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RISK FACTORS FOR THE OUTCOME AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: A SINGLE-CENTER EXEPERIENCE

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Abstract

Allogeneic stem cell transplantation (AlloSCT) is a therapeutic procedure for the treatment of a large number of malignant and non-malignant hematological diseases, unfortunately still associated with significant morbidity and mortality. Disease relapse and non-relapse mortality remain the main causes of treatment failure following AlloSCT. Identification of the risk factors associated with this continue to be a subject of extensive scientific research. The aim of our study is to estimate the risk factors that would have prognostic significance for the outcome of AlloSCT for our patient population. We evaluated 96 patients who received AlloSCT in the transplant unit at Specialized Hospital for Active Treatment of Hematological Diseases (SHATHD), between 2017-2022, with the following diagnoses: acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia (ALL. They were prospectively followed up to June 2023. Our results regarding success rates and

complications related to the procedure did not differ from data reported in the literature. Along with the common risks for the outcome of AlloSCT, we found as an independent prognostic factors the lymphocyte recovery at D+21 after transplantation and the indicators of cytokine response in the pre engraftmen period.

Key words: allogeneic stem cell transplantation, risk factors, transplant outcomes, absolute lymphocyte count

1. **Introduction:**

Allogeneic stem cell transplantation is a proven therapeutic method for treating a variety of malignant and benign hematological diseases, but it is still associated with significant morbidity and mortality [1,2,3]. Disease relapse and mortality from the procedure itself remain the main reasons for failure of AlloSCT. The intent of AlloSCT is to ensure the engraftment of transfused hematopoietic stem cells-from peripheral blood/bone marrow, obtained after mobilization with or without a growth factor from a related/unrelated donor with optimal HLA compatibility, and the engraftment to be for the recipient's entire future life, with subsequent partial or complete recovery of their lymphohematopoietic system [4]. The antileukemic effect of AlloSCT results from two key biological processes: the elimination of residual, chemosensitive tumor cells by the conditioning chemotherapy and the graft-versus-leukemia (GVL) effect. The importance of the GVL effect was described by the Seattle group in 1970 and emphasized by the success of non-myeloablative allogeneic transplantation [5,6]. On the other hand, GVL is invariably associated with acute and chronic graft versus host disease (GVHD), but the GVL effect is not entirely dependent on GVHD. The effector mechanism of GVL and GVHD is complex and still not fully understood. Medicine continues to search for and model risk factors directly associated with improving the outcomes of alloSCT. For this reason, our center initiated a study to identify risk factors related to the outcomes of AlloSCT, specific to the population of patients with malignant hematological diseases in Bulgaria, who are directed towards transplantation.

2. Aim of the study

For this purpose, the demographic and morbidity profile of the patients, peri transplant factors (pre-transplantation + post-transplantation – CMV reactivation, aGVHD, cGVHD) were analyzed. OS, PFS, CIR, NRM, and the risk factors associated with them were evaluated.

3. Materials and methods

3.1. Patients and transplant procedures

During the period 2017-2022, the electronic medical records of 96 patients diagnosed with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphoblastic leukemia (ALL), who underwent AlloSCT following a decision by the transplantation committee and after signing informed consent, were analyzed. The demographic, clinical, and laboratory data were obtained from the hospital information system (HIS). The selection criteria included patients with myeloablative or reduced-intensity conditioning, according to the CIBMTR classification [7], followed by the infusion of hematopoietic stem cells from peripheral blood mobilized with a growth factor from compatible related, unrelated, or haploidentical donors.

The choice of conditioning regimen intensity was at the discretion of the treating team, based on the patient's age and comorbidity index. Patients with AML and MDS suitable for MAC (myeloablative conditioning) were preferentially conditioned with a busulfan-based regimen, while those with ALL were conditioned with a total body irradiation (TBI)-based regimen. Most patients transplanted from a compatible unrelated donor underwent in vivo T-cell depletion with anti-thymocyte globulin (ATG). All patients received standard prophylaxis for infectious diseases, veno-occlusive disease (VOD), and immunosuppression with cyclosporin A (CycA) + methotrexate (MTX)/ mycophenolic acid (MMF) + tacrolimus (TAC)/ post-transplant cyclophosphamide (PTCy) + MMF + TAC/CycA + MMF. Patients who relapsed or died within 1 month of AlloSCT were excluded from analysis and evaluation.

3.2. Definitions and Transplantation-Related Outcomes

Overall survival (OS) is calculated from the date of transplantation to the date of death or last follow-up. Progression-free survival (PFS) is measured from the time of transplantation to death from any cause or relapse. Non-relapse mortality (NRM) is calculated from the date of transplantation to death from any cause without evidence of disease relapse [8]. Acute and

chronic GVHD are diagnosed and staged according to the standard criteria set by the EBMT [9]. Hematological recovery is defined as achieving an absolute neutrophil count (ANC) of 0.5x109/L or higher for 3 consecutive days and a platelet count higher than 20x109/L for 7 consecutive days without transfusion support.

3.3. Statistical Analysis

The analysis includes the assessment of quantitative variables, presented with mean and standard deviation or median and range (minimum and maximum), and categorical variables with absolute and relative frequencies. The chi-square (χ^2) analysis (Fisher's exact test) was used to examine the relationship between categorical variables. The significance of the difference between the means of two independent samples was assessed using the non-parametric Mann-Whitney test. Cox regression analysis and log-rank test (Mantel-Cox) were applied to identify significant factors related to survival and other time-dependent events. The distribution form was determined with the Kolmogorov–Smirnov test. Single and multiple analyses were performed to evaluate the main characteristics of the patients related to the transplantation outcomes - OS, PFS, and NRM. P-values <0.05 were considered significant.

4. Results

4.1. Patient Characteristics and Transplant Program

The main characteristics of the 96 patients included in the analysis are presented in **Table 1.** The median age is 43 years (range 19-68 years), with 56.3% of patients being over 40 years old. The majority of recipients and donors are male, accounting for 67.7% and 57.3%, respectively. The leading indication for AlloSCT is the diagnosis of AML, at 63.5%. More than half of the patients were transplanted in the first complete remission (CR1) - 53.1%, with a calculated DRI (Disease Risk Index) [10] being low/intermediate - 54.2%. The physical condition and comorbidity of patients relevant to AlloSCT were assessed using ECOG-PS [11] and HCT-CI [12], with over 90% of patients being transplanted in good condition and with a low comorbidity index. Regarding the transplant program profile, 55.2% of patients were transplanted from a fully compatible unrelated donor. The proportion of haploidentical transplants is 17.7%. In 25% of the cases, the gender match was female donor to male recipient. Myeloablative conditioning was applied to 53%, with a busulfan-based regimen in 61.5%. ATG prophylaxis for GVHD was used in 46.9% of the analyzed patients.

Table 1. Characteristics of the Patients and Transplant Program

Characteristics		Number (n)	Percentage(%)
Age	< 40	42	43,8%
	≥ 40	54	56,3%
Recepient sex	male	65	67,7%
	female	31	32,3%
Donor sex	male	31	57,3%
	female	55	42,7%
Diagnose	AML	61	63,5%
	MDS	5	5,2%
	ALL	28	29,2%
ECOG PS	0-1	93	96,9%
	2	3	3,1%
HSCT CI	0-2	89	92,7%
	3-5	7	7,3%
DRI	Low + Intermediate	52	54,2%
	High + Very high	44	45,8%
Responce to AlloSCT	CR1	51	53,1%
	CR2/CR3	16	16,7%
	RR	29	30,2%
ABO - compatibility	Minor	22	22,9%
	Major	16	16,7%
	Bidirectional	5	5,2%
	Common	53	55,2%
HLA-compatibility	MRD	26	27,1%
	MURD	53	55,2%
	Haplo	17	17,7%
Donor-recipient sex	Female-male	25	26,0%

Characteristics		Number (n)	Percentage(%)
	останалите	54	74,0%
Conditioning regimen	MAC	53	55,2%
	RIC	43	44,8%
	TBI - based	32	33,3 %
	Bu -based	59	61,5%
	ATG - prophilaxys	45	46.90%
	other	51	53,1 %

Legend: AML - Acute Myeloid Leukemia; MDS - Myelodysplastic Syndrome; ECOG PS - Eastern Cooperative Oncology Group Status; HCT CI - Hematopoietic Cell Transplantation-specific Comorbidity Index; DRI - Disease Risk Index; CR - Complete Remission; RR – Relapse/Refractory Disease; MRD - Matched Related Donor; MURD - Matched Unrelated Donor; Haplo - Haploidentical Donor; MAC - Myeloablative Conditioning; RIC - Reduced Intensity Conditioning; TBI - Total Body Irradiation; Bu - Busulfan; ATG - Anti-Thymocyte Globulin;

4.2. Graft Composition and Hematologic Recovery

In all patients, hematopoietic stem cells were obtained from peripheral blood after stimulation with a growth factor. The composition of the graft and hematologic recovery are presented in **Table 2** and **Table 3**.

Table 2. Composition of the graft

Parameter	Median value	Minimal value	Maximal value
CD34 + x 10^6/kg	4,97	2,10	9,85
CD3 + x 10^8/kg	2,149	0,471	10,700

Table 3. Hematologic recovery

Parameter, recovery in days	Median value	Minimal value	Maximal value
Neu	16	11	29
PLT	15	10	45

4.3. Lymphocyte Recovery

Table 4 provides information on the dynamics of lymphocyte recovery, monitored from Day +14 to Day +100.

Table 4. Dynamics of Lymphocyte Recovery

Parameter	Median value	Minimal value	Maximal value
Ly +14 day cells/µl	90,0	,0	1260,0
Ly +21 day cells/µl	245,0	,0	950,0
Ly +30 day cells/µl	525,0	,0	1850,0
Ly +60 day cells/µl	775,0	40,0	6560,0
Ly +100 day cells/µl	1140,0	110,0	7180,0

Legend: Ly – Lymphocytes.

4.4 Immune Reconstitution

Immune reconstitution in the first month (28 to 35 days) post-AlloSCT was assessed through multiparametric flow cytometry of peripheral blood. The results are presented in **Table 5.**

Table 5. Immune reconstitution in the first month post- AlloSCT

cell/µl	Median	Minimum	Maximum	Percentile 25	Percentile 75
CD3+	348,5	,0	2297,0	166,0	564,0
CD4+	117,0	,0	566,0	48,0	228,0
CD8+	152,5	,0	1997,0	67,0	276,0
NK	168,0	,0	764,0	80,0	327,0

4.5. Evaluation of Outcomes from AlloSCT through OS, PFS, CIR, and NRM

With a median follow-up of 54.7 months (95% CI 1395.965 - 1936.035), the median OS has not been reached: 51.3% of patients are alive, **Figure 1.** The median PFS is 19.4 months, **Figure 2**. The median CIR has not been reached, **Figure 3.** The median NRM has also not been reached, **Figure 4.**

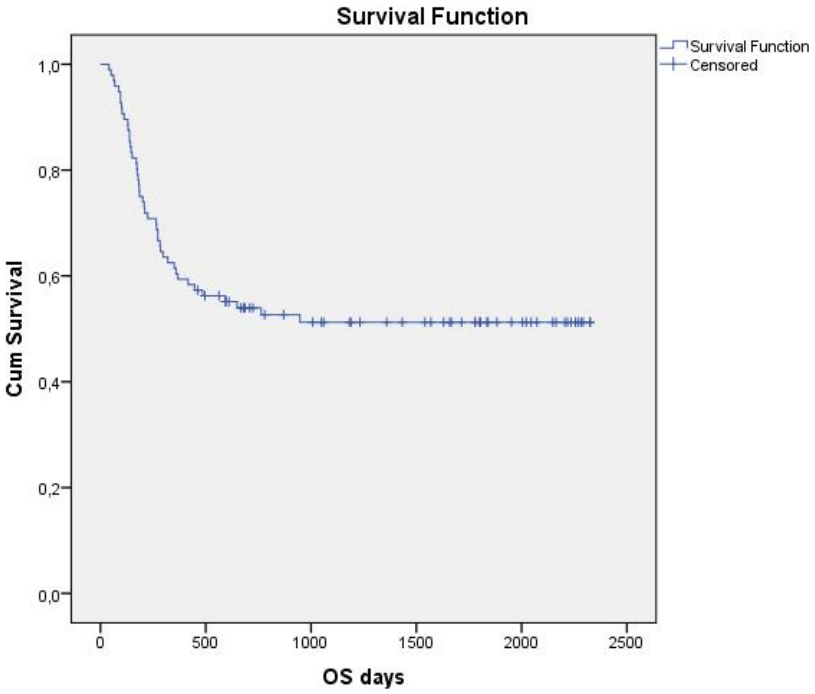

Figure 1. Transplantation Outcome – Overall Survival (OS)

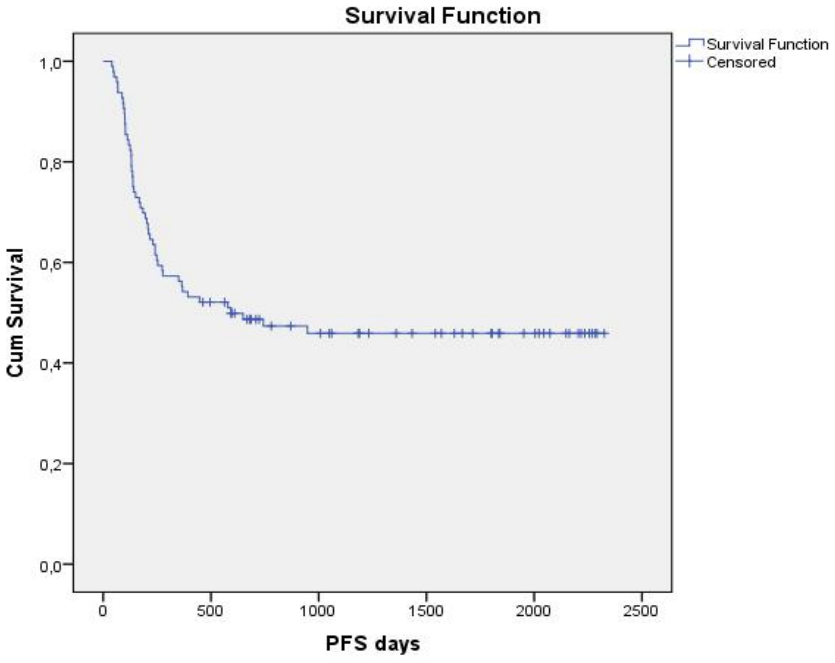

Figure 2. Transplantation Outcome – Progression-Free Survival (PFS)

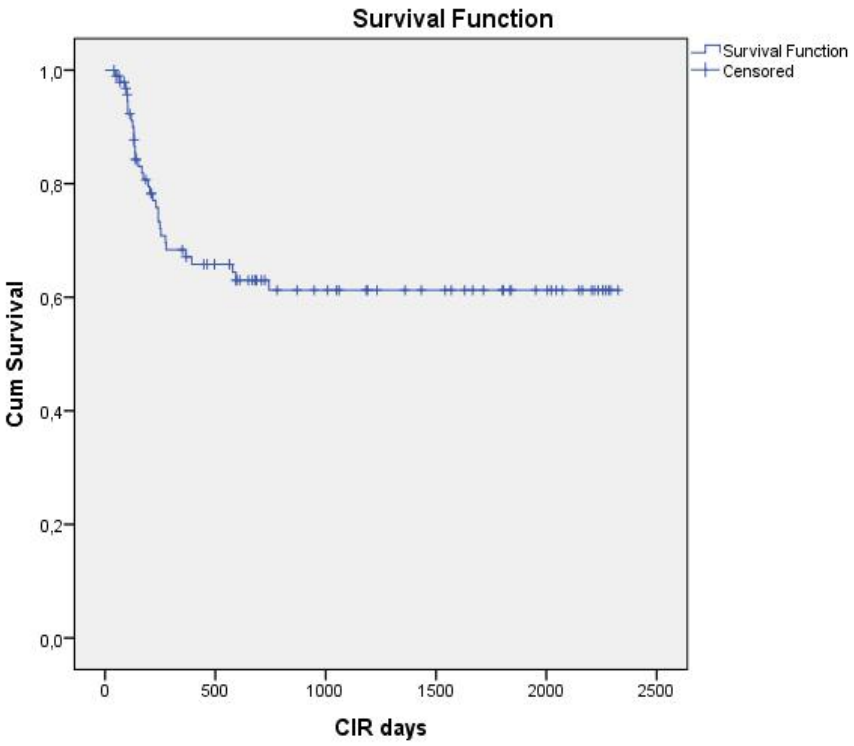

Figure 3. Transplantation Outcome – Cumulative incidence of relapse (CIR)

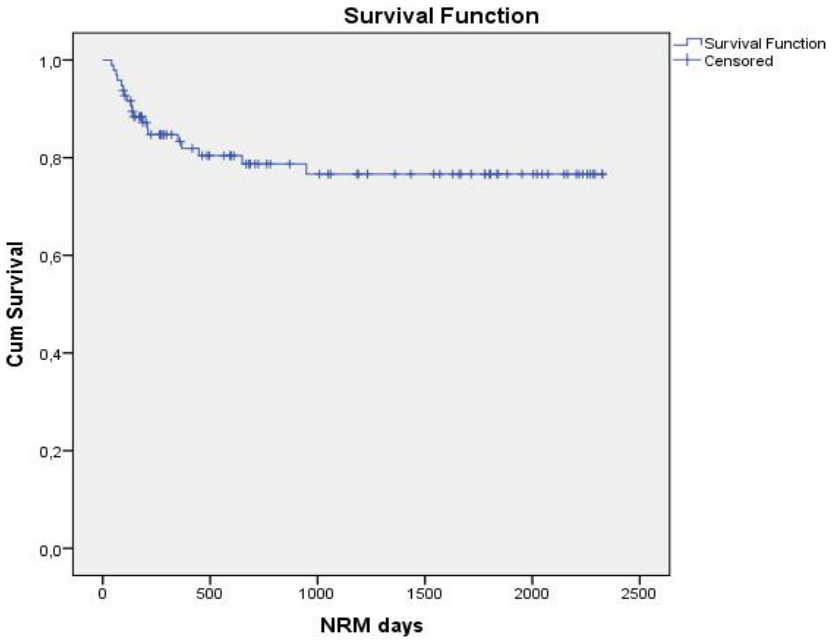

Figure 4. Transplantation Outcome – Non-relapse mortality (NRM)

4.6. Complications after AlloSCT and Causes of Mortality

The distribution of the followed-up patients in terms of complications that are significant for the outcome of the transplantation - acute and chronic graft-versus-host disease and cytomegalovirus reactivation, is shown in **Table 6**. The leading cause for mortality was disease relapse – 55% of the patients, followed by infectious complications in 23% and GvHD in 18%.

Table 6. Complications Associated with AlloSCT

Characteristics	Number (n)	Percent (%)
aGVHD	44	46,3%
1-2	28	63,6%
3-4	16	36,4%
cGvHD	24	31,6%
mild	9	37,5%
moderate	9	37,5%
severe	6	25,0%
CMV reactivation	52	54,2%

4.7. Peri transplant Risk Factors for Outcomes from AlloSCT

An analysis was conducted to evaluate the peri transplant risk factors related to the outcomes of the transplantation - OS, PFS, CIR, and NRM. We also studied the role of the degree of cytokine response in the preengraftment period, assessed by the maximum value of serum CRP (max CRP) and the maximum body temperature (max BT) during the first seven days after AlloSCT, the influence of early lymphocyte recovery of D + 21 and D+30 of AlloSCT, represented as absolute lymphocyte count, and NK-cell recovery at the first month of the procedure (D+28-D+35), by multiparametric flow cytometry of peripheral blood.

Risk Factors for OS

A Cox regression analysis was used to examine the relationship between patient characteristics and overall survival. Significant pretransplant risk factors for OS in the following group of patients include: ECOG PS, HCT CI, the response achieved to AlloSCT, donor choice, and the use of ATG. Patients who received AlloSCT from a compatible

unrelated donor had a 2.1 times lower risk of death compared to others, the reason being that over 50% of the transplants were from such donors. Patients who received a haploidentical transplant had the highest risk of death, being 2.2 times higher.

The use of ATG was an unfavorable factor regarding OS, increasing the risk of death by 2.1 times. In the post-transplant period, factors that carry a risk for reduced OS include an increase in temperature and CRP in the pre-engraftment period, delayed hematological and lymphocyte recovery, the manifestation of aGVHD, and CMV reactivation.

Table 7. Risk Factors for OS

Characteristic	p	HR	95% CI	
ECOG PS	0,012	2,733	1,088	5970
HSCT CI	0,005	1,373	1,101	1714
Disease risk index	<0,001	1,832	1,334	2523
Answer to AlloSCT	0,019	1,288	1,098	1591
HLA-type MRD	0,368	1,335	0,788	2,502
HLA-type MURD	0,013	0,478	0,297	0,857
HLA-type haplo	0,017	2,237	0,955	4,336
ATG - based	0,013	2,104	1,087	3,795
Neutrophil recovery	0,011	1,101	0,994	1,186
Platelet recovery	<0,001	1,079	1,018	1,124
Max t° in the period of preengraftment	0,024	1,451	0,926	2,005
max CRP in the period of pre engraftment	0,051	1,004	0,999	1,007
Ly +21 day cell/µl	0,004	0,998	0,997	0,999
Ly +30 day cell/µl	0,035	0,999	0,998	1,000
aGVHD	0,004	2,439	1,148	4445
cGvHD	0,765	0,881	0,425	2026
CMV reactivation	0,030	1,962	0,985	1,001
Conditioning regime RIC	0,052	1,779	0,948	3183

Risk Factors for PFS

Significant risk factors for PFS are presented in **Table 8**: ECOG PS, HCT CI, DRI, the response achieved to AlloSCT, the use of ATG, delayed platelet recovery, and lymphocyte recovery, manifestation of aGVHD, and post-transplant CMV reactivation. Patients who received AlloSCT from a compatible unrelated donor had a 1.9 times lower risk of progression compared to others.

Table 8. Risk factors for PFS

Characteristics	p	HR	95% CI	
ECOG PS	0,030	2,385	1,088	5,232
HCT CI	0,004	1,360	1,101	1,680
Disease risk index	<0,001	1,809	1,334	2,453
Answer to AlloSCT	0,004	1,344	1,098	1,644
HLA-type MRD	0,241	1,425	0,788	2,576
HLA-type MURD	0,020	0,517	0,297	0,899
HLA-type haplo	0,068	1,831	0,955	3,508
ATG - based	0,024	1,891	1,087	3,291
Neutrophil recovery	0,071	1,068	0,994	1,147
Platelet recovery	0,004	1,059	1,018	1,102
Ly +21 day cell/µl	0,004	0,998	0,997	0,999
Ly +30 day cell/µl	0,031	0,999	0,998	1,000
aGVHD	0,015	2,013	1,148	3,529

Risk Factors for CIR

A Cox regression analysis was performed to examine the relationship between patient characteristics and cumulative incidence of relapse, **Table 9**. Significant risk factors for CIR include: ECOG PS, DRI, choice of donor, the use of ATG, and choice of conditioning regimen. Patients who received AlloSCT from a compatible unrelated donor had a 2.1 times lower risk of relapse compared to others. Patients who received a transplant from a fully compatible related donor and those who underwent RIC had a 2.1 times higher risk of progression.

Table 9. Risk Factors for CIR

Characteristics	p	HR	95% CI
Disease risk index	<0,001	2,304	1,555
Answer to AlloSCT	<0,001	1,745	1,344
HLA-type MRD	0,035	2,141	1,057
HLA-type MURD	0,043	0,484	0,240
ATG - based	0,045	2,051	1,017
Conditioning RIC	0,038	2,095	1,040

Risk Factors for NRM

Significant risk factors for NRM include: HCT CI, choice of haploidentical donor, delayed hematological recovery, cytokine response indicators in the pre-engraftment period, delayed lymphocyte recovery, manifestations of aGVHD, post-transplant CMV reactivation, **Table 10.**

Table 10. Risk Factors for NRM

Characteristics	p	HR	95% CI	
HCT CI	0,021	1,466	1,059	2,030
HLA-type haplo	0,009	3,508	1,369	8,993
Neutrophil recovery	0,003	1,178	1,057	1,314
Platelet recovery	<0,001	1,104	1,048	1,162
Max t° during pre engraftment	0,004	2,532	1,343	4,773
max CRP during pre engraftment	0,045	1,005	1,000	1,010
Ly +21 day cell/µl	0,011	0,997	0,994	0,999
aGVHD	0,001	8,032	2,305	27,990
CMV reactivation	0,008	5,326	1,549	18,317

5. Discussion

The demographic characteristics and morbidity of the following population do not differ from the data presented in the literature. Regarding the distribution by diagnosis, there is a lower proportion of patients who received a transplant for MDS, due to the less frequent referral of these patients by treating teams to AlloSCT. The profile of the transplant program, including type of donor, source of cells, and choice of conditioning regimen, is fully comparable to the trends and data presented by other transplant centers [13]. The median infused amount of HSC, defined as CD34+ x 10^6/kg and hematological recovery, meet the target levels for AlloSCT from peripheral blood [14]. The results of the transplantation program in our center for the study period, evaluated as OS, PFS, CIR, NRM, and the frequency of post-transplant complications – aGVHD, cGVHD, and CMV reactivation, correspond to those cited in the literature. Besides the risk of relapse, significant problems for our center remain the mortality related to infectious complications and GvHD [15,16]. This is one of the reasons for identifying specific risk factors for adverse outcomes from AlloSCT in our patient population and searching for new ones. Distinctively, our study finds lymphocyte recovery on D+21 as an independent prognostic factor for OS, PFS, and NRM, and for OS and NRM, the indicators of cytokine response in the pre-engraftment period. No statistically significant association was demonstrated between NK-cell recovery and OS, PFS, CIR, NRM and ALC, possibly due to the small number of patients included in the analysis.A drawback of our study was that the role of the graft source for cellular reconstitution after AlloSCT could not be assessed because patients who received bone marrow stem cells were excluded from the study due to their extremely small number.

Several authors investigate the impact of lymphocyte recovery and immune reconstitution on the outcomes of AlloSCT. The results regarding the relationship between lymphocyte recovery and the frequency of relapse and/or NRM remain controversial, and whether lymphocyte recovery can be considered an indicator that defines high-risk groups for NRM or relapse after AlloSCT [17]. sL-index(30) is a promising tool that may be applied to various survival outcomes. A large-scale prospective study is needed to clarify whether medical interventions based on sL-index(30) values will improve the clinical prognosis of patients [18].

6. Conclusion

Despite this significant advance in allogeneic stem cell transplantation, the procedure is still associated with significant mortality and morbidity. The identification and management of risk in the context of personalized medicine is focused on the development of ever more precise and sensitive tools for risk stratification. To provide accurate probabilistic estimates of post-transplant events, prediction models should be developed on disease-specific cohorts and include granular information regarding patient, disease, and treatment features [19].

Acknowledgements

Institutional Review Board Statement

This study was approved by the Specialized Hospital for Active Treatment of Hematological Diseases (SHATHD) in Sofia; all patients signed an informed consent form.

Informed Consent Statement

Written informed consent has been obtained from the patient(s) who could be identified to publish this paper.

Conflicts of Interest

The authors declare no conflict of interest.

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