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Original Article

Analysis of Correlation between Body Mass Index and the Incidence of Graft-Versus-Host Disease in Allogeneic Hematopoietic Stem Cell Transplantation

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ABSTRACT

Background: Graft-versus-host disease (GVHD) is a life-threatening complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Identifiying the probable risk factors can help the clinicians manage the consequences of GVHD. The main aim of this study was to analyze the correlation of body mass index (BMI) as a risk factor with the GVHD incidence.

Methods: This retrospective study was conducted on 199 patients who received allo-HSCT during 2007-2017, as well as their donors. Almost all included patients received 10/10 human leukocyte antigen (HLA)-matched allogeneic stem cell transplants. The clinical data, including BMI, underlying disease and GVHD incidence, were collected from the clinical records.

Results: In the present study, GVHD was seen in 77 (38.6%) patients, including 59 acute and 18 chronic GVHD. The most frequent BMI range in both donors (35.5%) and recipients (45.2%) was between 18.5- 24.9 kg/m^2. The transplants in which the BMI of donors were below 18.5 kg/m^2 had 58% lower odds of GVHD incidence, compared to those with obese donors (CI: [0.21-0.85]; P = 0.05). Conversely, the donors with a BMI between 18.5 and 24.9 kg/m^2 led to a 19% higher odds of GVHD incidence, especially acute GVHD, than transplants from donors with BMI above 30 kg/m^2 (CI: [0.68-2.09]; P = 0.09). The recipients with a BMI between 18.5 and 24.9 kg/m^2 had the odds of GVHD incidence 63% more than those with a BMI above 30 kg/m^2 (CI: [0.89-3.06]; P= 0.3).

Conclusions: The findings of the present study suggest the donor's BMI as a probable GVHD risk factor so that the BMI lower than 18.5 kg/m^2 was statistically correlated with a decreased incidence of GVHD.

Keywords: Allo-HSCT, BMI, GVHD, Risk factor

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Introduction

Graft-versus-host disease (GVHD) is a prominent cause of morbidity and mortality following allogeneic hematopoietic stem cell transplantation (allo-HSCT), which can be clinically classified as acute (aGVHD) and chronic (cGVHD) forms (1-4). Activation of donor-derived T cells recognizing the allogeneic major histocompatibility complexes (MHCs) and minor histocompatibility antigens (MiHAs) of the recipients is regarded as the main mechanism underlying GVHD leading to inflammation in several organs such as eyes, skin, liver, and gastrointestinal system of the recipient (5). In refractory cases (to first-line corticosteroid-containing regimens), some of the most destructive diseases including skin sclerosis, severe ocular keratopathy, bronchiolitis obliterans (BO) syndrome, and fibrosis in the gastrointestinal tract, liver, and genitalia (6) cause poor survival (<5 years) in patients (7). Despite the use of various conditioning regimens, immunosuppressive drugs and effective anti-infective agents, both aGVHD and cGVHD have remained life-threatening complications of allo-HSCT (7-9). The frequency of GVHD and its lethal consequences accentuate the necessity of investigation to find any risk factors which correlate with the higher GVHD incidence or intensity.

Body mass index (BMI) is a medical indicator for identifying obesity and body fatness in individuals (10). This is a score obtained by dividing weight (in kilograms) by height (in meters squared) (11). In fact, the rate of obesity and weight loss is calculated on the basis of this global formula. Although some experts may not accept this indicator, BMI is an international standard, based on which the World Health Organization (WHO) identifies and classifies the countries with obese population (12). In the last report of the WHO, 210 countries around the world have been classified according to their obese population, in which Iran with 25.8% obese people and an average BMI of 26.2 kg/m^2 is ranked as the 62nd one (13, 14).

In recent studies of risk factors for GVHD in allo-HSCT, it has been reported that the recipient and donor BMI play important roles in GVHD incidence (15, 16). Obesity and low BMI are related to poor responses to chemotherapy regimen, infections, and mortality in hematological malignancy. A vast retrospective study by the Center for International Blood and Marrow Transplant Research (CIBMTR) confirmed that in patients who received stem cells from both related and unrelated donors, the overall survival (OS) in patients with low BMI (BMI<18.5 kg/m^2) was lower than those with normal BMI, mostly because of the increased risk of relapse (15). Also, an increased OS was seen in allo-HSCT patients with BMI ≥23 kg/m^2, compared to those with lower BMI (16). On the other hand, obesity was associated with an increased risk of some post-transplant complications such as infection and GVHD. It was revealed that minor obese patients undergoing allogeneic HSCT have worse outcomes with grade II to IV aGVHD (17). Therefore, BMI can be considered as a risk factor for GVHD prognosis. However, due to the inconsistency of the findings in this area, it was decided to investigate the impact of BMI on the incidence of GVHD in the Iranian allo-HSCT patients.

Materials and Methods

Patients

This retrospective study was performed on 199 patients (102 males and 97 females) with a mean age of 32.50 ±10.79 years who underwent allo-HSCT from 2007 to 2017 at Hematopoietic Stem Cell Transplantation Center of Taleghani Hospital, Tehran, Iran.

All included individuals signed the informed consent and the study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethical code: IR.SBMU.REC.1398.146). The demographic and clinical data such as age, BMI (of patient and donor), underlying disease, donor-recipient relationship, conditioning and GVHD prophylaxis regimens, and incidence of GVHD were collected from the clinical documents (Table1). The studied hematological disorders mainly included acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), Non-Hodgkin Lymphoma (NHL), Hodgkin's disease (HD), and aplastic anemia (AA). 194 (97.5%) of patients received allogeneic stem cell transplants, which were fully matched in HLA-A, -B, -C, -DRB1, and -DQB1 locus, while 5 (2.5%) of transplants were only miss-matched in one loci. HLA typing was performed using single specific primer-polymerase chain reaction (PCR-SSP) method described previously by Gaudet et al in 2009. (18).

Table 1. Descriptive analysis

Characteristics	Mean ± SD/Frequency (%)
Recipient Age (year)	32.50 ± 10.79
Missing	3(1.5%)
Donor-recipient Gender	
Male-Male	56(28.1%)
Male-Female	61(30.7%)
Female-Female	32(16.1%)
Female-Male	48(24.1%)
Missing	2(1%)
Recipient BMI (kg/m^2)	
Below 18.5	22(11.1%)
Between 18.5-24.9	90(45.2%)
Between 25-29.9	58(29.1%)
Above 30	26(13.1%)
Missing	3(1.5%)
Donor BMI (kg/m^2)	
Below 18.5	34(17.1%)
Between 18.5-24.9	71(35.5%)
Between 25-29.9	49(24.6%)
Above 30	32(16.3%)
Missing	13(6.5%)
Diagnosed disease	
NHL	13(6.5%)
HD	12(6%)
AML	102(51.3%)
ALL	54(27.1%)
Aplastic Anemia	8(4%)
Other	6(3%)
Missing	4(2%)
Donor-recipient relationship	
Sibling	148(74.4%)
Related	43(21.6%)
Missing	8(4%)
HLA	
Match	194(97.5%)
Mismatch	5(2.5%)
Missing	0(0%)

Table 1. Descriptive analysis

Conditioning regimen	
Bu/Cy	100(50.3%)
Bu/Flu	46(23.1%)
Bu/Flu/ATG	16(8%)
RIC	25(12.6%)
Aplastic anemia	8(4%)
Missing	4(2%)
Prophylaxis regimen	
CSA+MTX	179(89.9%)
CSA+MTX+ATG	20(10.1%)
Missing	0(0%)
GVHD incidence	
Yes-GvHD	77(38.6%)
No-GvHD	122(61.4%)
GVHD type	
Acute	59(76.6%)
Chronic	18(23.4%)

SD: Standard deviation; BMI: Body mass index; NHL: Non-Hodgkin lymphoma; HD: Hodgkin disease; AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; HLA: Human leukocyte antigen; Bu: Busulfan; Cy: Cyclophosphamide; Flu: Fludarabine; ATG: Anti-thymocyte globulin; RIC: Reduced-intensity conditioning; CSA: Cyclosporine A; MTX: Methotrexate; GVHD: Graft-versus-host disease.

Conditioning regimen

The myeloablative conditioning regimen received intravenously (IV) consisted of busulfan (BU) 0.8 mg/kg every 6 hours for 4 days followed by either two days of cyclophosphamide (CY) 60 mg/kg/day or fludarabine (Flu) 30 mg/m^2 of body surface area once a day intravenously for 5 days, started at 7 days before transplant. Reduced-intensity conditioning regimen (RIC) used for patients with HD and NHL comprised of Fludarabine 30 mg/m^2 IV for 5 days, CCNU 100 mg/m^2 P.O. for two days, and Melphalan 40 mg/m^2 IV for one day. Patients with aplastic anemia received CY (60 mg/kg/day) along with anti-thymocyte globulin (ATG) (1.5 mg/kg/day) for three days before transplant.

Peripheral blood stem cell isolation

Hematopoietic stem cells were mobilized to the peripheral blood after 4 days subcutaneous administration of 5-10 µg/kg granulocyte-colony stimulating factor (G-CSF) (filgrastim, Amgen, US) to the donors and harvested using apheresis Spectra Optia (Terumo BCT, Lakewood, CO) during 250 minutes depending on the volume and speed of donor peripheral blood stem cells (PBSCs) flow. The viability of cells in the apheresis product was evaluated using Trypan blue staining (Sigma-Aldrich, Germany). The CD34$^+$ (PE-conjugated, EXBIO) cells and mononuclear cells (through gating on forward scatter to side scatter) cells were counted using flow cytometry (Attune NxT; Life Technologies). All patients received 2-4×10^8 and 2-4×10^6 unmanipulated mononuclear cells (MNCs) and CD34$^+$ cells/kg, respectively.

GVHD Prophylaxis and Diagnosis

All patients received cyclosporine A (3 mg/kg/day) from day -2 to +5, intravenously (day of transplantation was considered as day 0) and P.O. (12.5 mg/kg/day) until day +180 in combination with methotrexate (MTX, 10 mg/kg) IV at day +1 followed by MTX IV (6 mg/kg) at days +3, +6, and +11 as GVHD prophylaxis. Twenty patients received ATG (2.5 mg/kg) for two days (-1 and -2) in addition to the routine GVHD prophylaxis.

The standard clinical signs such as rash, diarrhea, and liver function abnormalities along with biopsy and histopathological examination in the involved organ were the main criteria for diagnosis and categorizing GVHD, based on the National Institute of Health (NIH) criteria (19).

Statistical analyses

The univariable analysis of GVHD incidence data was performed using the Logistic regression model. The Hosmer–Lemeshow test was conducted for the goodness of fit of our Logistic model. The associations among different categories of GVHD and donor and recipient BMI were performed through Chi-square test. Computations were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, US) and SPSS version 19.0 (SPSS Inc., Chicago, IL, US). The level of statistical significance for univariable analyses was set at 20%.

Results

Patient characteristics

A total of 199 patients who had received allo-HSCT, were included in the present study. GVHD was seen in 77 (38.6%) patients. The most frequent BMI range in both donors (n = 71, 35.5%) and recipients (n = 90, 45.2%) was between 18.5 and 24.9 kg/m^2. Acute myeloid leukemia (AML) was the most prevalent leukemia among all types of leukemia. (n = 102, 51.3%), followed by acute lymphocytic leukemia (ALL) (n = 54, 27.1%), non-Hodgkin lymphoma (n = 13, 6.5%), Hodgkin's disease (n = 12, 6%), and aplastic anemia (n = 8, 4%). Other less frequent diseases, including adrenoleukodystrophy (ALD), myelodysplastic syndromes (MDS), and thalassemia were categorized as "others". Most of the patients (n = 148, 74.4%) received grafts from sibling donors and 43 (21.6%) patients received grafts from non-sibling related donors. Among 77 patients who developed GVHD, 59 patients (76.6%) manifested with acute GVHD and 18 individuals (23.4%) developed chronic GVHD (Table1).

Univariable Analysis

According to Tables 2 and 3, the donor's BMI significantly affected the incidence of GVHD. The donors with a BMI below 18.5 kg/m^2 had 58% lower odds of GVHD incidence, compared to those with a BMI above 30 kg/m^2 (CI: [0.21-0.85]; P = 0.05). Conversely, the donors with a BMI between 18.5 and 24.9 kg/m^2 had an odds of incidence 19% higher than those with a BMI above 30 kg/m^2 (CI: [0.68-2.09]; P = 0.09). The recipients whose BMI was between 18.5 and 24.9 kg/m^2 had an odds of incidence 63% greater than those with a BMI above 30 kg/m^2 (CI: [0.89-3.06]; P = 0.30). Table 3 illustrates the association of GVHD types and different levels of BMI in myeloablative and non-myeloablative conditioning regimens. Only one patient who received a non-myeloablative conditioning regimen developed chronic GVHD, while 17 patients with myeloablative conditioning regimen showed chronic GVHD. Twenty-three myeloablative transplants, in which the donors had a BMI below 18.5 kg/m^2 (85.2%), manifested no GVHD. As can be seen in the myeloablative transplants, donors with a BMI below 18.5 kg/m^2, significantly associated with not developing GVHD (P = 0.02), and the donors with BMI of 18.5-24.9 kg/m^2 revealed a significant association with acute GVHD (P=0.03).

Table 2. Univariable logistic regression models for graft-versus-host disease

Variables	Univariable	
	Odds Ratio (80% CI)	P-value
Recipient BMI		0.64
Below 18.5	1.05(0.47-2.33)	0.59
Between 18.5-24.9	1.63(0.89-3.06)	0.30
Between 25-29.9	1.56(0.83-3.03)	0.43
Above 30(RL[1])	-	-
Donor BMI		0.17*
Below 18.5	0.42(0.21-0.85)	0.05**
Between 18.5-24.9	1.19(0.68-2.09)	0.09**
Between 25-29.9	0.83(0.45-1.51)	0.91
Above 30(RL[1])	-	-

1. Reference level; *Significant at 0.2; **Significant at 0.1.

Table 3. Recipient and donor BMI and GVHD incidence

Type of Conditioning Regimen	BMI (KG/M^2)	GVhD		
	Recipient BMI	**Acute**	**Chronic**	**No-GVHD**
	Below 18.5	3(75%)	0(0%)	1(25%)
	18.5-24.9	8(47.1%)	0(0%)	9(25.9%)
	25-29.9	4(30.8%)	1(7.7%)	8(61.5%)
	Upper 30	0(0%)	0(0%)	3(100%)
Non-Myeloablative	**Donor BMI**			
	Below 18.5	4(57.1%)	0(0%)	3(42.9%)
	18.5-24.9	8(50%)	0(0%)	8(50%)
	25-29.9	1(12.5%)	1(12.5%)	6(75%)
	Upper 30	2(100%)	0(0%)	0(0%)
	Recipient BMI			
	Below 18.5	3(16.6%)	1(5.6%)	14(77.8%)
	18.5-24.9	23(31.5%)	7(9.6%)	43(58.9%)
	25-29.9	12(26.7%)	6(13.3%)	27(60%)
Myeloablative	Upper 30	4(17.4%)	3(13%)	16(69.6%)
	Donor BMI			
	Below 18.5	3(11.1%)	1(3.7%)	23(85.2%)*
	18.5-24.9	22(40%)*	3(5.5%)	30(54.5%)
	25-29.9	8(19.5%)	8(19.5%)	25(61%)
	Upper 30	9(30%)	4(13.3%)	17(56.7%)

*Significant at 0.05.

Discussion

The present study aimed to find a possible correlation between the donor and recipient BMI and GVHD in 199 Iranian allo-HSCT patients. The GVHD incidence in the recipients with a BMI between 18.5 and 24.9 kg/m^2 was higher than those with a BMI above 30 kg/m^2. However, this association was not statistically significant. In addition, the underweight recipients had insignificant lower GVHD incidence compared to those with normal and high level BMI. In general, with a little ignorance, it can be concluded that the GVHD incidence is higher in recipients with high BMI except for obese patients, compared to those with low BMI. In a study by Fuji et al. (2014) about the impact of pre-transplant BMI on allogeneic HSCT, it was illustrated that patients with a low BMI had the worst OS due to an increased risk of relapse caused by lower doses of received chemotherapy (10, 14, 20). In contrast, patients with a high BMI had the highest Non-Relapse Mortality (NRM) because of an increased risk of GVHD-related mortality. Besides, they assumed that the greater tissue damage caused by a higher dose of chemotherapy might lead to a cytokine storm, which precedes acute GVHD (21). One other hypothesis is the different immune status in those with different BMI values. According to the literature, in overweight patients, the number of adipose tissue-resident immune cells, such as macrophages, CD8$^+$ T cells, and IFN-γ^+ Th1 cells is increased, while the number of regulatory T cells is decreased. These adipose tissue-resident alloreactive cells in overweight patients might raise the alloimmune reaction after allo-HSCT leading to GVHD (10-14). Furthermore, the roles of adipokines in the control of immunity should be taken into account (22-24). Interestingly, leptin, an adipokine which its high level has been found to be associated with the body fat weight, can affect regulatory T cell (Treg) proliferation and function (25, 26). Thus, in overweight patients, a higher leptin level suppresses Treg activity and increases the risk of acute GVHD. Moreover, the inflammatory factors such as IL-1β, IL-6, and TNF- α were found to be high in overweight (BMI: 25–29.9 kg/m^2) patients (27).

In the present study, the recipients whose donors had a BMI ≤ 18.5 kg/m^2 and normal BMI (BMI: 18.5-24.9 kg/m^2) showed a lower and higher odds ratio of GVHD incidence, respectively, compared to those with a BMI above 30 kg/m^2. It might suggest the donor BMI as a probable factor deserves more attention in allo-HSCT. The results of this study are inconsistent with the results of previous research regarding donor obesity and BMI not being risk factors for GVHD (28). A study by Hadjibabaie (2012) on 192 patients with acute leukemia who underwent allo-HSCT reported that patients with higher BMI might have a shorter engraftment time, but lower survival rate compared to non-obese patients (29).

Given the results of this study, which revealed that the transplants from underweight donors had lower odds of GVHD incidence compared to those received from donors with either normal or higher BMI (overweight and obese), it can be concluded that high BMI in donors might lead to more GVHD incidence in recipients. It was also found that the donors with a BMI between 18.5 and 24.9 kg/m^2 caused more GVHD incidence in comparison with the obese donors (BMI above 30 kg/m^2). To explain this result, it should be noted that there are many factors capable of affecting the HSCT outcome and should be considered as GVHD risk factors including the type and dose of the conditioning regimen, the stem cell source and dose, the amount of transplanted immune cells, the underlying disease and etc.

To determine the exact association of different types of GVHD (acute and chronic) with BMI levels, individuals were separated based on different conditioning regimens (Myeloablative and non-Myloablative), and then, analyses were performed to determine any association between their BMI levels and GVHD type. According to the results, in the myeloablative transplants, the underweight donors were significantly associated with reducing the GVHD incidence, while donors with normal BMI increased the risk of acute GVHD. Interestingly, all the results of the analysis of whole 199 patients (Table 2) are consistent with those obtained from analysis of the patients who underwent transplants with myeloablative conditioning regimens (Table 3). It suggests that the associations mentioned above might be more critical in the myeloablative transplants.

Conclusion

According to the results of this study, there is a correlation between BMI of donors and GVHD occurrence in Iranian allo-HSCT patients, in whom the BMI <18.5 kg/m^2 is associated with lower GVHD incidence compared to donors with normal and high BMI. The recipient's BMI showed no statistically significant association with the GVHD, which needs more confirmatory investigations in different contexts to clarify the exact relationship between the BMI and HSCT outcomes. Overall, along with the other proved GVHD risk factors, BMI might also serve as a risk factor in HSCT complications, which strongly suggested to be taken into account in the future investigations with larger sample sizes.

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Authors' contributions

P.E, S.M, A.H, and S.S participated in designing experiments and critical revision of the manuscript. M.S, L.N, and M.A.N performed data collection and analysis. All authors revised the manuscript and approved the final manuscript.

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Conflict of interests

The authors declare that there is no conflict of interests.

Ethical approval

The study was confirmed by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethical code: IR.SBMU.REC.1398.146).

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