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ORIGINAL ARTICLE

The impact of HLA matching on unrelated donor hematopoietic stem cell transplantation in Korean children

Meerim Park[1], Kyung Nam Koh[1], Bo Eun Kim[1], Ho Joon Im[1], Kyung Duk Park[2], Hyoung Jin Kang[2], Hee Young Shin[2], Hyo Seop Ahn[2], Keon Hee Yoo[3], Ki Woong Sung[3], Hong Hoe Koo[3], Hyeon Jin Park[4], Byung-Kiu Park[4], Jong Jin Seo[1]

Department of Pediatrics, [1]University of Ulsan College of Medicine, Asan Medical Center Children's Hospital, [2]Seoul National University Hospital, Seoul National University College of Medicine, [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [4]Pediatric Oncology Center, National Cancer Center, Goyang, Korea

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Correspondence to
Jong Jin Seo, M.D.
Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center Children's Hospital, 388-1, Pungnap-2dong, Songpa-gu, Seoul 138-736, Korea
Tel: +82-2-3010-3383
Fax: +82-2-473-3725
E-mail: jjseo@amc.seoul.kr

Background
The impact of HLA matching on outcomes of unrelated donor (URD) hematopoietic stem cell transplantation (HSCT) varies in different racial or ethnic groups. Since little is known about the impact of such matching on URD HSCT in Korean children, we analyzed this issue.

Methods
We analyzed the outcomes of 142 patients who underwent URD HSCT at 4 Korean medical centers. All patient donor pairs were fully typed for HLA-A, -B, -C, and -DR alleles.

Results
At a median follow-up of 22 months, 3-year survival rates for patients with 8, 7, and ≤ 6 matched alleles were 88.4%, 70.7%, and 53.6%, respectively. A single mismatch (Mm) at HLA-B or -C was associated with lower survival compared with that associated with 8 matched alleles. No significant differences were observed between single-allele and single-antigen Mms with respect to survival rate or acute graft-versus-host disease (aGVHD) incidence rates. HLA disparity had a greater impact on the survival of patients with high-risk malignancy than of those with low-risk malignancy. Among pairs with a single Mm, only locus A showed a significant association and higher risk of grade III-IV aGVHD compared to those in patients with 8 matched alleles.

Conclusion
Disparity in HLA class I, regardless of antigen or allele Mm, adversely affected both survival and grade III-IV aGVHD development. An increased number of HLA Mms was associated with a higher risk of post-transplantation complications. Further investigations using larger cohorts are required to confirm the effects of HLA mismatching on URD HSCT patient outcomes.

Key Words URD HSCT, HLA, Korean children

INTRODUCTION

Allogeneic hematopoietic stem-cell transplantation (HSCT) is a well-established curative therapy for the treatment of lymphohematopoietic and congenital metabolic disease. Because there is a lack of HLA-identical related donors in approximately 75% of the cases, during the past few years, an increasing number of HSCTs have been performed using HLA-matched unrelated donors (URDs) [1]. Employment of URD introduces a number of questions and problems in donor selection that do not occur in transplantation from an HLA-identical sibling donor. The precise impact of HLA mismatching on HSCT outcomes remains unclear, because studies on the relative importance of various loci involved have yielded different results. Nearly every HLA locus has been reported to influence the outcome of URD HSCT; however, conflicting data have been obtained [2-4]. In American patients, a single mismatch (Mm) at HLA-B or -C was better tolerated than those at HLA-A or -DRB1 [5]. In Japanese

patients, however, the presence of a HLA-A or -B Mm significantly reduced survival, whereas a Mm at HLA-C or -DRB1/DQB1 did not [6]. Molecular typing techniques for all HLA loci have demonstrated that serological matching is insufficient to ensure an allelic match [7, 8]. High-resolution DNA-based typing of HLA alleles has markedly improved donor selection accuracy, resulting in improved HSCT patient outcomes. However, the relative importance of antigenic and allelic Mms remains unclear [5, 9].

The impact of HLA Mms on disease outcomes in Korean children has not been determined, and the relationship between Mms and disease status has not been explored. We, therefore, retrospectively assessed the impact of high-resolution donor-recipient matching results at the HLA-A, -B, -C, and -DR loci on patient outcomes in 142 Korean children treated with URD HSCT.

MATERIALS AND METHODS

1. Patients

This study included 142 patients aged ≤18 years, who received HSCT from URDs at 4 medical centers (Asan Medical Center, Seoul National University Hospital, Samsung Medical Center, and National Cancer Center) in Korea between April 2003 and September 2009. The median follow-up duration was 22 months (range, 1-78 months).

All patient-donor pairs were fully typed for HLA-A, -B, -C, and -DR alleles. Details of the study population are shown in Table 1. Underlying malignant diseases included acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), myelodysplastic syndrome (MDS), and chronic myeloid leukemia (CML). Nonmalignant diseases included bone marrow failure, immunodeficiency, hemophagocytic lymphohistiocytosis, and metabolic disease. Patients with hematological malignancies were divided into low-risk and high-risk subgroups based on disease status at transplantation. Low-risk individuals had ALL or AML in first complete remission (CR), MDS with either refractory anemia or refractory anemia with ringed sideroblasts subtypes, or CML in first chronic phase (CP). All other hematologic malignancies were considered high risk. Seventy-one patients were classified as low-risk and 38 as high-risk.

Stem cell sources included bone marrow in 69 (49%) and granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood in 73 (51%) patients. Recipients of cord blood were excluded in this study, because HLA Mms may have a different impact in this patient population.

2. HLA typing and matching

All donors and recipients were HLA-typed both serologically and using PCR by using sequence-specific primers (SSPs), and all donor-recipient pairs were fully typed for HLA-A, -B, -C, and -DR using high-resolution molecular typing. All Mms were classified according to the loci involved and whether they were detected at the low- or high-resolution level.

Table 1. Patient characteristics.

Characteristics	N	%	Median (range)
Age at transplantation (mo)			98 (4-244)
Patient gender (Male/Female)	85/57	60/40	
Disease			
ALL	33	23	
AML	52	37	
AmixL	2	1	
ABL	9	6	
JMML	3	2	
MDS	5	4	
CML	3	2	
SAA	18	13	
Lymphoma	2	1	
HLH	3	2	
Others[a)]	12	8	
Disease status			
Low risk	71	50	
High risk	38	27	
Nonmalignant disease	33	23	
ATG as GVHD prophylaxis			
Yes	84	59	
No	58	41	
Conditioning intensity			
Reduced intensity	46	32	
Myeloablative	96	68	
Source of stem cells			
Bone marrow	69	49	
Peripheral blood	73	51	
Total body irradiation			
Yes	37	26	
No	105	74	
Patient / Donor CMV status			
+/+	116	82	
+/−	11	8	
−/+	11	8	
−/−	2	1	

[a)]Others include Fanconi anemia (6 patients), pure red cell anemia (1 patient), congenital dyserythropoietic anemia (1 patient), Wiskott-Aldrich syndrome (1 patient), Krabbe disease (2 patients), and adrenoleukodystrophy (1 patient).
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AmixL, acute mixed lineage leukemia; ABL, acute basophilic leukemia; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; SAA, severe aplastic anemia; HLH, hemophagocytic lymphohistiocytosis; ATG, antithymocyte globulin; GVHD, graft versus host disease; CMV, cytomegalovirus.

3. Definitions of outcomes

The primary outcome was overall survival (OS), defined as the time from graft infusion to death from any cause. Treatment-related mortality (TRM) was defined as death during continuous CR of the primary disease. Secondary endpoints included neutrophil engraftment, defined as timing of the first 3 consecutive days on which a patient had neutrophil counts $>0.5\times10^9$/L, the cumulative incidence of grades II-IV acute graft-versus-host disease (aGVHD), and the cumulative incidence of relapse in patients with malignant disease. aGVHD was diagnosed and graded using established criteria [10]. Patients were considered evaluable for engraftment, if they survived for at least 21 days after HSCT.

Relapse-related death was defined as death caused by relapse after HSCT, regardless of any further treatment for relapse.

4. Statistical analysis

Continuous variables are expressed as median (range), whereas categorical variables are expressed as proportions and/or percentages. Descriptive statistical analysis was performed to compare patient baseline and post-transplantation characteristics. Two-sided Fisher's exact test was used in 2×2 table analysis. OS curves were calculated using Kaplan-Meier method and compared using the log-rank test. Cumulative incidence curves for TRM and relapse with or without death were constructed to reflect the time to relapse and time to transplant-related death as competing risks. Cumulative incidences were compared using Gray's test. Both analyses were performed using Cox regression for OS, TRM and relapse-related death, and logistic regression for aGVHD and engraftment. Variables considered included HLA match, patient age, donor-recipient gender match, disease status, stem cell source, and intensity of conditioning. All reported *P*-values are 2-sided, and *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS Version 18.0 software program or R 2.10.1.

Table 2. High-resolution HLA mismatch characteristics in 142 donor-recipient pairs.

	8/8 (%) N=59	7/8 (%) N=56	6/8 (%) N=20	≤5/8 (%) N=7
Allele match	59 (100)	0	0	0
Single allele Mm	0	25 (45)	0	0
2 allele Mm	0	0	6 (30)	0
3 or more allele Mm	0	0	0	1 (14)
Single antigen Mm	0	31 (55)	0	0
2 antigen Mm	0	0	1 (5)	0
3 or more antigen Mm	0	0	0	1 (14)
Single antigen+single allele Mm	0	0	13 (65)	0
Single antigen+2 allele Mm	0	0	0	4 (57)
Single antigen+3 allele Mm	0	0	0	1 (14)

Abbreviation: Mm, mismatch.

RESULTS

1. Types of HLA Mms present in the study population

Match/Mm characteristics of the 142 donor-recipient pairs are summarized in Table 2. High-resolution typing (4-digit level) revealed that 59 (41.5%) of donor-recipient pairs matched at all 8 loci, 56 (39.4%), had 1 HLA-A, -B, -C, or -DR Mm, 20 (14.1%), had 2 Mms, and 7 (4.9%) had 3 or more Mms at these loci. Of the 56 single-locus Mms, 25 (44.6%) were detectable upon low-resolution typing and 31 (55.4%) on high-resolution typing.

2. Overall survival

The 3-year OS in all patients was 74.1±4.0%. Univariate estimates of OS are shown in Table 3. Using multivariate analysis, HLA matching was shown to be the most significant factor associated with mortality.

Table 3. Cox regression analysis of overall survival.

Variable	HR	95% CI	*P*
High-resolution HLA matching			
Matched for all 8 loci	1		
1 locus Mm	2.94	1.04-8.32	0.04
≥2 loci Mm	6.07	1.94-19.01	0.002
Patient age (years)			
Younger than 5 years	1		
5-10 years	0.92	0.31-2.76	0.89
Older than 10 years	1.69	0.63-4.54	0.29
Gender Mm			
Match	1		
Mm	1.04	0.47-2.32	0.92
Conditioning regimen			
Reduced intensity conditioning	1		
Myeloablative conditioning	9.52	2.16-41.94	0.003
Stem cell source			
Bone marrow	1		
Peripheral blood	1.67	0.74-3.77	0.22
Disease status at HSCT			
Low risk	1		
High risk	2.12	0.87-5.15	0.09
Non-malignant disease	0.56	0.17-1.86	0.35

Abbreviations: HR, hazard ratio; Mm, mismatch; HSCT, hematopoietic stem cell transplantation.

Table 4. Adjusted hazard ratios of HSCT outcomes according to total number of HLA mismatches.

	No.	Overall survival			Transplant-related mortality			Acute GVHD Grade II-IV		
		HR	95% CI	*P*	HR	95% CI	*P*	RR	95% CI	*P*
8/8 matched	59	1			1			1		
7/8 matched	56	2.94	1.04-8.32	0.04	3.39	1.06-10.85	0.05	2.12	0.94-4.82	0.07
A locus Mm	13	3.93	0.92-16.72	0.06	4.68	0.41-15.38	0.08	3.03	0.87-10.61	0.08
B locus Mm	3	17.67	2.08-52.61	0.03	17.5	3.13-98.42	0.01	1.77	0.15-21.01	0.65
C locus Mm	29	3.37	1.12-9.32	0.04	3.73	1.05-13.23	0.06	2.16	0.82-5.71	0.12
DR locus Mm	11	0.00	0.00	0.99	0.00	0.00	0.99	1.33	0.31-5.73	0.71
≤6/8 matched	27	4.42	1.63-11.97	0.003	5.45	1.68-17.7	0.005	6.02	2.23-16.26	0.00

Abbreviations: HSCT, hematopoietic stem cell transplantation; Mm, mismatch; HR, hazard ratio; RR, relative ratio.

Mm at a single locus was associated with a lower survival rate than was observed for 8/8 HLA-matched pairs. Table 4 shows the association between HLA Mm and survival. A single Mm at HLA-B, or -C was associated with a significantly lower survival rate compared to that of patients with 8 matched alleles, whereas a single Mm at HLA-A or DR was not. Risks associated with single allele vs. single antigen Mms with regard to OS were not statistically significant. An increase in the number of HLA Mms was associated with reduced OS (Fig. 1A). The 3-year survival rates for patients with 8, 7, and ≤6 matched alleles were 88.4%, 70.7%, and 53.6%, respectively (P=0.006). There was a significant survival difference between patients with 8 and 7 matched alleles (P=0.015); however, there was no significant survival difference between patients with 7 and ≤6 matched alleles (P=0.39).

We also evaluated the association between the number of HLA-Mms and survival in patients with high- or low-risk hematologic malignancies (Fig. 1B and C). HLA Mms had a significantly greater effect on the survival of patients with high- compared to low-risk malignancies (P=0.003). The adjusted OS hazard ratios for pairs of patients with single Mms compared to those for high-risk and low-risk patients with 8 matched alleles were 12.14 (95% CI=1.13-123.62, P=0.04) and 1.24 (95% CI=0.32-4.86, P=0.76), respectively.

3. Engraftment

In this study, 136 of the 142 patients (95.8%) underwent successful graft procedures. The median time to neutrophil engraftment was 14 days (range, 9-35 days). Six patients (4.2%) showed graft failure; 4 had malignant diseases, and 2 had non-malignant diseases. There was no association between the numbers of HLA Mms (either allele or antigen) and engraftment.

4. Acute GVHD

The overall incidences of grade II-IV aGVHD for patients with 8, 7 and ≤6 matched alleles were 22.0%, 37.5%, and 63.0%, respectively. Additionally, the incidences of grade III-IV aGVHD in these 3 groups were 6.8%, 23.2%, and 33.2%. An increased number of HLA Mms was associated with an elevated risk of grade III-IV aGVHD (P=0.003). No significant difference was observed in aGVHD incidence between a single high- and a single low-resolution Mm.

Although a single locus Mm was not significantly associated with grade II-IV aGVHD, the incidence of grade II-IV aGVHD was significantly higher in recipients with ≥2 Mm than in recipients with 8 matched alleles (Table 4). Among pairs with a single locus Mm, only those in whom the Mm was at HLA-A were at a significantly higher risk of grade

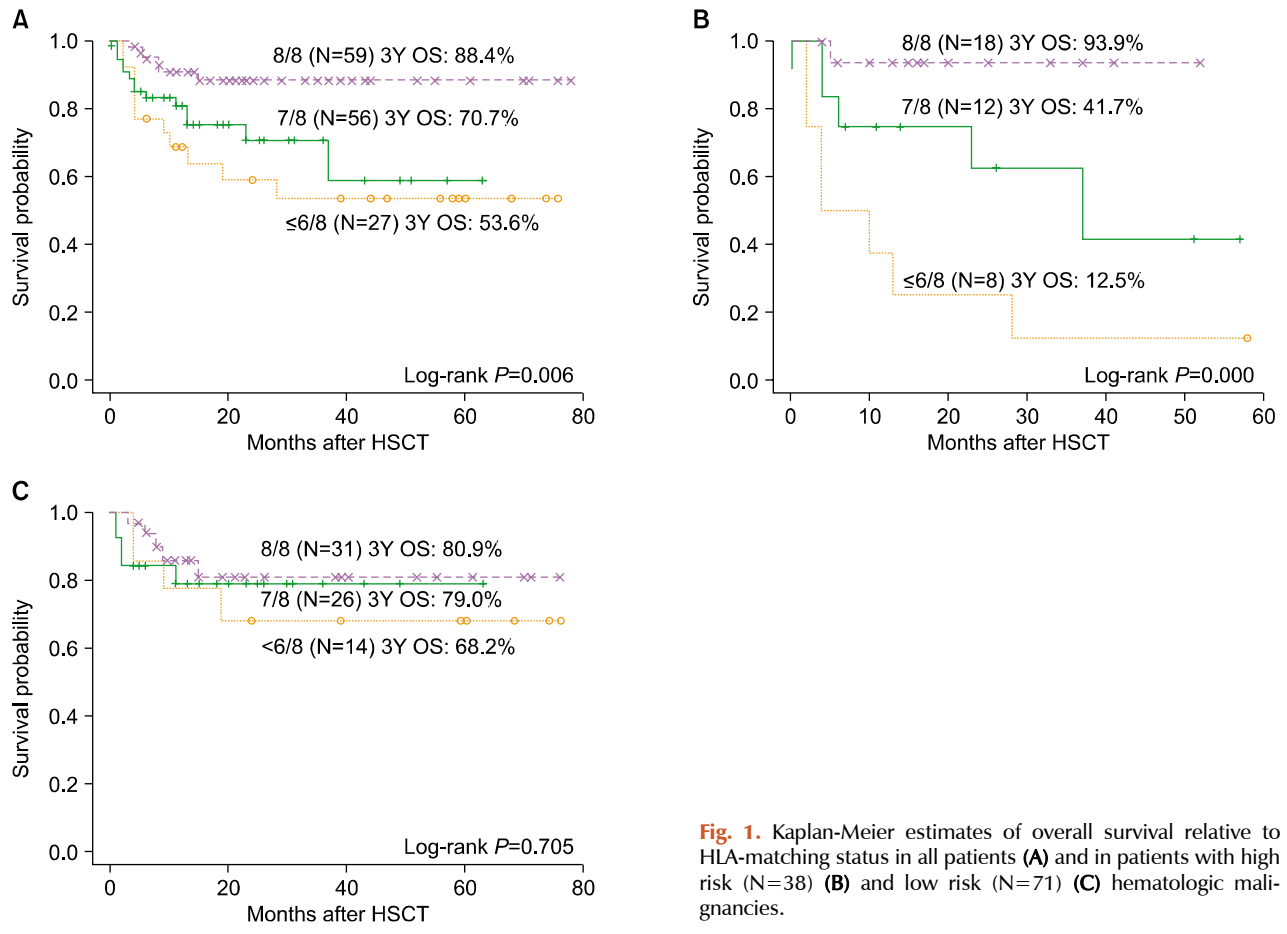

Fig. 1. Kaplan-Meier estimates of overall survival relative to HLA-matching status in all patients **(A)** and in patients with high risk (N=38) **(B)** and low risk (N=71) **(C)** hematologic malignancies.

III-IV aGVHD (RR=8.59, 95% CI=1.89-38.88, *P*=0.005), although a single Mm at locus C generally increased the risk of grade III-IV aGVHD, with borderline statistical significance (RR=3.59, 95% CI=0.93-13.91, *P*=0.06). Other significant non-HLA factors present in the multivariate model included stem cell source (*P*=0.05) and conditioning regimen (*P*=0.003).

5. Relapse/Relapse-related death

The 3-year cumulative incidence of relapse in patients with malignancies was 21.7±0.3%. There was no association between the numbers of HLA Mms (either allele or antigen) and relapse, or between HLA matching status and relapse-related death. According to multivariate analysis, no non-HLA factor was associated with relapse.

6. Transplant-related mortality

The 3-year cumulative incidence of TRM is shown in Fig. 2A. The major cause of TRM was infection. TRM incidence was significantly higher in recipients with a single Mm at the HLA-B locus than in those with a single Mm at the other loci, HLA-A, -C, or -DR (33.3 vs. 19.4%, *P*=0.007); among 3 patients with HLA-B Mm, 2 died of TRM, including veno-occlusive disease and infection.

Associations between the number of HLA-Mms and TRM in patients with high- and low-risk hematologic malignancies are illustrated in Fig. 2B and C. The number of HLA Mms had a significantly greater effect on TRM in patients with high-compared to low-risk disease (*P*=0.002). Compared with adjusted hazard ratios of TRM for recipients with 8 matched alleles, the adjusted hazard ratios of TRM for recipients with ≤6 matched alleles were 51.0 (95% CI=3.89-669.41, *P*=0.003) in patients with high-risk disease and 2.55 (95% CI=0.44-14.59, *P*=0.29) in patients with low-risk disease. Multivariate analysis identified donor/patient gender Mm (*P*=0.04) and conditioning regimen (*P*=0.02) as significant non-HLA factors associated with TRM.

DISCUSSION

Extensive recent research has shown that mismatches at each HLA locus can affect clinical outcomes of patients undergoing URD HSCT [11-13]. The role of HLA on HSCT outcomes had not previously been assessed in Korean children; thus, we evaluated the effects of patient-donor HLA compatibility in these children. This is the first multicenter study to analyze the relative clinical importance of HLA matching on major transplantation outcomes in Korean children. Several important results emerged from our analysis.

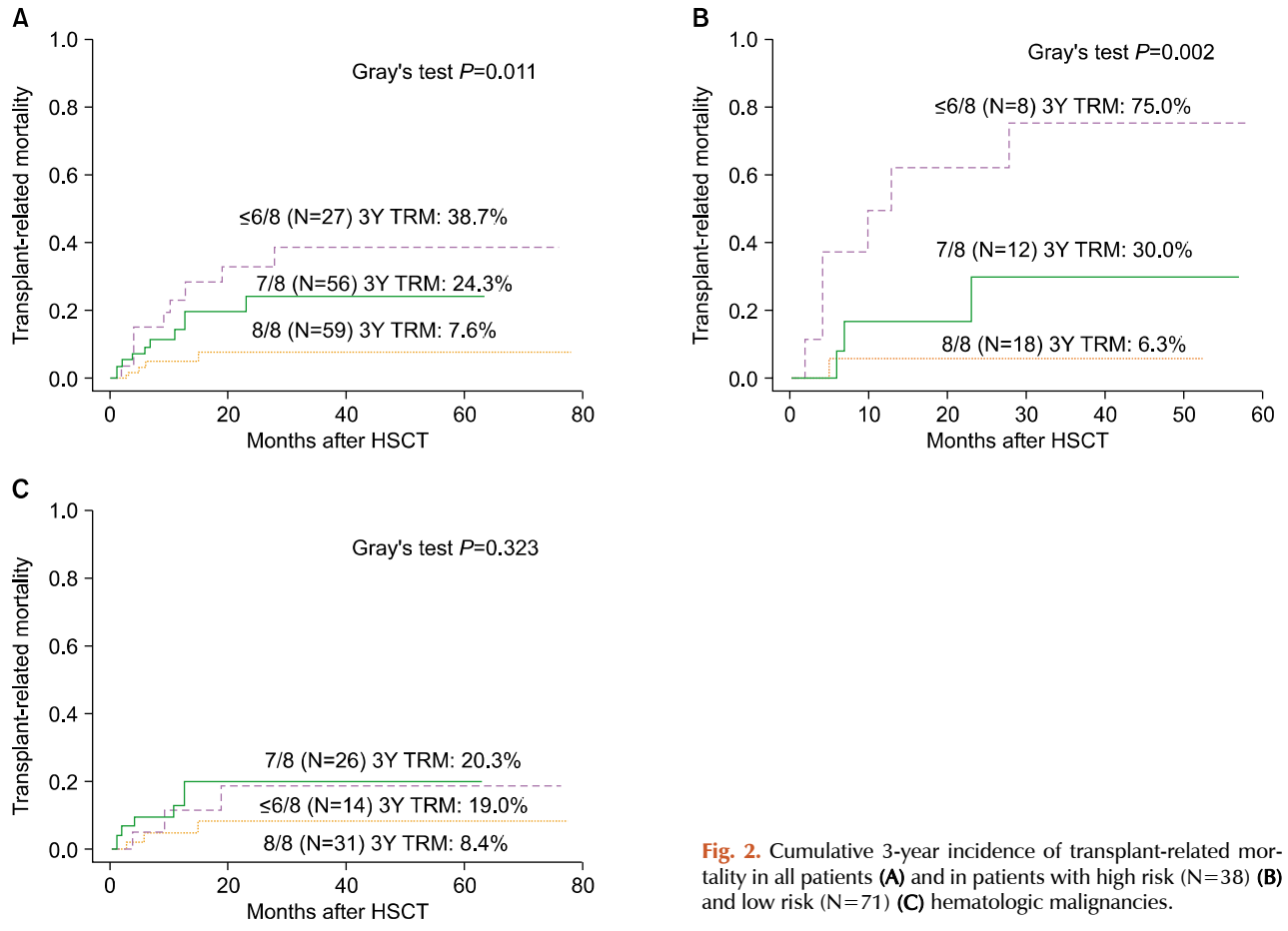

Fig. 2. Cumulative 3-year incidence of transplant-related mortality in all patients **(A)** and in patients with high risk (N=38) **(B)** and low risk (N=71) **(C)** hematologic malignancies.

First, there were no differences in survival, aGVHD, and relapse when single allele and single antigen Mms were compared, in contrast to the common perception that allele Mms are better tolerated than are antigen Mms. Previous studies have reported conflicting results, with single allele and antigen Mms showing either equivalent [4, 5, 9] or different [14] effects on outcomes. Although particular high-resolution Mms have been regarded as more permissive than their low-resolution counterparts, data on pooled high-resolution Mms showed that adverse effects on transplantation outcomes were detectable [14]. Our results suggest that both low- and high-resolution Mms should be considered equivalent when determining optimal donor-patient HLA matches. However, our inability to detect significant differences may be because the donor-recipient population in this study was relatively small.

Our results demonstrate the negative effects of a single Mm on survival. Some Mms exhibit worse transplant outcomes than other Mms. A recent National Marrow Donor Program (NMDP) study [14] found that single Mms at HLA-A, -B, -C, and -DR loci had similar adverse effects on mortality, and other reports have described a deleterious effect of HLA-C Mms on survival [3, 14, 15]. In this study, we found that single Mms at HLA-B and -C, but not at HLA-A and -DR, were associated with significantly lower survival rates, compared to those in patients with 8 matched alleles. These findings agree with the hypothesis that Mms at some loci are better tolerated than those at the others. As the strong linkage disequilibrium between HLA-B and -C results in frequent coordinate matching, information on both loci is of importance in determining optimal donor-patient HLA matches [16]. Moreover, HLA-A Mms are associated with a significantly higher risk of grades III-IV aGVHD. Although reports have yielded different results when the association between HLA disparity and aGVHD were compared, our findings confirm that HLA-A Mms have significant adverse effects on severe aGVHD [14].

An elevated number of HLA Mms also increased the risk of post-transplantation complications, including poorer overall survival, TRM, and aGVHD incidence and severity. In this study, each additional Mm was associated with a 17-18% absolute decrease in survival. Most previous studies have shown that multiple Mms increase mortality and the risk of post-transplantation complications.

Notably, the impact of HLA Mms differed among patients at various stages of disease. Some previous studies have reported that high-risk disease before HSCT had a greater absolute impact on survival than did HLA mismatching [5, 9, 15]. In this study, however, the impact of single HLA Mms on survival was more detrimental in patients with high- compared to low-risk malignancies. These differences may be due to higher incidence of grade III-IV aGVHD (P=0.05) and the use of a myeloablative conditioning regimen (P=0.01) in high-risk malignancies compared to those in low-risk malignancies; differences may also reflect higher intensities of immunosuppression and the tendency to have an infection. We also found that TRM rates were proportional to the extent of HLA mismatching in both the high- and low-risk disease categories; thus, the greater impact of single Mms on survival in patients with high- rather than low-risk disease is likely attributable to augmentation in patients with higher-risk disease of the negative effect of HLA disparity associated with TRM. Because the major cause of TRM in this study was sepsis, early identification and proper treatment of infections is imperative, if HSCT is performed in a patient with high-risk disease using an incompletely matched donor.

The acceptable Mm level remains controversial. This is important in donor selection, when a fully matched donor is not available, and a choice must be made between accepting a mismatched donor, searching for other sources of stem cells or a haploidentical donor, and completely avoiding HSCT. Guidelines of the International Histocompatibility Working Group (IHWG) state that a full application of the rules governing the acceptability of HLA Mms should include side-by-side evaluation of ethnically and racially diverse transplantation populations (www.ihwg.org). Analysis of very large numbers of pairs, characterized at high resolution and for whom complete clinical data are available, is of crucial importance in addressing locus- and allele-specific rules for mismatching [17]. The apparent discrepancy between our results and those of other studies may be attributable to both study power and ethnicity. A discrepancy between Korean and other patients may reflect disparities in the HLA and non-HLA genetic backgrounds of the more homogeneous Korean population compared with more heterogeneous populations. Some HLA alleles and haplotypes are distributed at different frequencies among various racial/ethnic groups [11]. Thus, specific Mms among HLA-loci may be better tolerated within certain ethnic groups. For example, a study in Japan suggested that discrepancies of responsible HLA locus for aGVHD between ethnically diverse HSCT may be explained by the proportions of nonpermissive Mm combinations in each HLA locus [18].

Although several studies have found lower relapse risks, of the graft-vs.-leukemia effect in patients with Mms at multiple loci or at a specific locus [3, 19], we did not find an association between HLA disparity and relapse; there may be an association of donor/patient HLA mismatching with low rate of discontinuation of immunosuppression and prolonged immunosuppressive therapy for GVHD compared to HLA-matched transplantation. However, as other studies did not observe an effect of HLA disparity on relapse, further investigations should be conducted to address this issue [4, 5].

Our present study had several limitations. First, our patient sample was relatively small and heterogeneous, and transplantation protocols were not uniform. Only 3 patients had HLA-B Mm; therefore, results should be interpreted with caution. However, some analyses regarding HLA-B Mm show a $P< 0.05$. Second, subset comparisons have specific strengths, but confounding by Mms at other loci is avoided. Thus, this method may overlook a functional role of HLA-A, -B, -C, or -DR mismatching that operates only in combination

with one or more Mms. Membership in groups with double and triple Mms was too low to permit statistical analysis. Third, we did not analyze the effect of HLA-DP and -DQ, which generally showed additive effects when additional HLA Mms were present at other loci [6, 20].

In summary, we showed that outcomes in single-allele Mm patients are not equivalent to those in patients with 8/8 matches. Disparity in HLA class I status, regardless of antigen or allele Mm, had adverse effects on survival and grade III-IV aGVHD, whereas HLA class II disparities had little impact on transplantation outcomes. An increased number of HLA Mms was associated with higher rates of post-transplantation complications, including poorer survival and increased aGVHD incidence or severity. HLA disparities impacted survival differently when recipients had low- or high-risk malignancies. Physicians overseeing HSCT for high-risk patients using HLA-mismatched donors should avoid and treat infections and associated complications to reduce TRM.

This study provides useful information regarding the significance of HLA matching on outcomes of Korean pediatric patients undergoing URD HSCT, thus assisting physicians in their search for a suitable donor. Further investigations, including analyses of larger cohorts, are warranted to confirm the effects of HLA Mms on outcomes of patients undergoing HSCT.

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