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CD44s and CD44v6 Are Predominantly Expressed in the Non-germinal Center B-Cell-like Type of Diffuse Large B-Cell Lymphomas

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Background: CD44 protein is known as a homing cellular adhesion molecule that is linked to diverse cellular functions such as adhesion, migration and invasion, which are all important in cancer progression and metastasis. The expression of CD44 standard and variant isoforms (CD44 standard isoform [CD44s] and CD44 splice variants containing exon v6 [CD44v6], respectively) is associated with an unfavorable clinical outcome in various neoplasms. **Methods:** Forty patients who were diagnosed with diffuse large B-cell lymphoma (DLBCL) through biopsy at Hanyang University Hospital between 1996 and 2003 were included in this study. CD44 proteins expression was analyzed by immunohistochemical staining on a tissue microarray and the correlation of CD44 with the types of DLBCL and clinical parameters, including the factors defined by the International Prognostic Index, was evaluated. **Results:** A high CD44s and intermediate to strong CD44v6 expression, including cytoplasmic membranous staining patterns, was present in 35% (14/40) and 25% (10/40) of DLBCL patients, respectively. High CD44s expression was correlated significantly with non-germinal center B-cell-like types (non-GCB, $p = 0.004$) and patients with old age ($p = 0.041$). **Conclusions:** High CD44s expression may be significantly associated with the non-GCB type compared to the GCB type and may be essential to the prediction of disease outcome in tumor stage III in DLBCL patients.

Key Words: Lymphoma, large B-cell, diffuse; CD44S antigen; CD44v6 antigen

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group of neoplasms and is characterized by aggressive progress and high mortality without treatment.[1] A Korean nationwide survey suggested that the incidence of DLBCL among non-Hodgkin's lymphomas is 42.7%, similar to the incidence of other studies.[2,3] With intensive combination chemotherapy, 60% to 80% of patients achieve a complete remission, and 40% to 50% are cured. Therefore, it is important to identify those patients who may benefit from combination chemotherapies or intensive care.

The categorization of DLBCL related to clinical outcome may help to identify groups of patients with distinct prognoses who may benefit from particular treatments. Using a complementary DNA (cDNA) microarray, DLBCL can be classified into 3 types with germinal center B-cell-like (GCB), activated B cell-like (ABC) and type 3 gene expression profiles.[4,5] Hans *et al.*[6] have shown that the immunohistochemical stains (CD10, Bcl-6, and MUM-1) can determine GCB and non-GCB types (ABC and type 3) of DLBCL. GCB type has a good survival rate, while non-GCB type has a poor outcome.

CD44 protein is basically a cell adhesion protein associated with lymphocytic migration, homing and activation.[7] It is encoded by a single gene containing 20 exons, 10 of which (v1-v10) are variant exons inserted by alternative splicing. The CD44 variant isoforms are necessary for tumor spread and metastasis associated with poor prognoses.[8] CD44 splice variants containing exon v6 (CD44v6) have been shown to be expressed in high-grade lymphomas with poor prognoses.[9] The CD44 standard isoform (CD44s) is most abundant on lymphocytes and is expressed on activated lymphocytes and on aggressive lymphoma cells.[10,11] These findings suggest that CD44s and CD44v6 are important mediators of lymphoma dissemination and that they are prognostic factors in the types of DLBCL.

In this study, 2 types (GCB and non-GCB) of DLBCL were divided by immunohistochemistry (IHC) using a tissue microarray (TMA) platform in DLBCL. We investigated the relationships between CD44 protein expression and the clinicopathological parameters defined by the International Prognostic Index (IPI).

MATERIALS AND METHODS

Patients

This study included a total of 40 patients with pathologically proven DLBCL of lymph nodes who were diagnosed at the Department of Pathology, Hanyang University Hospital between 1996 and 2003.

The following information was collected from the medical records and the following parameters were analyzed: the factors defined by the IPI[1] (age, serum lactate dehydrogenase [LDH], performance status, tumor stage, and extranodal involvement), gender, types of DLBCL, date of first disease progression or recurrence and date of last contact or death. All pathological slides from the primary biopsy were thoroughly reviewed by more than 2 pathologists who were blind to clinical information.

TMA construction

The most morphologically representative and non-necrotic area was carefully selected and marked on the hematoxylin and eosin-stained slide. The TMA specimens were assembled using a tissue-array instrument (AccuMac Arrayer, Isu Abxis Co. Ltd., Seoul, Korea) consisting of thin-walled stainless steel punches and stylets for emptying and transferring the needle content. The assembly was held in an X-Y position guide equipped with semiautomatic micrometers, with a 1-mm increment between individual samples and a 4-mm punch depth stop device. The instrument was briefly used to create holes in a recipient block with defined array cores. fits the needle, was used to transfer the tissue cores into the recipient block. Taking into account the limitations of the representative areas of the tumor, we used duplicate 3-mm-diameter tissue cores from each donor block.

Immunohistochemistry

Table 1 lists primary antibodies against CD44s, CD44v6, CD10, bcl-6, and MUM-1, as well as their dilutions and pretreatment conditions. Bound secondary antibodies were visualized by standard avidin-biotin-peroxidase techniques using diaminobenzidine as a chromogen. Each slide was interpreted semiquantitatively by the expressed area of malignant cells showing cytoplasmic membranous staining with reference to previous studies (Fig. 1).[10,12] Because weak staining for CD44s was con-

Table 1. Antibodies and antigen retrieval techniques used

Antibody	Clone	Source	Antigen retrieval	Dilution	Cutoff value (%)
CD44s	1563C11	Neomarker, Fremont, CA, USA	Benchmark XT protocol	1 : 300	≤20, 20-70, >70
CD44v6	2F10	Zymed, San Francisco, CA, USA	Benchmark XT protocol	1 : 200	≤20, 20-70, >70
CD10	SP67	Ventana, Tucson, AZ, USA	Citrate/Autoclave	1 : 1	30
Bcl-6	GI191E/A8	Ventana, Tucson, AZ, USA	Citrate/Autoclave	1 : 1	30
MUM-1	MUM1p	Dako, Glostrup, Denmark	Citrate/Autoclave	1 : 100	30

CD44s, CD44 standard isoform; CD44v6, CD44 splice variants containing exon v6.

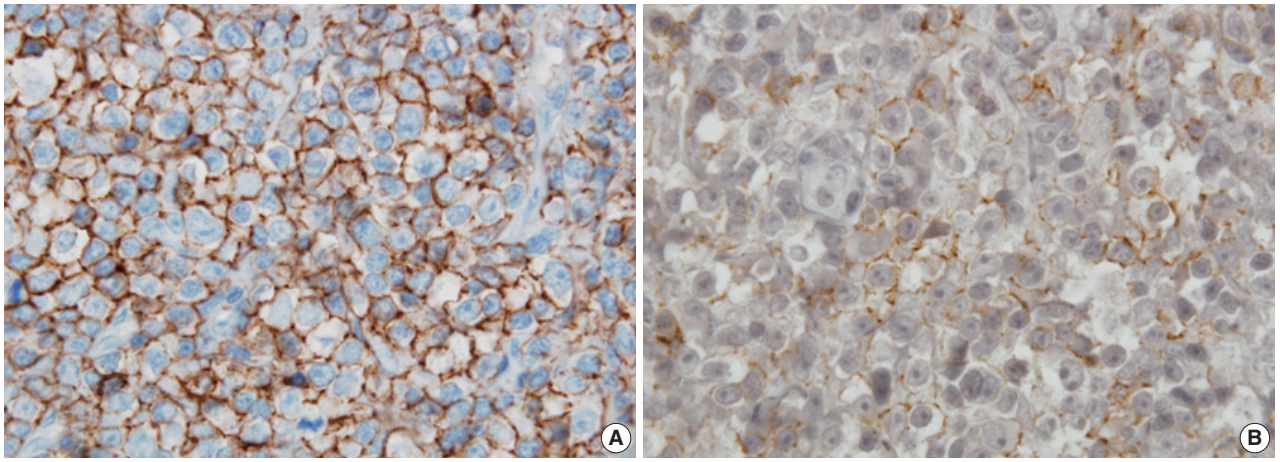

Fig. 1. Representative microphotographs exhibit cytoplasmic membranous expression of CD44 standard isoform (CD44s) (A) and CD44 splice variants containing exon v6 (CD44v6) (B) by immunohistochemical staining in diffuse large B-cell lymphoma.

sistently present in up to 20% of the small reactive background lymphocytes, similar staining patterns in lymphomas were not considered to be specific tumor-associated CD44s expression. Membranous staining in 20-70% of the tumor cells was considered to be low expression, and in membranous staining >70% of the tumor cells was considered to be high expression.[12] CD44v6 staining was considered weakly positive in ≤20% of the tumor cells, intermediately positive in 20-70% and strongly positive in >70%.[10] The classification of DLBCL types was determined with reference to previous studies.[6] Based on the immunohistochemically detectable expression of CD10, bcl-6 and MUM-1, DLBCLs were classified into GBC type (CD10+/bcl-6±/MUM-1± or CD10-/bcl-6+/MUM-1-) and non-GCB type (CD10-/bcl-6-/MUM-1± or CD10-/bcl-6+/MUM-1+). Cases in which immunoreactivity could not be assessed for technical reasons (failure of the tissue cores to stick to the slide) were excluded from the study.

Statistical analysis

Statistical analysis was performed using the SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA). Comparison between clinicopathological parameters and types of DLBCL was analyzed by the χ^2 test and the Fisher's exact test. The χ^2 test was used to examine the relationship between CD44s or CD44v6 expression and clinicopathological characteristics including types of DLBCL. The overall survival was analyzed by the life table method and compared using the log rank test. Multivariate analysis for the survival analysis with the Cox regression hazard model was used to evaluate independent prognostic factors. A 2-tailed p-value of <0.05 was considered statistically significant.

Table 2. Correlation between types and factors defined by the International Prognostic Index (IPI) in 40 patients with diffuse large B-cell lymphoma

Clinical parameters	No. of cases	Type		p-value (χ^2 test)
		GCB (n=18)	Non-GCB (n=22)	
Age (yr)				
≤60	23	12 (52.2)	11 (47.8)	0.289
>60	17	6 (35.3)	11 (64.7)	
Gender				
Male	19	9 (47.4)	10 (52.6)	0.775
Female	21	9 (42.9)	12 (57.1)	
Serum LDH (IU/L)				
≤220 (normal)	25	12 (48)	13 (52)	0.622
>220 (elevated)	15	6 (40)	9 (60)	
Performance status				
0 or 1	35	17 (48.6)	18 (51.4)	0.355[a]
2-4	5	1 (20)	4 (80)	
Stage				
I or II	28	13 (46.4)	15 (53.6)	0.781
III or IV	12	5 (41.7)	7 (58.3)	
Extranodal involvement				
≤1 site	39	17 (43.6)	22 (56.4)	0.450[a]
>1 site	1	1 (100)	0 (0)	
No. of IPI factors				
≤1 factor	25	14 (56)	11 (44)	0.071
>1 factors	15	4 (26.7)	11 (73.3)	

Values are presented as number (%).
[a]Chi-square test and Fisher's exact test.
GCB, germinal center B cell-like; LDH, lactate dehydrogenase.

RESULTS

Clinicopathological characteristics according to DCBCL types

The age of 40 patients with DLBCL ranged between 19 and 76 years at the time of lymph node biopsy. The mean age at diagnosis was 51.7 years. The types of DLBCL were classified by IHC. There were 18 cases (45%) of GCB type and 22 cases (55%) of non-GCB type. There was no significant difference in the factors defined by the IPI between the GCB and non-GCB types (Table 2).

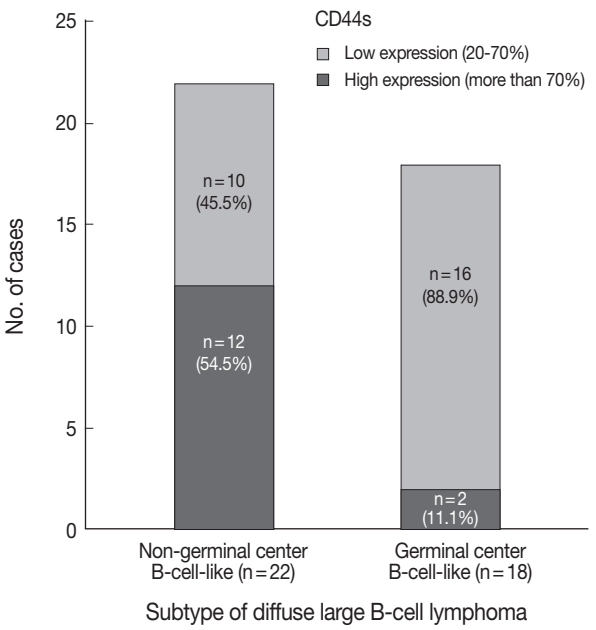

Fig. 2. High CD44 standard isoform (CD44s) expression is more frequently seen in non-germinal center B-cell-like type than in germinal center B-cell-like type (p=0.004).

Correlation between CD44s/CD44v6 expression and clinicopathological parameters in DLBCL

We performed IHC to investigate the correlation between CD44s expression and clinicopathological parameters in DLBCL. There were 26 cases (65%) with low CD44s expression and 14 cases (35%) with high CD44s expression. High CD44s expression was more frequently seen in the non-GCB type than in the GCB type (p=0.004) (Fig. 2). Also, CD44s expression was more increased in patients >60 years than those aged ≤60 years (p=0.041) (Table 3). High CD44 expression was more frequently seen in female patients than in male patients, but the difference was not statistically significant (p=0.079). The other characteristics including serum LDH, performance status, tumor stage, extranodal involvement and the number of the factors defined by the IPI were not significantly correlated with high CD44 expression.

The non-GCB type tended to have a frequent intermediate or strong expression of CD44v6 compared to the GCB type. However, there were no significant differences between GCB and non-GCB types in CD44v6 expression of DLBCL (p=0.464). Intermediate or strong CD44v6 expression was more frequently seen in early tumor stages (I or II) than in advanced tumor stages (III or IV), but the difference was not statistically significant (p=0.693). The other characteristics including age, gender, serum LDH, performance status, extranodal involvement and the number of the factors defined by the IPI were not significantly correlated with high CD44 expression (Table 4).

Table 3. Correlation between CD44s expression and factors defined by the International Prognostic Index (IPI) or types

Clinical parameters	No. of cases	CD44s expression		p-value (χ^2 test)
		Low (n=26)	High (n=14)	
Age (yr)				
≤60	23	18 (78.3)	5 (21.7)	**0.041**
>60	17	8 (47.1)	9 (52.9)	
Gender				
Male	19	15 (78.9)	4 (21.1)	0.079
Female	21	11 (52.4)	10 (47.6)	
Serum LDH (IU/L)				
≤220 (normal)	25	15 (60)	10 (40)	0.392
>220 (elevated)	15	11 (73.3)	4 (26.7)	
Performance status				
0 or 1	35	23 (65.7)	12 (34.3)	>0.999[a]
2-4	5	3 (60)	2 (40)	
Stage				
I or II	28	18 (64.3)	10 (35.7)	>0.999[a]
III or IV	12	8 (66.7)	4 (33.3)	
Extranodal involvement				
≤1 site	39	25 (64.1)	14 (35.9)	>0.999[a]
>1 site	1	1 (100)	0 (0)	
No. of IPI factors				
≤1 factor	25	18 (72)	7 (28)	0.231
>1 factors	15	8 (53.3)	7 (46.7)	
Type				
GCB	18	16 (88.9)	2 (11.1)	**0.004**
Non-GCB	22	10 (45.5)	12 (54.5)	

Values are presented as number (%). p<0.05 is denoted in boldface type.
[a]Chi-square test and Fisher's exact test.
CD44s, CD44 standard isoform; LDH, lactate dehydrogenase; GCB, germinal center B-cell-like.

Correlation between overall survival and CD44s/CD44v6 expression in DLBCL types

The GCB type had a significantly longer overall survival compared to the non-GCB type (p=0.002) (Fig. 3). The 5-year overall survival was 82.4% in the GCB type and only 33.3% in the non-GCB type. In multivariate analysis, the overall survival according to types of DLBCL significantly differed after adjustment for confounders such as the factors defined by the IPI (age,

Table 4. Correlation between CD44v6 expression and factors defined by the international prognostic index or type

Clinical parameters	No. of cases	CD44v6 expression		p-value (χ^2 test)
		Weak (n=30)	Intermediate or strong (n=10)	
Age (yr)				
≤60	23	17 (73.9)	6 (26.1)	>0.999[a]
>60	17	13 (76.5)	4 (23.5)	
Gender				
Male	19	15 (78.9)	4 (21.1)	0.721[a]
Female	21	15 (71.4)	4 (28.6)	
Serum LDH (IU/L)				
≤ 220 (normal)	25	19 (76)	6 (24)	>0.999[a]
> 220 (elevated)	15	11 (73.3)	4 (26.7)	
Performance status				
0 or 1	35	26 (74.3)	9 (25.7)	>0.999[a]
2-4	5	4 (80)	1 (20)	
Stage				
I or II	28	20 (71.4)	8 (28.6)	0.693[a]
III or IV	12	10 (83.3)	2 (16.7)	
Extranodal involvement				
≤1 site	39	29 (74.4)	10 (25.6)	>0.999[a]
>1 site	1	1 (100)	0 (0)	
No. of IPI factors				
≤1 factor	25	18 (72)	7 (28)	0.715[a]
>1 factors	15	12 (80)	3 (20)	
Type				
GCB	18	15 (83.3)	3 (16.7)	0.464[a]
Non-GCB	22	15 (68.2)	7 (31.8)	

Values are presented as number (%).
[a]Chi-square test and Fisher's exact test.
CD44v6, CD44 splice variants containing exon v6; LDH, lactate dehydrogenase; IPI, international prognostic index; GCB, germinal center B-cell-like.

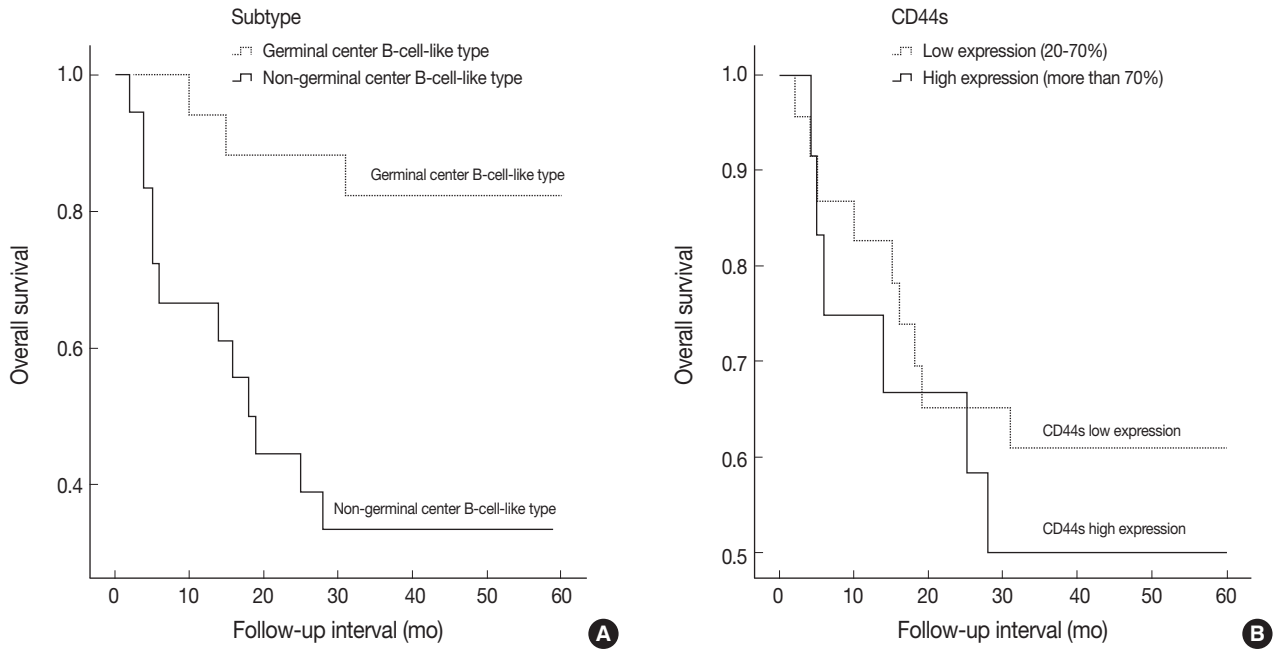

Fig. 3. Overall survival curves of life table according to type (A) and CD44 standard isoform (CD44s) expression (B) in diffuse large B-cell lymphoma (log rank test, p = 0.002 and p = 0.547, respectively).

serum LDH, performance status, tumor stage, and extranodal involvement) (p = 0.007, Cox regression hazard model). Therefore, the classification of DLBCL types according to IHC results was an independent prognostic predictor, which is similar to those reported by previous studies using a cDNA microarray.[4,5]

The 5-year overall survival according to CD44s expression patterns was 60.9% in patients with high CD44s expression and 50% in those with low CD44s expression, but the difference was not statistically significant (p = 0.547) (Fig. 3). For each stage, there were no significant correlations between CD44s expression and survival rate (stage I, p = 0.759; stage II, p = 0.749; and stage IV, p = 0.617). In patients with stage III tumors, those with low CD44s expression had a better prognosis than those with high CD44s expression (p = 0.039). However, in this group the number of patients is too small for any meaningful relationship, although CD44s expression was statistically significant. No significant correlations were found between CD44v6 expression and survival rate (p = 0.807).

DISCUSSION

Heterogeneous outcomes in non-Hodgkin's lymphomas, such as DLBCL, require the development of standard prognostic factors. Published studies have suggested that the IPI provides useful prognostic information and is applicable to aggressive non-Hodgkin's lymphoma.[1] However, the clinical parameters, including the factors defined by the IPI, have limitations in predicting the prognosis, because of biological variable determining disease heterogeneity.[13] Identification of these unknown biological variables may be helpful in predicting outcomes and improving prognostic models in DLBCL patients.

CD44, a transmembrane glycoprotein involved in cell-cell and cell-matrix interactions, appears in a standard form (CD44s) as well as a variety of splicing variants (CD44v);[14-16] their expressions have been reported in various malignant tumors.[17-20] Previous studies suggested that CD44s expression as well as CD44v6 expression is associated with poor survival and therapeutic resistance in non-Hodgkin's lymphoma.[9,21-23] A previous study by Drillenburg *et al.*[24] of patients with DLBCL reported that the expression of CD44s and CD44v6 does not predict survival and is not correlated with gender or the factors defined by the IPI, such as tumor stage, serum LDH and age. However, CD44s-negative tumors have more favorable prognoses than CD44s-positive tumors in patients with stage I disease. Tzankov *et al.*[12] demonstrated that CD44v6 expression is correlated directly with poor survival, whereas CD44s expression is correlated inversely with poor survival. Thus, controversy still exists regarding the relationship between various CD44 proteins and clinical outcomes in DLBCL. In our study, CD44s expression

was significantly correlated with non-GCB type, which has been reported to have a poor prognosis,[6] but was related to a poor survival rate only in patients with stage III tumors. The number of patients in the group of stage III tumors was too small to demonstrate a significant correlation with survival rate. Similar to the CD44s analysis, there was no significant difference in clinical features and overall survival in the CD44v6 analysis. The discrepancy of the correlations between CD44 proteins and clinical outcomes can be explained by several factors, including study designs, ethnic factors and the number of study cases. Additionally, other biological functions of CD44, especially its previously described roles in counteracting apoptosis[25] and supporting tumor suppressor function,[26] can be assessed by its expression.

In our result, high CD44s expression was associated with the non-GCB type of DLBCL. In addition, DLBCL showed a poorer survival rate in patients with the non-GCB type than those with the GCB type. Therefore, these findings suggest that CD44s expression may contribute to aggressive tumor growth in DLBCL.

The results of this study are subject to several limitations. First, the number of cases is relatively small, which may limit statistical power for analysis. Although some data tended to show a positive relationship between clinicopathological parameters and CD44s or CD44v6 expression, this relationship was not statistically significant. Second, representative areas may not have been evaluated because CD44s or CD44v6 IHC was carried out only on 2 cut surfaces of each tumor specimen. Third, similar to retrospective and cross-sectional studies, our study did not show continuous relationships over time compared to longitudinal studies, making it difficult to ascertain our conclusion. Further longitudinal studies with step-by-step reliability monitoring are needed to clarify a cause-effect relationship.

In summary, the results of this study suggest that high CD44s expression may be significantly associated with non-GCB type, an important predictor of overall survival in DLBCL patients. Therefore, CD44s may be a potential factor of an aggressive phenotype with the development and progression of DLBCL. Additionally, CD44s expression was statistically correlated with poor survival only in DLBCL patients with stage III tumors. Large scale studies including stage III tumors are necessary for further evaluation.

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