Original paper

Prognostic values of myeloid differentiation factor 88 (MYD88) and transducin (β)-like receptor 1 (TBLR1) expression in tissues of diffuse large B-cell non-Hodgkin lymphoma patients – an immunohistochemical study

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Introduction: Diffuse large B-cell non-Hodgkin lymphoma (DLBCL) is the largest common category of adult lymphoma. Recurrence and treatment resistance occurs in one-third of cases, triggering them to the progressive stage of DLBCL after treatment. Detection of novel predictive and prognostic biomarkers leads to improvement of its treatment and prognosis.

Aim of the study: To assess the prognostic roles of protein expression of myeloid differentiation factor 88 (MYD88) and transducin (β)-like receptor 1 (TBLR1) in tissues of DLBCL patients.

Material and methods: In the current study we included tissues from 100 cases of DLBCL. For immunohistochemistry, tissues were stained with MYD88 and TBLR1. We followed patients for about 3 years, and then we correlated their expression with clinicopathological and prognostic parameters.

Results: Higher MYD88 and TBLR1 expressions were associated with presence of B symptoms, fever, night sweat, advanced stage, bone marrow involvement and bulky nodal size, presence of extra-nodal extension, unfavourable relapse-free survival, and unfavourable overall survival rates ($p < 0.001$).

Conclusions: overexpression of MYD88 and TBLR1 expression was present in DLBCL patients and was associated with unfavourable clinicopathological and prognostic parameters.

Key words: MYD88, TBLR1, immunohistochemistry, diffuse large B-cell lymphoma, prognosis.

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Introduction

Diffuse large B-cell non-Hodgkin lymphoma (DLBCL) is the largest common category of adult lymphoma [1]. B-cell lymphomas are heterogeneous tumour as regards histomorphology, clinical manifestations, immunophenotyping, and prediction of prognosis [2]. It is the commonest subtype of non-Hodgkin lymphoma, which occurs in several nodal and extra-nodal sites [3].

The standard chemotherapy protocol is Rituximab, Doxorubicin, Cyclophosphamide, Vincristine, and Prednisone (R-CHOP), which leads to about 70% complete remission [4]. Recurrence and treatment resistance happened in one-third of cases, leading to the progressive disease of DLBCL after treatment [5]. Myeloid differentiation factor 88 (MYD88) was recently found to play a role as a disease-related main gene, an adaptor-soluble cytoplasmic protein that is intended in signal inflammatory pathways downriver followers of interleukin (IL-1) and toll-like receptor [6], and playing a main role in native immunity [7]. Myeloid differentiation factor 88 was recently found to play roles in the molecular classification of DLBCL cases, particularly cases that have worse prognosis [8], which points to the possibility of using it as prognostic parameter that could help in the detection of targeted therapy [9].

Transducin (β)-like (1) X linked receptor 1 (TBL1XR1) is the central element of the NCoR/SMRT dictation co-repressor complex. The prognostic values of TBL1XR1 as a tumour progression biomarker was recently pointed out in many cancers [10], including cervical cancer [11], breast cancer [12], nasopharyngeal carcinoma [13], hepatocellular carcinoma [14], digestive cancers [15–17], and ovarian cancer [18]. The prognostic roles of both MYD88 and trans-ducin β-like receptor-1 (TBLR1) expression have not been sufficiently assessed in DLBCL patients.

In the present study we aimed to assess the clinicopathological correlation and prognostic roles of both MYD88 and TBLR1 expression in tissues of DLBCL patients using immunohistochemistry (IHC) (Table 1, 2).

Table 1. Clinical outcome of patients in correlation with transducin (β)-like receptor 1 and myeloid differentiation factor 88 expression

		TBLR1 expression				*p*	MYD88 expression				*p*
		Low *N* = 58		High *N* = 42			Low *N* = 54		High *N* = 46		
		n	%	*n*	%		*n*	%	n	%	
Response	OAR	58	100.0	8	19.0	< 0.001	48	88.9	18	39.1	< 0.001
	NR	0	0.0	34	81.0		6	11.1	28	60.9	
Response	PD	2	3.4	4	9.5	< 0.001	0	0.0	6	13.0	0.001
	SD	0	0.0	4	9.5		2	3.7	2	4.3	
	PR	0	0.0	6	14.3		0	0.0	6	13.0	
	CR	56	96.6	28	66.7		52	96.3	32	69.6	
Relapse	No	54	96.4	2	25.0	< 0.001	44	91.7	12	75.0	0.081
	Yes	2	3.6	6	75.0		4	8.3	4	25.0	
Mortality	Alive	58	100.0	8	19.0	< 0.001	48	88.9	18	39.1	< 0.001
	Died	0	0.0	34	81.0		6	11.1	28	60.9	

CR – complete response, MYD88 – myeloid differentiation factor 88, NR – no response, OAR – overall response, PD – progressive disease , PR – partial response, SD – stable disease, TBLR1 – transducin (β)-like receptor 1

Table 2. Overall and relapse free survival analysis of patients in correlation with transducin (β)-like receptor 1 and myeloid differentiation factor 88 expression

Marker	RFS					*p*	OS					*p*
	Total *N*	*n* of events relapse	Censored		%		Total *N*	*n* of events deaths	Censored		%	
			N	%					*N*	%		
TBLR1 expression												
Low	56	2	54	96.4	96.3	< 0.001	58	0	58	100	100	< 0.001
High	8	6	2	25.0	25.0		42	34	8	19	19.0	
MYD88 expression												
Low	48	4	44	91.7	91.5	0.051	54	6	48	88.9	88.9	< 0.001
High	16	4	12	75.0	71.4		46	28	18	39.1	37.5	
Received regimen												
R-CHOP	18	6	12	66.7	100	< 0.001	30	12	18	60.0	95	< 0.001
CHOP	38	0	38	100.0	66.7		40	2	38	95.0	60	
Overall	64	8	56	87.5	87.0		100	34	66	66.0	65.7	

MYD88 – myeloid differentiation factor 88, OS – overall survival, RFS – relapse-free survival, TBLR1 – transducin (β)-like receptor 1

Material and methods

The current prospective study included tissues derived from 100 patients with DLBCL, who were admitted and treated in Medical Oncology, Clinical Oncology, Nuclear Medicine, and Internal Medicine Departments, Faculty of Medicine, Zagazig University hospitals in the period from August 2016 and July 2019. The cases were diagnosed by excisional biopsy in the General Surgery Department, and samples were sent to Pathology Department where they were processed, diagnosed, and graded.

Treatment protocols were R-CHOP, CHOP, R-CVP, CVP, or best supportive care only ± involved field radiotherapy (Table 3, 4).

Inclusion criteria

All cases diagnosed with DLBCL (NOS) CD20 +ve after histopathological and immunohistochemical confirmation according to the World Health Organization (2016) diagnostic principles of lymphoid and hematopoietic tumour were included [19].

Approval from the local Ethics Committee and written informed consent from all included patients were acquired. Presentation and follow-up data were collected from patients' files.

Exclusion criteria

Patients diagnosed with other histopathological subtypes of non-Hodgkin lymphoma, cases diagnosed with primary mediastinal large B-cell lymphoma, HIV-related lymphoma, primary central nervous system lymphoma, special morphologic DLBCL subtypes (e.g. anaplastic subtype), positive EBV lymphoma, patients with incomplete data, and patients lost to follow-up were excluded.

Immunohistochemistry

The tissue samples from 100 cases with DLBCL were incubated with primary monoclonal anti-MYD88 and TBLR1 antibodies (cat. no. ab 133739 and ab 117761, respectively; Abcam, U.S.A, dilution 1 : 200).

Myeloid differentiation factor 88 was confined to the cytoplasm of lymphoma cells. Staining intensity scores were recorded as negative: 0, weak: 1, moderate: 2, and intense: 3. The staining extent scores were recorded as 0: 0% of tumour cell stained 1: < 10%, 2: 10 –50%, and 3: > 50%. Then we summed the 2 scores to give a total score from 0 to 6. The score (0, 1) represents negative and (2–6) represents positive MYD88 expression [9].

Transducin (β)-like receptor 1 was confined to the nuclei of lymphoma cells, the staining intensity scores were recorded as (0: negative, 1: weak, 2: moderate, and 3: strong), and the extent of tumour cell staining scores were recorded as 0 ≤ 20%, 1: 21–50%, 2: 51–80%, 3: 81–100%. The total score was found by multiplying the percentage score with the intensity score, giving a result of 0–9. A score of IHC less than 4 was assumed as low TBLR1 expression. Scores more than or equal to 4 were assumed as high TBLR1 expression [10].

Due to different localizations of both markers in malignant lymphocytes, we used different evaluation methods and different cut-off points (Fig. 1).

Statistical analysis

The collected information was computerized then analysed by using Statistical Set for Social Sciences (24 Inc., SPSS, Chicago, IL, U.S.A.). Information was verified by normal dispersal using the Shapiro-Wilk test. Fisher exact and chi-square (χ^2) tests were performed to estimate difference among the variable quantities, as shown in Figure 2.

Survival analysis

The Kaplan-Meier method was performed for evaluation of overall and event-free survival. The log rank test was used for the survival curves. Overall survival (OS) was designed as interval among information of date of latter follow-up, diagnosis until date death or study end. Relapse-free survival (RFS) was estimated from the time of documented remission to the date of documented disease relapse or study end. Model of Cox hazards proportional was performed for univariate analysis. Variable quantities with statistically significant of univariate analysis were involved in multivariate model of Cox proportional hazards. A p-value ≤ 0.05 specified significance, while $p < 0.001$ specified a highly significant difference (Fig. 3–5).

Results

Clinicopathological parameters and associations with included marker expressions are shown in Table 5.

The 100 DLBCL patients included 62 males and 38 female patients with age ranges 40 to 70 years. Stage I was represented in 22 cases, stage II was found in 32 cases, stage III was found in 26 cases, and stage IV was found in 20 cases (Table 5).

Immunohistochemical results

Myeloid differentiation factor 88 expression

High cytoplasmic MYD88 expression in tumour cells was found in 46% (46/100), and it was significantly associated with older age, bone marrow involvement, presence of extra-nodal extension, presence of bulky nodes, and advanced stage of DLBCL cases ($p < 0.001$).

No significant association was found between MYD88 expression and sex.

Table 3. Treatment plan and response to therapy of the studied group

Variable		Total	
		n	%
Received regimen	0.00	4	4.0
	CVP	14	14.0
	R-CVP	16	16.0
	CHOP	36	36.0
	R-CHOP	30	30.0
Rituximab-based regimen	0.00	4	4.0
	No	50	50.0
	Yes	46	46.0
Number of cycles	4	14	14.0
	4–6	46	46.0
	6–8	40	40.0
Involved field radiotherapy	No	56	56.0
	Yes	44	44.0
Dose [Gy)]	Non	56	56.0
	30	18	18.0
	36	12	12.0
	40	14	14.0
Response	OAR	66	66.0
	NR	34	34.0
Response	PD	6	6.0
	SD	4	4.0
	PR	6	6.0
	CR	84	84.0
Relapse*		8	12.5
Mortality	Alive	66	66.0
	Died	34	34.0

CR – complete response, NR – no response, OAR – overall response, PD – progressive disease, PR – partial response, SD – stable disease
**Calculated from responders*

Transducin (β)-like receptor 1 expression

High nuclear TBLR1 expression in tumour cells was found in 42% (42/100) of cases, and it was significantly associated with older age, bone marrow involvement, presence of extra-nodal extension, presence of bulky nodes, and advanced stage of DLBCL cases ($p < 0.001$).

No significant association was found between TBLR1 expression and sex.

There is a positive association between both MYD88 and TBLR1 expression in tissues of DLBCL patients ($p < 0.001$).

According to univariate analysis, TBLR1 and MYD88 expression and age were independent prognostic factors, while only MYD88 expression was an unrestrained prognostic factor according to a multivariate analysis hazard ratio of 4.8 (1.6–14.0), with a confidence interval that positively correlated with OS (Table 6).

Table 4. Treatment plan in correlation with transducin (β)-like receptor 1 and myeloid differentiation factor 88 expression

		TBLR1 expression				*p*	MYD88 expression				*p*
		Low *N* = 58		High *N* = 42			Low *N* = 54		High *N* = 46		
		n	%	*n*	%		*n*	%	*n*	%	
Received regimen	CVP	4	6.9	10	23.8	< 0.001	8	14.8	6	13.0	< 0.001
	R-CVP	2	3.4	14	33.3		2	3.7	14	30.4	
	CHOP	38	65.5	2	4.8		34	63.0	6	13X.0	
	R-CHOP	14	24.1	16	38.1		10	18.5	20	43.5	
Number of cycles	4	8	13.8	6	14.3	< 0.001	8	14.8	6	13.0	0.006
	4–6	36	62.1	10	23.8		32	59.3	14	30.4	
	6–8	14	24.1	26	61.9		14	25.9	26	56.5	
Rituximab-based regimen	0.00	4	6.9	0	0.0	< 0.001	4	7.4	0	0.0	< 0.001
	No	38	65.5	12	28.6		38	70.4	12	26.1	
	Yes	16	27.6	30	71.4		12	22.2	34	73.9	
Involved field radiotherapy	No	42	72.4	14	33.3	< 0.001	38	70.4	18	39.1	0.002
	Yes	16	27.6	28	66.7		16	29.6	28	60.9	
Dose [Gy]	No	42	72.4	14	33.3	< 0.001	38	70.4	18	39.1	0.003
	30	12	20.7	6	14.3		8	14.8	10	21.7	
	36	4	6.9	8	19.0		6	11.1	6	13.0	
	40	0	0.0	14	33.3		2	3.7	12	26.1	

MYD88 – myeloid differentiation factor 88, TBLR1 – transducin (β)-like receptor 1

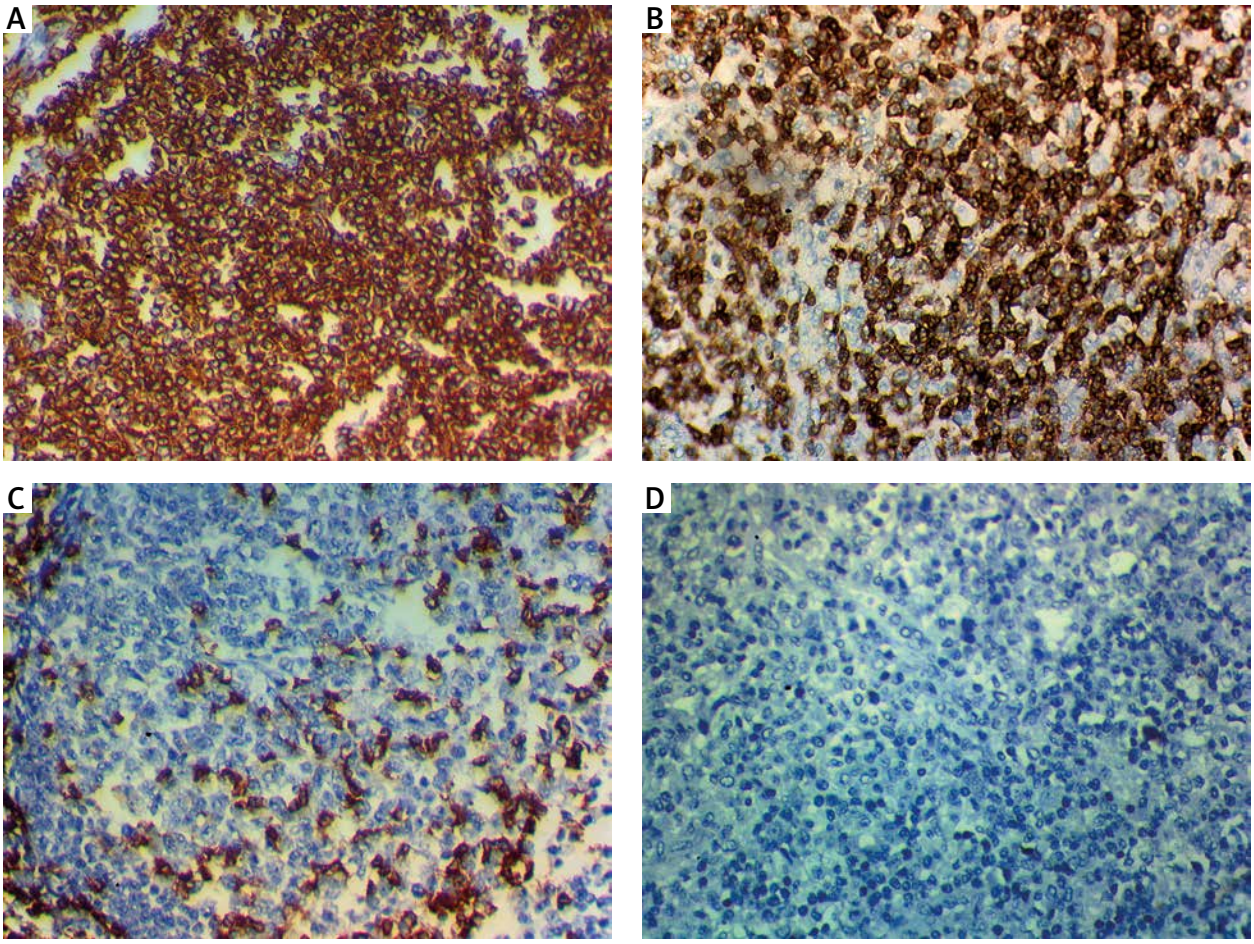

Fig. 1. Expression of myeloid differentiation factor 88 (MYD88) in the cytoplasm of cells of primary diffuse large B-cell non-Hodgkin lymphoma (DLBCL). High cytoplasmic expression of MYD88 in DLBCL; stage IV × 400 (**A**), high cytoplasmic expression of MYD88 in DLBCL; stage III × 400 (**B**), low cytoplasmic expression of MYD88 in DLBCL; stage II × 400 (**C**), negative cytoplasmic expression of MYD88 in DLBCL; stage I × 400 (**D**)

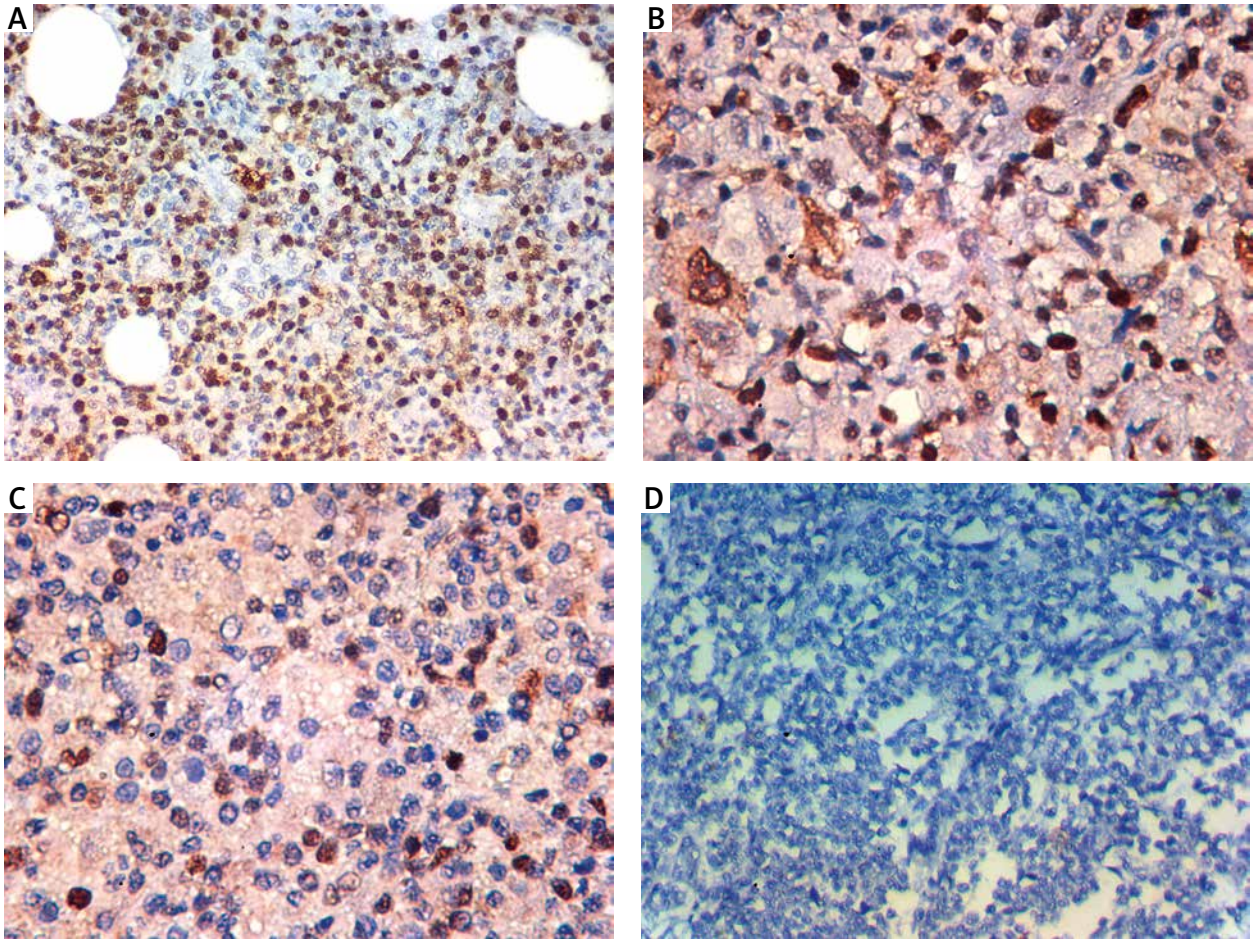

Fig. 2. Expression of transducin (β)-like receptor 1 (TBLR1) in the nuclei of cells of primary diffuse large B-cell non-Hodgkin lymphoma (DLBCL). High nuclear expression of TBLR1in DLBCL; stage IV × 400 (**A**), high nuclear expression of TBLR1 in DLBCL; stage III × 400 (**B**), low nuclear expression of TBLR1 in DLBCL; stage II × 400 (**C**), negative nuclear expression of TBLR1 in DLBCL; stage I × 400 (**D**)

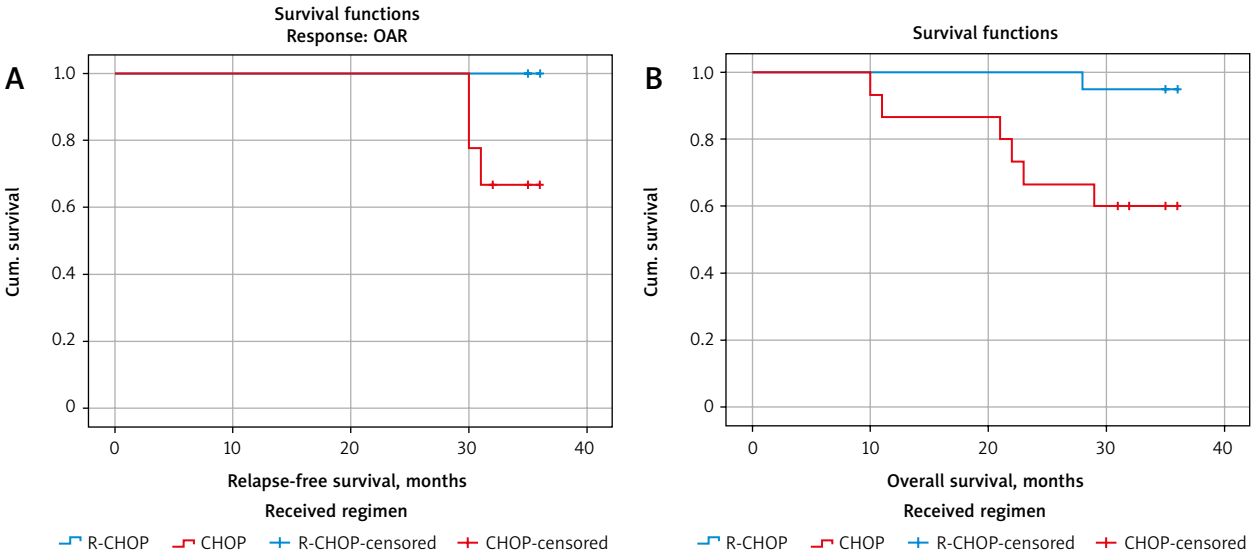

Fig. 3. Kaplan-Meier survival curves of 3-year relapse-free survival (RFS) rate and 3-year overall survival (OS) rate of patients with primary diffuse large B-cell non-Hodgkin lymphoma (DLBCL). RFS rate stratified according to treatment regimen (**A**), OS rate stratified according to treatment regimen (**B**)

Patients with higher TBLR1 and MYD88 expression have higher incidence of disease recurrence and progression, and unfavourable RFS and OS rates ($p < 0.001$), as the 3-year RFS was 91.5% in patients with low MYD88 expression while it was 71.4% in high expression patients ($p = 0.005$). Patients with high MYD88 expression had shorter 3-year OS compared to those with low expression (37.5% vs. 88.9%, respectively) ($p < 0.001$).

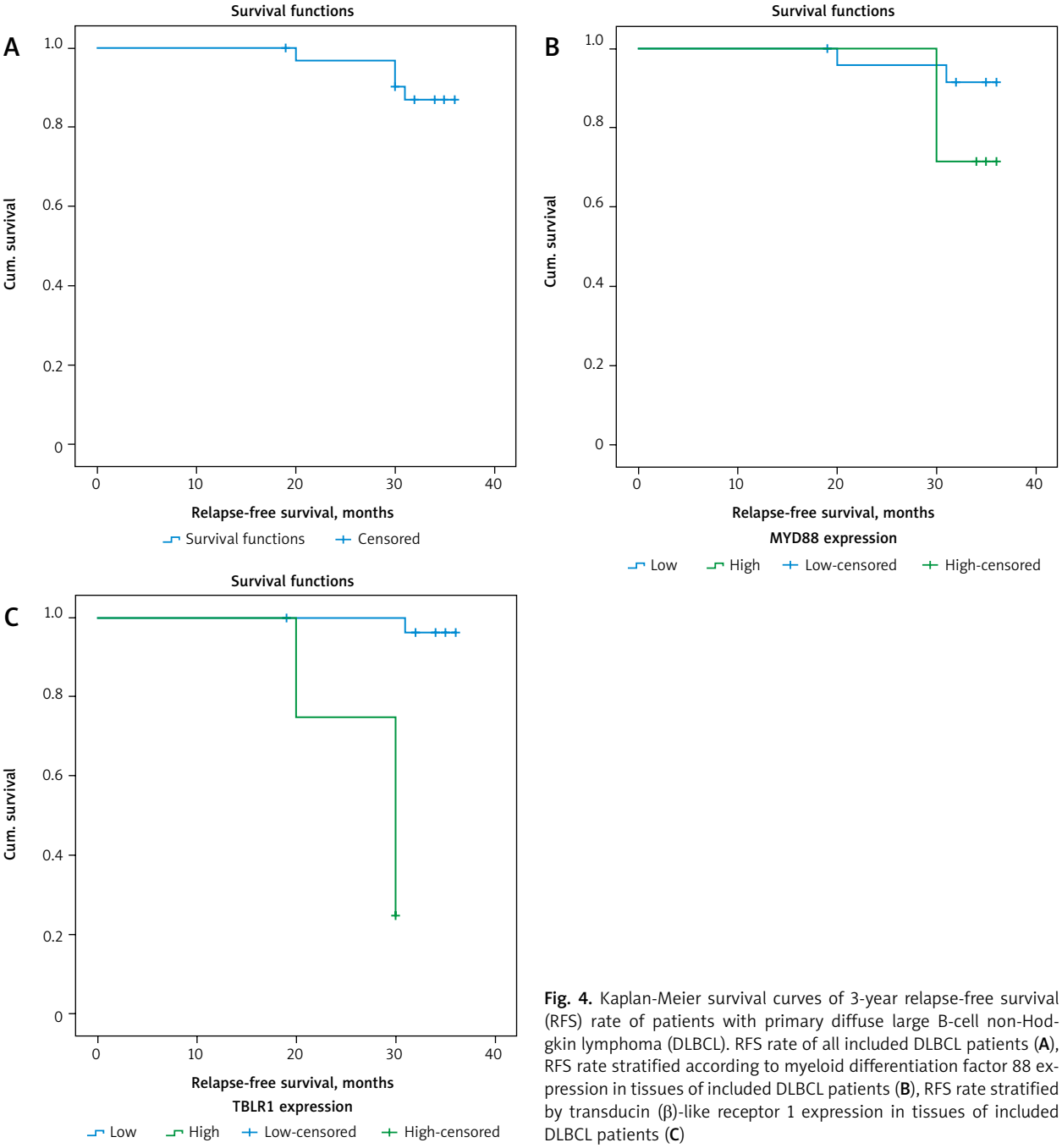

Fig. 4. Kaplan-Meier survival curves of 3-year relapse-free survival (RFS) rate of patients with primary diffuse large B-cell non-Hodgkin lymphoma (DLBCL). RFS rate of all included DLBCL patients (**A**), RFS rate stratified according to myeloid differentiation factor 88 expression in tissues of included DLBCL patients (**B**), RFS rate stratified by transducin (β)-like receptor 1 expression in tissues of included DLBCL patients (**C**)

Also, patients with high TBLR1 expression had poorer 3-year RFS compared to low-expression patients (25% vs. 96.3%, respectively – $p < 0.001$) and shorter 3-year OS (19% vs. 100%, respectively – $p < 0.001$).

Discussion

The prognostic mutations and many precipitated genes in DLBCL have been recognized in recent years. The expression of their encoded proteins with a probable relationship to patient outcome is mainly unknown.

In the study by Niu *et al*. [1] the MYD88 expressions in DLBCL were examined by performing immunohistochemical methods to evaluate MYD88 protein expression. Limited research has been performed by immunohistochemical method to detect expression of MYD88 protein.

It was previously found that overexpression of MYD88 protein was in 38.7% of DLBCL patients [20]. Those results were consistent with our study finding (38%). Also, MYD88-positive expression was associated with survival status.

The higher Bcl-2 expression was associated with positive MYD88 protein expression in the Niu *et al*. [1] study, which might show that Bcl-2 and MYD 88 expression impede apoptosis of tumour cells, encourage its proliferation, augmenting the other oncogenes' role in lymphoma cells. The progress of lymphoma is accelerated by Bcl-2 protein,

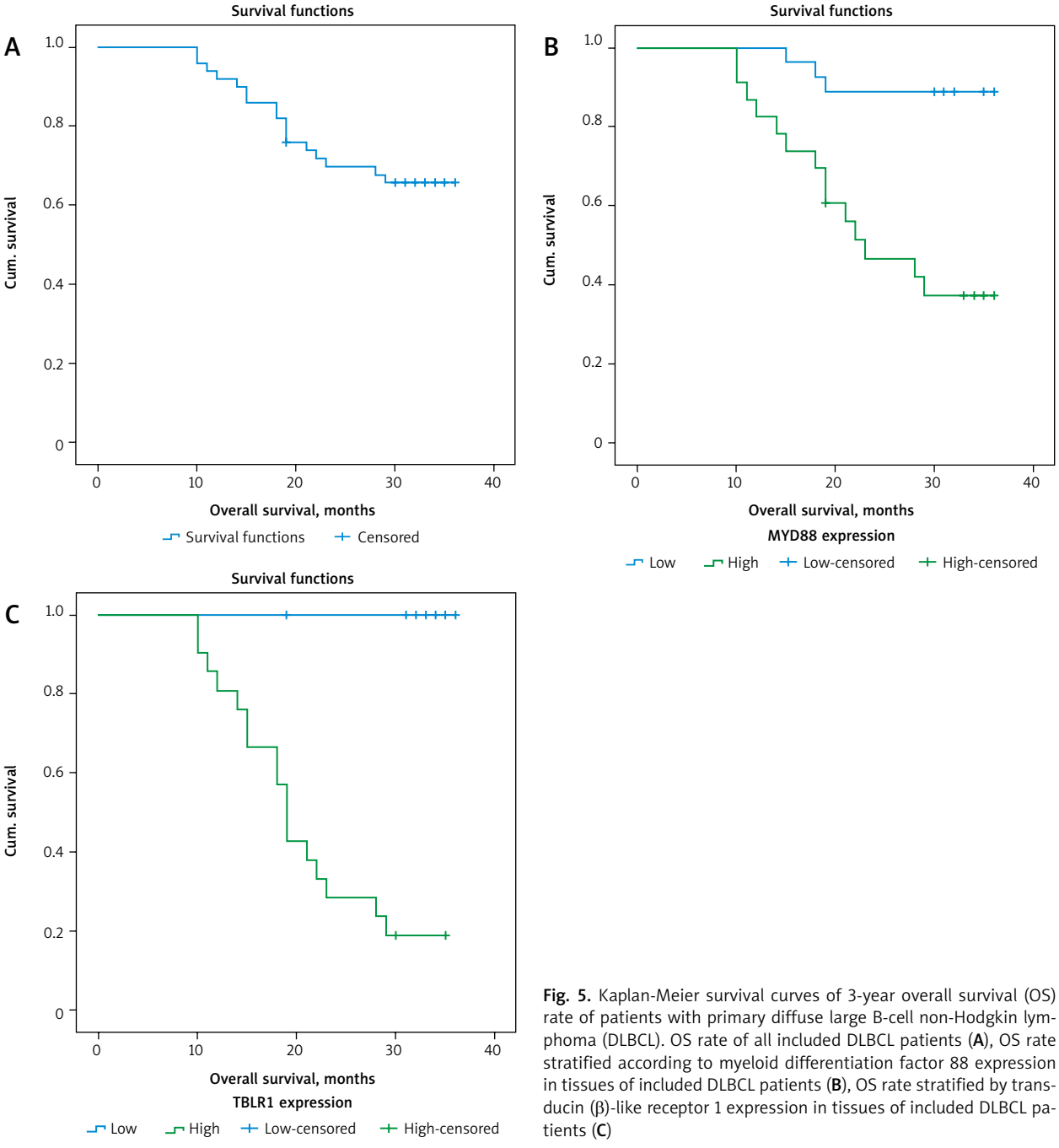

Fig. 5. Kaplan-Meier survival curves of 3-year overall survival (OS) rate of patients with primary diffuse large B-cell non-Hodgkin lymphoma (DLBCL). OS rate of all included DLBCL patients (**A**), OS rate stratified according to myeloid differentiation factor 88 expression in tissues of included DLBCL patients (**B**), OS rate stratified by transducin (β)-like receptor 1 expression in tissues of included DLBCL patients (**C**)

and it encourages lymphoma cell resistance to chemotherapy drugs [21]. Positive expression of MYD88 was positively associated with higher Ki-67 expression. This conclusion suggests that MYD88 protein expression might impede apoptosis of cancer cells and encourage its proliferation [1].

According to our study, we observed that MYD88 expression in DLBCL patients correlated to their survival status, and high expression correlated to low OS and RFS. These findings are in agreement with [1, 22] that provided MYD88 (L265P) mutation is related to the worse prognosis of DLBCL cases who already treated with typical R-CHOP immunochemotherapy. Nevertheless, other studies have established that mutation of MYD88 protein expression is not associated with OS rates of lymphoma cases [23].

In prior studies, MYD88 (L265P) mutation was observed in DLBCL cases (6.5–19%) [6, 22]. In the Niu *et al.* [1] study, MYD88 (L265P) mutation was observed in DLBCL cases (29%). Also, this genetic mutation was positively associated with Eastern Cooperative Oncology Group scores; the high score (72.4%) had high mutation rates compared with the low score (27.6%). The Eastern Cooperative Oncology Group score was a guide performed for appreciate tolerance to treatment, general health status, and patients' physical status. It was previously found that MYD88 (L265P) gene mutation of lymphoma patients that observed MYD88 (L265P) mutation was associated with immune-phenotyping, prognostic outcome, and age, but this mutation was not correlated with sex and stage [24].

Table 5. Clinicopathological parameters of patients in correlation with transducin (β)-like receptor 1 and myeloid differentiation factor 88 expression

		TBLR1 expression				*p*	MYD88 expression				*p*
		Low *N* = 58		High *N* = 42			Low *N* = 54		High *N* = 46		
		n	%	*n*	%		*n*	%	*n*	%	
Age group [years]	< 40	16	27.6	0	0.0	< 0.001	12	22.2	**4**	8.7	< 0.001
	40–60	32	55.2	8	19.0		28	51.9	12	26.1	
	61–74	8	13.8	26	61.9		14	25.9	20	43.5	
	> 75	2	3.4	8	19.0		0	0.0	10	21.7	
Sex	Men	38	65.5	24	57.1	0.394	38	70.4	24	52.2	0.062
	Female	20	34.5	18	42.9		16	29.6	22	47.8	
B symptoms	No	48	82.8	14	33.3	< 0.001	44	81.5	18	39.1	< 0.001
	Yes	10	17.2	28	66.7		10	18.5	28	60.9	
Fever	No	48	82.8	14	33.3	< 0.001	44	81.5	18	39.1	< 0.001
	Yes	10	17.2	28	66.7		10	18.5	28	60.9	
Weight loss	No	48	82.8	14	33.3	< 0.001	44	81.5	18	39.1	< 0.001
	Yes	10	17.2	28	66.7		10	18.5	28	60.9	
Night sweat	No	48	82.8	14	33.3	< 0.001	44	81.5	18	39.1	< 0.001
	Yes	10	17.2	28	66.7		10	18.5	28	60.9	
ECOG PS	1	54	93.1	20	47.6	< 0.001	46	85.2	28	60.9	0.006
	2–4	4	6.9	22	52.4		8	14.8	18	39.1	
Bulky nodes	No	38	65.5	8	19.0	< 0.001	34	63.0	12	26.1	< 0.001
	Yes	20	34.5	34	81.0		20	37.0	34	73.9	
Extra-nodal involvement	No	38	65.5	8	19.0%	< 0.001	34	63.0	12	26.1	< 0.001
	Yes	20	34.5	34	81.0		20	37.0	34	73.9	
Stage	I	18	31.0	4	9.5	< 0.001	18	33.3	4	8.7	< 0.001
	II	26	44.8	6	14.3		22	40.7	10	21.7	
	III	10	17.2	16	38.1		8	14.8	18	39.1	
	IV	4	6.9	16	38.1		6	11.1	14	30.4	
LDH	≤ UNL	36	62.1	4	9.5	< 0.001	32	59.3	8	17.4	< 0.001
	> 1 to < 3 UNL	16	27.6	12	28.6		12	22.2	16	34.8	
	> 3 UNL	6	10.3	26	61.9		10	18.5	22	47.8	
LDH	Normal	36	62.1	4	9.5	< 0.001	32	59.3	8	17.4	< 0.001
	Elevated	22	37.9	38	90.5		22	40.7	38	82.6	
IPI risk group	Low	38	65.5	6	14.3	< 0.001	34	63.0	10	21.7	< 0.001
	Low-intermediate	6	10.3	4	9.5		6	11.1	4	8.7	
	High-intermediate	6	10.3	8	19.0		2	3.7	12	26.1	
	High	8	13.8	24	57.1		12	22.2	20	43.5	

ECOG PS – Eastern Cooperative Oncology Group Performance Status, IPI – International Prognostic Index, LDH – lactate dehydrogenase, MYD88 – myeloid differentiation factor 88, TBLR1 – transducin (β)-like receptor 1

The preceding findings showed that genetic mutation MYD88 (L265P) of was related to the staging (Ann-Arbor), which was related to worse prognosis [1].

The main role of MYD 88 protein in NF-κB pathway is that its higher expression can cause the aberrant stimulation of this pathway even though activation of NF-κB pathway continues the proliferation DLBCL cells [25]. The gene mutation of MYD88 has great significance in the assessment of the progression and prognosis of DLBCL cases, signifying that this is of great value as an immunotherapy target [26].

Transducin (β)-like receptor 1 is a silencing mediator in retinoic acid with thyroid hormone receptor (SMRT/NCo R), which plays a role in a transcriptional repression and triggering NF-κB signalling activation. Diffuse large B cell lymphoma depends on activation of NF-κB pathway [25].

Table 6. Univariate and multivariable analyses for overall and relapse-free survival

Variable	OS				RFS		
	Univariate		Multivariate		Univariate		Multivariate
	Sig.	HR (95% CI)	Sig.	HR (95% CI)	Sig.	HR (95% CI)	Sig.
Age group	< 0.001	15.7 (5.5–44.8)	0.884		0.008	6.5 (1.6–26.0)	0.920
Sex	0.686				0.524		
History of HBV	0.004	3.0 (1.4–6.3)	0.889		0.557		
TBLR1 Expression	0.001	244.6 (8.8–6822.7)	0.836		0.765		
MYD88 Expression	< 0.001	7.7 (3.2–18.6)	0.005	4.8 (1.6–14.0)	0.072	3.6 (0.9–14.3)	0.923
IPI risk group	Ref (low)		Ref (low)		Ref (low)		
Low-intermediate	0.114	2.8 (0.8–9.8)	0.111		1.000		
High-intermediate	0.253	2.1 (0.6–7.4)	0.135		0.920		
High	< 0.001	7.3 (2.9–18.3)	0.433		0.917		

HBV – hepatitis B virus, HR – hazard ratio, IPI – International Prognostic Index, MYD88 – myeloid differentiation factor 88, OS – overall survival, RFS – relapse-free survival, Sig. – significance, TBLR1 – transducin (β)-like receptor 1

This mechanism can describe the augmented violence of lymphoma, detected in cases with higher TBLR1 protein expression. In [27] it was found that protein expression of TBLR1 has value in the assessment of prognostic outcomes and progression in DLBCL cases. According to our study, high TBLR1 expression was associated with poor RFS and OS. Our results are consistent with those in the study by Ednersson *et al*. and Schmitz *et al*. [27, 28]. Also, expression of TBLR1 protein evaluated by immunohistochemical method is correlated with worse outcome of cervical cancer [29], serous ovarian carcinoma [10], and gastric cancer [15]. The TB1R1 protein expression also encourages invasion and migration of ovarian tumour cells [18].

Conclusions

The immunohistochemical expressions of MYD88 protein and TBLR1 protein were correlated with shortened OS and RFS rates and progression in DLBCL cases.

The limitations of our study are the small samples sizes, and the fact that we should use molecular ways for better assessment of gene mutation in DLBCL cases.

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We included tissues from DLBCL (NOS) only, without inclusion of other subtypes.

We recommend the assessment of both marker expressions in other subtypes.

The authors declare no conflict of interest.

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