Donor and Recipient Individual Factors as Predictive Markers of Overall Survival After Allogeneic Hematopoietic Stem Cell Transplantation; Dream or Reality

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Abstract- Low overall survival (OS) still is a major concern of allogeneic hematopoietic stem cell transplantation (allo-HSCT), which is affected by many individual and environmental factors. In this study, we retrospectively evaluated the association of donor and recipient individual factors with the overall survival of 206 patients who underwent allo-HSCT. Donor and recipient prognostic factors consisted of donor and recipient age, donor-recipient gender status, recipient body mass index (BMI), underlying disease, recipient cytomegalovirus (CMV) serostatus, and time from diagnosis to transplant (DTT) were included in the overall survival analysis. In univariable analysis, recipient age, donor-recipient gender status, underlying disease, recipient CMV serostatus, and DTT were significantly associated with the OS. The hazard of death in patients with DTT less than 14 months was 38% lower than those with a DTT higher than 14 months (*P*=0.06). Multivariate analysis showed that patients with aplastic anemia (HR=3.58; *P*=0.11) and Hodgkin's disease (HR=3.89; *P*=0.11) have a much lower survival than unclassified diseases. Moreover, patients with acute myeloid leukemia and acute lymphoblastic leukemia showed better outcomes compared to the unclassified group. The donor and patient characteristics such as age, CMV serostatus, underlying disease, and time from diagnosis to transplantation could influence the overall survival of patients after allo-HSCT.
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Keywords: Individual factors; Allogeneic hematopoietic stem cell transplantation (allo-HSCT); Overall survival

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has become a curative treatment for hematological malignancies (1). Despite the considerable improvement in transplantation practices, immunosuppressive drugs, and supportive care, some life-threatening complications like graft-versus-host disease (GvHD) affect the patients' survival. Many factors are considered as prognostic markers in allo-HSCT, including source of stem cells, conditioning regimen, infection, cytomegalovirus (CMV) serological status in donor and patient, underlying diseases, and blood group incompatibility. Moreover, the genetic disparity between donor and recipient, especially in human leukocyte antigen (HLA) loci, might considerably affect the allo-HSCT outcomes such as overall survival (OS), GVHD incidence, relapse, etc. (2).

Recently, some authors claimed that the donor and individual recipient factors such as age and body mass index (BMI) as well as donor-recipient gender matching status in allo-HSCT could have an influence on the patients' outcomes after transplantation (3-5). It has been proved that HSCT from younger donors can improve survival after transplantation (6). The fact that hematopoiesis and bone marrow cellularity decrease with age could be due to the diminished repopulating ability of hematopoietic stem cells of the aged donors after

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transplantation leading to delayed neutrophil and platelet engraftment (4,7).

Moreover, according to the BMI, which classified people as underweight, normal, overweight, and obese (5,8,9), it has been reported that patients with higher BMI show better outcomes with higher OS after allo-HSCT (5). Besides, donor-recipient gender disparity is considered as a risk factor of GVHD in the European Society for Blood and Marrow Transplantation (EBMT), and in many transplantation centers matching the genders is being used as a criterion for donor selection (6).

Accordingly, it seems necessary to evaluate the effects of the donor and recipient characteristics, including gender combination, age, BMI, underlying disease, and CMV serological status on the outcome of allo-HSCT. In the current study, we investigated the effects of recipient and donor characteristics on the patients' overall survival after allo-HSCT.

Materials and Methods

Patient and donor selection

This retrospective study was carried out on 206 patients who underwent allogeneic hematopoietic stem cell transplantation at Taleghani hospital, Tehran, Iran, between January 2008 and December 2017. Ethical approval was waived by the local Ethics Committee of the University (IR.SBMU.REC.1398.147). A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. The required data were collected by reviewing the patients' clinical records. Patients who had insufficient documentation or died before neutrophil and platelet engraftment were excluded from the study. Donors with 6/6 HLA-matched were considered as a fully matched donor. Recipient and donor characteristics are given in Table1.

Table 1. Prognostic Factors Descriptive Analysis

Characteristics		Mean SD/ Frequency (%)
Recipient Age		32.30 10.80
Missing		0(0%)
Donor Age		33.12 11.70
Missing		3(1.5%)
	Male-Male	58(28.2%)
	Male-Female	67(32.5%)
Donor-Recipient Gender	Female-Female	33(16%)
	Female-Male	48(23.3%)
	Missing	0(0%)
	Under 18.5	22(10.7%)
	Between 18.5-24.9	94(45.6%)
Recipient BMI	Between 25-29.9	61(29.6%)
	Upper 30	27(13.1%)
	Missing	2(1%)
	NHL	10(4.9%)
	HD	16(7.8%)
	AML	113(54.9%)
Diagnosed disease	ALL	50(24.3%)
	Aplastic Anemia	9(4.4%)
	Unclassified	8(3.9%)
	Missing	0(0%)
	Negative	85(41.3%)
Recipient CMV IgG	Positive	12(12.4%)
	Missing	109(52.9%)
	Sibling	195(94.7%)
Donor-recipient relationship	Related	11(5.3%)
	Missing	0(0%)
	Under 14 Months	136(66%)
DTT2	Upper 14 Months	70(34%)
	Missing	0(0%)

BMI. Body Mass Index; NHL. Non-Hodgkin Lymphoma; HD. Hodgkin Lymphoma; AML. Acute Myeloid Leukemia; ALL. Acute Lymphoid Leukemia; DTT. Diagnosis of transplant time

All patients with acute myeloid leukemia (AML) were received a standard myeloablative conditioning regimen consisting of intravenous (IV) busulfan (BU) 0.8 mg/kg, every 6 hours for four days, followed by IV cyclophosphamide (CY) 60 mg/kg or IV fludarabine (Flu) 30 mg/m^2 of body surface area once a day for five days. Reduced-intensity conditioning (RIC) regimen comprised of fludarabine 30 mg/m^2 IV for five days, CCNU 100 mg/m^2 P.O. for two days, and melphalan 40 mg/m^2 IV for one day used for patients with Hodgkin's disease (HD) or Non-Hodgkin lymphoma (NHL). Conditioning regimen for aplastic anemia patients

consisted of IV cyclophosphamide 50 mg/kg and rabbit anti-thymocyte globulin (ATG) 2.5 mg/kg IV for four days. Patients received cyclosporine A (CsA) 3 mg/kg/day IV from the day -2 until +5 (day of AHSCT considered as day zero) and 12.5 mg/kg/day P.O. until day +180 in combination with IV methotrexate (MTX) with dose of 10 mg/kg on day +1 and 6 mg/kg at days +3, +6 and +11.

Risk factors

The following risk factors were assessed in the study: donor-recipient gender combination (male-female, male-male, female-female and female-male), donor and recipient age, donor and recipient BMI:$\leqslant$18.5 kg/m^2 (underweight); 18.5-24.9 kg/m^2 (normal-weight); 25-29.9 kg/m^2 (overweight); $\geqslant$30 kg/m^2 (obese), recipient CMV serological status, underlying diseases (AML, ALL, HD, NHL, Aplastic anemia (severe aplastic anemia -Fanconi Anemia) and unclassified diseases including adrenoleukodystrophy (ALD), myelodysplastic syndromes (MDS) and thalassemia), and the diagnosis to transplant time (DTT).

Outcome

The outcome of the study was overall survival (OS). OS was defined as the interval from the date of transplantation to the time of death of any cause as an event or last follow-up.

Statistical analysis

OS was estimated using the Kaplan-Meier method. Univariable and multivariable analyses of time to event data were performed using the Cox proportional hazards model. The proportional hazard assumption was assessed by the score process plot and Kolmogorov-type supremum test (Significant level=0.05). Multivariable Model Selection was made with the backward method for selecting the features with the highest prognostic value. Computations were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). The Significant levels for univariable and multivariable analyses were assigned 0.20 and 0.10, respectively.

Results

Patient characteristics

The current study included 206 patients undergoing allo-HSCT. Overall, the mean±SD age of the recipient was 33.12±11.70. The male-male and male-female gender combinations were 28.2% and 32.5%, respectively. It was 16% for female-female and 23.3% for

female-male. The greatest part of the patients, 94 patients (45.6%), had a normal BMI (18.5-24.9). The most prevalent disease was acute myeloid leukemia (n=113(54.9%) followed by acute lymphocytic leukemia (n=50, (24.3%)), Hodgkin disease (n=16, (7.8%)), non-Hodgkin lymphoma (n=10, (4.9%)), and aplastic anemia (n=9(4.4%)). Other less frequent diseases included adrenoleukodystrophy, myelodysplastic syndromes, and thalassemia was categorized as "unclassified." Twelve patients (12.4%) were serologically positive for CMV. One hundred and ninety-five (94.7%) patients received grafts from matched sibling donors, and 11 patients received grafts from related donors. Among 206 patients, 201 patients were 6/6 full match, and in the other five patients, two donors were Haplo-identical match with the recipient, and three donors were mismatch in 1 allele (HLA-C) with the recipient. The diagnosis to transplant (DTT) time in 66% of patients was less than 14 months (Table 1).

Overall survival

The median and meantime of follow-up were 62 (95% CI:35-91) and 53 (95% CI: 45-61) months, in all patients, in the order given. One-year and 5-year OS in all patients were 65% and 52.15%, respectively (Figure 1A). A total of 66 patients (40.5%) died during the follow-up period, and the survival record of 43 patients (20.9%) was missing.

Univariable analysis

The donor age was not significantly associated with the OS in the patients (HR=0.99; 80% CI: (0.97-1.004); P=0.36). However, the recipient age significantly affected the OS (HR=0.978; 80% CI: (0.963-0.994); P=0.07), such that each year increase in the recipient age led to a 2.2% decrease in the hazard of death (Table 2). In donor-recipient gender status, the hazard of death in male-male and female-male was significantly lower than that of male-female (P=0.01; HR=0.47; 80%CI:(0.31-0.71)), (P=0.19; HR=0.64; 80%CI:(0.42-0.99)), respectively. Regarding the BMI, patients were divided into four groups, and the hazard of death in underweight, normal weight, and overweight recipients, compared to obese recipients was 1.56 (80% CI=(0.83-2.91)), 0.95 (80% CI=(0.57-1.58)), and 0.86 (80%CI=(0.49-1.48)), separately. However, none of these three reported HRs in BMI were statistically significant. Underlying diseases were significantly associated with the OS (P=0.02). The hazard of death in patients with aplastic anemia and HD was 2.93 (80% CI=(1.27-6.76) and 1.17 (80% CI=(0.51-2.69) times higher than those with unclassified diseases.

In ALL, AML and NHL patients, the hazard of death was lower than those diagnosed with "unclassified" diseases (HR=0.65; 80% CI=(0.31-1.35)), (HR=0.62; 80% CI=(0.31-1.24), and (HR=0.88; 80% CI=(0.33-2.35), respectively. (Figure 1B). As shown in Figure 1B, the patients with AML had the highest survival among other diagnoses, and patients with NHL had the lowest

survival. The hazard of death in CMV seronegative patients was 64% lower than those who were seropositive for CMV (HR=0.36; 80% CI=(0.21-0.64); *P*=0.02). Moreover, the death hazard in patients with DTT less than 14 months (HR=0.62; 80% CI=(0.45-0.86); *P*=0.06) was 38% lower than those whose DTT was more than 14 months (Table 2).

Table 2. Univariate and Multivariable Cox Proportional Hazard Models for Overall Survival

Variables		Univariable	
		HR(80% CI)	**P**
Recipient Age		0.978(0.963-0.994)	0.07*
Donor Age		0.990(0.97-1.004)	0.36
Donor-Recipient Gender			0.11*
	Female-Female	0.64(0.40-1.04)	0.24
	Female-Male	0.64(0.42-0.99)	0.19
	Male-Male	0.47(0.31-0.71)	0.01
	Male-Female(RL1)	-	-
Recipient BMI			0.52
	Under 18.5	1.56(0.83-2.91)	0.35
	Between 18.5-24.9	0.95(0.57-1.58)	0.90
	Between 25-29.9	0.86(0.49-1.48)	0.72
	Upper 30(RL1)	-	-
Diagnosis			0.02*
	ALL	0.65(0.31-1.35)	0.45
	AML	0.62(0.31-1.24)	0.38
	Aplastic Anemia	2.93(1.27-6.76)	0.09
	HD	1.17(0.51-2.69)	0.80
	NHL	0.88(0.33-2.35)	0.87
	Unclassified(RL[1])	-	-
Recipient CMV IgG	**Missing**		0.02*
	Negative	0.36(0.21-0.64)	0.02
	Positive	-	-
Donor-recipient relationship			0.23
	Related	1.66(0.96-2.88)	0.23
	Sibling(RL1)	-	-
DTT			0.06*
	Under 14 Months	0.62(0.45-0.86)	0.06
	Upper 14 Months(RL[1])	-	-

BMI. Body Mass Index; NHL. Non-Hodgkin Lymphoma; HD. Hodgkin Lymphoma; AML. Acute Myeloid Leukemia; ALL. Acute Lymphoid Leukemia; DTT. Diagnosis of transplant time

Multivariable analysis

The features with the highest prognostic value were entered in the final Cox proportional hazard model with backward selection method (Table 2). The proportional hazard assumption based on the score process plot and Kolmogorov-type supremum test for prognostic factors was established, and this model was validated. The diagnosed disease (*P*=0.01) and CMV seropositivity (*P*=0.6) were significantly associated with the overall survival of the patients. The adjusted survivals of the prognostic factors based on multivariable model indicate

that patients with HD (HR= 3.89; 90% CI=(0.92-16.35)); *P*=0.11) and then aplastic anemia (HR= 3.58; 90% CI=(0.95-24.23)); *P*=0.11) have much lower survival than unclassified diseases. Also CMV seronegative patients (HR= 0.4; 90% CI=(0.18-0.89)); *P*=0.06) have better survival than those with CMV seropositive (Figure 1C). Based on the multivariable analysis results, we also used our final model to predict the hazard of death for patients undergoing Allo-HSCT (Table 3). The highest association between CMV seropositivity and mortality rate was seen in aplastic anemia (HR=4.8; 90% CI=(0.95-

24.23)) and HD (HR=3.89; %90CI=((0.92-16.35)) patients (Table 3). The mortality rate in terms of diseases in the model at pairwise comparisons was obtained as well (Table 4). The mortality rate in aplastic anemia patients was higher than those diagnosed with "unclassified" diseases (HR=4.80; 90% CI=(0.95-24.23), NHL (HR=3.79; 90% CI=(0.44-32.84), and HD (HR=1.23; 90% CI=(0.23-6.47). Moreover, pairwise comparisons of the diseases revealed a higher mortality rate in HD patients compared to patients with unclassified diseases. (HR=3.89; 90% CI= (0.92-16.35) and then patients with NHL (HR=3.08; 90% CI=(0.45-21). Hazard ratio in NHL patients was also higher than those with "unclassified" diseases (HR=1.26; 90% CI=(0.18-8.86) (Table 4).
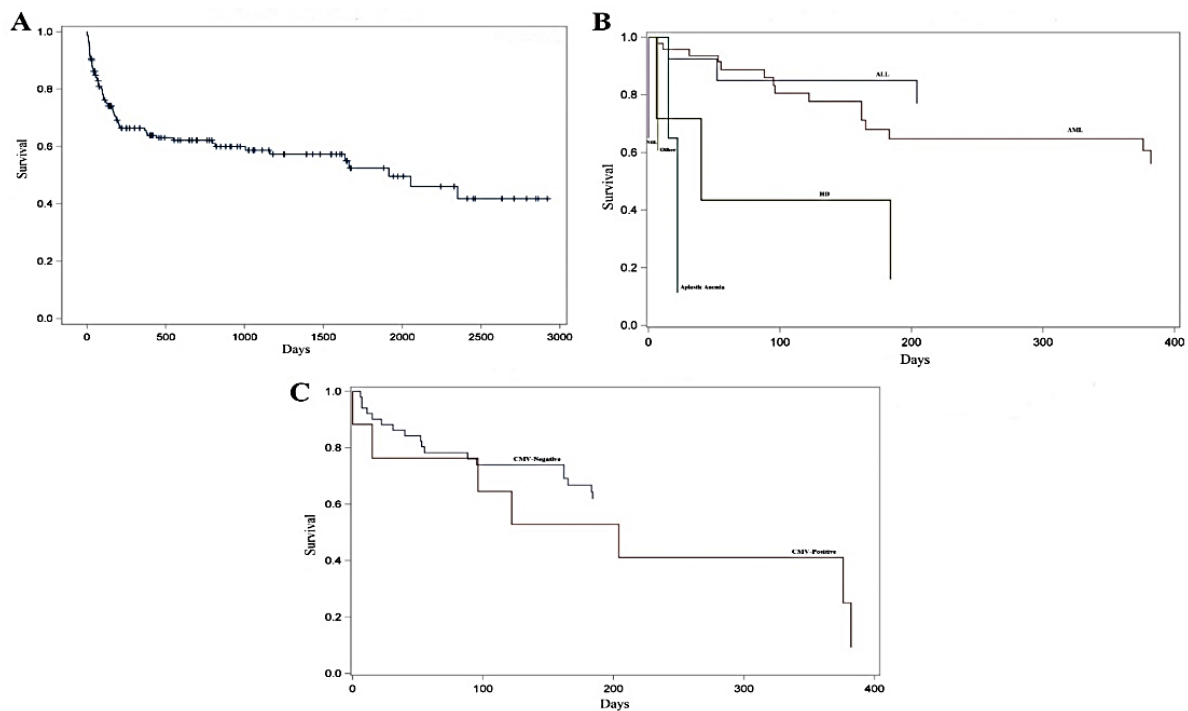

Figure 1. Overall survival plot and adjusted survival plots for risk factors in the multivariable model

Table 3. Hazard Ratios for all settings of significant prognostic factors based on final multivariable cox proportional hazard model

Setting	Diagnosis	Recipient CMV IgG	HR	(90% CI)
1	ALL	Negative	0.14	(0.03-0.59)
2	ALL	Positive	0.35	(0.08-1.39)
3	AML	Negative	0.26	(0.08-0.84)
4	AML	Positive	0.65	(0.22-1.91)
5	Aplastic Anemia	Negative	1.93	(0.31-11.99)
6	Aplastic Anemia	Positive	4.80	(0.95-24.23)
7	HD	Negative	1.57	(0.38-6.38)
8	HD	Positive	3.89	(0.92-16.35)
9	NHL	Negative	0.51	(0.07-3.55)
10	NHL	Positive	1.26	(0.18-8.86)
11	Unclassified	Negative	0.40	(0.18-0.89)
12	Unclassified	Positive	1	(-)

BMI. Body Mass Index; NHL. Non-Hodgkin Lymphoma; HD. Hodgkin Lymphoma; AML. Acute Myeloid Leukemia; ALL. Acute Lymphoid Leukemia; DTT. Diagnosis of transplant time

Table 4. Hazard Ratios for diagnosis in the model at pairwise comparisons of levels

Pair wises	Diagnoses	HR	(90% CI)
1	ALL vs. AML	0.54	(0.19-1.53)
2	ALL vs. Aplastic Anemia	0.07	(0.01-0.38)
3	ALL vs. HD	0.09	(0.02-0.35)
4	ALL vs. NHL	0.27	(0.04-1.86)
5	ALL vs. Unclassified	0.35	(0.08-1.39)
6	AML vs. Aplastic Anemia	0.13	(0.04-0.55)
7	AML- vs. HD	0.16	(0.05-0.48)
8	AML- vs. NHL	0.51	(0.09-2.84)
9	AML- vs. Unclassified	0.65	(0.22-1.91)
10	Aplastic Anemia vs. HD	1.23	(0.23-6.47)
11	Aplastic Anemia vs. NHL	3.79	(0.44-32.84)
12	Aplastic Anemia vs. Unclassified	4.80	(0.95-24.23)
13	HD vs. NHL	3.08	(0.45-21)
14	HD vs. Unclassified	3.89	(0.92-16.35)
15	NHL vs. Unclassified	1.26	(0.18-8.86)

* Significant at 0.20; ** Significant at 0.1; RL. Reference Level; BMI. Body Mass Index; NHL. Non-Hodgkin Lymphoma; HD. Hodgkin Lymphoma; AML. Acute Myeloid Leukemia; ALL. Acute Lymphoid Leukemia; DTT. Diagnosis of transplant time

BMI. Body Mass Index; NHL. Non-Hodgkin Lymphoma; HD. Hodgkin Lymphoma; AML. Acute Myeloid Leukemia; ALL. Acute Lymphoid Leukemia; DTT. Diagnosis of transplant time

Discussion

In the current retrospective study of 206 patients who received allo-HSCT, the median follow-up was 62 months, and 5-years OS was 52.5%. The most common disease in our study was AML, followed by ALL, HD, NHL, aplastic anemia, and other disorders.

Our result implies that the underlying diseases as an independent factor can significantly influence the OS rate. The greatest hazard of death was mostly observed in patients with less frequent diseases, including ALD, MDS, and thalassemia, while the most favorable outcomes were seen in patients with AML, followed by ALL patients. In a study conducted by Ghavamzadeh *et al.*, in 2013, thalassemia patients who underwent allo-HSCT showed a superior OS (79.3% (SE: 2.1%)), compared with other hematological disorders (10). This contrary could be due to the few thalassemia cases (totally four patients) in our report. Similar to our findings, Vaezi *et al.*, have shown that AML patients had better survival than those with ALL (11). Therefore, the success of allo-HSCT is heavily influenced by the type of underlying disease.

We have also found that the lower DTT significantly decreased the hazard of death after allo-HSCT. These findings are in line with some previous studies (12,13). Gratwohl *et al.*, in a large cohort study on 56605 patients with hematologic malignancy who underwent allo-HSCT, showed a significant effect of DTT on the OS.

However, they could not find any significant association between DTT and OS in patients who underwent allogeneic-HSCT who were in their first complete remission (CR) (12). According to some studies on atypical chronic myeloid leukemia (CML) (14) and on AML patients in the first CR, (15) the ones with DTT more than 12 months had a greater hazard of death compared to the patients with DTT less than six months; however, it was nonsignificant (14). We did not consider the remission status of the patients in our regression models, which could be another cause of the differences. Nevertheless, it should be noted that the role of DTT in predicting the allo-HSCT outcomes has long been controversial, and assessing DTT in patients with different CRs is likely to be effective in resolving this conflict.

Based on our data, OS in CMV seronegative patients was better than CMV seropositive patients. These results confirm previous studies showing an association between the CMV seropositivity of recipients with poor prognosis in acute leukemia patients who underwent allo-HSCT (16,17). Kollman *et al.*, showed that the CMV status of the recipient at the time of transplantation could be considered as a predictive factor of survival (6). Although there are considerable advances in strategies for managing and prophylaxis of CMV, seropositivity of CMV in donor and recipient remains a significant risk factor for complications after transplantation. Multivariate analyses confirmed the prognostic value of

CMV serologic status. Delayed treatment of CMV and treatment unresponsiveness has been reported to be associated with a high mortality rate (18). CMV infections affect the allo-HSCT through several ways, including interfering with hematopoiesis, bone marrow stromal damage (19-21), and induction of immune suppression through MHC downregulation, production of MHC-like protein to disrupt NK cell cytotoxicity, and suppression of T-cell proliferation (22).

Although the recipient age (2,23) and BMI (5,24-26) and also the donor-recipient gender status have been considered in various studies as independent risk factors affecting OS after the allo-HSCT, no significant effect was found in our multivariate regression model. In this study, there was no significant association between BMI and overall survival, but survival appears to be increased with increasing BMI as patients with BMI $\geq$24 kg/m^2 had higher survival compared to those with lower BMI. In a report by Flegal *et al.*, 97 studies with a sample size of 2.88 million individuals and 270,000 deaths were analyzed and suggested that overweight and class I obese (BMI 30 to 34.9) recipients had a significantly decreased risk of mortality, compared to recipients with normal weight (29). Yang *et al.*, in a study, indicated the association of recipient BMI before transplantation and the OS of patients with allo-HSCT in which overweight and obese patients showed significantly lower mortality rate (40% HR=0.60; 95% CI: 0.38-0.95) than underweight patients (5). One possible reason is that the weight-loss which is caused by GvHD-related gut injury and chemotherapy-induced gastrointestinal toxicity will take more time in obese and overweight patients so that patient nutrition can be considered as a prognostic factor for patient survival (5,30). Moreover, busulfan and cyclophosphamide that are used in conditioning regimen are lipophilic drugs, and obese or overweight patients have a larger volume of distribution and reduced drug clearance, which may affect the metabolism of these drugs, and as a result, overweight and obese patients might have more prolonged exposure to drug leading better outcomes (31,32). Interestingly, it has been reported in a study that adipose tissue-derived mesenchymal stromal cells could inhibit GvHD incidence after allo-HSCT in recipients (30), so it can probably result in lower GvHD incidence and better survival in obese or overweight recipients having more such adipose-derived stromal cells.

HSCT from a matched sibling donor is the best treatment option for patients with severe aplastic anemia. However, post-transplant complications such as graft rejection, GvHD, and engraftment failure lead to a low survival rate in these patients (31). The limited number of these patients in our study, as well as severe disease status, may explain the unfavorable post-transplant outcome of these patients, compared to other diseases such as HD and NHL.

Patients with HD who relapsed after autologous transplantation are considered as an allo-HSCT candidate in our center. These patients were not in the first CR, and their conditions might have a role in the worsening their allo-HSCT outcome. Therefore, patient clinical status at the time of admission should be considered as a critical factor that can affect the outcome of transplantation. Results in our study showed a higher mortality rate in ALL patients as compared with those with AML. This difference in mortality rates might be due to the better condition of AML patients at the admission time as they are admitted in partial remission or after 2 or 3 complete remissions, while patients with ALL are admitted after first complete remission. Conclusively, after adjusting of potential confounding factors, CMV seropositivity and underlying diseases were determined as significant independent OS predictive factors after allo-HSCT. Based on our findings, individual characteristics of donor and recipient have no significant OS predictive value after allo-HSCT.

Acknowledgments

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