Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Treatment Outcomes and Clinical Relevance in Patients with Double Expressor DLBCL

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Competing interests: The authors declare no conflict of Interest.

Abstract. ***Background*: Double-expressor lymphoma *(*DEL*)* was found to account for 20- 30% of DLBCL. We conducted this study to analyze the survival, the clinical presentation, and the factors associated with treatment outcomes in DEL-DLBCL.**
***Methods*: A retrospective study of 291 patients diagnosed with DLBCL during January 2015 - December 2018 was conducted.**
***Results*: Of the 291 patients, the median age was 63 years, germinal center B cell-like DLBCL *(*GCB*)* and non-GCB subtypes were found in 32% and 68%, respectively. DEL was found in 46% of 264 patients with available immunohistochemistry staining for MYC protein. Patients with DEL was significantly more common in elderly patients *(p*= 0.017*)* and non-GCB subtype *(p*= 0.006*)*. High serum lactate dehydrogenase *(*LDH*)* levels and high Ki-67 index were significantly found in DEL patients than non-DEL patients *(p*= 0.024 and *p*= 0.04, respectively*)*. The 3y-OS rate was shorter in the DEL group than in the non-DEL group, 58.7% versus 78.9% *(p*=0.026*)*, whereas no significant difference in 3y-DFS was identified between these groups *(*58.4% versus 67.7%, *p*= 0.343*)*. Independent factors affecting OS and DFS in DEL patients were ECOG 3-4, high LDH levels, extranodal involvement> 1 site, high IPI, and stage III-IV in univariate analysis.**
***Conclusions*: High incidence of DEL was observed in this study, especially in patients aged 60 years or older and non-GCB subtype. Patients with DEL showed dismal DFS and OS.**

Keywords: Diffuse large B cell lymphoma; Double expressor lymphoma; GCB, Non GCB; Survival.

Citation: Rungwittayatiwat S., Boonsakan P., Chantrathammachart P., Puavilai T., Pukiat S., Phusanti S., Boonyawat K., Wacharapornin P., Angchaisuksiri P., Ungkanont A., Chuncharunee S., Niparuck P. Treatment outcomes and clinical relevance in patients with double expressor DLBCL. Mediterr J Hematol Infect Dis 2021, 13(1): e2021063, DOI: http://dx.doi.org/10.4084/MJHID.2021.063

Published: November 1, 2021 **Received: July 18, 2021** **Accepted: October 15, 2021**

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Introduction. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive B-cell non-Hodgkin lymphoma (NHL), accounting for 65% of NHL in Thailand.[1] It is a heterogeneous disease classified as germinal center-like B-cell (GCB) and non-germinal B-cell subtypes that arise from different cells of origin (COO). Hans algorithm including CD10, BCL6, and MUM1

protein expressions are used for the classification of COO of DLBCL, and the common methods for determining the COO are immunohistochemistry (IHC) and gene expression profiling (GEP).[2] MYC and BCL2 protein expressions are found in 30- 50% and 20- 35% DLBCL, respectively.[3] Translocations of MYC and BCL2 and/or BCL6 are called triple and double-hit lymphomas (TH/DHL), whereas the coexpression of MYC and BCL2 proteins without MYC/BCL2 and/or BCL6 rearrangement is described as double-expressor lymphoma (DEL).[4] The progression-free survival (PFS) and overall survival (OS) were dismal in DEL patients receiving R-CHOP therapy. Rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) exhibited a favorable outcome for DLBCL-GCB (2y-PFS of 64% and 2y-OS of 74%), compared with those in non-GCB subtypes (2y-PFS of 28% and 2y-OS of 46%).[5] The OS in patients with DEL and non-DEL were 20 and 36 months, respectively; DEL patients receiving R-CHOP had a higher relapse rate than treatment with R-EPOCH (80% versus 18%).[5] The previous study of Italian patients with DEL illustrated that R-DA-EPOCH every three weeks had 2y-OS longer than that in DEL patients treated with R-CHOP, 90%, and 67%, respectively, whereas 2y-PFS in DEL patients receiving R-DA-EPOCH and R-CHOP were 57% and 51%, respectively.[6] Although the previous studies have demonstrated worse outcomes in patients with DEL, the survival and the prognostic factors affecting outcome in this subtype of DLBCL in the Asian population are not well known. Hence, we conducted this study to analyze the survival, clinical presentation, and factors associated with treatment outcomes in DEL.

Materials and Methods.

Patients. Patients with newly diagnosed DLBCL receiving chemotherapy plus rituximab or chemotherapy alone at Ramathibodi Hospital between January 2015 and December 2018 were recruited and reviewed. All patients were 18 years of age and older. The diagnosis and subtypes of DLBCL were reviewed and classified according to the 2016 revision of WHO classification by an experienced hemato-pathologist.[4,7,8] DLBCL with the cut-off level of 40% for MYC positivity and 50% for BCL2 protein coexpression was classified as double expressor (DE)-DLBCL, whereas this subtype with MYC and BCL2 and/or BCL6 rearrangement was classified as THL/DHL.[7] In this study, fluorescence in situ hybridization (FISH) testing for MYC, BCL2, and BCL6 rearrangement was performed in DLBCL patients with MYC protein expression > 40%.

Demographic characteristics of patients including age, serum lactate dehydrogenase (LDH), ECOG, site of lesion (extranodal/nodal), number of extranodal involvement, bulky lesion, International prognostic index (IPI) score, chemotherapy regimen, treatment with and without surgery or radiation therapy were recorded. We excluded primary CNS lymphoma, primary mediastinal B cell lymphoma, and indolent lymphoma with large cell transformation. Patients receiving prior chemotherapy and/or radiation therapy were also excluded. Six to eight cycles of intrathecal methotrexate administration at a dose of 15 mg were performed for all DLBCL patients with a high (4-6 points) CNS-IPI score[9] and/or testicular, adrenal/kidney or breast involvement.

Statistical analysis. The primary endpoints were to analyze the rates of overall survival (OS) and disease-free survival (DFS) in patients with double expressor lymphoma (DEL), and secondary endpoints were to evaluate the response and the complete remission (CR) rates between DEL and non-DEL and identify factors affecting survival in DEL and non-DEL patients. The response rate (RR) was defined as the percentage of patients who achieved at least partial remission (reduction in tumor size> 50% after treatment) and CR (no evidence of tumor after treatment).

Kaplan-Meier analysis and log-rank test were used to evaluate and compare DFS and OS between patients with DEL and non-DEL. The Cox regression model was applied for multivariate survival analysis and identify independent prognostic factors for survival. A Chi-square test was used to compare the clinical factors and treatment outcomes between DEL and non-DEL groups. Finally, all statistical analysis was performed using SPSS version 18, and a P value less than 0.05 was considered statistically significant.

This retrospective study was approved by the Local Ethics Committee on Human Rights related to research involving human subjects at Ramathibodi Hospital, Mahidol University.

Results.

Patient characteristics. The study included 291 DLBCL patients with a median age of 63 years (19- 92 years), 157 of whom were female, and 184 patients were older than 60 years. The tissue diagnosis was taken from lymph nodes (51%), bone marrow (0.3%), and other organs (51%). Extranodal involvement was found in 169 patients (58%), which the common sites of extranodal involvement were the gastrointestine (22%), bone marrow (17%), and nasal cavity (11%). GCB and non-GCB subtypes were found in 92 (32%) and 199 patients (68%), respectively. In the GCB group, 75 patients had CD10+, and 17 patients were BCL6+/MUM1-. DEL was seen in 121 out of 264 patients with available IHC

Table 1. Characteristics of patients diagnosed with DEL versus non-DEL subtypes.

Parameters	DLBCL (all subtypes) N= 291 (%)	DEL versus non DEL			DLBCL, unknown subtype (insufficient tissue) N= 27 (%)
		DEL; N= 121 (%)	non-DEL; N= 143 (%)	*p*	
Sex					
- Male	134 (46)	50 (41.3)	69 (48.3)	0.305	15 (55)
- Female	157 (54)	71 (58.7)	74 (51.7)		12 (44)
Age (years)					
- < 60	107 (36.8)	36 (29.7)	62 (43.4)	0.017	9 (33)
- ≥ 60	184 (63.2)	85 (70.2)	81 (56.6)		18 (66)
ECOG					
- 0- 2	256 (68)	105 (86.8)	125 (87.4)	0.795	26 (96)
- 3- 4	35 (12)	16 (13.2)	18 (12.6)		1 (4)
LDH level					
- Normal	101 (34.7)	34 (28.1)	61 (42.6)	0.024	6 (22)
- High	190 (65.3)	87 (71.9)	82 (57.4)		21 (78)
Stage					
- I- II	119 (40.9)	50 (41.3)	59 (41.3)	0.859	10 (37)
- III- IV	172 (69.1)	71 (58.7)	84 (58.7)		17 (63)
Extranodal involvement					
- No	122 (41.9)	53 (43.8)	59 (41.3)	0.81	10 (37)
- Yes	169 (58.1)	68 (56.2)	84 (58.7)		17 (63)
Number of extranodal site involvement					21 (78)
- 0- 1	244 (83.8)	100 (82.6)	123 (86)	0.383	
- > 1	47 (16.2)	21 (17.4)	20 (12)		6 (22)
Bulky lesion≥ 5 cm					
- No	188 (64.6)	74 (61.2)	95 (66.5)	0.413	19 (70)
- Yes	103 (35.4)	47 (38.8)	48 (33.5)		8 (30)
Bulky lesion≥ 7.5 cm					
- No	152 (52.2)	58 (47.9)	76 (53)	0.397	18 (67)
- Yes	139 (47.8)	63 (52.1)	67 (47)		9 (33)
COO					
- GCB	92 (31.6)	28 (23.1)	57 (40)	0.006	7 (26)
- Non-GCB	199 (68.4)	93 (76.9)	86 (60)		20 (74)
Subtype	N= 120	N = 106	N = 14		
- DHL	4 (3.4)	3 (2.8)	1 (7.1)	0.208	0
- Non-DHL	100 (83.3)	89 (84)	11 (78.6)		0
- Uninterpretable	16 (13.3)	14 (13.2)	2 (14.3)		0
IPI					
- Low	91 (31.3)	31 (25.6)	53 (37)	0.113	7 (26)
- Low- intermediate	92 (31.6)	43 (35.5)	43 (30)		6 (22)
- High- intermediate	68 (23.4)	25 (20.7)	31 (21.7)		12 (44)
- High	40 (13.7)	22 (18.2)	16 (11.3)		2 (8)
BCL6 expression					
- No	64 (22)	22 (18.2)	37 (26)	0.127	5 (19)
- Yes	227 (78)	99 (81.8)	106 (74)		22 (81)
MUM1 expression					
- No	71 (24.4)	19 (15.7)	49 (34)	0.001	3 (11)
- Yes	220 (75.6)	102 (84.3)	94 (66)		24 (89)
Rituximab based regimen					
- No	87 (29.9)	34 (28.1)	46 (32.2)	0.589	7 (26)
- Yes	204 (70.1)	87 (71.9)	97 (67.8)		20 (74)
Chemotherapy regimens					
- CHOP	59 (20.3)	21 (17.4)	32 (22.5)	-	6 (22)
- R-CHOP	184 (63.2)	74 (61.2)	90 (63)		20 (74)
- DA-EPOCH	2 (0.7)	1 (0.8)	1 (0.7)		0
- R-DAEPOCH	15 (5.2)	12 (10)	3 (2)		0
- Other regimens	26 (8.9)	11 (9)	14 (9.7)		1 (3.7)
- R- other regimens	5 (1.7)	2 (1.6)	3 (2.1)		0
RT					
- No	199 (68.4)	83 (68.6)	97 (67.8)	0.809	19 (70)
- Frontline	92 (31.6)	38 (31.4)	46 (32.2)		8 (30)

Tumor resection - No - Frontline - Relapse/ refractory	 259 (89) 29 (10) 3 (1)	 111 (91.7) 7 (5.8) 3 (2.5)	 122 (85.3) 21 (14.7) 0 (0)	0.015	 26 (96) 1 (4) 0
Ki-67 (%) - < 50 - 50- 80 - > 80	 8 (2.7) 130 (44.7) 153 (52.6)	 1 (0.8) 46 (38) 74 (61.2)	 5 (3.5) 73 (51) 65 (45.5)	0.04	 2 (7) 11 (41) 14 (52)

Abbreviation: ECOG: Eastern Co-Operative Oncology Group, LDH: lactate dehydrogenase, COO: cell of origin, GCB: germinal B-cell subtype, DHL: double hit lymphoma, IPI: international prognostic index, RT: radiation therapy.

staining for MYC protein (45.8%), and it was detected in non-GCB subtype (77%) greater than GCB-DLBCL (23%). BCL6+ and MUM1+ were found in 82.6% and 84.3% of DEL patients, respectively.

Of 121 DEL patients, the median age was 67 years (28- 90 years). Patients aged> 60 years, stage III-IV, extranodal involvement and ECOG performance 3-4 were observed in 70%, 59%, 56.2%, and 13% of DEL patients, respectively, whereas high LDH levels, high IPI, and bulky lesion (maximum tumor diameter> 7.5 cm) were found in 72%, 18% and 52% of DEL patients, respectively. In the group of DE-DLBCL patients, extranodal involvement was found in 68 patients (56%), the common sites of lymphoma involvements were BM (14%), nasal cavity (12%), stomach, small and large bowel (12%), lung and pleura (10%). Central nervous system involvement was found in only 3% of DEL patients. FISH for MYC, BCL2, and BCL6 gene rearrangement was done in 87.6% of 121 DEL patients (only available tissue samples), and DHL was detected in three patients, including two patients with GCB and one patient with non-GCB. BCL6+ and MUM1+ were found in 82.6% and 84.3% of DEL patients, respectively. In the non-DEL group (143 patients), MYC+/BCL2- DLBCL was detected by IHC in 17 patients which FISH for MYC/BCL2/ BCL6 gene rearrangement was performed in 82% of 17 patients.

Patients aged> 60 years, high LDH levels, Ki-67 >80%, non-GCB subtype, and MUM1+ DLBCL were found significantly in DEL patients compared to those in non-DEL DLBCL. Patients' characteristics are shown in **Table 1**.

Treatment outcomes. During the entire study period, Thai patients with DLBCL treated under the civil servant medical benefit scheme and health insurance could access treatment with rituximab-based chemotherapy. In contrast, patients with DLBCL who were treated under the universal coverage and social security schemes could not claim rituximab therapy reimbursement. Therefore, only 204 patients (70%) received rituximab based chemotherapy, 184 (63%), 59 (20%), 15 (5%), 2 (1%) and 31 patients (11%) were treated with R-CHOP, CHOP, R-DA-EPOCH, DA-EPOCH, and other chemotherapy regimens, respectively. In addition, DA-EPOCH was given depending on the personalized chemotherapy selection for patients with DLBCL who were younger than 60 years and suitable for DA-EPOCH therapy; however, the current frontline standard of treatment DLBCL (non-THL/DHL) remains CHOP regimen.

The CR rate and survival analysis were performed only in patients with DEL (87 patients) and non-DEL DLBCL (97 patients) treated with rituximab-based chemotherapy. CR rates were seen in 87% and 93% of DEL and non-DEL patients, respectively. In addition, 91% of non-GCB patients with DEL and 76% of GCB patients with DEL achieved CR. ECOG 0-2, normal LDH levels, stage I-II, extranodal involvement< 1 site, and low or intermediate IPI were significantly associated with higher CR rates in both DEL and non-DEL subtypes (**Table 2**).

In the entire study population, 1y-OS, 3y-OS, 1y-DFS and 3y-DFS were 79.5%, 62.9% 68.5% and 58.4%, respectively. The survival analysis was restricted to DEL and non-DEL patients who received rituximab-based chemotherapy (R-chemo). After a median follow-up of 26.5 months, 1y-OS, 3y-OS, 1y-DFS and 3y-DFS rates in DEL patients were 86.7%, 58.7%, 69.7%, 58.4%, respectively. The 3y-OS rate was significantly shorter in the DEL group than in the non-DEL group who were treated with R-chemo (58.7% vs. 78.9%, p = 0.026), whereas there was no significant difference in 3y-DFS was identified between these groups (58.4% vs. 67.7%, p = 0.343). The survival curves are shown in **Figure 1**. After a median follow-up duration of 25 months, the 1y-OS rates in patients with DEL and non-DEL who received R-CHOP were 86.7% and 94.3%, respectively, whereas the 3y-OS rates in these groups were 58.7% and 82.6%, respectively (p = 0.004). In addition, the 1y-DFS rates in the DEL and non-DEL patients treated with R-CHOP were 68.4% and 84.9%, respectively, whereas the 3y-DFS rates in these groups were 50.2% and 70.5%, respectively (p = 0.19). **Figure 2** Patients with refractory or relapsed (R/R) DEL and non-DEL after R-chemo therapy were treated with salvage chemotherapy regimens such as ifosfamide, carboplatin, and etoposide (ICE); cisplatin, cytarabine, and dexamethasone (DHAP); etoposide, methylprednisolone, cytarabine, and platinum (ESHAP); ifosfamide, methotrexate, and etoposide (IMVP-16); rituximab and bendamustine (RB); or PD-1 inhibitors. Among 33 patients with DEL,

Table 2. Factors affecting response of rituximab based regimens in patients with DEL and non-DEL subtypes.

Factors	DEL (N= 87)		non-DEL (N= 97)	
	CR (%)	*P*	CR (%)	*P*
Age (years) - < 60 - ≥ 60	 19/24 (79) 57/63 (90)	 0.303	 41/45 (91) 49/52 (94)	 0.554
ECOG - 0- 2 - 3- 4	 73/82 (89) 3/5 (60)	 0.048	 83/88 (94) 7/9 (78)	 0.068
LDH level - Normal - High	 30/31 (97) 46/56 (80)	 0.019	 41/43 (95) 49/54 (91)	 0.384
Stage - I- II - III- IV	 37/39 (95) 39/48 (81)	 0.019	 42/43 (98) 48/54 (89)	 0.097
Extranodal involvement - No - Yes	 29/33 (88) 47/54 (87)	 0.608	 30/31 (97) 60/66 (91)	 0.298
Number of extranodal site involvement - 0- 1 - >1	 67/73 (92) 9/14 (64)	 0.024	 79/84 (94) 11/13 (85)	 0.221
Bulky lesion (MTD≥ 5 cm) - Negative - Positive	 37/41 (90) 39/46 (85)	 0.251	 52/54 (96) 38/43 (88)	 0.134
Bulky lesion (MTD≥ 7.5 cm) - Negative - Positive	 47/51 (92) 29/36 (81)	 0.163	 63/68 (93) 27/29 (93)	 0.937
COO - GCB - Non-GCB	 16/21 (76) 60/66 (91)	 0.103	 51/55 (93) 39/42 (93)	 0.98
IPI-risk - Low - Low- intermediate - High- intermediate - High	 24/24 (100) 32/37 (86) 12/14 (86) 8/12 (67)	 0.034	 36/37 (97) 31/34 (91) 18/19 (95) 5/7 (71)	 0.105
KI-67 (%) - < 50 - 50- 80 - > 80	 1/1 (100) 12/14 (86) 63/72 (88)	 0.901	 4/4 (100) 23/24 (96) 63/69 (91)	 0.647
Chemotherapy regimen - R-CHOP -R-DA-EPOCH	 64/75 (85) 10/12 (83)	0.989	 85/94 (90) 3/3 (100)	0.888
RT -No -Frontline	 48/55 (87) 28/32 (88)	 0.727	 61/67 (91) 29/30 (97)	 0.323
RT (MTD≥ 5 cm) -No -Frontline	 20/24 (83) 19/23 (83)	 0.880	 24/28 (86) 14/15 (93)	 0.458
RT (MTD≥ 7.5 cm) -No -Frontline	 13/16 (81) 16/19 (84)	 0.935	 15/16 (94) 12/13 (92)	 0.879

52% received more than one salvage chemotherapy regimen, versus 56% of patients in the non-DEL group (27 patients). In total, 12% and 11% of patients with R/R DEL and non-DEL, respectively, had CNS involvement. CR was achieved after salvage chemotherapy for 6% and 22% of patients in the R/R DEL and non-DEL groups, respectively. In the group of patients with R/R DE-DLBCL, 94% did not respond to salvage chemotherapy and died from progressive disease (PD), whereas 22% of non-DEL patients with R/R disease achieved CR after salvage therapy and were still alive at the end of the study.

In univariate analysis, parameters significantly associated with poorer OS in both DEL and non-DEL patients were ECOG 3-4 and high IPI. In contrast, high LDH level, stage III-IV, extranodal involvement> 1 site, GCB subtype, and high-intermediate or high IPI were independent factors affecting OS only in DEL patients (**Table 3**). Only high LDH levels and stage III-IV were

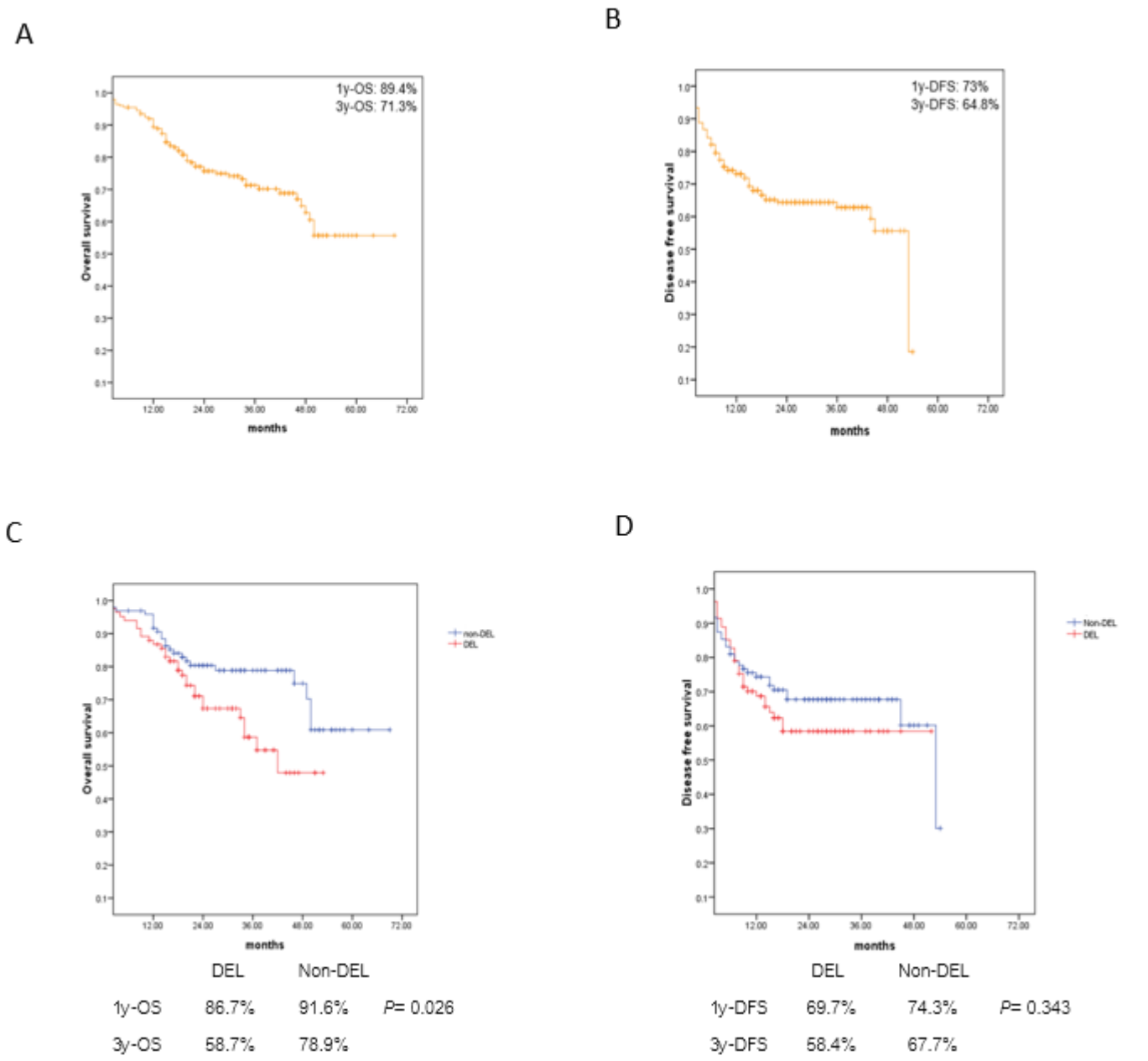

Figure 1. OS in DLBCL patients treated with rituximab based therapy (**A**), DFS in DLBCL patients treated with rituximab based therapy (**B**), OS in DEL patients treated with rituximab based therapy compared with that in non-DEL patients treated with rituximab based therapy (**C**), DFS in DEL patients treated with rituximab based therapy compared with that in non-DEL patients treated with rituximab based therapy (**D**).

significantly associated with dismal OS in DEL patients who were treated with both R-chemo and R-CHOP in multivariate Cox regression analysis, p= 0.005 (R-chemo) versus p= 0.01 (R-CHOP) for high LDH level group and p= 0.034 (R-chemo) versus p= 0.031 (R-CHOP) for stage III-IV group. The results of the multivariate Cox regression analysis are shown in **Table 4**. DEL patients with high LDH levels and stage III-IV treated with R-CHOP had 3y-OS of 41.8% and 37.6%, respectively. In the non-DEL group, ECOG 3–4 was significantly associated with poorer OS in multivariate Cox analysis, p< 0.001.

In addition, the univariate analysis showed that the parameters significantly affecting DFS in both DEL and non-DEL patients were ECOG 3-4, stage III-IV, and high IPI. Whereas high LDH levels, extranodal involvement >1, maximum tumor diameter (MTD) >5 or 7.5 cm, and BM involvement were independent factors for poorer DFS in DEL patients. (**Table 5**) Nevertheless, in multivariate analysis, only high LDH levels (p= 0.011) and stage III-IV (p= 0.035) were the independent factors affecting DFS in DEL patients receiving R-chemo. Stage III-IV (p= 0.028) was also associated with shorter DFS in DEL patients treated with R-CHOP in multivariate analysis. (**Table 6**) DEL patients with high LDH levels and stage III-IV treated with R-CHOP had 3y-DFS of 45.3% and 37.5%, respectively. Factors affecting DFS in non-DEL patients receiving R-chemo were ECOG3-4 (p< 0.001), stage III-IV (p= 0.017) and MTD) >5 (p= 0.001) in multivariate analysis.

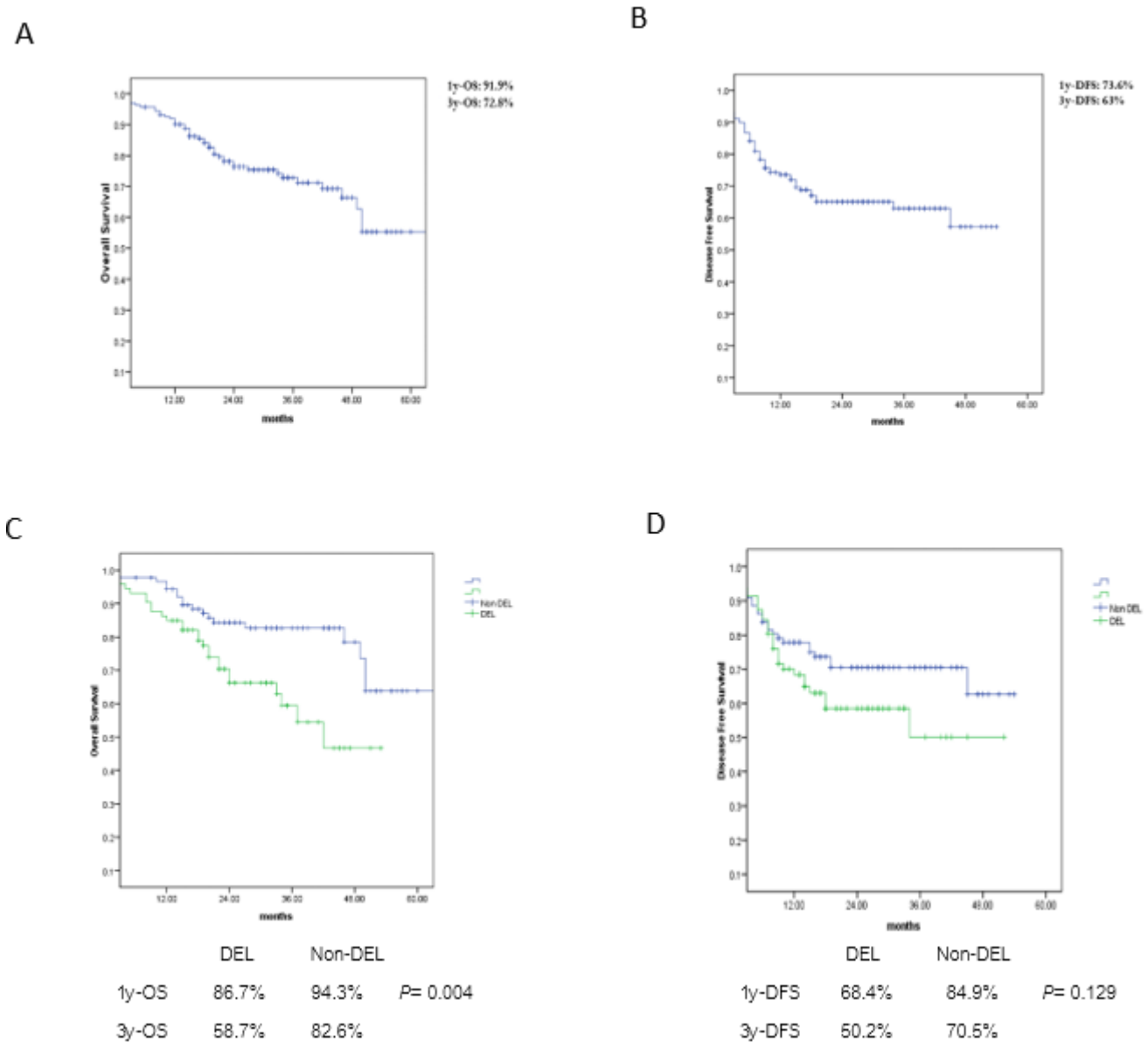

Figure 2. OS in DLBCL patients treated with R-CHOP (**A**), DFS in DLBCL patients treated with R-CHOP (**B**), OS in DEL patients treated with R-CHOP compared with that in non-DEL patients treated with R-CHOP (**C**), DFS in DEL patients treated with R-CHOP compared with that in non-DEL patients treated with R-CHOP (**D**).

Table 3. Factors affecting overall survival in 184 DLBCL patients treated with rituximab based chemotherapy.

Factors	**DEL patients receiving R-CHOP (N= 75)**				**DEL patients receiving** R-chemo **(N= 87)**				**Non-DEL patients receiving** R-chemo **(N= 97)**			
	mOS (Mo)	***p***	**1y-OS**	**3y-OS**	**mOS (Mo)**	***p***	**1y-OS**	**3y-OS**	**mOS (Mo)**	***p***	**1y-OS**	**3y-OS**
Age (years)												
- < 60	NR	0.692	78.6	61.9	NR	0.492	86.4	62.1	NR	0.156	97.8	86
- ≥ 60	37		85.7	55.8	42		86.9	56.9	NR		86.1	72.5
ECOG												
- 0- 2	42	0.045	86.4	60.5	42	0.004	88.4	61.3	NR	<0.001	97.7	86.3
- 3- 4	8		50	NA	14		60	20	15		55.6	0
LDH level												
- Normal	NR	0.001	90.9	90.9	NR	<0.001	100	92.3	NR	0.841	95.3	79.5
- High	24		76.6	41.8	34		80.3	40.8	NR		90.6	78.1
Stage												

- I- II	NR	0.001	93.9	81.5	NR	0.001	94.6	82.9	NR	0.245	92.9	81.8
- III- IV	24		75.7	37.6	24		80.4	40.2	NR		90.6	76.6
Extranodal involvement												
- No	NR	0.308	85.7	69.4	NR	0.65	89.1	69.1	NR	0.073	97.4	88.4
- Yes	37		83.3	53.5	37		84.8	50.7	NR		87.8	72.7
Number of extranodal site involvement												
- 0- 1	NR	<0.001	88.1	65.5	NR	<0.001	91.4	65.5	NR	0.806	92.8	79.2
- >1	18		63.6	NA	18		69.2	15.8	NR		84.6	76.9
BM involvement												
- No	42	0.17	82,5	61.9	42	0.283	84.9	61.4	NR	0.007	92.8	81.8
- Yes	22		83.3	NA	24		100	39.4	49		84.6	59.8
IPI												
- Low	NR	<0.001	83.3	83.3	NR	<0.001	100	100	NR	0.007	97.3	88
- Low- intermediate	42		82.1	57.3	42		85.7	55.3	NR		91	76.6
- High- intermediate	22		84.6	21.5	22		92.3	21.5	NR		94.7	77.3
- High	15		60	NA	15		66.7	15	13		57.1	42.9
Bulky lesion (MTD≥ 5 cm)												
- No	37	0.658	88.2	51.4	37	0.916	89.7	57.7	NR	0.061	96.3	86.3
- Yes	42		80.6	62.2	42		84.1	58.5	NR		85.8	69.9
Bulky lesion(MTD≥ 7.5 cm)												
- No	42	0.45	90.7	59.8	42	0.282	92	63.2	NR	0.395	92.5	83
- Yes	NR		74.1	54.9	NR		78.8	50.4	NR		89.7	69.9
COO												
- GCB	42	0.026	70.6	31.8	22	0.014	70.6	31.8	NR	0.74	90.1	78.6
- Non-GCB	22		84.8	65.1	NR		90	64.3	NR		92.7	79.3
DHL												
- Non-DHL	NR	<0.001	89.1	70.9	NR	0.001	87.4	68.6	NR	0.017	100	83.3
- DHL	3		50	0	15		66.7	0	1		0	0
- Uninterpretable	42		84.6	57.9	42		83.3	55	NR		100	100
Ki-67 (%)												
- < 50	-	0.658	-	-	NR	0.274	100	100	21	0.12	100	33.3
- 51- 79	NR		62.5	62.5	NR		88.2	67.3	NR		92.5	76.5
- ≥ 80	NR		86.9	55.6	NR		87.8	51.4	NR		89.7	86
RT												
- No	37	0.22	83.7	51.9	37	0.222	88.9	51.8	NR	0.831	89.5	81.6
- Yes	NR		85.2	70.2	NR		86.2	71.9	NR		96.6	71.5
Frontline RT (MTD≥ 5 cm)												
- No	42	0.362	77.8	57.1	34	0.192	83.3	57.9	50	0.961	81.7	74.3
- Frontline	NR		83.3	68.2	NR		85	70.8	NR		93.3	60.5
Frontline RT(MTD≥ 7.5 cm)												
- No	20	0.431	66.7	50	34	0.252	75	27.5	NR	0.364	87.5	81.3
- Frontline	NR		80	61	NR		82.4	64.9	NR		92.3	52.7
COO												
- GCB	42	0.026	70.6	31.8	22	0.014	70.6	31.8	NR	0.74	90.1	78.6
- Non-GCB	22		84.8	65.1	NR		90	64.3	NR		92.7	79.3
DHL												
- Non-DHL	NR	<0.001	89.1	70.9	NR	0.001	87.4	68.6	NR	0.017	100	83.3
- DHL	3		50	0	15		66.7	0	1		0	0
- Uninterpretable	42		84.6	57.9	42		83.3	55	NR		100	100
Ki-67 (%)												
- < 50	-	0.658	-	-	NR	0.274	100	100	21	0.12	100	33.3
- 51- 79	NR		62.5	62.5	NR		88.2	67.3	NR		92.5	76.5
- ≥ 80	NR		86.9	55.6	NR		87.8	51.4	NR		89.7	86

RT												
- No	37	0.22	83.7	51.9	37	0.222	88.9	51.8	NR	0.831	89.5	81.6
- Yes	NR		85.2	70.2	NR		86.2	71.9	NR		96.6	71.5
Frontline RT (MTD≥ 5 cm)												
- No	42	0.362	77.8	57.1	34	0.192	83.3	57.9	50	0.961	81.7	74.3
- Frontline	NR		83.3	68.2	NR		85	70.8	NR		93.3	60.5
Frontline RT(MTD≥ 7.5 cm)												
- No	20		66.7	50	34		75	27.5	NR		87.5	81.3
- Frontline	NR	0.431	80	61	NR	0.252	82.4	64.9	NR	0.364	92.3	52.7

Table 4. Multivariate Cox regression analysis of factors contributing to overall survival of DE-DLBCL patients treated with R-chemo and R-CHOP.

Parameters	R-chemo				R-CHOP			
	OS *(P)*	OS (HR)	95% CI		OS *(P)*	OS (HR)	95% CI	
			Lower	Upper			Lower	Upper
Age≥ 60 years	0.113	2.412	0.814	7.155	0.146	2.393	0.737	7.763
ECOG 3-4	0.313	1.814	0.570	5.778	0.476	1.614	0.433	6.014
High LDH levels	0.005	6.028	1.700	21.375	0.01	5.635	1.525	20.827
Stage III-IV	0.034	3.496	1.101	11.097	0.031	3.62	1.128	11.62
Extranodal involvement> 1 site	0.086	2.238	0.893	5.611	0.068	2.412	0.936	6.215
GCB	0.884	0.933	0.365	2.386	0.695	0.823	0.310	2.182

Table 5. Factors affecting disease free survival in 184 DLBCL patients treated with rituximab based chemotherapy.

Factors	**DEL patients receiving R-CHOP (N= 75)**				**DEL patients receiving** R-chemo **(N= 87)**				**Non-DEL patients receiving** R-chemo **(N= 97)**			
	mDFS (Mo)	***p***	**1y-DFS**	**3y-DFS**	**mDFS (Mo)**	***p***	**1y-DFS**	**3y-DFS**	**mDFS (Mo)**	***p***	**1y-DFS**	**3y-DFS**
Age (years)												
- < 60	NR	0.489	69.2	69.2	NR	0.762	71.9	68.3	45	0.211	73.4	73.4
- ≥ 60	34		68.9	44.9	44		70.8	65.5	53		67.2	56.8
ECOG												
- 0- 2	NR	0.091	70	52.3	44	0.002	73.7	70.4	53	<0.001	75.3	68.9
- 3- 4	8		25	NA	3		25	0	3		20	NA
LDH level												
- Normal	NR	0.008	86.5	64.9	44	0.001	88	44	53	0.093	75	75
- High	18		60.4	45.3	NR		60.4	51.7	45		66.1	54.5
Stage												
- I- II	NR	<0.001	90.9	61.4	NR	<0.001	86.6	86.6	NR	0.004	85.2	78.4
- III- IV	12		48.7	37.5	16		55.2	48.9	45		81.7	50.7
Extranodal involvement												
- No	NR	0.097	80.7	50.2	NR	0.22	75.1	75.1	NR	0.077	80.5	76
- Yes	18		61.5	48.9	44		67	62.1	45		83	60.5
Number of extranodal site involvement												
- 0- 1	NR	<0.001	75.4	56.6	NR	<0.001	76.2	72.8	45	0.570	71.2	63.2
- >1	7		34.1	NA	3		41.7	21.8	53		60	60
BM involvement												
- No	NR	0.008	72.1	53.9	44	0.022	73.4	71.7	53	0.119	85.5	69.2
- Yes	6		42.9	NA	10		50	16.7	15		50.3	42
IPI												
- Low	NR	<0.001	94.7	71.1	NR	<0.001	93.3	93.3	NR	0.004	86.4	86.4
- Low- intermediate	NR		73.2	73.2	NR		67.7	63.2	45		68.7	61.2
- High- intermediate	12		42.2	28.1	15		56.1	44.9	22		58.8	44.1

- High	7		40	NA	4		16.7	0	7		46.2	36.9
Bulky lesion (MTD≥ 5 cm)												
- No	34	0.274	64.3	27.5	NR	0.017	80.5	77.6	53	0.223	78.1	66.4
- Yes	NR		73.8	62.4	NR		59.9	53.3	45		64.1	58
Bulky lesion(MTD≥ 7.5 cm)												
- No	34	0.903	66.9	45.3	44	0.009	76.7	74.6	53	0.360	71.3	65
- Yes	NR		72.7	55.7	15		56.5	45.2	45		66.3	57.6
COO												
- GCB	NR	0.085	72.7	54.1	NR	0.576	73.4	67	53	0.877	70.9	62.3
- Non-GCB	14		57.8	37.1	44		66.5	66.5	45		66.7	63.3
DHL												
- Non-DHL	NR	0.012	81.9	57.4	NR	0.02	81.6	51	NR	0.445	83.3	62.5
- DHL	5		0	0	5		0	0	-		-	-
- Uninterpretable	NR		77.4	61.9	NR		75.2	59.1	NR		100	100
Ki-67 (%)												
- ≤ 50	NR	0.791	-	-	NR	0.884	66.7	66.7	1	0.005	0	0
- 51- 79	NR		71.4	0	NR		68.8	61.1	NR		78	78
- ≥ 80	NR		68.2	58.4	44		70	68	53		69.2	60.2
RT												
- No	34	0.084	61.3	34.5	44	0.813	70.3	65.4	53	0.34	72.6	65.2
- Yes	NR		81.3	69.6	NR		72.8	68.7	NR		59.1	54.2
Frontline RT (MTD≥ 5 cm)												
- No	NR	0.439	64.7	57.5	15	0.468	52.9	46.3	45	0.436	66.4	61.7
- Frontline	NR		83	67	NR		66	59.4	14		58.3	48.6
Frontline RT(MTD≥ 7.5 cm)												
- No	NR	0.479	63.6	NA	15	0.841	57.1	38.1	45	0.350	70.6	62.7
- Frontline	NR		79.4	58.8	15		56.2	48.2	14		58.3	48.6

Table 6. Multivariate Cox regression analysis of factors contributing to disease free survival of DE-DLBCL patients treated with R-chemo and R-CHOP.

Parameters	R-chemo				R-CHOP			
	DFS *(P)*	DFS (HR)	95% CI		DFS *(P)*	DFS (HR)	95% CI	
			Lower	Upper			Lower	Upper
Age≥ 60 years	0.625	1.283	0.472	3.483	0.179	2.276	0.685	7.565
ECOG 3-4	0.203	2.229	0.649	7.655	0.364	1.942	0.463	8.147
High LDH levels	0.011	5.099	1.442	18.035	0.050	3.125	0.999	9.775
Stage III-IV	0.035	3.279	1.084	9.915	0.028	3.649	1.149	11.585
Extranodal involvement > 1 site	0.419	1.466	0.580	3.706	0.379	1.594	0.564	4.506
GCB	0.650	1.225	0.510	2.943	0.868	1.083	0.422	2.776
BM involvement	0.619	1.305	0.457	3.728	0.247	1.953	0.629	6.064
MTD ≥ 5 cm	0.771	0.837	0.247	2.819	0.474	0.620	0.167	2.294
MTD ≥ 7.5 cm	0.634	0.746	0.224	2.489	0.696	0.765	0.199	2.936

DEL with BCL6 expression had no significant difference in 3y-OS and 3y-DFS compared with those in DEL with BCL6 negative DLBCL (71.3% versus 68.8%, p= 0.729 and 60.7% versus 62.5%, p= 1.00, respectively). Patients receiving R-DA-EPOCH had 1y-OS of 91.67% and 3y-OS of 64.3%, whereas 1y-OS and 3y-OS in patients receiving R-CHOP were 86.7% and 58.7%, respectively (p= 0.497). The 1y-DFS of 75% and 3y-DFS of 60% following R-DA-EPOCH therapy, and 1y-DFS of 68.4% and 3y-DFS of 50.2% following R-CHOP therapy, (p= 0.959).

Discussion. In this study, the frequency of DEL was 46% of DLBCL patients, and 77% of DE-DLBCL was non-GCB subtype, and the prevalence of both DEL and non-GCB with DE was higher than those reported in the previous studies.[10-13] Therefore, DEL is commonly found in non-GCB compared to GCB subtype.[11-13] Nevertheless, non-DEL DLBCL was also often observed in non-GCB in our study (60%) which was in contrast to

the previous report that non-DEL was commonly found in GCB patients.[11] In addition, DHL had an extremely low prevalence in our cohort (3.4%), and the prevalence of DEL and DHL differed from that in previous studies, which might be attributable to the fact that our study was a single-center retrospective study conducted at an academic tertiary referral hospital and we only recruited DLBCL patients undergoing DLBCL treatment at our center. Patients with DEL had significantly older age, high LDH levels and high Ki-67 proliferation than those with non-DEL, in line with the clinical manifestations in patients with DEL in previous reports. However, only small population of our DEL patients had poor performance status, high IPI or multiple extranodal sites of involvement.[11] GCB with DEL subtype had lower CR rate than that in non-GCB with DE patients which might be associated with the small number of GCB with DE patients receiving R-chemo (21 patients).

Among patients who received R-CHOP therapy, our study demonstrated that the DFS rate in non-DEL patients was higher than that in DEL patients with a 16.5% difference in DFS at 1 year (84.9% versus 68.4%) and 20% difference in DFS at three years (70.5% versus 50.2%), even though the result was not statistically significant between these groups. This result is consistent with the fact that DE-DLBCL is more aggressive than the non-DEL subtype.[3,6,10-16] Conversely, the OS rate was significantly lower in the DEL group than in the non-DEL group. We found that 94% of R/R DE-DLBCL patients did not respond to salvage chemotherapy and died from progressive disease (PD). Meanwhile, 22% of patients with R/R non-DEL achieved CR after salvage therapy and remained alive at the end of the study. Similar results were observed in patients who received R-chemo, and a lower 3-year OS rate was observed in patients with DEL than in patients with non-DEL (58.7% vs. 78.9%), and the cause of significantly shorter OS in DEL patients was PD after salvage therapy.

Conversely, there was no difference in DFS between the DEL and non-DEL arms among patients treated with receiving R-chemo at 1 (69.7% versus 74.3%) and three years (58.4% versus 66.7%). The possible cause of slightly higher DFS rates at 1 and 3 years in the non-DEL patients than in the DEL group might be the higher rate of treatment with R-DAEPOCH in the DEL group. Furthermore, our data also illustrated that both OS and DFS were markedly decreased in patients with DEL within two years after diagnosis, confirming that DEL is an aggressive lymphoma and did not respond to salvage therapy. In previous studies, the 2-year OS and PFS rates in patients with DEL treated with R-CHOP were approximately 50%-70% and 50%-54%, respectively,[6,11] and the 5-year OS and PFS rates were 30%–36% and 27%-32%, respectively.[9,10] Similarly, the 2-year OS and DFS rates among patients with DEL treated with R-CHOP in this study were 66.3% and 58.5%, respectively (**Figure 2**). However, the study's median duration of follow-up time was only two years, and we also lacked data on molecular features in our DLBCL patients. Therefore a long-term follow-up (5 years) and further study on the molecular biology in our DLBCL patients are needed.

Factors affecting OS and DFS in DE-DLBCL patients were ECOG 3-4, high LDH levels, extranodal involvement >1 site, stage III-IV and high-intermediate/ high IPI. Nevertheless, only high LDH levels and stage III-IV were independent factors for OS in the DEL patients treated with both R-chemo and R-CHOP in multivariate analysis, in line with previous studies.[11,12,14] High LDH levels and stage III-IV were the independent factors affecting DFS in DEL patients receiving R-chemo, whereas stage III-IV was associated with shorter DFS in DEL patients treated with R-CHOP in multivariate analysis. ECOG 3-4, high LDH levels, extranodal involvement >1 site, stage III-IV and high-intermediate/ high IPI were also significantly associated with lower CR rate in DEL patients. There was no significant difference in OS and DFS rate between DEL patients who received R-CHOP (75 patients) and R-DA-EPOCH (12 patients), as previously reported in a retrospective study from MD Anderson;[15] however, the limitation of our survival analysis was a small number of patients treated with R-DA-EPOCH since the major population of DEL patients were older patients which could not tolerate high-intensity chemotherapy. In the group of DEL patients, non-GCB patients had significantly better OS than GCB-DLBCL patients in the univariate analysis; nevertheless, the median age of GCB patients was 70 years (range, 48-86 years) and all of whom receiving R-CHOP therapy with 53% of recorded deaths from disease progression. Frontline rituximab-based chemotherapy combined with RT did not show benefit on DFS and OS in our DEL patients with either MTD> 5 or 7.5 cm. In the study of Japanese patients with relapsed/refractory DEL, poor outcomes in OS and EFS were seen even in patients who underwent allogeneic stem cell transplantation.[17] Although FISH is a standard test for diagnosis of DHL, it is expensive and time-consuming; therefore, we performed FISH testing for MYC/BCL2/BCL6 rearrangement only in DLBCL patients with MYC protein expression> 40%, since the report of Zhang et al. illustrated that MYC translocation was found only in DLBCL with MYC protein expression and the other previous studies showed that MYC protein expression> 50% and > 70% were predicted to have a rearrangement of MYC gene.[14,17,18] The limitations of our study were the retrospective study population, the small number of DE-DLBCL patients receiving R-DA-EPOCH therapy, and poor FISH quality on formalin-fixed paraffin-embedded tissues that have been stored for a long period. Therefore, it is impossible to draw

definitive conclusions regarding the best treatment for these patients.

Conclusions. A high incidence of double-expressor lymphoma was observed in this study, especially in patients aged 60 years or older and non-GCB subtype. Patients with DEL showed dismal DFS and OS. Poor performance status, high LDH and extranodal involvement >1 site, DHL, high IPI, and stage III-IV were significantly associated with dismal OS and DFS in DE-DLBCL patients.

Acknowledgments. We would like to thank all patients who participated in the study. We want to thank Ramathibodi Comprehensive Cancer Center, Ramathibodi Hospital, Mahidol University for providing research funding.

Funding. This work was supported by Ramathibodi Comprehensive Cancer Center, Ramathibodi Hospital, Mahidol University.

Ethics approval and consent to participate. This retrospective study was approved by the Local Ethics Committee on Human Rights related to research involving human subjects at Ramathibodi Hospital, Mahidol University.

Authors' Contributions. SR collected clinical data, FISH testing results, analyzed the data, and wrote the manuscript. PB performed the histological examination. PC, TP, SP, SP, KB, PW, PA, AU, SC carried out the experiment. PN designed the study, analyzed the data, and edited the manuscript. All authors read and approved the final manuscript.

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