A Prospective Trial Comparing Haploidentical Donor Transplantation With Cord Blood Versus HLA-Matched Sibling Donor Transplantation for Hematologic Malignancy Patients

Wenyi Lu¹,², Xin Jin³, Hairong Lyu¹,², Xue Bai¹,², Haibo Zhu¹,², Xin Li¹,², Xia Xiao¹,², Juana Xia Meng¹,², Ting Yuan¹,², Qing Li¹,², Juan Mu¹,², Cuicui Lyu¹,², Yili Jiang¹,², Yunxiong Wei¹, Xia Xiong¹, Meng Zhang¹, and Mingfeng Zhao¹,²

Abstract
Although haploidentical donor (HID) hematopoietic stem cell transplantation (HSCT) has achieved similar survival to HLA-identical sibling donor (ISD) transplantation, the delayed hematopoietic engraftment as well as higher incidence of graft-versus-host-disease (GVHD), results in prolonged hospitalization, higher costs, and increased morbidity. In this study, a prospective, non-randomized clinical study was designed to evaluate the outcomes of patients who underwent HID HSCT supported by cord blood or ISD HSCT. Between May 2017 and November 2020, 113 patients were enrolled to undergo HID HSCT supported by cord blood (n=88) or ISD HSCT (n=25). The cumulative incidence of neutrophil and platelet engraftment at 30 days was comparable in these two groups. Importantly, there was no significant difference in the cumulative incidence of grade II-IV aGVHD at 100 days (20.5% [95% confidence interval [CI]: 12.2%–28.8%] versus 12.0% [95% CI: 0.2%–23.8%], P = 0.32) and cGVHD at 1 year (19.5% [95% CI: 11.2%–27.8%] versus 16.6% [95% CI: 1.3%–31.9%] P = 0.70) between the two groups. Among the HID and ISD groups, the 2-year disease free survival was 76.8 and 80.0% (P = 0.83), the 2-year overall survival was 82.4 and 88.0% (P = 0.66), the 2-year GVHD-free, relapse-free survival was 68.9 and 75.3% (P = 0.62), respectively. Our results indicate that HID transplantation supported by cord blood may offer a good alternative to ISD HSCT for patients with hematopoietic malignancies. **Trial registration:** Effect of co-infusion third party umbilical cord blood stem cells on haploidentical hematopoietic stem cell transplantation [https://www.chictr.org.cn Reg. No. ChiCTR-OIN-17011426].

Keywords
haploidentical donor, hematopoietic stem cell transplantation, cord blood, HLA-identical sibling donor, graft-versus-host disease

Introduction
Allogeneic hematopoietic stem cell transplantation (HSCT) from a sibling donor is the preferred first choice of treatment for patients with hematopoietic malignancies. Unfortunately, only <30% patients have HLA-matched siblings. This is especially true in China, where the one-child policy has been implemented during the past three decades. Haploidentical donor (HID) transplantation provides an appealing option for patients who lack matched donors or require urgent transplantation. Furthermore, HID transplantation exhibits a stronger graft-versus-leukemia effect compared to HLA-identical sibling donor (ISD) transplantation¹. Chang et al demonstrated that HID transplantation is superior to ISD transplantation for eradicating pre-transplantation MRD². Although several studies have reported that HID transplantation achieved a similar survival to ISD transplantation, the

¹ Department of Hematology, Tianjin First Central Hospital, Tianjin, PR China
² Nankai University Affiliated First Central Hospital, Tianjin, PR, China
³ School of Medicine, Nankai University, Tianjin, PR China

Submitted: April 17, 2021. Revised: November 29, 2021. Accepted: January 10, 2022.

Corresponding Author:
Mingfeng Zhao, Department of Hematology, Tianjin First Central Hospital, No. 24 Fu Kang Road, Tianjin, 300192, China.
Email: mingfengzhao@sina.com
delayed platelet engraftment, a high incidence of graft-versus-host-disease (GVHD), and non-relapse mortality (NRM) remain major problems after HID transplantation. Cord blood as an alternative source of stem cells, has advantages of low incidences of GVHD and good graft-versus-leukemia activity. To balance the potential benefits of the greater alloimmunity with the concern for increased in GVHD, some recent studies have combined haploidentical transplantation with third-party cord blood cells. This transplantation model could result in rapid engraftment, low incidences of GVHD, and relapse in patients with hematological malignancy. Our group recently published a retrospective study that demonstrated that HID transplantation supported by cord blood resulted in a lower risk of relapse and prolonged progressive free survival compared with HLA-matched unrelated donor transplantation. However, it is still unknown that whether HID HSCT supported by cord blood would be a good alternative to ISD HSCT for patients with hematopoietic malignancies. In this study, the outcome of HID HSCT supported by cord blood is prospectively compared with ISD HSCT.

**Subjects and Methods**

**Study Design**

A prospective non-randomized trial was conducted from May 2017 to November 2020. Patients were enrolled to undergo HID HSCT supported by cord blood (n = 88) or ISD HSCT (n = 25) according to donor availability. The primary end points were disease free survival (DFS) and NRM. Secondary end points were the incidence of aGVHD, the incidence of cGVHD, relapse rates, hematopoietic engraftment, and overall survival (OS). The cutoff date was November 25, 2021. This clinical trial was registered to www.chictr.org as ChiCTR-OIN-17011426.

**Eligibility Criteria**

The eligible patients ranged in age from 15 to 65 years with hematopoietic malignancies including acute myeloid leukemia, acute lymphoblastic leukemia (ALL), chronic leukemia, high-grade lymphoma, and high-risk myelodysplastic syndromes. All of the patients had transplantation indications and had received a myeloablative conditioning regimen. This study was approved by the Institutional Research and Ethics Committee of Tianjin First Central Hospital. It was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all of the patients or their legal guardians.

**Donor Selection**

If an HLA-ISD was unavailable, patients without an HLA-matched unrelated donor or whose disease state left insufficient time for an unrelated donor search were eligible for HID transplantation.

**Procedure**

High-resolution HLA typing was used for HLA-A, B, C, DRB1, and DQB1 to select donors. Donor peripheral blood stem cells were mobilized using G-CSF (5 μg/kg/day) for 5 days. In the HID group, the haploidentical stem cells were infused into the recipient on day 1 and cord blood on day 2. Cord blood units were selected based on the HLA typing and cell count. Cord blood and recipient were matched for 4–5/6 HLA loci and the minimum cell count was 1 × 10^7/kg nucleated cells.

The conditioning therapy for the HID group was as follows: For patients with myeloblastic and hybrid malignancies, Busulfan was given at a total dose of 8 mg/kg divided on days 9 to 7, anti-thymocyte globulin (ATG-F) at 4 mg/kg on days -7 to -4, cyclophosphamide at 40 mg/kg on days -6 and -5, fludarabine at 30 mg/m² on days -4 to -2, cytarabine at 4 g/m² day on days -4 to -2. For ALL patients, fractionated total body irradiation(TBI) was given at a dose of 8–10 Gy, cyclophosphamide at 40 mg/kg on days -7 and -6, ATG-F at 4 mg/kg on days -7 to -4, fludarabine at 30 mg/m² on days -4 to -2, and cytarabine at 4 g/m² on days -4 to -2.

The conditioning therapy for the ISD group was as follows: For patients with myeloblastic malignancies, Busulfan was given at a total dose of 8 mg/kg divided on days -9 to -7, cyclophosphamide at 40 mg/kg on days -6 and -5, fludarabine at 30 mg/m² on days -4 to -2, cytarabine at 4 g/m² day on days -4 to -2. For ALL patients, fractionated TBI was given at a dose of 8–10 Gy, cyclophosphamide at 40 mg/kg on days -7 and -6, fludarabine at 30 mg/m² on days -4 to -2, and cytarabine at 4 g/m² on days -4 to -2.

**GVHD Prophylaxis**

The GVHD prophylaxis consisted of cyclosporineA, mycophenolate mofetil, and methotrexate. Cyclosporine A initiated on day -4 at a dose of 2.5 mg/kg/d as a continuous infusion. The dose was adjusted to a serum level of 200–250 ng/ml. Mycophenolate mofetil was given at 500 mg twice per day from day-5 until day +30. Moreover, methotrexate was administered at 15 mg/m² on day +1 and 10 mg/m² on days +3, +6, and +11 posttransplant.

**Supportive Care**

All patients received levofloxacin (200 mg twice per day) and albendazole before conditioning. Prophylactic posaconazole, acyclovir was administered during the conditioning and immunosuppressive period. Trimethoprim/sulfamethoxazole was given at 0.96 g twice per day from 1 week before conditioning until three months after stopping immunosuppressive drugs.
**Post-Transplantation Evaluations**

The remission status and chimerism were evaluated every 2 weeks during the first month and every month thereafter. The chimerism analysis was conducted using multiplex polymerase chain reaction (PCR) amplification of short tandem repeat as previously described\(^\text{10}\). Both peripheral blood and bone marrow chimerism studies were included. Cytomegalovirus (CMV) and EBV DNA were also detected every 1- or 2-weeks using PCR. aGVHD and cGVHD was scored based on the published criteria\(^\text{11,12}\).

**Statistical Analysis**

Categorical variables were compared using X\(^2\) testing and the continuous variables were tested using t tests. The incidence of engraftment, GVHD, relapse, and NRM were estimated using the cumulative incidence estimates to accommodate competing risks. DFS, OS and GVHD-free, relapse-free survival (GRFS) were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to perform the multivariate analysis. A \(P\)-value less than 0.05 was considered statistically significant. R software (version3.1.2; http://www.r-project.org) and SPSS 19.0 (Chicago, IL, USA) were used for the statistical analyses.

**Results**

**Patients and Graft Characteristics**

Between May 2017 and November 2020, 113 patients were enrolled to undergo HID HSCT supported by cord blood \((n = 88)\) or ISD HSCT \((n = 25)\). The characteristics of the patients and donors prior to transplantation are summarized in Table 1. The baseline characteristics in the two groups were matched. The median follow-up periods for the surviving patients were 925 days \((\text{range: 265–1667 days})\) in the HID group and 840 days \((\text{range: 301–1688 days})\) in the ISD group.

The median counts of donor derived mononuclear cells in the HID group and the ISD group were \(6.2 \times 10^6/\text{kg} \) \((\text{range: 1.8–13.0})\) and \(6.8 \times 10^6/\text{kg} \) \((\text{range: 2.8–12.9})\). The median counts of donor derived CD34\(^+\) cells in the HID group and the ISD group were \(4.5 \times 10^6/\text{kg} \) \((\text{range: 1.9–9.5})\) and \(4.1 \times 10^6/\text{kg} \) \((\text{range: 1.4–9.6})\), respectively. The infused mononuclear cell of the unrelated cord blood in the HID group was \(1.5 \times 10^7/\text{kg} \) and the infused CD34\(^+\) cells of the cord blood was \(0.5 \times 10^5/\text{kg} \).

**Hematopoietic Recovery and Engraftment**

At 30 days after transplantation, 97.6\% of the surviving patients \((83/85)\) in the HID group achieved full haploidentical chimerism. Among them, nine patients showed cord blood microchimerism on day +14 \((1.1\%, \text{range: 0.2–4.9})\), but this was superseded rapidly by stable engraftment of HID cells after day +30 \((0\%, \text{range: 0.0%–4.8})\). Only one patient had sustained detectable cord blood microchimerism until six months after transplantation. There are three patients died within 30 days after transplantation, one died due to infection at day +8, one died due to hepatic failure at day +24 and another died due to heart failure at day +18. Except for the three patients who died early due to transplant-related mortality, all achieved neutrophil engraftment at 30 days after transplantation, with a median time to engraftment of 12 days \((\text{range: 10–30, } P = 0.98, \text{Figure 1})\). The cumulative incidence of platelet engraftment at 30 days was 92.0\% \((95\% \text{ confidence interval [CI]: 86.2%–97.9\%}, \text{Figure 1})\), with a median time to engraftment of 15 days \((\text{range: 8–62})\).

In the ISD group, 100\% of the surviving patients \((25/25)\) achieved full donor chimerism on day +30. The cumulative incidence of neutrophil engraftment in the surviving patients at 30 days was also 100\%, with a median time to engraftment of 12 days \((\text{range: 11–22})\). The cumulative incidence of platelet engraftment at 30 days was 84.0\% \((95\% \text{ CI: 68.6%–99.4})\), with a median time to engraftment of 15 days \((\text{range: 9–34})\).

**Immune Recovery of T Cells**

We further investigate the immune reconstitution after transplantation in HID and ISD group \((\text{Figure 2})\). At 3 months after transplantation, the proportion of CD4\(^+\) T cells in HID group were significantly lower than of ISD group and comparable by 6 months after transplantation. However, the absolute number of the CD4\(^+\) T cells between the two groups were comparable. Furthermore, the proportion and absolute number of CD3\(^+\) T cells and CD8\(^+\) T cells in HID group was higher than that of ISD group at 6 months after transplantation, which indicated the cytotoxic T lymphocytes were expanded in HID group.

**GVHD**

At day 100 after transplantation, the cumulative incidence of aGVHD \((\text{grades II-IV})\) was 20.5\% \((95\% \text{ CI: 12.2%–28.8})\) in the HID group versus 12.0\% \((95\% \text{ CI: 0.2%–23.8})\) in the ISD group \((P = 0.32, \text{Figure3})\). Grades III-IV aGVHD was present in four patients in the HID group and one patient in the ISD group. The cumulative incidence of cGVHD at 1 year in the HID group was 19.5\% \((95\% \text{ CI: 11.2–27.8})\), which was comparable to the ISD group at 16.6\% \((95\% \text{ CI: 1.3%–31.9\%}, \text{Figure 3})\).

The variable which may influence the outcomes of transplantation was included in the COX model analysis. The included variables were donor type \((\text{HID vs ISD})\), disease \((\text{ALL vs AML/MDS})\), age \((>40\text{y vs ≤40y})\) and CIBMTR-DRI score. Backward elimination was used to identify
### Table 1. Patient Characteristics.

|                           | HID with cord blood | ISD | P value |
|---------------------------|--------------------|-----|---------|
| Total patients            | 88                 | 25  |         |
| Median age, y (range)     | 31.5 (15–64)       | 38  (17–63) | 0.052   |
| Male/female               | 57/31              | 13/12| 0.246   |
| Diagnosis                 |                    |     | 0.483   |
| AML/MDS                   | 43                 | 16  |         |
| CR1                       | 26                 | 11  |         |
| CR2                       | 3                  | 4   |         |
| Other                     | 14                 | 1   |         |
| ALL                       | 33                 | 6   |         |
| CR1                       | 23                 | 5   |         |
| CR2                       | 8                  | 1   |         |
| Other                     | 2                  | 0   |         |
| HAL                       | 2                  | 0   |         |
| CR1                       | 1                  | 0   |         |
| CR2                       | 1                  | 0   |         |
| Other                     | 10                 | 3   |         |
| Cytogenetic characteristic|                    |     | 0.583   |
| Normal                    | 46                 | 11  |         |
| t(8;21)                   | 3                  | 1   |         |
| -5/5q                      | 3                  | 0   |         |
| -7/7q                      | 2                  | 0   |         |
| i(8)                      | 2                  | 1   |         |
| Complex cytogenetic aberrations | 5     | 3   |         |
| Ph                        | 7                  | 1   |         |
| Others                    | 11                 | 2   |         |
| Unavailable                | 9                  | 6   |         |
| Molecular characteristic  |                    |     | 0.501   |
| Normal                    | 16                 | 4   |         |
| TP53                      | 7                  | 0   |         |
| FLT3-ITD                  | 9                  | 3   |         |
| MLL                       | 4                  | 3   |         |
| C-KIT                     | 4                  | 1   |         |
| CEBPA                     | 4                  | 3   |         |
| BCR-ABL                   | 8                  | 4   |         |
| Others                    | 20                 | 4   |         |
| Unavailable                | 16                 | 3   |         |
| CIBMTR-DRI               |                    |     | 0.146   |
| Low                       | 2                  | 3   |         |
| Intermediate              | 57                 | 17  |         |
| High                      | 25                 | 4   |         |
| Very high                 | 4                  | 1   |         |
| Conditioning regimens     |                    |     |         |
| AML/MDS                   | Bu/Flu/Cy/Ara-C/ATG | Bu/Flu/Cy/Ara-C |         |
| ALL                       | TBI/Flu/Cy/Ara/ATG  | TBI/Flu/Cy/Ara-C |         |
| HAL                       | Bu/Flu/Cy/Ara-C/ATG |     |         |
| MNC (×10^6/kg)            | 6.2 (1.8–13.0)     | 6.8 (2.8–12.9) | 0.117   |
| CD34^+ (×10^6/kg)         | 4.5 (1.9–9.5)      | 4.1 (1.4–9.6) | 0.179   |
| Sex mismatch              | 35                 | 10  | 0.984   |
| ABO mismatch (Haplo or ISD)|                    |     | 0.480   |
| Major                     | 17                 | 7   |         |
| Minor                     | 14                 | 5   |         |
| Major and minor           | 5                  | 0   |         |
| Match                     | 52                 | 13  |         |
| HLA compatibility         |                    |     | 0.00    |
| Haplo HLA match           |                    |     |         |
| 5/10                      | 66                 | 0   |         |
| 6/10                      | 12                 | 0   |         |
| 7/10                      | 7                  | 0   |         |
| 8/10                      | 3                  | 0   |         |
| ISD HLA match             |                    |     |         |
| 10/10                     | 0                  | 25  |         |
| CB MNC cells (×10^7/kg)   | 1.5 (0.8–2.7)      |     |         |
| CB CD34^+ cells (×10^5/kg)| 0.5 (0.08–1.6)     |     |         |

HID: haploidentical donor; ISD: identical sibling donor; AML/MDS: acute myeloid leukemia/myelodysplastic syndromes; ALL: acute lymphoblastic leukemia; CR: complete remission; HAL: hybrid acute leukemia; CEBPA: CCAAT enhancer binding protein alpha; FLT3-ITD: FMS-like tyrosine kinase-3 internal tandem duplication; CIBMTR-DRI: Center for International Blood and Marrow Transplantation Research-disease risk index; MNC: mononuclear cell; HLA: human leukocyte antigen; CB: cord blood; TBI: total body irradiation; ATG: anti-thymocyte globulin.
covariates that influenced outcomes. According to the multivariate analysis (Table 2), there was no significant difference in the risk of grades II-IV aGVHD (hazard ratio [HR] = 1.875; 95% CI = 0.552–6.365; \( P = 0.314 \)) and cGVHD (HR = 1.280; 95% CI: 0.404–4.056; \( P = 0.675 \)) in the HID group relative to the ISD group.

**Infections**

By 1-year post HSCT, the HID group had a comparable incidence of CMV viremia (HID group 18.2% vs. ISD group 8%, \( P = 0.22 \)) and EBV viremia (HID group 3.4% vs. ISD group 4.0%, \( P = 0.89 \)) compared with ISD group. Furthermore, there was no statistical significance in the

---

**Figure 1.** The hematopoietic engraftment after transplantation in the HID group and the ISD group. (A) cumulative incidence of neutrophil engraftment, and (B) cumulative incidence of platelet engraftment. HID: haploidentical donor, ISD: identical sibling donor.

**Figure 2.** The proportion (A) and absolute number (B) of T cells after transplantation in the HID group and the ISD group. HID: haploidentical donor, ISD: identical sibling donor.
incidence of probable and proven fungal infection (HID group 13.6% vs. ISD group 8.0%, \(P = 0.45\)).

**NRM, Causes of Deaths and Relapse**

The cumulative incidence curves are shown in Figure 4. The 2-year cumulative incidence of NRM in the HID group and the ISD group was 10.2% (95% CI: 2.6%–17.8%) and 8.0% (95% CI: 0.1%–15.9%, \(P = 0.64\)), respectively. In the HID group, non-relapse deaths were due to infection in three patient, cGVHD in two patients, hemorrhage in three patients, and toxicity in two patients. In the ISD group, non-relapse deaths were due to infection in one patient and hemorrhage in one patient. The 2-year cumulative incidence of relapse in the HID group was 14.2% (95% CI: 6.8%–21.5%), which is comparable to the ISD group 12.0% (95% CI: 0.3%–23.7%, \(P = 0.71\)). The multivariate analysis showed significant differences in relapse rates and the DFS between the different CIBMTR-DRI scores. However, there was no statistical difference in the relapse risk between the donor types (HR = 0.720; 95% CI: 0.194–2.675; \(P = 0.623\), Table 2).

**Survival**

The OS at two years was 82.4% (95% CI: 73.8%–91.0%) for the HID group and 88.0% (95% CI: 76.2%–99.8%) for the ISD group (\(P = 0.66\), Figure 5). The 2-year DFS for the HID patients was 76.8% (95% CI: 67.8%–85.8%), compared with 80.0% (95% CI: 64.3%–95.7%) for ISD patients (\(P = 0.83\), Figure 5). Furthermore, the 2-year GRFS for the HID patients was 68.9% (95% CI: 59.1%–78.7%), compared with 75.3% (95% CI: 58.1%–92.5%) for ISD patients (\(P = 0.62\), Figure 5). According to the multivariate analysis (Table 2), no difference in OS (HR = 0.892; 95% CI: 0.246–3.236; \(P = 0.862\)), DFS (HR = 0.818; 95% CI: 0.296–2.262; \(P = 0.699\)) and GRFS (HR = 1.058; 95% CI: 0.428–2.619; \(P = 0.903\)) was seen in the HID with cord blood group relative to the ISD transplants.

**Discussion**

With the wide use of reduced-intensity conditioning, post-transplantation cyclophosphamide, ATG, and better supportive therapy, the survival of haploidentical transplantation has been largely improved. However, the delayed hematopoietic engraftment and high incidence of GVHD still remain significant challenges. In this prospective study, haploidentical transplantation was combined with cord blood, and it was found that it could achieve similar outcomes compared with ISD transplantation.

NRM is a significant cause of treatment failure after HID HSCT. According to the data during 2011–2015 from the European society of Blood and Marrow Transplantation, the NRM was higher with haplo-identical donor transplantation compared with ISD transplantations. In this study, the 2-year NRM rate in the HID group was 10.2%, which was similar to contemporaneous patients undergoing ISD transplantation.
These data were comparable with previous studies about HID transplantation supplied with cord blood5. However, the cumulative incidence of NRM in this study was similar to some studies using the HID graft alone3. Several factors may contribute to the hidden advantages. First, the maximum age of these patients was older than in the other studies. Second, the proportion of patients with high-risk features and high HCT-CI scores was also higher. These characteristics may have been attributed to the higher NRM rate of both of the two groups in this study. Third, the composition of the disease entities was different from previous studies, which made it hard to compare these results with other studies.

Several studies have reported that HID transplantation combined with third-party cord blood cells could result in rapid engraftment, low incidences of GVHD and disease relapse5,7,13–16. In our past experience, the cumulative incidences of II-IV aGVHD and cGVHD in HID HSCT alone were 33.3% and 40%, respectively, which was higher than HID transplantation supported by cord blood10. In this analysis, the incidence of grades II-IV aGVHD in haploidentical transplantation combined with cord blood was 20.5%, which was also lower compared with historical data of HID HSCT alone. It was also lower than the reported results of haploidentical transplantation with post-transplantation cyclophosphamide or ATG17. Some studies revealed that patients receiving HID transplantation have a slower hematopoietic engraftment, higher incidence of aGVHD and inferior survival compared to ISD transplantation18. In our study, by

| Table 2. Multivariate Analysis Results. |
|----------------------------------------|
| **Outcome point** | **HR** | **95% CI** | **P** |
|-------------------|--------|------------|-------|
| **Acute GVHD**    |        |            |       |
| Donor: HID vs ISD | 1.875  | 0.552–6.365| 0.314 |
| Disease: ALL vs. AML/MDS | 0.346 | 0.114–1.047| 0.060 |
| Age: >40y vs.≤40y | 0.636  | 0.253–1.603| 0.338 |
| CIBMTR-DRI        | 1.221  | 0.597–1.603| 0.585 |
| **Chronic GVHD**  |        |            |       |
| Donor: HID vs ISD | 1.280  | 0.404–4.056| 0.675 |
| Disease: ALL vs. AML/MDS | 1.116 | 0.417–2.984| 0.828 |
| Age: >40y vs.≤40y | 1.271  | 0.536–3.018| 0.586 |
| CIBMTR-DRI        | 0.819  | 0.400–1.678| 0.586 |
| **NRM**           |        |            |       |
| Donor: HID vs ISD | 1.108  | 0.233–5.258| 0.898 |
| Disease: ALL vs. AML/MDS | 4.349 | 1.068–17.714| 0.040 |
| Age: >40y vs.≤40y | 4.469  | 1.376–14.519| 0.013 |
| CIBMTR-DRI        | 1.149  | 0.408–3.234| 0.792 |
| **Relapse**       |        |            |       |
| Donor: HID vs ISD | 0.720  | 0.194–2.675| 0.623 |
| Disease: ALL vs. AML/MDS | 0.777 | 0.189–3.194| 0.726 |
| Age: >40y vs.≤40y | 0.493  | 0.157–1.547| 0.226 |
| CIBMTR-DRI        | 2.949  | 1.528–5.692| 0.001 |
| **OS**            |        |            |       |
| Donor: HID vs ISD | 0.892  | 0.246–3.236| 0.862 |
| Disease: ALL vs. AML/MDS | 1.958 | 0.618–6.200| 0.253 |
| Age: >40y vs.≤40y | 2.649  | 0.974–7.200| 0.056 |
| CIBMTR-DRI        | 1.743  | 0.807–3.765| 0.157 |
| **DFS**           |        |            |       |
| Donor: HID vs ISD | 0.818  | 0.296–2.262| 0.699 |
| Disease: ALL vs. AML/MDS | 1.336 | 0.486–3.668| 0.574 |
| Age: >40y vs.≤40y | 1.114  | 0.475–2.612| 0.805 |
| CIBMTR-DRI        | 2.114  | 1.156–3.865| 0.015 |
| **GRFS**          |        |            |       |
| Donor: HID vs ISD | 1.058  | 0.428–2.619| 0.903 |
| Disease: ALL vs. AML/MDS | 0.807 | 0.337–1.932| 0.630 |
| Age: >40y vs.≤40y | 1.453  | 0.719–2.938| 0.298 |
| CIBMTR-DRI        | 1.653  | 0.970–2.818| 0.065 |

CI: confidence interval; GVHD: graft-versus-host-disease; HID: haploidentical donor; ISD: identical sibling donor; NRM: non-relapse mortality; OS: overall survival; DFS: disease free survival; GRFS: GVHD-free, relapse-free survival; AML/MDS: acute myeloid leukemia/myelodysplastic syndromes; CIBMTR-DRI: Center for International Blood and Marrow Transplantation Research-disease risk index.
combination of haploidentical and cord blood graft, the incidence of aGVHD was similar to the ISD transplantation. A possible mechanism may have been the higher proportion of T regulatory cells in cord blood, which may reduce the immune response. From another perspective, the main composition of T cells in cord blood is naïve T cells, which may also lead to a superior graft-versus-leukemia effect. Our previous work found that HID transplantation combined with cord blood resulted in a lower relapse rate and favorable progressive free survival compared to HLA-identical unrelated donor transplantation. In this study, no statistical significance was found for the relapse rate or the DFS between the HID and ISD groups. This may have been due to the short follow-up time, small sample size, and disease heterogeneity.

In this study, all of the patients in the HID group finally achieved haploidentical engraftment. This result was different with cord blood transplantation combined with haploidentical CD34+ cells, which had sustained cord blood engraftment\(^{19,20}\). Several factors likely contributed to the different outcomes. First, the amount of infused cord cells in this study was lower than in the cord blood transplantation. Second, the infused haploidentical cells in the cord blood transplantation was CD34 selected. The lack of haplo-identical T cells may have led to an engraftment failure of the haploidentical cells. In our study, there are nine patients who had a minority fraction of cord blood chimerism after HID transplantation. It seemed that the infused CD34 dose from haploidentical donor, the infused dose of cord blood cells and the degree of HLA matching between the haplo-graft and the host may contribute to the pattern of engraftment\(^{21,22}\). However, we did not find a significant difference of infused donor cell dose, the degree of HLA matching between the nine patients and other patients. It should also be noted that none of the nine patients relapsed and only one suffered grade II-IV aGVHD after transplantation. It seemed that cord blood microchimerism may induce immune tolerance, which decreased the incidence of aGVHD without compromising graft-versus-leukemia effect.

It has been shown that the incidence of infection after HID HSCT is higher than HLA-matched transplantation due to the delayed immunologic reconstitution\(^{23,24}\). The higher incidence of infection increases the mortality rate, days of hospitalization and extra costs. By combination of cord blood with HID transplantation, we found that the incidence of infection in HID transplantation was similar to ISD transplantation. The rapid hematopoietic recovery and immunologic reconstitution might contribute to the favorable outcome. Moreover, other complications after transplantation were also comparable between the two groups, such as hepatic veno-occlusive disease, diffuse alveolar hemorrhage, periengraftment respiratory distress syndrome, kidney injury, and so on.

The main limitation of this study was the non-randomized design and small sample size, which was due to the ethical and practical reasons. The availability of a matched donor might have minimized this limitation to some extent. Furthermore, the imbalanced factors were adjusted using a

Figure 4. Comparisons of outcomes between the HID group and the ISD group. (A) cumulative incidence of NRM, (B) cumulative incidence of relapse. HID: haploidentical donor, ISD: identical sibling donor, NRM: non-relapse mortality.
multivariate analysis. However, the influence of imbalanced factors on outcomes between the two cohorts cannot be totally eliminated. Thus, a large-scale, multicenter, prospective, randomized study is needed. The other important limitation was the unequal sample size between the two group. As the one-child policy was carried out in China in the past three decades, the number of patients who can find an ISD in China was less than that in other countries. On the contrary, it is easy to find an eligible HID. Thus, the number of patients in HID group in our study was higher than that in ISD group. When trying to infer from experience in previous studies of ISD transplantation, we found that the disease entities in our study was different from those studies\textsuperscript{8,26,27}. Therefore, it is unsuitable to compare our studies with those studies. However, in our study, the baseline characteristics between the two group were not significantly different. Furthermore, we have adjusted the imbalanced factors by multivariate analysis. These efforts may minimize the imbalance between the two groups.

In summary, this study indicated that haploidentical transplantation combined with cord blood could result in similar outcomes compared with ISD transplantation. Thus, it is a
good alternative to ISD transplantation for patients with hematopoietic malignancies. Further large-scale, randomized, multicenter clinical trials should be to conducted to confirm the findings.

Acknowledgments
We thank patients for their participation in our clinical trials.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from the National Natural Sciences Foundation of China (81970180, 81800105), Tianjin Municipal Science and Technology Key Support Program (20YFZCSY00800), Tianjin Key Natural Science Foundation (17JCZDJC35800), as well as Tianjin First Central Hospital (CM201807). This work was also funded by Tianjin Key Medical Discipline (Specialty) Construction Project.

Ethical Approval
This study was approved by the Institutional Research and Ethics Committee of Tianjin First Central Hospital.

Statement of Human Rights
This study was approved by the Institutional Research and Ethics Committee of Tianjin First Central Hospital. It was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all of the patients or their legal guardians.

Statement of Informed Consent
Informed consent was obtained from all of the patients or their legal guardians.

ORCID iD
Wenyi Lu https://orcid.org/0000-0002-3975-6636

Reference
1. Shouval R, Fein JA, Labopin M, Kroger N, Duarte RF, Bader P, Chabannon C, Kuball J, Basak GW, Dufour C, Galimard JE, et al. Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis. Lancet Haematol 2019;6(11):e573–84.

2. Chang YJ, Wang Y, Liu YR, Xu LP, Zhang YW, Lan SY, et al. Haploidentical allograft is superior to matched sibling donor allograft in eradicating pretransplantation minimal residual disease of AML patients as determined by multiparameter flow cytometry: a retrospective and prospective analysis. J Hematol Oncol 2017;10(1):134.

3. Wang Y, Liu QF, Xu LP, Liu KY, Zhang XH, Ma X, Fan ZP, Wu DP, Huang XJ. Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study. Blood 2015;125(25):3956–62.

4. Orfali N, van Besien K. Combining haplo-identical and cord blood stem cells grafts—might the whole be greater than the sum of its parts? Leuk Lymphoma 2020;61(4):753–56.

5. Chen J, Wang RX, Chen F, Sun AN, Qiu HY, Jin ZM, Tang XW, Han Y, Fu ZZ, He GS, Miao M, et al. Combination of a haploidentical SCT with an unrelated cord blood unit: a single-arm prospective study. Bone Marrow Transplant 2014;49(2):206–11.

6. Liu L, Zhang Y, Jiao W, Zhou H, Wang Q, Qiu H, Tang X, Han Y, Fu C, Jin Z, Chen S, et al. Combination of haploidentical haematopoietic stem cell transplantation with an unrelated cord-blood unit in patients with severe aplastic anemia: a report of 146 cases. Bone Marrow Transplant 2020;55:2017–25.

7. Huang J, Arzt A, Mayer SA, Guarner D, Bishop MR, Reich-Slotky R, Smith SM, Greenberg J, Kline J, Ferrante R, Phillips AA, et al. Combined haploidentical and umbilical cord blood allogeneic stem cell transplantation for high-risk lymphoma and chronic lymphocytic leukemia. Biol Blood Marrow Transplant 2018;24(2):359–65.

8. Ke P, Bao XB, Hu XH, Zhuang J, Wu XJ, Liu Y, Ye XF, Wu DP, Xue SL, Ma X. Myeloablative conditioning regimens with combined of haploidentical and cord blood transplantation for myelodysplastic syndrome patients. Bone Marrow Transplant 2018;53(2):162–68.

9. Xu J, Zhao R, Yang L, Gong H, Ma S, Chen J, Liu H, Shen H, Zhu M, Chen S, Ma X, et al. Haploidentical stem cells combined with a small dose of umbilical cord blood transplantation exert similar survival outcome of HLA-matched stem cells transplantation in T-cell acute lymphoblastic leukemia. Bone Marrow Transplant 2020;55:1197–99.

10. Lyu H, Lu W, Yao J, Xiao X, Li Q, Wang J, Mu J, Qi Y, Zhu H, Jiang Y, Li X, et al. Comparison of outcomes of haploidentical donor hematopoietic stem cell transplantation supported by third-party cord blood with HLA-matched unrelated donor transplantation. Leuk Lymphoma 2020;61(4):840–47.

11. Thomas ED, Storb R, Clift RA, Fefer A, Johnson L, Neiman PE, Lerner KG, Glucksberg H, Buckner CD. Bone-marrow transplantation (second of two parts). N Engl J Med 1975;292(17):895–902.

12. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, Hackman R, Tsoi MS, Storb R, Thomas ED. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 1980;69(2):204–17.

13. van Besien K, Koshy N, Gergis U, Mayer S, Cushing M, Rennert H, Reich-Slotky R, Mark T, Pearse R, Rossi A, et al. Cord blood chimerism and relapse after haplo-cord transplantation. Leuk Lymphoma 2017;58(2):288–97.

14. Kwon M, Bautista G, Balsalobre P, Sanchez-Ortega I, Montesinos P, Bermudez A, de Laiglesia A, Herrera P, Martin C, Humala K, Zabalza A, et al. Haplo-Cord transplantation compared to haploidentical transplantation with post-transplant cyclophosphamide in patients with AML. Bone Marrow Transplant 2017;52(8):1138–43.
15. Kwon M, Bautista G, Balsalobre P, Sanchez-Ortega I, Serrano D, Anguita J, Buno I, Forés R, Regidor C, García Marco JA, Vilches C, et al. Haplo-cord transplantation using CD34+ cells from a third-party donor to speed engraftment in high-risk patients with hematologic disorders. Biol Blood Marrow Transplant 2014;20(12):2015–22.

16. Liu H, Rich ES, Godley L, Odenike O, Joseph L, Marino S, Kline J, Nguyen V, Cunningham J, Larson RA, del Cerro P, et al. Reduced-intensity conditioning with combined haploidentical and cord blood transplantation results in rapid engraftment, low GVHD, and durable remissions. Blood 2011;118(24):4384–45.

17. Bashey A, Zhang X, Sizemore CA, Manion K, Brown S, Holland HK, Morris LE, Solomon SR. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. J Clin Oncol 2013;31(10):1310–16.

18. Chen D, Zhou D, Guo D, Xu P, Chen B. Comparison of outcomes in hematological malignancies treated with haploidentical or HLA-identical sibling hematopoietic stem cell transplantation following myeloablative conditioning: a meta-analysis. PLoS One 2018;13(1):e0191955.

19. Politikos I, Devlin SM, Arcila ME, Barone JC, Malion MA, Naputo KA, Ruiz JD, Mazis CM, Scaradavou A, Aveccia ST, Dahi B, et al. Engraftment kinetics after transplantation of double unit cord blood grafts combined with haplo-identical CD34+ cells without antithymocyte globulin. Leukemia 2020;35:850–62.

20. van Besien K, Artz A, Champlin RE, Guarneri D, Bishop MR, Chen J, Gergis U, Shore T, Liu H, Rondon G, Mayer SA, et al. Haploidentical vs haplo-cord transplant in adults under 60 years receiving fludarabine and melphalan conditioning. Blood Adv 2019;3(12):1858–867.

21. van Besien K, Koshy N, Gergis U, Mayer S, Cushing M, Rennert H, Reich-Slotky R, Mark T, Pearse R, Rossi A, Phillips A, et al. Haplo-cord transplant: HLA-matching determines graft dominance. Leuk Lymphoma 2017;58(6):1512–14.

22. Tsai SB, Liu H, Shore T, Fan Y, Bishop M, Cushing MM, Gergis U, Godley L, Kline J, Larson RA, Martinez G, et al. Frequency and risk factors associated with cord graft failure after transplant with single-unit umbilical cord cells supplemented by haploidentical cells with reduced-intensity conditioning. Biol Blood Marrow Transplant 2016;22(6):1065–72.

23. Yu S, Huang F, Fan Z, Xuan L, Nie D, Xu Y, Yang T, Wang S, Jiang Z, Xu N, Lin R, et al. Haploidentical versus HLA-matched sibling transplantation for refractory acute leukemia undergoing sequential intensified conditioning followed by DLI: an analysis from two prospective data. J Hematol Oncol 2020;13(1):18.

24. Huang J, Huang F, Fan Z, Xu N, Xuan L, Liu H, Shi P, Jiang L, Zhang Y, Sun J, Liu Q. Haploidentical related donor vs matched sibling donor allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia and myelodysplastic syndrome aged over 50 years: a single-center retrospective study. Cancer Med 2020;9(17):6244–55.

25. Tischer J, Engel N, Fritsch S, Prevalsek D, Hubmann M, Schulz C, Zoellner AK, Bucklein V, Reibke R, Mumm F, Rieger CT, et al. Virus infection in HLA-haploidentical hematopoietic stem cell transplantation: incidence in the context of immune recovery in two different transplantation settings. Ann Hematol 2015;94(10):1677–88.

26. Ottinger HD, Ferencik S, Beelen DW, Lindemann M, Peceny R, Elmaagaci AH, Husing J, Grosse-Wilde H. Hematopoietic stem cell transplantation: contrasting the outcome of transplantations from HLA-identical siblings, partially HLA-mismatched related donors, and HLA-matched unrelated donors. Blood 2003;102(3):1131–37.

27. Wang Y, Liu DH, Xu LP, Liu KY, Chen H, Chen YH, Han W, Shi HX, Huang XJ. Superior graft-versus-leukemia effect associated with transplantation of haploidentical compared with HLA-identical sibling donor grafts for high-risk acute leukemia: an historic comparison. Biol Blood Marrow Transplant 2011;17(6):821–30.