

## Research Article

# Early lymphocyte recovery after allogeneic transplantation of hematopoietic stem cells in patients with haematological malignancies: a single-centre experience

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## Summary

**Introduction:** Allogeneic hematopoietic stem cell transplantation (AlloHSCT) is a therapeutic method for the treatment of many malignant and non-malignant hematological diseases but is still associated with significant morbidity and mortality. Disease relapse recurrence and non-relapse mortality (NRM) remain the main causes of failure from AlloHSCT. The identification of the risk factors associated with this continue to be a subject of extensive scientific research.

**Aim:** The aim of our study was to identify the prognostic significance of the early lymphocyte recovery (ELR), presented as absolute lymphocyte count (ALC) for the outcome of AlloHSCT.

**Materials and methods:** 96 patients with diagnoses of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia(ALL) who underwent AlloSCT at the Hematopoietic Stem Cell Transplantation Unit of SHATHD between 2017 and 2021 were included in the study. Based on our previous study on the prognostic role of ELR such as absolute lymphocyte count (ALC) on the outcome of AlloSCT, in terms of overall survival (OS), patients were divided and evaluated into two groups.

**Results:** At a median follow-up of 54.7 months, median OS, progression-free survival (PFS), cumulative incidence of relapse (CIR), and NRM for patients with ELR were not reached. Disease risk index (DRI), response to AlloSCT and choice of haploidentical donor were identified as significant risk factors for ELR. Analysing the data regarding the significance of ELR in post-transplant complications led to important conclusions regarding aGvHD, cGvHD and associated survival.

**Conclusion:** ELR is an established, clinically significant prognostic factor for transplant outcome. Identification and modelling of risk factors and complications associated with ELR can significantly improve outcomes of AlloSCT.

**Key words:** Absolute lymphocyte count, acute leukaemia, stem cell transplantaion, survival



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## Introduction

AlloHSCT (allogeneic haematopoietic stem cell transplantation) is a proven therapeutic modality for the treatment of malignant and benign haematological diseases, but it is still associated with significant morbidity and mortality (Fallen et al. 2003; Appelbaum 2007; Mahmoud et al. 2015). The leading causes of failure remain disease relapse and treatment-related mortality. The antileukemic effect of AlloHSCT is the result of two key biological processes: the elimination of residual chemosensitive tumour cells from the conditioning chemotherapy and the graft-versus-leukaemia (GVL) effect. The importance of the GVL effect was described and emphasised by the Seattle group in 1970 and highlighted by the success of non-myeloablative allogeneic transplantation (Weiden et al. 1979; Berger et al. 2008). The effector mechanism of GVL and GvHD is complex and not fully understood (Horowitz et al. 1990). Medicine continues searching for risk factors directly related to improving the outcome of AlloHSCT. Timely and functionally adequate immune reconstitution is critical for improving overall survival and reducing relapse-free mortality after allo-HSCT. A surrogate marker for this is the recovery of the donor lymphoid system, represented by lymphocytes circulating in the peripheral blood. The role of ELR as a biologically relevant prognostic marker for transplant outcomes has been investigated in several studies (Chakrabarti et al. 2003; Fowler 2006; Heining et al. 2007; Bühlmann et al. 2011).

## Aim of the study

Our study aimed to identify the prognostic significance of the early lymphocyte recovery (ELR), presented as absolute lymphocyte count (ALC), for the outcome of AlloSCT.

## Materials and methods

### Patients

The medical records of 96 patients with acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and acute lymphoblastic leukaemia (ALL) who received AlloHSCT between 2017 and 2021. We obtained demographic, clinical and laboratory data from the hospital information system (HIS). Patients were selected according to the following criteria. The inclusion criteria were as follows: 1. Patients aged  $\geq 18$  years. 2. Diagnosis: AML, MDS, ALL. 3. Indication for AlloHSCT. 4. Signed informed consent. 5. Documented engraftment. 6. Survival 30 days after AlloHSCT. Exclusion criteria were 1. Patients with acute promyelocytic leukaemia. 2. Patients with relapsed or de novo acute leukaemia after first allo-HSCT. 4. Patients with primary graft failure, graft rejection, poor graft function according to generally accepted definitions (Valcárcel and Sureda 2019).

### Methods

The choice of regimen intensity was at the discretion of the treating team, based on the patient's age and comorbidity index. MAC-eligible patients with AML and MDS were preferentially treated with a busulfan-based regimen (busulfan

3.6 mg/kg for 4 days), while patients with ALL received a total body irradiation (TBI)-based regimen (10–12 Gy). Patients transplanted from a matched unrelated donor (MUD) undergo in vivo T-cell depletion with antithymocyte globulin (ATG, thimoglobulin 2.5 mg/kg for 2 days), and those from haploidentical donors received post-transplant cyclophosphamide (PTCy) at a dose of 50 mg/kg for 2 days. All patients received standard anti-infective prophylaxis (ciprofloxacin, fluconazole, acyclovir), veno-occlusive disease (VOD) prophylaxis with ursodeoxycholic acid and immunosuppression with cyclosporin A (CycA) + methotrexate (MTX) / mycophenolate (MMF) + tacrolimus (TAC) / PTCy and + MMF+TAC/CycA +MMF.

### Statistical analysis

Statistical analysis included the evaluation of both quantitative and categorical variables, using absolute and relative frequencies. Cumulative incidence of relapse (CIR) was calculated from the date of transplant until relapse or date of last follow-up. Cumulative incidence of non-relapse mortality (NRM) was calculated from the date of transplant until death of any cause without evidence of disease relapse. The Kolmogorov-Smirnov test was used to determine the type of distribution, the Chi-squared ( $\chi^2$ ) analysis (Fisher's exact test) – to test the relationship between categorical variables, a non-parametric Mann-Whitney test – to assess the significance of the difference between two independent sample means, and the Cox regression analysis and the log-rank test (Mantel-Cox) – to identify significant factors associated with survival and other time-dependent events. The mean and median times to event were assessed using the Kaplan-Meier method. Values  $p < 0.05$  were considered significant. Analyses were performed using IBM SPSS v. 22.

## Results

### Characteristics of the patients and transplantation program

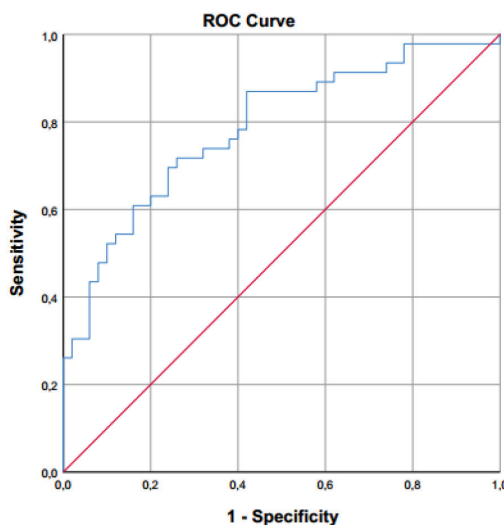
The baseline characteristics of all 96 patients included in the analysis are shown in Table 1. The median follow-up was 54.7 months (95% CI, 45.86–63.6). The median age was 43 years (range, 32–52), with ages ranging from 19 to 68 years. The leading indication for AlloHSCT was AML in 63.5% of patients. All patients received G-CSF mobilised haematopoietic stem cells from peripheral blood.

### Early lymphocyte recovery and absolute lymphocyte count

Assessment of ELR as ALC was performed on D+21 and D+30. Considering that the lowest normal reference value for ALC ( $0.5 \times 10^9/l$ ) is not clinically relevant for this patient population, we used Cox regression analysis to test the significance of ALC factors – D+21 and D+30 for assessment of OS. Only D+21 proved to be a significant factor for OS ( $p = 0.004$ ; HR = 0.998; 95% CI, 0.996–0.999). The function thus obtained from the Cox analysis was converted into an ROC curve to determine the optimal cut-off value of D+21 in terms of OS (Fig. 1). The area under the curve is 0.797 (at a population value of 0.5) and is statistically significant ( $p < 0.001$ ). The limit value of the function was

**Table 1.** Characteristics of the patients (n = 96).

Characteristics		Number (n)	Percentage (%)
Age	< 40	42	43.8%
	≥ 40	54	56.3%
Recipient sex	Male	65	67.7%
	Female	31	32.3%
Donor sex	Male	55	57.3%
	Female	41	42.7%
Diagnoses	AML	61	63.5%
	MDS	5	5.2%
	ALL	30	31.3%
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%
Response rate	CR1	51	53.1%
	CR2/CR3	16	16.7%
	RR	29	30.2%
ABO – incompatibility	Minor	22	22.9%
	Major	16	16.7%
	Bidirectional	5	5.2%
	Compatible	53	55.2%
HLA-match	MRD	26	27.1%
	MUD	53	55.2%
	Haplo	17	17.7%
Sex ratio donor-recipient	Female donor-male recipient	25	26.0%
	others	54	74.0%
Conditioning	MAC	53	55.2%
	RIC	43	44.8%
	TBI-based	32	33.3%
	Bu-based	59	61.5%
	ATG –containing	45	46.90%



**Figure 1.** ROC curve determining cut-off value of D+21 for OS based on Cox Proportional hazard function model with area under the curve 0.797.

determined to be 0.5376, corresponding to an ALC of  $0.220 \times 10^9/l$  of D+21. Based on the newly created variable, we grouped the patients into two categories: DLR with  $ALC < 0.220 \times 10^9/L$  and ELR with  $ALC \geq 0.220 \times 10^9/L$ .

### The role of early lymphocyte recovery for transplant outcome

Stratified by lymphocyte recovery, median OS was not achieved for ELR compared to 225 days for DLR ( $p < 0.001$ ). In terms of PFS, a significant difference was also observed between the two cohorts, with the median PFS not being achieved in the ELR group compared to 196 days in the DLR group ( $p < 0.000$ ). Median CIR was not achieved in patients with ELR compared to those with DLR, which was 393 days ( $p = 0.022$ ). The median NRM was not achieved in either group; however, the time to event was significantly longer in patients with ELR, at 2261 days, compared to 1889 days in the DLR group ( $p = 0.003$ ). The results at 1 and 3 years after AlloSCT stratified by lymphocyte recovery are shown in Table 2. Significantly better results were reported at both 1 and 3 years in patients who achieved ELR on D+21 after stem cell infusion.

**Table 2.** Transplant-related outcomes at 1<sup>st</sup> year and 3<sup>rd</sup> year.

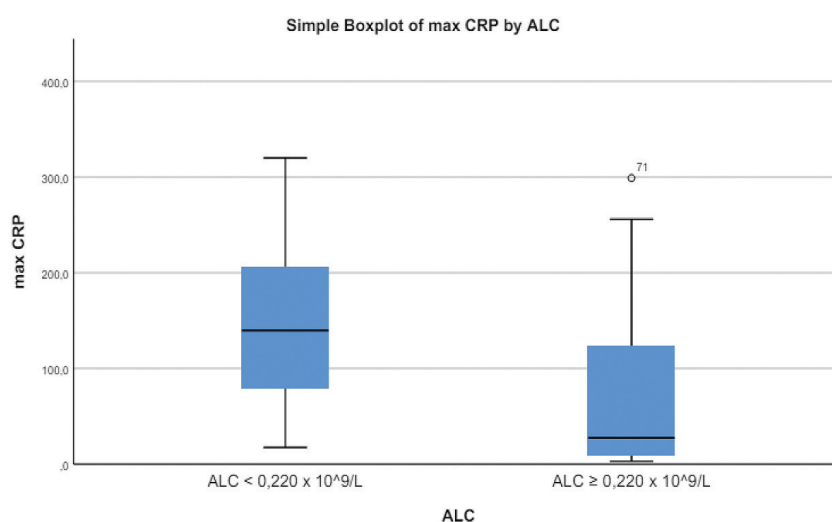
Variable	ALC +21 $< 0.220 \times 10^9$	ALC +21 $\geq 0.220 \times 10^9$	p
OS 1 <sup>st</sup> year	35.7%	75.9%	$p < 0.000$
PFS 1 <sup>st</sup> year	33.3%	70.4%	$p < 0.000$
CIR 1 <sup>st</sup> year	49.4%	25.2%	$p < 0.022$
NRM 1 <sup>st</sup> year	39.1%	8.1%	$p = 0.003$
OS 3 <sup>rd</sup> year	29.5%	67.8%	$p < 0.000$
PFS 3 <sup>rd</sup> year	27.1%	60.2%	$p < 0.000$
CIR 3 <sup>rd</sup> year	53.0%	30.1%	$p < 0.022$
NRM 3 <sup>rd</sup> year	39.1%	12.9%	$p = 0.003$

### Factors associated with early lymphocyte recovery

A statistically significant relationship was found between ALC D+21 and DRI, as well as the response rate before alloHSCT and haploidentical donor selection (Table 3). Comparing the type of in vivo T-cell depletion – ATG vs. PTCy vs. standard – expectedly, PTCy was associated with significantly delayed lymphocyte recovery, with a median ALC of  $0.06 \times 10^9/l$  on day +21, for the ATG and standard groups,  $0.220 \times 10^9/l$  and  $0.350 \times 10^9/l$ , respectively ( $p <$ ). Graft composition, represented by the median of transfused CD34+ and CD3+ donor cells, was not identified as a statistically significant factor correlating with lymphocyte recovery, with p-values of 0.0547 and 0.0842, respectively. We performed univariable and multivariable analysis to estimate the relationship between ELR and these factors in terms of OS. The univariable model identified ECOG PS, HCT CI, DRI, and response rate before AlloHSCT as significant, of which only DRI was confirmed by multivariable analysis ( $p = 0.04$ , HR 1.926, 95% CI 1.030–3.603). We investigated the degree of cytokine response in the pre-engraftment period, assessed by the maximum level of serum CRP (max CRP) during the first seven days after allo-HSCT and the maximum body temperature (max BT) (Fig. 2). It is known that CRP can be a net surrogate marker for early disease/

**Table 3.** Post-transplantation complications stratified based on D+21 lymphocyte recovery.

	ALC D+21				p
	< 0.220 x 10 <sup>9</sup> /L		≥ 0.220 x 10 <sup>9</sup> /L		
	N	%	N	%	
aGvHD	25	56.8%	19	43.2%	0.014
1–2	15	53.6%	13	46.4%	0.565
3–4	10	62.5%	6	37.5%	
cGvHD	5	20.8%	19	79.2%	0.035
mild	0	0.0%	9	100.0%	0.065
moderate	2	22.2%	7	77.8%	
severe	3	50.0%	3	50.0%	
CMV reactivation	25	48.1%	27	51.9%	0.35

**Figure 2.** Max CRP stratified by lymphocyte count ( $p = 0.001$ )

syndrome leading to the development of a/cGVHD and eventually NRM [17]. Our results showed that high levels of max CRP (normal values up to 5 mg/L for our laboratory) during this period led to delayed early lymphocyte recovery. The median max CRP in the group of patients with ALC D+21 below  $0.220 \times 10^9/L$  was 139.5 mg/L, in contrast to only 27.5 mg/L in patients with ALC D+21 above  $0.220 \times 10^9/L$  ( $p = 0.001$ ).

### Analysis of post-transplantation complications according to lymphocyte reconstitution

The frequency of a/cGvHD was statistically significantly higher in patients with DLR (Table 3). To assess the relationship between ALC and a/cGvHD in the context of NRM, we divided the sample into two groups: with and without manifestations of a/cGvHD. In both groups, a lower non-relapsed mortality was observed in patients with ELR, although this difference was not statistically significant ( $p > 0.05$ ). Regarding CMV reactivation, the results were similar in both groups – ELR and DLR (Table 3). One explanation for this is that ALC may represent the speed of immune recovery of CMV-specific cytotoxic T lymphocytes. We could not estimate the significance of ERL/DLR for other types of

viral infections, such as adenovirus and BKV, as we had only two patients with proven adenovirus infection and six cases with BKV cystitis. The immunohaematological recovery, dynamically followed in both groups, is shown in Table 4. A significant delay in neutrophil and platelet recovery was observed in the DLR group, as well as lower values of WBC, Hb, PLT, and NK cells at the end of the first month of AlloSCT, without statistical significance for NK cells and Neu.

**Table 4.** ELR and haematological recovery.

	ALC D+21						p
	< 0.220 x 10 <sup>9</sup> /L			≥ 0.220 x 10 <sup>9</sup> /L			
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	
Neu recovery in days	17	15	20	15	13	19	0.042
PLT recovery in days	19	15	25	14	12	15	<0.001
NK -cells / µl +1 month	150.5	62.0	362.0	176.5	96.0	322.0	0.626
WBC x 10 <sup>9</sup> /L +1 month	3.4	2.1	4.3	4.9	3.4	5.8	0.006
Hb x g/L +1 month	98	88	109	113	103	121	<0.001
PLT x 10 <sup>9</sup> /L +1 month	86	30	141	148	114	199	<0.001
Neu x 10 <sup>9</sup> /L +1 month	2	1	3	3	2	4	0.156

## Discussion

Several studies have investigated the influence of lymphocyte recovery and immune reconstitution on the outcome of AlloSCT. Most of them include a small number of patients and are limited to a specific disease type, donor type, conditioning regimen and graft source. Le Blank (Le Blank et al. 2009) and Michaelis (Michaelis et al. 2014) analysed only AML patients, Kumar (Kumar et al. 2003) only bone marrow transplant cases, and Amandine Le Bourgeois (Amandine Le Bourgeois et al. 2016) only umbilical cord transplant cases. They covered a wide range of time points for post-transplant assessment (days 21 to 100 after allo-HSCT) and offered different thresholds for defining low ALC (0.175 × 10<sup>9</sup>/L cells to 0.5 × 10<sup>9</sup>/L).

Rigoni and colleagues (Rigoni et al. 2014) demonstrated the association of ELR at D+21 with higher OS in a patient population with a profile similar to ours, using an arbitrary cut-off value of 0.300 × 10<sup>9</sup>/L for ALC analysis. Another study (Kim et al. 2015) identified an ALC of 0.350 × 10<sup>9</sup>/L on D+21 as a cut-off value with prognostic significance for OS. Kumar et al. concluded that an ALC below 0.175 × 10<sup>9</sup>/L on D+21 is a predictor of relapse risk in transplanted ALL patients.

The study of the relationship between ELR and other clinical endpoints, assessing the effectiveness and safety of AlloHSCT – PFS, CIR, and NRM, proved that patients with ELR on D+21 had longer relapse-free survival and a time-delayed NRM-related event. Regarding NRM, the medians were not reached in either group, but the time to event was statistically significantly longer for patients with ELR. In contrast to Rigoni et al., their study, after a median follow-up of 20 months, demonstrated a significantly longer disease-free survival, but not NRM, for patients with ALC > 0.300 × 10<sup>9</sup>/L on D+21. Kim et al. demonstrated significantly longer relapse-free survival and a lower relapse rate in patients with ALC > 0.350 × 10<sup>9</sup>/L on D+21, but a non-significant difference in NRM. Kumar et al. reported significantly longer risk-free survival and a lower relapse rate in patients with ALC > 0.175 × 10<sup>9</sup>/L on D+21, but did not assess NRM.

Our study is the first one to identify risk factors for delayed lymphocyte recovery – DRI, response to AlloHSCT and severity of cytokine response in the pre-transplant period. Known factors leading to DLR include an HLA-incompatible donor, the dose of infused CD34+ cells, administration of ATG, administration of G-CSF to stimulate engraftment, and aGvHD (De Koning et al. 1969; Kumar et al. 2003; Henig and Zuckerman 2014).

Our results confirmed that the choice of a haploidentical donor is an unfavourable factor for ELR – eight of the patients (72.7%) with a haploidentical donor had DLR ( $p = 0.029$ ). This was also confirmed by the significant recovery of deleted lymphocytes after *in vivo* T-cell depletion with PTCy. The influence of the haploidentical donor on lymphocyte recovery is well known (Kollman et al. 2016). Delayed immune reconstitution in haploidentical transplantation is a hallmark of the immunopathogenesis of this type of procedure. In contrast to the published results by Kim and Damlaj (Damlaj et al. 2017), the relationship between the amount of infused CD34+ cells and DLR was not confirmed in our study. In terms of OS, only DRI was confirmed by multivariable analysis as a significant risk factor for DLR ( $p = 0.04$ , HR 1.926, 95% CI 1.030–3.603).

Analysis of the data regarding the significance of ELR in terms of post-transplant complications led to important conclusions regarding aGvHD, cGvHD and their association with survival. ELR correlated with the clinical manifestation of an acute graft reaction, also found by Rigoni et al. Analysis stratifying patients based on median D+21 lymphocyte recovery also showed a statistically significant difference in median D+21 ALC between patients with and without aGvHD manifestations. These results, although not statistically significant, translated into a lower NRM, thereby raising the question of further research aimed at clarifying the dynamics of immune reconstitution and identifying the lymphocyte subpopulations involved in the immunopathogenesis of aGvHD, as well as the role of immunoregulatory cells.

We also found a higher frequency of cGvHD in patients with ELR, in contrast to Rigoni et al., who only demonstrated a correlation between ALC and the incidence of aGvHD. Despite the higher frequency of cGvHD in ELR, the NRM was lower but not statistically significant. A significant association between early lymphocyte recovery, as measured by the LD index (lymphopenia duration), and cGvHD was also observed by Yanagi and colleagues (Yanagi et al. 2022). Further studies on the lymphocyte subpopulation composition in the setting of cGvHD are needed to elucidate the immunopathogenesis of these findings.

Our study confirms that ELR can be a statistically proven surrogate marker for stable graft engraftment, tracking the time to haematological recovery for neutrophils and platelets (and D+30 haematological recovery from AlloSCT).

## Conclusion

We can conclude that ELR presented as ALB of D+21  $\geq 0.220 \times 10^9/L$  is a clinically significant prognostic factor for the outcome of transplantation – universal, accessible, easily measurable, and inexpensive. It could serve as a starting point in the early post-transplant period to initiate risk-adapted immunomodulatory strategies in patients with high or very high DRI and those not transplanted in CR1.

## Acknowledgements

This study was approved by the Specialised Hospital for Active Treatment of Haematological Diseases in Sofia. All the patients signed an informed consent form.

## Additional information

### Conflict of interest

The authors have declared that no competing interests exist.

### Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: National Specialized Hospital For Active Treatment of Hematological Diseases

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

### Use of AI

No use of AI was reported.

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No funding was reported.

### Author contributions

Data curation: KV. Formal analysis: EN. Supervision: IDT. Writing – original draft: KMK. Writing – review and editing: YL.

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### Data availability

All of the data that support the findings of this study are available in the main text.

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