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Impact of Donor Type on Outcomes After Allogeneic Hematopoietic Cell Transplantation in Myelofibrosis: A Study on Behalf of the Chronic Malignancies Working Party of the EBMT

Juan Carlos Hernández-Boluda[1] | Vipul Sheth[2] | Simona Iacobelli[3] | Linda Koster[4] | Nicolaus Kröger[5] | Patrizia Chiusolo[6] | Thomas Schroeder[7] | Marie Robin[8] | Massimiliano Gambella[9] | Didier Blaise[10] | Henrik Sengeloev[11] | Jakob Passweg[12] | Mattias Stelljes[13] | Robert Zeiser[14] | Ibrahim Yakoub-Agha[15] | Andrew Clark[16] | Urpu Salmenniemi[17] | Piero Galieni[18] | Werner Rabisch[19] | Kavita Raj[20] | Joanna Drozd-Sokolowska[21] | Giorgia Battipaglia[22] | Nicola Polverelli[23] | Tomasz Czerw[24] | Donal P. McLornan[20]

[1]Hospital Clínico Universitario, INCLIVA, University of Valencia, Valencia, Spain | [2]Rajiv Gandhi Cancer Research Institute and Research Center, RGCIRC, New Delhi, India | [3]Department of Public Health and Infectious Diseases, University of Rome Sapienza, Rome, Italy | [4]EBMT Leiden Study Unit, Leiden, the Netherlands | [5]University Hospital Eppendorf, Hamburg, Germany | [6]Ematologia e Trapianto-Dipartimento di Scienze di Laboratorio ed Ematologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy | [7]University Hospital Essen, Duesseldorf, Germany | [8]Saint-Louis Hospital, BMT Unit, Paris, France | [9]IRCCS Ospedale Policlinico San Martino, Genova, Italy | [10]Programme de Transplantation & Therapie Cellulaire, Marseille, France | [11]Rigshospitalet, Copenhaguen, Denmark | [12]University Hospital Basel, Basel, Switzerland | [13]University of Muenster, Muenster, Germany | [14]University of Freiburg, Freiburg, Germany | [15]CHU de Lille, Univ Lille, INSERM U1286, Lille, France | [16]Glasgow Royal Infirmary, Glasgow, UK | [17]HUCH Comprehensive Cancer Center, Helsinki, Finland | [18]Mazzoni Hospital, Ascoli Piceno, Italy | [19]Medizinische Universitaet Wien, Vienna, Austria | [20]University College London Hospitals NHS Trust, London, UK | [21]Central Clinical Hospital, The Medical University of Warsaw, Warsaw, Poland | [22]Hematology Department, Federico II University of Naples, Naples, Italy | [23]Unit of Bone Marrow Transplantation – Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy | [24]Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice, Poland

Correspondence: Juan Carlos Hernández-Boluda (juan.carlos.hernandez@uv.es) | Donal P. McLornan (donal.mclornan@nhs.net)

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ABSTRACT

Selecting the optimal donor is crucial for optimizing results of allogeneic hematopoietic cell transplantation (allo-HCT). We analyzed outcomes based on donor type in 2809 myelofibrosis (MF) patients undergoing first allo-HCT between 2015 and 2021 at EBMT centers. Study outcomes included overall survival (OS), progression-free survival (PFS), relapse, non-relapse mortality (NRM), engraftment, and graft-versus-host disease (GvHD). Four groups were compared: matched sibling donor (MSD, $n = 742$), matched unrelated donor (MUD, $n = 1401$), mismatched unrelated donor (MMUD, $n = 379$) and haploidentical donor (HD, $n = 287$). After a median follow-up of 33.5 months, 3-year OS rates were 65.8%, 61.5%, 53.2%, and 57.7% for MSD, MUD, MMUD, and HD, respectively. Multivariable analyses (MSD as reference) showed that donor type significantly correlated with OS (HR: 1.63 for MMUD, HR: 1.42 for HD), PFS (HR: 1.38 for MMUD), NRM (HR: 1.73 for MMUD, HR: 1.47 for HD), engraftment (HR: 0.72 for MMUD, HR: 0.40 for HD), grade 2–4 acute GvHD (HR: 1.53 for MUD, HR: 1.69 for MMUD, HR: 1.49 for HD), and extensive chronic GvHD (HR: 0.77 for MUD, HR: 0.65 for HD). Donor type was not associated with relapse risk. In patients

Juan Carlos Hernández-Boluda and Vipul Sheth contributed equally to this study.

over 60 years, correlations between donor type and outcomes were consistent with those in the overall study population. In summary, with current practices, MF patients receiving MSD or MUD grafts achieve comparable outcomes. In contrast, MMUD and HD transplants have worse OS due to increased NRM. MMUD transplants have a higher risk of GvHD than HD transplants, but this difference seems to disappear with post-transplant cyclophosphamide.

1 | Introduction

Myelofibrosis (MF), whether primary (PMF) or secondary to essential thrombocythemia or polycythemia vera (SMF), is a hematological malignancy that remains incurable without allogeneic hematopoietic cell transplantation (allo-HCT) [1]. Retrospective data comparing allo-HCT with medical treatment options suggest that allo-HCT may provide improved long-term overall survival (OS) for MF patients within the intermediate-2 and high-risk categories, but this comes at the cost of increased risk of early non-relapse mortality (NRM) [2–4]. Donor type is a well-recognized factor influencing transplantation outcomes [5, 6]. Historically, CIBMTR data showed that MF patients undergoing allo-HCT from a matched sibling donor (MSD) had superior OS compared to those receiving a graft from a matched unrelated donor (MUD) [7]. Furthermore, transplants from mismatched unrelated donors (MMUD) and haploidentical donors (HD) had a significantly higher NRM [5, 6, 8]. However, advancements with in vivo T cell depletion strategies have expanded the use of HLA-mismatched donors, particularly utilizing post-transplant cyclophosphamide (PT-Cy) for graft-versus-host disease (GvHD) prophylaxis, leading to improved outcomes [9–11]. In a recent CIBMTR study analyzing transplants performed between 2013 and 2019, MSD-HCTs were associated with superior OS during the first 3 months post-HCT compared to other donor types (MUD, MMUD, HD), but beyond this landmark OS did not significantly differ among donor types. Notably, transplant outcomes between MUD and HD were comparable [12].

Patients over 60 years now represent a significant proportion of those undergoing allo-HCT for MF [13, 14]. These patients are often transplanted using an MSD of a similar advanced age. Several studies have shown that the risk of GvHD and overall mortality is higher with older donor age [15–18]. As results with alternative donors continue to improve, a clinically relevant question is whether using younger donors (MUD, MMUD or HD) could lead to better allo-HCT outcomes in older MF patients compared to older MSDs. This issue has been examined in other hematological malignancies with conflicting results [19–23].

In the present study, we aimed to evaluate the impact of donor type on outcomes after allo-HCT in a contemporary series of MF patients from the EBMT registry. Additionally, we conducted an exploratory analysis to assess the impact of donor type specifically in patients older than 60 years.

2 | Methods

2.1 | Patient Selection

Inclusion criteria were adult PMF and SMF patients undergoing first allo-HCT between 2015 and 2021 at EBMT centers. Patients transplanted utilizing cord blood as a stem cell source or with a history of transformation to blast phase were excluded. HD was defined as a family donor mismatched by 2 or more HLA loci; MUD as matched at the allele level HLA-A, -B, -C, -DRB1, and -DQB1; MMUD as unrelated with at least one mismatch. All HD transplants received PT-Cy. The study was approved by the Chronic Malignancies Working Party (CMWP) of the EBMT and conducted in accordance with the Declaration of Helsinki.

2.2 | Endpoints and Definitions

The primary endpoint was OS. Secondary endpoints were progression-free survival (PFS), cumulative incidence of relapse/progression, NRM, engraftment, acute GvHD (aGvHD), and chronic GvHD (cGvHD).

Primary graft failure (PGF) was defined as failing to reach neutrophil $>0.5\times10^9$/L in the first 60 days post-transplant or documentation of autologous reconstitution by chimerism analysis in the absence of relapse [23, 24]. Disease status at HCT was defined by the treating physician as per EBMT criteria (Table S1). Conditioning intensity was defined as per standard EBMT criteria [25].

2.3 | Statistical Analysis

All time-to-event endpoints were computed from the time of HCT except cGvHD starting on day 80 (a minority of cases reported with earlier onset and still alive on day 80 were considered as having the event on day 81). Competing events for aGvHD and cGvHD were relapse/progression, second allo-HCT, and death; aGvHD was evaluated until day 120. Events considered as failures for engraftment were: PGF, second allo-HCT, and death (in absence of engraftment or of primary failure), and no engraftment until 60 dd. NRM and relapse were mutually competing. Median follow-up was determined using the reverse Kaplan–Meier method. OS and PFS were estimated using the Kaplan–Meier product limit estimation method, and differences in subgroups were assessed by the log-rank test. For endpoints with competing risks, we estimated crude cumulative incidence and compared subgroup differences using Gray's test.

Multivariable Cox proportional hazards models adjusted for potential confounders were fitted to assess the association between the donor type groups (MRD, MUD, MMUD, HD) and the (cause-specific) hazard for all endpoints. Factors considered as candidates for the adjusted analysis were: patient age, donor age, patient sex and combination with donor sex (mismatch female to male), MF subtype, driver mutations (*JAK2*, *MPL*, or *CALR*), splenomegaly and splenectomy, disease status at allo-HCT, Dynamic International Prognostic Scoring System (DIPSS), Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), Karnofsky performance status (KPS), use of ATG,

graft source (peripheral blood or bone marrow), CMV status of recipient/donor, and interval MF diagnosis to transplant. Conditioning intensity was not considered as it is part of the transplant strategy and could hide differences between donor groups. A "missing value" category for covariates was added to enable analysis using the complete dataset. Calendar year and center effect (including a shared "frailty" term) were included in all models regardless of statistical significance to minimize potential bias.

All estimates were reported with 95% confidence intervals. All p-values were two-sided and $p < 0.05$ was considered significant. Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL) and R version 4.1.1 (R core team, Vienna, Austria) using packages "prodlim," "survival," and "cmprsk."

3 | Results

3.1 | Patient and Transplant Characteristics

Baseline characteristics of the 2809 MF patients included in the study are shown in Table 1. Four transplant cohorts were compared based on the donor type: MSD ($n = 742$, 26.4%), MUD ($n = 1401$, 49.9%), MMUD ($n = 379$, 13.5%), and HD ($n = 287$, 10.2%). Key differences were younger patient age ($p < 0.001$) and older donor age ($p < 0.001$), higher frequency of female donor to male recipient ($p < 0.001$), and lower frequency of CMV patient+/donor− ($p < 0.001$) in MSD; more splenectomized patients in MMUD and HD ($p = 0.004$); more ATG use in MUD and MMUD ($p < 0.001$); longer period from diagnosis to transplant ($p = 0.041$), worse KPS ($p = 0.034$), and more frequent use of myeloablative conditioning ($p < 0.001$) and bone marrow graft source ($p < 0.001$) in HD. All HD transplants received PT-Cy, whereas this agent was uncommonly used in the other transplant cohorts.

3.2 | Survival

The median follow-up was 33.5 months (range: 0.2–98.9). In univariate analysis, 3-year estimated OS rates were 65.8% (95% Confidence Interval [CI]: 62.1–69.6) for MSD, 61.5% (95% CI: 58.7–64.3) for MUD, 53.2% (95% CI: 47.6–58.7) for MMUD, and 57.7% (95% CI: 51.6–63.7) for HD ($p < 0.001$)(Figure 1A). The main causes of death according to donor type are elicited in Table S2. Fewer deaths due to GvHD but more due to infection were seen for HD transplants (Figure S1).

Multivariable analyses (MVA) adjusting for confounding factors (MSD as reference) showed that MMUD and HD had significantly reduced OS (Hazard Risk [HR]: 1.63, 95% CI: 1.33–2.00; $p < 0.001$ for MMUD; HR: 1.42, 95% CI: 1.12–1.80; $p = 0.004$ for HD). Notably, the HR for HD was non-proportional—indicating a time-dependent effect. The increased risk associated with HD was most prominent early in the follow-up period, gradually diminishing over time. Other baseline risk factors associated with decreased OS after HCT were older patient age (per year, HR: 1.03, 95% CI: 1.02–1.03; $p < 0.001$), relapsed/refractory disease (HR: 1.23, 95% CI: 1.08–1.40; $p = 0.002$), KPS ≤ 80 (HR: 1.42, 95% CI: 1.25–1.63; $p < 0.001$), high-risk classification by the DIPSS (HR: 1.39, 95% CI: 1.18–1.64; $p < 0.001$), and a high HCT-CI (HR: 1.30, 95% CI: 1.13–1.50; $p < 0.001$). By contrast, a *CALR/MPL* genotype was associated with improved OS (HR: 0.76, 95% CI: 0.63–0.91; $p = 0.004$) (Table 2).

3.3 | Engraftment

The cumulative incidence of neutrophil engraftment at day +28 was 91.3% (95% CI: 89.3–94.3), 89.3% (95% CI: 87.6–90.9), 84.2% (95% CI: 80.4–87.9), and 73.4% (95% CI: 68.0–78.7), for MSD, MUD, MMUD, and HD groups, respectively ($p < 0.001$). The cumulative incidence of neutrophil engraftment at day +59 was 97.3% (95% CI: 96.2–98.5), 96.4% (95% CI: 95.5–97.4), 94.7% (95% CI: 92.4–97.0), and 86.7% (95% CI: 82.6–90.8), for MSD, MUD, MMUD, and HD groups, respectively ($p < 0.001$) (Figure 2A).

At MVA, MMUD (HR: 0.72, 95% CI: 0.63–0.83, $p < 0.001$) and HD (HR: 0.40, 95% CI: 0.34–0.48, $p < 0.001$) were significantly associated with a lower probability of engraftment (Table 2). Factors associated with better engraftment were the presence of the *CALR/MPL* genotype (HR: 1.33, 1.19–1.49, $p < 0.001$) and a female recipient (HR: 1.26, 1.15–1.37, $p < 0.001$).

3.4 | GvHD

The cumulative incidence of grade 2–4 aGVHD at day +120 was 21.3% (95% CI: 18.3–24.3), 30.3% (95% CI: 27.8–32.7), 31.2% (95% CI: 26.4–36), and 27.2% (95% CI: 21.9–32.5), for MSD, MUD, MMUD, and HD groups, respectively ($p < 0.001$) (Figure 2B). In MVA, MUD (HR: 1.53, 95% CI: 1.26–1.87; $p < 0.001$), MMUD (HR: 1.69, 95% CI: 1.31–2.18; $p < 0.001$), and HD (HR: 1.49, 95% CI: 1.11–2.01; $p = 0.009$) were associated with a higher risk of grade 2–4 aGVHD as compared to MSD. No other factor was significantly associated with the risk of this complication (Table 2).

The cumulative incidence of grade 3–4 aGVHD at day +120 was 11.2% (95% CI: 8.9–13.6), 14.7% (95% CI: 12.8–16.6), 14.9% (95% CI: 11.2–18.6), and 12.1% (95% CI: 8.25–16), for MSD, MUD, MMUD, and HD groups, respectively ($p = 0.13$) (Figure 2C). In MVA, MMUD (HR: 1.48, 95% CI: 1.04–2.11; $p = 0.031$) and MUD (HR: 1.35, 95% CI: 1.03–1.77; $p = 0.030$) were significantly associated with a higher risk of grade 3–4 acute GVHD compared to MSD. By contrast, prior splenectomy (HR: 0.52, 95% CI: 0.28–0.97; $p = 0.040$) was significantly protective for this complication (Table 2).

The cumulative incidence of any grade cGVHD at year 5 was 49.0% (95% CI: 44.9–53.2), 45.8% (95% CI: 42.7–48.9), 49.0% (95% CI: 42.6–55.4), and 37.1% (95% CI: 30.1–44.2), for MSD, MUD, MMUD, and HD groups, respectively ($p = 0.032$). The cumulative incidence of extensive cGVHD at year 5 was 32.5% (95% CI: 28.6–36.4), 26.8% (95% CI: 24.2–29.5), 29.2% (95% CI: 23.4–35.1), and 18.7% (95% CI: 13.4–24), for MSD, MUD, MMUD, and HD groups, respectively ($p = 0.0054$) (Figure 2D). In MVA, MUD (HR: 0.77, 95% CI: 0.64–0.94; $p = 0.010$) and HD (HR: 0.65, 95% CI: 0.45–0.94; $p = 0.023$) were associated with a lower risk of extensive cGVHD compared to MSD. By contrast, a female donor for a male recipient had a higher risk for this complication (HR: 1.27, 95% CI: 1.01–1.58; $p = 0.037$) (Table 2).

TABLE 1 | Baseline characteristics of 2809 myelofibrosis patients undergoing allogeneic hematopoietic cell transplantation at EBMT centers based on donor type.

Category	Subcategory	Missing values (%)	MSD count	MSD $N=742$	MUD count	MUD $N=1401$	MMUD count	MMUD $N=379$	HD count	HD $N=287$	p
Patient age, year	median (IQR)	0.0%		57.9 (52.6–63.3)		61.1 (55.4–66.2)		58.1 (52.5–62.8)		60.4 (53.8–66.3)	**< 0.001**
Patient age, year	< 60	0.0%	438	59.0%	614	43.8%	222	58.6%	140	48.8%	**< 0.001**
	> 60		304	41.0%	787	56.2%	157	41.4%	147	51.2%	
Patient sex	Male	0.0%	467	62.9%	883	63.0%	222	58.6%	181	63.1%	0.433
	Female		275	37.1%	518	37.0%	157	41.4%	106	36.9%	
Myelofibrosis type	Primary myelofibrosis	0.0%	555	74.8%	1014	72.4%	280	73.9%	209	72.8%	0.669
	Post-ET/PV myelofibrosis		187	25.2%	387	27.6%	99	26.1%	78	27.2%	
Genotype	Triple negative/JAK2	28.6%	363	74.1%	808	76.9%	212	77.7%	148	76.7%	0.611
	CALR/MPL		127	25.9%	243	23.1%	61	22.3%	45	23.3%	
Splenectomy at HCT	No	56.1%	267	92.7%	587	93.3%	139	88.0%	135	85.4%	**0.004**
	Yes		21	7.3%	42	6.7%	19	12.0%	23	14.6%	
Disease status at HCT	Other	4.0%	427	60.8%	811	60.0%	214	58.8%	166	59.5%	0.93
	Relapse/progressive/ refractory		275	39.2%	540	40.0%	150	41.2%	113	40.5%	
DIPSS at HCT	Low risk	18.8%	13	2.2%	20	1.7%	7	2.3%	10	4.0%	0.382
	Int-1 risk		230	39.4%	454	39.6%	117	38.6%	102	41.0%	
	Int-2 risk		230	39.4%	435	38.0%	114	37.6%	100	40.2%	
	High risk		111	19.0%	237	20.7%	65	21.5%	37	14.9%	
HCT-CI risk group	Low risk (0)	7.4%	354	51.8%	610	47.0%	185	53.0%	129	47.3%	0.081
	Intermediate risk (1, 2)		182	26.6%	333	25.7%	81	23.2%	69	25.3%	
	High risk (≥ 3)		147	21.5%	354	27.3%	83	23.8%	75	27.5%	
Karnofsky performance status	> 80	4.1%	482	67.6%	840	63.1%	254	68.3%	168	60.2%	**0.034**
	≤ 80		231	32.4%	491	36.9%	118	31.7%	111	39.8%	
ATG given	No	0.5%	315	42.8%	235	16.8%	97	25.8%	260	90.6%	**< 0.001**
	Yes		421	57.2%	1160	83.2%	279	74.2%	27	9.4%	

(Continues)

TABLE 1 | (Continued)

Category	Subcategory	Missing values (%)	MSD count	MSD $N=742$	MUD count	MUD $N=1401$	MMUD count	MMUD $N=379$	HD count	HD $N=287$	p
Conditioning intensity	Standard	1.2%	239	32.5%	419	30.4%	125	33.4%	136	47.6%	**<0.001**
	Reduced		497	67.5%	961	69.6%	249	66.6%	150	52.4%	
Source of cells	Bone marrow	0.0%	26	3.5%	33	2.4%	14	3.7%	85	29.6%	**<0.001**
	Peripheral blood		716	96.5%	1368	97.6%	365	96.3%	202	70.4%	
Donor age, year	median (IQR)			55.9 (49.4–61.9)		29.3 (24.0–36.0)		30.2 (24.7–37.5)		35.9 (28.5–43.0)	**<0.001**
Gender mismatch	Other combination	0.5%	548	73.9%	1244	89.4%	321	85.4%	236	82.5%	**<0.001**
	Male patient/Female donor		194	26.1%	147	10.6%	55	14.6%	50	17.5%	
CMV patient/donor	−/−	1.4%	145	20.1%	494	35.6%	77	20.6%	53	18.7%	**<0.001**
	−/+		75	10.4%	103	7.4%	20	5.3%	24	8.5%	
	+/−		116	16.0%	291	21.0%	111	29.7%	78	27.6%	
	+/+		387	53.5%	501	36.1%	166	44.4%	128	45.2%	
GvHD prophylaxis	CNI + MTX (±ATG)	0.9%	264	35.6%	481	34.3%	148	39.1%	0	0%	
	CNI + MMF (±ATG)		272	36.7%	590	42.1%	118	31.1%	0	0%	
	CNI (±ATG)		90	12.1%	116	8.3%	15	4.0%	0	0%	
	PT-Cy		45	6.1%	87	6.2%	54	14.2%	259	90.2%	
	PT-Cy + ATG		8	1.1%	19	1.4%	21	5.5%	27	9.4%	
	other		52	7.0%	99	7.1%	19	5.0%	1	0.3%	
	Missing		11	1.5%	9	0.6%	4	1.1%	0	0%	
Time diagnosis-HCT	<12 months	0.0%	218	29.4%	358	25.6%	86	22.7%	59	20.6%	**0.041**
	12–24 months		113	15.2%	217	15.5%	70	18.5%	46	16.0%	
	24–60 months		143	19.3%	260	18.6%	87	23.0%	60	20.9%	
	>60 months		268	36.1%	566	40.4%	136	35.9%	122	42.5%	

Note: Numbers in bold are those with a significant p-value on the statistical analysis ($p < 0.05$).

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; CNI, calcineurin inhibitor; DIPSS, dynamic international prognostic scoring system; ET, essential thrombocythemia; GvHD, graft-versus-host disease; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; HD, haploidentical donor; IQR, interquartile range; MMF, mycophenolate mofetil; MMUD, mismatched unrelated donor; MSD, matched sibling donor; MTX, methotrexate; MUD, matched unrelated donor; PT-Cy, postransplant cyclophosphamide; PV, polycythemia vera.

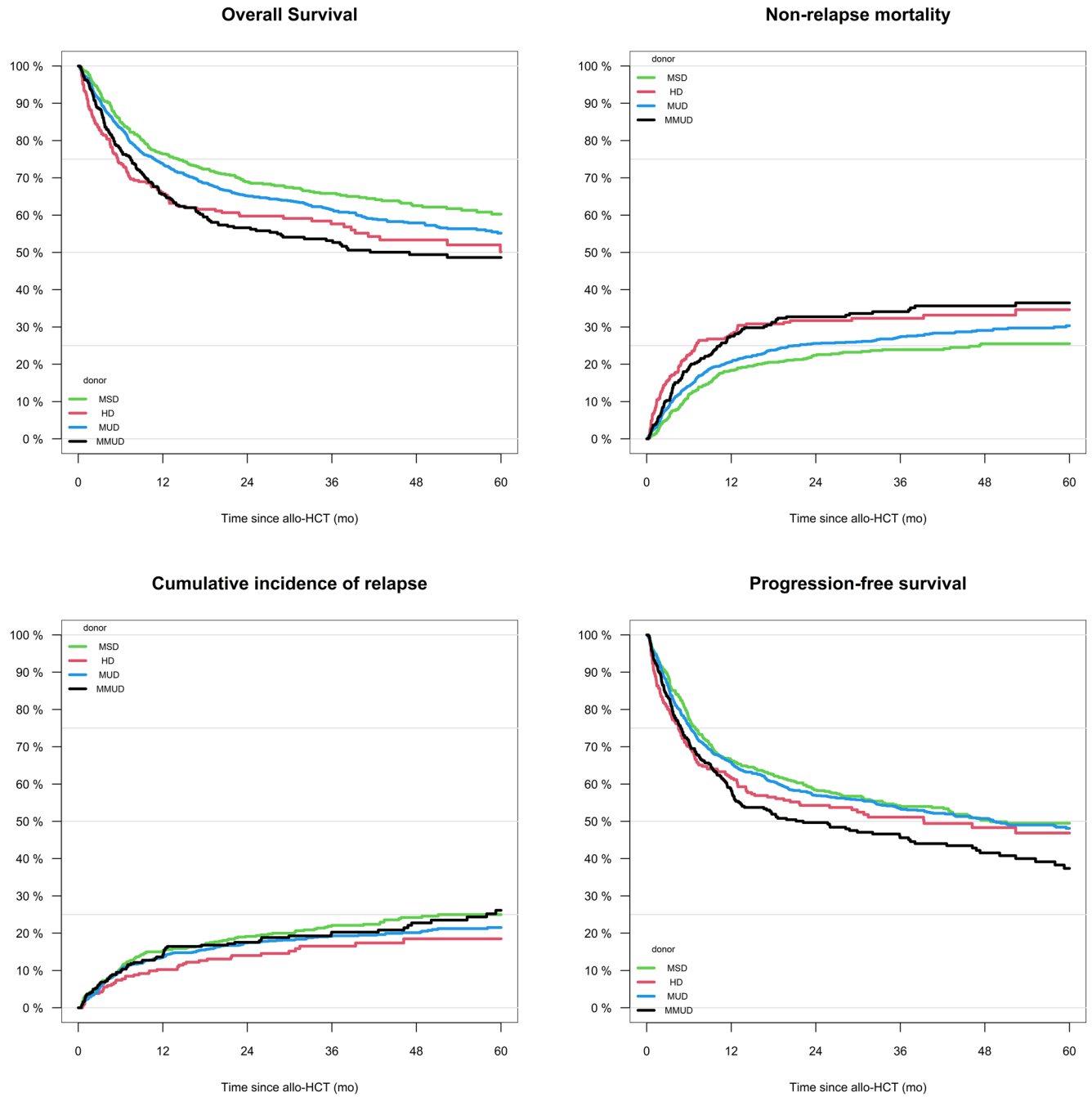

FIGURE 1 | Outcomes after transplant in a series of 2809 myelofibrosis patients based on donor type. (A) Overall Survival, (B) Non-relapse mortality, (C) Cumulative incidence of relapse, and (D) Progression-free survival.

3.5 | Non-Relapse Mortality

The 3-year NRM rate was 23.9% (95% CI: 20.6–27.2) for MSD, 27.3% (95% CI: 24.8–29.8) for MUD, 34.1% (95% CI: 29.0–39.3) for MMUD, and 32.3% (95% CI: 26.8–37.9) for HD ($p < 0.001$) (Figure 1B).

In MVA, MMUD and HD had an increased risk of NRM (HR: 1.73, 95% CI: 1.36–2.20; $p < 0.001$ for MMUD; HR: 1.47, 95% CI: 1.11–1.94; $p = 0.006$ for HD). Other adverse risk factors were older patient age (per year, HR: 1.03, 95% CI: 1.02–1.05; $p < 0.001$), relapsed/refractory disease (HR: 1.18, 95% CI: 1.01–1.38; $p = 0.041$), KPS ≤ 80 (HR: 1.27, 95% CI: 1.08–1.49; $p = 0.004$), high-risk DIPSS score (HR: 1.27, 95% CI: 1.05–1.54; $p = 0.016$), high HCT-CI (HR: 1.30, 95% CI: 1.10–1.54; $p = 0.002$), and the female donor/male patient combination (HR: 1.22, 95% CI: 1.01–1.48; $p = 0.040$). By contrast, the *CALR/MPL* genotype was associated with a lower risk of NRM (HR: 0.77, 95% CI: 0.62–0.95; $p = 0.017$) (Table 2).

3.6 | Relapse/Progression

The 3-year cumulative incidence of relapse/progression was 22.1% (95% CI: 18.8–25.4) for MSD, 19.2% (95% CI: 17.0–21.4) for MUD, 20.3% (95% CI: 15.8–24.7) for MMUD, and 16.5% (95% CI: 11.8–21.2) for HD ($p = 0.12$) (Figure 1C). In MVA, donor type was not significantly associated with relapse risk. Factors associated with increased risk of relapse were relapsed/refractory

TABLE 2 | Multivariable analysis of outcomes after allogeneic hematopoietic cell transplantation in a series of 2809 myelofibrosis patients.

	Overall survival				Progression free survival				Non-relapse mortality				Relapse			
Variable	**HR**	**95% CI**		***p***	**HR**	**95% CI**		***p***	**HR**	**95% CI**		***p***	**HR**	**95% CI**		***p***
HD	1.42[a]	1.12	1.80	**0.004**	1.15	0.93	1.42	0.207	1.47	1.11	1.94	**0.006**	0.76	0.53	1.08	0.124
MUD	1.15	0.98	1.36	0.087	1.00	0.87	1.15	0.956	1.14	0.94	1.39	0.180	0.88	0.72	1.08	0.236
MMUD	1.63	1.33	2.00	**<0.001**	1.38	1.15	1.65	**<0.001**	1.73	1.36	2.20	**<0.001**	1.07	0.81	1.41	0.627
Patient age	1.03	1.02	1.03	**<0.001**	1.02	1.01	1.03	**<0.001**	1.03	1.02	1.05	**<0.001**	1.00	0.99	1.01	0.914
Disease status Rel/Ref	1.23	1.08	1.40	**0.002**	1.23	1.09	1.38	**0.001**	1.18	1.01	1.38	**0.041**	1.28	1.07	1.53	**0.007**
Disease status_NA	0.89	0.62	1.27	0.519	0.84	0.61	1.17	0.307	0.83	0.53	1.28	0.397	0.84	0.51	1.36	0.474
KPS ≤ 80	1.42	1.25	1.63	**<0.001**	1.23	1.09	1.39	**0.001**	1.27	1.08	1.49	**0.004**	1.18	0.98	1.42	0.077
KPS_NA	1.38	0.99	1.91	0.055	1.27	0.95	1.69	0.11	1.42	0.97	2.08	0.068	1.08	0.69	1.69	0.749
Genotype CALR/MPL	0.76	0.63	0.91	**0.004**	0.71	0.60	0.84	**<0.001**	0.77	0.62	0.95	**0.017**	0.60	0.46	0.80	**<0.001**
DIPSS_High	1.39	1.18	1.64	**<0.001**	1.33	1.15	1.54	**<0.001**	1.27	1.05	1.54	**0.016**	1.37	1.09	1.72	**0.007**
HCT-CI_High	1.30	1.13	1.50	**<0.001**	1.28	1.12	1.46	**<0.001**	1.30	1.10	1.54	**0.002**	1.22	0.99	1.50	0.058
Pat/Donor sex_M/F	1.16	0.98	1.37	0.077	NE				1.22	1.01	1.48	**0.040**	NE			
Splenectomy_Yes	NE				NE				NE				2.29	1.60	3.29	**<0.001**
Year	0.99	0.96	1.03	0.772	0.99	0.96	1.02	0.44	0.98	0.94	1.03	0.433	0.98	0.94	1.04	0.563

	Engraftment				Grade II-IV aGvHD				Grade III-IV aGvHD				Extensive cGvHD			
Variable	**HR**	**95% CI**		***p***	**HR**	**95% CI**		***p***	**HR**	**95% CI**		***p***	**HR**	**95% CI**		***p***
HD	0.40	0.34	0.48	**<0.001**	1.49	1.11	2.01	**0.009**	1.12	0.73	1.72	0.607	0.65	0.45	0.94	**0.023**
MUD	0.91	0.82	1.01	0.077	1.53	1.26	1.87	**<0.001**	1.35	1.03	1.77	**0.03**	0.77	0.64	0.94	**0.010**
MMUD	0.72	0.63	0.83	**<0.001**	1.69	1.31	2.18	**<0.001**	1.48	1.04	2.11	**0.031**	0.94	0.71	1.23	0.635
Genotype CALR/MPL	1.33	1.19	1.49	**<0.001**	NE				NE				NE			
Patient sex Female	1.26	1.15	1.37	**<0.001**	NE				NE				NE			
Pat/Donor sex_M/F	NE				NE				NE				1.27	1.01	1.58	**0.037**
Splenectomy_Yes	NE				0.68	0.45	1.03	0.07	0.52	0.28	0.97	**0.04**	0.61	0.35	1.08	0.091
Year	1.02	1.00	1.04	0.095	1.01	0.97	1.06	0.504	1.01	0.95	1.08	0.662	0.99	0.95	1.04	0.786

Note: Numbers in bold are those with a significant p-value on the statistical analysis ($p < 0.05$).
Abbreviations: CI, confidence interval; HD, haploidentical donor; HR, hazard risk; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; NE, not evaluated.
[a]The HR of HD was nonproportional (i.e., time-dependent). The increased risk associated with HD diminished over time.

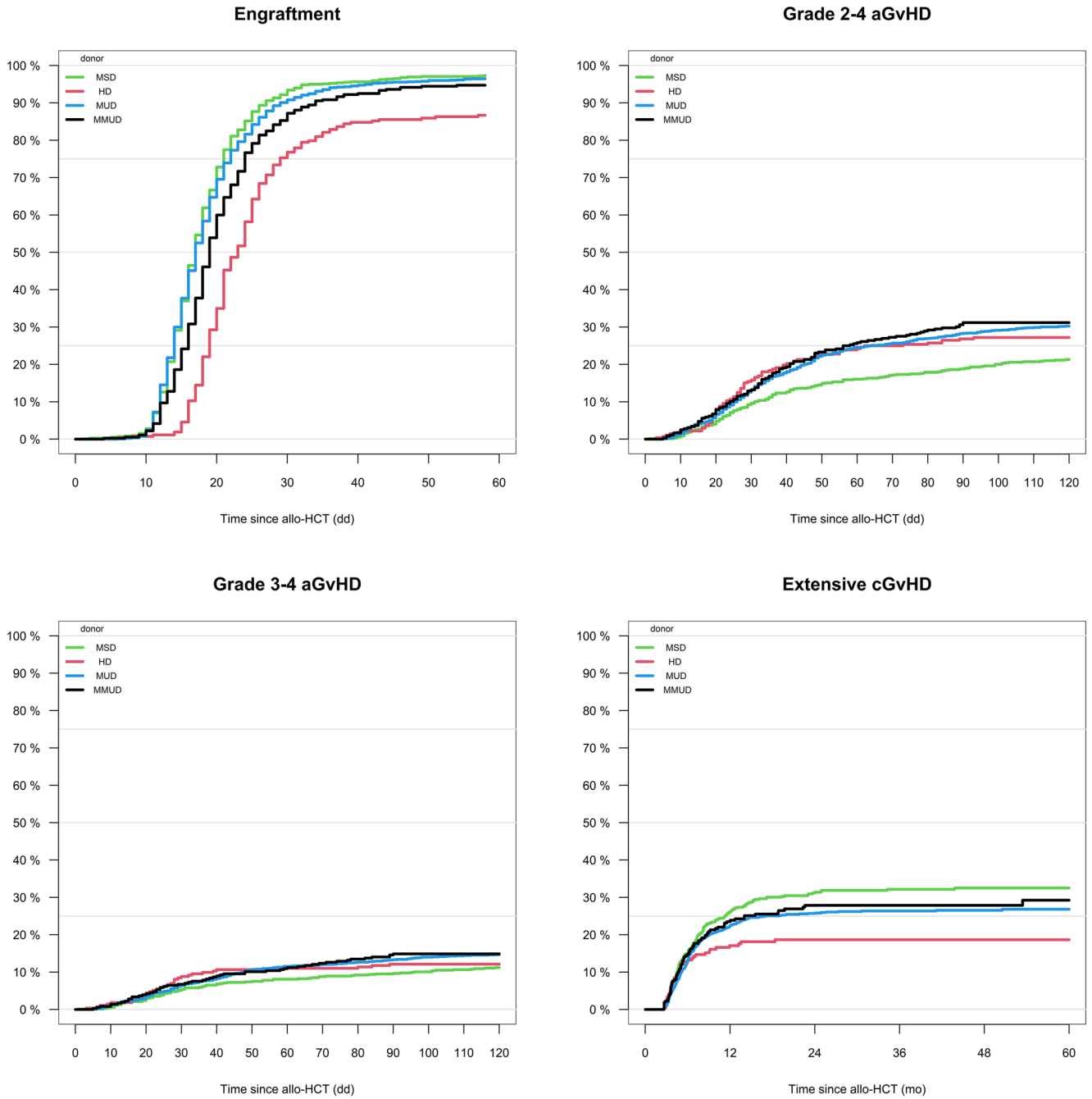

FIGURE 2 | Outcomes after transplant in a series of 2809 myelofibrosis patients based on donor type. Cumulative incidence of engraftment (A), grade 2–4 aGvHD (B), grade 3–4 aGvHD (C), and (D) Extensive cGvHD.

disease (HR: 1.28, 95% CI: 1.07–1.53; $p = 0.007$), high-risk DIPSS score (HR: 1.37, 95% CI: 1.09–1.72; $p = 0.007$), and splenectomy (HR: 2.29, 95% CI: 1.60–3.29; $p < 0.001$). By contrast, the *CALR/MPL* genotype was associated with lower relapse risk (HR: 0.60, 95% CI: 0.46–0.80; $p < 0.001$) (Table 2).

3.7 | Progression-Free Survival

The 3-year PFS rates were 54.0% (95% CI: 50.0–57.9) for MSD, 53.5% (95% CI: 50.6–56.3) for MUD, 45.6% (95% CI: 40.0–51.2) for MMUD, and 51.1% (95% CI: 44.9–57.3) for HD ($p = 0.0025$) (Figure 1D). In MVA, MMUD had significantly worse PFS (HR: 1.38, 95% CI: 1.15–1.65; $p < 0.001$). Other factors associated with decreased PFS were older patient age (per year, HR: 1.02, 95% CI: 1.01–1.03; $p < 0.001$), relapsed/refractory disease (HR: 1.23, 95% CI: 1.09–1.38; $p = 0.001$), KPS ≤ 80 (HR: 1.23, 95% CI: 1.09–1.39; $p = 0.001$), high-risk DIPSS score (HR: 1.33, 95% CI: 1.15–1.54; $p < 0.001$), and high HCT-CI (HR: 1.28, 95% CI: 1.12–1.46; $p < 0.001$). By contrast, the *CALR/MPL* genotype was associated with improved PFS (HR: 0.71, 95% CI: 0.60–0.84; $p < 0.001$) (Table 2).

3.8 | Transplant Outcomes in Elderly Patients by Donor Type

The key question in this sub-analysis was whether an elderly MF patient (over 60 years old) with a likely elderly sibling donor

would have better outcomes with the latter compared to a younger MUD, MMUD, or HD.

The study population consisted of 1395 patients, distributed as follows: MSD ($n=304$, 22%), MUD ($n=787$, 56%), MMUD ($n=157$, 11%), and HD ($n=147$, 11%). As expected, the median donor age was significantly higher in the MSD group: 60.5 years (Interquartile range [IQR]: 56.4–65.6) for MSD, 29.8 years (IQR: 24.0–36.0) for MUD, 30.4 years (IQR: 24.8–38.7) for MMUD, and 37.9 years (IQR: 32.3–42.5) for HD ($p<0.001$).

The main transplantation outcomes of the series based on donor type are shown in Figures S2 and S3. Overall, the impact of donor type on the main outcomes was consistent with findings from the all-age study population (Table S3). The 2-year estimated OS rates were 63.0% (95% CI: 57.2–68.8) for MSD, 61.4% (95% CI: 57.7–65) for MUD, 51.2% (95% CI: 42.8–59.6) for MMUD, and 53.9% (95% CI: 45.6–62.1) for HD ($p=0.0032$). In MVA, MMUD were significantly associated with worse OS (HR: 1.57, 95% CI: 1.17–2.10; $p=0.003$) and PFS (HR: 1.40, 95% CI: 1.08–1.82; $p=0.011$) than MSD. MMUD and HD were associated with higher NRM (HR: 1.80, 95% CI: 1.28–2.52; $p=0.001$ for MMUD; HR: 1.58, 95% CI: 1.10–2.27; $p=0.014$ for HD). HD was associated with a lower probability of engraftment (HR: 0.47, 95% CI: 0.37–0.60; $p<0.001$) and decreased relapse risk (HR: 0.55, 95% CI: 0.32–0.95; $p=0.031$). MUD and MMUD were associated with a higher risk of grade 2–4 aGvHD (HR: 1.47, 95% CI: 1.10–1.97; $p=0.010$ for MUD; HR: 1.54, 95% CI: 1.04–2.29; $p=0.031$ for MMUD), whereas no significant differences were observed by donor type regarding grade 3–4 aGvHD or extensive cGvHD.

3.9 | Comparison of Outcomes in MMUD and HD Using PT-Cy

In this sub-analysis, we aim to evaluate the outcomes of patients transplanted with HD ($n=287$) and MMUD ($n=75$) using the same GvHD prophylaxis strategy based on PT-Cy.

The main post-transplant outcomes are elicited in Figures S4 and S5. The 2-year estimated OS rates were 57.6% (95% CI: 44.4–70.7) for MMUD, and 59.7% (95% CI: 53.9–65.6) for HD ($p=0.45$). The 2-year estimated PFS rates were 54.2% (95% CI: 41.2–67.2) for MMUD, and 54.3% (95% CI: 48.4–60.2) for HD ($p=0.72$). The 2-year cumulative incidence of relapse was 15.5% (95% CI: 6.5–24.5) for MMUD, and 14% (95% CI: 9.85–18.2) for HD ($p=0.48$). The 2-year NRM rate was 30.2% (95% CI: 18.3–42.2) for MMUD, and 31.7% (95% CI: 26.2–37.2) for HD ($p=0.37$). The cumulative incidence of engraftment was 91.8% in MMUD compared to 86.7% in HD ($p=0.076$). At 120 days, the incidence of grade 2–4 and 3–4 aGvHD was 35.7% (95% CI: 24.5–46.9) and 18.6% (95% CI: 9.5–27.7) for MMUD, and 27.2% (95% CI: 21.9–32.5) and 12.1% (95% CI: 8.3–16) for HD ($p=0.18$ and $p=0.16$, respectively). The incidence of extensive cGvHD was 16% (95% CI: 5.5–26.5) for MMUD, and 18.7% (95% CI: 2.7–13.4) for HD ($p=0.50$). Overall, no significant differences were observed in any of the study outcomes between these two patient cohorts.

3.10 | Comparison of Outcomes in MMUD Using PT-Cy Versus Other GvHD Prophylaxis Strategies

Finally, we compared the outcomes of patients transplanted with MMUD using PT-Cy ($n=75$) or other GvHD prophylaxis strategies ($n=300$).

As shown in Figures S6 and S7, there were no significant differences between the two groups in terms of OS, PFS, NRM, relapse, or aGVHD rates. However, MMUD transplants with PT-Cy had a lower probability of engraftment (91.8% vs. 95.4%, $p=0.023$) and a reduced incidence of extensive cGvHD (16% vs. 30.8%, $p=0.026$).

4 | Discussion

In this study, we analyzed outcomes in a contemporary series of 2809 MF patients who underwent allo-HCT at EBMT registered centers, comparing results across different donor types (MSD, MUD, MMUD, and HD) using multivariable analyses. Our data show that transplants from MSD and MUD currently yield similar outcomes in terms of OS, PFS, or NRM. In contrast, MMUD and HD-HCTs are associated with significantly lower OS compared to MSD-HCTs, primarily due to increased NRM. The increased risk associated with HDs was most prominent early in the follow-up period, with the effect diminishing over time, consistent with findings by Jain T et al. [12]. This higher NRM in MMUD and HD-HCTs is driven by both an increased risk of graft failure and grade 2–4 aGvHD. Notably, the relapse risk did not significantly differ among donor groups. In elderly patients, MUD-HCTs showed comparable outcomes to MSD-HCTs, despite the significantly younger donor age in the MUD cohort (median 29.8 vs. 60.5 years). In this age group, MMUDs and HDs remained associated with higher NRM. However, the long-term OS of HD-HCTs approached that of MSD-HCTs, possibly due to a lower risk of relapse and cGvHD.

Our data highlights that the survival difference between MSD-HCTs and transplants from alternative donors has narrowed in recent years. This trend is consistent with a similar study from the CIBMTR including 1032 MF patients transplanted between 2013 and 2019, which had a comparable donor type distribution [12]. Advances in GvHD prophylaxis and its treatment, and improved supportive care may have contributed to this progress. Overall, our results confirm that multiple options are currently available to successfully transplant MF patients with high-risk disease [9, 10].

Our findings reinforce the preference for an MSD as the optimal graft source for MF patients, including those over 60 years of age. Notably, the potential benefit of using a younger alternative donor did not translate into improved outcomes in our study, consistent with similar studies [20–23], though not all [19], conducted in other hematological malignancies. However, since MUD-HCTs yielded results comparable to MSD-HCTs, MUD could serve as a suitable alternative when MSD donation is not feasible due to health issues or other constraints.

MMUDs and HDs were associated with a higher risk of graft failure, a well-recognized complication of HLA mismatched

transplants that appears not to be fully prevented by using ATG or PT-Cy [12, 26]. Additionally, grade 2–4 aGvHD was more common in MUD, MMUD, and HD-HCTs than in MSD-HCTs, with MUD and MMUD also carrying a higher risk of grade 3–4 aGvHD. Interestingly, the proportion of less severe cases (grade 2 within grade 2–4 aGvHD) was slightly higher in HD-HCTs than in MSD- and MUD-HCTs (55.4% vs. 47.3% vs. 51.5%, respectively). Of note, MMUD-HCTs using PT-Cy had a lower risk of extensive cGvHD compared to those using other GvHD prophylaxis strategies, with overall outcomes closely resembling those of HD-HCTs. However, the size of the patient series was insufficient to draw definitive conclusions regarding the optimal GvHD prophylaxis in this setting. Increasing evidence suggests that PT-Cy may be preferable to ATG in MMUD-HCTs, not only for its positive impact on reducing GvHD but also for its potential to lower relapse risk [24, 27–29]. However, further advancements are needed to optimize outcomes in HLA-mismatched transplant for MF. In this regard, posttransplant use of JAK inhibitors [30], as well as PT-Cy at standard or reduced dose [31] in combination with ATG [32], deserves investigation.

Several limitations of this study should be acknowledged. As a retrospective analysis, it lacks the controlled conditions of a clinical trial, which would be the ideal setting to compare allo-HCT outcomes by donor type. Moreover, the EBMT dataset does not include information on donor-directed antibodies, which could help interpret the non-engraftment data in the context of HLA disparities. It is also possible that the optimal donor source may vary depending on the disease risk characteristics, but this aspect was not analyzed in our study. Additionally, data on spleen size at the time of allo-HCT and graft cell dose were not available. Regarding the latter, a previous EBMT study showed that a CD34+ cell dose $> 7 \times 10^6$/kg was associated with faster engraftment in MSD- and MUD-HCTs using reduced intensity conditioning [33]. In that study, higher CD34+ cell counts were also linked to improved OS, specifically in MSD-HCTs. The impact of graft cell dose may be particularly relevant in the setting of PT-Cy, as its use in MF patients has been associated with delayed engraftment [34]. Indeed, a recent EBMT study found that in HD-HCTs using PT-Cy, a CD34+ cell dose $> 7 \times 10^6$/kg from peripheral blood correlated with faster neutrophil recovery [35]. Interestingly, in the present study, female patients had a higher probability of engraftment—and association that, to our knowledge, has not been previously reported. It would be of interest for future studies to explore whether this observation could be explained by a smaller spleen size at the time of allo-HCT or a higher CD34+ cell dose per kg of body weight in female recipients compared to males.

In conclusion, our data suggest that MSD and MUD are the preferred graft sources for MF patients requiring transplantation. We found no clinical benefit of using a younger MUD over an MSD in MF patients over 60 years. However, given the comparable outcomes, MUDs represent a suitable alternative when MSD donation is not feasible due to health issues or other constraints. While alternative donors can provide favorable outcomes, they remain associated with higher NRM. Our findings support the role of PT-Cy in MMUD-HCTs to decrease the risk of extensive cGVHD, though further studies are needed to confirm this benefit, coupled with longer follow-up. Although our data cover a recent period (2015–2021), clinical practices in allo-HCT continue to evolve, potentially influencing outcomes. This is particularly evident with the expanding use of PT-Cy beyond HD transplants to other donor types, including MSD-HCTs. As transplant strategies change, updated studies will be necessary to determine whether these findings remain relevant in future clinical practice.

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Disclosure

This retrospective study was approved by the Chronic Malignancies Working Party (CMWP) of EBMT.

Consent

Informed consent for inclusion in the EBMT registry was obtained in all patients.

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. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Cumulative incidence of death due to infection (A) and GvHD (B) according to donor type. **Figure S2:** Outcomes after transplant in a series of 1395 myelofibrosis patients aged 60 years or older based on donor type. (A) Overall Survival, (B) Non-relapse mortality, (C) Cumulative incidence of relapse, and (D) Progression-free survival. **Figure S3:** Outcomes after transplant in a series of 1395 myelofibrosis patients aged 60 years or older based on donor type. Cumulative incidence of engraftment (A), grade 2–4 aGvHD (B), grade 3–4 aGvHD (C), and (D) Extensive cGvHD. **Figure S4:** Outcomes after transplant in myelofibrosis patients engrafted from mismatched unrelated donors or haploidentical donors using post-transplant cyclophosphamide. (A) Overall Survival, (B) Non-relapse mortality, (C) Cumulative incidence of relapse, and (D) Progression-free survival.

Figure S5: Outcomes after transplant in myelofibrosis patients engrafted from mismatched unrelated donors or haploidentical donors using post-transplant cyclophosphamide. Cumulative incidence of engraftment (A), grade 2–4 aGvHD (B), grade 3–4 aGvHD (C), and (D) Extensive cGvHD. **Figure S6:** Outcomes after transplant in myelofibrosis patients engrafted from mismatched unrelated donors using post-transplant cyclophosphamide or other GvHD prophylaxis strategies. (A) Overall Survival, (B) Non-relapse mortality, (C) Cumulative incidence of relapse, and (D) Progression-free survival. **Figure S7:** Outcomes after transplant in myelofibrosis patients engrafted from mismatched unrelated donors using post-transplant cyclophosphamide or other GvHD prophylaxis strategies. Cumulative incidence of engraftment (A), grade 2–4 aGvHD (B), grade 3–4 aGvHD (C), and (D) Extensive cGvHD. **Table S1:** Disease status at the time of transplantation according to the EBMT definitions. **Table S2:** Main causes of death according to donor type in 2809 myelofibrosis patients undergoing allogeneic hematopoietic cell transplantation. **Table S3:** Multivariable analysis of outcomes after allogeneic hematopoietic cell transplantation in a series of 1395 myelofibrosis patients aged 60 years or older.