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## CELL-OF-ORIGIN FAILS TO PREDICT SURVIVAL IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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### Abstract

Diffuse large B-cell lymphoma (DLBCL) includes two prognostically-important subtypes, the germinal center B-cell (GCB) and the non-GCB types. The aim of this study was to evaluate immunohistochemical approaches for predicting the survival of patients with DLBCL following autologous hematopoietic stem cell transplantation (AHSCT). We identified 62 patients with DLBCL who either had an initial complete remission (17 patients) or received salvage chemotherapy for relapsed or refractory disease (45 patients), followed by AHSCT. Tissue microarrays were immunostained with monoclonal antibodies against GCET1, CD10, BCL6, MUM1, FOXP1 and LMO2. Using the Hans algorithm, we classified 50% of the cases as GCB type, whereas the Choi algorithm classified 58% as GCB type and LMO2 was positive in 69%. However, no significant differences were found in the five-year overall or event-free survivals using any of these approaches. In conclusion, cell-of-origin fails to predict survival of DLBCL patients treated with AHSCT.

### Keywords

cell-of-origin; algorithm; immunophenotype; diffuse large B-cell lymphoma; autologous hematopoietic stem cell transplantation; survival

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## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL) worldwide [1]. Morphological, biological and clinical studies have subdivided DLBCL into a variety of morphological variants and distinct disease entities [2]. However, a large number of cases do not belong to a specific disease entity and are classified as DLBCL, not otherwise specified. This group of lymphomas is biologically heterogeneous and constitutes 25-30% of adult NHL in western countries, and a higher percentage in developing countries [2].

Currently, the International Prognostic Index (IPI) is the most important tool used to predict the response to treatment and prognosis of patients with DLBCL [3]. However, even in the IPI risk groups, substantial variability in outcome has been observed. Gene expression profiling (GEP) for the cell-of-origin also has prognostic value in DLBCL independent of the IPI [4-6]. Patients with a GEP resembling that of germinal center B-cells (GCB) have a better outcome than those with a profile resembling activated B-cells (ABC). A cell-of-origin algorithm using only three immunostains can also successfully translate GEP data into practical application and subdivide DLBCL patients into similar prognostic groups, the GCB and the non-GCB types [7]. This algorithm is also useful when rituximab is added to standard chemotherapy [8]. Recently, a new immunostain algorithm using five antibodies was developed to improve the accuracy of this classification [9].

In addition to these cell-of-origin algorithms, studies looking for new prognostic markers have been conducted. One of these markers, LMO2, has been found to be a promising predictor of survival in de novo DLBCL [10]. LMO2 is a cysteine-rich LIM domain-containing transcription factor which plays a role in erythropoiesis, and is frequently involved in a chromosomal translocation in childhood T-cell acute lymphoblastic leukemia [11,12]. LMO2 is not expressed in normal T lymphocytes [13], but is expressed at high levels in germinal center B cells [4]. LMO2 expression is reported to be a predictor of survival in DLBCL, with positive immunostaining (>30%) correlating with longer survival [10].

Addition of rituximab (R) to the standard CHOP regimen (cyclophosphamide, adriamycin, vincristine and prednisone) increases the complete remission (CR) rate and improves the event-free survival (EFS) and overall survival (OS) of patients with DLBCL [14-16]. Both of the cell-of-origin algorithms and LMO2 expression have prognostic value for DLBCL patients receiving R-CHOP or similar regimens [8,17]. However, patients who are resistant to initial treatment or whose disease recurs after conventional therapy have smaller chance of a durable remission with salvage therapy [18-20]. In patients with a relapse of chemotherapy-sensitive DLBCL, high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (AH SCT) can lead to a cure in 40 -60% of cases and currently constitutes the standard of care [21].

The aim of this study was to evaluate the use of immunohistochemical approaches including the cell-of-origin algorithms of Hans et al [7] and Choi et al [9], and LMO2 expression alone [10], for predicting the survival of patients with DLBCL following AH SCT.

## Materials and Methods

### Patients

We identified patients diagnosed with DLBCL who received CHOP or R-CHOP chemotherapy as the first-line treatment. These patients either had an initial CR, with or without a subsequent relapse, or had primary refractory disease (primary induction failure – PIF). They were all later treated with high-dose salvage therapy followed by AHSCT. A total of 179 patients with DLBCL underwent AHSCT from 1996 through 2007 at the University of Nebraska Medical Center and met the above inclusion criteria. However, tissue blocks were only available from 85 patients. These patients were divided into three groups based on their treatment response prior to AHSCT. In Group 1, the patients were either in initial CR or had a relapse post-CR that was sensitive to salvage therapy. In Group 2, the patients had PIF with initial chemotherapy but were sensitive to salvage therapy. In Group 3, the patients had PIF or relapsed post-CR and were resistant to salvage therapy. The Institutional Review Board of the University of Nebraska Medical Center approved this study.

### Immunohistochemistry on tissue microarrays

Tissue microarrays were prepared with three representative 0.6 mm tissue cores obtained from formalin-fixed, paraffin-embedded tissue blocks from each of the 85 cases with available blocks, as described previously [22]. Briefly, hematoxylin and eosin-stained slides from each tissue block were reviewed to define diagnostic areas of DLBCL. PAX5 and CD3 immunostains were used to aid in the interpretation of immunostains performed with monoclonal antibodies against GCET1, CD10, BCL6, MUM1, FOXP1 and LMO2 on tissue microarray sections using previously described methods [9,10]. Classification of DLBCL into the GCB and non-GCB types was performed using the algorithm of Hans et al [7], and the algorithm recently proposed by Choi et al [9] (Figure 1). Insert Figure 1. The positive cutoff for the antibodies in the Hans algorithm (CD10, BCL6 and MUM1) was 30%; for the Choi algorithm, we used a 30% cutoff for CD10 and BCL6, and 80% for the other stains (GCET1, FOXP1 and MUM1). A positive cutoff of 30% was used for LMO2 [10]. Among the 85 cases, only 62 cases yielded interpretable immunostaining results for all of these antibodies, and the rest of the cases were excluded from further analysis. In 50 cases (81%), tissue was available from the initial diagnostic biopsy for immunostaining. In the remaining 12 cases, the initial diagnostic tissue was not available and tissue from a later biopsy was used.

### Statistical analysis

Patient characteristics were compared by clinical group, cell-of-origin subtype (GCB and non-GCB), and LMO2 expression using the ANOVA model and Fisher's exact test. Cumulative incidence estimation methods were used to estimate the two-year progression rates by group, which were compared with the log-rank test. The Kaplan-Meier method was used to estimate the OS and EFS distributions. OS was calculated as the time since transplantation to the date of death or last contact. Patients who were alive at last contact were treated as censored for OS analysis. EFS was calculated as the time since transplantation to the date of progression, death, or last contact. Patients who were alive at

last contact and who had not progressed were treated as censored for EFS analysis. The log-rank test was used to compare survival distributions. All statistical tests were 2-sided and p-values of less than 0.05 were considered to be statistically significant. The data analysis was conducted using SAS software (SAS Institute Inc., Cary, NC, USA).

## Results

### Clinical characteristics

The median age of the patients at the time of AHSCT was 56 years (range, 17 – 75 years), and 42 patients (68%) were male (Table 1). Insert Table 1. Forty-nine patients (79%) received R-CHOP as the initial therapy and thirteen patients (21%) received only CHOP. Group 1 included 39 patients, of which 17 were in initial CR at the time of AHSCT. Group 2 included 12 patients, and Group 3 included 11 patients, seven of whom had PIF and four who relapsed post-CR with disease resistant to salvage therapy. There were no significant differences in the clinical characteristic between these groups. However, the patients in Group 3 tended to have more adverse prognostic factors and had a significantly higher two-year progression rate compared to Groups 1 and 2 (Table 1). We identified only five cases with immunoblastic morphology (5/62, 8.1%) including three cases in group 3, none in group 2, and two in group 1.

The clinical characteristics of the patients according to the cell-of-origin algorithms and LMO2 expression are given in Table 2. Insert Table 2. There were no significant differences in any of these characteristics in any of the groups, and no significant differences in the two-year progression rates were found. There was no enrichment of GCB cases in Groups 1 or 3, but there was an increased number of GCB cases in Group 2 (Table 2).

### Survival by clinical groups

The survival after AHSCT of patients receiving either R-CHOP or CHOP as initial therapy was compared, and those treated with rituximab appeared to have a better OS ( $p=0.048$ ) and in EFS ( $p=0.10$ ) (Figure 2). Insert Figure 2. The survival after AHSCT among Groups 1-3 was also analyzed, and those in Group 3 with chemotherapy-resistant disease had the worst OS and EFS (Figure 3). Insert Figure 3.

### Survival by immunophenotype groups

Using the Hans algorithm, 50% of the cases were classified as GCB type and 50% as non-GCB type, whereas the Choi algorithm classified 58% of the cases as GCB type and only 42% as non-GCB type (Table 2). However, no significant differences were found in the survival of patients after AHSCT using either of these cell-of-origin algorithms (Figure 4). Insert Figure 4. LMO2 was positive in 69% of the cases, but no significant difference was found in the survival of patients after AHSCT based on LMO2 expression (Figure 4).

Since significant survival differences were found for patients receiving R-CHOP versus CHOP (Figure 2), and for Groups 1 and 2 versus Group 3 (Figure 3), we performed additional survival analysis of the patients in Groups 1 and 2 who received R-CHOP as first-

line treatment (38 patients). However, no significant differences were found in these cases based on the cell-of-origin algorithms or LMO2 expression (Figure 5). Insert Figure 5.

## Discussion

The IPI and GEP or cell-of-origin algorithms using immunostaining are currently the most important tools available to predict the response to chemotherapy and survival of newly-diagnosed patients with DLBCL. In DLBCL patients with chemosensitive disease at the time of progression or relapse, high-dose therapy (HDT) followed by AHSCT is considered the standard of care [21]. Also, for patients with poor-risk DLBCL in first CR or partial remission (PR), HDT and AHSCT is a feasible and effective treatment option [23]. It has been our policy at Nebraska to do HDT and AHSCT for patients with DLBCL in first CR who were intermediate/high or high risk by the IPI. However, few biological markers to predict outcome have been evaluated in DLBCL patients receiving AHSCT.

A few studies have used cell-of-origin algorithms in an attempt to predict the outcome of patients with relapsed or refractory DLBCL following AHSCT. Using the Hans algorithm [7], Moskowitz et al [24] found no difference in OS by cell-of-origin for patients with relapsed or primary refractory chemosensitive disease following AHSCT. Similarly, Costa et al [25] found no difference in the risk of progression or in OS for patients with relapsed or primary refractory chemosensitive disease following AHSCT using the same algorithm. However, in a series of poor-risk DLBCL patients treated with AHSCT as first line therapy, van Imhoff et al [26] found that the GCB type had a favorable impact on OS using the Hans algorithm. In contrast, Nyman et al [27] failed to confirm this finding in a similar group of high-risk DLBCL patients treated with AHSCT as first-line therapy, and concluded that dose intensification seems to eliminate the adverse prognostic impact of the non-GCB type in high-risk DLBCL.

To address this issue, we used two cell-of-origin algorithms, Hans et al [7] and Choi et al [9], to investigate the outcome of DLBCL patients who underwent AHSCT. Since the phenotype (GCB or non-GCB) present at initial diagnosis appears to be unchanged at the time of progression [24,25], we included 12 cases with only tissue obtained during progression. However, neither of these algorithms or LMO2 expression predicted the survival of our patients, confirming other similar studies using the Hans' algorithm [24,25]. We are not able to address this issue in patients receiving AHSCT as part of first-line therapy due to the small number of patients in our series. However, Hallack Neto et al [28] have suggested that AHSCT in first CR improves survival regardless of cell of origin. Further studies are needed to clarify the findings for AHSCT as first-line therapy in DLBCL.

As expected, we found that patients with PIF and those who relapsed post-CR and were resistant to standard salvage therapy (Group 3) derived no benefit from AHSCT. In this group, all 11 patients had received rituximab as part of their initial treatment. Therefore, it appears that AHSCT will not improve the survival outcome of such patients, and other innovative salvage therapies should be attempted.

A recent study found that AHSCT was equally effective in DLBCL patients in relapse after first-line therapy whether they had received rituximab or not, and should remain the standard of care for relapsed DLBCL [29]. However, we found that a major predictive factor for patients receiving AHSCT for DLBCL was the use of rituximab as part of initial therapy (Figure 2). This finding is in keeping with the results of a large study which concluded that pre-transplant rituximab is associated with a lower rate of progression and improved survival following AHSCT [30]. Therefore, we also performed a survival analysis of our patients in Groups 1 and 2 who received R-CHOP as first-line treatment (38 patients, Figure 5). However, neither of the cell-of-origin algorithms or LMO2 expression was predictive of outcome in this favorable subgroup.

In the recent CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study, Gisselbrecht et al [31] found that patients with DLBCL who were initially treated with a CHOP-like regimen and rituximab before AHSCT had a significantly worse response rate and survival than those who had not received rituximab initially. All of the patients received rituximab as part of HDT prior to AHSCT. However, this adverse effect was only seen in the patients who relapsed early (<12 months) after initial therapy with rituximab, and not in those who relapsed later. In our study, the small number and heterogeneous nature of the patients precluded such a detailed analysis.

LMO2 expression has been reported to be a useful tool in predicting the survival in DLBCL patients who receive CHOP or R-CHOP therapy [10,17]. The present study is the first, to our knowledge, to explore the use of LMO2 in predicting the outcome of patients with DLBCL receiving AHSCT. However, our data indicate that LMO2 expression does not predict the survival of the patients with DLBCL receiving AHSCT.

In summary, neither the cell-of-origin algorithms nor LMO2 expression predicted the survival of patients with DLBCL receiving AHSCT in this patient cohort. However, the number of patients in this study was small and our results should be confirmed by larger studies.

## Acknowledgements

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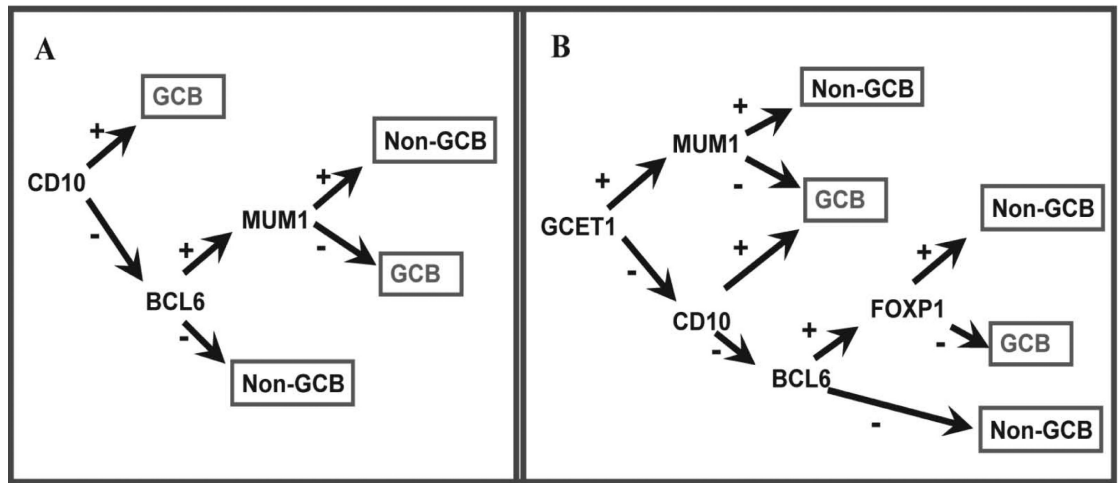
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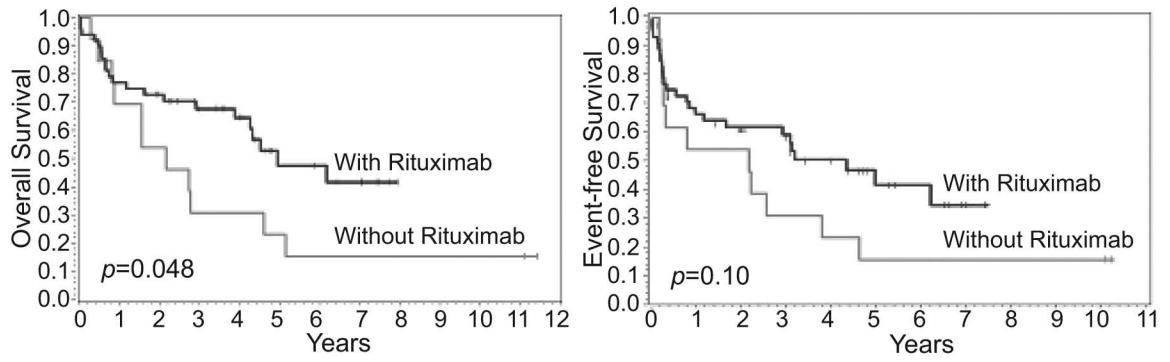
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**Figure 1.** Diagrams of the Hans (A) and Choi (B) algorithms based on the expression of three (CD10, BCL6 and MUM1) and five (CD10, BCL6, MUM1, GCET1 and FOXP1) markers, respectively



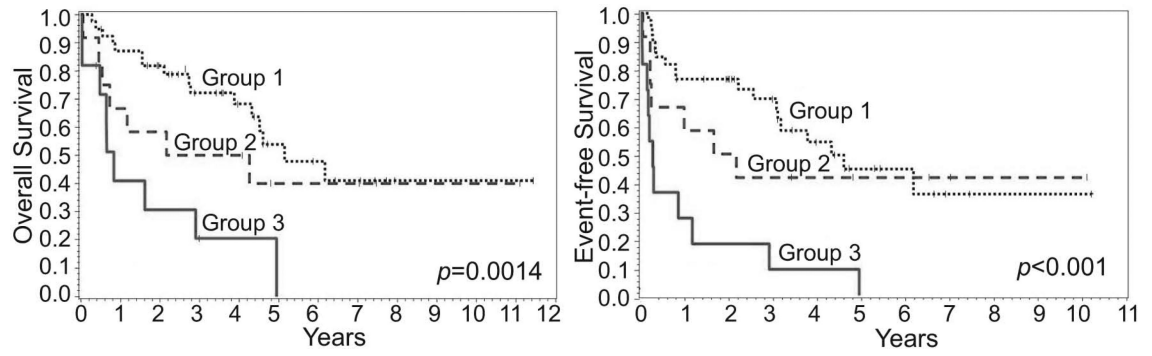
**Figure 2.** Overall and event-free survival of patients after autologous hematopoietic stem cell transplantation according to the initial use of rituximab

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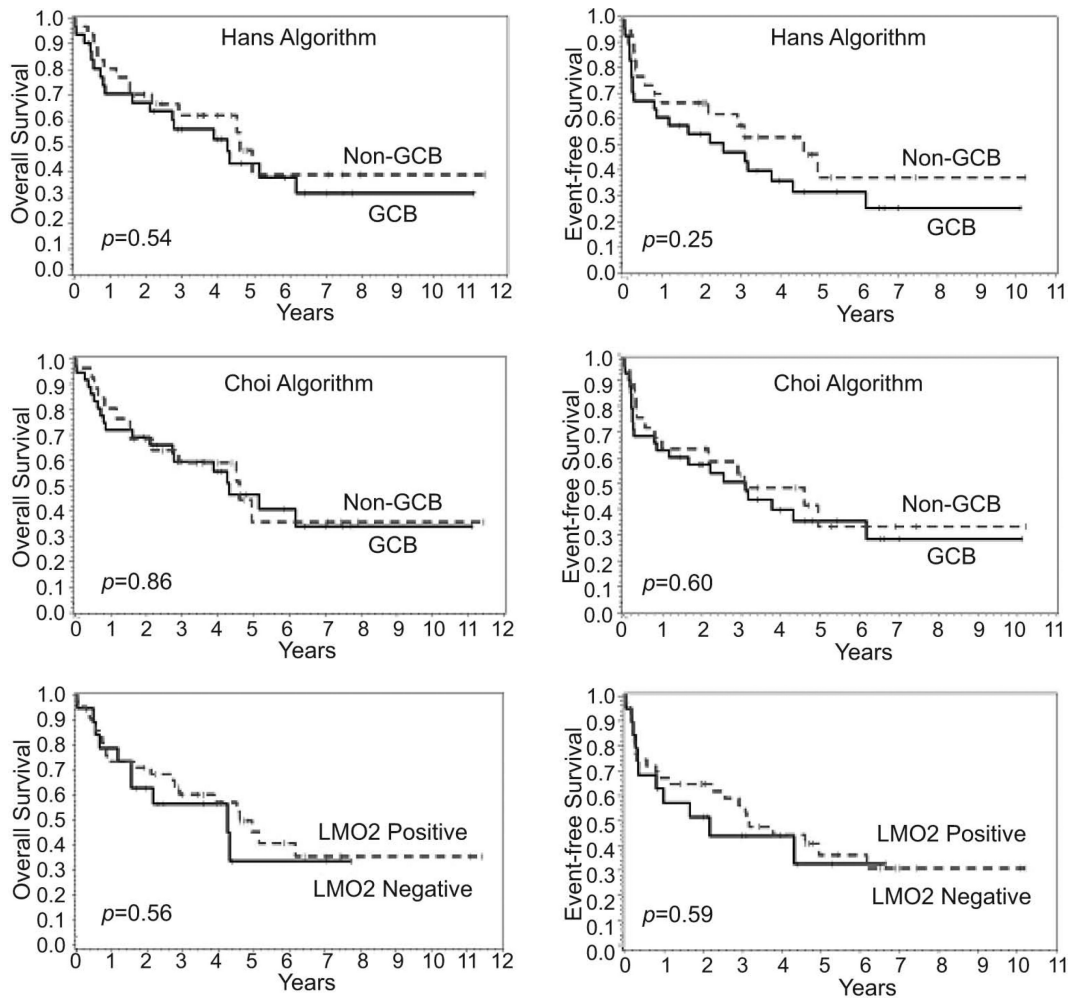
**Figure 3.** Overall and event-free survival of patients after autologous hematopoietic stem cell transplantation by clinical groups

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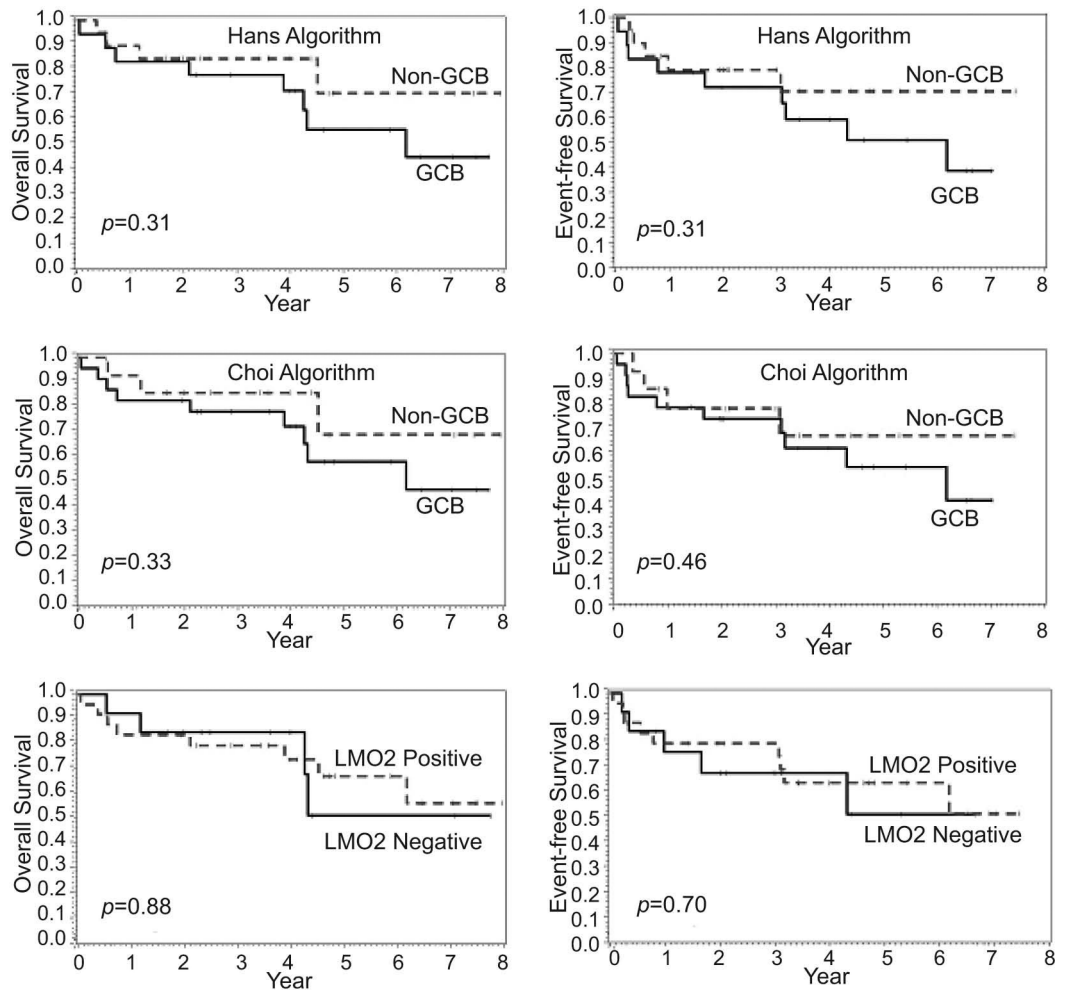
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**Figure 4.** Overall and event-free survival of patients after autologous hematopoietic stem cell transplantation according to the cell-of-origin algorithms and LMO2 expression



**Figure 5.** Overall and event-free survival of patients after autologous hematopoietic stem cell transplantation according to the cell-of-origin algorithms and LMO2 expression for patients in Groups 1 and 2 receiving rituximab as initial treatment (38 patients)

**Table 1**

Patient characteristics by clinical groups.

	Total (n=62)	Group 1 (n=39)	Group 2 (n=12)	Group 3 (n=11)	P=
<b>Age at AHSCT (years)</b>					
Median (range)	56 (17-75)	58 (17-75)	49 (38-58)	57 (30-67)	0.35
<b>Gender</b>					
Male	42 (68%)	24 (62%)	10 (83%)	8 (73%)	0.40
Female	20 (32%)	15 (38%)	2 (17%)	3 (27%)	
<b>Receiving rituximab</b>	49 (79%)	29 (74%)	9 (75%)	11 (100%)	0.19
<b>Number of prior chemotherapy regimens</b>					
1	11 (20%)	8 (24%)	3(25%)	0 ( 0%)	0.023
2	27 (50%)	20 (61%)	4(33%)	3 (33%)	
3	16 (30%)	5 (15%)	5(42%)	6 (67%)	
<b>LDH at AHSCT</b>					
Normal	36 (62%)	25 (69%)	6 (55%)	5(45%)	0.28
Elevated	22 (38%)	11 (31%)	5 (45%)	6(55%)	
<b>Extranodal involvement at AHSCT</b>					
No	37 (69%)	25 (74%)	6 (50%)	6 (75%)	0.30
Yes	17 (31%)	9 (26%)	6 (50%)	2 (25%)	
<b>Stage at AHSCT</b>					
CR	12 (23%)	11 (33%)	0 (0%)	1 (13%)	
I/II	22 (41%)	13 (39%)	6 (50%)	3(38%)	0.15
III/IV	19 (36%)	9 (27%)	6 (50%)	4(50%)	
<b>2-year progression</b>	33%	21%	42%	64%	0.0072

Table 1: Note: Clinical data were not available in some cases and, therefore, addition of the numbers may not equal the total number at the top. AHSCT: autologous hematopoietic stem cell transplantation, LDH: serum lactate dehydrogenase, CR: complete remission.



**Table 2**

Patient characteristics according to the cell-of-origin algorithms and LMO2 expression.

	Total (n=62)	Hans Algorithm (n=31)		Choi Algorithm (n=36)		LMO2 (n=43)		P=	
		GCB (n=31)	non-GCB (n=31)	GCB (n=36)	non-GCB (n=26)	positive (n=43)	negative (n=19)	P=	
<b>Age at AHST (years)</b>									
Median (range)	56 (17-75)	57 (22-75)	54 (16-70)	56 (22-75)	55 (17-70)	56 (22-75)	55 (17-67)	0.67	0.56
<b>Gender</b>									
Male	42 (68%)	23 (74%)	19 (61%)	26 (72%)	16 (62%)	30 (70%)	12 (63%)	0.37	0.61
Female	20 (32%)	8 (36%)	12 (39%)	10 (28%)	10 (38%)	13 (30%)	7 (37%)		
<b>Receiving rituximab</b>									
	49 (79%)	23 (74%)	26 (84%)	28 (78%)	21 (81%)	33 (77%)	16 (84%)	0.78	0.51
<b>Numbers of prior chemotherapy regimens</b>									
1	11 (20%)	6 (21%)	5 (20%)	6 (19%)	5 (23%)	7 (18%)	4 (25%)	0.53	0.50
2	27 (50%)	14 (48%)	13 (52%)	18 (56%)	9 (41%)	21 (55%)	6 (38%)		
3	16 (30%)	9 (31%)	7 (28%)	8 (25%)	8 (36%)	10 (26%)	6 (38%)		
<b>Clinical groups</b>									
Group 1	39 (63%)	17 (55%)	22 (71%)	21 (58%)	18 (69%)	27 (62%)	12 (63%)		
Group 2	12 (19%)	9 (29%)	3 (10%)	10 (28%)	2 (8%)	8 (19%)	4 (21%)	0.13	1.0
Group 3	11 (18%)	5 (16%)	6 (19%)	5 (14%)	6 (23%)	8 (19%)	3 (16%)		
<b>LDH at AHST</b>									
Normal	36 (62%)	20 (69%)	16 (55%)	23 (68%)	13 (54%)	24 (60%)	12 (67%)	0.30	0.63
Elevated	22 (38%)	9 (31%)	13 (45%)	11 (32%)	11 (46%)	16 (40%)	6 (33%)		
<b>Extranodal involvement at AHST</b>									
No	37 (69%)	17 (63%)	20 (74%)	20 (65%)	17 (74%)	25 (66%)	12 (75%)	0.46	0.51
Yes	17 (31%)	10 (37%)	7 (26%)	11 (35%)	6 (26%)	13 (34%)	4 (25%)		
<b>Stage at AHST</b>									
CR	12 (23%)	6 (21%)	6 (24%)	6 (20%)	6 (26%)	9 (24%)	3 (19%)		
I/II	22 (41%)	12 (43%)	10 (40%)	12 (40%)	10 (43%)	14 (38%)	8 (50%)	0.75	0.71
III/IV	19 (36%)	10 (36%)	9 (36%)	12 (40%)	7 (30%)	14 (38%)	5 (31%)		
<b>2-year progression</b>	33%	39%	26%	36%	28%	28%	43%	0.30	0.52

Table 2: Note: Clinical data were not available in some cases and, therefore, addition of the numbers may not equal the total number at the top. AHST: autologous hematopoietic stem cell transplantation; LDH: serum lactate dehydrogenase; CR: complete remission; GCB: germinal center B-cell.