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Age-Related Considerations in Allogeneic Hematopoietic Stem Cell Transplantation for Acute Leukemia: A 10-Year Retrospective Study

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ABSTRACT

Background: Allogeneic hematopoietic stem cell transplantation (HSCT) has long been a curative intervention for acute leukemia, though outcomes in older patients remain suboptimal due to higher non-relapse mortality (NRM) and relapse rates. Innovations in conditioning regimens and supportive care have made HSCT accessible to patients over 50, but age-related disparities in outcomes persist.

Materials and Methods: This 10-year retrospective cohort study reviewed all patients who underwent first-time allogeneic HSCT for acute leukemia. Patients were stratified by age at HSCT (≥ 50 years and < 50 years), and outcomes were assessed for overall survival (OS), disease-free survival (DFS), NRM, and relapse incidence (RI).

Results: Of the 1199 patients, 152 were 50 years or older. Five-year OS rates were markedly lower in patients ≥ 50 years compared to younger patients (48.70% vs. 59.35%; *P*= 0.024 for AML and 23.60% vs. 41.96%; *P*= 0.025 for ALL). Moreover, older patients demonstrated significantly higher NRM rates (35.95% vs. 23.53%; *P*= 0.045 for AML and 78.14% vs. 26.76%; *P*= 0.005 for ALL) and a notably increased incidence of grade III-IV acute graft-versus-host disease (aGVHD). Interestingly, no significant differences were observed between the two age groups regarding DFS rates and RI.

Conclusion: Older acute leukemia patients undergoing allogeneic HSCT face significant challenges, including elevated NRM and GVHD rates. While relapse rates were comparable, survival outcomes favored the younger cohort. These findings emphasize the need for age-adapted transplantation strategies, using reduced-intensity conditioning (RIC) regimens and further research to refine risk stratification and improve management approaches for older patients.

Keywords: Hematopoietic stem cell transplantation; Acute leukemia; Age; Overall survival; Non-relapse mortality

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a well-established treatment that offers a potential cure for patients diagnosed with various hematologic malignancies. Considering that most hematologic malignancies occur over the age of 60 years, achieving long-term disease control and the outcome of older acute leukemia patients remains unsatisfactory due to higher NRM and relapse rates. Historically, patients older than 55 years of age have been regarded as unsuitable candidates for allogeneic HCT. Contemporary enhancements in conditioning regimens, supportive care, and the

implementation of reduced-intensity conditioning (RIC) regimens have facilitated the transplantation of elderly patients[1,2]. Reduced-intensity conditioning results in less NRM but is associated with a higher relapse rate. Findings from retrospective studies using the RIC regimen show that age alone does not adversely affect the outcomes of allogeneic HSCTs, and that performance status was better predictive for outcome rather than age[3-5]. Despite the proposition of various risk assessments and prognostic factors to improve the outcomes of allogeneic SCT in older patients, the variability in treatment policies and care strategies for these patients across different facilities complicates the interpretation and comparison of the results of these studies[6]. In this study, we aimed to investigate the outcomes of patients with acute leukemia transplanted at 50 years of age or above at our institution and compare their outcomes with those of patients who received HSCT at younger ages.

Materials and Methods

Study Design

This retrospective cohort study was conducted at the Research Institute for Oncology, Hematology, and Cell Therapy (RIOHCT) of Shariati Hospital, Tehran, Iran, after obtaining approval from the ethics committee. From January 2010 to December 2020, all consecutive first-time recipients of allogeneic HSCT diagnosed with acute leukemia and aged 16 years or more were included in the study. Patients underwent transplantation with morphological and pathologic complete remission (CR) status. Patients' and donors' demographic, clinical, and laboratory data were extracted from their medical records using a structured checklist. The data were updated periodically, and the patients were followed up until the end of 2022. Before HSCT, written informed consent was obtained from the patients or their designated caregivers to allow for the utilization of their data within the research context.

Transplant Procedure

Peripheral blood stem cells (PBSCs) were the preferred source of grafts for all participants. As previously described[7], a uniform MAC regimen with busulfan and cyclophosphamide was used for all recipients, and prophylaxis against GVHD comprised of intravenous cyclosporine A (CyA) and methotrexate (MTX). Moreover, rabbit anti-thymocyte globulin (ATG) and post-HSCT cyclophosphamide (40 mg/kg/day on days +3 and +4) were used as a part of the GVHD prophylaxis regimen for the alternative HSCT recipients(8). Details of conditioning regimens and supportive care employed in allo-HSCT procedures at our institution have been previously published[8, 9].

Outcomes and definitions

The primary outcomes focused on assessing the probability of 5-year overall survival (OS) and disease-free survival (DFS). The secondary outcomes included evaluating the incidence of non-relapse mortality (NRM) and relapse within 4 years, grade III-IV aGVHD within 90 days, and extensive cGVHD over 3 years. OS was described as the duration from HSCT until the death of the patient. The process for diagnosing and classifying both acute and chronic GVHD adhered to the Glucksberg criteria and consensus guidelines provided by the National Institutes of Health[10, 11].

Statistical analysis

Comparisons between groups regarding demographic, clinical, and laboratory data were obtained using the Mann-Whitney U test for continuous variables and the chi-squared test for categorical variables. The median follow-up duration was established by applying the reverse Kaplan–Meier method. Furthermore, the Kaplan–Meier method was utilized to calculate the OS and DFS, and comparisons across various categories of each covariate were performed using the log-rank $\chi 2$ test. The Fine and Gray tests were also employed to determine and compare the cumulative incidences (CIs) of NRM, RI, grade III-IV aGVHD, and extensive cGVHD. Univariate and multivariable analyses using the Cox proportional hazard regression model were conducted to examine the impact of patient age on OS and DFS. Moreover, the Fine and Gray proportional subdistribution hazard regression model, both in univariate and multivariable forms, was employed to examine the associations between the recipient's age and the incidences of NRM and

relapse. Covariates such as recipient age (≥ 50 vs. < 50), primary disease (AML vs. ALL), pre-transplant disease status (CR≥ 2 vs. CR1), donor type (alternative vs. MRD), ABO matching (mismatch vs. match), and sex matching (F to M vs. others) were included in the initial univariate analyses. Only those variables that showed a p-value below 0.2 in these preliminary analyses were included in the subsequent multivariate analysis. A p-value of 0.05 was adopted as the criterion for statistical significance throughout the analysis process. STATA version 17 (StataCorp, LP, College Station, TX, USA) was used for statistical analyses.

RESULTS

The study cohort comprised 1199 patients undergoing allogeneic HSCT; 760 (63.40%) individuals were diagnosed with AML and 439 (36.60%) patients with ALL. Among AML patients, 126 (16.60%) were ≥ 50 years old, whereas only 26 (5.90%) patients with ALL were ≥ 50 years old. Females constituted 38.60% and 42.80% of patients aged < 50 and ≥ 50 years old in the study, respectively. There were significant differences in recipient sex and sex matching (F to M vs. others) between the two age groups (P= 0.006 for recipient sex and P= 0.027 for sex matching). However, no remarkable differences were observed in terms of donor sex, disease status, donor type, ABO matching, and graft cell dose (CD3+ and CD34+) between the two age groups in the entire cohort. The baseline characteristics and transplant-related data of the patients are presented in Table 1.

Table 1: Patients' baseline and transplant-related characteristics

		< 50 yr			≥ 50 yr			P
		AML	ALL	Total	AML	ALL	Total	
Number (%)		634 (60.55%)	413 (39.45%)	1047 (100%)	126 (82.89%)	26 (17.11%)	152 (100%)	-
Sex Recipient								
	Male	370 (57.50%)	273 (42.50%)	643 (100%)	72 (82.80%)	15 (17.20%)	87 (100%)	0.006-
	Female	264 (65.30%)	140 (34.70%)	404 (100%)	54 (83.10%)	11 (16.90%)	65 (100%)	
Donor								
	Male	339 (63.60%)	194 (36.40%)	533 (100%)	70 (89.70%)	8 (10.30%)	78 (100%)	0.249-
	Female	259 (59.10%)	179 (40.90%)	438 (100%)	48 (76.20%)	15 (23.80%)	63 (100%)	
Disease status								
	CR1	437 (58.60%)	309 (41.40%)	746 (100%)	101 (84.20%)	19 (15.80%)	120 (100%)	0.074-
	CR≥ 2	191 (65.20%)	102 (34.80)	293 (100%)	25 (83.30%)	5 (16.70%)	30 (100%)	
Donor type								
	MRD	524 (59.60%)	355 (40.40%)	879 (100%)	118 (83.70%)	23 (16.30%)	141 (100%)	0.240
	Alternative	110 (65.50%)	58 (34.50%)	168 (100%)	8 (72.70%)	3 (27.30%)	11 (100%)	
ABO matching								
	Matched	314 (59.40%)	215 (40.60%)	529 (100%)	65 (86.70%)	10 (13.30%)	75 (100%)	0.061
	Mismatched	251 (65.70%)	131 (34.30%)	382 (100%)	45 (80.40%)	11 (19.60%)	65 (100%)	
Sex matching								
	F to M	144 (57.40%)	107 (42.60%)	251 (100%)	27 (79.40%)	7 (20.60%)	34 (100%)	0.027
	Others	428 (64.00%)	241 (36.00%)	669 (100%)	83 (84.70%)	15 (15.30%)	98 (100%)	
Graft Cell Dose, mean±SD ($\times 10^6$/kg)								
	$CD34^+$	5.65±2.84	5.38±3.21	5.55±2.99	5.85±2.79	5.81±2.56	5.84±2.75	0.44
	$CD3^+$	292.48±96	289.08±111.98	291.13±102.61	279.96±83.98	252.75±106.61	275.36±88.36	

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CR, complete remission; F, female; M, male; MRD, matched related donor; SD, standard deviation

As shown in Table 2 and Figure 1, both AML and ALL patients who received HSCT at a younger age than 50 years were significantly more likely to have augmented OS at five years post-transplant than patients aged 50 years or older (59.35% vs. 48.70%; *P*= 0.024 for AML and 41.96% vs. 23.60%; *P*= 0.025 for ALL). In terms of five-year DFS, patients aged less than 50 years at transplantation were found to have enhanced DFS probability than patients 50 years or older in both AML and ALL groups; nevertheless, these differences turned out to be insignificant statistically (76.18% vs. 73.29%; *P*= 0.62 for AML and 57.27% vs. 50.64%; *P*= 0.96 for ALL) (Table 2).

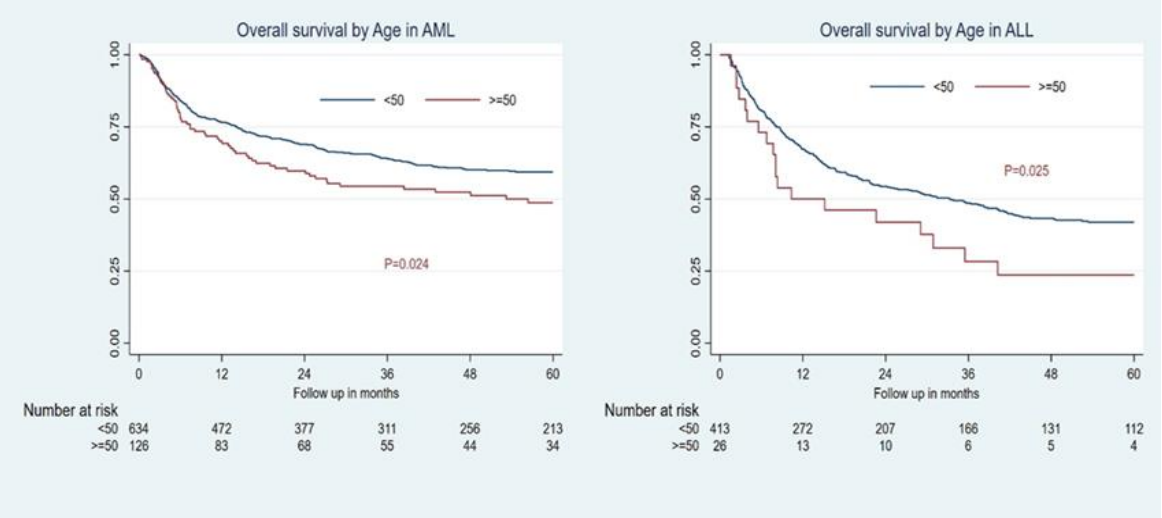

Figure 1. OS by Primary Disease and Age

Both AML and ALL patients aged 50 years and older demonstrated a significantly escalated NRM rate compared to patients under 50 years of age (35.95% vs. 23.53%; *P*= 0.045 for AML and 78.14% vs. 26.76%; *P*= 0.005 for ALL) (Table 2 and Figure 2). Regarding the four-year RI, however, patients aged less than 50 years showed a comparable rate to patients who received the graft at older ages within both AML and ALL groups (26.86 % vs. 26.24%; *P*= 0.504 for AML and 55.51% vs. 54.81%; *P*= 0.881) (Table 2).

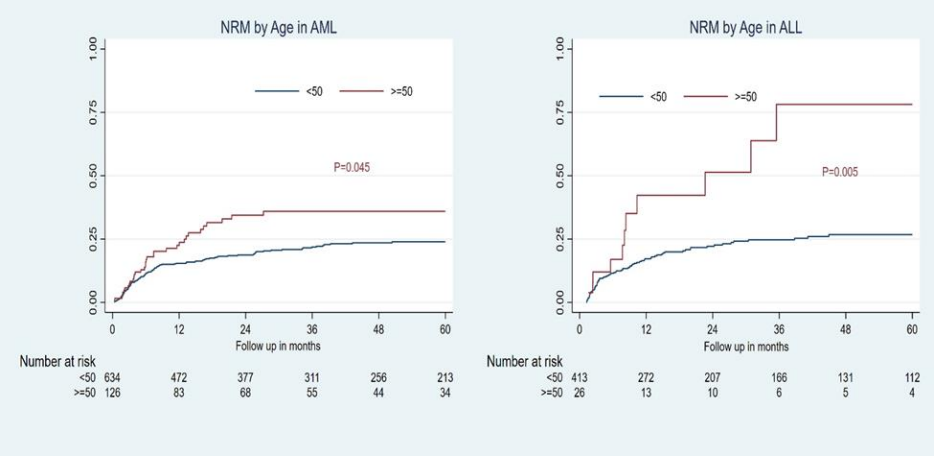

Figure 2. NRM by Primary Disease and Age

For grade III-IV aGVHD incidence, a notably increased rate was detected in older AML patients compared to younger patients (28.31% vs. 15.82%; *P*= 0.009). A similar trend was observed in the ALL group, although the difference was not statistically significant (21.12% vs. 14.11%; *P*= 0.406) (Table 2). Furthermore, older individuals in both AML and ALL groups were more likely to develop extensive cGVHD compared to their younger counterparts during the three-year post-transplant period; however, these differences were not significant (37.24% vs. 27.10%; *P*= 0.305 for AML and 31.42% vs. 21.47%; *P*= 0.511 for ALL) (Table 2).

Table 2: HSCT outcomes according to primary disease and age groups

Primary Disease		OS (%)	DFS (%)	Cumulative Incidence of NRM (%)	Cumulative Incidence of Relapse (%)	Cumulative Incidence of Grades III-IV aGVHD (%)	Cumulative Incidence of Extensive cGVHD (%)
		5 Yrs (95% CI)	***5 Yrs (95% CI)***	***4 Yrs (95% CI)***	***4 Yrs (95% CI)***	***90 days (95% CI)***	***3 yrs (95% CI)***
AML	< 50	59.35 (55.16-63.28)	76.18 (72.10-79.74)	23.53 (19.54-28.34)	26.86 (22.28-32.37)	15.82 (12.68-19.74)	27.10 (22.63-32.45)
	≥ 50	48.70 (39.11-57.62)	73.29 (62.19-81.60)	35.95 (25.51-50.66)	26.24 (16.87-40.83)	28.31 (19.45-41.21)	37.24 (25.69-53.97)
ALL	< 50	41.96 (36.91-46.91)	57.27 (51.68-62.46)	26.76 (21.30-33.61)	55.51 (46.66-66.05)	14.11 (10.80-18.43)	21.47 (16.49-27.95)
	≥ 50	23.60 (9.07-41.95)	50.64 (20.76-74.49)	78.14 (40.68-150.08)	54.81 (23.83-126.07)	21.12 (8.77-50.87)	31.42 (12.54-78.68)

aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; cGVHD, chronic graft-versus-host disease; CR, complete remission; DFS, disease-free survival; GFRFS, GVHD-free relapse-free survival; NRM, non-relapse mortality; OS, overall survival

Recipient age, disease status, donor type, and sex matching significantly predicted poor OS in univariate analysis. In contrast, the primary disease (AML vs. ALL) was the only factor associated with a better OS in the univariate analysis. The model fitted for multivariable analysis showed that recipient age (HR= 1.47, *P*= 0.004) and disease status (HR= 1.66, *P*= 0.000) posed a significant hazard for a diminished OS. On the other hand, patients suffering from AML (HR= 0.63, *P*= 0.000) were significantly associated with an elevated OS probability in the multivariable analysis (Table 3). Analyzing the factors affecting DFS, recipient age, primary disease, disease status, donor type, and sex matching showed a notable correlation with DFS in the univariate analysis. In the multivariable model, AML (HR= 0.61, *P*= 0.000) remained the only predictor of better DFS, while recipient age (HR= 1.46, *P*= 0.005) and disease status (HR= 1.67, *P*= 0.00) were the two factors predicting a worse DFS (Table 3).

Table 3. Univariate and multivariable analysis for OS and DFS

Factor	OS					DFS				
	Univariate			Multivariable		Univariate			Multivariable	
	HR (95% CI)		P Value	HR (95% CI)	P Value	HR (95% CI)		P Value	HR (95% CI)	P Value
Recipient age (≥ 50 vs. < 50)	1.29	(1.02-1.63)	0.034	1.47 (1.13-1.92)	0.004	1.26	(1.00-1.59)	0.052	1.46 (1.12-1.90)	0.005
Primary disease (AML vs. ALL)	0.66	(0.56-0.78)	0.000	0.63 (0.52-0.76)	0.000	0.64	(0.55-0.76)	0.000	0.61 (0.51-0.73)	0.000
Disease status (CR≥ 2 vs. CR1)	1.61	(1.35-1.92)	0.000	1.66 (1.36-2.02)	0.000	1.64	(1.37-1.95)	0.000	1.67 (1.37-2.04)	0.000
Donor type (alternative vs. MRD)	1.37	(1.10-1.70)	0.005	1.20 (0.94-1.52)	0.138	1.38	(1.11-1.71)	0.004	1.21 (0.96-1.54)	0.108
ABO matching (mismatch vs. match)	1.06	(0.89-1.27)	0.497			1.03	(0.86-1.24)	0.723		
Sex matching (F to M vs. others)	1.30	(1.07-1.57)	0.008	1.19 (0.98-1.45)	0.080	1.30	(1.07-1.57)	0.007	1.19 (0.98-1.44)	0.081

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete remission; F, female; M, male; MRD, matched related donor; HR, hazard ratio; DFS, disease-free survival; OS, overall survival

Univariate analysis conducted for NRM showed that recipient age, disease status, donor type, ABO matching (mismatch vs. match), and sex matching were significantly associated with higher NRM rates. Additionally, recipient age (HR= 1.65, *P*= 0.006) was the most robust predictor of NRM in the multivariable analysis. In addition to recipient age, donor type (HR= 1.54, *P*= 0.011), ABO matching (HR= 1.35, *P*= 0.027), and sex matching (HR= 1.53, *P*= 0.003) were also significant risk factors for NRM in the multivariable analysis (Table 4). In the univariate analysis of RI, the primary disease of AML and ABO matching were associated with decreased RI. In contrast, disease status of ≥ 2 was the unique risk factor for RI. Moreover, the multivariable analysis for RI revealed the primary disease of AML as the only protective factor (HR= 0.53, *P*= 0.000) and disease status of ≥ 2 as the only risk factor (HR= 1.96, *P*= 0.000) (Table 4).

Table 4. Univariate and multivariable analysis for NRM and RI

Factor	NRM					RI				
	Univariate			Multivariable		Univariate			Multivariable	
	HR (95% CI)		P Value	HR (95% CI)	P Value	HR (95% CI)		P Value	HR (95% CI)	P Value
Recipient age (≥ 50 vs. < 50)	1.62	(1.18-2.24)	0.003	1.65 (1.15-2.36)	0.006	0.93	(0.65-1.33)	0.704		
Primary disease (AML vs. ALL)	0.92	(0.71-1.20)-	0.549			0.51	(0.41-0.64)	0.000	0.53 (0.41-0.68)	0.000
Disease status (CR≥ 2 vs. CR1)	1.36	(1.04-1.79)	0.025	1.31 (0.97-1.77)	0.078	1.86	(1.47-2.34)	0.000	1.96 (1.52-2.53)	0.000
Donor type (alternative vs. MRD)	1.74	(1.28-2.35)	0.000	1.54 (1.10-2.15)	0.011	1.13	(0.82-1.55)	0.461		
ABO matching (mismatch vs. match)	1.44	(1.11-1.88)	0.006	1.35 (1.03-1.77)	0.027	0.80	(0.62-1.03)	0.078	0.81 (0.63-1.05)	0.116
Sex matching (F to M vs. others)	1.55	(1.18-2.04)	0.002	1.53 (1.16-2.02)	0.003	1.14	(0.87-1.49)	0.341		

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete remission; F, female; M, male; MRD, matched related donor; HR, hazard ratio; NRM, non-relapse mortality; RI,

During a median follow-up of five years, 479 (45.75%) patients in the group of patients transplanted at less than 50 years of age and 83 (54.60%) individuals who received the graft at older ages died, reflecting a considerable correlation between advanced age at HSCT and transplant-related mortality (TRM). Relapse was the leading cause of mortality in both age groups (57.20% in < 50 years group and 45.80% in ≥ 50 years group). Apart from relapse, GVHD (16.10%) was the most common cause of death among the patients receiving the transplant under 50 years old, while infection (22.90%) was the most common cause in patients aged 50 or older.

DISCUSSION

Our study encompassed 1199 patients who underwent allogeneic HSCT, with a significant proportion diagnosed with AML over ALL. Notably, a smaller percentage of older patients (≥ 50 years) were observed, especially within the ALL subgroup, indicating a potential selection bias or reflecting the incidence patterns of the disease with age. The outcomes of HSCT varied significantly with age, particularly highlighting the challenges older patients face. NRM rates were considerably higher in patients aged 50 years or above, a finding consistent across both AML and ALL cohorts.

Incidence of acute GVHD (grade III-IV) was significantly higher in the older age group among AML patients, pointing towards an age-related vulnerability to severe immune-mediated complications. While similar trends were observed in ALL patients and in extensive cGVHD rates across both diseases, these did not reach statistical significance, possibly due to the smaller sample size of older ALL patients or the inherent variability in GVHD manifestation.

Interestingly, the study found no significant difference in RI between the age groups, suggesting that once engrafted, the disease control aspects of the transplant process, such as the graft-versus-leukemia effect, may function comparably across ages. However, a significant discrepancy in OS and DFS favors younger patients, underscoring the compounded effect of non-relapse complications on older individuals. Multivariable analysis identified recipient age, disease status at transplant, donor type, and sex matching as significant predictors of NRM, with recipient age being a particularly potent risk factor. It also should be noted that one of the reasons for the increased NRM in individuals over 50 years old is that all these patients received MAC, while the use of RIC in older individuals leads to a reduction in NRM.

Recent years have witnessed a noteworthy discourse regarding the influence of patient age on allogeneic HSCT outcomes. The preference for allogeneic HSCT has been predominantly observed in younger patients, primarily driven by concerns regarding the elevated occurrence of morbidity and mortality associated with the treatment. Advanced age is widely acknowledged as a significant unfavorable factor in predicting outcomes following HSCT. The primary factors contributing to this include (1) the presence of underlying medical complexities or organ impairment, (2) a delayed drug metabolism process that amplifies the toxicity of conditioning regimens, and (3) a previously reported elevated incidence of GVHD in older patients[12-15].

During the initial phase of HSCT development, the maximum age limit was established at 40 years[16]. However, advancements in HSCT therapy have led to the opportunity to offer HSCT to patients older than 40 years[17-19]. The introduction of RIC and non-myeloablative conditioning (NMC) regimens as alternatives to MAC regimens has played a pivotal role in broadening the scope of HSCT to encompass patients with comorbidities and older age[1, 20-26].

A study conducted by Brunner et al.[23] investigated the outcomes of 54 allotransplanted patients aged ≥ 70 years using RIC regimens found a cumulative incidence of 56% and 5.6% for relapse and NRM at 2 years after the transplant, which their results in terms of NRM was obviously lower than the results obtained in our study for older patients who received MAC regimen. Another research effort in Japan, focusing on AML patients 50 years or older, showed no significant differences in survival or relapse rates between RIC and MAC, though RIC was associated with significantly lower NRM rates[26].

McClune et al.'s study on 1080 AML or myelodysplastic syndromes (MDS) patients over 40 years who had received RIC found no significant age-related differences in NRM, relapse, DFS, or OS in the

multivariable analysis, highlighting the impact of RIC regimen in older patients. Factors like HLA mismatch and poor cytogenetic profiles, however, did impact 2-year NRM, DFS, and OS[3]. Our analysis adds that ABO matching, donor type, and disease status at transplant are critical for NRM, OS, and DFS outcomes.

This study has several limitations and advantages. We performed this study in a homogeneous group of acute leukemia patients who underwent allo-HSCT using the identical Bu-based MAC regimen, graft source, and transplant approach with as few confounding variables as possible. Our study's limitations were its retrospective nature, single-center design, and use of an identical conditioning regimen for both age groups. Immune reconstitution data were lacking, and insufficient data on cytogenetic or molecular assessments made it difficult to perform routine MRD surveillance after transplantation or establish initial risk categorization.

CONCLUSION

Our study highlights the distinct challenges and outcomes of allogeneic HSCT in patients aged 50 years and above. Notably, older patients face higher NRM rates and increased incidence of GVHD, emphasizing the need for tailored treatment approaches. While relapse rates did not significantly differ between the two age groups, OS and DFS favored younger patients. These findings underscore the importance of age-adapted transplantation strategies, including enhanced pre-transplant screening and the use of RIC regimens, to improve outcomes for older patients undergoing HSCT. Further research is needed to refine risk stratification and optimize treatment approaches for this patient population.

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Ethical approval

Approval was obtained from the ethics committee of the Research Institute for Oncology, Hematology, and Cell Therapy (RIOHCT), Tehran University of Medical Sciences, Tehran, Iran (Approval Number: IR.TUMS.HORCSCT.REC.1401.022). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate

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

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Data availability statement

The corresponding author can provide the datasets created during the current investigation upon reasonable request.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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