



Impact of graft-versus-host disease on outcomes of cord blood transplantation according to HLA disparity and its prophylaxis type

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Abstract

This study evaluated the impact of acute graft-versus-host disease (aGVHD) on cord blood transplantation (CBT) outcomes based on human leukocyte antigen (HLA) disparity and GVHD prophylaxis type. Data from 4,196 adult patients with acute myeloid leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome were analyzed. Patients were classified by HLA mismatch (8/8–6/8, 5/8, and 4/8–2/8) and further by GVHD prophylaxis type (methotrexate [MTX] or mycophenolate mofetil [MMF]). The impact of aGVHD was assessed using a time-dependent Cox model. Grade I–II aGVHD improved overall survival (OS) in all groups, regardless of HLA mismatches or prophylaxis type. However, grade III–IV aGVHD worsened OS across MMF groups, while in MTX groups, it was unfavorable only in the HLA 8/8–6/8-matched group (HR 1.6, $P=0.01$). Grade III–IV aGVHD increased non-relapse mortality (NRM) across all groups but was more pronounced in HLA 4/8–2/8-matched patients receiving MMF. Notably, relapse risk decreased in HLA 4/8–2/8-matched patients with MTX prophylaxis, partially offsetting the negative impact of grade III–IV aGVHD on NRM. These findings suggest that the impact of aGVHD varies with HLA mismatches and prophylaxis type. MTX prophylaxis may mitigate the adverse effects of severe aGVHD in highly mismatched cases, unlike MMF prophylaxis. Careful donor selection considering HLA mismatches is essential when using MMF prophylaxis to manage severe aGVHD and reduce NRM risk.

Keywords Cord blood transplantation · Acute graft-versus-host disease · HLA matching · GVHD prophylaxis

Introduction

Acute graft-versus-host disease (aGVHD) is a major complication associated with allogeneic hematopoietic stem cell transplantation (HSCT). aGVHD development causes organ damage via the alloreactive immune response and complications of aGVHD treatments, such as immunosuppressants, which lead to increased non-relapse mortality (NRM) after HSCT [1, 2]. The impact of aGVHD on HSCT outcomes is different between donor sources [3–6]. In bone marrow (BMT) or peripheral blood stem cell transplantation (PBSCT), grade II or higher aGVHD and chronic GVHD increase NRM and worsen disease-free survival [4–7]. Contrastingly, in cord blood transplantation (CBT), grade I–II aGVHD (aGVHD I–II) and localized chronic GVHD reduce

the incidence of both relapse and NRM and improve survival [5–9], with some exceptions [4, 10, 11].

Recently, some studies have reported that the impact of aGVHD on HSCT outcomes might depend not only on the donors but also on other factors in HSCT. Konuma et al. found that the benefit of aGVHD I–II and chronic GVHD on CBT outcomes was noted only in human leukocyte antigen (HLA) 4/6-matched cases but not in HLA 6/6–5/6-matched cases, while the GVHD prophylaxis type did not show such an effect [6]. Furthermore, through the analysis of patients who developed grade II–IV aGVHD, Fuji et al. showed that HLA 2- or HLA 1-locus allele-mismatched unrelated donors who received BMT or PBSCT had significantly worse overall survival (OS) than HLA-matched related donor, while HLA allele-mismatch effects were not noted in CBT [5].

Although these studies suggest that HLA mismatch might affect the impact of aGVHD I–II and grade III–IV GVHD (aGVHD III–IV) on CBT outcomes, none have analyzed the

impact of aGVHD considering both HLA allele mismatch and GVHD prophylaxis type simultaneously. Therefore, we conducted this study to obtain useful information for selecting suitable cord blood units and GVHD prophylaxis types.

Methods

Patients

Patients aged ≥ 16 years who received their first single-unit CBT for acute myeloid leukemia, acute lymphoblastic leukemia, and myelodysplastic syndrome between 2008 and 2020 and achieved neutrophil engraftment were retrospectively analyzed. Patients who received GVHD prophylaxis other than calcineurin inhibitor (CNI)–methotrexate (MTX) or CNI–mycophenolate mofetil (MMF) and those who received in vivo T-cell depletion, using components, such as anti-thymocyte globulin, were excluded. Furthermore, patients with HLA 7 and 8 allele mismatches in the HLA-A, -B, -C, and -DRB1 loci (HLA 1/8 match or 0/8 match) were excluded because of the small number of patients and difficulty of analysis. The analyzed data were obtained from the Transplant Registry Unified Management Program, which included data from the Japanese Society for Transplantation and Cellular Therapy and the Japan Cord Blood Bank Network [12–14]. Informed consent was waived for patients who received transplants before 2017 because of the retrospective nature of this study; nevertheless, these patients were offered the opportunity to opt out. Informed consent was obtained from all other patients. This study conformed to the principles of the Declaration of Helsinki and was approved by the ethics committee of the Tohoku University School of Medicine.

Definitions

HLA disparity was assessed based on the number of mismatches among eight alleles at the HLA-A, -B, -C, and -DRB1 loci. A regimen of total-body irradiation (≤ 8 Gy) and administration of busulfan (< 9 mg/kg) and melphalan (≤ 140 mg/m²) was defined as reduced-intensity conditioning [15]. For patients with insufficient data about doses of the conditioning regimen, we used clinician-reported conditioning intensity, such as myeloablative or reduced intensity. Adverse cytogenetic risk is defined as follows; A complex karyotype (three or more abnormalities), monosomal karyotype (two or more autosomal monosomies or one single autosomal monosomy with one or more structural abnormalities), $-5/\text{del}(5q)$, $-7/\text{del}(7q)$, 11q23 abnormality except for $t(9;11)$, $\text{inv}(3)$, $t(3;3)$, $t(6;9)$, and $t(9;22)$ in acute myeloid leukemia, and abnormal chromosome 7 and complex karyotype (three or more abnormalities) in myelodysplastic

syndrome. None of the chromosomal abnormalities in acute lymphoblastic leukemia were included in the adverse cytogenetic risk category.

Statistical analysis

Chi-square and Kruskal–Wallis tests were used to compare categorical and continuous variables in patient characteristics. The landmark method was used with univariate analysis to assess the impact of aGVHD on OS, relapse, and NRM, and the landmark was set at 90 d post CBT. Cumulative incidence of aGVHD, relapse, and NRM was evaluated by considering death as a competing risk, and Gray test and log-rank test were used to compare the cumulative incidences and OS, respectively. Multivariate adjustment for possible confounding variables using a cause-specific Cox proportional hazards regression model was used to assess the impact of aGVHD on the relapse rate, NRM, and OS. aGVHD development was considered a time-dependent covariate. The variables used in multivariate analysis are as follows: aGVHD I–II development, aGVHD III–IV development, age (< 55 or ≥ 55 years), karyotype risk (low/intermediate, adverse, or unknown karyotype), complete remission status at CBT, HCT-specific comorbidity index (HCT-CI) (< 3 or ≥ 3), performance status (PS) (0/1 or ≥ 2), recipient CMV serostatus, donor/recipient sex combination (female donor-to-male recipient, others, or unknown), number of transfused CD34⁺ cells (< 0.8 or $\geq 0.8 \times 105/\text{kg}$), conditioning regimen intensity (myeloablative or reduced-intensity), total body irradiation for conditioning, and transplantation year (< 2016 or ≥ 2016). EZR (version 1.61; Saitama Medical Center, Jichi Medical University, Saitama, Japan). Statistical significance was set at P -value < 0.05 , except in the analysis of the interaction effect between GVHD prophylaxis and aGVHD or HLA disparity and aGVHD, where P -value < 0.1 was considered significant.

Results

Patient characteristics

The number of eligible cases was 4,619, including 1,429 HLA 8/8–6/8-matched cases, 1,596 HLA 5/8-matched cases, and 1,594 HLA 4/8–2/8-matched cases. Each group was further divided into groups that received CNI–MTX (MTX prophylaxis) and CNI–MMF (MMF prophylaxis) as GVHD prophylaxis. The clinical characteristics of these groups are shown in Table 1. Cumulative incidence of aGVHD development is shown in Figure S1. aGVHD developed before day 90 post CBT in most cases, and aGVHD III–IV development was higher with MMF prophylaxis than with MTX prophylaxis (16.4% vs 9.2%, $P < 0.001$).

Table 1 Clinical characteristics of the patients included in the study

Factor	HLA 8/8–6/8 match		HLA 5/8 match		HLA 4/8–2/8 match	
	MTX (n = 753)	MMF (n = 676)	MTX (n = 886)	MMF (n = 710)	MTX (n = 1005)	MMF (n = 589)
Age						
median	52	50	51	60	50	60
[range]	[16, 76]	[16, 80]	[16, 79]	[17, 80]	[16, 80]	[16, 77]
< 55	419 (55.6)	232 (34.3)	531 (59.9)	236 (33.2)	612 (60.9)	191 (32.4)
≥ 55	334 (44.4)	444 (65.7)	355 (40.1)	474 (66.8)	393 (39.1)	398 (67.6)
Disease						
ALL	156 (20.7)	129 (19.1)	215 (24.3)	115 (16.2)	238 (23.7)	79 (13.4)
AML	466 (61.9)	450 (66.6)	528 (59.6)	496 (69.9)	601 (59.8)	416 (70.6)
MDS	131 (17.4)	97 (14.3)	143 (16.1)	99 (13.9)	166 (16.5)	94 (16.0)
Disease status						
CR	378 (50.2)	283 (41.9)	468 (52.8)	287 (40.4)	567 (56.4)	235 (39.9)
non-CR	375 (49.8)	392 (58.1)	418 (47.2)	423 (59.6)	438 (43.6)	354 (60.1)
Cytogenetic risk						
high	123 (16.3)	130 (19.2)	176 (19.9)	162 (22.8)	180 (17.9)	135 (22.9)
low and intermediate	476 (63.2)	358 (53.0)	523 (59.0)	379 (53.4)	613 (61.0)	319 (54.2)
unknown	154 (20.5)	188 (27.8)	187 (21.1)	169 (23.8)	212 (21.1)	135 (22.9)
PS						
0, 1	689 (91.5)	576 (85.5)	834 (94.1)	622 (88.0)	942 (93.7)	523 (88.9)
≥ 2	64 (8.5)	98 (14.5)	52 (5.9)	85 (12.0)	63 (6.3)	65 (11.1)
HCT-CI						
0, 1, 2	625 (83.7)	479 (71.9)	723 (82.3)	483 (68.8)	819 (82.0)	415 (71.1)
≥ 3	122 (16.3)	187 (28.1)	155 (17.7)	219 (31.2)	180 (18.0)	169 (28.9)
Recipient CMV serostatus						
negative	139 (18.5)	117 (17.3)	186 (21.0)	130 (18.3)	179 (17.8)	104 (17.7)
positive	614 (81.5)	558 (82.7)	700 (79.0)	580 (81.7)	825 (82.2)	485 (82.3)
The number of CBT with female donor-to-male recipient						
absent	514 (68.3)	481 (71.2)	599 (67.6)	464 (65.4)	632 (62.9)	372 (63.2)
present	165 (21.9)	153 (22.6)	197 (22.2)	226 (31.8)	255 (25.4)	177 (30.1)
unknown	74 (9.8)	42 (6.2)	90 (10.2)	20 (2.8)	118 (11.7)	40 (6.8)
Number of transfused CD34 cells						
median	0.8	0.8	0.88	0.88	0.91	0.85
[range]	[0.04, 6.45]	[0.05, 3.75]	[0.08, 12.69]	[0.05, 6.32]	[0.04, 14.02]	[0.05, 4.06]
< 0.8	369 (49.8)	329 (50.2)	364 (41.8)	275 (39.9)	396 (40.0)	257 (44.6)
≥ 0.8	372 (50.2)	327 (49.8)	507 (58.2)	415 (60.1)	593 (60.0)	319 (55.4)
Intensity of conditioning regimen						
MAC	516 (68.5)	423 (62.7)	628 (70.9)	496 (69.9)	692 (68.9)	387 (65.7)
RIC	237 (31.5)	252 (37.3)	258 (29.1)	214 (30.1)	313 (31.1)	202 (34.3)
TBI						
absent	161 (21.4)	262 (38.8)	158 (17.8)	339 (47.8)	146 (14.5)	231 (39.2)
present	592 (78.6)	414 (61.2)	728 (82.2)	370 (52.2)	859 (85.5)	358 (60.8)
CBT year						
median	2015	2017	2016	2017	2015	2016
[range]	[2008, 2020]	[2008, 2020]	[2008, 2020]	[2008, 2020]	[2008, 2020]	[2008, 2020]
< 2016	393 (52.2)	241 (35.7)	442 (49.9)	263 (37.0)	525 (52.2)	257 (43.6)
≥ 2016	360 (47.8)	435 (64.3)	444 (50.1)	447 (63.0)	480 (47.8)	332 (56.4)

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *CR* complete remission, *PS* performance status, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *CMV* cytomegalovirus, *MAC* myeloablative regimen, *RIC* reduced-intensity conditioning regimen, *TBI* total body irradiation, *CBT* cord blood transplantation, *MTX* calcineurin inhibitor with methotrexate, *MMF* calcineurin inhibitor with mycophenolate mofetil

Difference in the impact of aGVHD on OS according to GVHD prophylaxis type and HLA disparity

The unadjusted OS for patients who developed aGVHD in each group stratified by HLA disparity and GVHD prophylaxis is shown in Figure S2A–C. With the HLA 8/8–6/8 match, the impact of aGVHD III–IV was similar regardless of the GVHD prophylaxis type used. However, with the HLA 5/8 and 4/8–2/8 matches, aGVHD III–IV development had a more detrimental effect on patients receiving MMF prophylaxis than on those receiving MTX prophylaxis. Multivariate analysis was therefore performed to compare the impact of aGVHD on OS between these groups. aGVHD I–II development had a favorable impact on OS compared to the absence of aGVHD, regardless of HLA disparity and GVHD prophylaxis type (Fig. 1A–C). aGVHD III–IV development worsened OS in the HLA 8/8–6/8-matched group that received CBT with MTX prophylaxis (hazard ratio [HR] 1.66, $P = 0.021$) (Fig. 1A), whereas no adverse impact on OS was noted in the HLA 5/8- and 4/8–2/8-matched groups using MTX prophylaxis (Fig. 1B and C). In the MMF prophylaxis group, the impact of aGVHD III–IV development was unfavorable, regardless of HLA disparity (Fig. 1A–C). These differences in the impact of aGVHD III–IV development on OS between HLA disparity and GVHD prophylaxis types were supported by the P -value for the interaction effect between aGVHD III–IV and GVHD prophylaxis type (Fig. 1A–C).

Impact of aGVHD grade on relapse and NRM according to GVHD prophylaxis type and HLA disparity

The cumulative incidence of relapse and NRM in patients who developed aGVHD before day 90 post CBT in each group stratified by HLA disparity and GVHD prophylaxis type is shown in Figures S3 and S4. The incidence of relapse was the lowest with aGVHD III–IV development in the HLA 4/8–2/8-matched group. aGVHD III–IV development worsened NRM similarly in the HLA 8/8–6/8-matched groups that received MTX and MMF prophylaxes. In contrast, in the HLA 5/8- and 4/8–2/8-matched groups, aGVHD III–IV development with MMF prophylaxis increased NRM substantially; this increase was relatively small with MTX prophylaxis. We subsequently performed multivariate analysis to examine the effect of aGVHD I–II and III–IV onset on the incidence of relapse and NRM. As shown in Fig. 2A and B, the onset of aGVHD had no impact on relapse in patients with HLA 8–6/8 and HLA 5/8 matches who received MTX or MMF prophylaxis. In contrast, the onset of aGVHD I–II and III–IV in HLA 4/8–2/8-matched patients who received MTX prophylaxis significantly reduced the incidence of relapse (HR 0.62, $P = 0.0019$ and HR 0.44, $P = 0.0086$, respectively), while no effect was noted in those

who received MMF prophylaxis (Fig. 2C). The difference in the impact of aGVHD III–IV between GVHD prophylaxis types in HLA 4/8–2/8-matched patients was demonstrated by analyzing the interaction effect.

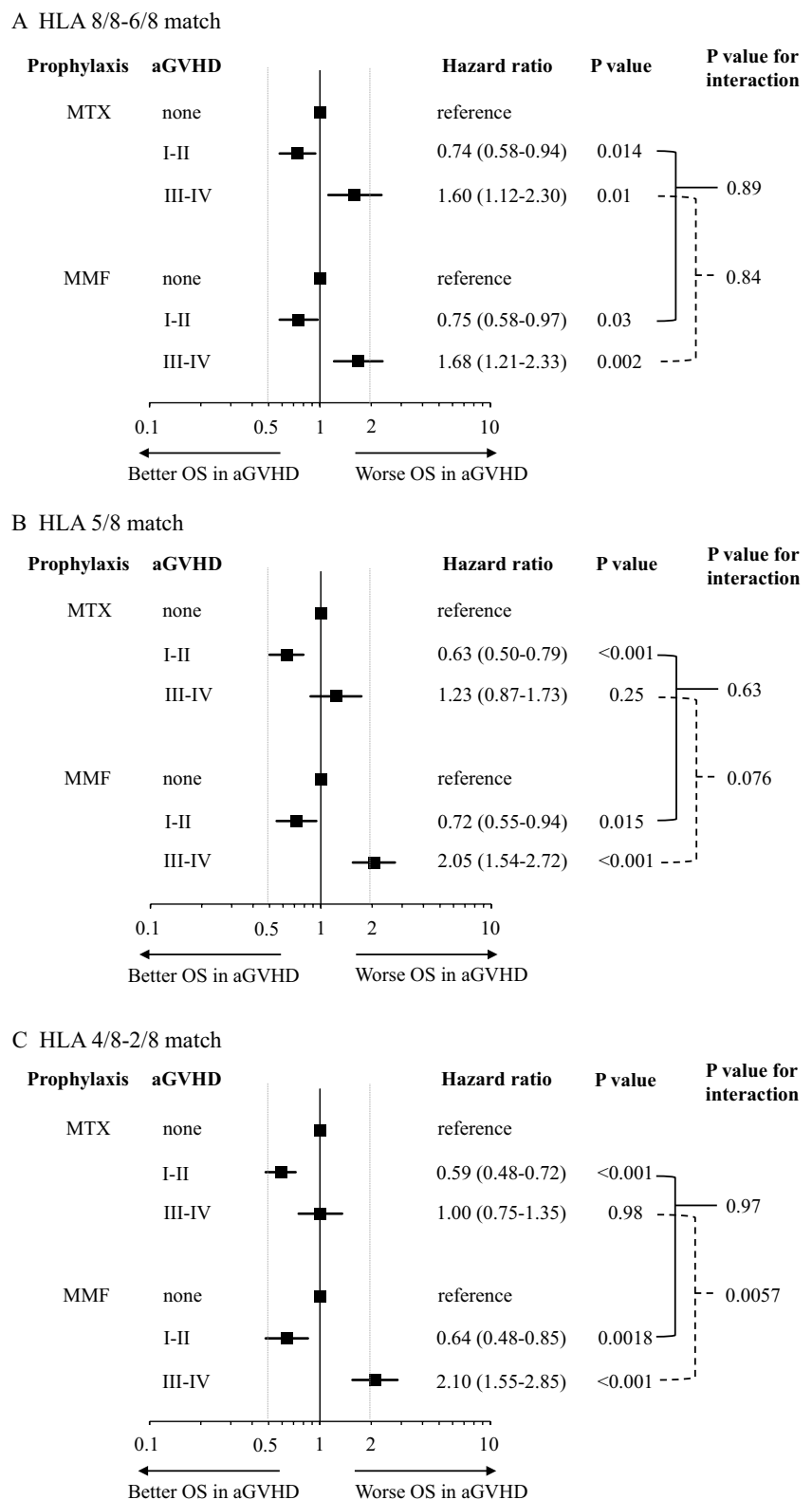
As shown in Fig. 3A–C, aGVHD I–II development improved NRM regardless of HLA disparity and GVHD prophylaxis type, although this effect was marginal in HLA 8/8–6/8-matched groups that received MMF prophylaxis. In contrast, aGVHD III–IV development worsened NRM in all groups (Fig. 3A–C). Analysis of the interaction effect between aGVHD III–IV and GVHD prophylaxis showed that the impact of aGVHD III–IV was similar to that of MTX and MMF prophylaxis in the HLA 8/8–6/8- and 5/8-matched groups (Fig. 3A and B), whereas a more unfavorable impact of aGVHD III–IV development was noted in the HLA 4/8–2/8-matched group that received MMF prophylaxis than in the group that received MTX prophylaxis, which was supported by the analysis of the interaction effect (Fig. 3C).

Discussion

The study findings suggest that the impact of aGVHD was influenced by the number of HLA matches and GVHD prophylaxis type. In the HLA 4/8–2/8-matched group that received MTX prophylaxis, but not the group that received MMF prophylaxis, the unfavorable impact of aGVHD III–IV on NRM might be offset by the reduced incidence of relapse, which might be the reason for the difference in the impact of aGVHD III–IV on OS by GVHD prophylaxis type. When MMF prophylaxis is used, the number of HLA mismatches may need to be considered when selecting cord blood donors to prepare for the risk of severe aGVHD, which leads to a high rate of NRM. This consideration is not necessary in the case of MTX prophylaxis.

Several studies have demonstrated inconsistent effects of aGVHD on CBT outcomes. Lazaryan et al. reported that aGVHD onset had no effect on NRM, relapse, and OS in patients who underwent HSCT from an HLA-matched sibling donor [4]. aGVHD worsened OS in the EBMT/Eurocord registry analysis [11], whereas no significant impact of aGVHD was noted in the CIBMTR cohort [10]. Although these studies did not analyze aGVHD I–II onset alone, they suggested that the effect of aGVHD can be changed by the nature of CBT, as shown herein. Another study examined the impact of aGVHD I–II and III–IV separately and found that aGVHD I–II development in CBT improved relapse incidence and NRM, resulting in improved OS, while the onset of aGVHD III–IV worsened NRM and OS despite the decrease in relapse [6, 8, 9]. Subgroup analysis was conducted according to HLA disparity or GVHD prophylaxis type; however, HLA disparity was assessed using HLA low-resolution data without considering these effects

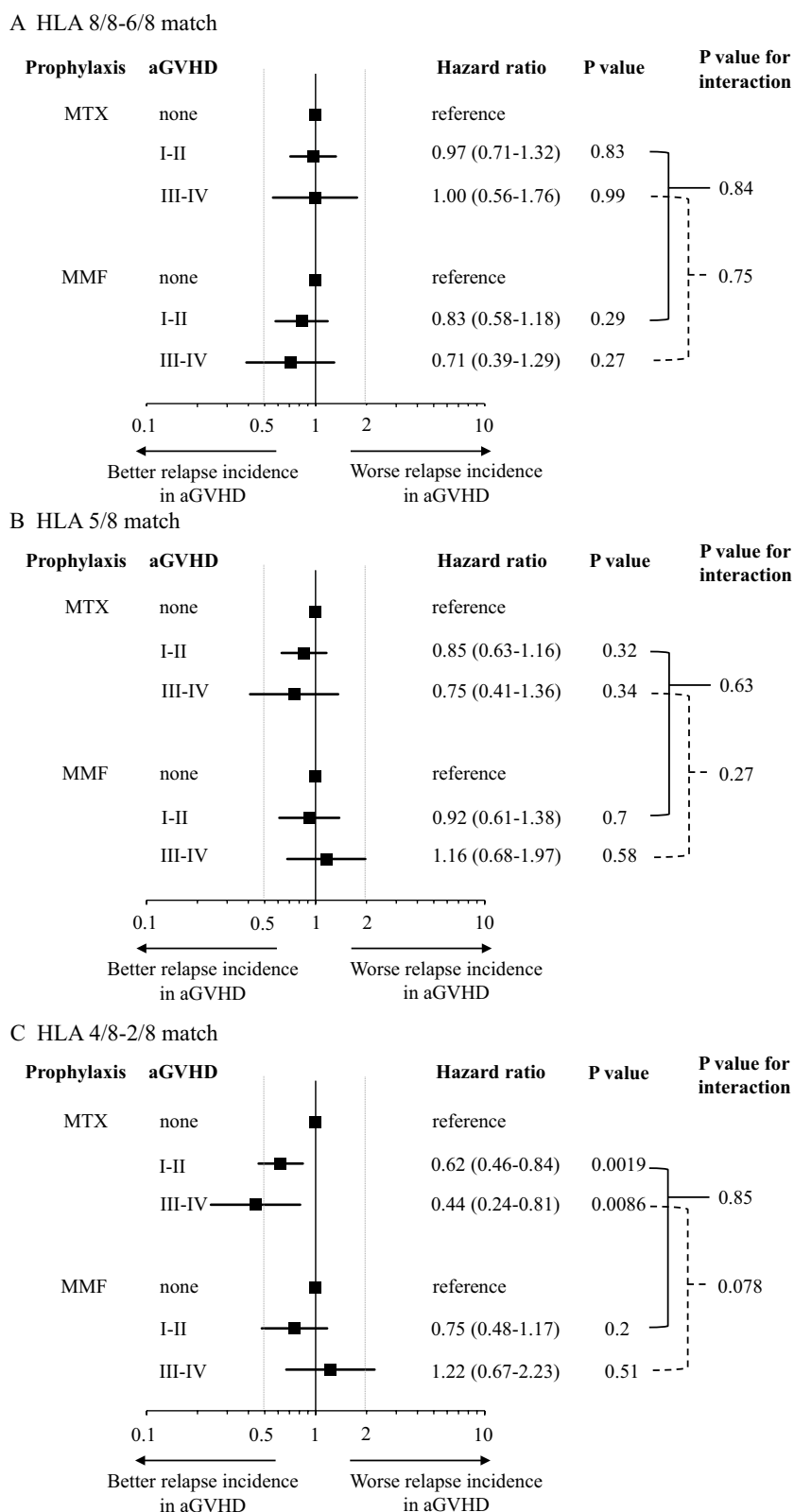
Fig. 1 Impact of acute graft-versus-host disease (aGVHD) development on overall survival (OS). The impact of aGVHD I-II and III-IV development on OS was analyzed by multivariate adjustment using the Cox proportional hazards regression model for each group stratified by HLA disparity: **(A)** HLA 8/8–6/8 match, **(B)** HLA 5/8 match, and **(C)** HLA 4/8–2/8 match. Each GVHD prophylaxis was analyzed separately; hence, the reference cases were distinct for MTX and MMF prophylaxes. Abbreviations: OS, overall survival; aGVHD, acute graft-versus-host disease; MTX, calcineurin inhibitor and methotrexate for GVHD prophylaxis; MMF, calcineurin inhibitor and mycophenolate mofetil for GVHD prophylaxis; I-II, grade I-II; III-IV, grade III-IV; CI, confidence interval



simultaneously. Our analysis demonstrated the importance of estimating the impact of aGVHD based on both high-resolution HLA allele mismatch and GVHD prophylaxis. The results also indicate that in the case of CBT with HLA

4/8–2/8 matches, MTX prophylaxis might be preferred over MMF prophylaxis, and special attention should be paid to the development of severe GVHD when MMF prophylaxis is used.

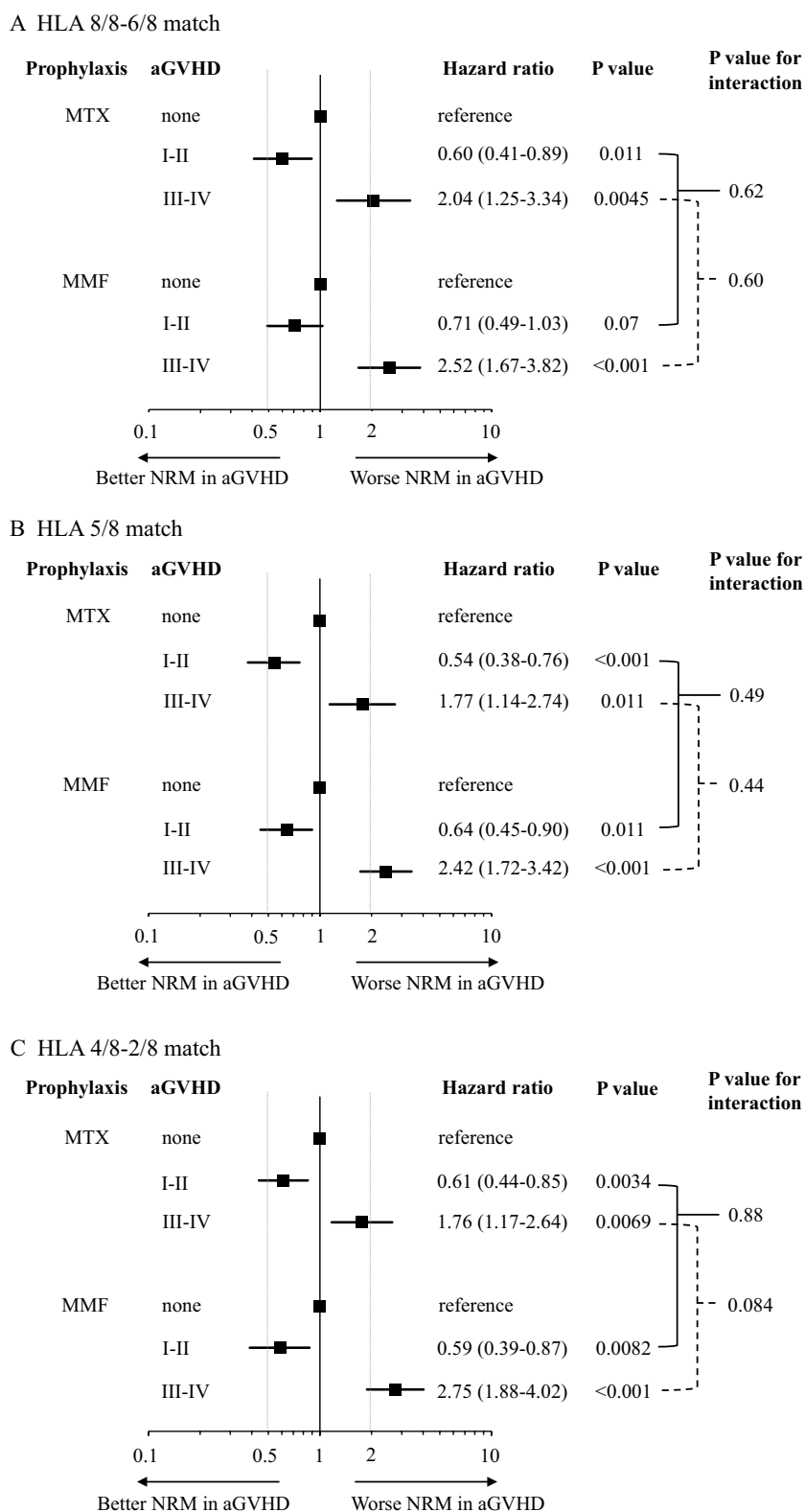
Fig. 2 Impact of aGVHD development on relapse incidence. The impact of aGVHD I-II and III-IV development on the incidence of relapse was analyzed by multivariate adjustment using a cause-specific Cox proportional hazards regression model for each group stratified by HLA disparity: **(A)** HLA 8/8–6/8 match, **(B)** HLA 5/8 match, and **(C)** HLA 4/8–2/8 match. Each GVHD prophylaxis was analyzed separately; hence, the reference cases were distinct for MTX and MMF prophylaxes. Abbreviations: aGVHD, acute graft-versus-host disease; MTX, calcineurin inhibitor and methotrexate for GVHD prophylaxis; MMF, calcineurin inhibitor and mycophenolate mofetil for GVHD prophylaxis; I-II, grade I-II; III-IV, grade III-IV; CI, confidence interval



In this study, the impact of aGVHD I-II on NRM was almost equally favorable across all groups, consistent with previous reports [6, 9]. Although the exact mechanism has

not been elucidated, it has been speculated that mild GVHD may stimulate immune reconstitution and decrease relapses through its alloreactivity. Conversely, the impact of aGVHD

Fig. 3 Impact of aGVHD development on the incidence of non-relapse mortality (NRM). The impact of aGVHD I-II and III-IV development on NRM was analyzed by multivariate adjustment using a cause-specific Cox proportional hazard regression model for each group stratified by HLA disparity: **(A)** HLA 8/8–6/8 match, **(B)** HLA 5/8 match, and **(C)** HLA 4/8–2/8 match. Each GVHD prophylaxis was analyzed separately; hence, the reference cases were distinct for MTX and MMF prophylaxes. Abbreviations: NRM, non-relapse mortality; aGVHD, acute graft-versus-host disease; MTX, calcineurin inhibitor and methotrexate for GVHD prophylaxis; MMF, calcineurin inhibitor and mycophenolate mofetil for GVHD prophylaxis; I-II, grades I-II; III-IV, grades III-IV; CI, confidence interval



III-IV was inconsistent among all groups, possibly due to varying responses to treatment of severe GVHD according to whether MTX or MMF prophylaxis was administered. Although the severity of aGVHD III-IV might increase with

the degree of HLA disparity, patients with MTX prophylaxis might respond better to GVHD treatments, such as those involving steroids, while patients with MMF prophylaxis might have poorer responses.

This study had some limitations. First, owing to the limited number of cases, it was not possible to analyze HLA disparities based on the individual number of HLA mismatches, and the analysis was divided into three major groups. Therefore, the effect of the number of HLA mismatches was not completely elucidated. Furthermore, the patients' characteristics were not balanced between the MTX and MMF prophylaxis groups. Although multivariate analysis was performed, the aforementioned differences might not have been completely adjusted. Additionally, to assess aGVHD impact, cases without engraftment were excluded from this study, which might have affected the results, especially in cases with MTX prophylaxis.

The study findings provide important information for selecting cord blood units and GVHD prophylaxis. However, this was a retrospective analysis, and further accumulation of cases and more detailed analyses are required.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00277-025-06415-w>.

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Author contributions H.Y., S.F., M.M., M.H., A.W., and S.M. designed the study. N.U., M.T., M.O., S.T., N.D., Y.M., K.I., Y.U., T.N., M.S., T.K., and T.E. collected data. F.I., K.K., T.I and Y.A. managed the data collection. H.Y., S.F., M.M., M.H., A.W., and S.M. analyzed and interpreted the data. H.Y. wrote the first draft of the manuscript. S.T. and S.M. were responsible for the GVHD Working Group and HLA Working Group of the JSTCT. All authors have reviewed and revised the manuscript.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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