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ABO incompatibility in mismatched unrelated donor allogeneic hematopoietic cell transplantation for acute myeloid leukemia: A report from the acute leukemia working party of the EBMT

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Abstract

ABO incompatibility is commonly observed in stem cell transplantation and its impact in this setting has been extensively investigated. HLA-mismatched unrelated donors (MMURD) are often used as an alternative stem cell source but are associated with increased transplant related complications. Whether ABO incompatibility affects outcome in MMURD transplantation for acute myeloid leukemia (AML) patients is unknown. We evaluated 1,013 AML patients who underwent MMURD transplantation between 2005 and 2014. Engraftment rates were comparable between ABO matched and mismatched patients, as were relapse incidence [34%; 95% confidence interval (CI), 28–39; for ABO matched vs. 36%; 95% CI, 32–40; for ABO mismatched; $P = .32$], and nonrelapse mortality (28%; 95% CI, 23–33; for ABO matched vs. 25%; 95% CI, 21–29; for ABO mismatched; $P = .2$). Three year survival was 40% for ABO matched and 43% for ABO mismatched patients ($P = .35$), Leukemia free survival rates were also comparable between groups (37%; 95% CI, 32–43; for ABO matched vs. 38%; 95% CI, 33–42; for ABO mismatched; $P = .87$). Incidence of grade II-IV acute graft versus host disease was marginally lower in patients with major ABO mismatching (Hazard ratio of 0.7, 95% CI, 0.5–1; $P = .049$]. ABO incompatibility probably has no significant clinical implications in MMURD transplantation.

1 | INTRODUCTION

For acute myeloid leukemia (AML) patients lacking a matched sibling donor or a fully HLA matched unrelated donor, alternative stem cell donor sources must be sought to proceed with allogeneic hematopoietic cell transplantation. At present, these include transplantation from an haploidentical related donor, using an umbilical cord blood stem cell product or using a partially HLA-mismatched unrelated donor (MMURD).[1]

While MMURD transplantation presents an attractive and readily available option for some patients, widespread use has been limited to some degree by an increased risk for graft failure,[2–4] higher rates of GVHD,[5,6] and an increased risk of nonrelapse mortality (NRM),[7] all of which may lead to compromised survival. Thus, improving on transplant related outcomes in MMURD is a major priority in the field of alternative donor transplantation. ABO incompatibility involves antibody production against donor red blood cells (major ABO incompatibility) or against the recipient's red blood cells (minor ABO incompatibility) and is seen in 25–50% of allogeneic stem cell transplantations.[8,9] Yet, it remains unclear whether ABO incompatibility is of actual clinical significance for transplanted patients. A multitude of published reports in a wide range of hematologic malignancies, conditioning regimens, and donor sources have yielded conflicting data with regard to the actual impact of ABO mismatching on patient outcome.[9–16] Previous publications in AML patients undergoing MMURD did not address the potential clinical significance of ABO mismatching on clinical and transplanted related outcomes. In this analysis of the acute leukemia working party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) we set out to investigate the clinical effects of ABO incompatibility in a large group of adult AML patients undergoing MMURD transplantation.

2 | METHODS

2.1 | Study design and data collection

This multicenter retrospective analysis was approved by the ALWP, in accordance with the EBMT guidelines for retrospective studies. The EBMT is a voluntary working group of more than 500 transplant departments that are required to report all consecutive stem cell transplantations and follow-ups on a yearly basis. Audits are routinely performed to determine the accuracy of the data. The study protocol was approved by the institutional review board at each site and complied with country-specific regulatory requirements. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent authorizing the use of their personal information for research purposes. The list of institutions reporting data included in this study is provided in the Supporting Information data.

For the purpose of this analysis, eligible patients were adults over the age of 18 with AML who were transplanted from an HLA mismatched donor at one or two loci (8/10; 9/10) (-A, -B, -C, DRB1, -DQB1). Patients who had undergone previous allogeneic stem cell transplantation were excluded from the analysis. Major ABO incompatibility was defined as serological evidence for recipient derived antibodies directed against donor red cells, minor ABO incompatibility was defined as serological evidence for donor derived antibodies directed against the recipient's red cells, while bi-directional incompatibility comprised serological evidence of both donor and recipient derived red cell directed antibodies. Regimens were classified as myeloablative conditioning (MAC) or reduced intensity conditioning (RIC) based on published criteria.[17]

2.2 | Statistical analysis

The primary end point of the study was overall (OS) and leukemia-free survival (LFS). Secondary endpoints included disease relapse incidence (RI), NRM, engraftment, incidences, GVHD-free/relapse-free survival (GRFS), defined as events including grade 3–4 acute GVHD, systemic therapy-requiring chronic GVHD, relapse, or death in the first post-HCT year, and severity of acute and chronic GVHD. NRM was defined as death without previous relapse. RI was defined on the basis of morphological evidence of leukemia in bone marrow or other extramedullary organs. LFS was defined as the time from transplantation to first event (either relapse or death in complete remission. Engraftment was defined as sustained achievement of an absolute neutrophil count of over 0.5×10^9/l. Grading of acute and chronic GVHD was performed using established criteria.[18] Chronic GVHD was classified as limited or extensive according to usual criteria.[19] GRFS after HSCT was defined as survival in the absence of grade 3–4 acute GVHD, extensive chronic GVHD and relapse. Cumulative incidence curves were used for RI and NRM in a competing risks setting, since death and relapse are competing. Competing events considered for acute and chronic GVHD were relapse and death. Probabilities of OS and LFS were calculated using the Kaplan–Meier estimate. All tests were two-sided with the type I error rate fixed at 0.05. Statistical analyses were performed with SPSS 22 (SPSS, Chicago, IL), and R 3.2.3 (R Development Core Team, Vienna, Austria) software packages.

3 | RESULTS

3.1 | Patient demographics

A total of 1,013 AML patients who underwent HLA mismatched allogeneic stem cell transplantation between 2005 and 2014 was identified and analyzed. As most of the patients were transplanted with peripheral blood mobilized grafts ($n = 876$), we decided to initially focus our analysis on this group of patients. As summarized in Table 1, the median age of patients was comparable between the various ABO matched and mismatched groups. Most patients were transplanted at first complete remission (CR1) with RIC being the most commonly used conditioning modality. The vast majority of patients in our cohort (range, 88–91%) were mismatched at a single allele, namely 9/10. Cyclosporine based regimens for GVHD prophylaxis were used for most of the patients (889 of 1013; 87%) in the cohort while the rest were given prophylaxis with various combinations consisting of mycophenolate mofetil, tacrolimus, sirolimus, and post-transplant cyclophosphamide. As outlined in Supporting Information Table S1, leukemia, GVHD, and infection accounted for most deaths in the analyzed cohort whereas ABO status had no clinical impact on cause of death both in patients transplanted with PB grafts ($P = .94$) and those receiving BM derived grafts ($P = .84$).

3.2 | Engraftment

ABO matched patients and the three groups of ABO mismatched patients (major, minor, bidirectional) did not significantly differ with regard to engraftment rates at 30 days post transplantation (96, 95, 98, and 97%, respectively, $P = .32$). Univariate analysis for engraftment rates also confirmed the absence of a statistically significant difference between ABO matched and mismatched patients (93 vs. 95%; $P = .96$).

TABLE 1 Patient characteristics-peripheral blood grafts

Variable	ABO matched n = 349	Minor ABO mismatch n = 241	Major ABO mismatch n = 215	Bidirectional ABO mismatch n = 71	P^a
Follow up duration in m, median (range)	24 (1.84–113.85)	34 (2.99–117.44)	32 (0.62–112.74)	41 (1.74–117.96)	
Age in y, median (range)	52 (18–75.3)	54 (18.1–71.5)	52 (18.6–70.8)	50 (21.8–68.8)	.266
Gender, n (%)					
Male	193 (55.3)	134 (55.6)	120 (55.81)	33 (47.14)	.6
Female	156 (44.7)	107 (44.4)	95 (44.19)	37 (52.86)	
Performance status (Karnofsky)					
KPS < 90%	98 (30)	64 (28.9)	50 (24.7)	13 (19.4)	.234
KPS > = 90%	228 (69.9)	157 (71)	152 (75.2)	54 (80.6)	
Disease status at transplant					
CR1	190 (54.4)	127 (52.7)	113 (52.5)	41 (57.7)	.11
CR2/3	89 (25.5)	62 (25.7)	64 (29.7)	9 (12.6)	
Active disease	70 (20.06)	52 (21.5)	38 (17.6)	21 (29.5)	
CMV D–/R–	88 (25.8)	68 (28.8)	50 (23.4)	17 (25.3)	.92
CMV D+/R–	41 (12)	23 (9.7)	24 (11.2)	8 (11.9)	
CMV D–/R+	105 (30.8)	70 (29.6)	61 (28.6)	18 (26.8)	
CMV D+/R+	106 (31.1)	75 (31.7)	78 (36.6)	24 (35.8)	
T-cell depletion ex-vivo					
Yes	8 (2.2)	11 (4.5)	10 (4.6)	1 (1.4)	.246
No	341 (97.7)	230 (95.4)	205 (95.3)	70 (98.5)	
T-cell depletion in-vivo					
Yes	301 (86.2)	204 (85)	190 (88.3)	60 (84.5)	.725
No	48 (13.7)	36(15)	25 (11.6)	11 (15.4)	
HLA matching					
9/10	311 (89.1)	216 (89.6)	190 (88.3)	65 (91.5)	.895
8/10	38 (10.8)	25 (10.3)	25 (11.6)	6 (8.4)	
Female donor to male recipient	48 (13.7)	26 (10.8)	38 (17.7)	10 (14.4)	.216
No female donor to male recipient	300 (86.2)	213 (89.1)	176 (82.2)	59 (85.5)	
Conditioning regimen					
Myeloablative	156 (44.7)	87 (36.1)	93 (43.2)	33 (46.4)	.15
Reduced intensity	193 (55.3)	154 (63.9)	122 (56.7)	38 (53.5)	

^{a}P value of a test of the null hypothesis that all the groups are the same.
Abbreviations: CR1, first complete remission; CMV, cytomegalovirus.

ABO matched, minor mismatched, and major mismatched patients engrafted after a median of 16 days compared to 15 days required for patients with a bidirectional mismatch (P = .9).

3.3 | Acute and chronic GVHD

To evaluate the impact of ABO incompatibility we initially performed a univariate analysis, which as shown in Table 2, demonstrated that the incidence of grade II–IV acute GVHD did not differ to a statistically significant degree between ABO matched and mismatched patients (33 vs. 28%; P = .09). Severe acute GVHD, defined as grade III–IV GVHD, was also not seen more frequently among ABO mismatched patients (15 vs. 11%; P = .14).

Additionally, the rates of 3 year chronic GVHD (38 vs. 35%; P = .43) and extensive chronic GVHD (17 vs. 14%, P = .26) were also comparable between ABO compatible and incompatible patients. Patients who underwent in-vivo T-cell depletion were less likely to experience chronic GVHD (35 vs. 47%; P = .049) and extensive chronic

GVHD (14 vs. 24%; P = .003) compared with those who did not undergo T-cell depletion.

Multivariate analysis (Table 3) also confirmed the absence of a statistically significant association between ABO matching and chronic GVHD, however grade II–IV acute GVHD was significantly lower in patients with major ABO mismatching [Hazard ratio (HR) of 0.7, 95% confidence interval (CI), 0.5–1; P = .049].

3.4 | RI and NRM

In univariate analysis there was no difference in RI at 3 years between ABO matched and mismatched patients (34%; 95% CI, 28–39; for ABO matched vs. 36%; 95% CI, 32–40; for ABO mismatched; P = .32). Neither conditioning intensity patients (33%; 95% CI, 28–38; for MAC vs. 37%; 95% CI, 32–41; for RIC; P = .26) nor degree of HLA mismatching patients (36%; 95% CI, 32–39; for 9/10 mismatch vs. 31%; 95% CI, 21–41; for 8/10 mismatch; P = .29) were found to affect RI in a statistically significant manner. Multivariate analysis (Table 3) also did not establish ABO compatibility to affect RI.

TABLE 2 Univariate analysis of clinical outcome

	3 year RI	P	3 year NRM	P	3 year LFS	P	3 year OS	P	3 year GRFS	P	3 year acute GVHD II–IV	P	3 year chronic GVHD	P	3 year extensive chronic GVH D	P
ABO matched	34.4% (28.9–39.9)	.48	28% (23.1–33)	.52	37.6% (32–43.3)	.52	40.7% (34.9–46.6)	.36	27.6% (22.4–32.9)	.68	33.6% (28.6–38.6)	.19	38% (32.5–43.5)	.7	17.7% (13.4–22.3)	.59
Minor ABO mismatch	38.7% (32.1–45.1)		25.6% (19.9–31.5)		35.8% (29.2–42.4)		40.6% (33.8–47.4)		28.9% (22.6–35.2)		30.3% (24.5–36.3)		33.5% (27.2–39.9)		13.1% (8.8–18.2)	
Major ABO mismatch	32.5% (26–39)		26.3% (20.3–32.7)		41.3% (34.3–48.3)		43.4% (36.1–50.6)		31% (24.5–37.6)		25.4% (19.7–31.5)		36.8% (29.9–43.7)		15.9% (11.1–21.6)	
Bidirectional mismatch	38.7% (26.6–50.5)		21.7% (12.8–32.2)		39.6% (27.5–51.6)		54.7% (42.5–66.9)		30.4% (19–41.8)		29.7% (19.2–40.8)		40.7% (28.4–52.7)		14.4% (7–24.4)	
ABO matched	34.4% (28.9–39.9)	.32	28% (23.1–33)	.2	37.6% (32–43.3)	.87	40.7% (34.9–46.6)	.35	27.6% (22.4–32.9)	.46	33.6% (28.6–38.6)	.09	38% (32.5–43.5)	.43	17.7% (13.4–2 2.3)	.26
ABO mismatched	36.4% (32–40.7)		25.3% (21.5–29.3)		38.3% (33.9–42.8)		43.7% (39.1–48.3)		29.8% (25.6–34.1)		28.2% (24.4–32.2)		35.8% (31.5–40.2)		14.5% (11.4–17.9)	
Disease status at Tx																
CR1	32.6% (28.1–37.2)	.0002	23.4% (19.5–27.6)	.024	44% (39–48.9)	<.0001	49% (44–54)	<.0001	33.6% (28.9–38.3)	<.0001	27.7% (23.6–31.8)	.16	41.3% (36.4–46)	.025	17.6% (14–21.6)	.12
CR2	32.2% (25.8–38.8)		27.4% (21.3–33.7)		40.4% (33.4–47.4)		44.3% (37.2–51.5)		31.5% (24.9–38)		32.9% (26.7–39.2)		33% (26.5–39.7)		15% (10.3–20.5)	
Active disease	47% (39.1–54.5)		32.6% (25.7–39.7)		20.3% (13.9–26.7)		24.4% (17.6–31.2)		14.3% (8.7–20)		34.3% (27.3–41.5)		29.2% (22.3–36.5)		11.6% (7.1–17.3)	
HLA																
9/10	36% (32.4–39.6)	.29	25.3% (22.1–28.6)	.02	38.7% (35–42.5)	.22	43.1% (39.2–46.9)	.42	29.4% (25.9–32.9)	.38	31% (27.7–34.3)	.19	36.4% (32.8–40.1)	.47	15.6% (12.9–18.5)	.71
8/10	31.5% (21.7–41.7)		35.4% (25.3–45.5)		33.1% (22.8–43.5)		38.5% (27.5–49.5)		25.8% (16.4–35.3)		24.9% (16.4–34.3)		38.9% (28.4–49.3)		16.3% (9.1–25.4)	
Conditioning regimen																
MAC	33% (28–38)	.26	22.8% (18.6–27.4)	.19	44.2% (38.8–49.6)	.028	47.6% (42–53.2)	.036	33.9% (28.7–39.2)	.043	30.4% (25.7–35.2)	.85	39.6% (34.2–45)	.13	14.9% (11.1–19.2)	.98
RIC	37.3% (32.7–41.8)		29.1% (24.9–33.3)		33.7% (29.1–38.2)		39% (34.3–43.7)		25.4% (21.2–29.6)		30.4% (26.3–34.5)		34.8% (30.3–39.2)		16.4% (13.1–20.1)	

Abbreviations: LFS, leukemia free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; RI, relapse incidence; NRM, non-relapse mortality; GVHD, graft versus host disease; GRFS, GVHD-free/relapse-free survival.

TABLE 3 Multivariable analysis of patient outcome following transplantation

Parameter	RI HR (95% CI)	OS HR (95% CI)	LFS HR (95% CI)	NRM HR (95% CI)	Acute GVHD grade II–IV HR (95% CI)	Chronic GVHD HR (95% CI)
Matched ABO (ref)	1	1	1	1	1	1
Minor ABO mismatch	1.17 (0.86–1.61), P = .32	1.03 (0.8–1.33), P = .78	1.1 (0.87–1.4), P = .4	1.04 (0.73–1.48), P = .82	0.93 (0.66–1.31), P = .7	1.002 (0.71–1.4), P = .98
Major ABO mismatch	1.11 (0.79–1.56), P = .53	1.02 (0.78–1.32), P = .87	1.01 (0.79–1.3), P = .9	0.92 (0.63–1.35), P = .69	0.71 (0.49–1.04), P = .08	0.94 (0.66–1.33), P = 0.73
Bi–directional ABO mismatch	1.004 (0.61–1.63), P = .98	0.73 (0.47–1.12), P = .16	0.83 (0.56–1.24), P = .37	0.63 (0.32–1.24), P = .18	0.84 (0.47–1.48), P = .55	0.9 (0.53–1.51), P = .69
Patient age (10 year increment)	1.08 (0.96–1.21), P = .17	1.1 (1.006–1.21), P = .037	1.09 (1.003–1.19), P = .041	1.11 (0.97–1.27), P = .11	0.91 (0.8–1.04), P = .18	1.04 (0.92–1.18), P = .45
Donor age (10 year increment)	0.96 (0.83–1.1), P = .57	1.04 (0.94–1.16), P = .39	1.03 (0.93–1.14), P = .53	1.12 (0.96–1.3), P = .12	0.93 (0.81–1.08), P = .38	0.93 (0.8–1.07), P = .34
Disease status at transplant						
CR1 (reference)	1	1	1	1	1	1
CR2	1.14 (0.81–1.62), P = .43	1.15 (0.88–1.51), P = .28	1.11 (0.86–1.43), P = .39	1.08 (0.74–1.57), P = .66	1.27 (0.88–1.82), P = .18	0.88 (0.63–1.23), P = .46
Active disease	2.34 (1.69–3.24), P < .0001	2.04 (1.58–2.62), P < .0001	2.11 (1.66–2.7), P < .0001	1.85 (1.27–2.67), P = .001	1.28 (0.88–1.85), P = .18	1.06 (0.71–1.58), P = .74
CMV donor/ recipient matching						
D–/R– (ref)	1	1	1	1	1	1
D+/R–	1.04 (0.65–1.66), P = .84	0.73 (0.49–1.09), P = .12	0.89 (0.61–1.29), P = .54	0.68 (0.36–1.29), P = .24	0.93 (0.56–1.54), P = .79	1.26 (0.79–2.02), P = .32
D–/R+	1.28 (0.91–1.8), P = .15	1.34 (1.03–1.76), P = .029	1.37 (1.06–1.77), P = .016	1.48 (1–2.2), P = .05	1.08 (0.75–1.56), P = .64	1.23 (0.85–1.79), P = .26
D+/R+	0.99 (0.69–1.41), P = .96	1.04 (0.78–1.37), P = .77	1.11 (0.85–1.45), P = .42	1.29 (0.86–1.94), P = .21	0.7 (0.47–1.04), P = .08	1.38 (0.95–1.99), P = .08
Female donor to male recipient vs. others	0.73 (0.49–1.1), P = .14	0.9 (0.66–1.22), P = .5	0.83 (0.62–1.12), P = .23	0.96 (0.63–1.47), P = .88	1.22 (0.83–1.8), P = .3	0.88 (0.6–1.3), P = .54
RIC vs. MAC conditioning	1.005 (0.74–1.35), P = .97	1.02 (0.81–1.28), P = .86	1.01 (0.81–1.26), P = .87	1.03 (0.74–1.44), P = .84	1.01 (0.71–1.42), P = .95	0.82 (0.6–1.12), P = .22
KPS≥90% vs. KPS<90%	0.8 (0.6–1.06), P = .13	0.68 (0.55–0.85), P < .0001	0.74 (0.6–0.91), P = .005	0.67 (0.49–0.92), P = .014	1.01 (0.72–1.41), P = .94	1.03 (0.73–1.44), P = .85

Abbreviations: LFS, leukemia free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; RI, relapse incidence; NRM, non-relapse mortality; GVHD, graft versus host disease; CR, complete remission; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; KPS, Karnofsky performance status.

The NRM incidence at 3 years was also equivalent between the ABO compatible and incompatible groups (28%; 95% CI, 23–33; for ABO matched vs. 25%; 95% CI, 21–29; for ABO mismatched; P = .2). Of note, patients 9/10 HLA matched patients had significantly decreased rates of NRM at 3 years compared to 8/10 HLA matched patients (25%; 95% CI, 22–28; for 9/10 HLA matched patients vs. 35%; 95% CI, 25–45; for 8/10 HLA mismatched patients; P = .02). Conditioning intensity did not significantly impact on NRM (22%; 95% CI, 18–27; for MAC vs. 29%; 95% CI, 24–33; for RIC; P = .19). In the multivariate analysis presented in Table 3, NRM incidence was not significantly different between ABO matched and mismatched patients.
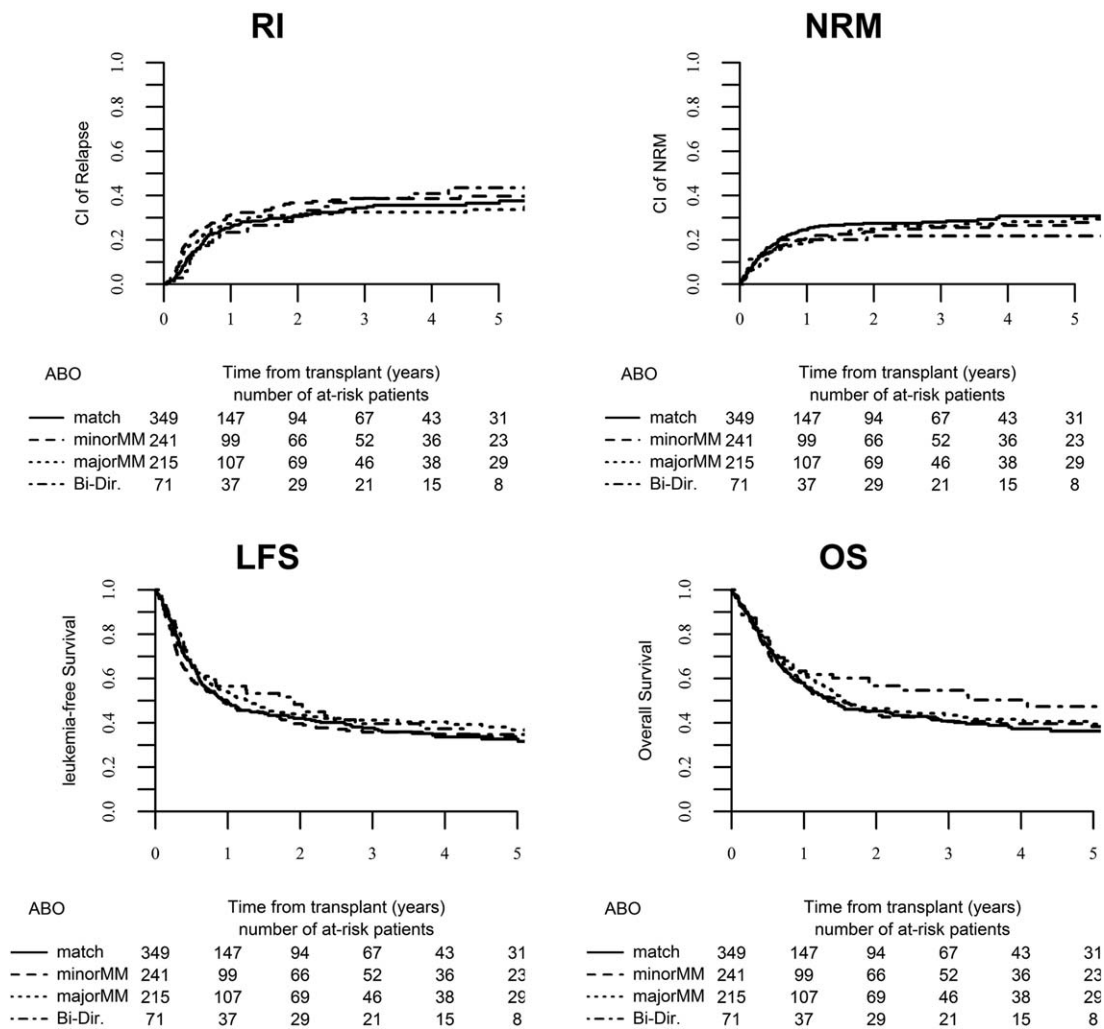
FIGURE 1 Impact of ABO incompatibility on clinical outcome indices in MMURD transplantation

3.5 | GRFS, LFS, and OS

As shown in Table 2, univariate analysis of GRFS, LFS, and OS at 3 years was comparable between ABO matched and mismatched patients. Conversely, disease status at transplant and the conditioning regimen significantly affected LFS with active disease correlating significantly with inferior LFS at 3 years (20%; 95% CI, 13–26; $P < .0001$) while MAC was associated with a 3 year of 44% compared with 33% with RIC ($P = .028$). Similar correlations were also observed for OS and GRFS (Table 2). In multivariate analysis, ABO compatibility status did not significantly affect LFS and OS (Table 3) while increasing age, active disease at transplant, and a decreased performance status were all predictive of inferior LFS and OS. Figure 1 depicts the various clinical parameters stratified per ABO compatibility status

3.6 | Bone marrow graft cohort

To assess whether HLA mismatched patients transplanted with bone marrow derived grafts were differentially affected by ABO mismatching status we performed an additional separate analysis for this group of patients. In all, a cohort of 137 patients was analyzed with their baseline demographic data presented in Supporting Information Table S2. A uni-

variate analysis demonstrated that none of the clinical outcomes analyzed (RI, NRM, LFS, OS, GRFS, acute GVHD, and chronic GVHD) were significantly affected by ABO compatibility status (Supporting Information Figure S1). A subsequent multivariate analysis also did not confirm a statistically significant difference between ABO matched and mismatched patients with regard to the clinical outcome indices noted above.

3.7 | HLA mismatch focused analysis

As HLA-DQ mismatching has a minor impact on prognosis compared with other HLA mismatches[20] we wanted to assess whether exclusion of this group of patients would influence the outcome of ABO mismatched patients. First, we confirmed that in our cohort there was no statistically significant difference in the distribution of HLA-DQ mismatches between ABO matched and mismatched patients ($P = .15$).

Next, we reanalyzed the data excluding the 156 patients who were HLA-DQ mismatched. A univariate analysis showed that ABO incompatible patients experienced decreased grade II–IV acute GVHD rates compared to ABO matched patients (28 vs. 38%; $P = .011$). A subsequent multivariate analysis (Supporting Information Table S3) confirmed that patients with major ABO mismatching experienced less

grade II–IV acute GVHD than ABO matched patients (HR of 0.57, 95% CI, 0.37–0.88; $P = .01$).

4 | DISCUSSION

ABO incompatibility is commonly seen in allogeneic hematopoietic cell transplantations with a yet undecided consensus regarding the clinical implications it holds on patient outcome. In this analysis, comparing the outcomes of over a thousand adult AML patients who underwent MMURD transplantations, we determine that in this specific clinical setting, ABO mismatching does not affect prognosis in a clinical meaningful way. Furthermore, we establish this lack of clinical significance to be true both for peripheral blood mobilized grafts as well as for bone marrow derived grafts.

Whereas the use of donors with one or two HLA mismatches affords physicians the possibility of transplanting patients who would otherwise may not have been able to benefit from a transplanted based approach,[4] this comes at a price of increased transplant related morbidity and mortality. Multiple publications including those from the Center for International Blood and Marrow Transplant Research (CIBMTR)[21] and the Japanese Society of Hematopoietic Cell Transplantation[22,23] as well as others[6,24] have consistently demonstrated the incremental detrimental consequences of increased HLA mismatching regardless of graft source or conditioning intensity.[4,25] Consequently, attempts at optimizing transplant related factors are highly warranted. Consistent with most major prior publications, we did not find ABO mismatching to correlate with inferior neutrophil engraftment. Whereas neutrophils can express the ABO antigens which may theoretically lead to slower engraftment following transplantation, several large registry based analyses failed to show slower engraftment kinetics with ABO mismatching,[26–28] although Kimura and colleagues previously suggested that major ABO incompatibility resulted in delayed engraftment of neutrophils, platelets, and red blood cells.[9]

Our data did indicate a potential mitigating role for major ABO mismatching on the incidence of grade II–IV acute GVHD. These data are in agreement with those reported by Bacigalupu and colleagues[29] showing that patients with major ABO incompatibility experienced lower acute GVHD rates compared with ABO matched and minor ABO mismatched patients. More recently published data did not confirm the same effect but did suggest a correlation between minor ABO incompatibility and severe acute GVHD.[30,31] While this observation currently lacks a clear biological rationale, a possible explanation for this phenomenon may involve the absorption of anti A/B antibodies by donor lymphocytes thus eliminating at least part of the cellular repertoire responsible for the induction and propagation of GVHD.[29,32] Our findings also concur with most prior publications in the field with regard to the incidence of disease relapse in the setting of ABO incompatibility. Indeed, data from major cooperative groups in the field, namely the CIBMTR,[33] the National Marrow Donor Program[28] and others,[16,30,32] support our findings essentially confirming that across multiple datasets and conditioning regimens, ABO incompatibility has no bearing on the risk for relapse.

Lastly, as the stem cell source may in itself impact on clinical outcome post-transplantation,[34] we performed a separate analysis for a smaller group of patients who received bone marrow derived grafts.

Again, similar to our earlier observations in the PB group, ABO status did not affect outcome in MMURD transplanted patients. We note that in general, studies examining ABO incompatibility both in bone marrow derived grafts and in PB grafts indicated the lack of a prognostic effect of ABO status.[35] Interestingly, we also found that upon exclusion of HLA-DQ mismatched patients, major ABO incompatibility impacted favorably on the incidence of acute GVHD. The reasons for this observation are not completely clear but are supported by data previously published by Bacigalupo et al.[29]

We recognize the challenge of comparing the results of our analysis, of a rather homogeneous AML cohort, to those of prior studies, which consisted of a multitude of diseases comprising both malignant and nonmalignant hematologic conditions. Additionally, as with any retrospective multicenter analysis, there are recognized inherent limitations affecting data collection and analysis. Importantly, we note that as our registry data was not annotated for clinical data on transfusion requirements, clinically significant hemolysis, and additional potentially prognosis modifying clinical factors we cannot fully exclude a potential role for ABO incompatibility in influencing outcome in MMURD.

In aggregate, our findings support the prevailing clinical notion that ABO incompatibility has no major impact on patient prognosis probably extends also to the population of adult AML patients undergoing MMURD allogeneic stem cell transplantation.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.