Prognostic impact of HLA supertype mismatch on outcomes after single-unit cord blood transplantation

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Abstract

Backgrounds: The “human leukocyte antigen (HLA) supertype” is a functional classification of HLA alleles, which was defined by structural features and peptide specificities, and has been reportedly associated with the clinical outcomes of viral infections and autoimmune diseases. Although the disparity in each HLA locus was reported to have no clinical significance in single-unit cord blood transplantation (sCBT), the clinical significance of the HLA supertype in sCBT remains unknown.

Methods: The clinical data of 1,603 patients who received sCBT in eight institutes in Japan between 2000 and 2017 were retrospectively analyzed. Each HLA allele was categorized into 19 supertypes, and the prognostic effect of disparities was then assessed.

Results: An HLA-B supertype mismatch was identified as a poor prognostic factor (PFS: hazard ratio [HR] = 1.23, p= 0.00044) and was associated with a higher cumulative incidence (CI) of relapse (HR = 1.24, p = 0.013). However, an HLA-B supertype mismatch was not associated with the CI of acute and chronic graft-versus-host-disease. The multivariate analysis for relapse and PFS showed the significance of an HLA-B supertype mismatch independent of allelic mismatches, and other previously reported prognostic factors.

Conclusion: HLA-B supertype-matched grafts should be selected in sCBT.

Introduction

Cord blood is an important alternative donor source for patients without human leukocyte antigen (HLA)-identical donor. Because of the low incidence of severe graft-versus-host disease (GVHD), two mismatches in HLA-A, HLA-B serotype, and HLA-DRB1 allele are considered feasible[1,2]. In peripheral blood stem cell transplantation or bone marrow transplantation, some HLA allelic mismatches were reported as non-permissive mismatch because of the high risk of severe GVHD incidence[3,4]. Considering these reports, each pair of HLA allelic mismatch is not equivalent. HLA is not only a target of allogeneic immunity but also an important molecule that induces GVHD and graft-versus-tumor effects through antigen presentation of allogeneic antigens[5]. The allo-antigens presented by each mismatched HLA are possibly different; however, few reports have discussed this issue. The HLA supertype is a functional classification based on predicted structural similarities in epitope-binding specificities of HLA molecules[6–9]. HLA alleles belonging to each supertype have either experimentally proven or predicted ability to present antigenic peptides with similar anchoring amino acids. For the classification of the HLA class I supertype, Sette et al. made the latest classification for HLA-A and HLA-B based on a compilation of published motifs, peptide-binding data, and primary sequence of the B and F peptide-binding pockets[6]. This updated HLA-I classification agrees with those previously defined by other approaches from other groups[10,11]. For HLA-C, Doytchinova et al. classified into two supertypes based on the three-dimensional protein structure[12], which was consistent with the killer Ig-like receptor-binding specificities for HLA-C[13].

In contrast to HLA-I supertypes, HLA-II supertypes have been less intensively studied because of the less availability of peptide-binding data due to higher structural complexity. Doytchinova et al. defined 12 HLA-II supertypes, including five DRs (DR1, DR3, DR4, DR5, and DR9), three DQs (DQ1, DQ2, and DQ3), and four DPs (DPw1, DPw2, DPw4, and DPw6) by in silico analysis using both protein sequence and structural data of 2,225 HLA-II molecules[14]. The clinical significance of the HLA supertype to immune susceptibility to infection[15–17], cancer[18,19], and efficacy of the immune checkpoint inhibitor[20] has been reported. Moreover, this classification is now widely accepted and has been used for vaccine development[6, 21–23]. In hematopoietic stem cell transplantation (HSCT), Lazaryan et al. analyzed the clinical significance of HLA supertype mismatch in the context of HLA 1 allelic mismatched transplantation and reported that an HLA-B supertype mismatch was associated with a higher incidence of severe acute GVHD[24]. However, the clinical significance of HLA supertype mismatch is still unknown in single-unit cord blood transplantation (sCBT). Therefore, we conducted this retrospective analysis of a large sCBT cohort to identify the clinical significance of the HLA supertype mismatch.

Materials and Methods

Data collection

Data from 1,716 patients who underwent sCBT between 2000 and 2018 in Fukuoka Blood and Marrow Transplantation Group were collected. Among them, 113 patients with ≥ 3 mismatches in HLA-A, HLA-B serotype, and HLA-DRB1 allele and > 2 of past HSCTs were excluded, and 1,603 were analyzed in this study (Fig. S1). Patient backgrounds such as date and age at transplantation, sex, conditioning regimen, GVHD prophylaxis, experience in previous HSCT, and pre-transplant complications were collected to calculate HCT-CI[25]. To adjust for the prognostic effect of disease type and status, disease status information at transplantation in all patients and cytogenetics change in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) cases were collected, and the disease risk index proposed by Armand et al. was calculated.[26]

This study was approved by the Institutional Ethics Committee of the Kyushu University Graduate School of Medical Sciences and Toranomon Hospital.

Definitions

Progression-free survival (PFS) was defined as the number of days from transplantation to disease progression or death from any cause. Treatment-related mortality (TRM) was defined as any death related to transplantation toxicity without disease progression. The day of sustained engraftment was defined as the first of three consecutive days with an absolute neutrophil count exceeding 0.5×10^9/L. Acute GVHD was defined and graded by standard criteria, and only patients who experienced engraftment were evaluated. Chronic GVHD was evaluated according to standard criteria in patients who survived for > 100 days after transplantation. Patients were divided into two groups according to the conditioning regimen: full-intensity conditioning (FIC) and reduced-intensity conditioning (RIC). FIC and RIC were

defined according to the proposals of Giralt et al.[27] and Bacigalupo et al.[28] respectively, with slight modifications. In this study, conditioning regimens that included ≥ 8 Gy of total body irradiation in multiple fractions, intravenous administration of busulfan at > 6.4 mg/kg, or melphalan at > 140 mg/m^2 were considered FIC; all other regimens were classified as RIC. Alleles at the HLA-A, HLA-B, HLA-C, and HLA-DRB1 loci were identified by high-resolution DNA typing. The assignment algorithm for HLA-A and HLA-B supertypes was based on an updated supertype classification with revised main HLA anchor specificities. This method extends the previously described nine HLA-A and HLA-B supertype designations (A1, A2, A3, A24, B27, B44, B58, and B62) to 12 supertype groups (A01, A01A03, A01A24, A02, A03, A24, B07, B08, B27, B44, B58, and B62), because certain HLA-A alleles have peptide-binding repertoires with overlapping supertype specificities, resulting in newly defined A01A03 and A01A24 supertype categories[6]. This revised classification of HLA-A and HLA-B supertypes captured 99% of the allelic diversity of allograft recipients and their donors. The remaining 1% of unclassified HLA-A and HLA-B alleles were grouped into supertypes using bioinformatics methods[12]. Two HLA-C supertypes (C1 and C2) were derived from the hierarchical cluster analysis with distinct amino acid fingerprints in the protein structure for HLA-C1 (Ser77) and HLA-C2 (Asn77)[12], which also coincide with killer Ig-like receptor-binding specificities for HLA-C[13]. The grouping of HLA-DRB1 alleles into five supertypes (DR1, DR3, DR4, DR5, and DR9) was accomplished according to previously described in silico methods based on the common structural and functional features of HLA class II molecules[14]. In total, we categorized each HLA allele into 19 supertypes and then assessed the prognostic effect of disparities as used in the previous analysis for patients with PBSCT.

Statistical analysis

Cases with and without supertype mismatch at each HLA locus were compared across major clinical endpoints including PFS, relapse, TRM, acute and chronic GVHD, and time-to-neutrophil recovery (absolute neutrophil count ≥ 0.5 × 10^9/L). The probability PFS was estimated according to the Kaplan–Meier method. Cumulative incidence (CI) rates of TRM, relapse, and acute GVHD grades II–IV and III–IV were estimated by CI function analysis, wherein the competing risks of these included relapse, TRM, death or disease progression without grade 0–I acute GVHD, and death or disease progression without grade 0–II acute GVHD. Univariate and multivariate models for PFS, relapse, TRM, acute GVHD, chronic GVHD, and neutrophil engraftment were built using Cox proportional hazards models. All statistical analyses were performed using R version 4.1.0 (The R Foundation for Statistical Computing).

Results

Patient background

Baseline patient and clinical characteristics are summarized in Table 1. In total, we analyzed 1,603 patients (acute myeloid leukemia/myelodysplastic syndrome, n = 1,050; lymphoma, n = 309; acute lymphoblastic leukemia/lymphoblastic lymphoma, n = 179; lymphoma, n = 309; others, n = 65 [myelodysplastic/myeloproliferative neoplasm, n = 41; myeloma, n = 17; mixed phenotype acute leukemia,

n = 7]) who received sCBT between 2000 and 2017. The median age at transplantation was 57 (range 18–75) years. In total, 372 patients (23.2%) had a history of HSCT. RIC and FIC were used in 56.5% and 43.2% of all patients, respectively. GVHD prophylactic regimens consisted of calcineurin inhibitor (CNI) plus mycophenolate mofetil (CNI + MMF, 50.4%), CNI plus methotrexate (CNI + sMTX, 27.8%), or CNI alone (19.2%). The median follow-up of the surviving patients after CBT was 3.79 years (Table 1).

HLA alleles and supertypes

In 1,603 patients, allele-level mismatch in GVHD direction was observed as follows: HLA-A in 822 patients, HLA-B in 1,181, HLA-C in 1,006, and HLA-DRB1 in 1,145. Of the patients with allele-level mismatches at each HLA locus, supertype mismatches were observed in 55.2% (454/822) for HLA-A, 61.1% (722/1,181) for HLA-B, 15.5% (156/1,006) for HLA-C, and 54.3% (622/1,145) for HLA-DRB1, respectively (Fig. S2).

Clinical outcomes

The results of the univariate Cox proportional hazard regression analysis for post-transplant outcomes by the supertype mismatch in each HLA loci are summarized in Fig. 1A and 1B. An HLA-B supertype mismatch in the GvH direction was associated with a lower PFS rate (hazard ratio [HR] = 1.23 [95% confidence interval [CI] 1.10–1.38], p = 0.00044) and higher CI of relapse (HR = 1.24 [95% CI 1.05–1.46], p = 0.013) (Fig. 1A). However, an HLA-B supertype mismatch was not associated with GVHD development including acute GVHD grades II–IV, III–IV, and I–IV and chronic GVHD (Fig. 1A), whereas all supertype mismatch status in the host-versus-graft (HvG) direction were not prognostic (Fig. 1B). The two Kaplan–Meier curves for patients with and without an HLA-B supertype mismatch began to diverge after 2 months, and a landmark analysis at 2 months post-transplant showed a significantly worse prognosis and more recurrences in patients with an HLA-B supertype mismatch. Conversely, no difference in PFS and relapse at 2 months was found between the two groups (Fig. 1C). The univariate analysis of HLA mismatch in the allele or serotype level was also conducted for post-transplant outcomes. HLA-B serotype mismatch was also significantly associated with a lower PFS rate and a higher TRM rate rather than the relapse rate. In addition, a significant decrease in the neutrophil engraftment rate was found in these groups, which was considered a cause of increased TRM (Fig. S3). HLA-DRB1 mismatch was also associated with engraftment rates in both GvH and HvG directions and tended to increase TRM; however, it also tended to decrease the relapse rates, without affecting OS and PFS (Fig. S3). The HLA-A allelic mismatch in the GvH direction was associated with an increased risk of grade II–IV acute GVHD, but it was not associated with a higher TRM rate (Fig. S3). The subgroup analysis of recipients with HLA-B allele mismatch (n = 1,181) or serotype mismatch (n = 1,094) showed that an HLA-B supertype mismatch was a significant prognostic factor in both subgroups (Fig. 1D). We could not find any significant difference in patient backgrounds between recipients of HLA-B supertype-mismatched allograft and those of matched allografts (Table 2). The independent effect of HLA-B supertype matching on the PFS rate and CI of relapse was confirmed by the multivariable analysis adjusted for patient backgrounds or allelic mismatch of each HLA locus (Fig. 2). The subgroup analysis of patients with and without previous transplantation revealed that patients with an HLA-B supertype mismatch had a poor prognosis,

especially those who received their first CBT (HR = 1.22 [95% CI 1.08–1.37], p = 0.001, Fig. 3). Interestingly, the effect of an HLA-B supertype mismatch on the CI of relapse was significant in younger recipients (HR = 1.40 [95% CI 1.11–1.76], p = 0.0040), CNI + MTX (HR = 1.62 [95% CI 1.19–2.21], p = 0.002), and RIC (HR = 1.39 [95% CI 1.09–1.77], p = 0.008). An HLA-B supertype mismatch was not prognostic in those with CNI + MMF (Fig. 3). Patients who received GVHD prophylaxis consisting of CNI + MTX had a low frequency of chronic GVHD irrespective of HLA-B supertype disparity (Fig. S4), suggesting that excess immune suppression by MTX therapy synergistically increased the incidence of relapse. An HLA-B supertype mismatch was associated with relapse regardless of disease status at the time of transplantation and contributed to prognostic stratification, especially in acute lymphocytic leukemia and AML/MDS (Fig. 3).

Discussion

By using the HLA supertype, a functional classification, we identified the factors associated with the graft-versus-tumor effect on sCBT that could not be identified by conventional allelic typing. An HLA-B supertype mismatch is associated with increased relapse rates and poor prognosis, suggesting that an HLA-B supertype mismatch diminishes a graft-versus-tumor effect. Our multivariate and subgroup analyses revealed that an HLA-B supertype mismatch had a prognostic effect independent of the HLA mismatch in the allelic level.

Lazaryan et al. reported the prognostic effect of an HLA supertype mismatch in the context of PBSCT from an HLA 1 allele-mismatched donor. In this study, patients with an HLA-B supertype mismatch tended to have higher recurrence rates even if they had a significantly higher incidence of severe acute GVHD[24]. A pair of supertype-matched HLAs can present the same antigen even if they are mismatched at the allelic levels [6,9,12,14,24]. This means that an HLA of the supertype-matched donor can present neoantigens restricted to the recipient HLA (Fig. 4). This difference may have led to the difference in the graft-versus-tumor effect. A landmark analysis showed that the prognostic difference between the HLA-B supertype-matched and mismatched groups began to diverge 2 months after transplantation. At this time, the amount of T cells that differentiated from the transplanted donor stem cells increases, and they become the main source of T cells by approximately 6 months[29,30], whereas immediately after the transplantation, the T cells expanded from mature T cells in the graft [31,32]. A previous study identified that the poor recovery of thymic function after HSCT was associated with higher rates of relapse and TRM[30]. In HLA-mismatched HSCT, radioresistant thymus epithelial cells (TECs) express the recipient's haplotype, whereas donor T cells derived from the engrafted donor stem cells have different haplotypes. Such differences in MHC restriction are historically thought to influence the selection of the thymic T-cell repertoire and thus the peripheral T-cell pool[33]. Several data have been reported to substantiate this inference: recipients of HLA-matched blood donors show little loss of diversity in their TCR repertoire, whereas recipients of unrelated or HLA-mismatched blood donors show a bias in their TCR repertoire[34–36]. In CBT, the reconstitution of donor antigen presenting cell (APC) was reportedly more rapid than transplantation using other sources, reaching normal levels at 100 days post-transplant[37], and play a

critical role in the graft-versus-tumor effect[38]. Therefore, donor T cells must recognize the neoantigens presented on donor APC to induce an antitumor effect efficiently. However, these donor T cells receive positive selection by recipient TECs using recipient HLA. In other words, these T cells are educated to recognize the antigens presented on recipient HLA. Thus, we hypothesized that the graft-versus-tumor effect should be efficiently induced in HLA supertype-matched transplantation because the donor HLA on the donor APC can present similar antigens as recipient HLA in the supertype-matched transplantation (Fig. 4). We believe that HLA-B has a significant prognostic effect because of its high expression level[15] and diversity compared with other loci. HLA-B is thought to be the molecule that has undergone the most change in response to various environments and pathogens and is more diverse by region than HLA-A and HLA-C[39,40]. It may also be more important than other loci for antitumor immunity, given the correlation of HLA-B diversity with endogenous antigen diversity, such as viral genomes in populations [20,39,40], and the importance of HLA-B-binding antigens for antiviral and antitumor immunity[20,41,42].

In this study, an HLA-B supertype mismatch was not associated with the incidence of acute and chronic GVHD, suggesting that grafts with matched HLA-B supertype exhibit antitumor effects without GVHD. We believe that a successful negative selection is the underlying mechanism of these results. Failed negative selection of donor T cells in the thymus has been proven to result in GVHD[43–45]. In allogeneic HSCT, donor dendritic cells engrafted in the recipient's thymus present tissue antigens on donor HLA during negative selection[43,46]. Since dendritic cells reconstituted earlier in CBT than in other donor sources[37], negative selection may continue regardless of the supertype mismatch. The differences in subgroup analysis were more pronounced in first transplantation, young patients, and transplant patients in RIC, possibly because the thymic function is preserved in those patients[29, 47–50]. According to the other subgroup analysis, the prognostic effect of an HLA-B supertype mismatch was mainly emphasized in patients treated with CNI + MTX for GVHD prophylaxis. MTX therapy was reported to be a risk factor for disease recurrence after CBT because of excessive immunosuppression[51]. In this study, MTX therapy was also associated with a low frequency of chronic GVHD independent of an HLA-B supertype mismatch. Collectively, we considered that an HLA-B supertype mismatch and excess immune-suppression by MTX may have increased the relapse rate synergistically.

The major limitations of this study are inherent to its retrospective design and statistical challenges in analyzing multiple endpoints across various HLA class I supertypes. Thus, the significance of the HLA-B supertype must be validated by conducting similar analyses in another cohort. In addition, the reason why the HLA-B supertype was prognostic, instead of other loci, was not clarified in this study. Thus, antigens presented by supertype-matched HLA-B must be identified to elucidate the target of the graft-versus-tumor effect.

In conclusion, we identified an HLA-B supertype mismatch as a poor prognostic factor independent of other patient backgrounds including complications, disease risk, conditioning regimen, and GVHD prophylaxis. We recommend choosing HLA-B supertype-matched donor to enhance a graft-versus-tumor effect in sCBT.

Declarations

Disclosure of Conflicts of Interest: No COI declared.

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Authorship Contributions

TS, NU, KM, SM, and KK designed experiments and wrote the manuscript. TS and NU collected the clinical data. TS, NU, KM, and KK analyzed the data. YO, TE, YM, GY, KY, YK, KN, HI, TK, RO, TM, ST, and KA reviewed the data.

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Tables

Tables 1 to 2 are available in the Supplementary Files section

Figures

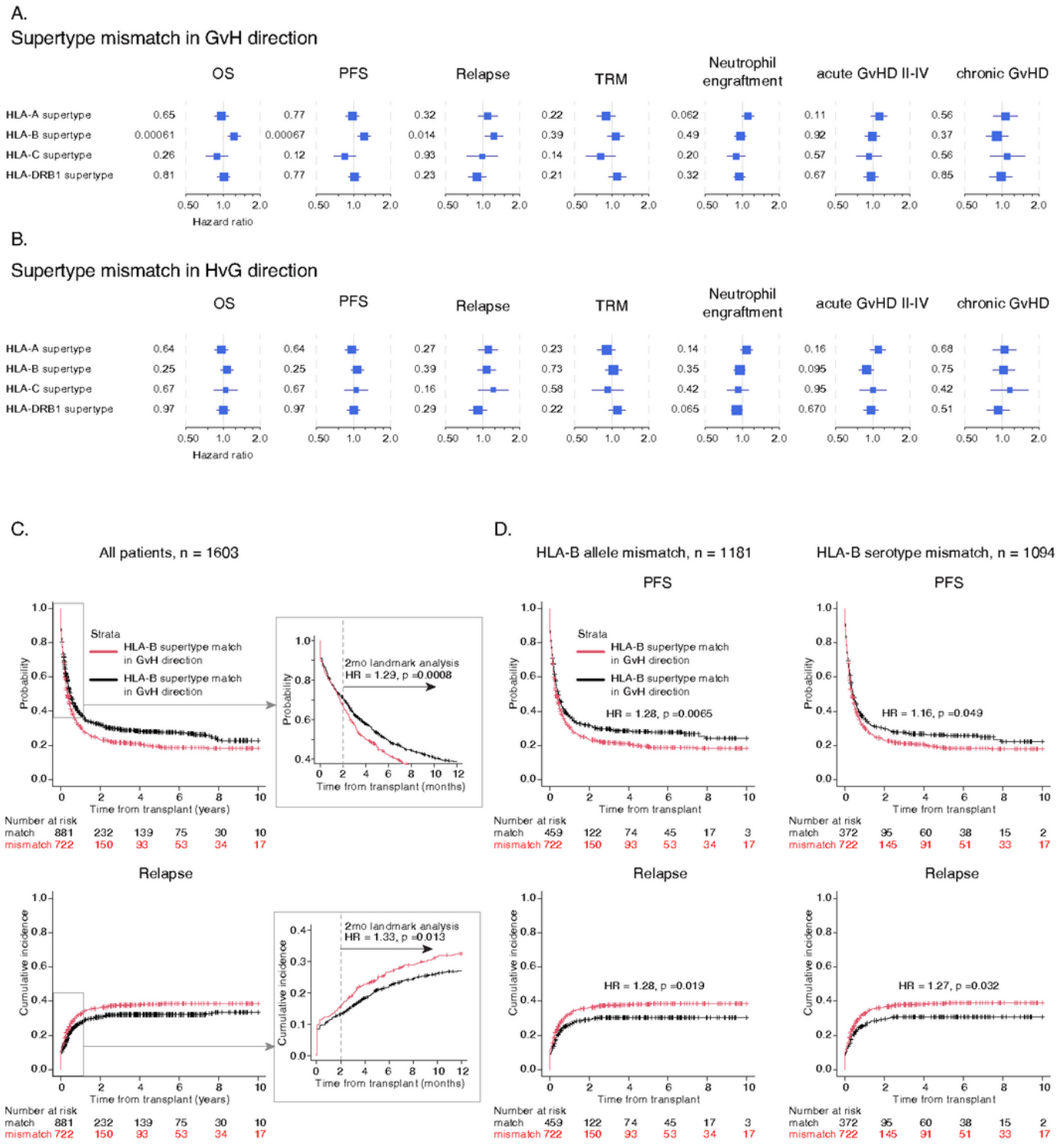

Figure 1

Relationship between post-transplant outcomes and HLA supertype compatibility

A, B. All the graph shows the hazard ratio of HLA supertype-mismatched cases compared with matched cases for each event. The size of the box reflects the number of mismatched patients, and each line shows the 95% confidential interval of the hazard ratio. **A.** Prognostic effect of an HLA supertype mismatch on the graft-versus-host direction. **B.** Prognostic effect of an HLA supertype mismatch on the host-versus-graft direction. **C.** Curves for the PFS and CI of relapse in all patients (left) and enlarged view of the curve within 1 year after transplantation (right). **D.** Curves for PFS and CI of relapse in patients with HLA-B allele mismatch and serotype mismatch. PFS, progression-free survival; CI, cumulative incidence

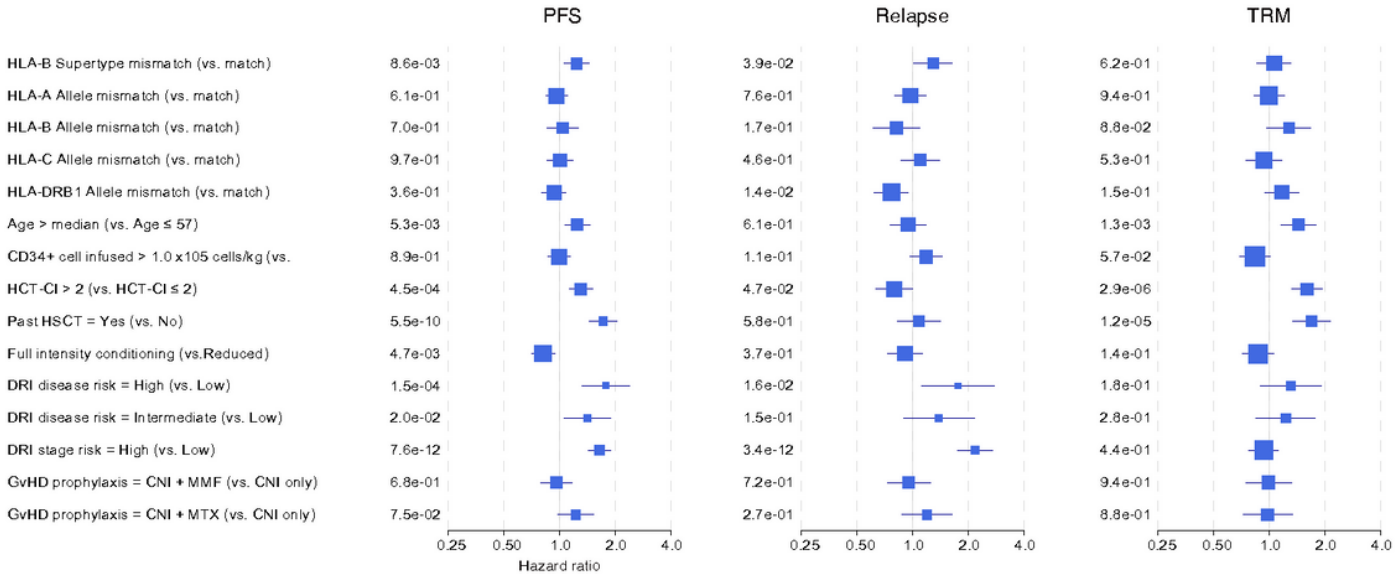

Figure 2

Multivariate analysis

All the graph shows the hazard ratio for each event adjusted by all the conditions in each figure. The size of the box reflects the number of mismatched patients, and each line shows the 95% confidential interval of the hazard ratio.

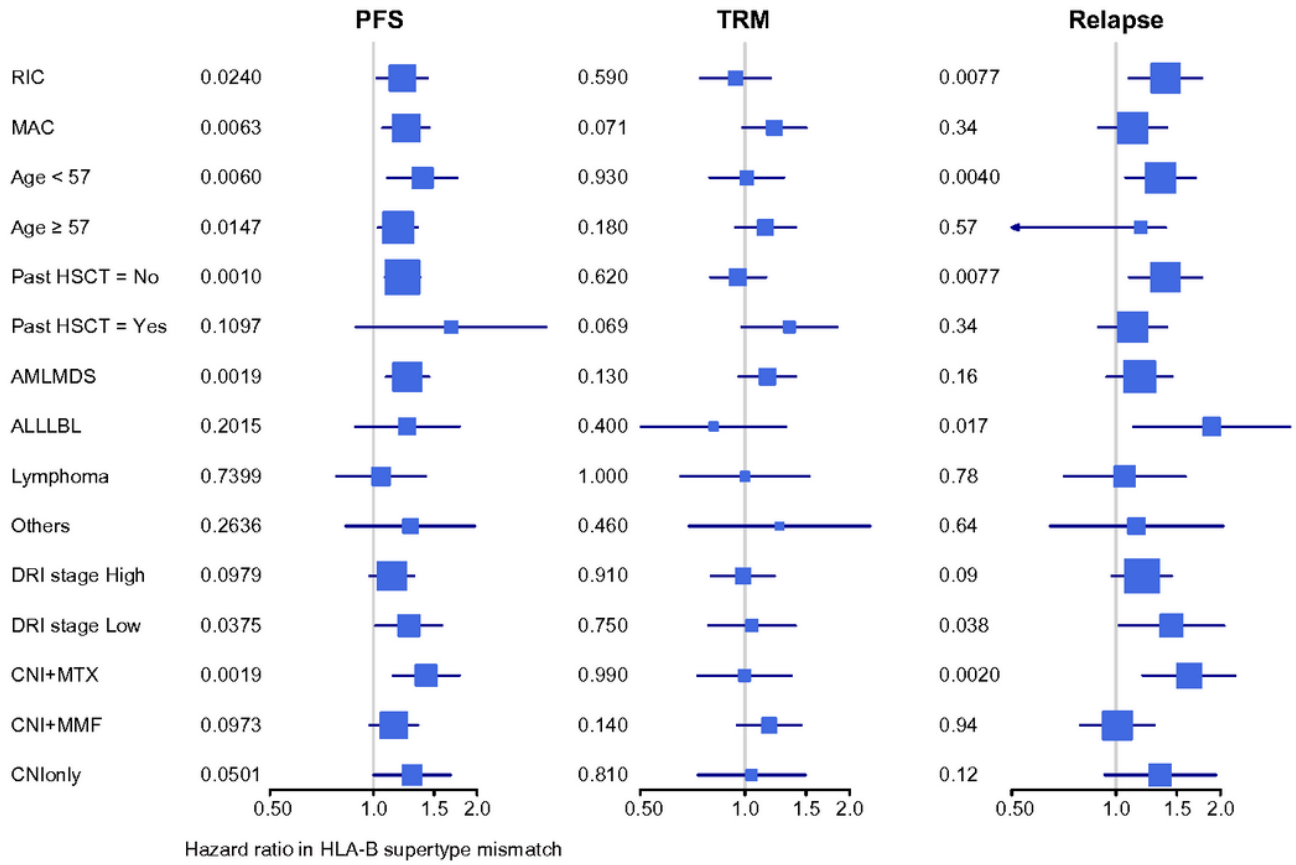

Figure 3

Subgroup analysis

Subgroup analysis of the patients by conditioning regimens, age, number of previous HSCT, diagnosis, disease status at the transplantation, and graft-versus-host disease prophylaxis.

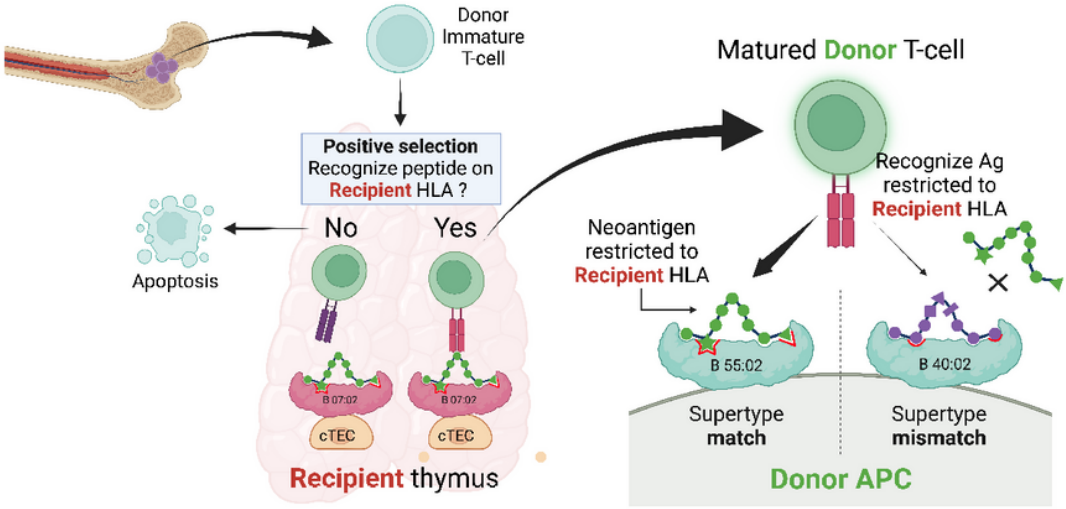

Figure 4

Schema of the effect of supertype matching on the graft-versus-tumor effect

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20230501SupplementalFig.pdf
- Table1.xlsx
- Table2.xlsx