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Risk Factors of Graft-Versus-Host Disease in the Iranian Allogeneic Hematopoietic Stem Cell Transplantation: A 10-Year Experience

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Abstract

Background: Graft-versus-host disease (GVHD) is a serious complication associated with allogeneic hematopoietic stem cell transplantation (allo-HSCT). Thus, it is necessary to evaluate the risk factors of GVHD in allo-HSCT. Herein, we studied the effects of some risk factors on GVHD incidence in patients with allo-HSCT.

Methods: We retrospectively evaluated the GVHD incidences and risk factors in 199 patients diagnosed with hematological disorders who underwent allo-HSCT in Taleghani hospital, Tehran, Iran, between 2007 and 2017. The univariable and multivariable analyses of time to event data were performed using the Logistic regression model. Computations were performed using SAS, and the level of statistical significance for univariable and multivariable analyses was set at 20% and 10%, respectively.

Results: Acute GVHD (aGVHD) was seen in 59 (29.6%) patients, and 18 (9%) patients developed chronic GVHD (cGVHD). The odds of GVHD incidence in male to female transplants was 3.49 times greater than the male-to-male transplantations (CI, 1.16, 11.5; p<0.001). The patients with body mass index (BMI) below 18.5 had 96% lower odds of GVHD incidence compared with those with BMI above 30 (CI, 0.007-0.27; p=0.013). The odds of GVHD incidence in patients who were negative for cytomegalovirus (CMV) antigen was 76% lower than patients with positive CMV antigen (CI, 0.06-0.93; p=0.081).

Conclusion: In a nutshell, our results indicated that the donor-recipient gender disparity, the recipient's BMI, and CMV infection/reactivation status might be pivotal risk factors, which should be taken into account for prevention and management of GVHD.

Keywords: Hematopoietic Stem Cell Transplantation, Graft-Versus-Host Disease, Body Mass Index, Cytomegalovirus

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important therapeutic choice for hematological disorders (1, 2). Graft-versus-host disease (GVHD), however, is a deadly consequence of allo-HSCT (3, 4). The reported incidence of GVHD is 20% to 60% and the incidence ranges of acute GVHD (aGVHD) and chronic GVHD (cGVHD) is 30% to 50% and 30% to 70%, respectively (5). The criteria of GVHD classification to acute

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↑What is "already known" in this topic:
Graft-versus-host disease (GVHD) is a serious consequence of allogeneic hematopoietic stem cell transplantation (allo-HSCT). The risk factors of GVHD are controversial and vary in different populations.

→What this article adds:
The 10-year experience from our HSCT center shows donor-recipient gender disparity, patients' BMI, and cytomegalovirus infection are risk factors of GVHD in allogeneic HSCT that should be taken into account for GVHD prevention and management.

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and chronic were previously based on the day of occurrence before or after 100 days post-HSCT, while the new classification criteria are based on the clinical manifestation (6-8). GVHD starts when the recipients' organs are attacked by donor T lymphocytes (9). Antigen presenting cells (APCs) are responsible for recognizing and presenting host-derived antigens and activating donor T lymphocytes for releasing the proinflammatory cytokines, including tumor-necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-12, and IL-1, which lead to organ damage by immune cells (10-12). The most susceptible organs in GVHD are skin (81% of patients), gastrointestinal system (54%), and liver (50%). Their damages cause keratoconjunctivitis, oral mucositis, hepatic veno-occlusive disease, diarrhea, and hemorrhagic cystitis, with high mortality rate (11-14). The grades of acute and chronic GVHD, based on the severity of organ involvements, include grade I (mild), II (medium), III (severe), and IV (very severe) (14). The grades III and IV with the 5-year survival of 25% and 5%, in that order, have poor prognosis (13). The treatment in high stages is irksome, hence, prevention is the best strategy.

Over the past 3 decades, many studies have identified various risk factors associated with GVHD, including (1) patient and donor age; (2) underlying disease; (3) donor-recipient relationship; (4) donor-recipient sex mismatch; (5) human leukocyte antigens (HLA) mismatch; (6) GVHD prophylaxis; (7) conditioning regimen; (8) total body irradiation (TBI); and (9) viral infections, such as cytomegalovirus (CMV) in the recipient or even in the donor (15-17).

The evaluation of GVHD risk factors is required in the HSCT recipient and donor on admission date. Some risk factors of GVHD had been defined by the National Institutes of Health consensus criteria (NCC) (8, 18); however, the evaluation of other risk factors and their relationship with GVHD could be more beneficial in prevention and management of the disease. In this study, we described the effect of some risk factors on GVHD incidence based on our 10-year experience in 199 allo-HSCT patients.

Methods

Patients

This retrospective study was performed on 199 patients (102 (51.3%) men and 97 (48.7%) women), with a mean age of 32.50±10.79 years and various hematological disorders, who underwent allo-HSCT from 2007 to 2017 at the Hematopoietic Stem Cell Transplantation and Cell Therapy Center of Taleghani Hospital, Tehran, Iran. The study received the ethical approval from Shahid Beheshti University of Medical Sciences. The dataset for the analysis was extracted from the clinical records, and informed consent was obtained from all patients.

The studied hematological disorders mainly included acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD), and aplastic anemia (AA). All patients received allogeneic stem cell transplants, which are fully matched in HLA-A, -B, -C, -DRB1, and -DQB1 loci, except for 5 transplantations in which 1 locus was mismatched. HLA typing was performed using the single specific primer-polymerase chain reaction (PCR-SSP) method (19). Patients were kept in isolated rooms with HEPA air filtration.

Conditioning Regimen

The myeloablative conditioning regimen was administered intravenously to all patients, which consisted of busulfan (BU; Otuska) 0.8 mg/kg every 6 hours for 4 days succeeded by 2 days of either cyclophosphamide (CY; Sandoz) 60 mg/kg/day or fludarabine (Flu; Genzyme) 30 mg/m^2 once a day for 5 days. Reduced Intensity Conditioning (RIC) regimen utilized for HD and NHL patients comprised fludarabine 30 mg/m^2 IV for 5 days, CCNU (Lomustine, Bristol Myers) 100 mg/m^2 P.O. for 2 days and Melphalan (Alkeran; GlaxoSmithKline) 40 mg/m^2 IV for 1 day.

Peripheral Blood Stem Cell Isolation

Hematopoietic stem cells mobilization is induced in the donors using subcutaneous administration of 5 to 10 µg/kg granulocyte-colony stimulating factor (G-CSF) (filgrastim, Amgen) for 4 consecutive days. Then, peripheral blood stem cells were harvested using apheresis Spectra Optia (Terumo BCT, Lakewood). The CD3$^+$ cells (FITC-conjugated human anti-CD3, Beckman Coulter) and CD34$^+$ cells (PE-conjugated human anti-CD34, EXBIO) were counted by flow cytometry (Attune NxT, Invitrogen). All patients received 5×10^8 and 2-4 $\times10^6$ mononuclear cells and CD34$^+$ cells/kg, respectively.

Neutropenia Phase Management

All patients received prophylactic antibiotic drugs during the neutropenia phase, including oral acyclovir, fluconazole, and ciprofloxacin for viral, fungal, and bacterial infection. Intravenous imipenem and vancomycin for febrile neutropenia and metronidazole for intestinal infection were administered. Moreover, patients intravenously received G-CSF (5 µg/kg/day) from the day after transplantation until the day at which neutrophil counts reached-up to 1.5×10^9/L.

GVHD Prophylaxis and Diagnosis

All patients received 3 mg/kg/day of cyclosporine A (CsA; Sandoz) intravenously between days -2 to +5 (The transplantation day was assumed as day zero) followed by 12.5 mg/kg/day P.O. for 6 months along with methotrexate (MTX; Sandoz) IV on days +1 (10 mg/kg), +3, +6, and +11 (6 mg/kg) as GVHD prophylaxis. Twenty patients received 2.5 mg/kg of anti-thymocyte globulin (ATG; Genzyme) for 2 days (-1 and -2) in addition to the routine GVHD prophylaxis.

We applied the NCC system for the evaluation of GVHD incidence in allo-HSCT patients (7). The standard clinical signs, including diarrhea, rash, and abnormalities in liver function tests, along with biopsy and histopathological criteria in the involved organs, were principal manifestations for diagnosis of GVHD. Moreover, the CMV Ag were measured before and after the HSCT using real time PCR detection kit (Dynabio), and positive cases were

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detected according to the manufacturer's protocol. All patients with negative CMV Ag and IgM at the admission day underwent HSCT and included to the study.

Risk Factors Evaluation

In this study, some risk factors were evaluated in Iranian allo-HSCT patients including: (1) recipient and donor age; (2) disease diagnosis (categorized as AML, ALL, HD, NHL, AA, and other); (3) gender disparity between the donor and the recipient; (4) donor and recipient relationship; (5) recipient ABO blood group; (6) ABO incompatibility between the donor and the recipient; (7) complete and (8) partial remission; (9) human leukocyte antigens (HLA) mismatch; (10) BMI of the recipient; (11) GVHD prophylaxis strategies; (12) conditioning regimen; (13) receiving ATG in patients; and (14) cytomegalovirus antigen (CMV Ag) status of recipient. These risk factors are listed in Table 1.

Statistical Analysis

The univariable and multivariable analyses of GVHD incidence were performed using the logistic regression model. The Hosmer–Lemeshow test was used for the goodness-of-fit of our logistic model. The multivariable model was achieved through a backward selection method to find the risk factors with the highest prognosis. Computations were done using SAS Version 9.4 (SAS Institute Inc). The significance level for univariable and multivariable analyses was set at 20% and 10%, respectively.

Results

Patient Characteristics

A total of 199 patients who had received allo-HSCT were included in the study. The donor-recipient gender combinations were 56 (28.1%) male-male, 61(30.7%) male-female, 32 (16.1%) female-female, and 48(24.1%) were female-male. The majority of the recipients 90 (45.2%) had a BMI of 18.5-24.9. AML was the most prevailing among all kinds of disorders ((n = 100; 50.3%) followed by ALL (n = 52; 26.1%), NHL (n = 13; 6.5%), HD (n = 12; (6.1%), and AA (n = 8; 4%)). Other less frequent diseases included adrenoleukodystrophy, myelodysplastic syndromes, and thalassemia were categorized as "other." Twenty patients (10.1 %) became positive for CMV Ag after HSCT. Most of the patients 148 (74.4%) received grafts from sibling donors and 43 (21.6%) patients received grafts from related donors. Only 5 recipients received mismatched HLA grafts, which were mismatched in 1 locus. The results revealed that type "O" was the most frequent blood group (31.2%) closely followed by type "A" (30.7%). According to the clinical manifestation, 59 (29.6%) patients developed acute GvHD, while 18 (9%) patients had chronic GVHD (Table 1).

Table 1. Prognostic Factors Descriptive Analysis For Graft-Versus-Host Disease

Characteristics	Mean±SD/ Frequency (%)
Recipient Age	32.50±10.79
Missing	3 (1.5%)
Donor Age	33.82±11.22
Missing	61 (30.7%)
DR[1] 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	
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 (6.1%)
AML	100 (50.3%)
ALL	52 (26.1%)
Aplastic Anemia	8 (4%)
Other	6 (3%)
Missing	8 (4%)
Recipient CMV Ag	
Negative	179 (89.9%)
Positive	20 (10.1%)
Missing	0 (0%)
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%)
Remission Status	
CR1	112 (56.3%)
CR2	19 (9.5%)
CR3	4 (2%)
PR1	4 (2%)
PR2	9 (4.5%)
PR3	2 (1%)
PR4	3 (1.6%)
Missing	46 (23.1)
ATG	
Yes	23 (11.6%)
No	176 (88.4%)
Missing	0 (0%)
Conditioning Regimen	
Bu/Cy	108 (54.3%)
Bu/Fu	46 (23.1%)
Bu/Fu/ATG	16 (8%)
RIC	25 (12.6%)
Missing	4 (2%)
Prophylaxis Regimen	
CSA+MTX	179 (89.9%)
CSA+MTX+ATG	20 (10.1%)
Missing	0 (0%)
Recipient Blood Group	
A	61 (30.7%)
B	42 (21.1%)
AB	24 (12%)
O	62 (31.2%)
Missing	10 (5%)
Compatibility Blood Group	
Compatible	108 (54.3%)
Incompatible	82 (41.2%)
Missing	9 (4.5%)
GVHD Type	
Acute	59 (29.6%)
Chronic	18 (9%)
No-GvHD	122 (61.4%)

[1] Donor-Recipient

Univariate Analysis

The risk factors, including donor-patient gender, recipient's BMI, recipient's CMV Ag, donor-recipient relationship, and blood group, were statistically significant on the incidence of GVHD. On the contrary, risk factors, such as the recipient and donor age, receiving ATG, conditioning, and prophylaxis regimen did not show any significance. The odds of GVHD incidence in male to female transplantations was 92% higher than the male-male HSCT (CI,

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1.17, 3.17; p=0.069); however, the odds in female-female gender were 20% lower than male-male gender (CI, 0.43-1.50; p=0.162). The BMI of the recipients below 18.5 had 58% lower odds of GVHD incidence compared with recipients with BMI above 30 (CI, 0.21-0.85; p=0.048). Conversely, BMI of the recipients between 18.5 and 24.9 had the odds of incidence 19% higher than recipients with BMI above 30 (CI, 0.68-2.09; p=0.088). The odds of recipients with negative CMV Ag were 74% lower than patients with positive CMV Ag (CI, 0.11-0.60; p=0.033). The odds of GVHD incidence in patients who received grafts from related donors was almost 45% lower than the patients who received grafts from sibling donors (CI, 0.33-0.89; p=0.109). The odds of GVHD incidence in

Table 2. Univariate and Multivariate Logistic Regression Models for Graft-Versus-Host Disease

	Univariate		Multivariate	
Variable	Odds Ratio (80% CI)	p	Adjusted Odds Ratio (90% CI)	p
Recipient Age	0.99 (0.97-1.008)	0.465		
Donor Age	1.01 (0.99-1.04)	0.252		
DP[1] Gender		0.173*		0.009**
Female-Female	0.80 (0.43-1.50)	0.162	0.11 (0.01-0.64)	0.033
Female-Male	1.58 (0.93-2.69)	0.367	0.47 (0.11-1.83)	0.556
Male-Female	1.92 (1.17-3.17)	0.069	3.49 (1.16-11.50)	0.001
Male-Male (RL[1])	-	-	-	-
Recipient BMI		0.170*		0.041**
Below 18.5	0.42 (0.21-0.85)	0.048	0.04 (0.007-0.27)	0.013
Between 18.5-24.9	1.19 (0.68-2.09)	0.088	0.30 (0.08-1.09)	0.566
Between 25-29.9	0.83 (0.45-1.51)	0.91	0.25 (0.06-0.94)	0.908
Above 30 (RL[1])	-	-	-	-
Diagnosed disease		0.912		
NHL	1.71 (0.45-6.41)	0.444		
HD	1.14 (0.29-4.49)	0.984		
AML	1.21 (0.38-3.79)	0.866		
ALL	1.51 (0.47-4.87)	0.420		
Aplastic Anemia	0.66 (0.14-3.06)	0.434		
Other (RL[1])	-	-		
Recipient CMV Ag		0.033*		0.081**
Negative	0.26 (0.11-0.60)	0.033	0.24 (0.06-0.93)	0.081
Positive (RL[1])	-	-	-	-
Donor-recipient relationship		0.109*		0.029**
Related	0.55 (0.33-0.89)	0.109	0.08 (0.01-0.60)	0.029
Sibling (RL[1])	-	-	-	-
HLA		0.393		
Match	2.60 (0.61-11.07)	0.393		
Mismatch (RL[1])	-	-		
Complete Remission		0.971		
CR2	1.01 (0.53-1.91)	0.844		
CR3	0.76 (0.15-3.73)	0.816		
CR1 (RL[1])	-	-		
Partial Remission		0.755		
PR2	3.75 (0.74-25.58)	0.402		
PR3	3 (0.28-36.33)	0.733		
PR4	1.5 (0.16-14.26)	0.770		
PR1 (RL[1])	-	-		
ATG		0.664		
No	1.22 (0.67-2.22)	0.664		
Yes (RL[1])	-	-		
Conditioning Regimen		0.644		
Bu/Cy	1.50 (0.71-3.13)	0.352		
Bu/Fu	1.13 (0.56-2.38)	0.866		
Bu/Fu/ATG	1.45 (0.34-2.01)	0.558		
RIC (RL[1])	-	-		
Prophylaxis Regimen		0.955		
CSA+MTX	0.97 (0.51-1.82)	0.955		
CSA+MTX+ATG (RL[1])				
Recipient Blood Group		0.170*		
A	2.1 (1.29-3.39)	0.048		
B	1.55 (0.9-2.65)	0.551		
AB	0.91 (0.46-1.80)	0.322		
O (RL[1])	-	-		
Compatibility Blood Group		0.588		
Incompatible	1.17 (0.79-1.73)	0.588		
Compatible (RL[1])	-	-		

[1] Reference Level
* Significant at 0.2
** Significant at 0.1

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patients who did not receive ATG were 22% higher than those who received ATG (CI, 0.67-2.22; p=0.664). Patients with blood group A have 2 times higher odds of GVHD incidence compared with those with blood group O (CI, 1.29-3.39; p=0.048). The patients with blood group B had the odds of incidence, which was 55% higher than patients with blood group O (CI, 0.9-2.65; p=0.551). The patients with type AB had 9% lower odds of incidence compared with type O patients (CI, 0.46-1.80; p=0.322) (Table 2).

Multivariate Analysis

The result of the Hosmer–Lemeshow test indicated that our model was valid. In this multivariable model, donor-patient gender, recipient BMI, CMV Ag, and donor-recipient relationship were presented as influential risk factors. Assuming that the effects of all the other factors were constant, for male-female gender, the odds of GVHD incidence was 3.49 times higher than male-male gender (CI, 1.16-11.5; p=0.001). The odds of GVHD incidence in female-female was 89% lower than male-male (CI, 0.01-0.64; p=0.033). The recipients with BMI below 18.5 had the odds of GVHD incidence 96% lower than recipients with BMI above 30 (CI, 0.007-0.27; p=0.013). The odds of GVHD incidence in recipients with negative CMV Ag was 76% lower than patients with positive CMV Ag (CI, 0.06-0.93; p=0.081). The patients who received grafts from related donors had the odds of GVHD incidence, which was 92% lower than the patients who received grafts from sibling donors (CI, 0.01-0.60; p=0.029) (Table 2).

As shown in Table 3, 29 (47.5%) of the male-female and 9 (28.1%) of female-female transplantations developed GVHD. The number of male-male transplantation was 18 (32.2%). The BMI of the recipients with GVHD incidence below 18.5 was the least frequent 8(23.5%) compared with the recipients with BMI above 30, which were 14 (43.75%). Among the recipients with positive CMV Ag, 11 (55%) and with negative CMV Ag, 70 (39.1%) patients developed GVHD. A total of 64 (43.25%) of the patients who had GVHD incidence received a graft from sibling donors compared with the ones who received a graft from related donors, which were 13 (30.23%).

Discussion

Despite all benefits of allo-HSCT for malignancy patients, this treatment is confined by high morbidity and mortality arising from GVHD (9, 20, 21). The aim of this research was to explain the influential risk factors that lead to GVHD incidence based on a 10-year recorded data of a single center in Iran. This was a relatively large study with a decent follow-up period and small attrition. In our study, aGVHD was observed in 59 (29.6%) patients and 9 (18%) of our patients developed cGVHD. Previous studies have reported the recipient, donor age, and donor-recipient gender as crucial risk factors for incidence of GVHD in allo-HSCT (22, 23). Our results have revealed that recipient and donor age were not significantly related to GVHD incidence. This is consistent with the study of Jagasia et al, which illustrated that recipient and donor age did not have any effect on aGVHD incidence (15). However, it has been shown that the donor-recipient gender is a significant factor for GVHD incidence. In this study, transplants from male donors to female recipients were associated with increased incidence of GVHD. Countering that, the female recipients who received transplants from females had lower GVHD incidence (24). It could be interpreted that the gender parity of donor and recipient might decrease the probability of GVHD. AW Loren et al have found that parity of the donor does not have an impact on the occurrence of acute GVHD and overall survival; nevertheless, it increases the incidence of chronic GVHD (25). One of the challenging contradictions between our results and several previous findings is that they have mentioned that GVHD incidence in female to male transplantations was significantly greater than the reverse combination (26-28).

Among the many risk factors for GVHD incidence and mortality after allo-HSCT, HLA compatibility is a pivotal criterion (29). HLA-identical sibling is the best standard source for allo-HSCT, but some patients do not have any HLA-identical sibling, and inevitably need grafts from a matched related (MRD)/unrelated donor (MUD) (30). Our result demonstrated that the GVHD incidence in patients who received grafts from related donors was significantly

Table 3. Distribution of frequency of risk factors in final multivariable logistic model by GVHD status

Variable	GVHD = Yes (Frequency/%)	GVHD = No (Frequency/%)
D-P Gender		
Female-Female	9 (28.1%)	23 (71.9%)
Female-Male	15 (31.25%)	33 (68.75%)
Male-Female	29 (47.5%)	32 (52.5%)
Male-Male	18 (32.2%)	38 (67.8%)
Recipient BMI		
Below 18.5	8 (23.5%)	26 (76.5%)
18.5-24.9	30 (42.25%)	41 (57.75%)
25-29.9	19 (38.7%)	30 (61.3%)
Upper 30	14 (43.75%)	18 (56.25%)
Recipient CMV Ag		
Positive	11 (55%)	9 (45%)
Negative	70 (39.1%)	109 (60.9%)
Donor-recipient relationship		
Sibling	64 (43.25%)	84 (56.75%)
Related	13 (30.23%)	30 (69.77%)

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lower than patients who received grafts from sibling donors. These data collected from patients whose HLA compatibility in sibling and MRD transplantations were 6/6 matched (HLA-A, -B, and -DRB1 loci) and 10/10 matched (HLA-A -B, -C, -DRB1, and -DQB loci), respectively. Hence, regarding the difference in HLA evaluation of sibling and MRD transplantations, this significant difference is not clinically valuable.

There are proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, in obese people, defined with BMI≥30kg/m^2 of body surface, and overweight people (BMI, 25-29.9 kg/m^2) (31). On that account, BMI index in recipients can be considered as a risk factor for GVHD prognosis. In our results, it has been observed that recipients with BMI≤18.5 kg/m^2, compared with recipients with obese ones, manifested much lower GVHD incidence. In addition to the more inflammatory factors in obese patients, the lower absorption of GVHD prophylaxis medications in overweight patients might be one of the explanations for higher rate of GVHD in obese recipients. However, Lucie M et al found no relationship between the recipient BMI index and incidence of GVHD (32).

Recent studies presented that the CMV replication is a risk factor for GVHD; however, this finding is still controversial (33, 34). The result of the current study revealed that the GVHD incidence in recipients whose CMV Ag is negative is significantly lower than patients with positive CMV Ag. Accordingly, CMV infection in a recipient could be a main factor for an initial phase of the GVHD. Our result is in line with the study of N. Cantoni et al that reported CMV replication as a risk factor for aGVHD incidence (35).

Conditioning regimen can cause tissue damage and activation of recipients' APCs leading to inflammation and GVHD incidence (36, 37). No significant difference was found in the incidence of GVHD among the different conditioning regimens. Furthermore, the patients who were given Bu/Cy, Bu/Fu, and Bu/Fu/ATG had a higher GVHD incidence compared with those who received RIC regimen, but it was not significant. These results are consistent with what have been reported by H Nakasone et al in which TBI is a significant risk factor for GVHD incidence, and there is no significant difference in myeloablative conditioning and RIC regimen (38). Ergo, the impact of the conditioning regimen intensity, and GVHD prophylaxis on GVHD incidence should be considered according to the patient physiology and background of patients. Having said that, it is still a matter of debate (39). As the preceding studies indicated, the use of prophylaxis drugs, such as cyclosporine that inhibits regulatory T cells, with short-term MTX decreased the incidence of acute GVHD (40, 41). In this study, this prophylaxis was utilized for allogeneic patients, and the difference in the incidence of GVHD was analyzed when CSA+MTX was used with or without ATG. The administration of ATG was not an influential prognostic factor for the decrement of GVHD incidence in transplant. This result is in contrast with the report of Redondo Velao et al who found that aGvHD incidence and toxicity have been lower in ATG-based prophylaxis (42). The controversy might be due to the small sample size of patients who received ATG in our study.

The blood group A compared with blood group O was an adverse prognostic factor for the incidence of GVHD. Contrastingly, there was no significant relationship between the donor-recipient ABO blood group incompatibility status and the incidence of GVHD. This result is in agreement with the study of Seebach JD et al that found no impact of ABO blood group incompatibility on outcomes of allo-HSCT (43). The most important limitation of the study is that this report was obtained from a single center. A multi-center study is highly suggested for more reliable results, especially for controversial findings. The data on disease relapse and survival of the patients was not included in the study because of incomplete documentation.

Conclusion

In summary, we report the risk factors, including donor-patient gender, recipient's BMI, recipient's CMV infection, were statistically significant on the incidence of GVHD. The results of this study can help a more rational choice of recipient's background, donor character, and treatment strategies to improve outcomes after allo-HCT.

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Conflict of Interests

The authors declare that they have no competing interests.

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