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ORAL ABSTRACTS

723.ALLOGENEIC TRANSPLANTATION: LONG-TERM FOLLOW-UP AND DISEASE RECURRENCE

Deciphering the Impact of Donor Telomere Length on Allogeneic Transplantation Outcomes: Telomere Length Matters More Than Age

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Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment for acute leukemia. The success of transplantation relies significantly on optimal donor selection, with the donor's age being a critical factor affecting recipient survival post allo-HSCT. Telomeres play a vital role in safeguarding genetic information and are considered biomarkers for biological aging. In patients with severe aplastic anemia undergoing allo-HSCT, shorter telomere length is strongly associated with adverse outcomes. However, the relationship between telomere length and transplant outcomes in patients with acute leukemia remains unexplored. Thus, this study aims to investigate the impact of donor telomere length on clinical outcomes following allo-HSCT.

Methods

This post hoc analysis included 863 patients with acute leukemia who underwent allo-HSCT at the First Affiliated Hospital of Zhejiang University between June 6, 2016, and March 4, 2022. The inclusion criteria were as follows: (1) patient age $\geq$ 10 years; (2) diagnosis of acute leukemia, including acute myeloid leukemia, acute lymphoblastic leukemia, and mixed phenotype acute leukemia; (3) availability of a pre-transplant blood sample from the donor before mobilization. Peripheral mononuclear cells were sorted and analyzed uniformly for telomere length using qPCR. Based on the quartiles of donor telomere length, patients were categorized into the shortest telomere group (Q1), intermediate length telomere group (Q2, Q3), and longest telomere group (Q4), and the transplant outcomes were compared among the different telomere length groups.

Results

Out of the 863 eligible patients, 137 underwent allo-HSCT with matched sibling donors, 88 with unrelated donors, and 638 with haploidentical related donors. There were 546 donors aged $<$ 40 years and 317 donors aged $\geq$ 40 years. An inverse linear correlation was observed between donor age and telomere length ($P < 0.001$, **Figure 1A**). However, this age-dependent association was mainly evident in younger donors (age $<$ 40 years, $P = 0.021$), while in donors aged $\geq$ 40 years (elderly donors), it did not reach statistical significance as observed in the younger donor group ($P = 0.36$).

In patients receiving grafts from younger donors, there was no significant correlation between telomere length and engraftment, acute graft-versus-host disease (aGVHD), chronic graft-versus-host disease (cGVHD), non-relapse mortality (NRM), relapse, relapse-free survival (RFS), or overall survival (OS).

In patients receiving grafts from elderly donors, the shortest telomere length was associated with an elevated incidence of aGVHD, while aGVHD incidence was similar between intermediate and longest telomere groups (49.4%, 38.5%, and 34.2% for shortest, intermediate, and longest, respectively, $P = 0.06$). Moreover, the intermediate telomere group exhibited improved OS (3-year OS for shortest, intermediate, and longest was 59.2%, 75.6%, and 59.9%, respectively, $P = 0.07$, **Figure 1B**) and prolonged RFS (3-year RFS for shortest, intermediate, and longest was 58.8%, 74.1%, and 55.1%, respectively, $P = 0.06$, **Figure 1C**). While the donor age has on impact on OS and RFS ($P > 0.05$). Even after adjusting for prognostic factors such as patient age, pre-transplant disease status, disease risk index stratification, and transplantation type, the multivariate analyses

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consistently indicated that intermediate telomere length remained an independent protective factor for OS (HR = 0.549, 95% CI, 0.328-0.920, P = 0.023, **Figure 1D**) and RFS (HR = 0.591, 95% CI, 0.361-0.967, P = 0.036, **Figure 1E**).
Notably, elderly donors with the longest and shortest telomeres showed significantly inferior OS compared to younger donors (**Figure 1F**). However, those elderly donors with intermediate telomere lengths demonstrated comparable OS to younger donors (**Figure 1G**).

Conclusion

This study has significantly advanced our comprehension of telomeres, revealing that both excessively long and short telomeres are linked to adverse clinical outcomes in allo-HSCT for acute leukemia. Remarkably, elderly donors with intermediate-length telomeres demonstrate comparable outcomes to younger donors, challenging the conception that "young donors are superior to elderly donors." These findings underscore the paramount importance of donor telomere length more than donor age, emphasizing its pivotal role in allo-HSCT success.

Disclosures No relevant conflicts of interest to declare.

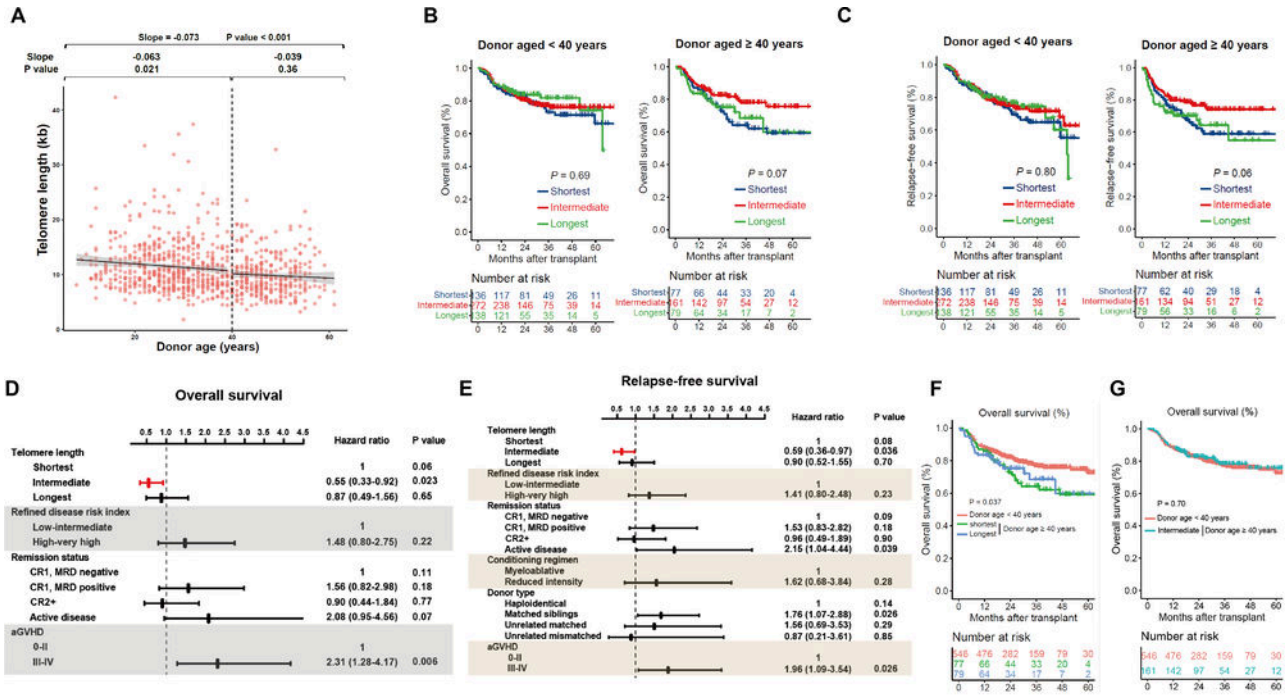

Figure 1. Donor telomere length and patients' clinical outcomes after allogeneic hematopoietic stem cell transplantation. (A) Association between donor telomere length and their age. By categorizing donors' age into < 40 years and ≥ 40 years, Kaplan-Meier curves for (B) overall survival (OS) and (C) relapse-free survival (RFS) of patients based on telomere length donors. Multivariable Cox regression model of (D) OS and (E) RFS for patients with donors aged ≥ 40 years. (F) Younger donors provided superior OS for patients compared to elder donors with the shortest and longest telomere length. (G) Patients having younger donors had similar OS to those having elder donors with intermediate telomere length.

Figure 1

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