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Impact of Donor Age on Allogeneic Haemopoietic Stem Cell Transplant Outcomes

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Abstract

Objective: To evaluate the impact of donor age on outcomes of matched sibling donor haemopoietic stem cell transplant (HSCT).

Methodology: This descriptive cross-sectional study was conducted in tertiary care bone marrow transplant centre Rawalpindi from Jan 2023 to Dec 2024, included 85 adult patients who met the inclusion criteria and underwent matched sibling donor hematopoietic stem cell transplantation (MSD-HSCT) for both malignant and non-malignant hematological disorders. Prior to transplantation, informed consent was obtained from all patients and donors. The study evaluated the influence of donor age on neutrophil and platelet engraftment, graft-versus-host disease (GVHD), and survival outcomes. All statistical analyses were conducted using SPSS version 25.0.

Results: The mean recipient age was 28.25±9.72 years. Aplastic anemia (42.4%), followed by AML (25.9%) and ALL (23.5%) were among the most frequent indications of transplant. Mean donor age was 29.4±12.5 years and 71.8% were male. The most common donor relation with patients was sibling donor (96.5%). Majority of recipients underwent allogeneic HSCT 69(81.2%) and 54(63.5%) had no ABO mismatch. HSCT from donors <30 years of age had early neutrophils and platelets engraftment, less chronic GVHD and better survival statistics compared to HSCT from donors > 30 years of age.

Conclusion: In our study, recipients of sibling-donor HSCTs with donors under 30 years of age experienced lower rates of chronic GVHD, faster platelet engraftment (P = 0.02), and there was a trend toward improvement in OS, DFS, and GRFS, although the latter outcomes were not statistically significant. Other than platelet engraftment, there was no notable difference in neutrophil engraftment, GVHD incidence, or survival metrics. Patients experiencing acute GVHD showed significantly worse OS and DFS compared to those without aGVHD.

Keywords: Hematopoietic and stem cell transplantation (HSCT), Donor age, Engraftment, Overall survival (OS)

Introduction

Hematopoietic stem cell transplantation (SCT) involves replacing a patient's damaged or dysfunctional blood-forming system with donor-derived stem cells to restore normal hematopoiesis.[1] It's an effective therapeutic modality for various benign and malignant hematological conditions. Before undergoing this procedure, conditioning chemotherapy is mandatory. The intension of conditioning is to prepare host bone marrow environment prior to stem cell infusion. The main types of conditioning chemotherapy are myeloablative (MAC), reduced-intensity (RIC), and non-myeloablative (NMA) regimens.[2,3] The conditioning regimens have three main objectives: (1) eradicating the patient's underlying disease before transplantation, (2) making room in the bone marrow for donor cell engraftment, and (3) inducing immunosuppression to avoid graft rejection. These effects are mediated by myeloablative or lymphodepleting mechanisms.

There are three primary techniques for collecting donor stem cells: bone marrow harvesting, peripheral blood stem cell apheresis, and umbilical cord blood collection. There is a long list of hematological diseases (benign and malignant) where SCT can be offered as a cure. These diseases include acute leukemia (acute myeloid leukemia, acute lymphoblastic leukemia), myeloproliferative neoplasms. lymphoproliferative neoplasm, aplasia (congenital and acquired) and myelodysplastic syndrome.[4,5]

With advances in health care facilities, supportive care and reduction in conditioning regimen intensity, a growing number of older patients are now becoming eligible for transplant.[6] Resultantly, the age of sibling donors in HSCT is indeed growing. There are extensive literature available and numerous studies demonstrated the impact of patient age and comorbidities on health outcomes in the past.[7] However, more investigation is

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needed into how donor age affects hematopoietic stem cell transplantation results.[8]

Studies have found inconsistent results on the influence of donor age on transplant outcomes. Some studies advocate that it's the disease and recipient characteristics which carries more importance than donor characteristics.[9-12] Conversely, some studies also reported that increasing donor age has an impact on transplant outcomes.[13,14] In addition patients having parent donors have higher chances of losing graft and lower survival.[11]

In this study the effect of aging donor hematopoietic cells is studied for their ability to engraft, and subsequently for any delay in neutrophil and platelet engraftment. In addition, GVHD (acute and chronic) and survival parameters were also analyzed.

Methodology

The data for this cross-sectional analysis was gathered through convenience sampling, a non-probability approach. Clinical records were reviewed of 85 adult patients who underwent MSD-HSCT from January 2023 to December 2024 at a tertiary care bone marrow transplant centre Rawalpindi for hematological diseases (malignant and non-malignant). Prior to transplantation, informed consent was obtained from all patients and donors. The study started after the approval by the institutional review board (IRB-025/AFBMTC/Approval/2024). Correlations were observed between donor age and key transplant outcomes including engraftment times, GVHD incidence, and survival metrics. All statistical evaluations employed SPSS 25.0.

Inclusion Criteria: All patients who are eligible for transplant with a matched sibling donor for non-malignant conditions or having disease in remission for malignant conditions irrespective of gender but age ≥15 years were included in the study.

Exclusion Criteria: All patients <15 years of age or with the following diseases or transplant category were excluded from study (Beta thalassemia major, Sickle cell disease, Osteopetrosis, SCID, Autologous SCT)

HLA typing: HLA typing of both recipient and donor were performed for HLA Class I (A, B, C) and Class II (DQB1 and DRB1)at low-intermediate resolution. Fully HLA Matched patients were considered for HSCT.

Conditioning regimens: Standard myeloablative conditioning (MAC), Non-myeloablative conditioning (NMA) or RIC regimens were given in accordance with disease, age, comorbid and performance status of the patient.

GVHD prophylaxis: HSCT recipients having MAC conditioning were given Cyclosporin A (CSA) (3mg/kg IV) starting on Day -2 and methotrexate (MTX) (10mg/m2) on Day+1 and 8mg/m2 on Day +3, and +6. Whereas, HSCT recipients having NMA conditioning received Cyclosporin A (CSA) (3mg/kg IV) alone as GVHD prophylaxis starting on Day-2.

Stem cell source: Stem cells were collected through Bone marrow harvest (BMH) as per institutional policy. Peripheral blood stem cell was used as graft sourceprovided there was donor recipient weight disparity or less than desired dose with BMH.

Definitions

1. **Neutrophil engraftment**: an absolute neutrophil count (ANC) of more than 0.5 x 10(9)/l for three consecutive days without need for GCSF.
2. **Platelet engraftment**: platelet count of more than 20,000/ul for seven successive days with no platelet transfusion.
3. **Primary graft failure**: failure to achieve ANC of more than 0.5 x 10(9)/l till day 28 post-transplant.
4. **GvHD and NRM:** NRM comprise all deaths occurring without relapse or progression of underlying disease. For analysis; GvHD and NRM we subdivided cohort into two groups. First with matched sibling donor age ≤ 30years and second group with matched sibling donor age ≥30years.

Statistical analysis: All statistical analyses were performed using IBM SPSS Statistics (version 25.0). Continuous variables are reported as mean ± standard deviation, while categorical variables are expressed as counts and percentages. To assess associations between donor age and categorical variables, the Chi-square test was employed. For comparing the means between two independent groups, the Independent t-test was utilized. Survival analysis was performed to evaluate time-to-

event data. Survival analysis was conducted using Kaplan-Meier curves, and intergroup differences were evaluated with the log-rank test. A significance level of $p< 0.05$ was applied.

Results

Patient, donor, and transplant characteristics: Eighty-five patients constitute the study cohort. Table I displays baseline demographics for recipients and donors, including transplant characteristics. The average age among recipients was 28.25 ± 9.72 years. This cohort comprise majority of male (57%) recipients and most frequent indication of transplant was Aplastic anemia (42.4%), followed by AML (25.9%) and ALL (23.5%).

Most transplant recipients with malignant conditions had their disease in remission before transplantation and they underwent myeloablative conditioning (56.5%). The mean donor age was 29.4 ± 12.5 years, and majority of donors (71.8%) were males. The most common donor relation with patients was siblings (96.5%), while 2.4% were mothers and (1.2%) were uncles respectively. Among donor-recipient pairs, all recipients were positive for CMV, and only one donor was negative for CMV. Majority of recipients underwent matched related donor allogeneic HSCT 69(81.2%) and 54(63.5%) had no ABO mismatch.

Neutrophil and platelet engraftment: For those recipients who underwent transplant with <30 years old donors achieved early neutrophil engraftment (mean days to engraftment =13.28) in comparison to those with donors >30 years age(mean days to engraftment =15.35), though the variation didn't reach the level of statistically significance (*P*=0.73). Similarly, recipients who underwent transplants with <30 years old donors achieved early platelet engraftment (mean days to engraftment=21.37) in comparison to those with donors >30 years age(mean days to engraftment=23.44) and the variation was found statistically significant (*P*=0.02).

Acute and chronic GVHD: The results for acute GVHD, chronic GVHD, neutrophil and platelet engraftment are summarized in Table 2. By day 100, the cumulative incidence of grade II–IV acute GVHD was 24.5% in recipients of HLA-matched related donor transplants younger than 30 years, compared with 16.7% in those with donors older than 30 years (P = 0.38).

Table I: Baseline demographics of recipients and donors, and transplant characteristics.

Variable		n	%
Recipient Gender	Male	57	67.1
	Female	28	32.9
Recipient Age (Years)	28.25±9.72		
Diagnosis	ALL	20	23.5
	AML	22	25.9
	CML	7	8.2
	Aplastic Anemia	36	42.4
CMV Status Patient	IgG Positive	85	100
CMV Status Donor	IgG Positive	84	98.8
	IgG Negative	1	1.2
ABO Mismatch	No ABO Mismatch	54	63.5
	Minor ABO Mismatch	17	20
	Major ABO Mismatch	11	12.9
	Bidirectional ABO Mismatch	3	3.5
Transplant Type	Allogeneic	69	81.2
	Haplo	16	18.8
GVHD Prophylaxis	CSA+MTX	50	58.8
	CSA+MMF	7	8.2
	CSA	17	20
	PtCy+CSA+MMF	11	12.9
Source of Stem cells	BMH	54	63.5
	BMH+PBSC	17	20
	PBSC	14	16.5
aGVHD	YES	18	21.2
	NO	67	78.8
cGVHD	YES	11	12.9
	NO	74	87.1
Cause of Death	TRM	12	14.1
	NRM	18	21.1
Donor Relation with Recipient	Brother	59	69.4
	Sister	23	27.1
	Mother	2	2.4
	Uncle	1	1.2
Donor Age (years)	28.25±9.72		
Donor Gender	Male	61	71.8
	Female	24	28.2
Conditioning intensity	MAC	48	56.5
	NMA	36	42.4
	RIC	1	1.2

MAC; Myeloablative conditioning, NMA; Non Myeloablative conditioning, RIC; Reduced intensity conditioning, CSA; Cyclosporin, MTX; Methotrexate, MMF; Mycophenolate mofetil, Cyclo; Cyclophosphamide, TRM; transplant related mortality, NRM; Non relapse mortality, BMH; Bone marrow Harvest, PBSC; Peripheral blood stem cells, aGVHD; acute graft versus host disease, CMV; Cytomegalovirus

Table II: Impact of donor age on aGVHD, cGVHD, Neutrophil and platelets engraftment.						
		Donor Age				
		<30 years		>30 years		
		N	%	N	%	p-value
aGVHD	YES	12	24.5	6	16.7	0.38
	NO	37	75.5	30	83.3	
cGVHD	YES	6	12.2	5	13.9	0.82
	NO	43	87.8	31	86.1	
Neutrophil Engraftment (Days)*	(Mean± SD)	13.28 ± 1.85		15.35 ± 1.63		0.73
Platelet Engraftment (Days)*	(Mean± SD)	21.37 ± 6.92		23.44 ± 5.20		0.02
Note: Chi square test was applied, independent t test was applied* aGVHD; acute graft versus host disease, cGVHD; chronic graft versus host disease						

Overall survival, TRM and NRM: The NRM cumulative incidence was 9.41% among patients who were transplanted from a less than 30 years age donor, compared with 11.7% among recipients with donors older than 30 years (P = 0.29). In contrast, treatment-related mortality (TRM) was 4.70% in the <30 years donor group versus 9.41% in the above 30 years donor group (P = 0.298).

Overall survival (OS) was 71.4% in recipients of transplants from HLA-matched related donors younger than 30 years, compared with 63.9% in recipients whose donors were older than 30 years (P = 0.53). Donor age did not significantly affect disease-free survival (DFS) or graft-versus-host–free, relapse-free survival (GFRS). OS, DFS, and GFRS are presented in Figures 1a, 1b and 1c respectively.

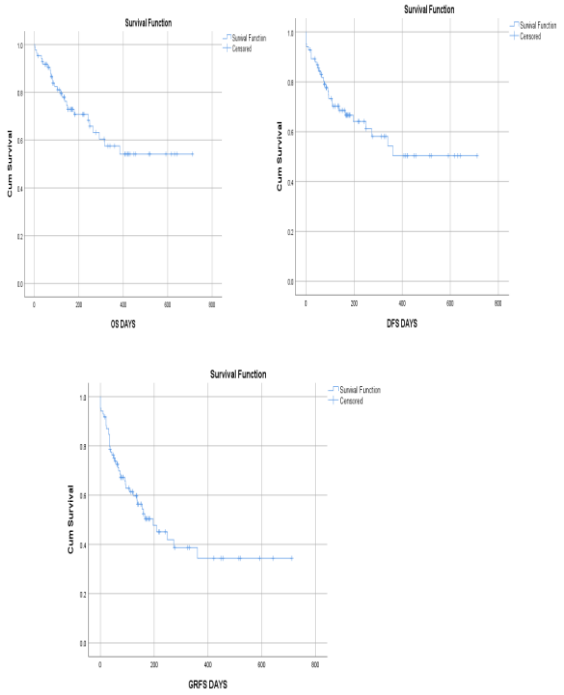

Figure 1: Cumulative overall survival [OS] (a), Disease free survival [DFS](b) and Graft-Versus-Host Disease (GVHD)-Free Relapse-Free Survival [GFRS] (c)

In contrast, acute GVHD (aGVHD) significantly impacted both OS and DFS, as shown in Figures 2a and 2b.

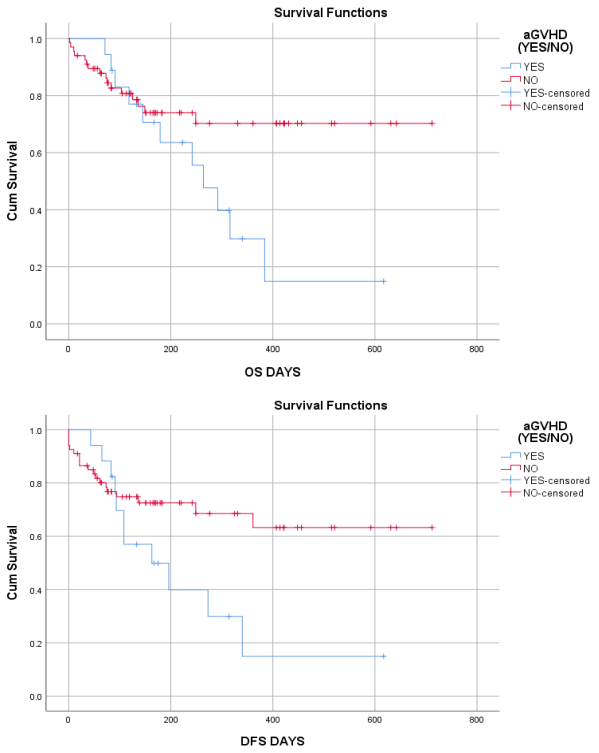

Figure 2. Impact of acute GVHD on Overall survival [OS](a) and Disease-free survival [DFS](b)

Discussion

Aging has an impact on hematopoietic stem cell transplant (HSCT) function due to both intrinsic and extrinsic changes. These changes lead to HSC functional decline, their ability to differentiate and do carry increased susceptibility to disease. The aged HSC has reduced the potential of self-renewal due to multiple mechanisms including DNA damage, telomerase attrition

and oxidative stress.[15] Aged HSC has an impaired engraftment potential compared to young HSCs.[16]

The aged HSC also exhibits epigenetic drift and dysregulated gene expression due to effected DNA methylation, histone modifications, inflammatory genes upregulation and down regulation of lymphoid-associated genes.[17] In addition, aged HSC do carry risks of malignancy and genomic instability due to defective repair mechanisms.[18] Aging also carries concerns for microenvironment (Niche) dysfunction due to altered stromal signaling, inflammatory microenvironment and mitochondrial dysfunction.[19]

The age of the donor can significantly impact neutrophil and platelet recovery in patients undergoing myeloablative HSCT from a MSD. The possible mechanisms include reduced HSC quality and quantity in older donors and decreased proliferative capacity. In our study patients undergoing HSCT from a MSD aged more than 30 years had a slower neutrophil and platelet recovery in comparison to patients with donors younger than 30 years. In a study reported by Kollman et al.[20] transplants from donors aged more than 40 years were found having delayed neutrophil engraftment. Similarly, older donors are linked with prolonged thrombocytopenia and delayed recovery of platelets as shown in a study by Rezvani et al.[21]Moreover, in CIBMTR 2008 analysis donor age above 40 years was reported a risk factor for delayed platelet engraftment in RIC/NMA transplants.

A secondary aim of this study was to assess how donor age influences overall transplant outcomes. This analysis is particularly challenging, as recipient age–related comorbidities may independently impact prognosis. Donor age impacts the development of chronic GVHD following matched sibling HSCT. The older donors carry higher risk of chronic GVHD whereas the impact on acute GVHD is less clear since the studies show varying results. There are multiple factors that carry an influence such as donor-recipient sex mismatch and recipient age. Therefore, careful consideration of donor age is essential in the selection process for allogeneic-HSCT to optimize patient outcomes. In our study, patients undergoing HSCT from a MSD aged less than 30 years had aGVHD and cGVHD incidence of 24.5% and 12.2% respectively. Whereas patients undergoing HSCT from a MSD aged more than 30 years had aGVHD and cGVHD incidence of 16.7 and 13.9% respectively. Our results are similar tothe findings reported by Zhang et al.[22] on a cohort of 68 patients, the grade II–IV acute GVHD was observed in 13.6% patients, and no significant association with donor age and the incidence of acute GVHD was found. Whereas in the same study the cGVHD was observed in 19.7% patients and especially higher risk was noted in male patients having female donor. Similarly, in another study a higher incidence of cGVHD with donors aged more than 35 years was reported.[23]

The impact of donor age on TRM and NRM is less pronounced in comparison to other donor types, though several studies have emphasized its significance. The younger donors are generally associated with lower NRM and TRM. Moreover, the literature review showed a less consistent impact of donor age on TRM. The leading factors influencing the impact include recipient age, conditioning regimen, and disease status. In our cohort, donor age did not have a statistically significant impact(p=0.29) on either TRM or NRM.

The preferred donor type are MSDs due to their HLA compatibility. Older donors are associated with decreased OS and DFS in certain patient populations. The recipients of older donors have shown lower survival rates and higher relapse rates in comparison to the recipients from younger donors. Hence donor age should be considered in donor selection for HSCT. In our study, overall survival (OS) was 71.4% for transplanted patients with donors under 30 years of age, compared to 63.9% when the donor was older than 30 years ($P = 0.53$).In a large CIBMTR analysis involving 6,978 transplant recipients, Kollman et al.[22] found that donor age over 40 years independently predicted poorer OS (HR 1.14; $p < 0.001$), primarily due to increased graft-versus-host disease and NRM. Yakoub et al.[23] also reported similar findings of significantly worsened OS (HR 1.25, p=0.02) with older donors due to higher chronic GVHD and NRM. In our study the a GVHD has an impact on OS and it was found to be statistically significant (p=0.04).

Older donors (≥40 years) are linked to lower DFS, primarily due to higher relapse and NRM. In our study no significant correlation of donor age with DFS was found. A Study by Flower et al.[24] reported a worse DFS (HR 1.12, p=0.02) in myeloablative transplants with donor age above 30 years. In our study we have found a statistically significant correlation of aGVHD on DFS (P=0.04).

Limitation: The limitations include Small sample size study and determining impact of donor age on multiple malignant and non-malignant conditions together.

Conclusion

In our study, recipients of sibling-donor HSCTs with donors under 30 years of age experienced lower rates of chronic GVHD, faster platelet engraftment (P = 0.02), and trends toward improved OS, DFS, and GRFS, though the latter outcomes are not statistically significant. Apart from time to platelet engraftment, no significant variations were noted in neutrophil engraftment, GVHD incidence, or survival metrics. Acute GVHD has significantly reduced OS and DFS compared to those patients without aGVHD. There is limited data available on Pakistani cohorts, and this is the first study reporting impact of donor age on transplant outcomes.

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