Haploidentical- versus identical-sibling transplant for high-risk pediatric AML: A multi-center study

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Abstract
Background: Human leukocyte antigen-identical sibling donor (ISD)-hematopoietic stem cell transplantation (SCT) is a potentially curative treatment for high-risk pediatric acute myeloid leukemia (AML). A haploidentical donor (HID) is readily available to almost all children. Previous studies have demonstrated that patients with HID-SCT had similar outcomes compared to ISD-SCT for pediatric and adult AML. However, the role of HID-SCT in high-risk pediatric AML is unclear.

Methods: To compare the overall survival of high-risk AML children who underwent either HID-SCT or ISD-SCT, we analyzed 179 cases of high-risk AML patients under 18 years of age treated with either ISD-SCT (n = 23) or HID-SCT (n = 156). Granulocyte colony-stimulating factor plus anti-thymocyte globulin-based regimens were used for HID-SCT. We also analyzed the subgroup data of AML patients at first complete remission (CR1) before SCT with known cytogenetic risk.

Results: The numbers of adverse cytogenetic risk recipients were 8 (34.8%) and 13 (18.8%) in the ISD-SCT group and the HID-SCT group, and the number of patients with disease status beyond CR1 were 6 (26.1%) and 14 (20.3%) in the two groups. The cumulative rates of grades II-IV acute graft-versus-host disease (GVHD) were 13.0% in the ISD-SCT group and 34.8% in the HID-SCT group (P = 0.062), with a
1 | BACKGROUND

The survival of pediatric acute myeloid leukemia (AML) has been increased up to 60%--70% after using more intensive chemotherapy and better supportive care [1-3]. Allogeneic hematopoietic stem cell transplantation (SCT) is a potentially curative treatment for high-risk or chemotherapy-refractory AML [4]. Although a human leukocyte antigen (HLA)-identical sibling donor (ISD) would be the first-line of choice for SCT, for patients lacking a suitable ISD, the haploidentical donor (HID)-SCT may represent a valid alternative option. HID-SCT has advantages such as rapid and universal availability as well as the ability to provide additional donor cells when needed for subsequent adoptive immunotherapies. Over the past decade, great progress has been made in the use of HID-SCT which has led to improvements in patients survival and increase in the number of HID-SCT procedures. According to a report from the European Society for Blood and Marrow Transplantation [5], the number of HID-SCT procedures grew by 291% from 2005 to 2015. The three most commonly used strategies are the granulocyte colony-stimulating factor (G-CSF) and anti-human thymocyte globulin (ATG)-based protocol [6], the post-transplantation cyclophosphamide (PT/Cy)-based protocol [7], and the T-cell depletion protocol [8]. HID-SCT could be employed in the absence of an ISD or for those in urgent need of a transplant.

Liu et al. [9] reported a five-year overall survival (OS) rate of 73.3% with acceptable non-relapse mortality of 12.6% in pediatric AML patients who underwent T cell replete HID-SCT. Recently, investigators have compared HID-SCT and HLA-matched SCT in adult AML. Bashey et al. [10] reported comparable results between PT/Cy-based HID-SCT and HLA-matched SCT, where the three-year OS, disease-free survival (DFS), non-relapse mortality and cumulative rates of relapse in the HID-SCT and the HLA-matched SCT were 67% and 62%, 58% and 51%, 9% and 17%, and 33% and 32%, respectively. Another promising result reported by Wang et al. [11] showed that HID-SCT with a G-CSF and ATG-based protocol achieved outcomes similar to those of ISD-SCT for adult AML patients in their first complete remission (CR1), where the three-year OS, DFS, non-relapse mortality, and relapse rates in the HID-SCT and ISD-SCT groups were 79% and 82%, 74% and 78%, 13% and 8%, 15% and 15%, respectively. However, previous studies either included both AML and acute lymphoblastic leukemia or high-risk and standard-risk AML [9, 12], as such data comparing HID-SCT with ISD-SCT in children with high-risk AML are lacking.

Herein, we performed a multi-center retrospective matched-pair study to compare the survival outcomes between high-risk AML children who underwent either unmanipulated HID-SCT or ISD-SCT at three large Chinese SCT centers.
FIGURE 1 Protocol of conditioning regimen for pediatric AML patients who underwent ISD-SCT or HID-SCT (A). Transplantation protocol for HID-SCT: Ara-C (4 g/m²/d) on days –10 to –9; Bu (3.2 mg/kg/d) on days –8 to –6; CTX (1.8 g/m²/d) on days –5 to –4; M-CCNU (250 mg/m²) on day –3; and ATG (2.5 mg/kg/d) on days –5 to –2. (B). Donor and stem cell harvesting: All donors received G-CSF (5 μg/kg/d) on days –3 to transplantation day. (C). Transplantation protocol for ISD-SCT: Bu (80 mg/kg) on day –10; Ara-C (2 g/m²/d) on day –9; Bu (3.2 mg/kg/d) on days –8 to –6; CTX (1.8 g/m²/d) on days –5 to –4; M-CCNU (250 mg/m²) on day –3. All recipients received G-CSF-mobilized, fresh, and unmanipulated bone marrow cells plus peripheral blood stem cells or peripheral blood stem cells alone. The GVHD prophylaxis plan included ATG, CSA, MMF and short-term MTX [39].

Abbreviations: /d, per day; SCT, stem cell transplantation; ISD, identical sibling donor; HID, haploidentical donor; Ara-C, cytarabine; Bu, busulfan; CTX, cyclophosphamide; M-CCNU, simustine; Hu, hydroxycarbamide; ATG, anti-human thymocyte globulin; G-CSF, granulocyte colony-stimulating factor; GVHD, graft-versus-host-disease; CSA, cyclosporine A; MMF, mycophenolate mofetil; MTX, methotrexate; BM, bone marrow; PB, peripheral blood.

one-year OS (56.8% vs. 73.0%) and higher one-year non-relapse mortality (35.1% vs. 18.0%). Furthermore, high-risk patients usually had insufficient time to wait for an unrelated matched donor (URD); thus, the proportions of both URD-SCT and CB-SCT cases were small in our centers. Therefore, we ruled out URD-SCT and CB-SCT cases. Patients aged 1-18 years who underwent transplant between January 1, 2013 and January 11, 2017 were enrolled in this study. Each SCT procedure took place in one of the following three transplantation centers: the Department of Bone Marrow Transplantation, Peking University People’s Hospital (Beijing, China); Department of Hematology, Xinqiao Hospital, Army Military Medical University (Chongqing, China); or Department of Pediatrics, Nanfang Hospital, Southern Medical University (Guangzhou, China). HLA-ISD was the first choice for SCT donors. If HLA-ISD was unavailable, HIDs were deemed eligible for the patients. The last follow-up date was December 1, 2018. The study protocol was approved by the ethics committee at each local institution. Informed consent was obtained from all the patients’ guardians.

2.2 | Transplant regimen

The treatment protocol is shown in Figure 1. The conditioning regimens for HID-SCT were as follows: cytarabine (Ara-C, 4 g/m²/d, intravenous infusion, Pfizer Pharmaceuticals Ltd., New York, USA) on days –10 (defined as 10 days before transplantation day) to –9; busulfan (Bu, 3.2 mg/kg/d, intravenous infusion, Otsuka Pharmaceutical Co. Ltd., Naruto, Tokushima, Japan) on days –8 to –6; cyclophosphamide (CTX, 1.8 g/m²/d, intravenous infusion, Baxter Oncology GmbH, Frankfurt, Hesse-Darmstadt, Germany) on days –5 to –4; simustine (M-CCNU, 250 mg/m², oral administration, ZheJiang Ruixin Pharmaceutical Co. Ltd., Lishui, Zhejiang, China) on day –3; and rabbit thymoglobulin (ATG, 2.5 mg/kg/d, intravenous infusion, Genzyme Polyclonals S.A.S., Lyon, Rhône, France) on days –5 to –2. Patients in the ISD-SCT group received the same treatment as the HID-SCT patients except for the following differences: the patients were additionally treated with hydroxyurea (Hu, 80 mg/kg, oral administration, Qilu Pharmaceutical Co. Ltd., Jinan, Shandong, China) on day –10 and Ara-C (2 g/m²/d) on
day −9, and the patients were not treated with ATG. All patients received cyclosporine A (CSA, intravenous infusion, Novartis Pharma Ltd., Basel, Switzerland), mycophenolate mofetil (MMF, oral administration, Roche Pharmaceutical Ltd., Basel, Switzerland), and short-term methotrexate (MTX, intravenous infusion, Pfizer Pharmaceuticals Ltd., New York, USA) as a prophylaxis for graft-versus-host disease (GVHD). CSA was used from day −9, of which the concentration was adjusted to 150-250 ng/mL. From day −9, 250-500 mg of MMF was administered every 12 hours until day +30. After graft infusion, a dose of 15 mg/m² MTX was administered on day +1 as well as a dose of 10 mg/m² on days +3 and +6 for the ISD-SCT recipients and on days +3, +5 and +11 for the HID-SCT recipients [14]. All recipients received G-CSF-mobilized (Chugai Pharmaceutical Co. Ltd., Tokyo, Japan) (5 μg/kg/d, subcutaneously for donor on day −3 to transplantation day), fresh, and unmanipulated (without T cell depletion of graft in vitro) bone marrow cells plus peripheral blood stem cells (PBSCs) or PBSCs alone. G-CSF (5 μg/kg/d) was provided to all HID-SCT recipients from day +6 until their white blood cell (WBC) count exceeded 2 × 10⁹/L for three consecutive days [6, 14].

2.3 | Definition and assessments

According to published criteria, “high-risk” was defined as follows: 1) relapsed AML [15, 16]; 2) therapy-related or myelodysplastic syndrome-derived AML [15, 16]; 3) ≥15.0% blasts in bone marrow (BM) smear or ≥0.1% blasts in a BM sample tested by flow cytometry after two cycles of induction [17]; 4) AML with adverse cytogenetic features [17]; 5) ≥0.1% blasts in a BM sample tested by flow cytometry after three cycles of chemotherapy [15]; and 6) FLT3-ITD without NPM1 mutation [17]. Adverse cytogenetic features were defined as abnormal 3q, monosomy 5, monosomy 7, monosomy 17, deletions of 5q, deletion of 7q, t(6;9)(q23;q34), t(9;22)(q34;q11), MLL re-arrangement except t(9;11), and complex cytogenetic abnormalities which was defined as at least four unrelated cytogenetic abnormalities [17]. Patients with t(16;16)(p13;q22) and t(8;21)(q22;q21) were considered to have favorable cytogenetic features [17]. All other patients were considered to have intermediate risk for cytogenetic disease.

Neutrophil engraftment was defined as the first day of neutrophil count of 0.5 × 10⁹/L or more for three consecutive days, and platelet engraftment was defined as the first day of a platelet count of 20 × 10⁹/L or more for seven consecutive days without transfusion. Primary engraftment failure was defined as the absence of donor-derived myeloid cells at day 60 in patients surviving beyond day 28 after transplantation or as the need for a second allogeneic transplant or reconstitution with autologous cells. ABO major mismatch was defined as: either group O patients who received grafts from group A, group B, or group AB donors; or group A and group B patients who received grafts from group AB donors. ABO minor mismatch was defined as: either group AB patients who received grafts from non-group AB donors or group A and group B patients who received grafts from group O donors. Bidirectional mismatch was defined as: either group A patients who received grafts from group B donors or group B patients who received grafts from group A donors. The diagnosis of acute GVHD (aGVHD) was in accordance with the Glucksberg criteria [18]. Chronic GVHD (cGVHD) was classified as mild, moderate, or severe according to the National Institutes of Health consensus criteria [19].

OS was defined as the time from transplantation to death from any cause. DFS was defined as survival in continuous CR. CR was defined as BM blasts at ≤ 5.0%. CR1 was defined as the first complete remission. Relapse was defined as recurrence of BM blasts at > 5.0%, the reappearance of blasts in the blood or development of extramedullary disease infiltrates at any site. Non-relapse mortality was defined as death after SCT without disease progression or relapse.

2.4 | Statistical analysis

Data were censored at the time of death or last contact. Propensity score matching was performed to reduce or eliminate confounding effects. Each ISD-SCT case was matched with three HID-SCT cases using the nearest neighbor-matching method. Age and sex of patients, disease status, cytogenetic risk, sex of donor, and graft type were included in the propensity score model. Continuous variables were compared using the Mann-Whitney U-test. Categorical variables were compared using the χ² and Fisher’s exact tests. Survival functions were estimated using the Kaplan-Meier method. Competing risk analysis was used to calculate the cumulative rates of GVHD, relapse, and non-relapse mortality, and the Gray’s test was used to test the differences between the HID-SCT and ISD-SCT groups. All reported P values were based on two-sided hypothesis tests, and P < 0.05 was considered as having statistical significance. Data analyses were primarily conducted with the SPSS software package 22.0 (SPSS Inc., Chicago, IL, USA), and R software (version 3.3.1; http://www.r-project.org) was used for propensity score matching [20], competing risk analysis [21] and estimating survival.

3 | RESULTS

3.1 | Patient characteristics

As a result, 23 cases of ISD-SCT and 156 cases of HID-SCT were enrolled in the study. In total, we matched 23 ISD-SCT
| Characteristic                        | ISD-SCT (n = 23) | HID-SCT (n = 69) | P value |
|--------------------------------------|-----------------|-----------------|---------|
| Age of recipients [years, median (range)] | 11 (4-18)       | 12 (1-16)       | 0.805   |
| Sex of recipients [cases (%)]        |                 |                 | 1.000   |
| Male                                 | 14 (60.9%)      | 42 (60.9%)      |         |
| Female                               | 9 (39.1%)       | 27 (39.1%)      |         |
| WBC at diagnosis (range, × 10^9/L)   | 19.9 (2.1-227.9) | 19.9 (0.3-404.0) | 0.334   |
| Time from diagnosis to SCT (range, months) | 5.5 (1.0-30.0) | 6.0 (1.0-84.0) | 1.000   |
| Cytogenetic risk                     |                 |                 | 0.126   |
| Favorable                            | 3 (13.0%)       | 3 (4.3%)        |         |
| Intermediate                         | 8 (34.8%)       | 40 (58.0%)      |         |
| Adverse                              | 8 (34.8%)       | 13 (18.8%)      |         |
| Unknown                              | 4 (17.4%)       | 13 (18.8%)      |         |
| Diseases status                      |                 |                 | 0.569   |
| CR1                                  | 17 (73.9%)      | 55 (79.7%)      |         |
| Beyond CR1                           | 6 (26.1%)       | 14 (20.3%)      |         |
| ABO incompatibility                  |                 |                 | 0.007   |
| Match                                | 21 (91.3%)      | 36 (52.2%)      |         |
| Minor mismatch                       | 0               | 21 (30.4%)      |         |
| Major mismatch                       | 1 (4.3%)        | 8 (11.6%)       |         |
| Bidirectional mismatch               | 1 (4.3%)        | 4 (5.8%)        |         |
| Age of donors (range, years)         | 16 (6-31)       | 37 (11-52)      | <0.001  |
| Sex of donors                        |                 |                 | 0.159   |
| Male                                 | 9 (39.1%)       | 39 (56.5%)      |         |
| Female                               | 14 (60.9%)      | 30 (43.5%)      |         |
| Graft source                         |                 |                 | 0.307   |
| BM+PBSC                              | 14 (60.9%)      | 50 (72.5%)      |         |
| PB                                   | 9 (39.1%)       | 19 (27.5%)      |         |
| Median MNC (range, × 10^9/kg)        | 8.48 (5.43-15.82) | 9.15 (3.19-29.60) | 0.630   |
| Median CD34(range, × 10^6/kg)        | 3.29 (1.10-6.20) | 3.29 (0.52-10.00) | 1.000   |
| Transplant center                    |                 |                 | 0.505   |
| Peking University People’s Hospital  | 14 (60.9%)      | 39 (56.5%)      |         |
| Xinqiao Hospital, Army Military Medical University | 7 (30.4%) | 17 (24.6%) |         |
| Nanfang Hospital, Southern Medical University | 2 (8.7%) | 13 (18.8%) |         |

AML, acute myeloid leukemia; SCT, stem cell transplantation; ISD, identical sibling donor; HID, haploidentical donor; WBC, white blood cell; CR1, first complete remission; BM, bone marrow; PBSC, peripheral blood stem cell; MNC, mononuclear cell.

Patients with 69 HID-SCT patients, and the characteristics are summarized in Table 1. The characteristics of CR1 patients in the two groups are shown in Table 2. There were 9 and 18 recipients who died in the ISD-SCT group and the HID-SCT group, respectively. The median follow-up period after SCT in survivors was 39.6 months (range: 15.0-65.1 months) for the ISD-SCT group and 43.6 months (range: 10.8-70.8 months) for the HID-SCT group (P = 0.153).

### 3.2 Engraftment

All patients achieved donor cell engraftment except one HID-SCT patient who died of cerebral hemorrhage on day +8. All patients achieved platelet engraftment, except one HID-SCT patient who died of thrombotic thrombocytopenic purpura on day +106. The median time to achieve neutrophil engraftment were 15 days (range: 11-23 days) and 13 days (range:
TABLE 2  Characteristics of pediatric AML patients who underwent ISD-SCT or HID-SCT in the subgroup for patients in CR1 with known cytogenetics

| Characteristic                              | ISD-SCT (n = 14) | HID-SCT (n = 44) | P value |
|---------------------------------------------|------------------|------------------|---------|
| Age of recipients (range, years)            | 14 (4-16)        | 12 (2-16)        | 0.741   |
| Sex of recipients                           |                  |                  |         |
| Male                                        | 8 (57.1%)        | 21 (47.7%)       | 0.380   |
| Female                                      | 6 (42.9%)        | 23 (52.2%)       |         |
| WBC at diagnosis (range, ×10^9/L)           | 19.9 (2.1-55.7)  | 25.1 (1.0-404.0) | 0.357   |
| Time from diagnosis to SCT (range, months)  | 4.0 (1.0-31.0)   | 5.2 (1.0-60.0)   | 0.440   |
| Cytogenetic risk                            |                  |                  |         |
| Favorable                                   | 2 (14.3%)        | 3 (6.8%)         | 0.172   |
| Intermediate                                | 6 (42.9%)        | 31 (70.5%)       |         |
| Adverse                                     | 6 (42.9%)        | 10 (22.7%)       |         |
| Resistant to first cycle of chemotherapy    | 5 (35.7%)        | 19 (43.2%)       | 0.547   |
| Number of chemotherapy cycles (range)       | 4.5 (1-16)       | 4 (2-20)         | 0.525   |
| ABO incompatibility                         |                  |                  |         |
| Match                                       | 13 (92.8%)       | 22 (50.0%)       | 0.026   |
| Minor mismatch                              | 0                | 5 (11.4%)        |         |
| Major mismatch                              | 0                | 14 (31.8%)       |         |
| Bidirectional mismatch                      | 1 (7.1%)         | 3 (6.8%)         |         |
| Age of donors (range, years)                | 16 (10-31)       | 38.5 (11-52)     | 0.002   |
| Sex of donors                               |                  |                  |         |
| Male                                        | 6 (42.9%)        | 25 (56.8%)       | 0.540   |
| Female                                      | 8 (57.1%)        | 19(43.2%)        |         |
| Graft source                                |                  |                  | 0.086   |
| BM+PBSC                                     | 10 (71.4%)       | 40 (90.0%)       |         |
| PB                                          | 4 (28.6%)        | 4 (9.1%)         |         |
| Median MNC (range, ×10^8/kg)                | 9.01 (5.43-15.82)| 8.95 (3.19-16.66)| 0.759   |
| Median CD34 (range, ×10^6/kg)               | 3.12 (1.10-6.20) | 3.09 (0.52-10.00)| 0.759   |

AML, acute myeloid leukemia; SCT, stem cell transplantation; CR, complete remission; ISD, identical sibling donor; HID, haploidentical donor; WBC, white blood cell; BM, bone marrow; PBSC, peripheral blood stem cell; MNC, mononuclear cell.

10-46 days) for the ISD-SCT group and HID-SCT group, respectively (P = 0.002). Platelet engraftment occurred at a median time of 12 days (range: 10-26 days) for the ISD-SCT group and 13 days (range: 7-61 days) for the HID-SCT group (P = 0.026).

### 3.3 GVHD

The cumulative rate of GVHD in HID-SCT group may be higher than that in the ISD-SCT group but there was no statistical difference observed between the two groups. At day +100, the cumulative rates of grades II-IV aGVHD were 13.0% (95% CI, 3.1%–30.2%) in the ISD-SCT group and 34.9% (95% CI, 23.2%–46.8%) in the HID-SCT group (P = 0.062) (Figure 2A). Meanwhile, the cumulative rates of grades III-IV aGVHD were 0.0% and 11.6% (95% CI, 5.4%–20.4%) in the ISD-SCT group and the HID-SCT group, respectively (P = 0.090).

The three-year cumulative rates of cGVHD were 14.1% (95% CI, 3.4%–32.4%) in the ISD-SCT group, and 34.9% (95% CI, 23.2%–46.8%) in the HID-SCT group respectively (P = 0.091) (Figure 2B). The three-year cumulative rates of moderate to severe cGVHD were 14.1% (95% CI, 3.4%–32.4%) in the ISD-SCT group and 16.2% (95% CI, 8.2%–26.6%) in the HID-SCT group (P = 0.890) (Figure 2C). The three-year cumulative rates of severe cGVHD were 5.0% (95% CI, 0.3%–21.1%) and 10.0% (95% CI, 4.0%–19.3%) in the ISD-SCT group and the HID-SCT group, respectively (P = 0.494).

### 3.4 Relapse and non-relapse mortality

The three-year relapse rate in the ISD-SCT group was significantly higher than that in the HID-SCT group (39.1% [95% CI, 19.4%–58.4%] vs. 16.4% [95% CI, 8.7%–26.3%], P = 0.027) (Figure 3A). Causes of death for relapse and
FIGURE 2 Illustration of the (A). Cumulative rate of grades II-IV acute GVHD, (B). chronic GVHD, and (C). moderate to severe chronic GVHD in the entire study population cohort.

Abbreviations: ISD, identical sibling donor; HID, haploidentical donor; GVHD, graft-versus-host disease.

FIGURE 3 Illustration showing the (A). Cumulative relapse rate in the entire study population, and (B). rate of relapse in the subgroup with known cytogenetic risk in CR1.

Abbreviations: ISD, identical sibling donor; HID, haploidentical donor; SCT, stem cell transplantation.

non-relapse mortality are shown in Table 3. The three-year cumulative rates of non-relapse mortality were 0.0% in the ISD-SCT group and 10.6 (95% CI, 4.7%–19.7%) in the HID-SCT group (P = 0.113).

Subgroup analysis of patients with known cytogenetic risk in CR1 showed that the three-year relapse rate in the ISD-SCT group was significantly higher than that in the HID-SCT group (50.0% [95% CI, 21.5%–73.2%] vs. 9.2% [95% CI, 2.8%–20.1%; P = 0.001) (Figure 3B), whereas the non-relapse mortality rates were 0.0% and 9.5% (95% CI, 3.0%–20.9%) in the ISD-SCT group and the HID-SCT group, respectively (P = 0.256).

3.5 Survival

There was no significant difference in the three-year DFS and OS rates between the ISD-SCT and the HID-SCT group. Their three-year DFS rates were 60.9% (95% CI, 40.9%–80.9%) and 72.9% (95% CI, 62.1%–83.7%; P = 0.297) (Figure 4A) and their three-year OS rates were 73.0% (95% CI, 54.4%–91.6%) and 74.6% (95% CI, 64.0%–85.2%; P = 0.689), respectively (Figure 4B).

Subgroup analysis of patients with known cytogenetic risk in CR1 showed that the three-year DFS rate in the HID-SCT group was significantly higher than that in the ISD-SCT group (81.2% [95% CI, 69.4%–93.0%] vs. 50.0% [95% CI, 23.7%–76.3%; P = 0.021) (Figure 4C), whereas the OS rates were comparable between the two groups (81.5% [95% CI, 69.9%–93.1%] vs. 68.8% [95% CI, 42.7%–94.9%; P = 0.196).

4 DISCUSSION

The present study compared the survival outcomes between undergoing HID-SCT or ISD-SCT in children with high-risk
TABLE 3 Causes of death in pediatric AML patients who underwent ISD-SCT or HID-SCT

| Causes of death  | ISD-SCT [cases (%)] | HID-SCT [cases (%)] |
|------------------|---------------------|---------------------|
| Total            | 9 (100.0)           | 18                  |
| AML Relapse      | 9 (100.0)           | 7 (38.9)            |
| Infections       | 0                   | 4 (22.2)            |
| aGVHD            | 0                   | 0                   |
| cGVHD            | 0                   | 1 (5.6)             |
| Organ failure    | 0                   | 2 (11.1)            |
| Others*          | 0                   | 4 (22.2)            |

*Included one case of diffuse alveolar hemorrhage, one case of cerebral hemorrhage and two cases with missing data.

AML, acute myeloid leukemia; ISD, identical sibling donor; SCT, stem cell transplantation; HID, haploidentical donor; aGVHD, acute graft-versus-host disease; cGVHD, chronic-graft-versus-host disease.

AML. Matched-pair analyses showed that, in high-risk pediatric AML, relapse rate among ISD-SCT recipients was significantly higher than that among HID-SCT recipients despite having comparable OS and DFS rates and that the subgroup of patients with known cytogenetic risk and transplanted in CR1 had higher relapse rate and lower DFS rate in ISD-SCT compared with HID-SCT. Our study findings also demonstrated that HID-SCT was comparable to ISD-SCT in terms of OS rate, DFS rate, and non-relapse mortality in pediatric high-risk AML patients. Therefore, the results showed the possibility for exploring the currently undefined role of T-cell-replete HID-SCT in pediatric high-risk AML.

In the current study, the relapse rate was 16.4% in the HID-SCT group, which is comparable to a recent study that enrolled 58 ISD-SCT patients, 75 URD-SCT patients, and 8 HID-SCT patients in the allogenic SCT group [22]. Mo et al. [23] observed that the relapse rates were comparable (22.2% vs. 7.6%) between the two groups that were resistant and sensitive to the first course of induction chemotherapy in pediatric AML patients, suggesting that HID-SCT could improve the outcomes of high-risk AML. In the current study, the proportion of HID-SCT recipients who were resistant to the first course of induction chemotherapy in the subgroup with known cytogenetic risk in CR1 was 43.2% and the relapse rate of the subgroup was 9.2%, which aligned with the results of a previous study [23]. However, in the current study, the strikingly low relapse rate in the HID-SCT might be explained by the fact that, in HID-SCT, the proportions of favorable and intermediate-risk patients were 62.3% in the whole population and 77.3% in the subgroup; whereas in ISD-SCT, the proportions of these two cytogenetic-risk groups were 47.8% in the whole population and 57.2% in the subgroup. Furthermore, the current study demonstrated that in both the entire population and the subgroup of patients with known cytogenetic risk in CR1, patients in the ISD-SCT group had higher relapse rate than those in the HID-SCT group. Chang et al. [24] reported that patients receiving HID-SCT experienced lower relapse rate than those who underwent ISD-SCT (19% vs. 57% in a retrospective cohort and 13% vs. 36% in a prospective cohort). In that study [24], among the patients receiving ISD-SCT, relapse rate was higher in the minimal residual disease (MRD)-positive group than in the MRD-negative group (36% vs. 7%), whereas relapse rates were comparable between the MRD-positive group and MRD-negative group among patients who received HID-SCT (13% vs. 7%); suggesting that HID-SCT had a stronger graft versus leukemia (GVL) effect than ISD-SCT [24]. The results from other studies also confirmed the stronger GVL effect in HID-SCT than in ISD-SCT [25, 26]. In theory, in HID-SCT, stronger alloimmune response would be achieved by leukemic cells which express HLA mismatched from donors and result in a decrease in relapse rate. However, since little is known about the mechanisms underlying the stronger GVL effect of HID-SCT compared to that of ISD-SCT [27-29], there may be some other possible reasons for the higher relapse rate in the ISD-SCT group compared to the HID-SCT group in the current study. First, in the present study...
study, both groups of patients received CSA, MTX, and MMF as GVHD prophylaxis. However, whether a strong immunosuppression strategy is also applicable to high-risk pediatric AML patients who underwent ISD-SCT needs to be reevaluated. Second, there were almost twice as many cytogenetically adverse-risk patients in the ISD-SCT group than in the HID-SCT group (34.8% vs. 18.8%). Third, in the subgroup of ISD-SCT, only 10 patients had MRD data: six were MRD positive before ISD-SCT, and four relapsed after SCT. The higher percentages of pre-MRD-positive patients in the ISD-SCT subgroup may explain the higher rate of relapse rate in the CR1 subgroup than in the whole population of ISD-SCT. To better understand the cause of the higher relapse rate of patients after ISD-SCT than HID-SCT warrants larger samples size of case-control studies and further biological experiments.

Liu et al. [9] demonstrated that the non-relapse mortality was 7.1% and 12.6% among ISD-SCT and HID-SCT groups. In our study, non-relapse mortality was 10.6% in the HID-SCT group, which was in agreement with a previous report [9]. All ISD-SCT recipients died of relapse which might be due to the relatively small sample size of this group. Meanwhile, no patients died of infections in the ISD-SCT group, whereas infection was the common cause of death in the HID-SCT group. This may be due to the intensive immunosuppressive regimen in the HID-SCT group which causes delayed immune reconstitution compared to the ISD-SCT group [30]. However, as the data of the present study was derived from multicenter database, details on immune reconstitution were not available. Furthermore, in the HID-SCT group, only 1% of HID-SCT recipients died of GVHD. Although the GVHD rate may be potentially higher in the HID-SCT group than in the ISD-SCT group, severe GVHD was manageable in our protocol. In addition, up to 39% of HID-SCT recipients died of relapse, which suggested that it might be necessary to improve the transplantation protocol to reduce the relapse of this highly malignant disease, for instance by optimizing the conditioning regimen and applying targeted drugs as maintenance therapy.

One of the major concerns regarding HID-SCT is the increased possibility of GVHD. In the current study, the difference in the cumulative incidences of grades II-IV and III-IV aGVHD and cGVHD was not significant between the ISD-SCT group and the HID-SCT group but there were trends that HID-SCT led to higher rates of GVHD than ISD-SCT, which were aligned with the findings from a previous study [9]. However, our previous studies showed that HID-SCT resulted in a comparable rate of GVHD as ISD-SCT in pediatric and adult recipients [31-33]. This may be due to the small number of patients, especially in the ISD-SCT group. Despite potentially higher rate of GVHD, as discussed above, the mortality of GVHD was low (1/18), suggesting that the prophylaxis strategies for GVHD that combined in vivo T cell depletion with ATG [34], CSA, MTX, MMF, and transfusing G-CSF mobilized PBSC [35] were effective for overcoming the HLA barrier in HID-SCT. Currently, PT/Cy prophylaxis is widely used due to its effectiveness in decreasing the incidence of GVHD. Our results showed that, despite the fact that the incidence of grades II-IV aGVHD was consistent with those in previous studies that employed PT/Cy prophylaxis for HID-SCT recipients (27%–33%) [36, 37], the rates of grades III-IV aGVHD (11.6%) and cGVHD (34.9%) of present study were higher than that for the PT/Cy protocols (5.0% for grades III-IV aGVHD and 13%-23% for cGVHD) [36, 37]. This may be partly explained by the fact that all recipients received PBSC infusion in our study, whereas 7.5% of patients were infused PBSC in one of the previous studies [36], and all recipients in another study were only infused with BM as the stem cell source [37].

The major limitation of our study was its retrospective design. Some of the HID-SCT recipients had advanced disease status, lacked an ISD and could not wait for a matched unrelated donor, thus it would be difficult to conduct a randomized study to compare the efficacy of HID-SCT and ISD-SCT. Second, not all the MRD statuses were available in our study. As discussed above, MRD status before SCT could impact the outcome of SCT [12, 24]. Third, the information of donor lymphocyte infusion was invalid. Yan et al. [38] found that DLI could reduce relapse and increase survival in patients with refractory/relapsed acute leukemia after SCT with the ATG and G-CSF-based protocol. Future studies should involve both MRD and information of donor lymphocyte infusion to analyze data in more details. Last, although we conducted matched pair analysis to reduce selection bias, the sample size of the ISD-SCT group was small, which could partially explain the slightly different results with our previous studies [9, 31, 32, 33].

5 | CONCLUSIONS

In conclusion, our findings underline that HID-SCT had comparable OS and DFS to ISD-SCT with acceptable complications in high-risk pediatric AML patients, and that HID-SCT can be a valid alternative option in this population. A prospective study to investigate the role of HID-SCT in this setting is warranted for confirmation.

DECLARATIONS ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the ethics committee of the local institution. Informed consent was obtained from all patients' guardians. All authors vouch for the accuracy and completeness of the reported data and analyses.
CONSENT FOR PUBLICATION
Not applicable.

AVAILABILITY OF DATA AND MATERIALS
The datasets analyzed during the current study are available from the corresponding authors on reasonable request.

COMPETING INTERESTS
The authors declare that they have no competing interests.

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AUTHORS’ CONTRIBUTIONS
XJH and YW designed the research; FMZ, XZ, CFL, YFC, LG, and YLH collected the clinical data; FMZ, XZ and CFL performed the statistical analyses and wrote the manuscript. All authors have read and approved the final manuscript.

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