

## BRIEF REPORT

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# Turkish Hematologists' Preferences for Relative Donor Selection: Results of a Multicenter Survey

Özkan S.G. et al: Hematologists' Donor Selection Preferences

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### Abstract:

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a widely utilized treatment for various hematological diseases. While selection criteria for unrelated donors are well-established, there is a lack of consistency and standardization in the selection of related donors.

To investigate the current approach of hematologists to the selection of relative donors at Turkish hematopoietic stem cell transplantation (HSCT) centers. The study employed a cross-sectional survey design, distributing a self-administered questionnaire to 95 adult and pediatric transplantation centers in Turkey to investigate their approach to related donor selection for allo-HSCT. The questionnaire collected data on various aspects including the center's experience in performing allo-HSCT, patient groups treated, number of allo-HSCT procedures conducted

between 2015 and 2021, preferences for related donors, considerations in related donor selection (such as gender and past pregnancies), guidelines utilized for related donor selection, upper age limit for related donors, and the use of specialized advanced analyses for elderly donors. The response rate to the survey was 38.9%. Variability was observed across centers in gender consideration and the impact of past pregnancies on related female donor rejection. Different guidelines were employed for related donor selection, with the European Bone Marrow Transplantation (EBMT) guidelines being the most commonly used. Regarding the upper age limit for related donors, 8.1% of centers accepted an upper age limit of 55, 48.7% preferred an upper age limit of 65, and 43.2% even selected related donors aged 65 and above. The lack of standardized guidelines for related donor selection in HSCT centers leads to variability in criteria and potential risks. Collaboration among centers is essential to establish consensus and develop standardized protocols.

**Keywords:** Donor selection, Hematopoietic stem cell transplantation, HSCT, Standardized protocols, Survey

## Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a rising treatment option for hematological malignancies and non-cancerous blood disorders. Stem cell sources may be from bone marrow, peripheral or cord blood from an identical twin, a sibling, or a related or unrelated donor, which can be human leukocyte antigen (HLA) matched, mismatched, or haploidentical. Outcomes of allogeneic HSCT depend on the underlying disease, the timing of the transplant, patient comorbidities, and the choice of donor. Donor-recipient histocompatibility is one of the key variables in allo-HSCT; nevertheless, non-HLA factors such as cytomegalovirus serostatus, gender, age, ABO compatibility, previous pregnancies, and greater body weight affect the transplant outcomes (1-4).

International regulatory bodies (such as the European Directives for Donation of Tissues and Cellular Therapy Products and the US Food and Drug Administration) have devised detailed donation processes to ensure the recipient's safety (5). The criteria for the selection of unrelated donors have been determined within the scope of the guidelines created by national and international authorities (such as those supplied by the Worldwide Network for Blood and Marrow Transplantation, the Center for International Blood and Bone Marrow Transplant Research, the Turkish Society of Hematology, and others) to ensure both the recipient's and the donor's safety and to receive high-quality cellular products (2, 5, 6). In many countries, lower and upper age limits have been set for an unrelated donor to be a stem cell donor by local authorities. World Marrow Donor Association (WMDA) standards require donor registries to stipulate an upper age limit not to exceed 60 years. In fact, many other donor registries have set upper age limits for joining: 55 years in Germany, 55 years in Turkey, 50 years in Canada, 40 years in Australia and the United Kingdom, and 54 years in Japan (7). However, the upper age limit for related donors is not clear, and it is left to the preference of transplant centers.

Inadequate definition of exclusion criteria for elderly related donors puts these donors at risk in terms of possible adverse events (6). Using older, related donors in these treatments is a field where the toxicity and long-term implications are not entirely established (8-14). We present a survey in which we show the differences in relative donor selection among Turkish hematologists before our main study, which will be conducted within the framework of the

Turkish Hematology Society Donor Research Team (DART) project to determine the upper age limit for related donors.

**Methods:**

*Study design, participants, and survey administration*

The study adopted a cross-sectional design to collect data on allogeneic HSCT practices and preferences among hematologists working at Turkish HSCT institutions. Between February 2021 and May 2021, an electronic mail-based survey was carried out among hematologists working in HSCT centers in Turkey. The survey was designed to acquire information about allogeneic HSCT practices and preferences. Participants were chosen based on their involvement in allogeneic HSCT procedures.

*Survey Instrument*

The survey included nine questions designed to collect valuable data. The questions covered a variety of topics, such as the number of years of experience performing allogeneic HSCT, the patient groups for whom allogeneic HSCT was performed, the number of patients who underwent allogeneic HSCT between 2015 and 2021, the preference for related donors, considerations of donor gender in related donor selection, the impact of the number of pregnancies on related female donor rejection, the guidelines used for related donor selection, the upper age limit for related donors, and whether specialized advanced analyses are conducted for elderly donors if selected.

*Data Collection*

The survey was emailed to hematologists working in HSCT centers throughout Turkey. We used SurveyMonkey, an online survey tool, to collect the data (<http://tr.surveymonkey.com/r/63QNNPJ>). The email briefly explained the study's goal and directions for completing the survey. Participants were asked to submit their responses to the survey questions electronically.

*Data Analysis*

The survey results were evaluated by SurveyMonkey as a percentile.

*Ethical Considerations*

The protocols employed in this study conformed to the ethical guidelines outlined in the 1975 Helsinki Declaration. Ethical approval was obtained from the Yeditepe University non-interventional clinical research ethics committee prior to conducting the survey (Decision date: January 20, 2022, decision no: 202111110).

**Results:**

Responses from 37 different centers were evaluated. 48.6% (n=18) of these centers had been pursuing allogeneic HSCT for more than 16 years. Adult bone marrow transplant units made up 83.8% of those who responded. When related donors are available, 86.5% of these centers said they consider the donor's gender. Concerning the selection of related female donors, 67.5% of the centers stated that the number of pregnancies had no bearing on the decision to reject the donor, while 29.7% considered three or more pregnancies to be a reason for donor rejection, and 2.8% considered five or more pregnancies to be a reason for donor rejection. Survey questions and answers are demonstrated in Table 1.

Between 2015 and 2020, 40.5% of the facilities did 201 or more allogeneic transplants, while 24.3% performed 101–200 transplants, 27% performed 51–100 transplants, and 8.1% performed 50 or fewer transplants. 46% of these facilities performed 76 or more transplants from related donors, while 2.7% performed 10–15 transplants. Regarding donor selection, the European Bone

Marrow Transplantation Guidelines were most commonly employed (48.6%), followed by the Turkish Society of Hematology Guidelines (24.3%).

While 8.1% of the centers accepted an upper age limit of 55 for related donors, 48.7% preferred an upper age limit of 65, and 43.2% even selected related donors aged 65 and above. Among the centers that preferred elderly related donors, 7 centers did not perform additional advanced investigations, 26 centers performed advanced cardiac evaluations, 21 centers performed bone marrow evaluations, 20 centers performed advanced pulmonary evaluations, and 8 centers requested serum and urine immunofixation electrophoresis.

### **Discussion:**

We report the results of a mailed survey sent to adult and pediatric transplantation centers in Turkey, which was conducted as part of the THS-DART project to gather information on allo-HSCT practices and preferences, especially the preference of an upper age limit for related donors. Most of the participants stated that they preferred a male-related donor. If a female donor is to be preferred, most of the participants replied that the number of pregnancies of the donor does not affect the donor selection. The upper age limit for donors for most participating hematologists is 56 and over. Agreement was highest for the EBMT guideline when choosing a related donor for transplantation. If an elderly donor was chosen, most participants agreed that the donor should undergo cardiac and pulmonary function evaluations.

The effect of donor sex, recipient gender, and donor-recipient gender matches has been fully studied in risk-explained disease cohorts and has been shown to affect transplantation outcomes. As such, the modified European Group for Blood and Marrow Transplantation risk score now includes F-M as a negative prognostic indicator (15). Although respondents had high agreement on male-related donors, in the modern transplantation era, recent studies have shown that outcome disparities are driven solely by recipient sex, with less influence from donor sex (16, 17).

Besides that, in our survey, most respondents agreed that the number of pregnancies does not affect donor selection. In a NMDP analysis of unrelated donor data, parity was identified as an independent risk factor for chronic GVHD (18).

Furthermore, another study shows that -parous female donors result in an increased risk of chronic graft-versus-host disease (GVHD) in all recipients; -the magnitude of this increased risk is similar in male and female recipients; and -nulliparous female donors increase the risk of chronic GVHD in male recipients to a degree comparable to that from parous donors. A decrease in the risk of relapse was not observed, and there was no effect on overall survival, acute GVHD, or transplant-related mortality (19). Although there are studies showing that the donor's gender and number of pregnancies adversely affect the transplant outcome, it was thought that the urgency of the transplant and the availability of donors may be related to the fact that most of the participants stated that the number of pregnancies did not affect the donor selection.

Due to advancements in allo-HSCT, more than 22% of allo-HSCT recipients for malignant diseases reported to the CIBMTR between 2007 and 2013 were over 60 years old (20).

Significant progress in allo-HSCT has extended its applicability to elderly patients, thanks to innovations such as the implementation of reduced-intensity conditioning (RIC) and nonmyeloablative (NMA) regimens (21) and advances in supportive care approaches (22) and more accurate HLA typing methods (10). The topic of stem cell transplantation from older donors is currently under consideration for stem cell recipients. This led to many studies examining how donor age affects allo-HSCT outcomes. Several studies have looked at the effect of donor age on allo-HSCT outcomes. In our survey, most of the participants agreed that the

upper age limit for the selection of relative donors was 56 and over. However, many studies demonstrated that increasing donor age by decade was associated with poorer overall survival (23, 24)

Besides that, there are a limited number of studies regarding the complications that develop in the donor when an elderly donor is selected. Different age limits for related donors impact potential donor availability. If age limits are set excessively low, otherwise healthy and qualified persons may be excluded from consideration as donors, decreasing the pool of available donors. On the other hand, if the age limit is too high, it can include people at a higher risk of health problems or who are less compatible as donors. Older donors may have a higher prevalence of age-related health disorders such as cardiovascular, cerebrovascular, peripheral vascular, chronic respiratory diseases, diabetes mellitus, and malignancies, which could affect the transplantation's success (14, 25). Consequently, hematological malignancies, such as myelodysplastic syndrome and chronic myeloproliferative disorders, can also develop in the recipients (26). Therefore, many of our survey participants plan to have a cardiac and pulmonary evaluation if they choose an older donor.

As a result, it is critical to thoroughly assess older donors' health status and eligibility individually, considering their overall health, comorbidities, and potential risks. It is essential to remember that the success of transplantation procedures depends on several variables. As a result, age limits are not the only factor determining transplantation success. Standardized selection criteria for related donors in HSCT have many advantages. It ensures consistency in assessments, improves safety by reducing hazards, supports quality assurance for high-quality stem cell products, simplifies the selection process to increase efficacy, and ultimately optimizes patient outcomes and donor safety (25).

Expertise is essential since skilled facilities may have developed their standards based on clinical expertise and data on outcomes. Practical considerations may force looser requirements due to resource limits, like equipment and donor availability. Different institutes use different procedures because there are no established standards for related donor selection. Inconsistent criteria make assessing the suitability of potential donors difficult (25). Inconsistent criteria can contribute to a lack of standardization in the evaluation process, making it difficult to compare and analyze donor data (12). The results of our investigation and recommendations from other studies (14, 15) show that additional research is required to establish common standards for related donor selection.

There are certain limitations to the study that should be considered. The cross-sectional design limits causal relationships and temporal changes. Relying on self-reported replies may lead to biases and inaccuracies. The findings may not be applicable outside of Turkish bone marrow transplant centers. Due to the survey instrument's limited scope, relevant aspects may have been overlooked. Finally, the implementation of standardized guidelines should still be addressed.

In conclusion, related donor selection guidelines in bone marrow transplant centers are inconsistent, leading to various criteria and potential risks. Standardized criteria for donor selection would ensure consistency, increase safety, improve quality assurance, shorten the process, and optimize patient outcomes and donor safety. Collaboration among centers is critical for reaching consensus and developing standardized methods. More study is required to define universal criteria and overcome implementation issues. In line with these goals, we will conduct a research project within the framework of the Turkish Hematology Society Donor Research Team (DART) project to determine the upper age limit for related donors.

**Previous Presentations:**

This study has not been previously presented or published elsewhere.

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**Conflict of Interest and Funding Statement:**

The authors declare that they have no conflicts of interest regarding the publication of this study. Additionally, there was no external funding received for this research.

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**Table 1: Survey questions and general responses**

Survey questions	Answers		
<b>1. How many years has allo-HSCT been performed at your transplantation center?</b>		<b>n</b>	<b>%</b>
	1-5 years	3	8.1
	6-10 years	8	21.6
	11-15 years	8	21.6
	>15 years	18	48.7
<b>2. In your transplantation center, which patient group undergoes allo-HSCT?</b>		<b>n</b>	<b>%</b>
	Pediatric patient	6	16.2
	Adult patient	31	83.8
<b>3. Please specify the total number of allo-HSCT performed at your transplantation center between the years 2015 and 2020.</b>		<b>n</b>	<b>%</b>
	<50	3	8.1
	51-100	10	27
	101-200	9	24.3
	>200	15	40.6
<b>4. Please specify the total number of related allo-HSCT performed at your</b>		<b>n</b>	<b>%</b>
	10-25	1	2.7



<b>transplantation center between the years 2015 and 2020.</b>	26-50	8	21.6
	51-75	11	29.7
	>75	17	46
<b>5. Do you have a gender preference when selecting a related donor for the transplantation?</b>		<b>n</b>	<b>%</b>
	Yes	32	86.5
	No	5	13.5
<b>6. If a related female donor candidate is available for a patient undergoing allo-HSCT, how many pregnancies would lead to the rejection of the donor?</b>		<b>n</b>	<b>%</b>
	>3	11	29.7
	>4	0	0
	>5	1	2.7
	The number of pregnancies does not affect the donor selection.	25	67.6
<b>7. Which donor selection guideline do you prefer when choosing a related donor for transplantation? (Multiple selections can be made)</b>		<b>n</b>	<b>%</b>
	CIBMTR	2	
	WBMT	5	
	EBMT	18	
	Chinese Society of Hematology consensus	1	
	NMDP	2	
	Turkish Society of Hematology Donor Guideline	9	
		<b>n</b>	<b>%</b>

<b>8. What is the upper age limit for related donors at your transplantation center?</b>	55	3	8.1
	56-65	18	48.7
	>65	16	43.2
<b>9. If you have chosen an older donor at your center, do you perform additional tests for the donor? (Multiple selections can be made)</b>		<b>n</b>	<b>%</b>
	No	7	
	Cardiac analysis	26	
	Bone marrow aspiration flow cytometry	8	
	Bone marrow biopsy	7	
	BM aspiration genetics	6	
	Pulmonary analysis	20	
	Immunofixation electrophoresis	8	
	Other	7	

Allo-HCT: Allogeneic hematopoietic cell transplantation, BM: bone marrow, EBMT: European Group for Blood and Marrow Transplantation, NMDP: National Marrow Donor Program, WBMT: Worldwide Network for Blood & Marrow Transplantation.