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RESEARCH ARTICLE

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Association of ABO mismatch with the outcomes of allogeneic hematopoietic cell transplantation for acute leukemia

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Abstract

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). While many factors influence the outcomes of allo-HCT, the independent impact of donor–recipient ABO mismatching remains unclear. Using the Center for International Blood and Marrow Transplant Research (CIBMTR) database, we identified patients aged ≥18 years with AML or ALL who underwent allo-HCT between 2008 and 2018. Our objectives were to analyze the outcomes of allo-HCT based on the donor–recipient ABO status (match, minor mismatch, major mismatch, bidirectional mismatch). Among 4946 eligible patients, 2741 patients (55.4%) were ABO matched, 1030 patients (20.8%) had a minor ABO mismatch, 899 patients (18.1%) had a major

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ABO mismatch, and 276 patients (5.6%) had a bidirectional ABO mismatch. In multivariable analyses, compared to ABO matched allo-HCT, the presence of a major ABO mismatch was associated with worse overall survival (HR 1.16, 95% CI 1.05–1.29; $p = 0.005$), inferior platelet engraftment (HR 0.83, 95% CI 0.77–0.90; $p < 0.001$), and higher primary graft failure (HR 1.60, 95% CI 1.12–2.30, $p = 0.01$). Relapse, acute graft versus host disease (GVHD) grades III-IV and chronic GVHD were not significantly associated with ABO status. While donor age was not significantly associated with outcomes, older recipient age was associated with worse survival and non-relapse mortality. Our study demonstrates that donor–recipient ABO status is independently associated with survival and other post-transplantation outcomes in acute leukemia. This underscores the importance of considering the ABO status in donor selection algorithms and its impact in acute leukemia.

1 | INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for several hematological disorders with its utilization increasing over time.[1] While planning allo-HCT, several factors such as donor–recipient HLA match, donor age, graft source, and conditioning strategies are considered given their strong impact on clinical outcomes. The compatibility of ABO antigens between donors and recipients is routinely evaluated although the priority of ABO matching status in donor selection algorithms is variable. In practice, ABO mismatches are classified as minor (donor antibodies against recipient blood group antigen), major (antibodies in recipient plasma against donor blood group antigen) or bidirectional (combination of major and minor mismatches).[2]

Several prior studies have evaluated the effect of ABO mismatch in allo-HCT, but their conflicting results have added complexity to understand its independent impact on outcomes.[3–10] Hence, allo-HCT is often performed across ABO mismatches and transplant centers utilize a variety of approaches to mitigate its impact pre- and/or post-transplant.[11,12] One important limitation to the prior studies is the heterogeneity of the disease types included. For example, most studies with large sample size have included a mix of underlying disorders including malignant and non-malignant conditions. Given the variations in transplant practice based on the underlying hematological disorder along with the biologic differences between these conditions, it is possible that the impact of ABO mismatch on allo-HCT was concealed or attenuated for individual hematologic diseases. When restricted to acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), a study from the Center for International Blood and Marrow Transplant Research (CIBMTR) by Logan et al. demonstrated that major ABO mismatch was associated with worse overall survival.[10] However, similar results have not been seen in the context of other hematological disorders,[3–10] raising the possibility that the influence of ABO mismatch could vary based on the underlying condition. Hence, we sought to evaluate the impact of ABO mismatch on the outcomes of allo-HCT for AML and acute lymphoblastic leukemia (ALL), hypothesizing that ABO mismatched allo-HCT would be associated with inferior outcomes.

2 | METHODS

2.1 | Study objectives

Our objectives are to investigate the association between donor–recipient ABO status and outcomes: overall survival, disease free survival, non-relapse mortality, relapse, engraftment, primary graft failure and acute and chronic graft versus host disease (GVHD) in patients with AML or ALL undergoing allo-HCT.

2.2 | Data source

The CIBMTR is a research affiliation between the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR captures data including, but not limited to, baseline recipient and donor characteristics, transplant outcomes, and follow-up data at day +100, day +180, and annually after allo-HCT.[13] Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The institutional review boards of the National Marrow Donor Program approved this study. Patients and donors provided written informed consent for research.

2.3 | Study population

Patients with age ≥18 years who underwent first allo-HCT in the United States for AML or ALL either from HLA-identical sibling or 8/8 matched unrelated donor (MUD) between the years 2008 to 2018 were included. Key exclusion criteria were allo-HCT from mismatched unrelated donor, haploidentical donor, syngeneic donor, cord blood, and the use of ex-vivo T-cell depleted, CD34 selected or cryopreserved grafts.

TABLE 1 Baseline characteristics of patients receiving peripheral blood stem cells

Characteristic	ABO matched	Minor mismatch	Major mismatch	Bi-directional mismatch
No. of patients	2318	859	741	232
No. of centers	110	103	92	72
Recipient age at transplant-no. (%)				
Median (min-max)	52.7 (18–81.5)	54.1 (18.4–78.3)	53.9 (18.2–77.7)	55 (18.9–75.2)
18–29	257 (11)	82 (10)	90 (12)	27 (12)
30–39	270 (12)	95 (11)	91 (12)	23 (10)
40–49	459 (20)	167 (19)	119 (16)	36 (16)
50–59	621 (27)	219 (25)	210 (28)	62 (27)
60–69	589 (25)	247 (29)	192 (26)	74 (32)
70+	122 (5)	49 (6)	39 (5)	10 (4)
Sex-no. (%)				
Male	1285 (55)	453 (53)	406 (55)	130 (56)
Female	1033 (45)	406 (47)	335 (45)	102 (44)
Race-no. (%)				
White	2050 (88)	723 (84)	647 (87)	193 (83)
Black or African American	86 (4)	58 (7)	30 (4)	9 (4)
Asian	92 (4)	44 (5)	36 (5)	17 (7)
Native Hawaiian or other Pacific Islander	8 (0)	2 (0)	0	1 (0)
American Indian or Alaska Native	18 (1)	2 (0)	3 (0)	1 (0)
More than one race	8 (0)	6 (1)	6 (1)	1 (0)
Missing	56 (2)	24 (3)	19 (3)	10 (4)
HCT-CI-no. (%)				
0	556 (24)	218 (25)	198 (27)	49 (21)
1	329 (14)	119 (14)	115 (16)	37 (16)
2	372 (16)	127 (15)	120 (16)	36 (16)
3+	1047 (45)	387 (45)	306 (41)	110 (47)
Missing	14 (1)	8 (1)	2 (0)	0
Karnofsky performance score-no. (%)				
90–100	1317 (57)	458 (53)	408 (55)	136 (59)
<90	986 (43)	395 (46)	322 (43)	93 (40)
Missing	15 (1)	6 (1)	11 (1)	3 (1)
Disease - no. (%)				
AML	1828 (79)	724 (84)	583 (79)	182 (78)
ALL	490 (21)	135 (16)	158 (21)	50 (22)
Disease status at time of HCT-no. (%)				
PIF	278 (12)	115 (13)	92 (12)	22 (9)
CR1	1485 (64)	508 (59)	442 (60)	148 (64)
CR2	372 (16)	152 (18)	140 (19)	40 (17)
≥CR3	23 (1)	10 (1)	6 (1)	1 (0)
Relapse	160 (7)	73 (8)	61 (8)	20 (9)
Missing	0	1 (0)	0	1 (0)
Conditioning intensity and TBI use-no. (%)				
MAC TBI	647 (28)	219 (25)	196 (26)	63 (27)
MAC non-TBI	822 (35)	302 (35)	260 (35)	72 (31)
RIC/NMA	837 (36)	336 (39)	281 (38)	94 (41)
Missing	12 (1)	2 (0)	4 (1)	3 (1)

TABLE 1 (Continued)

Characteristic	ABO matched	Minor mismatch	Major mismatch	Bi-directional mismatch
GVHD prophylaxis-no. (%)				
TAC +/− others	2020 (87)	734 (85)	612 (83)	194 (84)
CSA +/− others	221 (10)	86 (10)	86 (12)	27 (12)
PTCy +/− others	63 (3)	30 (3)	33 (4)	7 (3)
Other(s)	11 (0)	8 (1)	7 (1)	4 (2)
Missing	3 (0)	1 (0)	3 (0)	0
ATG/alemtuzumab-no. (%)				
ATG or alemutzumab	520 (22)	234 (27)	188 (25)	68 (29)
No ATG or alemtuzumab	1795 (77)	625 (73)	553 (75)	164 (71)
Missing	3 (0)	0	0	0
Donor type-no. (%)				
HLA-identical sibling	1026 (44)	239 (28)	226 (30)	57 (25)
Well-matched unrelated (8/8)	1292 (56)	620 (72)	515 (70)	175 (75)
Donor age at collection, unrelated donors only-no. (%)				
Median (min-max)	27.8 (18.3–60.8)	28.7 (18–60.4)	30.1 (18.2–59.6)	29.4 (18.9–56.8)
NA, HLA-identical sibling	1026 (44)	239 (28)	226 (30)	57 (25)
18–29	775 (33)	339 (39)	248 (33)	93 (40)
30–39	299 (13)	144 (17)	125 (17)	38 (16)
40–49	151 (7)	92 (11)	95 (13)	30 (13)
50–59	43 (2)	32 (4)	30 (4)	11 (5)
60–69	2 (0)	1 (0)	0	0
Missing	22 (1)	12 (1)	17 (2)	3 (1)
Donor/recipient Rh factor match-no. (%)				
+/+	1790 (77)	663 (77)	564 (76)	177 (76)
+/−	208 (9)	66 (8)	81 (11)	28 (12)
−/+	213 (9)	99 (12)	81 (11)	23 (10)
−/−	107 (5)	30 (3)	15 (2)	4 (2)
Missing	0	1 (0)	0	0
Donor/recipient sex match-no. (%)				
M-M	869 (37)	289 (34)	280 (38)	83 (36)
M-F	643 (28)	220 (26)	221 (30)	66 (28)
F-M	416 (18)	164 (19)	126 (17)	47 (20)
F-F	390 (17)	186 (22)	114 (15)	36 (16)
Donor/recipient CMV serostatus-no. (%)				
+/+	725 (31)	270 (31)	229 (31)	72 (31)
+/−	245 (11)	82 (10)	88 (12)	21 (9)
−/+	758 (33)	275 (32)	256 (35)	80 (34)
−/−	562 (24)	220 (26)	157 (21)	56 (24)
Missing-donor	6 (0)	0	1 (0)	1 (0)
Missing-recipient	1 (0)	0	0	0
Missing-recipient not tested, inconclusive	21 (1)	12 (1)	10 (1)	2 (1)
Year of transplant-no. (%)				
2008	301 (13)	107 (12)	119 (16)	35 (15)
2009	262 (11)	104 (12)	109 (15)	40 (17)
2010	222 (10)	96 (11)	71 (10)	22 (9)
2011	117 (5)	42 (5)	46 (6)	9 (4)

(Continues)

TABLE 1 (Continued)

Characteristic	ABO matched	Minor mismatch	Major mismatch	Bi-directional mismatch
2012	88 (4)	42 (5)	23 (3)	11 (5)
2013	223 (10)	106 (12)	71 (10)	18 (8)
2014	329 (14)	113 (13)	93 (13)	32 (14)
2015	308 (13)	82 (10)	89 (12)	29 (13)
2016	212 (9)	81 (9)	60 (8)	17 (7)
2017	129 (6)	45 (5)	27 (4)	8 (3)
2018	127 (5)	41 (5)	33 (4)	11 (5)
Follow-up-median (min-max)	61.7 (2.7–147.7)	71 (3.8–144.8)	72 (3–145.4)	71.3 (6–144.8)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; CR, complete remission; CSA, cyclosporine; GVHD, graft versus host disease; HCT-CI, hematopoietic cell transplantation comorbidity index; MAC, myeloablative conditioning; NMA, non-myeloablative conditioning; PIF, primary induction failure; PTCy, post transplant cyclophosphamide; RIC, reduced intensity conditioning; TAC, tacrolimus; TBI, total body irradiation.

3 | STATISTICAL ANALYSIS

Baseline characteristics of the study population were summarized using descriptive statistics with medians and ranges for continuous variables and proportions for categorical variables. The definitions of outcomes are provided in Data S1. Cumulative incidence estimates were calculated for competing risks outcomes including neutrophil and platelet recovery, acute GVHD, chronic GVHD, non-relapse mortality, and relapse; relapse was considered as a competing event for non-relapse mortality, while death was considered a competing event for all other outcomes. Kaplan–Meier method was used to estimate the probabilities for survival. To evaluate potential risk factors, multivariable Cox regression analysis was used. The proportional hazards assumption was examined using graphical methods and time-dependent covariates and covariates that violated the proportional hazards assumption were added as time-dependent covariates. Hazard ratios (HRs) and confidence limits were reported. Variables considered for multivariable analysis are provided in Data S1, including donor age which was investigated in all models. A stepwise selection method was used to identify the final model with a significance level of 0.05, forcing the main effect of ABO matching into the model. Interactions between the main effect (ABO status) and other significant risk factors were also tested. Cause specific proportional hazards models were used for analysis of non-relapse mortality, GVHD, and relapse. Marginal Cox models were used to adjust for center effects. Missing covariate categories were included in the models to avoid loss of data and power. Logistic regression was used to model the binary outcome of primary graft failure. All analyses were performed at a two-sided significance level of 0.05 using SAS 9.4 (SAS Institute, Cary, NC).

4 | RESULTS

4.1 | Baseline characteristics

Of 4946 patients who met the study criteria, 2741 patients (55.4%) were ABO matched, 1030 patients (20.8%) had minor ABO mismatch, 899 patients (18.1%) had major ABO mismatch, and 276 patients (5.6%) had bidirectional ABO mismatch. Baseline characteristics of the study population based on the graft source [peripheral blood (PB) and bone marrow (BM)] is summarized in Tables 1 and 2. The majority of the patients underwent allo-HCT using MUD, peripheral blood stem cells, myeloablative conditioning (MAC), and were in their first complete remission (CR). A higher proportion of patients underwent allo-HCT for AML (79.2%) than ALL (20.8%).

4.2 | Engraftment and primary graft failure

Median time to neutrophil recovery was 14 days (range 1–81) with PB grafts and 17 days (range 1–96) with BM grafts. Median time to platelet recovery was 16 days (range 1–510) for PB grafts and 24 days (range 1–444) for BM grafts. The incidence of primary graft failure was 3% in the PB cohort and 6% in the BM cohort (eTable 1). In multivariable analysis, major ABO mismatch was associated with a higher risk of primary graft failure (HR 1.60, 95% CI 1.12–2.30, $p = 0.01$) and delayed platelet engraftment (HR 0.83, 95% CI 0.77–0.90; $p < 0.001$) (eTables 2–4).

4.3 | Overall survival

In multivariable analysis, overall survival was significantly inferior in patients with a major ABO mismatched donor as compared to ABO matched allo-HCT (HR 1.16, 95% CI 1.05–1.29; $p = 0.005$) (Figure 1, Table 3). Other significant factors associated with overall survival were recipient age (higher risk with increasing age), disease status prior to allo-HCT (higher risk when not in CR1), GVHD prophylaxis (higher risk with regimens other than post-transplant cyclophosphamide [post-Cy]), hematopoietic cell transplantation comorbidity index (HCT-CI) (higher risk with increasing score), performance status (higher risk with increasing score), and year of transplant (lesser risk in subsequent periods) (eTable 5).

TABLE 2 Baseline characteristics of patients receiving bone marrow stem cells

Characteristic	ABO matched	Minor mismatch	Major mismatch	Bi-directional mismatch
No. of patients	423	171	158	44
No. of centers	80	57	50	31
Recipient age at transplant-no. (%)				
Median (min-max)	47.3 (18–75.1)	48.4 (18.4–76)	46.1 (18.1–76.4)	48.1 (19.4–71.9)
18–29	90 (21)	36 (21)	32 (20)	7 (16)
30–39	59 (14)	27 (16)	23 (15)	9 (20)
40–49	89 (21)	27 (16)	33 (21)	8 (18)
50–59	105 (25)	49 (29)	42 (27)	11 (25)
60–69	65 (15)	27 (16)	24 (15)	7 (16)
70+	15 (4)	5 (3)	4 (3)	2 (5)
Sex-no. (%)				
Male	228 (54)	94 (55)	82 (52)	24 (55)
Female	195 (46)	77 (45)	76 (48)	20 (45)
Race-no. (%)				
White	385 (91)	143 (84)	133 (84)	36 (82)
Black or African American	17 (4)	2 (1)	9 (6)	0
Asian	4 (1)	17 (10)	12 (8)	8 (18)
Native Hawaiian or other Pacific Islander	1 (0)	0	0	0
American Indian or Alaska Native	0	0	2 (1)	0
More than one race	2 (0)	3 (2)	0	0
Missing	14 (3)	6 (4)	2 (1)	0
HCT-CI-no. (%)				
0	120 (28)	35 (20)	45 (28)	15 (34)
1	72 (17)	28 (16)	23 (15)	5 (11)
2	72 (17)	25 (15)	28 (18)	8 (18)
3+	157 (37)	83 (49)	58 (37)	16 (36)
Missing	2 (0)	0	4 (3)	0
Karnofsky performance score-no. (%)				
90–100	266 (63)	113 (66)	107 (68)	34 (77)
<90	149 (35)	57 (33)	49 (31)	10 (23)
Missing	8 (2)	1 (1)	2 (1)	0
Disease - no. (%)				
AML	320 (76)	127 (74)	116 (73)	35 (80)
ALL	103 (24)	44 (26)	42 (27)	9 (20)
Disease status at time of HCT-no. (%)				
PIF	43 (10)	24 (14)	20 (13)	2 (5)
CR1	277 (65)	95 (56)	99 (63)	30 (68)
CR2	75 (18)	40 (23)	25 (16)	8 (18)
≥CR3	8 (2)	1 (1)	2 (1)	1 (2)
Relapse	20 (5)	11 (6)	12 (8)	3 (7)
Conditioning intensity and TBI use-no. (%)				
MAC TBI	120 (28)	50 (29)	58 (37)	15 (34)
MAC non-TBI	234 (55)	84 (49)	75 (47)	20 (45)
RIC/NMA	69 (16)	35 (20)	25 (16)	9 (20)
Missing	0	2 (1)	0	0
GVHD prophylaxis-no. (%)				

(Continues)

TABLE 2 (Continued)

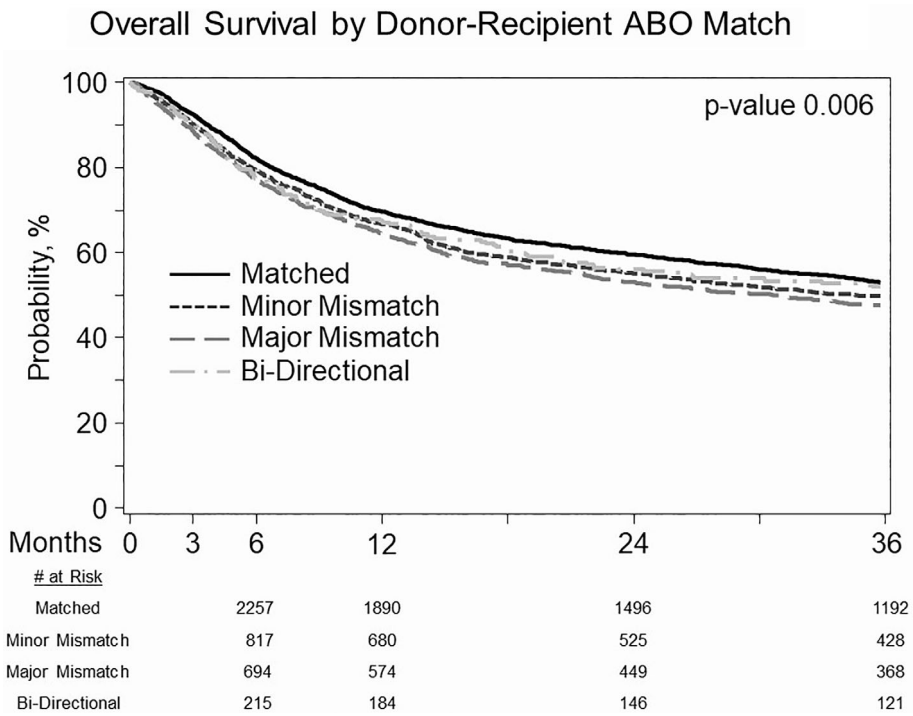
Characteristic	ABO matched	Minor mismatch	Major mismatch	Bi-directional mismatch
TAC +/− others	306 (72)	124 (73)	132 (84)	38 (86)
CSA +/− others	39 (9)	22 (13)	11 (7)	2 (5)
PTCy +/− others	73 (17)	23 (13)	14 (9)	4 (9)
Other(s)	5 (1)	2 (1)	0	0
Missing	0	0	1 (1)	0
ATG/alemtuzumab-no. (%)				
ATG or Alemtuzumab	74 (17)	40 (23)	38 (24)	11 (25)
No ATG or Alemtuzumab	349 (83)	131 (77)	120 (76)	33 (75)
Donor type-no. (%)				
HLA-identical sibling	121 (29)	17 (10)	20 (13)	9 (20)
Well-matched unrelated (8/8)	302 (71)	154 (90)	138 (87)	35 (80)
Donor age at collection, unrelated donors only-no. (%)				
Median (min-max)	28.8 (18.8–59.2)	28.8 (18.8–61)	27.8 (19.1–55.2)	29.7 (21.6–54.9)
NA- HLA-identical sibling	121 (29)	17 (10)	20 (13)	9 (20)
18–29	166 (39)	82 (48)	84 (53)	19 (43)
30–39	88 (21)	37 (22)	36 (23)	9 (20)
40–49	36 (9)	22 (13)	13 (8)	5 (11)
50–59	9 (2)	9 (5)	4 (3)	2 (5)
60–69	0	1 (1)	0	0
Missing	3 (1)	3 (2)	1 (1)	0
Donor/recipient Rh factor match-no. (%)				
+/+	310 (73)	123 (72)	117 (74)	31 (70)
+/−	42 (10)	23 (13)	16 (10)	8 (18)
−/+	49 (12)	21 (12)	19 (12)	2 (5)
−/−	22 (5)	4 (2)	6 (4)	3 (7)
Donor/recipient sex match-no. (%)				
M-M	169 (40)	78 (46)	60 (38)	16 (36)
M-F	135 (32)	53 (31)	51 (32)	15 (34)
F-M	59 (14)	16 (9)	22 (14)	8 (18)
F-F	60 (14)	24 (14)	25 (16)	5 (11)
Donor/recipient CMV serostatus-no. (%)				
+/+	101 (24)	46 (27)	42 (27)	16 (36)
+/−	59 (14)	20 (12)	13 (8)	3 (7)
−/+	125 (30)	67 (39)	57 (36)	17 (39)
−/−	136 (32)	37 (22)	46 (29)	6 (14)
Missing-recipient not tested, inconclusive	2 (0)	1 (1)	0	2 (5)
Year of transplant-no. (%)				
2008	39 (9)	19 (11)	27 (17)	9 (20)
2009	48 (11)	15 (9)	20 (13)	4 (9)
2010	33 (8)	12 (7)	13 (8)	1 (2)
2011	13 (3)	7 (4)	4 (3)	5 (11)
2012	21 (5)	8 (5)	7 (4)	3 (7)
2013	35 (8)	16 (9)	18 (11)	6 (14)
2014	42 (10)	28 (16)	18 (11)	7 (16)
2015	33 (8)	15 (9)	11 (7)	3 (7)
2016	60 (14)	16 (9)	19 (12)	2 (5)

TABLE 2 (Continued)

Characteristic	ABO matched	Minor mismatch	Major mismatch	Bi-directional mismatch
2017	62 (15)	22 (13)	7 (4)	3 (7)
2018	37 (9)	13 (8)	14 (9)	1 (2)
Follow-up-median (min-max)	50.1 (2.3–143.9)	59 (6.3–143.7)	64.7 (11.2–144.7)	62.4 (23.5–120.7)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; CR, complete remission; CSA, cyclosporine; GVHD, graft versus host disease; HCT-CI, hematopoietic cell transplantation comorbidity index; MAC, myeloablative conditioning; NMA, non-myeloablative conditioning; PIF, primary induction failure; PTCy, post transplant cyclophosphamide; RIC, reduced intensity conditioning; TAC, tacrolimus; TBI, total body irradiation.

FIGURE 1 Overall survival by ABO status



4.4 | Disease free survival

In multivariable analysis, inferior disease-free survival was seen in patients with a major ABO mismatched donor (HR 1.11, 95% CI 1.02–1.22, $p = 0.02$, overall $p = 0.09$) (Table 3, eFigure 1). Other factors significantly associated with disease free survival were recipient age (higher risk with increasing age), disease status prior to allo-HCT (higher risk when not in CR1), GVHD prophylaxis (higher risk with regimens other than post-Cy), HCT-CI (higher risk with increasing score), and performance status (higher risk with increasing score) (eTable 6).

4.5 | Relapse

Cumulative incidence of relapse was not significantly associated with donor–recipient ABO status in multivariable analysis (Table 3, eFigure 2). Other significant factors associated with relapse were disease status prior to allo-HCT (higher risk when not in CR1), conditioning intensity [higher risk if other than MAC/total body irradiation (TBI)], HLA match (lower risk with MUD), performance status (higher risk with worse score) (eTable 7).

4.6 | Non-relapse mortality

In multivariable analysis, higher non-relapse mortality was seen in patients with a major ABO mismatched donor (HR 1.21, 95% CI 1.03–1.44, $p = 0.02$, overall $p = 0.10$) (Table 3, eFigure 3). Other factors significantly associated with non-relapse mortality were recipient age (higher risk with increasing age), conditioning intensity (lower risk if other than MAC/TBI), HLA match (higher risk with MUD), GVHD prophylaxis (higher risk with regimens other than post-Cy), performance status (higher risk with increasing score), HCT-CI (higher risk with increasing score), year of transplant (lesser risk in subsequent periods) (eTable 8).

4.7 | GVHD

On multivariable analysis (Table 3), no significant difference in the risk of acute GVHD grade III-IV or chronic GVHD was observed based on the ABO matching status (eFigures 4–8). Other significant factors associated with acute (grade III-IV) and chronic GVHD were conditioning intensity (lower risk if other than MAC/TBI), antithymocyte globulin/alemtuzumab (lower risk), HLA match (higher risk with MUD),

TABLE 3 Multivariable analysis of main effect on outcomes

Outcome	*N*	Hazard ratio	95% CI lower	95% CI upper	*p*-value
Overall survival					0.04*
ABO matched	2738	Ref.			
Minor mismatch	1029	1.05	0.96	1.15	0.31
Major mismatch	899	1.16	1.05	1.29	0.005*
Bi-directional	275	1.02	0.86	1.21	0.79
Disease free survival					0.09
ABO matched	2710	Ref.			
Minor mismatch	1020	1.06	0.97	1.15	0.19
Major mismatch	892	1.11	1.02	1.22	0.02*
Bi-directional	273	1.14	0.96	1.36	0.13
Relapse					0.42
ABO matched	2710	Ref.			
Minor mismatch	1020	1.05	0.95	1.17	0.35
Major mismatch	892	1.06	0.94	1.19	0.33
Bi-directional	273	1.13	0.93	1.37	0.23
Non-relapse mortality					0.1
ABO matched	2710	Ref.			
Minor mismatch	1020	1.1	0.93	1.3	0.26
Major mismatch	892	1.21	1.03	1.44	0.02*
Bi-directional	273	1.22	0.93	1.59	0.15
Acute GVHD II-IV – Bone marrow					0.05
ABO matched	420	Ref.			
Minor mismatch	169	0.85	0.66	1.09	0.2
Major mismatch	157	1.18	0.82	1.69	0.38
Bi-directional	44	0.5	0.27	0.93	0.03*
Acute GVHD II-IV – Peripheral blood					<0.001*
ABO matched	2295	Ref.			
Minor mismatch	847	1.15	1.03	1.29	0.01*
Major mismatch	737	0.82	0.71	0.95	0.009*
Bi-directional	227	1.06	0.84	1.34	0.63
Acute GVHD III-IV					0.14
ABO matched	2711	Ref.			
Minor mismatch	1017	1.18	0.98	1.41	0.08
Major mismatch	894	0.94	0.77	1.16	0.56
Bi-directional	270	1.06	0.79	1.43	0.68
Chronic GVHD					0.3
ABO matched	2715	Ref.			
Minor mismatch	1018	1.02	0.93	1.13	0.65
Major mismatch	894	0.92	0.81	1.04	0.18
Bi-directional	271	0.88	0.74	1.04	0.13
Primary graft failure					0.007*[a]
ABO matched	2741	Ref.			
Minor mismatch	1030	0.86	0.57	1.31	0.48
Major mismatch	899	1.6	1.12	2.3	0.01*
Bi-directional	276	1.63	0.92	2.88	0.09
Neutrophil engraftment					0.08

TABLE 3 (Continued)

Outcome	N	Hazard ratio	95% CI lower	95% CI upper	p-value
ABO matched	2734	Ref.			
Minor mismatch	1025	1.04	0.98	1.11	0.2
Major mismatch	896	0.92	0.85	1	0.06
Bi-directional	272	1.02	0.92	1.13	0.73
Platelet engraftment					<0.001*
ABO matched	2738	Ref.			
Minor mismatch	1028	0.95	0.87	1.04	0.29
Major mismatch	898	0.83	0.77	0.9	<0.001*
Bi-directional	274	1.02	0.87	1.19	0.84

Abbreviation: GVHD, graft versus host disease.
*p < 0.05-significant.[a]Odds ratio.

graft source (higher risk with PB grafts), GVHD prophylaxis (higher risk with regimens other than post-Cy), HCT-CI (higher risk with increasing score), gender match (higher risk with female donor-male recipient) and year of transplant (lesser risk in subsequent periods) (eTables 9–15).

5 | DISCUSSION

The current study found a significant association between major ABO mismatching and inferior survival in a large cohort of patients with AML and ALL undergoing allo-HCT from HLA-matched sibling donor or MUD. ABO mismatched allo-HCT is usually known for its association with complications such as acute hemolysis, delayed engraftment, pure red cell aplasia, and passenger lymphocyte syndrome due to immune-mediated and non-immune-mediated mechanisms.[14–16] However, the significant association between ABO mismatch and outcomes such as survival, non-relapse mortality, and platelet engraftment seen in our study highlight its widespread effects and importance while selecting donors in the context of AML and ALL.

Prior studies have evaluated the impact of ABO mismatch on allo-HCT outcomes, albeit with contradictory results. A CIBMTR study by Kollman et al. with over 10 000 patients (AML, ALL, chronic myeloid leukemia, MDS) investigated the effect of donor characteristics on survival after allo-HCT and found that both minor and major ABO mismatches were associated with a significantly higher risk of mortality.[3] Another study by Seebach et al. with 3103 patients undergoing allo-HCT from matched-related donors using bone marrow grafts showed that bidirectional ABO mismatch was associated with a significantly higher risk of grade III–IV acute GVHD and major ABO mismatch was associated with higher and prolonged need for red blood cell transfusions and delayed neutrophil recovery.[17] Although numerous other studies have also evaluated the impact of ABO mismatch in allo-HCT, the heterogeneity of the underlying diseases included in addition to variations in transplant practice based on the underlying disease adds to the complexity of interpreting those results. We hypothesized that the impact of ABO mismatch could vary based on the underlying disease. For example, in alignment with our study, a post hoc analysis of the CIBMTR data set by Logan et al. in patients with AML and MDS showed major ABO mismatch significantly increased the risk of non-relapse mortality and inferior overall survival.[10] Although the mechanism behind this disease-specific variation remains unclear, our data provides valuable information for the donor selection process in AML and ALL and paves way for future studies.

The mechanisms by which ABO mismatch affect transplant outcomes and the impact of graft manipulation strategies were unfortunately not evaluable in this study due to changes in data collection strategies and manipulation techniques over the years. The reasons behind variations in graft manipulation across ABO subgroups could not be delineated as these data were taken as reported by the centers to the CIBMTR and evaluated only in a descriptive manner without statistical comparisons (eTables 16,17). In general, ABO incompatibility may exert direct effects on outcomes through alloreactive antibodies, transferred lymphocytes and consequent immune reactions or an indirect impact through graft processing and manipulation affecting infused cell doses.[2,18,19] Studies with more granular data collected on manipulation technique and pre-and-post manipulation cell counts are needed to inform the impact of individual graft manipulation techniques and mitigation strategies on the outcomes of allo-HCT.

In addition to ABO status, another factor associated with worse outcomes was older recipient age. Prior studies in allo-HCT for acute leukemia have also demonstrated inferior outcomes in older recipients, underscoring the adverse biological impact of aging in this context.[20,21] Although the impact of donor age on outcomes has been variable in prior reports based on donor type, our study did not find this as a significant factor when tested on all multivariable models likely indicating the heterogeneous impact and interplay between various pre-transplant factors.[3,22] To investigate whether the impact of ABO status differs based on other pre-transplant variables, we looked for interactions between ABO status and several clinical factors including graft type (BM or PB), donor-recipient gender match, donor age, and recipient age. An interaction was noted between ABO status and graft source only for acute GVHD grades II–IV and presented separately for BM versus PB (eTables 9–11). However, no significant

interactions were noted between ABO status and other factors, indicating the effect may not be constrained to a particular subgroup.

Despite the large sample size, our study is limited by its retrospective design and lack of detailed information on factors such as the graft manipulation techniques used and its impact on infused cell doses. We did not have information on aspects such as anti-A/anti-B antibody titers, non-ABO antigen match status, blood product transfusion needs post allo-HCT, and clinical outcomes such as pure red cell aplasia, passenger lymphocyte syndrome, and hemolytic reactions. We recognize that individual transplant centers vary with respect to the procedures done for ABO mismatched allo-HCT and adjusted for center-effect in multivariable analyses. To minimize the effect of HLA mismatching, we restricted our analyses to matched sibling donors and 8/8 MUD. Further studies in the HLA mismatched setting may be helpful.

6 | CONCLUSIONS

Our study demonstrates that donor–recipient ABO status is significantly associated with survival and other post-transplantation outcomes in a large cohort of patients with AML and ALL in the recent era. This demonstrates the importance of considering ABO status in the donor selection algorithms for acute leukemia, in addition to factors such as donor age, HLA-match, gender, and cytomegalovirus status. The impact of graft manipulation techniques, post-transplant immunomodulation as well as the impact of differential transfusion burden on the outcomes could not be evaluated and need to be investigated in the future studies. Additional mechanistic studies evaluating immunologic interactions in ABO mismatched transplants are also warranted.

AUTHOR CONTRIBUTIONS

Guru Subramanian Guru Murthy, Stephanie Bo-Subait, Brent R. Logan, Heather E. Stefanski, and Bronwen E. Shaw conceived and designed the study, collected and assembled the data, and wrote the manuscript; all authors performed data analysis and interpretation of data; and Guru Subramanian Guru Murthy, Brent R. Logan, and Bronwen E. Shaw provided final approval of the manuscript. Guru Subramanian Guru Murthy and Bronwen E. Shaw had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

Dr. Lazarus declares CSL Behring, Seattle Genetics, Jazz Pharmaceuticals, Actinium Pharmaceuticals, BioSight, BMS/Celgene, Partner Therapeutics as conflicts of interest. Dr. Sharma declares CRISPR Therapeutics, Vertex Pharmaceuticals, Medexus Inc., Spotlight Therapeutics, Vindico Medical Education as conflicts of interest. Dr. Pulsipher declares Honoraria for lectures, Novartis and Miltenyi, Advisory for Novartis, Gentibio, Bluebird, Vertex, Medexus, Equillium, Mesoblast, Study support from Adaptive and Miltenyi (Assays and discounted materials for IITs) as conflicts of interest. Dr. Guru Subramanian Guru Murthy reports the following outside the submitted work - Cardinal Health (Honoraria), TG Therapeutics (Advisory board), Gilead/Kite (Advisory board), Cancerexpert now (Consultancy), Qessential (Consultancy), Techspert (Consultancy), DAVA Oncology (Honoraria), Aptitude Health (Honoraria) and Curio science (Honoraria), all outside the submitted work.

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The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

DATA AVAILABILITY STATEMENT

CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified data sets that comply with all relevant global regulations regarding privacy and confidentiality.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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