0.113	0.92 (0.73–1.16)	0.482	0.77 (0.57–1.04)	0.089	0.9 (0.76–1.06)	0.208

Variable	aGVH_II.IV		aGVH_III.IV		cGVH		extcGVH	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Type of donors: Haplo vs. MSD	0.5 (0.36–0.7)	0.000	0.36 (0.2–0.63)	0.000	0.9 (0.66–1.23)	0.521	0.93 (0.57–1.53)	0.788
Type of donors: Haplo vs. MUD	0.84 (0.64–1.1)	0.196	0.8 (0.5–1.26)	0.331	1.13 (0.86–1.47)	0.382	1.19 (0.78–1.8)	0.428
Karnofsky score: ≥90 vs. <90	1.09 (0.93–1.28)	0.304	1.37 (1.05–1.79)	0.019	1 (0.85–1.17)	0.994	0.94 (0.74–1.19)	0.590
Age of the patient at HCT (per 10 years)	1.01 (0.94–1.09)	0.776	1.01 (0.89–1.15)	0.832	1.04 (0.96–1.11)	0.324	0.99 (0.88–1.1)	0.813
Age of the donor at HCT (per 10 years)	1.03 (0.96–1.11)	0.384	1.12 (0.99–1.26)	0.080	1.05 (0.98–1.13)	0.171	1.06 (0.96–1.19)	0.259
Female donor to male patient: No vs. Yes	0.96 (0.79–1.18)	0.722	0.77 (0.53–1.12)	0.173	1.34 (1.11–1.6)	0.002	1.14 (0.86–1.52)	0.356
Cytogenetic AML classification: Favorable/Int/Missing vs. Adverse	0.98 (0.84–1.14)	0.778	0.99 (0.75–1.3)	0.941	1.06 (0.9–1.24)	0.501	0.92 (0.72–1.18)	0.519
Months between diagnosis and HCT	0.96 (0.93–1)	0.025	0.93 (0.88–0.99)	0.014	0.99 (0.96–1.02)	0.488	1.03 (0.98–1.07)	0.273
RIC or MAC regimen: RIC vs. MAC	0.85 (0.71–1.01)	0.058	0.76 (0.57–1.01)	0.055	0.96 (0.81–1.13)	0.602	0.83 (0.65–1.06)	0.144
Main Gvh Prevention: ATG vs. PTCY	0.92 (0.72–1.18)	0.523	1.03 (0.68–1.55)	0.902	1.02 (0.81–1.3)	0.850	0.9 (0.62–1.3)	0.566

Abbreviations: AML, acute myeloid leukemia; ATG, anti thymocyte globulin; CI, confidence interval; GRFS, GVHD-free, relapse-free survival; GRFS, GVHD-free, relapse-free survival; GVHD, graft versus host disease; GVHD, graft-versus-host disease; Haplo, haploidentical donor; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; LFS, leukemia-free survival; MSD, matched sibling donor; MUD, matched unrelated donor; NRM, non-relapse mortality; OS, overall survival; Poly, polymorphonuclears; PTCy, post-transplant cyclophosphamide.

evident, whereas differences in OS, RI, and aGVHD were no longer statistically significant. Haplo recipients continued to show delayed neutrophil and platelet recovery compared with MSD and MUD. No clear differences in chronic GVHD were observed, although the protective effect of Haplo against acute GVHD was less pronounced. Interpretation of these findings is limited by the strong association between donor type and PTCy exposure.

4 | Discussion

This registry-based retrospective analysis provides valuable insights into the outcomes of HSCT in patients with sAML in CR1, focusing on the impact of different donor types. Our findings confirm the well-established advantages of MSD, which yielded the most favorable outcomes and is generally considered the best donor for allo-HCT [11]. This superiority was primarily driven by a lower risk of acute GVHD and reduced NRM in our cohort.

In the absence of an MSD, MUD remains a strong alternative, offering robust outcomes in our study. Interestingly, Haplo demonstrated outcomes comparable to MUD, except for a higher risk incidence of NRM. This aligns with some prior studies but contrasts with others [19], suggesting that the variability in Haplo outcomes may depend on center-specific factors, conditioning regimens, and post-transplant management strategies.

Notably, Haplo-HSCT achieved the lowest RI of 22%, compared to 40% with MSD and 27% with MUD. This translated into an encouraging OS rate of 56.9% in this high-risk patient population, highlighting that Haplo is an effective alternative when an MSD is unavailable. One possible contributor to the reduced RI observed in the Haplo group is the more frequent use of myeloablative conditioning regimens. However, in our multivariate analysis, myeloablative conditioning was not associated with lower relapse rates. Although still debated, the GVL effect may be stronger with non–T cell-depleted Haplo donors [20]. Haplo-HSCT with PTCy may overcome the poor prognosis of sAML, as outcomes are not significantly different from those of Haplo-HSCT in de novo AML [10]. Moreover, Haplo-HSCT with PTCy can serve as a rescue strategy for patients with primary refractory or relapsed sAML [11]. These results challenge the traditional preference for MUD in patients without a sibling match, particularly in younger patients with expected low NRM. Furthermore, Haplo offers practical advantages, including rapid donor availability and, in theory, reduced time to transplant (not in our study), both critical for patients with sAML due to the aggressive nature of the disease and the high risk of progression. Our study focused on patients in CR1, but prior evidence suggests that Haplo with PTCy can also rescue patients with primary refractory or relapsed sAML. These findings underscore the versatility of a Haplo as an option across different stages of disease [11].

It is worth noting that our analysis did not capture the impact of novel therapies such as Vyxeos (CPX-351) [21] or other targeted agents, which have shown promise in improving sAML outcomes [22]. Our study did not fully capture the use of PTCy-based GVHD prophylaxis in the matched donor setting, although this approach has been associated with improved GRFS and reduced toxicity compared to conventional regimens in both matched and mismatched donor settings [23, 24]. PTCy is now widely used by many centers for both MSD and MUD transplants. In our cohort, however, PTCy was primarily applied in the Haplo group, and in multivariate analysis, PTCy use was not associated with outcomes. A subgroup analysis restricted to PTCy-treated patients showed no significant donor-related differences, except for NRM, but interpretation remains limited due to the strong association of PTCy with Haplo and the small number of MSD and MUD recipients receiving PTCy. In our current study, we did not observe a significant difference in the risk of chronic GVHD between donor types, in contrast to previous reports suggesting that Haplo with PTCy may be associated with a lower risk of chronic GVHD [25]. This discrepancy could reflect underreporting of chronic GVHD in the registry or lack of updated data with longer follow-up. Further limitations of our study include its retrospective, registry-based design, which makes it subject to inherent selection bias. In addition, important clinical variables—including details of frontline therapy, molecular profiles, and measurable residual disease—were not available.

In conclusion, our findings highlight the importance of individualized donor selection in HSCT for sAML. In the absence of an MSD, both Haplo and MUD are viable options, each with distinct advantages. Future prospective studies are needed to validate these findings. Such studies should integrate novel therapies, MRD assessment, and standardized transplant protocols to enhance our understanding of how donor type, disease biology, and post-transplant interventions interact to influence outcomes in sAML.

Author Contributions

A.N. wrote the manuscript, designed the study, and interpreted the data. S.K. wrote the manuscript and interpreted the data. A.T.F. performed the statistical analyses, interpreted the data, and edited the manuscript. M.M. and F.C. designed the study, interpreted the data, and edited the manuscript. N.K., M.E., G. S., D.B., T.S., H.L-W., J.M., A.B., E.F., T.G-.D., A.R., C.E.B., G.B., A.B., E.B. and B.S. reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

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Disclosure

Data presented in part at the ASH 2024 meeting, San Diego, USA (oral presentation 505).

Ethics Statement

The scientific boards of the ALWP of the EBMT approved this study.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ajh70164-sup-0001-Supinfo.docx.