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Alternative donors, particularly haploidentical donors, are safe and effective for elderly patients with adverse-risk AML: a multicenter TROPHY study

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Dear editor,

Adverse-risk acute myeloid leukemia (AML) is one of the most life-threatening hematologic malignancies in adults [1], and allogeneic stem cell transplantation (allo-HSCT) is the standard consolidation therapy after achieving complete remission (CR) [2]. However, the incidence of AML increases with advancing age, with a median age at diagnosis ranging from 65 to 72 years [3]. Therefore, how to optimize the transplant strategies in elderly AML patients is crucial, particularly regarding donor selection.

Human leukocyte antigen (HLA) identical sibling donors (ISDs) are considered as the preferred option for allo-HSCT [4]. However, for elderly AML patients, ISDs are often also of advanced age or unsuitable for donation due to poor organ function, making alternative donors increasingly essential. In China, haploidentical related donors (HIDs) have become the most important source of alternative donors, and several studies reported that the outcomes of HID HSCT were comparable with or even better than those of ISD HSCT [5, 6]. In addition, Sun et al. [7] reported that HID HSCT might decrease relapse and improve survival compared with consolidation chemotherapy in elderly patients (≥ 55 years) with intermediate or high-risk AML. Nevertheless, it remains unclear whether alternative donor, particularly the HID HSCT can achieve comparable clinical outcomes with ISD HSCT in elderly patients with adverse-risk AML.

Older donors negatively impact the clinical outcomes of allo-HSCT [8]. In HID HSCT, younger donors were associated with a lower incidence of severe graft-versus-host disease (GVHD) [9] and a better overall survival (OS) [10]. Nath et al. [11] observed that young HID donors showed a similar survival compared to those of older ISDs; however, no subgroup analysis was conducted for adverse-risk AML patients in their study.

Therefore, in this real-world study of the TROPHY group, we aimed to compare the clinical outcomes among ISD, HID, and unrelated donor (URD) HSCT in elderly patients with adverse-risk AML.

This a multicenter, retrospective study based on the transplant database from 8 transplant center in China (Supplementary Table 1). Consecutive AML patients receiving allo-HSCT from March 2017 to April 2025 were screened, and the eligibility criteria were as follows: (1) aged ≥ 55 years; and (2) adverse-risk AML based on ELN 2022 criteria [12]. The last follow-up was September 30, 2025. The study was approved by the institutional review board of each participating hospital and was conducted in accordance with the *Declaration of Helsinki*. Detailed descriptions of the transplant regimens, measurable residual disease (MRD) monitoring protocols, and definitions of clinical endpoints are shown in the Supplementary Materials. Donors were categorized into younger (≤45 years) and older (>45 years) groups.

Surviving patients were censored at the date of last follow-up. The primary outcome was relapse. Independent variables with $P > 0.1$ were sequentially excluded from the model, and $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed using the R software 4.2.0 (https://www.r-project.org) and Statistical Package for the Social Sciences 26 (SPSS Inc., IBM, Armonk, NY, USA) (Supplementary Methods).

A total of 332 adverse-risk AML patients were enrolled (Supplementary Table 2). In the alternative donor group, most of them received HID HSCT ($n = 264$). The median follow-up was 1029 days (range 939–1118) days.

A total of 319 (96.0%) patients achieved neutrophil engraftment within 28 days after allo-HSCT, and 247 (93.2%) patients achieved platelet engraftment. The cumulative incidence of engraftment of neutrophil and platelet was comparable among ISD, HID, URD HSCT groups (Supplementary Table 3).

The cumulative incidence of total and grade II-IV acute GVHD (aGVHD) at 100 days after allo-HSCT were both comparable among ISD, HID, and URD HSCT recipients. Similarly, the 2-year cumulative incidence of total and moderate to sever chronic GVHD (cGVHD) after allo-HSCT were also comparable among ISD, HID, and URD HSCT recipients (Supplementary Table 4).

The 2-year cumulative incidence of relapse after allo-HSCT was 22.4% (95% CI: 7.4–37.4%), 24.3% (95 CI: 19.0–29.6%), and 15.5% (95% CI: 2.7–28.4%) ($P = 0.517$), respectively, in ISD, HID, and URD HSCT cohorts (Fig. 1A). In multivariable analysis, female patients and non-CR status before HSCT were associated with a higher risk of relapse (Supplementary Tables 5–6).

The 2-year cumulative incidence of non-relapse mortality (NRM) was 15.6% (95% CI: 2.7–28.4%), 18.3% (95% CI: 13.5–23.0%), and 20.8% (95% CI: 6.8–34.9%) ($P = 0.848$), respectively (Fig. 1B). In multivariable analysis, non-CR status before HSCT and ABO incompatibility were associated with a higher risk of NRM (Supplementary Tables 5–6).

The 2-year probability of leukemia-free survival (LFS) was 62.0% (95% CI: 47.1–81.6%), 57.2% (95% CI: 51.6–63.6%), and 63.6% (95% CI: 49.1–82.5%) ($P = 0.786$), respectively, in ISD, HID and URD HSCT cohorts (Fig. 1C). In multivariable analysis, *TP53* mutation, non-CR status before HSCT, and MRD positivity before HSCT were associated with a worse LFS (Supplementary Table 5–6).

The 2-year probability of GVHD-free/relapse-free survival (GRFS) was 43.0% (95% CI: 28.6–64.5%), 42.6% (95% CI: 36.9–49.1%), and 48.3% (95% CI: 33.8–69.1%) ($P = 0.715$), respectively, in ISD, HID and URD HSCT cohorts (Fig. 1D). In multivariable analysis, *TP53* mutation, non-CR status before HSCT, and a high hematopoietic

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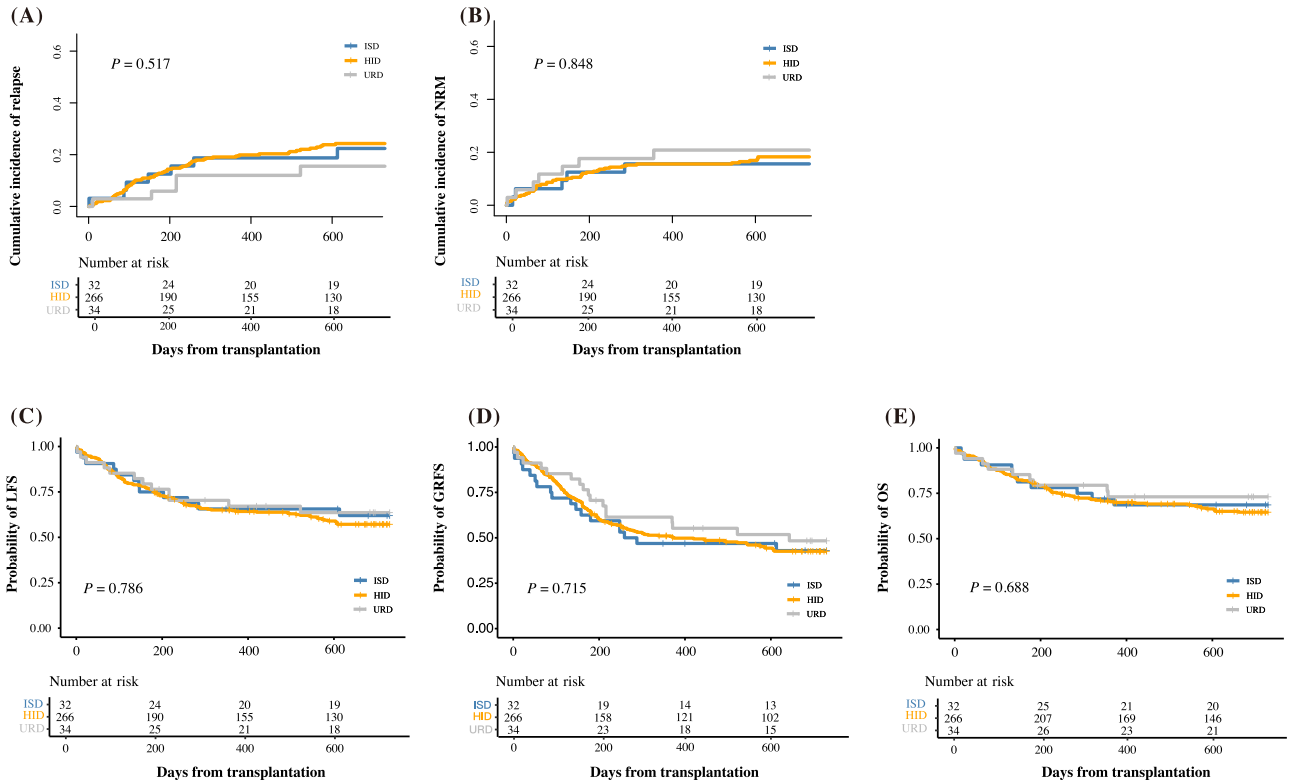

Fig. 1 2-year probabilities of clinical outcomes after allo-HSCT in total cohort. A Relapse; **B** NRM; **C** LFS; **D** GRFS and **E** OS.

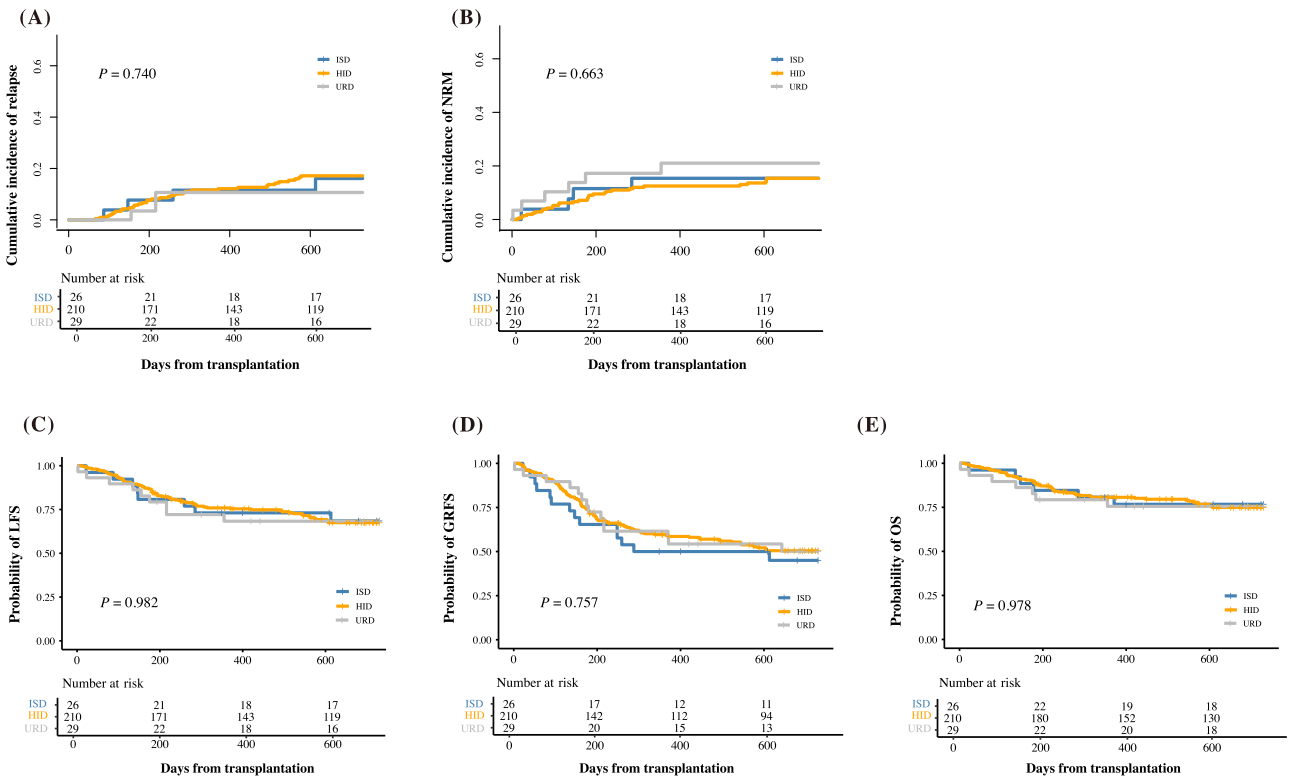

Fig. 2 2-year probabilities of clinical outcomes after allo-HSCT in patients achieving CR. A Relapse; **B** NRM; **C** LFS; **D** GRFS and **E** OS.

cell transplantation-comorbidity index were associated with a poorer GRFS (Supplementary Tables 5–6).

The 2-year probability of OS was 68.6% (95% CI: 54.2–86.8%), 64.6% (95% CI: 58.9–70.8%) and 73.1% (95% CI: 59.4–89.8%) ($P = 0.688$), respectively, in ISD, HID and URD HSCT cohorts (Fig. 1E). In multivariable analysis, *TP53* mutation and non-CR status before HSCT were associated with a poorer OS (Supplementary Tables 5–6).

The 2-year probabilities of relapse, NRM, LFS, GRFS, and OS were all comparable among ISD, HID, and URD cohorts both in patients who achieved CR (Fig. 2) and in those who did not achieve CR before allo-HSCT (Supplementary Table 7).

Subgroup analysis was further performed in patients who achieved CR before allo-HSCT ($n = 265$, Supplementary Table 8). Most post-transplant outcomes were comparable between the older ISD and younger alternative groups (especially the younger HID group) (Supplementary Tables 9–14), as well as between the younger HID and older HID groups (Supplementary Tables 15–17). However, in patients aged 55–59 years, the younger HID groups showed a lower 2-year total cGVHD rate compared to the older ISD group (42.7% vs. 80.0%, $P = 0.018$; Supplementary Table 12). In addition, in patients aged 55–59 years, the younger HID groups exhibited a higher 2-year LFS rate (67.0% vs. 33.3%, $P = 0.037$), and a higher 2-year OS rate (76.1% vs. 33.3%, $P = 0.010$) compared with those in the older HID group (Supplementary Table 17). In patients who achieved MRD negativity before allo-HSCT, the 2-year probability of LFS after allo-HSCT was higher in patients receiving younger HID HSCT (76.7%) than that of those receiving older HID HSCT (56.4%, $P = 0.026$) (Supplementary Table 17). The results of multivariate analysis were shown in Supplementary Table 18–19.

ISDs have traditionally been recommended as the preferred option for allo-HSCT. In the present study, the 2-year probability of LFS, OS, and GRFS was 62.0%, 68.6%, and 43.0%, respectively, for the elderly patients with adverse AML following ISD HSCT. These results are similar to previous studies enrolling young AML patients [13], confirming that ISDs should still be the first donor choice for elderly AML patients. However, their ISDs are often of advanced age, and the comorbidities may make them ineligible for donation. Thus, our findings broaden the scope of donor selection and allow more elderly patients without available ISDs to benefit from allo-HSCT.

In those receiving allo-HSCT in CR, patients aged 55–59 years receiving older HID HSCT had a NRM rate of 33.3%, which was nearly three times that of those receiving younger HID HSCT (13.2%), although this difference did not reach statistical significance due to the relatively small sample size. Thus, younger donors are preferred in unmanipulated HID HSCT [14]. However, for those who have an older HID as the only available donor, how to improve the survival of these patients should be further identified.

In the previous studies, the rates of aGVHD, particularly the grade III to IV aGVHD, in HID HSCT recipients were significantly higher than those of ISD HSCT recipients [15]. With the development of GVHD prophylaxis, the risk of severe aGVHD after HID HSCT has been decreased, and some authors reported that the rate of grade III to IV aGVHD after HID HSCT was comparable with ISD HSCT [5]. Considering that older donor age increases the risk of aGVHD [9], the disparity in aGVHD risk between younger HID and older ISD was attenuated. We observed that the total and grade III to IV aGVHD rates of younger HID group were not higher than those of older ISD group, suggested that the younger HID was safe and suitable. In addition, several new methods have been used as the treatment of severe GVHD [16–18], which further decreased the risk of GVHD-related mortality after HID HSCT.

Several studies have reported that myeloablative conditioning (MAC) could decrease the risk of post-transplant relapse compared with reduced intensity conditioning (RIC) [19]; however, a lower risk of relapse might be offset by increased NRM in MAC recipients, resulting in comparable survival rates between RIC and MAC HSCT [19]. This phenomenon may be more prominent in elderly patients with adverse-risk AML. Recently, Sun et al. [7] established a novel reduced-toxicity MAC regimen (busulfan, fludarabine, cytarabine, and rabbit antithymocyte globulin [ATG]) for elderly patients, which can achieve similar survival to younger patients receiving traditional MAC (busulfan, cytarabine, and ATG) [20]. In the present study, patients receiving this novel MAC conditioning regimen can achieve comparable NRM and survival rates to those receiving RIC, which further confirmed its safety in adverse-risk elderly AML patients. Randomized controlled trials should be performed to further compare the safety and efficacy between this novel reduced-toxicity MAC and RIC conditioning regimen in the future.

In summary, we firstly confirmed the undefined role of alternative donor, particularly the younger HID, in a disease-specific cohort of elderly patients with adverse-risk AML, and younger alternative donor, particularly the younger HID, could be used safely in these patients. A biologically randomized study may help to further compare the efficacy and safety between younger HID and older ISD HSCT in elderly patients with adverse-risk AML.

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DATA AVAILABILITY

The dataset supporting the conclusions of this article is available in the clinical data repository of each hospital. Individual participant data were not shared. For the original data, please contact moxiaodong@bjmu.edu.cn.

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AUTHOR CONTRIBUTIONS

XM, XH, JC, YZ, YC, WS, and HJ conceived the study. WH, CJ, CZ, ZS, MZ, JL, YC, JH, LW, YW, Y. Yang, CW, CZ, Y. Yu, and LX collected the clinical data. WH and XM analyzed the data and wrote the manuscript. XM, XH, JC, YZ, YC, WS, and HJ interpreted the results and provided feedback. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

INFORMED CONSENT

Informed consent was obtained from all individual participants or their guardians included in the study.

ADDITIONAL INFORMATION

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