# Haploidentical transplantation has a superior graft-versus-leukemia effect than HLA-matched sibling transplantation for Ph– high-risk B-cell acute lymphoblastic leukemia

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## Abstract

**Background:** Compared with human leukocyte antigen (HLA)-matched sibling donor (MSD) transplantation, it remains unclear whether haploidentical donor (HID) transplantation has a superior graft-versus-leukemia (GVL) effect for Philadelphia-negative (Ph–) high-risk B-cell acute lymphoblastic leukemia (B-ALL). This study aimed to compare the GVL effect between HID and MSD transplantation for Ph– high-risk B-ALL.

**Methods:** This study population came from two prospective multicenter trials (NCT01883180, NCT02673008). Immunosuppressant withdrawal and prophylactic or pre-emptive donor lymphocyte infusion (DLI) were administered in patients without active graft-versus-host disease (GVHD) to prevent relapse. All patients with measurable residual disease (MRD) positivity posttransplantation (post-MRD+) or non-remission (NR) pre-transplantation received prophylactic/pre-emptive interventions. The primary endpoint was the incidence of post-MRD+.

**Results:** A total of 335 patients with Ph– high-risk B-ALL were enrolled, including 145 and 190, respectively, in the HID and MSD groups. The 3-year cumulative incidence of post-MRD+ was 27.2% (95% confidence interval [CI]: 20.2%–34.7%) and 42.6% (35.5%–49.6%) in the HID and MSD groups ($P = 0.003$), respectively. A total of 156 patients received DLI, including 60 (41.4%) and 96 (50.5%), respectively, in the HID and MSD groups ($P = 0.096$). The 3-year cumulative incidence of relapse was 18.6% (95% CI: 12.7%–25.4%) and 25.9% (19.9%–32.3%; $P = 0.116$) in the two groups, respectively. The 3-year overall survival (OS) was 67.4% (95% CI: 59.1%–74.4%) and 61.6% (54.2%–68.1%; $P = 0.382$), leukemia-free survival (LFS) was 63.4% (95% CI: 55.0%–70.7%) and 58.2% (50.8%–64.9%; $P = 0.429$), and GVHD-free/relapse-free survival (GRFS) was 51.7% (95% CI: 43.3%–59.5%) and 37.8% (30.9%–44.6%; $P = 0.041$), respectively, in the HID and MSD groups.

**Conclusion:** HID transplantation has a lower incidence of post-MRD+ than MSD transplantation, suggesting that HID transplantation might have a superior GVL effect than MSD transplantation for Ph– high-risk B-ALL patients.

**Trial registration:** ClinicalTrials.gov: NCT01883180, NCT02673008.

**Keywords:** Haploidentical; HLA-matched sibling; Philadelphia-negative high-risk B-cell acute lymphoblastic leukemia; Graft-versus-leukemia; Transplantation

## Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapeutic option for patients with hematological malignancies and is recommended as the front-line treatment for high-risk adult acute lymphoblastic leukemia (ALL) patients.[1-3] For high-risk patients, timely transplantation is very important. However, the availability of a suitable donor source

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limits its application. With the development of haploidentical transplantation, almost all patients can have rapid access to a suitable donor.[4,5] A growing body of studies has demonstrated that haploidentical donor (HID) transplantation might attain comparable outcomes with human leukocyte antigen (HLA)-matched sibling donor (MSD) or matched unrelated donor (MUD) transplantation.[6-9]

With regard to the graft-versus-leukemia (GVL) effect, some reports from acute myeloid leukemia (AML) have suggested that HID transplantation might have a stronger GVL effect than MSD transplantation, making relapse lower, but data about ALL are lacking, especially for high-risk ALL patients.[10-14] More importantly, these comparisons mainly focused on hematological relapse and did not rule out the effect of pre-emptive treatment for measurable residual disease (MRD) on relapse. The presence of MRD pre- or post-transplantation was an independent predictor of relapse,[15-19] and MRD positivity (MRD+) was found to be positively correlated with relapse post-transplantation.[19-23] Our prospective multicenter cohort study showed that HID transplantation had a lower incidence of MRD+ post-transplantation (post-MRD+) than MSD transplantation for high-risk AML patients, whereas relapse was not different between the two cohorts due to pre-emptive interventions for post-MRD+ patients.[12] In this study, we also chose post-MRD+ as the evaluation point to investigate whether HID transplantation had a superior GVL effect in comparison with MSD transplantation in Philadelphia-negative (Ph–) high-risk B-cell ALL (B-ALL) patients.

## Methods

### Ethical approval

The study was conducted in accordance with the modified *Helsinki Declaration,* and the protocol was approved by the respective ethical review boards before study initiation (No. NFEC-2013–037). Informed consent was obtained from the donors and recipients.

### Study design and patients

The study population came from two prospective multicenter trials (NCT01883180, NCT02673008). Patients undergoing allo-HSCT between June 2013 and October 2018 were selected for this study if the following criteria were met: (i) aged 14 to 65 years, (ii) high-risk B-ALL, (iii) HID or MSD as a donor, and (iv) undergoing first allo-HSCT. Diagnosis of B-ALL was performed by morphologic analysis of bone marrow (BM) specimens along with flow cytometry immunophenotyping by using monoclonal antibodies reactive with B-cell-associated antigens. Patients with B-ALL were classified as high risk if they met one of the following criteria at diagnosis: high white blood cell (WBC) count ($\geq 30 \times 10^9$/L) at diagnosis, delayed first complete remission (CR1, remission required more than two cycles of induction therapy), refractory or non-remission (NR) at transplantation, or high-risk cytogenetic abnormalities according to the National Comprehensive Cancer Network 2012 guidelines, such as hypodiploidy, t(v;11q23) or *MLL* rearranged, or complex karyotype (five or more chromosomal abnormalities).[24] Patients with Ph– positive B-ALL were excluded from the study.

### Conditioning and transplantation

Patients were assigned to undergo HID or MSD transplantation according to donor availability.[25] MSD (6/6 matching HLA-A, -B, and -DR loci) was the first choice for allo-HSCT. If an MSD could not be obtained, subjects without a suitable MUD (>8 of 10 matching HLA-A, -B, -C, -DR, and -DQ loci) were qualified for HID transplantation. Patients in CR received myeloablative conditioning regimen of total body irradiation (TBI, 4.5 Gy/days, –5 days, –4 days), cyclophosphamide (CY, 60 $mg \cdot kg^{-1} \cdot day^{-1}$, –3 days, –2 days), and etoposide (VP-16, 15 $mg \cdot kg^{-1} \cdot day^{-1}$, –3 days, –2 days). Patients in NR received intensified conditioning regimen of fludarabine (Flu, 35 $mg \cdot m^{-2} \cdot day^{-1}$, –10 days to –6 days), cytarabine (Ara-c, 1 $g \cdot m^{-2} \cdot day^{-1}$, –10 days to –6 days), TBI (4.5 Gy/days, –5 days, –4 days), CY (60 $mg \cdot kg^{-1} \cdot day^{-1}$, –3 days, –2 days), and VP-16 (15 $mg \cdot kg^{-1} \cdot day^{-1}$, –3 days, –2 days). Cyclosporin A (CsA) and methotrexate (MTX) were administered in patients undergoing MSD transplantation, and CsA, MTX, mycophenolate, and anti-thymocyte globulin were used in patients undergoing HID transplantation for graft-versus-host disease (GVHD) prophylaxis.[13]

### Surveillance and intervention for MRD

BM samples were analyzed at 1 month, 2 months, 3 months, 4 months, 6 months, 8 months, 10 months, and 12 months within 1-year post-transplantation, then once every 3 months from the 13th to 36th month, and once every 6 months from the 37th to 60th month for the monitoring of morphology and MRD. If MRD was positive, the test was repeated within a week. Subjects were defined as MRD+ if they had two consecutive positive results. MRD was evaluated by eight-color multi-parameter flow cytometry (MFC).[10] A panel of ten antibody combinations that recognized CD10, CD19, CD20, CD34, CD38, CD45, CD58, CD99, CD123, and cTDT was used for MRD detection, and 0.3 million cells per tube were acquired.[26] For patients with leukemia-associated immuno-phenotype (LAIP) markers at diagnosis, MRD was identified as detection of at least two LAIP markers identified at diagnosis. For those without LAIP markers at diagnosis, MRD was identified as a cell population showing deviation from the normal patterns of antigen expression seen on specific cell lineages at specific stages of maturation compared with either normal or regenerating marrow.[12] A lower limit of detection of 0.01% was targeted, and the sensitivity of the MFC was $10^{-4}$.

The strategies for preventing leukemia relapse included immunosuppressant withdrawal and prophylactic or preemptive therapy with donor lymphocyte infusion (DLI). For patients in NR pre-transplantation, immunosuppressant was withdrawn by 10%/week in patients without acute GVHD (aGVHD) by day +30 post-transplantation, and prophylactic DLI was administered on day +90 posttransplantation if patients had no active

GVHD and available donor lymphocytes. Pre-emptive DLI was administered in patients with post-MRD+ from day +60 when patients had no active GVHD and available donor lymphocytes, and it was given monthly until MRD became negative or GVHD occurred or for a total of four times.[27,28] Donor lymphocytes were all obtained from granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells. The CD3+ T-cell count for each prophylactic or pre-emptive DLI was $3.0 \times 10^7$/kg of the recipient weight. Short-term immunosuppressant was used for the prevention of GVHD after DLI.[29]

### Infection prophylaxis

Infection prophylaxis was administered as previously described.[30,31] Oral sulfamethoxazole and norfloxacin were used in all patients. Antifungal agents were administered 5 days pre-transplantation. For patients without a history of invasive fungal infection (IFI), oral fluconazole was used until day +60 post-transplantation. Otherwise, for patients with a history of IFI, antifungal agents for secondary prevention based on response to the initial antifungal therapy were used until day +90 post-transplantation. Patients with Epstein-Barr virus (EBV) or cytomegalovirus (CMV) DNA-emia received pre-emptive therapy.

### Evaluation points and definitions

The primary endpoint was the incidence of post-MRD+. Secondary endpoints included hematopoietic engraftment, GVHD, infections, non-relapse mortality (NRM), relapse, overall survival (OS), leukemia-free survival (LFS), and GVHD-free/relapse-free survival (GRFS). Relapse was defined as reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the BM aspirate or biopsy not attributable to any other cause or reappearance or new appearance of extramedullary leukemia. CR was defined as <5% blasts in the BM and no persistence of extramedullary disease. NR was defined as a failure to obtain CR. NRM was defined as death from any cause not subsequent to relapse. OS was defined as the time from transplantation until death from any cause. LFS was defined as the time from transplantation until relapse or death from any cause. GRFS events were defined as grade III-IV aGVHD, chronic GVHD (cGVHD) requiring systemic immunosuppressive therapy, leukemia relapse, or death from any cause during follow-up after allo-HSCT.[32] Neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count exceeding $0.5 \times 10^9$/L. Platelet engraftment was defined as the first of 3 days with an absolute platelet count exceeding $20 \times 10^9$/L without transfusion support. aGVHD and cGVHD were graded according to the literature.[33,34] Prophylactic and pre-emptive therapies were defined as interventions for MRD-negative and MRD-positive patients without hematologic relapse, respectively.

### Statistical analysis

Analysis was performed on August 31, 2020. The $\chi^2$ test and $t$ test were used for categorical variables and continuous variables, respectively. Post-MRD+, relapse, NRM, engraftment, GVHD, and infections were considered to be competing risks. Competing risk for post-MRD+ was death without post-MRD+. Relapse was a competing risk for NRM, and NRM was a competing risk for relapse. Competing risk for engraftment was death without engraftment, competing risks for GVHD included death without GVHD and relapse, and competing risks for infections included death without infections and relapse. The Fine and Gray model was used for the analysis of endpoints involving competing risks.[35] OS, LFS, and GRFS were estimated using the Kaplan-Meier method and compared using the log-rank test. The corresponding hazard ratio (HR) and 95% confidence interval (CI) were estimated using the Cox proportional hazards model, which was also used for the analysis of risk factors for time-to-event variables. Only variables with $P < 0.10$ in the univariable analysis were included in the multivariable analysis. All statistical tests were two-tailed with a significance level of 0.05. SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and R version 3.3.0 (R Development Core Team, Vienna, Austria) were used for data analysis.

## Results

### Patient and transplant characteristics

There were 335 patients enrolled in this study, including 145 in the HID group and 190 in the MSD group. The median age was 28 (range, 14–59) years. There were 116 patients in CR and 29 in NR at transplantation in the HID group, whereas 148 in CR and 42 in NR in the MSD group. Patient and transplant characteristics are shown in Table 1. Baseline factors were well balanced between the two groups.

### Hematopoietic engraftment and disease response

All patients achieved neutrophil engraftment except for two patients who died of infections (one in the HID and one in the MSD group) and two who died of hepatic veno-occlusive disease (HVOD) in the MSD group. Of the 331 evaluable patients, the median time of neutrophil engraftment was 12 (range, 9–24) days and 11 (range, 9–21) days in the HID and MSD groups ($P = 0.850$), respectively. The 28-day cumulative incidence of neutrophil engraftment was 99.3% (95% CI: 95.2%–99.9%) and 98.4% (95% CI: 95.2%–99.5%), respectively, in the HID and MSD groups ($P = 0.462$). The median time of platelet engraftment was 14 (range, 9–108) days and 12 (range, 8–85) days, respectively, in the HID and MSD groups ($P = 0.959$). The 100-day cumulative incidence of platelet engraftment was similar between HID and MSD groups (94.5% [95% CI: 89.3%–97.2%] *vs.* 97.4% [95% CI: 93.8–98.9%], $P = 0.178$). All the patients achieved CR on day +30 post-transplantation, except four patients who died before neutrophil engraftment.

### MRD and DLI

Up to the last follow-up date, MRD+ was observed in 120 patients after transplantation, including 39 patients in the HID and 81 in the MSD groups. The 3-year cumulative

incidence of post-MRD+ was 27.2% (95% CI: 20.2%–34.7%) and 42.6% (95% CI: 35.5%–49.6%) in the HID and MSD groups, respectively ($P = 0.003$, HR = 0.564, 95% CI: 0.385–0.827) [Figure 1A]. The median time from allo-HSCT to post-MRD+ was 150 (range, 30–733) days and 103 (range, 30–615) days in the two groups, respectively ($P = 0.299$). Multivariable analysis revealed that HID was a protective factor for post-MRD+ ($P = 0.005$, HR = 0.576, 95% CI: 0.393–0.845); NR status pre-transplant was a risk factor for post-MRD+ ($P < 0.001$, HR = 2.064, 95% CI: 1.385–3.076) [Table 2].

According to the above-mentioned DLI strategy, a total of 156 patients received DLI for relapse prevention at a median time of 125 (range, 60–610) days post-transplantation, including 60 (41.4%) patients in the HID and 96 (50.5%) in the MSD groups ($P = 0.096$) [Figure 2]. Forty-two patients received prophylactic DLI (HID, $n = 18$; MSD, $n = 24$) and 114 pre-emptive DLI (HID, $n = 42$; MSD, $n = 72$). The median number of DLI was 1 (range, 1–4) per patient, with no difference between the two groups ($P = 0.975$).

### Graft-versus-host disease

The overall cumulative incidence of grade II-IV aGVHD was 46.2% (95% CI: 37.9%–54.1%) and 47.9% (95% CI: 40.6%–54.8%; $P = 0.771$), and that of grade III-IV aGVHD was 11.7% (95% CI: 7.1%–17.6%) and 14.7% (95% CI: 10.1%–20.2%; $P = 0.509$) in the HID and MSD groups, respectively. Of the 156 patients undergoing DLI, 70 (44.9%) patients developed grade II-IV aGVHD after DLI, including 23 (38.3%) in the HID and 47 (49.0%) in the MSD groups ($P = 0.194$). After ruling out the effects of

**Table 1: Characteristics of patients with HID and MSD of the study.**

| Characteristics | HID group ($n = 145$) | MSD group ($n = 190$) | Statistics | *P* value |
|---|---|---|---|---|
| Age (years) | 26 (14–58) | 29 (14–59) | 1.112* | 0.267 |
| Gender, male/female | 88 (60.7)/57 (39.3) | 120 (63.2)/70 (36.8) | 0.213† | 0.645 |
| WBC count at diagnosis | 35.5 (1.1–517.0) | 19.1 (0.7–699.6) | −1.130* | 0.259 |
| Cytogenetic risk | | | 0.041† | 0.839 |
| Standard risk | 39 (26.9) | 53 (27.9) | | |
| High risk | 106 (73.1) | 137 (72.1) | | |
| Disease status pre-transplant | | | 1.057† | 0.589 |
| CR1 | 99 (68.3) | 120 (63.2) | | |
| ≥CR2 | 17 (11.7) | 28 (14.7) | | |
| NR | 29 (20.0) | 42 (22.1) | | |
| Median MNC per graft ($\times 10^8$/kg) | 8.1 (4.2–12.3) | 7.8 (4.1–12.5) | −2.479* | 0.140 |
| Follow-up time in survivors from transplant (months) | 36.5 (0.1–88.2) | 38.0 (0.3–88.1) | 0.505* | 0.614 |

Data are presented as *n* (%) or median (interquantile range, IQR). * *t* statistic. † $\chi^2$ statistic. CR1: First complete remission; CR2: Second complete remission; HID: Haploidentical donor; MNC: Mononuclear cell; MSD: HLA-matched sibling donor; NR: Non-remission; WBC: White blood count.

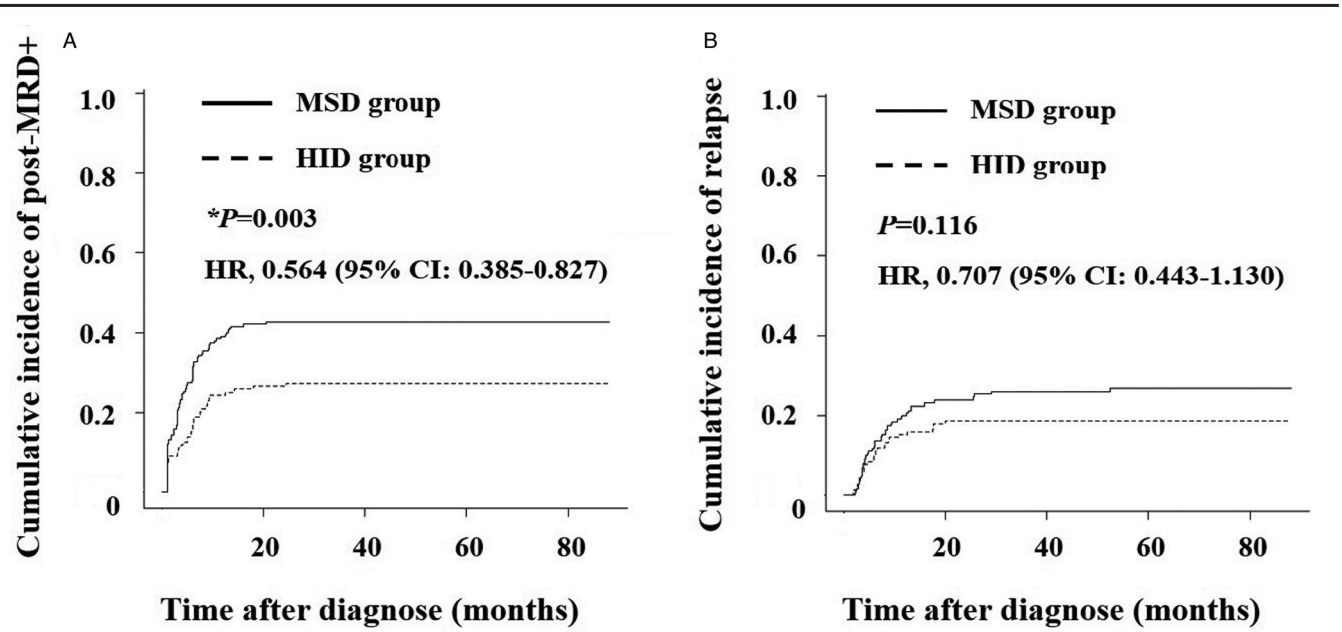


**Figure 1:** Cumulative incidence of post-MRD+ (A) and relapse (B) for all patients. * $P < 0.05$. CI: Confidence interval; HID: Haploidentical donor; HR: Hazard ratio; MRD: Measurable residual disease; MSD: HLA-matched sibling donor; post-MRD+: Measurable residual disease positivity post-transplantation.

**Table 2: Univariable and multivariable analysis for risk factors of MRD+ post-transplantation.**

| Parameters | Univariable *P* value | Multivariable *P* value, HR (95% CI) |
|---|---|---|
| Age, ≥28 years *vs.* <28 years | 0.512 | – |
| Patient gender, female *vs.* male | 0.170 | – |
| WBC count at diagnosis, ≥30 × $10^9$/L *vs.* <30 × $10^9$/L | 0.600 | – |
| Cytogenetic risk, high *vs.* standard risk | 0.162 | – |
| Disease status pre-transplant, NR *vs.* CR | <0.001 | <0.001, 2.064 (1.385–3.076) |
| Transplant modality, HID *vs.* MSD | 0.003 | 0.005, 0.576 (0.393–0.845) |

CI: Confidence interval; CR: Complete remission; HID: Haploidentical donor; HR: Hazard ratio; MRD: Measurable residual disease; MRD+: MRD positivity; MSD: HLA-matched sibling donor; NR: Non-remission; WBC: White blood count.

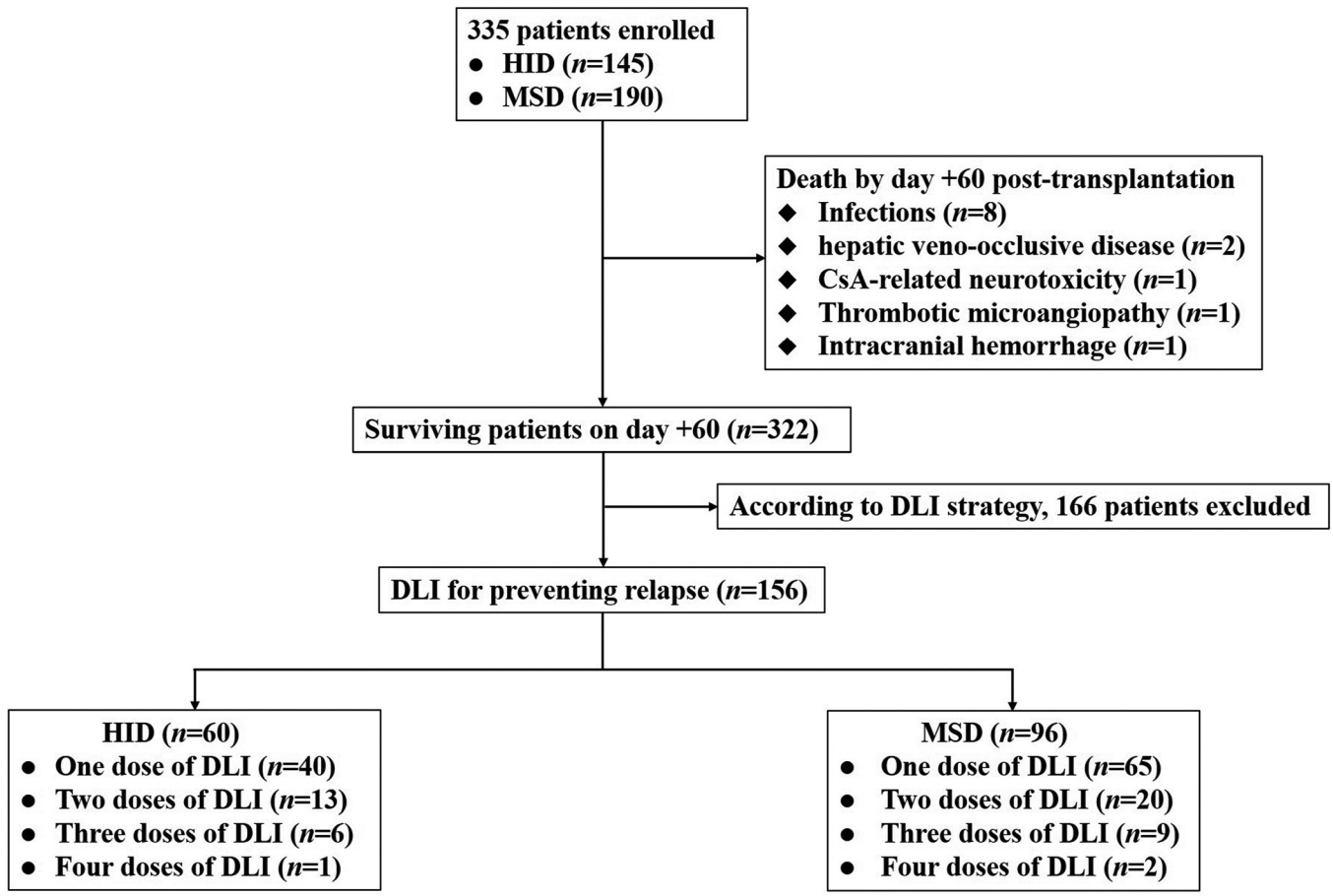


**Figure 2:** Flow diagram. CsA: Cyclosporin A; DLI: Donor lymphocyte Infusion; HID: Haploidentical donor; MSD: HLA-matched sibling donor.

DLI, the incidence of grade II-IV aGVHD by day +100 post-transplantation was 31.8% (95% CI: 24.2%–39.5%) and 23.2% (95% CI: 17.4%–29.4%; $P = 0.019$), and that of grade III-IV aGVHD was 10.3% (95% CI: 6.1%–16.0%) and 8.9% (95% CI: 5.4%–13.5%; $P = 0.617$) in the HID and MSD groups, respectively. Seven patients died of severe aGVHD, including three in the HID and four in the MSD groups.

The 3-year cumulative incidence of overall cGVHD was 46.3% (95% CI: 37.9%–54.2%) and 52.1% (95% CI: 44.7%–59.0%; $P = 0.210$), and extensive cGVHD was 13.1% (95% CI: 8.2%–19.2%) and 19.5% (95%CI: 14.9%–26.6%; $P = 0.105$) in the HID and MSD groups, respectively. Sixty-five (41.7%) patients developed cGVHD after DLI, including 21 (35.0%) in the HID and 44 (45.8%) in the MSD groups ($P = 0.182$). After ruling out the effects of DLI, the cumulative incidence of cGVHD was 33.7% (95% CI: 25.8%–41.8%) and 31.5% (95% CI: 24.7%–38.6%; $P = 0.803$), and extensive cGVHD was 9.8% (95% CI: 5.6%–15.4%) and 9.7% (95%CI: 6.0%–14.5%; $P = 0.965$) in the HID and MSD groups, respectively. Five patients died of extensive cGVHD, including one in the HID and four in the MSD groups.

### Relapse

With a median follow-up of 37.5 (range, 0.1–88.2) months post-transplantation, 27 and 50 patients relapsed in the HID and MSD groups, respectively. The median time of relapse was 5.9 (range, 1.7–19.9) months and 6.1 (range, 2.2–52.4) months post-transplantation in the HID and MSD groups ($P = 0.292$), respectively. The 3-year cumulative incidence of relapse post-transplantation was 18.6% (95% CI: 12.7%–25.4%) and 25.9% (95% CI: 19.9%–32.3%), respectively, in the HID and MSD groups ($P = 0.116$, HR = 0.707, 95% CI: 0.443–1.130) [Figure 1B].

Of the 77 relapsed patients, 15 patients abandoned treatment and 62 received salvage treatment, including 38 patients receiving DLI combined with chemotherapy, 17 receiving chemotherapy alone, 4 receiving chimeric antigen receptor T-cell immunotherapy, and 3 receiving second allo-HSCT. Of the 62 patients undergoing salvage treatment, 40 patients achieved CR and 13 were still alive. The multivariable analysis revealed that cGVHD was a protective factor for relapse ($P = 0.043$, HR = 0.617, 95% CI: 0.387–0.985); post-MRD+ was a risk factor for relapse ($P < 0.001$, HR = 17.218, 95% CI: 8.450–35.083) [Table 3].

### Infections

The 1-year cumulative incidence of EBV-DNAemia was 33.2% (95% CI: 23.0%–42.0%) and 18.6% (95% CI: 11.5%–25.1%; $P = 0.003$) in the HID and MSD groups, respectively. The 2-year cumulative incidence of EBV-associated diseases was 9.5% (95% CI: 5.3%–15.2%) and 5.6% (95% CI: 2.6%–10.2%; $P = 0.095$) in the two groups, respectively. Two patients died of EBV-associated diseases in the HID group, whereas none died in the MSD group. The 1-year cumulative incidence of CMV-DNAemia was 61.0% (95% CI: 49.9%–70.0%) and 42.1% (95% CI: 31.9%–50.9%; $P = 0.001$) in the HID and MSD groups, respectively. The 2-year cumulative incidence of CMV-associated diseases was 7.3% (95% CI: 3.4%–13.3%) and 7.0% (95% CI: 3.6%–12.0%; $P = 0.851$) in the two groups, respectively. Five patients died of CMV-associated diseases, including two in the HID and three in the MSD groups. In total, 43 patients died of infections, including 21 in the HID and 22 in the MSD groups. The 3-year infection-related mortality was 14.5% (95% CI: 9.3%–20.8%) and 12.3% (95% CI: 7.9%–17.8%) in the HID and MSD groups, respectively ($P = 0.394$).

### Survival

At the last follow-up, 215 patients survived, and 120 patients died (47 in the HID and 73 in the MSD groups). Causes of death included relapse ($n = 54$), infections ($n = 43$), GVHD ($n = 12$), intracranial hemorrhage ($n = 4$), heart failure ($n = 2$), thrombotic microangiopathy ($n = 2$), HVOD ($n = 2$), and CsA-related neurotoxicity ($n = 1$) [Table 4]. The 3-year NRM was 18.0% (95% CI: 12.2%–24.7%) and 15.9% (95% CI: 11.1%–21.5%), respectively, in the HID and MSD groups ($P = 0.558$). The 3-year OS was 67.4% (95% CI: 59.1%–74.4%) and 61.6% (95% CI: 54.2%–68.1%), in the HID and MSD groups, respectively ($P = 0.382$, HR = 0.850, 95% CI: 0.589–1.226) [Figure 3A]. The 3-year LFS was 63.4% (95% CI: 55.0%–70.7%) and 58.2% (95% CI: 50.8%–64.9%), respectively, in the HID and MSD groups ($P = 0.429$, HR = 0.870, 95% CI: 0.615–1.231) [Figure 3B]. The 3-year GRFS was 51.7% (95% CI: 43.3%–59.5%) and 37.8% (95% CI: 30.9%–44.6%), respectively, in the two groups ($P = 0.041$, HR = 0.736, 95% CI: 0.548–0.989) [Figure 3C].

Multivariable analysis revealed that cGVHD was the only protective factor for OS and LFS ($P < 0.001$, HR = 0.369, 95% CI: 0.247–0.551; $P < 0.001$, HR = 0.378, 95% CI: 0.259–0.550); post-MRD+, NR status pretransplant and grade II-IV aGVHD were risk factors for OS ($P < 0.001$, HR = 2.055, 95% CI: 1.420–2.973; $P = 0.003$, HR = 1.797, 95% CI: 1.217–2.653; $P = 0.022$, HR = 1.526, 95% CI: 1.064–2.188); post-MRD+ was a risk factor for LFS ($P < 0.001$, HR = 2.483, 95% CI: 1.745–3.533) [Table 3].

**Table 3: Univariable and multivariable analyses for risk factors of relapse, OS, and LFS.**

| | Relapse | | OS | | LFS | |
|---|---|---|---|---|---|---|
| Parameters | Univariable *P* value | Multivariable *P* value, HR (95% CI) | Univariable *P* value | Multivariable *P* value, HR (95% CI) | Univariable *P* value | Multivariable *P* value, HR (95% CI) |
| Age, ≥28 years *vs.* <28 years | 0.435 | – | 0.209 | – | 0.388 | – |
| Gender, female *vs.* male | 0.106 | – | 0.530 | – | 0.392 | – |
| WBC count at diagnosis, ≥30 × $10^9$/L *vs.* <30 × $10^9$/L | 0.285 | – | 0.287 | – | 0.206 | – |
| Cytogenetic risk, high *vs.* standard risk | 0.781 | – | 0.503 | – | 0.365 | – |
| Disease status at transplant, NR *vs.* CR | < 0.001 | 0.477, 1.189 (0.737–1.918) | < 0.001 | 0.003, 1.797 (1.217–2.653) | 0.002 | 0.106, 1.372 (0.936–3.533) |
| MRD status post-transplant, positive *vs.* negative | < 0.001 | <0.001, 17.218 (8.450–35.083) | < 0.001 | <0.001, 2.055 (1.420–2.973) | <0.001 | <0.001, 2.483 (1.745–3.533) |
| Transplant modality, HID *vs.* MSD | 0.092 | 0.642, 0.881 (0.517–1.501) | 0.385 | – | 0.472 | – |
| aGVHD, II-IV *vs.* 0–I | 0.686 | – | 0.038 | 0.022 1.526 (1.064–2.188) | 0.182 | – |
| cGVHD: cGVHD *vs.* no cGVHD | 0.001 | 0.043, 0.617 (0.387–0.985) | <0.001 | <0.001, 0.369 (0.247–0.551) | <0.001 | <0.001, 0.378 (0.259–0.550) |
| DLI *vs.* No DLI | 0.108 | – | 0.617 | – | 0.195 | – |

aGVHD: Acute graft-versus-host disease; cGVHD: Chronic graft-versus-host disease; CI: Confidence interval; CR: Complete remission; DLI: Donor lymphocyte infusion; GVHD: Graft-versus-host disease; HID: Haploidentical donor; HR: Hazard ratio; LFS: Leukemia-free survival; MRD: Measurable residual disease; MSD: HLA-matched sibling donor; NR: Non-remission; OS: Overall survival; WBC: White blood count.

**Table 4: Causes of death post-transplantation.**

| Causes of death | HID group ($n = 145$) | MSD group ($n = 190$) | Statistics | *P* value |
|---|---|---|---|---|
| Relapse | 17 (11.7) | 37 (19.5) | 3.653† | 0.056 |
| GVHD-related | 4 (2.8) | 8 (4.2) | 0.502† | 0.479 |
| aGVHD | 3 (2.1) | 4 (2.1) | 0.001† | 1.000 |
| cGVHD | 1 (0.7) | 4 (2.1) | 1.121† | 0.394 |
| Infections* | 21 (14.5) | 22 (11.6) | 0.620† | 0.431 |
| Intracranial hemorrhage, | 2 (1.4) | 2 (1.1) | 0.074† | 1.000 |
| Thrombotic microangiopathy | 2 (1.4) | 0 | 2.636† | 0.187 |
| Heart failure | 0 | 2 (1.1) | 1.535† | 0.508 |
| HVOD | 0 | 2 (1.1) | 1.535† | 0.508 |
| CsA-related neurotoxicity | 1 (0.7) | 0 | 1.314† | 0.433 |

Data are presented as *n* (%). * Included the patient who died of EBV-associated disease. † $\chi^2$ statistic. aGVHD: Acute graft-versus-host disease; cGVHD: Chronic graft-versus-host disease; CsA: Cyclosporin A; EBV: Epstein-Barr virus; GVHD: Graft-versus-host disease; HID: Haploidentical donor; HVOD: Hepatic veno-occlusive disease; MSD: HLA-matched sibling donor.

## Discussion

To identify whether HID transplantation has a superior GVL effect than MSD transplantation for Ph– high-risk BALL patients, we analyzed the data from two prospective multicenter trials. Our results showed that HID transplantation was associated with a lower incidence of post-MRD + compared with MSD transplantation, suggesting that HID transplantation might exert a superior GVL effect in comparison with MSD transplantation in Ph– high-risk BALL patients.

Leukemia relapse remains the major cause of transplant failure. Multiple factors may affect relapse, such as donor sources, underlying primary disease, transplant strategy, disease status at transplantation, and pre- or post-MRD status.[9,10,13,19] Now it remains unknown whether HID transplantation might have a stronger GVL effect than MSD transplantation, especially for ALL patients. Some studies showed that the relapse rate of ALL patients undergoing HID transplantation was similar to that of MSD transplantation.[9,13,14] Recently, Chang *et al*[36] conducted a prospective randomized study, and the findings suggested that HID transplantation was superior to MSD transplantation in regard to favorable anti-leukemia activity for ALL patients with MRD+ pre-transplantation. However, most studies comparing the GVL effect of HID and MSD transplantation were based on hematological relapse. Emerging evidence has suggested that MRD post-transplantation is an important indicator of relapse, and pre-emptive interventions based on MRD status can reduce relapse.[23,37-39] Therefore, in this study, post-MRD+ was used as the primary endpoint to compare the GVL effect between HID and MSD transplantation, and patients with post-MRD+ received pre-emptive DLI. Our results showed that the incidence of post-MRD+ in the HID group was lower than that of the MSD group (27.2% *vs.* 42.6%), and relapse was similar between the two groups (18.6% *vs.* 25.9%). These results were similar to our previous result in high-risk AML patients.[12] Based on these findings, we suggested that HID transplantation might have a stronger GVL effect than MSD transplantation in Ph– high-risk B-ALL patients. The potential mechanism underlying the stronger GVL effect of HID transplantation is still unclear. Guo *et al*[40] reported that HID transplantation had stronger anti-leukemia activity than MSD transplantation in both mouse models and clinical cohorts, probably due to the enhanced function of T cell and natural killer cells. The specific mechanism requires further exploration.

Although the incidence of post-MRD+ in the HID group was lower than that of the MSD group, the OS and LFS were similar between the two groups, with the 3-year OS and LFS of 67.4% and 63.4% in the HID group compared with 61.6% and 58.2% in the MSD group, respectively. A reasonable explanation for our results was that the post-MRD+ patients received pre-emptive interventions, which reduced relapse. This finding might also be related to the insufficient sample size and the fact that the HID group had a relatively higher NRM than the MSD group. Additionally, we found that the HID group had improved GRFS compared with the MSD group.

To prevent relapse after transplantation, post-transplantation interventions, including prophylactic or pre-emptive therapy hav3 received extensive attention in recent years.[13,27,36-38] Withdrawal of immune suppression, DLI, cytokines, and targeted therapies are utilized as prophylactic or pre-emptive interventions.[23,41-43] Multiple studies have shown that pre-emptive DLI based on MRD status and prophylactic DLI for high-risk patients has shown good efficacy in reducing relapse after allo-HSCT.[23,44,45] In this study, prophylactic DLI was administered to patients in NR pre-transplantation, and pre-emptive DLI was administered to patients with post-MRD+. Our results showed that the 3-year incidence of relapse post-transplantation was 18.6% and 25.9% in the HID and MSD groups, respectively, which was consistent with our previous studies.[13,27,36] The results once again demonstrated that prophylactic or pre-emptive therapy with DLI after transplantation could reduce relapse. Nonetheless, multivariable analysis revealed that post-MRD+ was a risk factor for relapse, suggesting that preemptive interventions could not completely overcome the negative effect of post-MRD+ on relapse. The means to completely overcome the negative effect of post-MRD+ on transplantation needs further research.

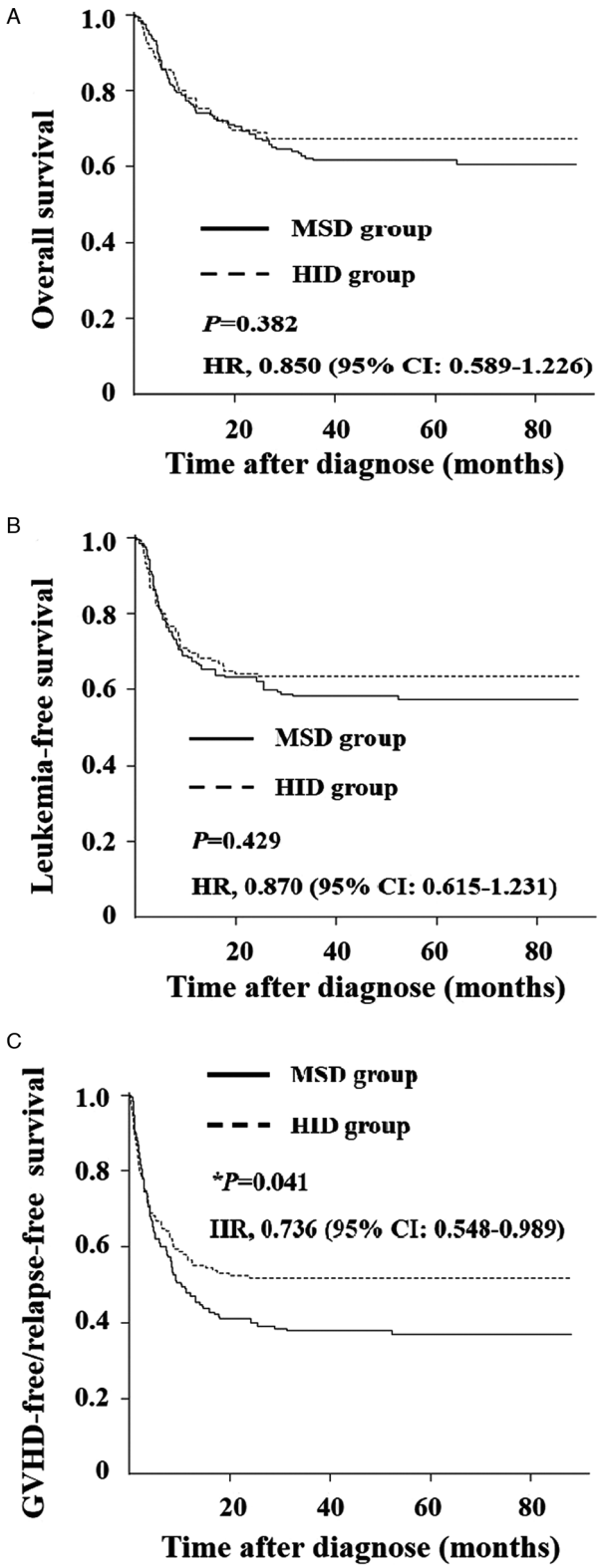


**Figure 3:** Cumulative incidence of overall survival (A), leukemia-free survival (B), and graft-versus-host disease-free/relapse-free survival (C) for all patients. $P < 0.05$. CI: Confidence interval; GVHD: Graft-versus-host disease; HID: Haploidentical donor; HR: Hazard ratio; MSD: HLA-matched sibling donor.

The main obstacle to successful HID transplantation is the high incidence and mortality of GVHD compared with the MSD transplantation. In recent years, great progress has been made in prophylaxis for GVHD in HID transplantation.[6,46,47] A growing body of research has suggested that HID and MSD transplantation have similar incidence and mortality of GVHD.[9,13,36,48] In the present study, after ruling out the effects of DLI, the incidence of grade II-IV aGVHD was higher in the HID group, whereas the incidences of severe aGVHD and cGVHD were similar between the HID and MSD groups, which was consistent with our previous results.[9,1] However, the incidences of overall aGVHD and cGVHD did not differ between the two groups. These results might be attributed to the fact that more patients in the MSD group received DLI.

Another concern in the HID transplantation is the high incidence and mortality of infection after transplantation, due to the use of strong immunosuppressive agents to prevent GVHD. In this study, the HID group had higher incidences of EBV-DNAemia and CMV-DNAemia than the MSD group, whereas there were no differences in the incidences of EBV- and CMV-associated diseases or infection-related mortality between the two groups, which might be attributed to the rich experience in infection management at the study centers.

Our study had a few limitations. First, the differences in post-MRD positivity between the two treatment groups provided indirect evidence of the strength of the GVL effect. Second, since testing to identify Ph– like ALL was not routine during the research period, Ph– like B-ALL patients were not enrolled in this study.

In conclusion, HID transplantation has a lower incidence of post-MRD+ than MSD transplantation, suggesting that HID transplantation might have a superior GVL effect than MSD transplantation for Ph– high-risk B-ALL patients. HID transplantation should be recommended as one of the optimal choices for Ph– high-risk B-ALL patients.

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## Conflicts of interest

None.

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