IMPACT OF INTENSITY OF CONDITIONING REGIMENS ON CLINICAL OUTCOME OF ALLOGENIC BONE MARROW TRANSPLANT

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ABSTRACT

Recent progress in hematopoietic cell transplantation has been associated with the development of stem cell sources such as peripheral blood or cord blood, alternative donors, novel strategies of immunosuppression, and reduced intensity conditioning (RIC) regimens. Many recipients often experience various complications, so identification of risk factors for these complications may help to further improve transplant outcomes. The impact of conditioning intensity on HCT outcomes has remained a matter of debate. This study was done to study the impact of intensity of the conditioning regimens on clinical outcome of patients who underwent allogenic hematopoietic stem cells transplant regarding, rate complications & early post-transplant mortality. This was an observational model single center study, and it was retrospective registry-based analysis. This study included adult Egyptian patients who underwent Allo-HSCT at Nasser institute from the reference year of 2012 through 2022. This study included adult patients ≥ 18 years of age, with allogeneic stem cell transplantation, with matched sibling donor, planned to have Myeloablative conditioning (MAC) or non-myeloablative conditioning/Reduced intensity conditioning (NMA/RIC) Allo-HSCT. The results showed that the conditioning intensity MAC vs. NMA/RIC had no significant impact on post-transplant complications. No significant impact on overall survival, MAC was associated with a trend towards lower incidence of non-relapse mortality (NRM)., we concluded that the conditioning intensity (MAC vs. NMA/RIC) Had no significant impact on post-transplant complications, although MAC is associated with longer time to hematopoietic recovery. No significant impact on overall survival, MAC was associated with a trend towards lower incidence of NRM

Keywords: Hematopoietic Cell Transplantation, Reduced- Intensity Conditioning, Non-Relapse Mortality, Myeloablative Conditioning, , Non-Myeloablative Conditioning/Reduced Intensity Conditioning

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INTRODUCTION

Since allogeneic hematopoietic cell transplantation (HCT) was introduced about 50 years ago, the procedure has spread widely because of its potential to cure hematological diseases [1]. Recent progress in HCT has been associated with the development of stem cell sources such as peripheral blood or cord blood, alternative donors, novel strategies of immunosuppression, and reduced- intensity conditioning (RIC) regimens [2, 3].

However, many recipients often experience various complications, including organ failure, infection, and acute and chronic graft versus host disease (aGVHD and cGVHD, respectively). The identification of risk factors for these complications may help to further improve transplant outcomes [4].

Preparative chemotherapy regimens for HCT have a different intensity, toxicity, and dependence upon a graft-versus-tumor effect .Preparative regimens for HCT have been classified as myeloablative, reduced intensity, and non myeloablative**[5]**. There is no optimal preparative chemotherapy regimen for all patients who undergo HCT . The choice of a preparative regimen depend on the comorbidities, underlying cause, disease status, donor, and graft source**[6]**.

MAC regimens are preferred for young patients with a excellent performance stat. RIC or non myeloablative (NMA) regimens may be indiated for patients who are not candidate for any

MAC regimens in whom the underlying disease has been in complete remission**[7]**.

. As recent progress in the modalities of HCT has spread the indications for allogeneic HCT, the impact of conditioning on the clinical outcome needs to be reassessed among recent HCT patients according to the patient background. So, this study was done to study the impact of intensity of the conditioning regimens on clinical outcome of patients who had allogenic hematopoietic stem cells transplant regarding, rate complications & early post-transplant mortality.

PATIENTS AND METHODS

This was an observational model single center study, and it was retrospective registry-based analysis. This study included adult Egyptian patients who underwent Allo-HSCT at Nasser institute from the reference year of 2012 through 2022. Data were collected from registered patients fulfilling the protocol eligibility criteria. This study included adult patients ≥ 18 years of age, with allogeneic stem cell transplantation, with matched sibling donor, planned to have MAC or NMA/RIC Allo-HSCT , but we excluded patients with prior allogeneic HCT, or receiving corticosteroids or other immunosuppressive therapy, or with seropositive for HIV-1 or -2 and/or with Concurrent malignancies or active disease within 1 year (excluding basal cell carcinoma).

Methods

For all patients, we collected their characteristics including Demographic information, CBC, and Bone marrow analysis. We evaluated them Pre-transplant, we did for all of them HLA matching, we established a GVHD prophylaxis for them, we assessed the complications after transplantation including infections and we assessed the graft versus host disease.

Outcomes

The Overall survival (OS) was defined as the time from transplant to the last follow-up or death due to any cause. Relapse incidence was calculated from the date of transplant to the date of documented relapse. NRM was defined as the time from transplantation until death without prior relapse.

Statistical Methods

Data were analyzed on a personal computer running SPSS© for windows (Statistical Package for Social Scientists) version 19. A p value of ≤ 0.05 was considered statistically significant. Chi Square Test was run for testing association between categorical variables. Correlations between variables were determined by Pearson's correlation coefficient or Kendall's Tau non-parametric correlation coefficient. Overall survival and Disease-free survival analyses were calculated by the Kaplan-Meier Product-Limit Estimator. Comparison of the survival was performed by the Log-Rank Test. Non-relapse mortality and Relapse incidences were determined using the competing-risk method. Exploring variables for their independent prognostic effect on survival was carried out using the multivariate stepwise Cox's proportional regression hazard model.

RESULTS

This study was a retrospective study applied on adult Egyptian who underwent Allo-HSCT at Nasser institute, Cairo, Egypt, from the reference year 2012 through 2022. The median age was 34 among the recipients (range 21-60), and 72% and 28% of recipients were male, and female, respectively. CMV seropositivity was present in 89.3% of patients, (Table 1). The median age was 34 years among the donors (range 14-72), and 64% and 36% of donors were male, and female, respectively. All donors were HLA typing full matching. 13.5% of the donors had HCV AB positive. 85.3% of the donors had CMV IGG positive, 82,7% of the donors were HBV negative (Table 2). AML was the most common underlying disease (52%), other diagnoses included (MF, HD, NHL), two patients were diagnosed with NHL, 2 patients diagnosed with MF, and one patient was diagnosed with HL. As regard patients with acute leukemia, 38 patients (80.9%) were transplanted at CR1, and 9 patients (19.1%) were transplanted at CR2+ (Fig. 1).

Table (1): Patient characteristics

		No	**%**
Gender (Patient)	**Male**	54	72.0%
	Female	21	28.0%
HBV Status	**Negative**	56	74.7%
	Immune=Protected	16	21.3%
	Resolved Infection	1	1.3%
	Chronic Infection	2	2.7%
CMV IgG	**Negative**	8	10.7%
	Positive	67	89.3%
Tox. IgG	**Negative**	47	62.7%
	Positive	28	37.3%

Table (2): The donor characteristics

		No	%
Gender (Donor)	**Male**	48	64.0%
	Female	27	36.0%
Sex Mismatch	**Matched**	37	49.3%
	Mismatch	38	50.7%
HCV Ab donor	**Negative**	64	86.5%
	Positive	10	13.5%
HCV Status (donor)	**Negative**	65	86.7%
	SVR	7	9.3%
	Chronic HCV Infection	3	4.0%
HBV (Donor)	**Negative**	62	82.7%
	Immune=Protected	12	16.0%
	Resolved Infection	0	0.0%
	Chronic Infection	1	1.3%
CMV IgG donor	**Negative**	11	14.7%
	Positive	64	85.3%
Tox. IgG donor	**Negative**	49	65.3%
	Positive	26	34.7%
CMV status (donor/recipient)	-/-	5	6.7%
	-/+	6	8.0%
	+/-	3	4.0%
	+/+	61	81.3%

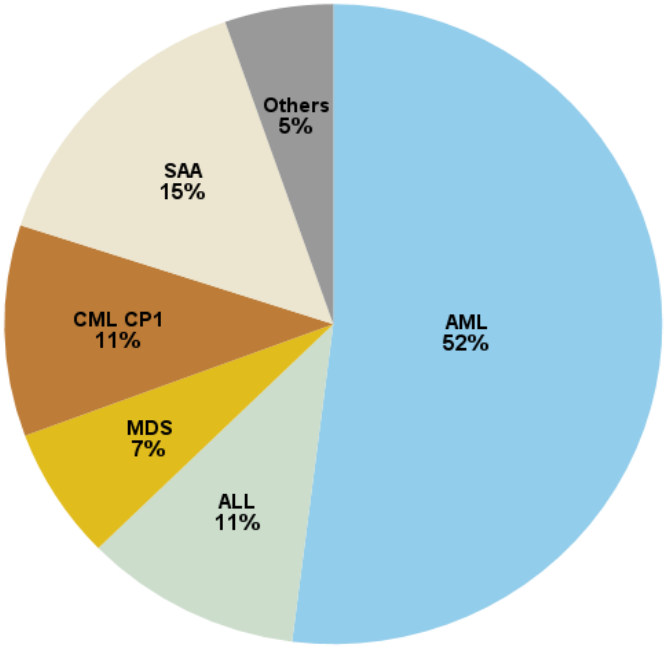

Figure (1): Underlying disease distribution

Myeloablative conditioning (MAC) was used in 48 patients (64%), and reduced intensity conditioning (RIC) was used in 27 patients (36%). The MAC regimens consisted of Busulfan/Cyclophosphamide (Bu/Cy), Cyclophosphamide/total body irradiation (Cy/TBI), and Fludarabine/Busulfan (FLU/BU) busulfan (16 mg/kg orally or 12.8 mg/kg by vein) with fludarabine (120 to 180 mg/m^2) administered over four days. The RIC regimens consisted of FLU/melphalan, Fludarabine/cyclophosphamide (FLU/CY) and Flu/Bu: Flu/Bu2 regimen combines fludarabine (150 to 160 mg/m^2) total dose administered over four to five days with oral busulfan (8 to 10 mg/kg) administered over two to three days. The median duration of hospital stay was 36 days. The median CD34 cells dose was 6.3 (range 1.8-19). Cyclosporine with methotrexate was the most common protocol used for GVHD Prophylaxis in 66.7% of the patients (Tables 3 & 4)

Table (3): Transplant related parameters

		No	%
Conditioning Regimen	**BuCy**	**30**	**40.0%**
	FluBu	**18**	**24.0%**
	TBICy	**8**	**10.7%**
	FluMel	**8**	**10.7%**
	FluCy	**11**	**14.7%**
Conditioning Intensity	**MAC**	**48**	**64.0%**
	RIC	**27**	**36.0%**
GVHD Prophylaxis	**CSA/MTX**	**50**	**66.7%**
	CSA/PostCy	**19**	**25.3%**
	CSA/MMF	**5**	**6.7%**
	CSA/ATG	**1**	**1.3%**
Apheresis Sessions	**1**	**67**	**89.3%**
	2	**8**	**10.7%**

Table (4): Hematopoietic recovery

	Median	Range
Neutrophil Recovery[1]	**14**	**10 - 25**
Platelet Engraftment[2]	**15**	**8 - 30**
Duration of Hospital Stay (Days)	**36**	**0 - 86**

1-Days from stem cell infusion till myeloid engraftment (count holding at 500 for 3 consecutive days)
2-Days from stem cell infusion till platelet engraftment (platelet count holding at 20K for 3 consecutive days)

Fifteen patients (20%) developed grade 2 to 4 acute GVHD, and Sinusoidal obstruction syndrome (SOS) was found in only five patients (6.8%), the median number of RBCS transfusion was 3 times (0-25)., and the median number of platelets transfusion was 3 times ranging from (0-15) (Table 5). The duration of hospital stay more than the median (> 35 days) was more common in patients received MAC than in patients received RIC (28vs9) with P- value =0.015. Eleven patient (22.9%) who received MAC developed grade II to IV hepatotoxicity, while 7 patients (25.9 %) who received RIC developed grade II to IV hepatotoxicity with no-significant difference (p =0.77) (Table 6)

Table (5): Transplant related complications

		No	%
Hepatotoxicity	**Absent/G 1**	57	76.0%
	Grade 2-4	18	24.0%
SOS	**Absent**	69	93.2%
	SOS	5	6.8%
aGVHD Organ Involvement	**Skin**	5	27.8%
	Skin+GIT	8	44.4%
	Liver+GIT	3	16.7%
	Skin+Liver	0	0.0%
	Skin+GIT+Liver	2	11.1%
aGVHD	**Grade 0 1**	60	80.0%
	Grade 2-4	15	20.0%
cGVHD-Lim/Ext	**Limited**	6	54.5%
	Extensive	5	45.5%
		Median	**Range**
Number of RBCs Transfusion		3	0 - 25
Number of Platelets Transfusion.		3	0 - 15

Table (6): Comparison of the study parameters between MAC VS RIC

		Myeloablative	NMA/RIC	p
		No (%)	No (%)	
Gender (patient)	**Male**	33 (68.8%)	21 (77.8%)	0.4
	Female	15 (31.3%)	6 (22.2%)	
Age (years)	**≤ 35**	28 (58.3%)	11 (40.7%)	0.14
	> 35	20 (41.7%)	16 (59.3%)	
Status at Transplantation	**CR1**	29 (76.3%)	9 (100.0%)	0.1
	CR2+	9 (23.7%)	0 (0.0%)	
CMV IgG	**Negative**	6 (12.5%)	2 (7.4%)	0.49
	Positive	42 (87.5%)	25 (92.6%)	
Tox. IgG	**Negative**	30 (62.5%)	17 (63.0%)	0.69
	Positive	18 (37.5%)	10 (37.0%)	
GVHD Prophylaxis	**Post-Cy**	6 (12.5%)	13 (48.1%)	0.001
	Other	42 (87.5%)	14 (51.9%)	
Duration of Hospital Stay (days)	**≤ 35**	19 (40.5%)	19 (67.8%)	0.011
	> 35	28 (59.5%)	9 (32.2%)	
aGVHD Grade	**Grade 0-1**	36 (75.0%)	24 (88.9%)	0.15
	Grade 2-4	12 (25.0%)	3 (11.1%)	
cGVHD	**Absent**	39 (81.3%)	25 (92.6%)	0.18
	cGVHD	9 (18.8%)	2 (7.4%)	
cGVHD-Lim/Ext	**Limited**	5 (55.6%)	1 (50.0%)	0.88
	Extensive	4 (44.4%)	1 (50.0%)	
Hepatotoxicity	**Absent/G 1**	37 (77.1%)	20 (74.1%)	0.77
	Grade 2-4	11 (22.9%)	7 (25.9%)	
SOS	**Absent**	43 (89.5%)	27 (100.0%)	0.15
	SOS	5 (10.4%)	0 (0.0%)	

At the end of follow-up, the median OS of studied cases was 44.2 months. Twenty-nine patients died (38.7%). 10 patients died after relapse (13.3%), and NRM was found in 19 patients (25.3%). In patients who received myeloablative conditioning regimen 12 patients died (25%), while in patients who received NMA/RIC conditioning regimen 10 patients died (37%) .

The median OS of studied cases was 44.2 months. The median OS was 44.2 month in patients receiving MA conditioning regimen, meanwhile it was not reached in patients receiving NMA/RIC conditioning regimen. The cumulative proportion surviving for at 1, 2, and 5-years of patients receiving MAC vs NMA/RIC conditioning regimens were 66% vs. 54%, 54% vs 54% and 54% vs. 48% respectively, the difference was not statistically significant (p=0.72) .

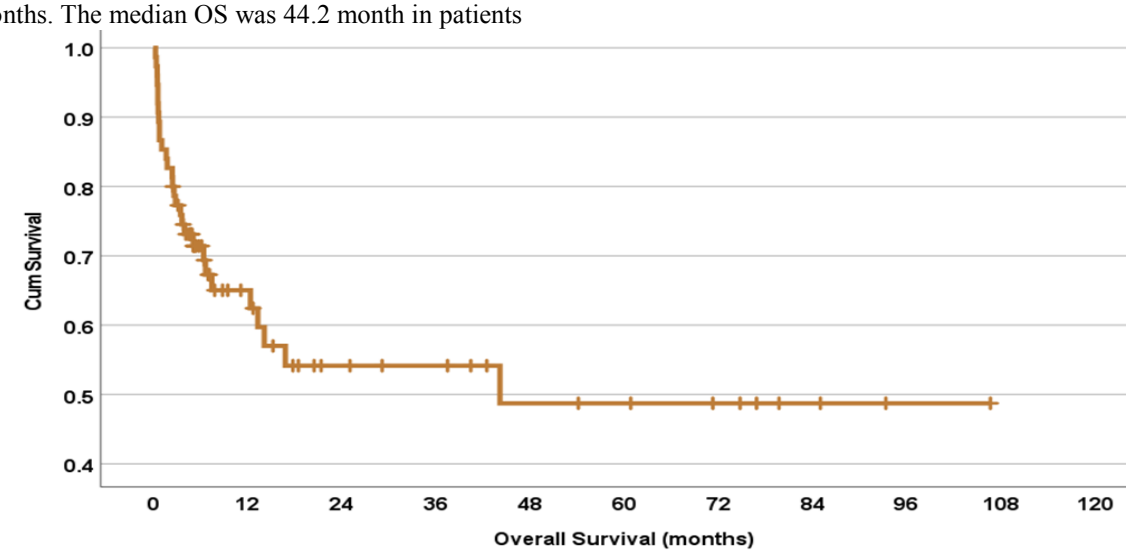

Figure (2): Overall survival

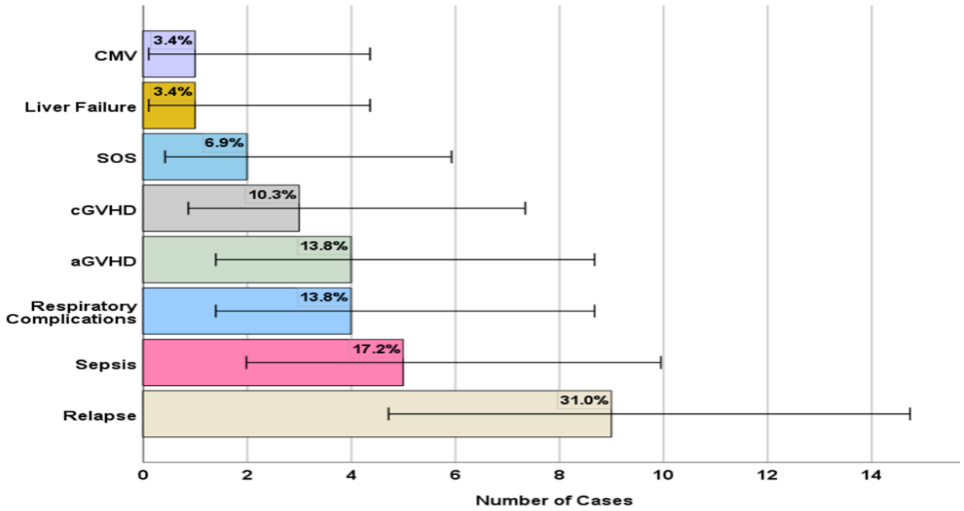

Figure (3): Causes of Death

Table (7): Relation between death causes and conditioning regimens

		Conditioning Intensity			
		Myeloablative		NMA/RIC	
		No	%	No	%
Causes of Death	**Sepsis**	**2**	**10.5%**	**3**	**30.0%**
	Respiratory Complications	**1**	**5.3%**	**3**	**30.0%**
	CMV	**1**	**5.3%**	**0**	**0.0%**
	aGVHD	**3**	**15.8%**	**1**	**10.0%**
	cGVHD	**1**	**5.3%**	**2**	**20.0%**
	SOS	**2**	**10.5%**	**0**	**0.0%**
	Relapse	**9**	**47.4%**	**0**	**0.0%**
	Liver Failure	**0**	**0.0%**	**1**	**10.0%**
Survival	**Censored**	**29**	**60.4%**	**17**	**63.0%**
	Relapsed	**9**	**20.8%**	**0**	**0.0%**
	NRM	**10**	**18.8%**	**10**	**37.0%**

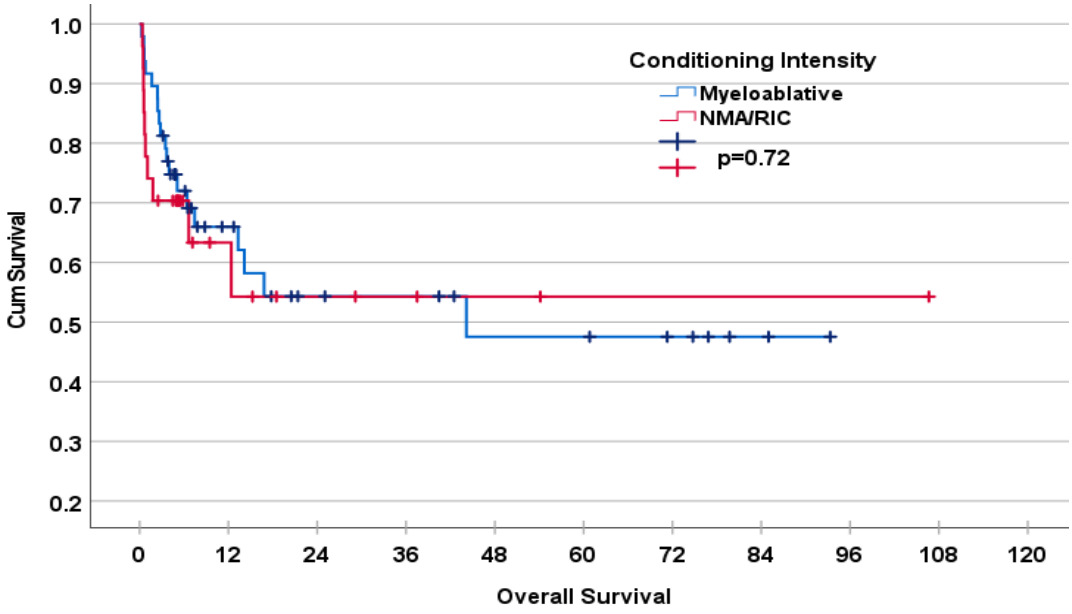

Figure (4): Relation between overall survival and conditioning intensity

Figure (4) shows impact conditioning intensity on NRM. The cumulative incidence of NRM at 1,2 and 3 years for patients who received MAC VR vs patients who received NMA/RIC were 15 vs 36%, 19 vs 46% and 24 vs 46% respectively. The difference was significant (p=0.054).

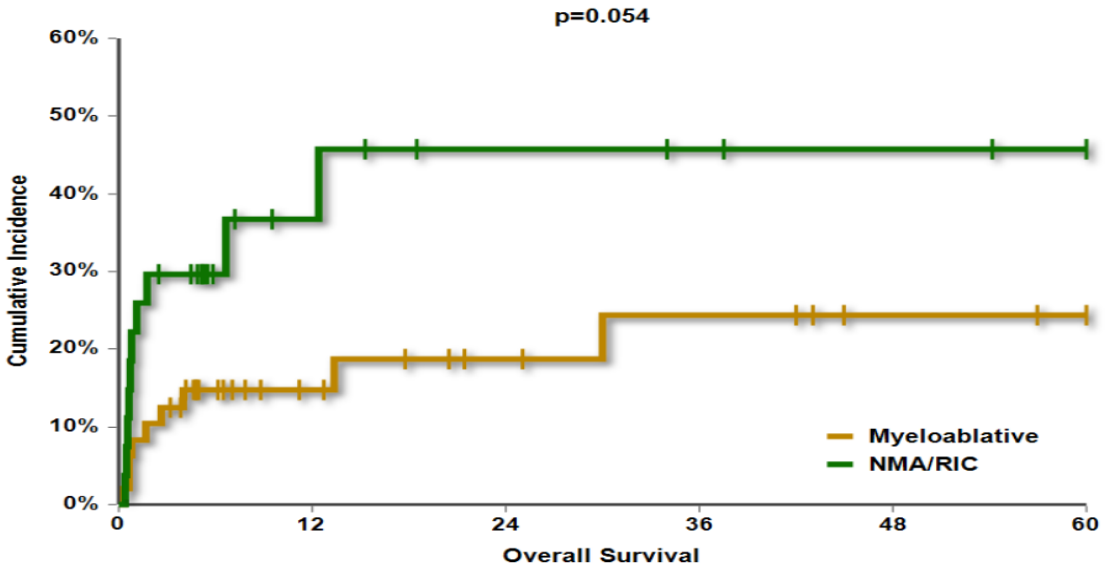

Figure (4): Impact conditioning intensity on NRM

On univariate analysis of prognostic factors of OS, HBV coinfection and sex mismatch, and donor age more than 35 years old (the median age) were prognostic factors for worse OS with hazard ratio =8.182, 3.526, and 2.526 respectively. ABO-Incompatibility, conditioning intensity, underlying disease, CMV infection, HCV chronic infection, and conditioning intensity had no significant impact on OS. On multivariate analysis, HBV coinfection and sex mismatch (female donor), and donor age above median cut off 35 years old were independent prognostic factors of OS. Multivariate and univariate analysis of prognostic factors of OS, including pretransplant variables, transplant related parameters shown in tables **(9, 10).**

Table (9): Univariate analysis

Univariate	**HR**	**95.0% CI**	**p**
Gender (Patient)	0.921	0.406 - 2.086	0.843
Female Gender (Donor)	2.193	1.042 - 4.619	0.039
Sex Mismatch	3.526	1.504 - 8.266	0.004
Age (Recipient)	1.931	0.909 - 4.101	0.087
Age (Donor)	2.526	1.196 - 5.337	0.015
Underlying Disease			
AML	0.859	0.554 - 1.734	0.108
ALL	0.559	0.254 - 1.229	0.148
SAA	0.775	0.292 - 2.057	0.609
CML	1.191	0.358 - 3.960	0.776
MDS	23.501	0.173 - 56.41	0.284
CR2+	0.769	0.223 - 2.649	0.677
ABO-Incompatibility	1.230	0.443 - 3.417	0.691
HCV (No SVR)	1.551	0.732 - 3.285	0.252
HBV Infection	8.182	1.83 - 36.52	0.006
HCV positive (Donor)	0.35	0.49 - 2.65	0.439
CMV + Recipient	0.910	0.274 - 3.021	0.877
CMV + Donor	0.817	0.281 - 2.374	0.711
CMV (donor/recipient)	0.85	0.151 - 6.23	0.680

Conditioning Intensity	0.880	0.408 - 1.896	0.744
GVHD Prophylaxis	0.916	0.372 - 2.254	0.848

Table (10): Multivariate analysis

Multivariate	**HR**	**95.0% CI**	**p**
Sex mismatch (Female Donor)	3.188	1.25 – 8.1	0.015
Donor Age (> 35 years)	2.777	1.26 = 6.1	0.011
HBV Infection	9.077	1.88 = 43.2	0.006

DISCUSSION

Allo-hematopoietic stem cell transplantation (HSCT) is a potentially curative option for many patients with hematologic disorders in patients with CR1 after induction chemotherapy or in patients with relapsed/refractory disease **[8]**. The number of Allo-HSCTs has increased in Egypt in the last years. AML and ALL were the most common malignancies treated with Allo-HSCT in Egypt and the Middle East in the last years **[9, 10]**.

NRM and relapse of the underlying disease are the main reasons of failure of Allo-HSCT. NRM after Allo-HSCT may result from organ damage from the preparative regimen and infection flaring which lead to increase the risk GVHD **[11]**.

Liver complications influence morbidity and mortality in patients undergoing HCT. Liver injury is common early after HCT because of veno-occlusive disease (SOS), Graft-versus-Host Disease (GVHD), drug toxicity, post-transplantation viral hepatitis and disease relapse **[12]**.

The impact of intensity of conditioning regimens on outcome of patients who underwent allogeneic hematopoietic cell transplantation (HCT) remains a matter of debate. In this study, we had retrospectively examined the impact of intensity of the conditioning regimens on recipient who underwent allogeneic HCT in this study. The median age of recipients and donors was 34 years for both. This was similar to the known median age of Allo-HSCT recipients in the middle east and developing countries **[13, 14]**.

Among the recipients, 52 % had AML, while 14.7% had severe aplastic anemia. this finding is consistent with **Nakasone *et al.*, [15]** who found 55% of the patients who underwent allogenic HCT had AML.

Among our studied cases, 24 % developed acute GVHD. In allogenic transplant, the rate of acute GVHD was reported to range from 20 to 50 percent **[16, 17].** similar to our findings

Reduced-intensity conditioning (RIC) was developed to decrease transplant-related mortality (TRM) after Allo-HSCT and to allow allogenic bone marrow transplant in patients who would not be eligible otherwise for transplantation due to comorbidities or old age. Due to the fact that it is less toxic than the established myeloablative conditioning (MAC), the use of RIC has increased **[18].**

In our study, platelet engraftment was slightly faster with RIC than MAC, and there is no increase in the speed of engraftment of ANC. The explanation of this finding may be that patients received RIC are mostly frail, and complain from another comorbidity. The duration of hospital stay was lower in patients received RIC. this finding is consistent with **Ringden *et al.*, [19]** who found that platelet engraftment was faster with RIC than MAC, The time of discharge from hospital was faster.

In this study, the median OS was 44.2 month. The cumulative proportion surviving for at 1, 2, and 5-years of patients receiving MAC vs NMA/RIC conditioning regimens were 66% vs. 54%, 54% vs. 48% respectively, the difference was not statistically significant (p=0.72). This finding is in agreement with **Ringden *et al.*, [19]** who found that Five-year survival was 62% in patients conditioned with MAC and 76% in those conditioned with RIC (P = 0.30).

Among the studied cases, HBV coinfection had poor prognostic impact on overall survival. our finding is consistent with **Tomblyn *et al.*, [20]** who found that transplant related mortality(TRM) was higher for cases with seropositive For both HBV and HCV compared to cases in which only one virus was present. the frequencies of SOS, hepatic acute GVHD, and hepatic chronic GVHD were similar in both groups, suggesting that infection or other organ toxicities may be causing the higher TRM.

In our study, sex mismatch between recipient and donor had poor prognostic impact on overall survival with ratio (HR)= 3.526; 95% confidential interval (CI): 1.504 - 8.266, P-value =0.004. The explanation of this finding may be that that human minor histocompatibility antigens (mHAs) encoded on Y chromosome contribute to the allo-reactive immunogenicity in male recipients from female donors **[21]**.

Conflict of interest: The investigators declare no conflict of interest.

Sources of funding: The current study didn't receive any specialized grant from funding agencies.

CONCLUSION

We concluded that the conditioning intensity (MAC vs. NMA/RIC) Had no significant impact on post-transplant complications, although MAC is

associated with longer time to hematopoietic recovery. No significant impact on overall survival, MAC was associated with a trend towards lower incidence of NRM.

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