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.

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 [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 transducin 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).
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).

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

| Marker          | TBLR1 expression |     | MYD88 expression |     |
|-----------------|------------------|--|------------------|--|
|                 | Low          | High          |     | Low          | High          |
| N = 58          | N = 42        |     | N = 54          | N = 46        |
| Response        | n            | %          | n            | %          | n            | %          | n            | %          |
| OAR             | 58           | 100.0      | 8           | 19.0      | < 0.001      |
| NR              | 0            | 0.0        | 34          | 81.0      | < 0.001      |
| Response        | 2            | 3.4        | 4           | 9.5       | < 0.001      |
| PD              | 0            | 0.0        | 4           | 9.5       | < 0.001      |
| SD              | 0            | 0.0        | 6           | 14.3      | < 0.001      |
| PR              | 56           | 96.6       | 28          | 66.7      | < 0.001      |
| CR              | 6            | 11.1       | 28          | 60.9      | < 0.001      |
| Relapse         | 54           | 96.4       | 2           | 25.0      | < 0.001      |
| Yes             | 2            | 3.6        | 6           | 75.0      | < 0.001      |
| Mortality       | 58           | 100.0      | 8           | 19.0      | < 0.001      |
| Died            | 0            | 0.0        | 34          | 81.0      | < 0.001      |

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          |     | OS           |     |
|-----------------|--------------|--|--------------|--|
|                 | Total        | n of events | Censored   | %    | Total        | n of events | Censored   | %    |
| TBLR1 expression| N = 56       | 2          | 54         | 96.4 | 96.3    | < 0.001      |
| Low             | 56           | 6          | 2          | 25.0 | 25.0    | < 0.001      |
| High            | 42           | 34         | 8          | 19.0 | 19.0    | < 0.001      |
| MYD88 expression| N = 54       | 4          | 44         | 91.7 | 91.5    | 0.051        |
| Low             | 48           | 4          | 44         | 91.7 | 91.5    | 0.051        |
| High            | 46           | 28         | 18         | 39.1 | 37.5    | < 0.001      |
| Received regimen| R-CHOP       | 18         | 12         | 66.7 | 100     | < 0.001      |
| CHOP            | 38           | 0          | 38         | 100.0 | 66.7   | < 0.001      |
| Overall         | 64           | 8          | 56         | 87.5 | 87.0    | 0.001        |

MYD88 – myeloid differentiation factor 88, OS – overall survival, RFS – relapse-free survival, TBLR1 – transducin (β)-like receptor 1
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 (χ²) 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. No significant association was found between MYD88 expression and sex.

**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.

**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 |          | MYD88 expression |          |
|------------------|------------------|----------|------------------|----------|
|                  | Low N = 58       | High N = 42 | Low N = 54       | High N = 46 |
| **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 |
| **Number of cycles** |                  |          |                  |          |
| R-CHOP           | 14 24.1          | 16 38.1  | < 0.001          | 10 18.5  | 20 43.5 |
| 4                | 8 13.8           | 6 14.3   |                  | 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** |                  |          |                  |          |
| No               | 38 65.5          | 12 28.6  | < 0.001          | 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   |
| 36               | 12 20.7          | 6 14.3   |                  | 8 14.8   | 10 21.7 |
| 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)
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 \((37.5% \text{ vs. } 88.9\%, \text{ respectively})\) \((p < 0.001)\).
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,
Prognostic values of myeloid differentiation factor 88 and transducin (β)-like receptor 1 expression in tissues of diffuse large B-cell non-Hodgkin lymphoma patients – an immunohistochemical study

Survival functions

Overall survival, months

Cum. survival

Censored

Survival functions

Overall survival, months

MYD88 expression

Low

High

Low-censored

High-censored

Survival functions

Overall survival, months

TBLR1 expression

Low

High

Low-censored

High-censored

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 |                | MYD88 expression |                |
|--------------------------|------------------|----------------|------------------|----------------|
|                          | Low              | High           | p               | Low            | High           | p               |
|                          | N = 58           | N = 42         | p               | N = 54         | N = 46         | p               |
| Age group [years]        | n %              | n %            | < 0.001         | n %            | n %            | < 0.001         |
| < 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        |                |                 |
| Sex                      |                  |                |                 |                |                |                 |
| > 75                     | 2 3.4            | 8 19.0         | 0 0.0           | 10 21.7        |                |                 |
| Men                      | 38 65.5          | 24 57.1        | 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/NCoR), 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].
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 TBLR1 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.

Acknowledgements

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

| Variable            | Univariate OS | Multivariate OS | Univariate RFS | Multivariate RFS |
|---------------------|---------------|-----------------|----------------|------------------|
| 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         |                 |               |                  |
| 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                 | 0.253         | 2.1 (0.6–7.4)   | 0.135         |                  |
| High                 | < 0.001       | 7.3 (2.9–18.3)  | 0.433         | 0.920            |

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
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