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HLA Factors Versus Non-HLA Factors for Haploidentical Donor Selection

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Abstract

When multiple haploidentical donors are available for transplantation, those of younger generations are generally selected over those of older generations. However, it is unclear who is the optimal donor when selecting candidates from within a generation, such as a father vs mother, son vs daughter, or brother vs sister. Although traditionally, male donors are favored over female donors, particularly for male recipients and significant associations of individual HLA mis(matches) on outcomes are being recognized, the hierarchy of factors for donor selection is indeterminate. To assess whether HLA factors take precedence over non-HLA factors and to isolate the influence of specific characteristics on outcomes, we analyzed 412 patients stratified by donor relationship: child donor [son (n=202) vs daughter (n=96)]; parent [(father: n=28 vs mother: n=29)] and sibling [non-inherited maternal (NIMA, n=29) vs paternal (NIPA, n=28)-mismatched]. Among siblings, NIMA-mismatch was associated with a lower risk of acute graft-versus-host disease (aGVHD); B-leader mismatch was associated with high non-relapse mortality (NRM), poor progression-free survival, and a trend towards poor overall survival (OS); A-mismatch was associated with lower aGVHD. Among parent donors, the relationship did not impact any

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Authorship Contributions

R.S.M. conceptualized the study design, collected the data, helped with the interpretation of data, and wrote the manuscript; K.C. provided the HLA data and classified HLA mismatches; R.M.S. designed and performed all statistical analysis, contributed to data interpretation, and wrote the statistical section of the manuscript; G.R. provided patient data; G.A. provided important feedback on the clinical significance of HLA factors, and enrolled patients in the study; K.L. and C.R. reviewed and provided feedback on the manuscript; A.A.A. provided critical feedback on outcomes and GVHD assessment enrolled patients in the study and monitored responses; Q. B., C.M.H, P.K., I.K., D.M., Y.N., B.O., U.P., M.H.Q., J.R., K.R., R.E.C., and E.J.S, enrolled patients in the study and monitored responses. Y.C. helped with HLA data collection. R.S.M., R.M.S., and G.R. had full access to the raw data. All authors approved the manuscript. The corresponding author had the final responsibility to submit for publication.

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outcome; B-leader mismatch was associated with higher NRM and a trend towards poor OS; A-mismatch was associated with lower NRM and improved PFS and OS. Among child donors, no individual HLA mismatch predicted any outcome, and daughter donors were not associated with any adverse outcomes in multivariate analyses. Our data suggest that certain HLA factors may be more significant in some cases and should be given priority than simply selecting a donor based on relationship/gender.

Keywords

HLA haploidentical donor; NIMA (non-inherited maternal antigen); NIPA (non-inherited paternal antigen); post-transplantation cyclophosphamide; HLA B-leader mismatch; HLA A-mismatch; donor gender; gender mismatch; donor age; father vs mother; son vs daughter

Introduction

Recent studies in the haploidentical hematopoietic stem cell transplantation (HCT) setting showed a significant prognostic impact of certain HLA (mis)matches at specific loci, such as HLA class II mismatches and HLA B-leader mismatch on survival,[1,2] while some of the non-HLA factors which are traditionally thought to be of significance,[3] such as the donor gender and donor-recipient gender mismatch (female-to-male) and donor relationship did not affect survival.[1,2] Donor age, on the other hand, is a well-recognized prognostic factor across studies because of which the European Society for Blood and Marrow Transplantation (EBMT) guidelines suggest using a younger donor over an older donor.[3] This was also corroborated in the Center for International Blood and Marrow Transplant Research (CIBMTR) analysis that showed a significantly higher risk of mortality with increasing donor age.[1] Therefore, if a patient has several haploidentical donors belonging to different generations (parents, siblings, or children), a preference is almost always given to the donor from the youngest generation. Thus, practically, a donor is selected from within one of the siblings (brother vs sister), within one of the children (son vs daughter), or within parents (father vs mother) in patients for whom younger donors are not available. Only rarely does one have to decide whether they should choose a donor across donor generations, such as selection between a child donor vs a parent donor. But, when several similarly aged donors are available (e.g. multiple children), it is unclear which factors should be given precedence in donor selection.

Although recent studies suggest that HLA factors and donor age may supersede other non-HLA factors (donor relationship, gender, gender mismatch) for prognostication[1], these factors are all firmly correlated with each other and with donor age. For instance, most child donors are expected to be younger and parent donors are expected to be older. Similarly, the effect of donor-recipient gender mismatch is better studied within-generations of donors (e.g. father vs mother donor), rather than across-generation comparisons (son vs mother donor), again due to the confounding effect of donor age. Including these factors together in analyses can be problematic due to multicollinearity, making it impracticable to isolate the effects of these factors. Moreover, except in cases with sibling donors, the patient age and the donor age in many donor-recipient pairs are inversely correlated with each

other– i.e. older patients (poor prognosis) usually have a younger donor (good prognosis) and vice-a-versa, which may nullify the statistical significance of each other in analyses. These issues can be partly resolved by performing analyses stratified by donor relationship/generation, such as performing separate analyses for sibling donors (brother vs sister), parent donors (father vs mother), and child donors (son vs daughter), which is also more clinically relevant. Such a study also produces an obligatory equivalence of donor age among comparator groups as well as patient age, minimizing biases related to donor and patient age.

To complicate matters further, as an alternative to gender classification, sibling donors can be categorized as non-inherited maternal (NIMA) or paternal (NIPA) antigen mismatched based on the non-shared haplotype. A few studies using conventional graft-versus-host disease (GVHD) prophylaxis with a calcineurin inhibitor, mycophenolate mofetil, anti-thymocyte globulin, and/or methotrexate showed that a NIMA-mismatched sibling donor was associated with improved outcomes compared to a NIPA-mismatched donor due to lower risk of GVHD and non-relapse mortality (NRM).[4–6] This is based on the hypothesis that exposure to maternal antigens in utero can lead to immunologic tolerance.[7] However, this has not been studied with post-transplant cyclophosphamide (PTCy) prophylaxis.

To address these questions, we performed a retrospective analysis with the chief goal to identify the characteristics of an “ideal” haploidentical donor, by comparing donors from within generations. Specifically, our aims were to (a) compare outcomes of son vs daughter donors among patients with child donors, (b) compare outcomes of father vs mother donors among patients with parent donors, and (c) compare outcomes of NIMA-mismatched vs NIPA-mismatched HCT among patients with sibling donors. All analyses were in the setting of T cell-replete haploidentical HCT with PTCy prophylaxis.

METHODS

We included adult patients with a hematologic malignancy who underwent first allogeneic HCT at the MD Anderson Cancer Center using a haploidentical donor between January 2009 and December 2021 with any conditioning regimen and PTCy-based GVHD prophylaxis. We excluded pediatric patients, those with non-malignant disease, and those who received ex vivo T cell depleted grafts. The objectives were to compare the rates of acute and chronic GVHD, non-relapse mortality (NRM), relapse, progression-free survival (PFS), and overall survival (OS) between the groups.

Definitions

Acute GVHD (aGVHD) was staged and graded as per the consortium criteria[8], and cGVHD was staged and graded per the 2014 NIH criteria.[9] Relapse or progression was defined as the time to recurrence or progression of the underlying malignancy, with NRM (death before relapse or progression) as a competing risk. PFS was defined as the time from HCT to relapse/progression or death. OS was the time from HCT to death from any cause. High-resolution typing of HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQB1, and -DPB1 alleles was performed using sequence-based typing or next-generation sequencing methodologies. HLA-B mismatches were categorized as leader matched or mismatched as previously

reported.[1] HLA-DPB1 mismatch was further categorized as permissive or nonpermissive based on the T-cell-epitope groups.[10] The study was conducted per the Helsinki Declaration and was approved by the institutional Investigational Review Board [MDACC 2021–0106].

Statistical analysis

Descriptive analyses were performed to summarize clinical and demographic characteristics. Characteristics were compared across donor types using Fisher's exact test for categorical variables, and Wilcoxon rank-sum test for continuous variables. The cumulative incidence method accounting for competing risks was used to estimate the rate of NRM and GVHD. Competing risks included relapse/progression for the estimation of NRM, and relapse/progression, or death before GVHD for the estimation of GVHD. Kaplan-Meier curves were used to estimate PFS and OS. Predictors of outcomes were evaluated using Cox's proportional hazards regression analysis for OS and PFS, and Fine and Grey competing-risk regression analysis for all other outcomes. Predictors that were significant in univariate analysis were considered in multivariate analysis. Backward elimination was used to identify the final multivariate model. The proportionality of the hazards assumption was tested, and first-degree interaction effects were evaluated between donor type and significant predictors. Statistical significance was determined at the 0.05 level. Statistical analyses were performed using primarily STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp L).

RESULTS

We included 412 patients who had complete HLA information available. Of these, 298 had a child donor, 57 had a parent donor and 57 had a sibling donor. There was no difference in graft failure or the median time to neutrophil engraftment between son vs daughter (child donor), father vs mother (parent donor), and NIMA- vs NIPA-mismatched (sibling donor) [data not shown].

Child donor

Among patients with a child donor, the donor was a son in 202 patients and a daughter in 96 patients. The median age at HCT was 58 years vs 56 years, respectively (p=0.05), and the median donor age was 29 years vs 27 years, respectively (p=0.1). More patients with a son donor had high/very-high disease risk index (DRI; 41% vs 20%, respectively; p<0.001), received bone marrow (BM) graft (74% vs 56%, p=0.002), and had 0–2 HLA-class II mismatches (27% vs 15%, respectively, p=0.03). HLA-C mismatch was less common in those with son donor (88%) than those with daughter donors (97%), p=0.01. Other characteristics were similar (Table 1). The median follow-up among survivors was 27 months vs 24 months, respectively [Table 1].

The incidence of grade III-IV acute GVHD at day 180 was numerically higher in those with a daughter (12%) than those with a son donor (6%), p=0.1, and chronic GVHD at 3 years was 21% (daughter) vs 13% (son), p=0.2. The 3-year cumulative incidence of relapse was 24% (daughter) vs 31% (son), p=0.3, NRM was 32% vs 33%, respectively, p=0.6, PFS was 43% (daughter) and 36% (son), p=0.2 and OS was 41% (daughter) vs 42% (son),

p=0.5 [Table 2]. The univariate analyses are shown in table S1. In multivariate analysis after adjusting for covariates, the rate of acute GVHD grade II-IV [Hazard ratio (HR) 1.2, 95% confidence interval (CI) 0.8–1.9, p=0.3], chronic GVHD (HR 1.05, 95% CI 0.5–2.3, p=0.9) and NRM (HR 0.9, 95% CI 0.6–1.4, p=0.7) were similar with daughter vs son donors. Son-to-mother was associated with a higher risk of relapse (HR 1.7, 95% CI 1.02–2.7, p=0.04). The analysis of PFS and OS revealed significant statistical interactions between donors and DRI. Son donors in patients with high/very-high DRI were associated with inferior PFS (HR 2.8, 95% CI 1.9–4.1, p<0.001) and OS (HR 3.3, 95% CI 2.1–5.0, p<0.001) [Fig 1A]. Among HLA factors, the presence of three class-II mismatches was associated with a higher risk of cGVHD (HR 3.3, 95% CI 1.3–8.7, p=0.01). None of the mismatches at individual HLA loci, including B-leader, predicted the risk of any outcome [Fig 1B, 1C]. Other predictors are shown in table 3.

Parent donor

Among patients with a parent donor, the donor was a father in 28 patients and a mother in 29 patients. The median age at HCT was 27 years vs 23 years, respectively (p=0.1), and the median donor age was 52 years vs 50 years, respectively (p=0.9). There were no significant differences in the baseline characteristics of the groups including conditioning intensity, graft source, HCT-CI, DRI, and HLA mismatches (Table 1). More donor/recipient pairs were cytomegalovirus seropositive in mother donor group (79%) than those with father donors (50%), p=0.04. The median follow-up was shorter in patients with father donors (28 months) than those with mother donors (54 months) [Table 1].

The incidence of grade III-IV acute GVHD at day 180 was numerically higher in those with a mother (31%) than those with a father donor (11%), p=0.1, and chronic GVHD at 3 years was 31% (mother) vs 15% (son), p=0.2. The cumulative incidence of relapse was 21% (mother) vs 32% (father), p=0.3, NRM was 35% vs 26%, respectively, p=0.5, PFS was 39% (mother) and 36% (father), p=0.9 and OS was 53% (mother) vs 41% (father) [Table 2]. The univariate analyses are shown in table S2. In multivariate analysis, donor relationship (mother vs father) was not found to be a significant predictor of either acute or chronic GVHD, NRM, relapse, PFS, or OS [Fig 2A]. Among HLA factors, B-leader mismatch was associated with a significantly higher risk of NRM (HR 2.7, 95% CI 1.03–7.02, p=0.04) [Fig 2B] and a trend towards inferior OS (HR 2.2, 95% CI 0.9–4.9, p=0.06) [Fig 2C]; HLA-A mismatch was associated with a lower risk of NRM (HR 0.3, 95% CI 0.1–0.8, p=0.02) and superior PFS (HR 0.2, 95% CI 0.1–0.4, p<0.001) and OS (HR 0.1, 95% CI 0.05–0.4, p<0.001). Other predictors are shown in table 4.

Sibling donor

Among patients with a sibling donor, 29 patients had a NIMA-mismatched and 28 patients had a NIPA-mismatched donor. The median age at HCT was 31 years vs 37 years, respectively (p=0.1), and the median donor age was 32 years vs 41 years, respectively (p=0.1). A significantly higher proportion of patients in the NIMA-mismatched group had female-to-male gender mismatch (55%) than in the NIPA-mismatched (21%) group, p=0.005. There were no other significant differences between the groups regarding conditioning intensity, graft source, HCT-CI, DRI, or HLA mismatches (Table 1). However,

the median follow-up was considerably longer in patients with NIMA-mismatched donors (38 months) than in those with NIPA-mismatched donors (13 months) [Table 1].

The incidence of grade II-IV acute GVHD at day 180 was significantly lower in those with a NIMA-mismatched donor (31%) than those with a NIPA-mismatched donor (58%), p=0.04, with no differences in grade III-IV aGVHD (10% vs 11%, respectively, p=0.9), chronic GVHD (11% vs 13%, respectively, p=0.9), NRM (28% vs 33%, respectively, p=0.9), relapse (21% vs 11%, respectively, p=0.4), PFS (48% vs 56%, respectively, p=0.4) and OS (54% vs 55%, respectively, p=0.8) at 3 years [Table 2]. The univariate analyses are shown in table S3. In multivariate analysis, a NIMA-mismatched donor was associated with a significantly lower risk of grade II-IV aGVHD (HR 0.1, 95% CI 0.02–0.6, p=0.001) [Fig 3A] without differences in other outcomes. Among HLA factors, HLA-A mismatch was associated with a lower risk of grade II-IV aGVHD (HR 0.2, 95% CI 0.1–0.6, p=0.005), and HLA-B leader mismatch was associated with a higher NRM (HR 3.8, 95% CI 1.04–13, p=0.04) [Fig 3B] and worse PFS (HR 2.7, 95% CI 1.1–6.7, p=0.03) and OS (HR 2.4, 95% CI 0.9–6.3, p=0.06) [Fig 3C]. Other predictors are shown in table 5.

Discussion

In this study, we sought to address whether HLA factors or non-HLA factors are more critical (defined as a variable that would affect survival) in the hierarchy of donor selection for haploidentical HCT when several similarly aged donors are available. To assess this, we performed separate analyses categorizing donors by generations (children, parents, and siblings), as it may be otherwise difficult to differentiate the impact of individual non-HLA factors (donor relationship, donor age, and gender/gender-mismatch) given the high correlation of these factors to each other.

Our analysis revealed several key findings. First, it is interesting to note that the effect of HLA factors was not consistent across all groups. For instance, HLA B-leader mismatch was associated with a significantly high NRM and a trend towards poor OS in patients with sibling or parent donors, but it did not impact any outcome in patients with a child donor. As HLA B-leader sequences affect the expression of HLA-E, which influences NKG2A- and NKG2C-mediated immune responses,[11] different effects of HLA B-leader noted across donor groups could be related to possible underlying diversities in natural killer (NK) cell receptors, their ligands or other factors. Next, previous studies showed that non-permissive DP-mismatch was associated with improved OS[1,2] and HLA-DR mismatch was associated with lower relapse[1] or improved OS.[2] In contrast, we did not find similar associations in our study when donors are categorized by generations. Other reasons for disparities in the results of our study and the CIBMTR study[1] could be related to different study populations. For example, the CIBMTR study[1] included both adult and pediatric patients with AML, MDS or ALL, while our study included other malignancies also but was restricted to adults only.

Further, in contrast to the previous studies we noted a distinctive effect of HLA-A mismatch on outcomes. Having an HLA-A donor-recipient mismatch was associated with a lower risk of aGVHD in the sibling donor group, and lower risk of NRM and better PFS and OS in the parent donor group. The immune modulatory effect of HLA-A in several autoimmune

diseases is well recognized.[12,13] Some HLA-A alleles (e.g., HLA-A*01, HLA-A*11 and HLA-A*31) are protective while others (e.g. HLA-A*24) predispose to type 1 diabetes.[12] Similarly, HLA-A*0201 has a protective effect while A*0301 increases the risk of multiple sclerosis.[13] This is hypothesized to be related to the up/down-regulation of immune response by T-cell clones restricted to specific HLA A-alleles.[13] Also, T cells restricted by certain HLA-A alleles (e.g. HLA-A3) have reduced proliferative capacity than HLA-B alleles (e.g. HLA-B27/-B57),[14] and certain HLA A-alleles (e.g. HLA-A02) recognizing viral epitopes are much more susceptible to regulatory T cell (Treg)-mediated suppression than HLA-B*27–restricted T cells.[15] Lastly, the beneficial effect of HLA-A mismatch on GVHD is not an entirely new finding in our study. This was also observed in a study that showed that HLA-A mismatched transplants where the HLA-A–mismatched antigens were for the donor NIMA involved the least GVHD.[5] Similarly, studies in the renal transplantation setting showed that the graft survival rates were significantly better for NIMA HLA-A mismatched transplants.[16] Then, why some HCT studies show this apparent protective effect of HLA-A mismatch while others do not, remains unclear. It is conceivable that it may be related to underlying differences in HLA-A alleles and supertypes of the donor-recipient pairs in our study versus others.[17,18] Studies categorizing HLA-A as supertype matched vs mismatched may provide further answers.

Next, our analyses challenge the traditional conviction where donor selection is prioritized on non-HLA factors such as gender/gender mismatch. Our study indicates that these factors may not be as critical as thought previously (no survival prognostic significance) once the HLA factors are accounted for. Nevertheless, the significance of donor gender and gender mismatch cannot be ignored from these analyses, and these factors may help in donor selection if the HLA factors are similar across donors. Lastly, similar to previous studies using conventional GVHD prophylaxis,[4–6] our study with PTCy prophylaxis also noted a lower risk of aGVHD with NIMA-mismatched sibling donors but without any effect on other outcomes.

We recognize the limitations of our study. Although the sample size in our study is reasonably large for patients with a child donor (n=298), it was limited for those with sibling donors (n=57 with available NIMA/NIPA information) and those with parent donors (n=57). Next, by virtue of the study design, the significance of donor age cannot be addressed from our analyses. This has been performed in multiple studies previously[1,3] that showed better survival with younger donors, and is reflected in the current national practice where children account for most of the donors and only about 10% of donors are parents.[1] Similarly, because of the study design, the question of selecting a brother vs a sister haploidentical donor cannot be addressed in this study. Also, the information about anti-HLA-antibodies was not included as our center generally avoids donors against which recipients carry significant antibodies. Lastly, data on other variables were lacking, such as the information on donor parity and killer Ig-like receptors (KIRs) which may be of added significance.

Conclusion

Child donor:

Our analysis does not support the traditional notion of prioritizing a son over a daughter as a haploidentical donor. There was no difference in the risk of acute or chronic GVHD, or NRM between son vs daughter donors. None of the individual HLA mismatches, including HLA B-leader mismatch, which is noted to be of significance in other donor relationships, was a predictor of any outcome in patients with a child donor.

Parent donor:

Acknowledging the limitations of sample size, our data suggest that HLA factors, such as B-leader match and HLA-A mismatch should be prioritized over donor relationship (mother vs father) as the latter did not impact any outcome after HCT, while the HLA factors did (lower NRM with B-leader match, and lower aGVHD and improved PFS and OS with HLA-A mismatch).

Sibling donor:

Within the constraints of a small sample, our data suggest that HLA factors should be prioritized for donor selection, especially B-leader match (lower NRM, better PFS, and OS) and HLA-A mismatch (lower aGVHD). Among patients with multiple siblings with similar HLA factors, a NIMA-mismatched donor could be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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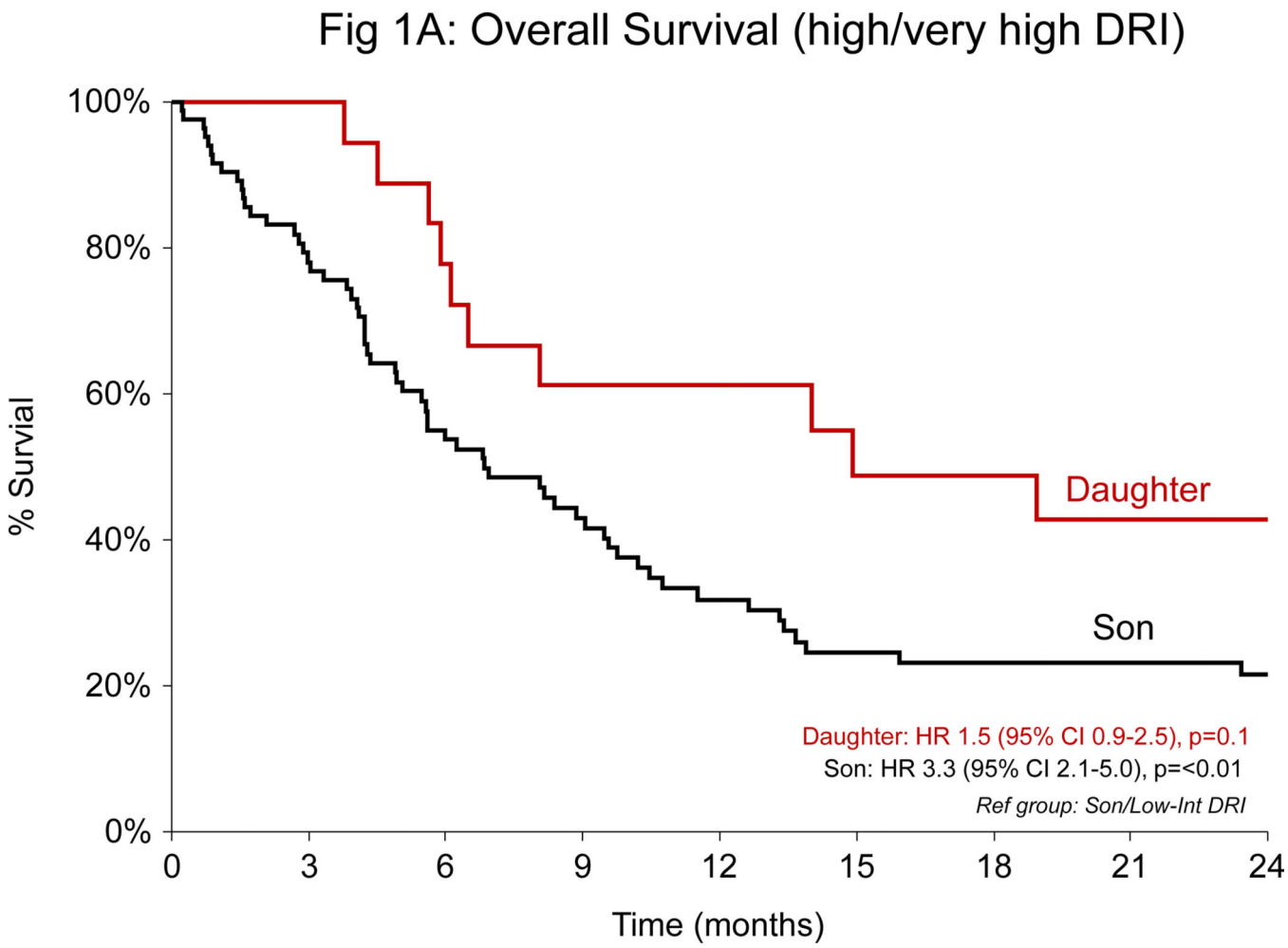
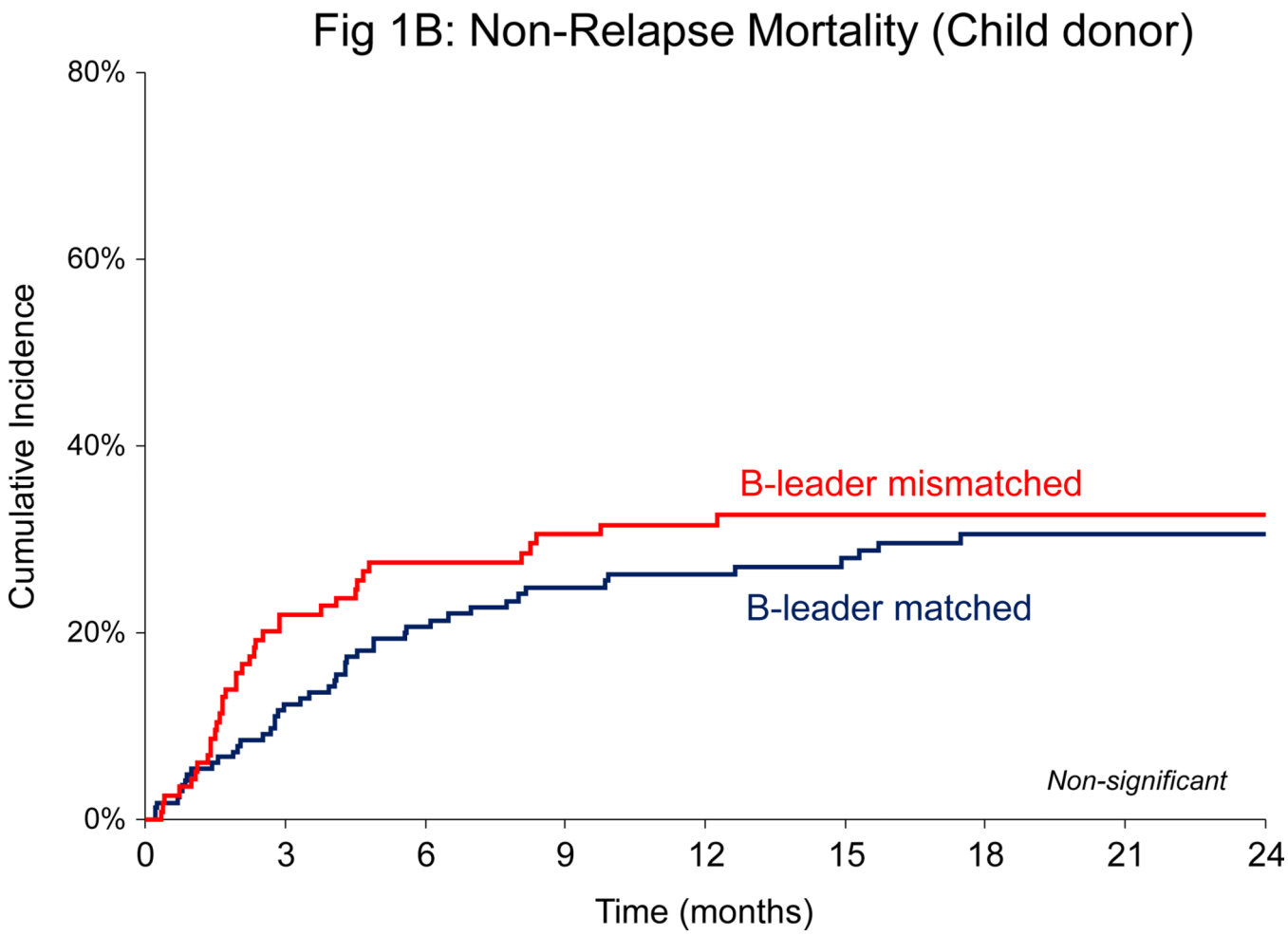
Key Points:

1. B-leader mismatch was associated with significantly higher NRM and a trend towards poor OS in parent and sibling haploidentical donor groups.
2. HLA A-mismatch was associated with a lower risk of aGVHD (haploidentical sibling) and lower NRM and better PFS and OS (parent donors).
3. Among non-HLA donor factors, female donors did not have adverse effect on any outcome.





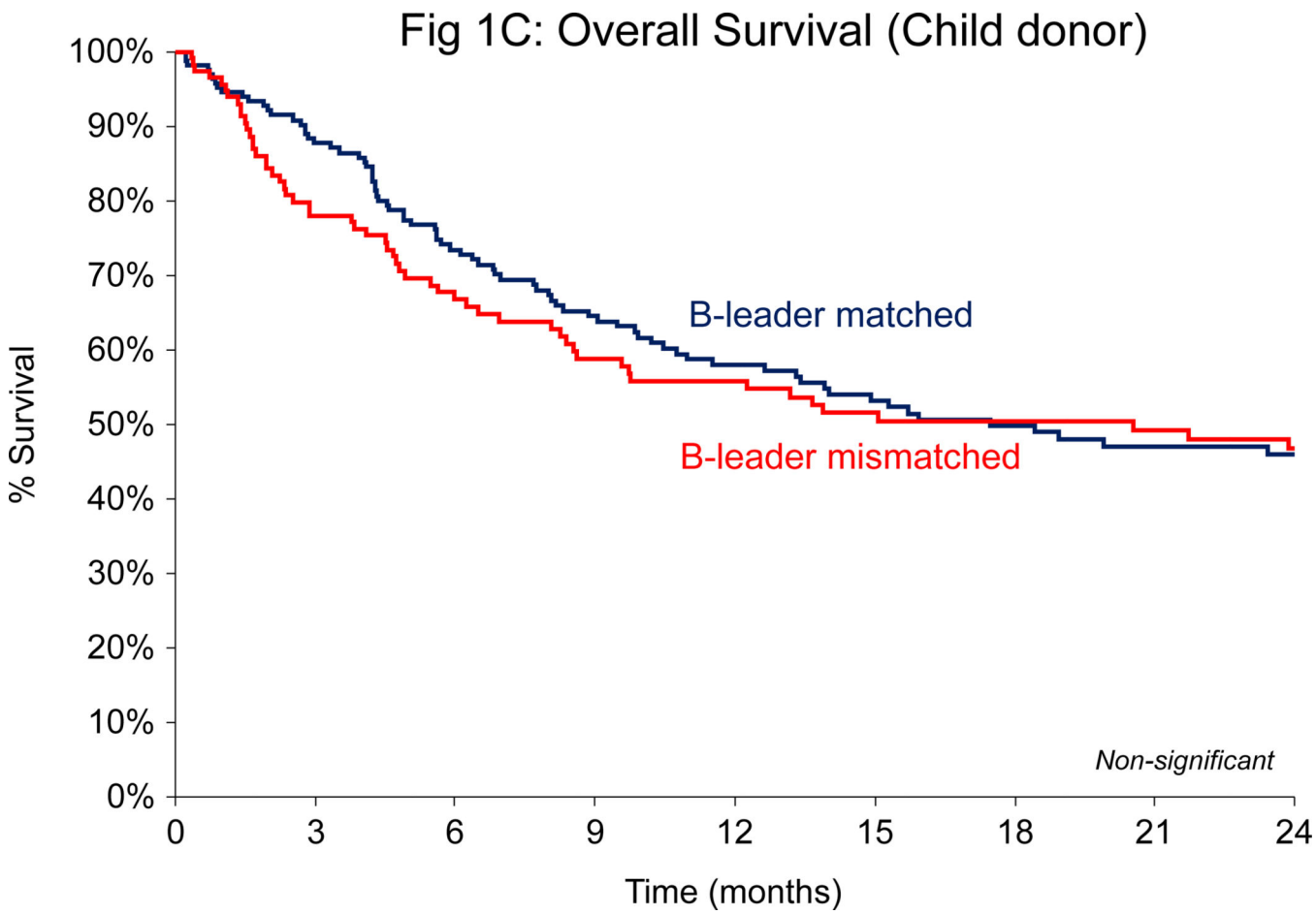
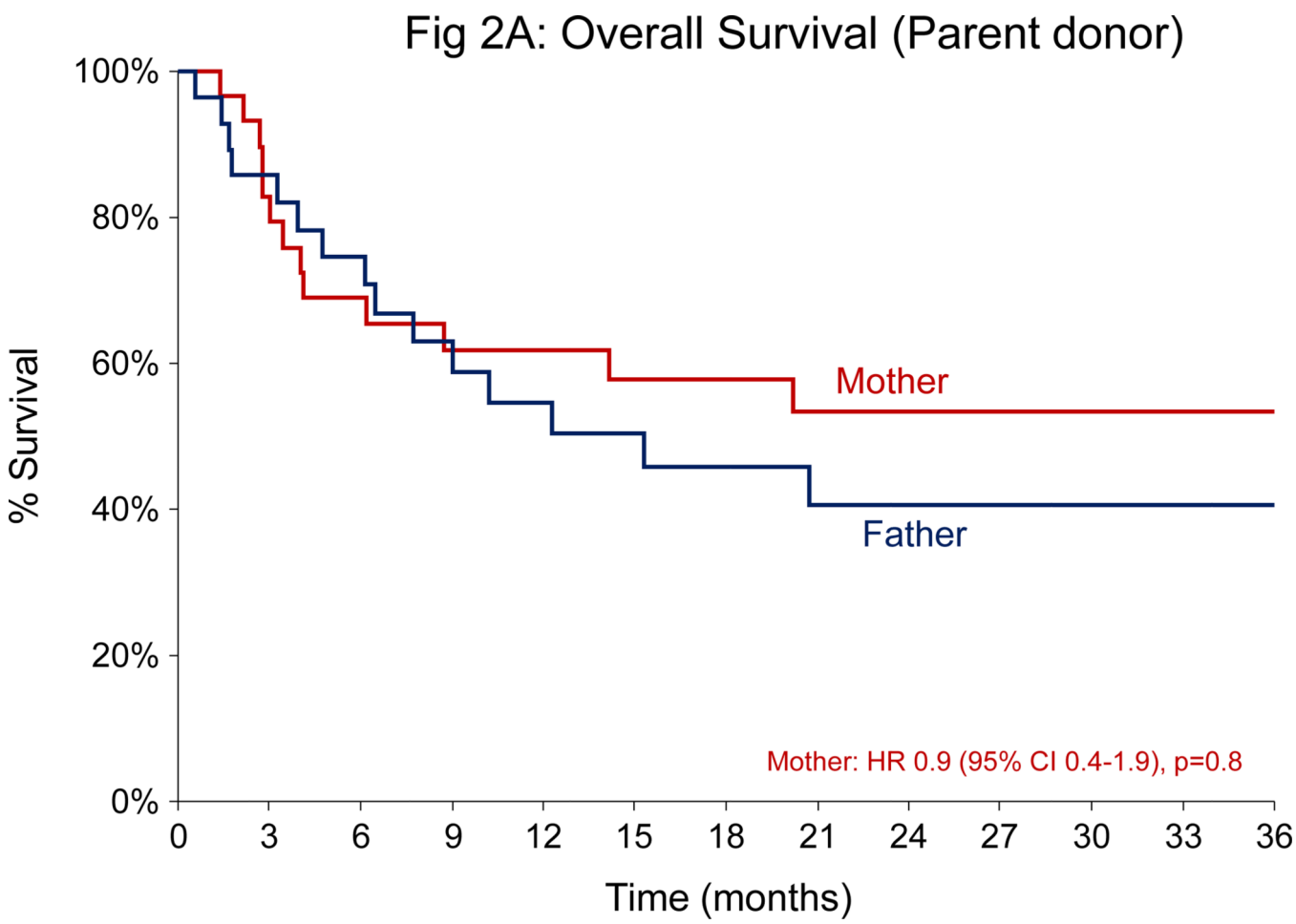
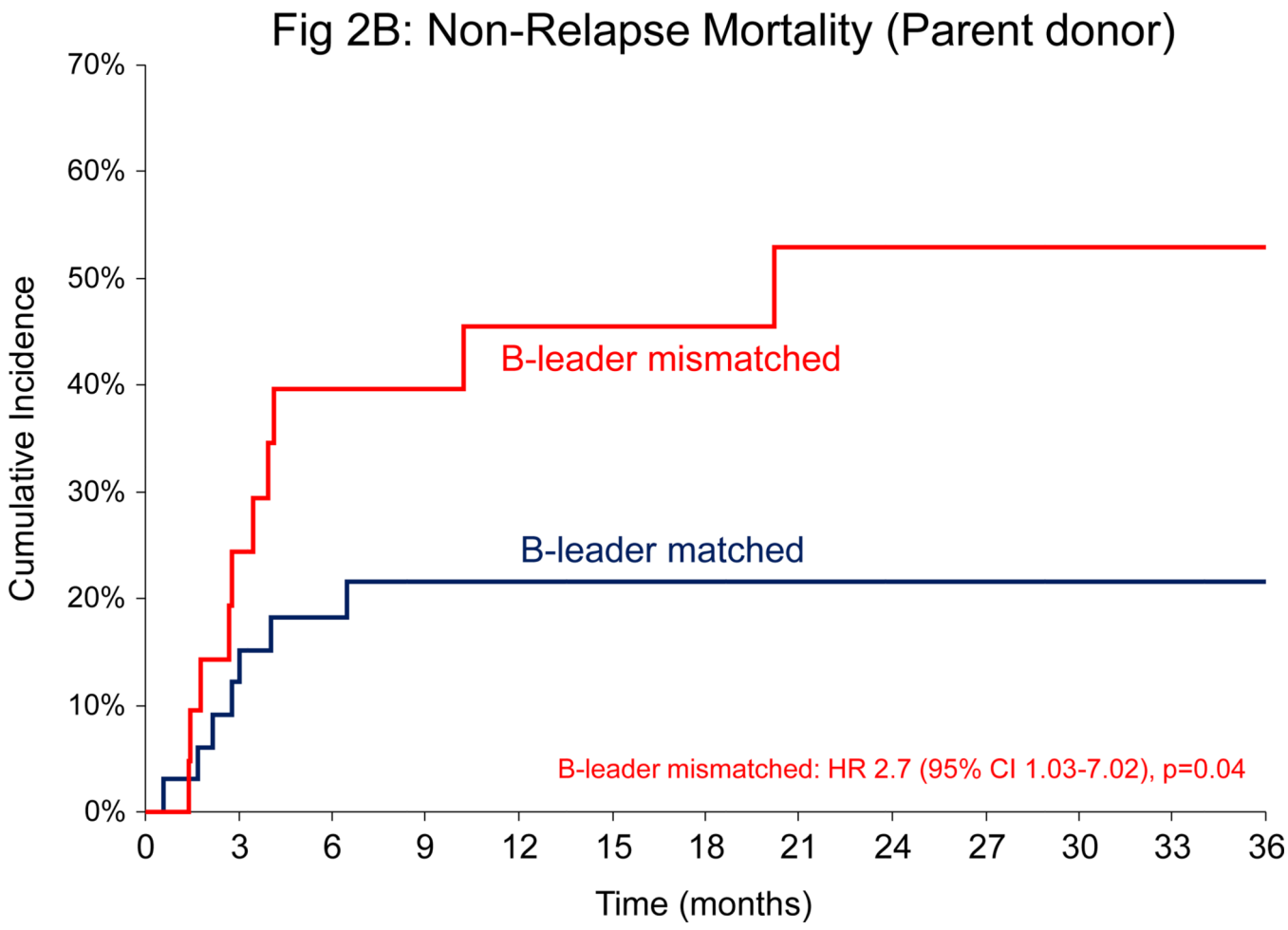


Figure 1:

(A) Overall survival in daughter vs son donors among patients with high/very-high DRI, (B) non-relapse mortality in HLA B-leader matched vs B-leader mismatched child haploidentical donor, and (C) OS in in HLA B-leader matched vs B-leader mismatched child haploidentical donor.





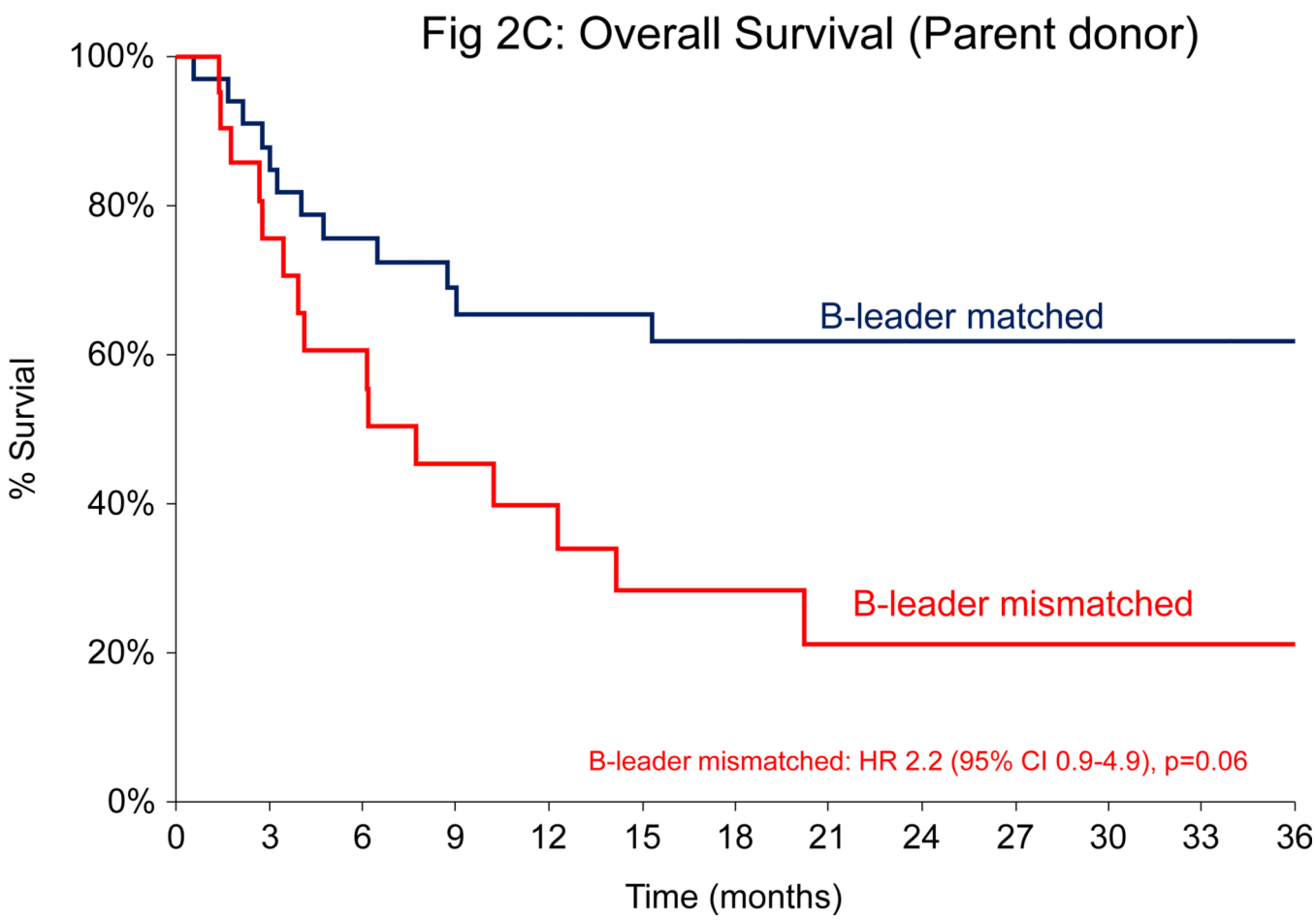
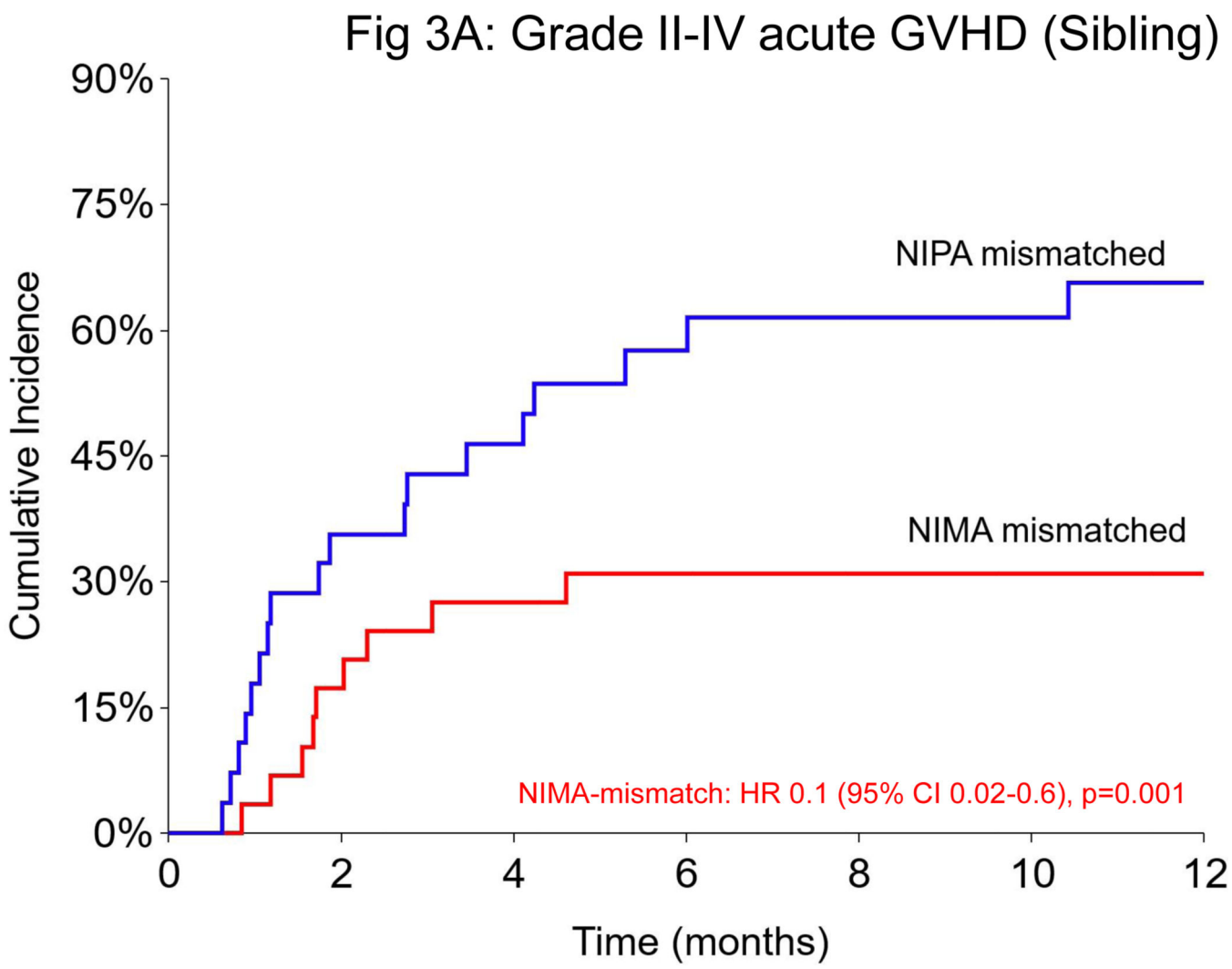
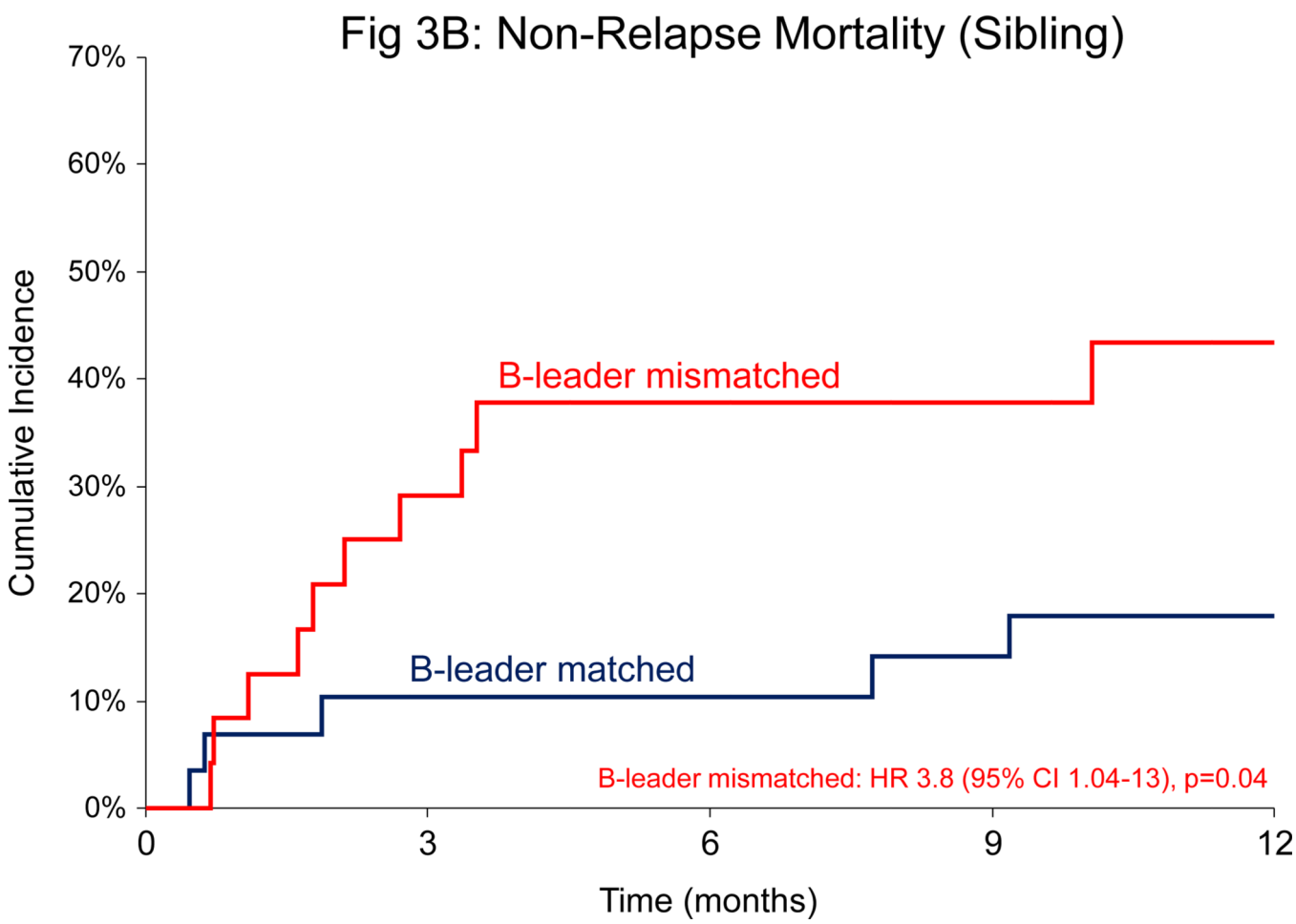


Figure 2:

(A) Overall survival in mother vs father donors, (B) non-relapse mortality in HLA B-leader matched vs B-leader mismatched parent haploidentical donor, and (C) OS in in HLA B-leader matched vs B-leader mismatched parent haploidentical donor.





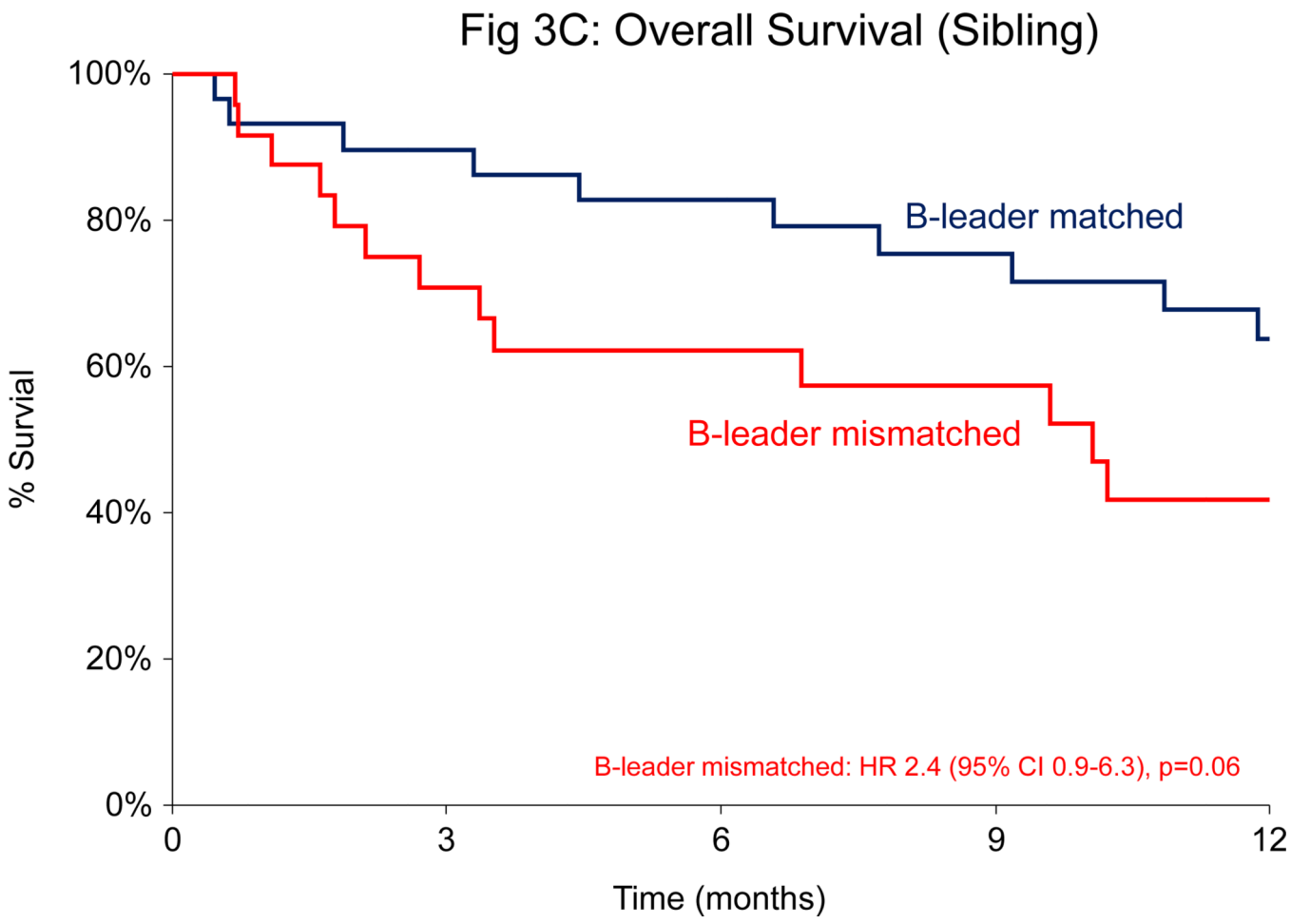


Figure 3:

(A) Grade II-IV acute GVHD in NIMA-mismatched vs NIPA-mismatched sibling donor, (B) non-relapse mortality in HLA B-leader matched vs B-leader mismatched sibling haploidentical donor, and (C) OS in in HLA B-leader matched vs B-leader mismatched sibling haploidentical donor.

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Table 1:

Baseline characteristics

	Child donor			Parent donor			Sibling donor		
	Son N=202	**Daughter N=96**	**P-value**	**Father N=28**	**Mother N=29**	**P-value**	**NIMA-mismatched N=29**	**NIPA- mismatched N=28**	**P-value**
Recipient age, median (range), in years	58 (32–75)	56 (34–72)	0.05	27 (18–42)	23 (18–47)	0.1	31 (20–64)	37 (21–69)	0.1
Donor age, median (range), in years	29 (11–68)	27 (11–46)	0.1	52 (25–67)	50 (40–69)	0.9	32 (19–65)	41 (18–66)	0.1
Donor/Recipient Gender			NA			NA			0.005
Female/Male	0 (0)	45 (47)		-	17 (59)		16 (55)	6 (21)	
Male/Male	127 (63)	0 (0)		17 (61)	-		6 (21)	16 (57)	
Female/Female	0 (0)	51 (53)		-	12 (41)		1 (3)	4 (14)	
Male/Female	75 (37)	0 (0)		11 (39)	-		6 (21)	2 (7)	
Disease			0.003			0.06			0.1
AML/MDS	142 (70)	58 (60)		14 (50)	6 (21)		14 (48)	14 (50)	
ALL	20 (10)	6 (6)		9 (32)	14 (48)		4 (14)	8 (29)	
MPD/ CML	12 (6)	21 (22)		0	4 (14)		3 (10)	3 (11)	
CLL/Lymphoma/ Myeloma	28 (13)	11 (11)		5 (18)	5 (17)		4 (13)	3 (11)	
Disease Risk Index			<0.001			0.8			0.4
High/v High	83 (41)	19 (20)		10 (36)	12 (41)		9 (31)	12 (43)	
Low/intermediate	111 (55)	70 (73)		15 (54)	13 (45)		18 (62)	15 (54)	
Missing	8 (4)	7 (7)		3 (11)	4 (14)		2 (7)	1 (4)	
HCT-CI median (range)	3 (0–10)	3 (0–9)	0.6	3 (0–10)	2 (0–9)	0.6	4 (0–9)	3 (0–8)	0.9
≥3	110 (54)	49 (52)		18 (64)	13 (46)	0.2	16 (55)	15 (54)	
Conditioning intensity			0.9			0.5			0.5
MAC	41 (20)	20 (21)		4 (14)	6 (21)		7 (24)	9 (32)	
RIC/NMA	161 (80)	76 (79)		24 (86)	23 (79)		22 (75)	19 (68)	
Graft source			0.002			0.5			0.8
Bone marrow	150 (74)	54 (56)		21 (75)	24 (83)		23 (79)	23 (82)	
Peripheral blood	52 (26)	42 (44)		7 (25)	5 (17)		6 (21)	5 (18)	

	Child donor			Parent donor			Sibling donor		
	Son N=202	Daughter N=96	P-value	Father N=28	Mother N=29	P-value	NIMA-mismatched N=29	NIPA- mismatched N=28	P-value
HLA-A mismatch	173 (96)	87 (91)	0.2	23 (82)	24 (83)	0.9	25 (86)	25 (89)	0.5
HLA-B mismatch	190 (94)	92 (96)	0.4	26 (93)	28 (96)	0.5	28 (96)	25 (89)	0.3
HLA B-leader mismatch	75 (37)	41 (43)	0.6	10 (48)	11 (52)	0.9	15 (52)	9 (32)	0.2
HLA-C mismatch	178 (88)	93 (97)	0.01	26 (93)	27 (93)	0.9	26 (90)	22 (79)	0.2
HLA-DRB1 mismatch	189 (94)	88 (92)	0.5	28 (100)	27 (93)	0.2	28 (96)	27 (96)	0.7
HLA-DQB1 mismatch	182 (90)	83 (86)	0.3	27 (96)	26 (90)	0.3	26 (90)	24 (86)	0.5
HLA-DPB1			0.4			0.7			0.6
Matched/Permissive mismatch	147 (73)	72 (75)		23 (82)	25 (86)		22 (76)	22 (79)	
Non-Permissive mismatch	55 (27)	24 (25)		5 (18)	4 (14)		7 (24)	6 (21)	
Total number of HLA mismatches			0.8			0.2			0.8
2	0 (0)	0 (0)		1 (4)	0		0 (0)	1 (4)	
3	7 (3)	4 (4)		0	0		1 (3)	1 (4)	
4	22 (11)	8 (8)		1 (4)	4 (14)		4 (14)	4 (14)	
5	73 (36)	32 (33)		12 (43)	7 (24)		8 (28)	9 (32)	
6	100 (49)	52 (54)		14 (50)	18 (62)		16 (55)	13 (46)	
Number of HLA class I mismatches			0.03			0.8			0.3
0–2	55 (27)	15 (15)		6 (21)	7 (24)		5 (17)	8 (29)	
>2	147 (73)	81 (85)		22 (79)	22 (76)		24 (83)	20 (71)	
Number of HLA class II mismatches			0.4			0.3			0.9
0–2	64 (32)	35		9 (32)	6 (21)		10 (35)	10 (36)	
>2	138 (68)	61 (63)		19 (68)	23 (79)		19 (65)	18 (64)	
Donor/Recipient CMV			0.09			0.04			0.8
Reactive/Reactive	83 (42)	52 (54)		14 (50)	23 (79)		16 (55)	14 (50)	
Non-reactive/ Reactive	78 (39)	28 (29)		8 (29)	2 (7)		7 (24)	9 (32)	
Reactive/Non-reactive	9 (4)	7 (7)		4 (14)	4 (14)		2 (7)	2 (7)	
Non-reactive/Non-reactive	29 (15)	9 (9)		2 (7)	0		4 (14)	2 (7)	

	Child donor			Parent donor			Sibling donor		
	Son N=202	**Daughter N=96**	**P-value**	**Father N=28**	**Mother N=29**	**P-value**	**NIMA-mismatched N=29**	**NIPA- mismatched N=28**	**P-value**
Missing	-	-		-	-		0	1 (4)	
ABO matching			0.9			0.5			0.8
Matched	124 (61)	58 (60)		18 (64)	22 (76)		19 (65)	20 (71)	
Minor mismatch	36 (18)	16 (17)		3 (11)	3 (10)		5 (17)	4 (14)	
Major mismatch	36 (18)	20 (21)		7 (25)	4 (14)		5 (17)	3 (11)	
Bi-directional	6 (3)	0		0	0		0	1 (4)	
Year of HCT, median (range)	2018 (2009–21)	2017 (2009–21)	0.3	2017 (2010–21)	2015 (2009–21)	0.05	2017 (2010–2021)	2018 (2009–2021)	0.6
Follow-up, median (range) in **months**	27 (1.2–124)	24 (0.9–110)	NA	28 (2–122)	54 (4–114)	NA	38 (6–125)	13 (3–89)	NA

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMV, cytomegalovirus; DRI, Disease Risk Index; HCT, hematopoietic cell transplantation; HCT-CI, Hematopoietic Cell Transplantation-Specific Comorbidity Index; HLA, human leukocyte antigen; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; NIMA, non-inherited maternal antigen; NIPA, non-inherited paternal antigen; NMA, non-myeloablative; RIC, reduced-intensity conditioning.

Table 2:

Outcomes

	Child Donor Estimate (95% CI)				Parent Donor Estimate (95% CI)				Sibling Donor Estimate (95% CI)			
	Overall N=298	**Son N=202**	**Daughter N=96**	**P**	**Overall N=57**	**Father N=28**	**Mother N=29**	***P***	**Overall N=57**	**NIMA**	**NIPA**	**P**
Acute GVHD, grade II-IV, day 180	36% (31–42)	34% (28–42)	39% (31–51)	0.5	63% (52–77)	56% (40–78)	65% (50–85)	0.3	48% (36–63)	31% (18–53)	58% (42–79)	0.04
Acute GVHD, grade III-IV, day 180	8% (6–12)	6% (4–11)	12% (7–21)	0.1	23% (14–37)	11% (4–32)	31% (18–53)	0.09	10% (5–22)	10% (3–30)	11% (4–31)	0.9
Chronic GVHD, 3 years	16% (12–21)	13% (9–20)	21% (13–33)	0.2	16% (8–30)	15% (6–37)	31% (18–53)	0.2	12% (6–25)	11% (4–31)	13% (4–37)	0.9
Non-relapse mortality, 3 years	33% (28–39)	33% (27–41)	32% (23–44)	0.6	31% (21–46)	26% (14–50)	35% (21–59)	0.5	43% (30–60)	28% (15–50)	33% (18–59)	0.9
Relapse, 3 years	28% (23–34)	31% (24–38)	24% (16–35)	0.3	29% (19–44)	32% (18–57)	21% (11–44)	0.3	25% (15–42)	21% (10–43)	11% (4–32)	0.4
Progression-free survival, 3 years	38% (32–44)	36% (28–43)	43% (32–54)	0.2	38% (25–51)	36% (16–56)	39% (21–58)	0.9	30% (16–44)	48% (29–64)	56% (34–73)	0.4
Overall survival, 3 years	42% (35–48)	42% (34–49)	41% (30–53)	0.5	47% (33–61)	41% (21–60)	53% (34–72)	0.5	41% (27–56)	54% (35–70)	55% (33–72)	0.8

Abbreviations: CI, Confidence Interval; GVHD, Graft Versus Host Disease; NIMA, non-inherited maternal antigen; NIPA, non-inherited paternal antigen

Table 3:

Multivariate Analysis*: Child Donor

		Acute GVHD, grade II-IV	Chronic GVHD	NRM	Relapse	PFS	OS
		HR (95% CI), p-value	**HR (95% CI), p-value**	**HR (95% CI), p-value**	**HR (95% CI), p-value**	**HR (95% CI), p-value**	**HR (95% CI), p-value**
DONOR	Daughter	1.2 (0.8–1.9), 0.3	1.05 (0.5–2.3), 0.9	0.9 (0.6–1.4), 0.7			
	Son				**Son to mother**: 1.7 (1.02–2.7), 0.04		
	Donor/DRI						
	Son/Low-intermediate	-	-	-	-	1.0	1.0
	Daughter/Low-intermediate	-	-	-	-	1.2 (0.7–1.9), 0.4	1.5 (0.9–2.5), 0.1
	Son/high-very high	-	-	-	-	2.8 (1.9–4.1), <0.001	3.3 (2.1–5.0), <0.001
	Daughter/high-very high	-	-	-	-	1.4 (0.7–2.7), 0.3	1.7 (0.8–3.5), 0.1
HLA	>2 class II mismatches	-	3.3 (1.3–8.7), 0.01	-	-	-	-
OTHER	PB graft	-	3.1 (1.5–6.4), 0.003	-	-	-	-
	Patient age >50 years	-	-	2.03 (1.1–3.7), 0.02	-	1.5 (1.02–2.3), 0.04	1.6 (1.0–2.5), 0.05
	High/ v high DRI	-	-	-	2.4 (1.5–3.9), <0.001	-	-
	Donor/Recipient CMV (NR/R)	1.7 (1.2–2.6), 0.006	0.4 (0.1–0.9), 0.04	-	-	-	-

*Analysis not done for grade III-IV acute GVHD as there were no significant predictors in univariate analysis

-: factors were not included in the multivariate model as they were not significant predictors in the univariate analyses

Abbreviations: CI, Confidence Interval; CMV, cytomegalovirus; DRI, disease risk index; GVHD, Graft Versus Host Disease; HR, hazard ratio; PB, peripheral blood; NR/R, non-reactive/reactive; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival

Table 4:

Multivariate Analysis*: Parent Donor

		Acute GVHD, grade III-IV	NRM	Relapse**	PFS	OS
		HR (95% CI), p-value	**HR (95% CI), p-value**	**HR (95% CI), p-value**	**HR (95% CI), p-value**	**HR (95% CI), p-value**
DONOR	Mother	2.6 (0.7–9.8), 0.1	1.2 (0.5–3.1), 0.7	0.5 (0.2–1.3), 0.2	1.3 (0.6–2.6), 0.5	0.9 (0.4–1.9), 0.8
HLA	HLA B leader mismatch	-	2.7 (1.03–7.02), 0.04	-	-	2.2 (0.9–4.9), 0.06
	HLA-A mismatch	-	0.3 (0.1–0.8), 0.02	-	0.2 (0.1–0.5), 0.001	0.2 (0.1–0.5), 0.001
OTHER	Patient age >30 y	4.8 (1.4–16.5), 0.01	-	-	-	-
	HCT-CI ≥3	-	-	-	3.1 (1.4–6.7), 0.004	3.0 (1.2–7.5), 0.02

*No multivariate analysis of grade II-IV acute GVHD or chronic GVHD as there were no significant predictors in univariate analysis

-: factors were not included in the multivariate model as they were not significant predictors in the univariate analyses

**HLA-DQ mismatch: HR 0.2, 95% CI 0.06–0.5, p=0.002 based on a very small number of events, as there were very few donor-recipient pairs that were -DQ matched (n=4/57)

Abbreviations: CI, Confidence Interval; CMV, cytomegalovirus; DRI, disease risk index; GVHD, Graft Versus Host Disease; HCT-CI, hematopoietic cell transplantation comorbidity index; HR, hazard ratio; PB, peripheral blood; R/R, reactive/reactive; NRM, non-relapse mortality; PFS, progression-free survival; OS, overall survival

Table 5:

Multivariate Analysis*: Sibling Donor

		Acute GVHD, grade II-IV	NRM	PFS	OS
		HR (95% CI), p-value	**HR (95% CI), p-value**	**HR (95% CI), p-value**	**HR (95% CI), p-value**
DONOR	**NIMA**	0.1 (0.02–0.6), 0.001	0.9 (0.3–3.1), 0.9	1.4 (0.6–3.4), 0.4	1.1 (0.4–2.9), 0.8
HLA	HLA-B leader mismatch	-	3.8 (1.04–13), 0.04	2.7 (1.1–6.7), 0.03	2.4 (0.9–6.3), 0.06
	HLA-A mismatch	0.2 (0.1–0.6), 0.005	-	-	-
OTHER	Patient age >50 years	2.7 (1.1–6.9), 0.04	-	-	-
	HCT-CI ≥3	-	-	2.4 (0.9–6.4), 0.08	2.9 (0.9–8.8), 0.05
	High/v high DRI	-	4.4 (1.513), 0.008	2.5 (0.9–5.5), 0.07	2.6 (1.0–6.6), 0.05

*No multivariate analysis of grade III-IV acute GVHD, chronic GVHD or relapse as there were no significant predictors in univariate analysis

-: factors were not included in the multivariate model as they were not significant predictors in the univariate analyses

Abbreviations: CI, Confidence Interval; CMV, cytomegalovirus; DRI, disease risk index; GVHD, Graft Versus Host Disease; HCT-CI, hematopoietic cell transplantation comorbidity index; HR, hazard ratio; NRM, non-relapse mortality; PFS, progression-free survival; OS, overall survival