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Comparison of c-MYC Expression between Patients with Germinal Center and Non-Germinal Center B-cell-like Diffuse Large B Cell Lymphoma

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ABSTRACT

Background: c-MYC expression has been used as a prognostic marker to predict prognosis and determine therapeutic strategies in both Diffuse Large B Cell Lymphoma (DLBCL) subtypes. No study on c-MYC expression associated with DLBCL has ever been conducted in Indonesia. Our study aimed to evaluate differences in c-MYC expression in both DLBCL subtypes and assess the immunophenotype profile.

Method: We selected 40 DLBCL cases and divided them into Germinal Center B-cell (GCB) and non-GCB subtypes using Hans Criteria. We evaluated c-MYC expression, and a cut-off value of 60.4% was determined using Receiver Operating Characteristic (ROC) curve analysis.

Results: We found that c-MYC expression was significantly higher in GCB subtypes compared to non-GCB subtypes (n = 17 (42.5%) vs n = 20 (7.5%), p < 0.000 and mostly had an immunophenotype of CD10+/BCL6+/MUM1+.

Conclusion: Higher c-MYC expression is found more frequently in GCB subtypes. These findings suggest that c-MYC may play a subtype-specific role in DLBCL pathogenesis, potentially influencing therapeutic decisions for Indonesian patients. Future studies should validate these results in larger, multi-center cohorts and explore the mechanistic link between c-MYC and the GCB subtype and its clinical implications for targeted therapies.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of malignant lymphoma, particularly non-Hodgkin lymphoma (NHL), accounting for 30% to 40% of all lymphoma cases. It may present as de novo cases or transformed DLBCL, which arises from low-grade malignant lymphoma, such as follicular lymphoma [1].

DLBCL has been subdivided clinically, morphologically, and biologically into heterogeneous groups with widely variable clinical courses. Hans' criteria use immunohistochemistry (IHC) to classify DLBCL into two subtypes: germinal center B cell-like (GCB) and non-germinal center B cell-like (non-GCB) [2–7]. Patients with GCB subtypes have better overall survival than those with non-GCB subtypes [1]. Aberrant phenotypes are commonly found in DLBCL and may be responsible for confusion when diagnosing [2,3].

The treatment regimen of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) has significantly improved overall survival and has become the standard initial treatment for DLBCL; however, 30%–40% of DLBCL patients will eventually have a relapse or may develop refractory disease [3,4]. Therefore, it is essential to evaluate predictive biomarkers, including c-MYC, to identify the risk of DLBCL cases failing treatment [5–10].

c-MYC is a regulator gene essential in cell cycle progression, apoptosis, and cellular transformation [11]. Current studies show that c-MYC translocation has been an independent predictor of a less favorable outcome in DLBCL patients treated with RCHOP, and only 5%–14% of DLBCL cases harbor c-MYC translocation [6,12]. Most studies have demonstrated that c-MYC expression is more often found in GCB than non-GCB subtypes, where CD10 and BCL6 are positive and MUM1 is negative, but data among different regions, particularly in Indonesia, are limited.

c-MYC expression has been known to cause various outcomes in DLBCL subtypes. They may serve as prognostic markers that predict overall survival and provide assistance in determining treatment strategies. Several studies have demonstrated that c-MYC expression is associated with shorter survival, which is shared among the GCB subtype. Nevertheless, the data among patients with GCB and non-GCB subtypes in different geographical regions remains controversial. There is no study on c-MYC expression among DLBCL subtypes in Indonesia. This study aimed to evaluate the differences in c-MYC expression between both DLBCL subtypes and to assess the immunophenotype profile.

METHODS

We conducted a cross-sectional analytical study at the Department of Pathology Anatomy, Cipto Mangunkusumo Hospital, Universitas Indonesia, Jakarta, Indonesia, in January to May 2016.

Study population

The medical records of B-cell lymphoma patients at the Department of Pathology Anatomy (PA) at the Faculty of Medicine, Universitas Indonesia, were reviewed. DLBCL cases diagnosed at Cipto Mangunkusumo Hospital between 2011 and 2015 were retrieved retrospectively. Inclusion criteria were data recorded at the PA Department Cipto Mangunkusumo Hospital between 2011 and 2015 retrospectively, with the diagnosis of DLBCL determined through the Hans Criteria, and GCB and non-GCB subtype classifications determined. The cases were divided into two subtypes of GCB and non-GCB, with 20 cases for each group using consecutive sampling. (Each subtype must have a good paraffin block, HE slide, Ki67, CD20, CD10, BCL6, and MUM1 immunohistochemical slide.) We excluded cases with incomplete immunohistochemistry staining, inadequate paraffin blocks, and/or those with unrecognised subtypes were excluded.DLBCL diagnosis was made according to the current World Health Organization (WHO) classification. All DLBCL cases were reviewed by two pathologists (SFH and HE). The cases were divided into GCB and non-GCB subtype groups, with 20 cases for each group using consecutive sampling. The classification of GCB and non-GCB subtypes was determined using Hans Criteria. Cases with incomplete immunohistochemistry staining, inadequate paraffin blocks, and/or unrecognised subtypes were excluded. Clinical data, including age, sex, site of origin (nodal/extranodal sites), morphologic features (centroblastic, immunoblastic, anaplastic), and treatment regimen, were obtained from medical records.

Immunohistochemistry (IHC)

Immunohistochemistry (IHC) was performed on formalin-fixed paraffin-embedded blocks using routine methods. The following antibodies were used: CD10 (clone 56C6; Invitrogen Life Technologies, Carlsbad, CA, USA), BCL6 (clone PG-B6P; Dako, Carpinteria, CA, USA), MUM1 (clone MUM1p, Dako), and Ki67 (clone SP6, Abcam, Cambridge, UK). Immunohistochemical results were interpreted as positive when ≥ 30% of tumor cells showed nuclear immunoreactivity in accordance with other studies [13,14]. All cases with a Ki67 proliferation index of ≥ 75% (55% sensitivity; 45% specificity) were included.

The determination of GCB or non-GCB subtypes was based on an immunophenotype profile according to Hans' criteria using CD10, BCL6, and MUM1 immunostaining. GCB subtype was considered for all cases with CD10 positive results and those with CD10(-)/BCL6(+)/MUM1(-); while non-GCB subtype included cases with MUM1 (+) regardless of their BCL6 status (CD10 (-)/BCL6(+)/MUM1 (-)/(+)) [9,15].

Immunohistochemistry Assay for c-MYC expression

Detection of c-MYC expression was performed on formalin-fixed paraffin-embedded (FFPE) tissue sections using rabbit anti-human MYC primary monoclonal antibody (clone Y69, Epitomics, Burlingame, CA, USA) at a 1:200 dilution. Tissue sections treated with phosphate-buffered saline (PBS) were used as negative controls, while adenocarcinoma colon cells with positive c-MYC expression were used as positive controls.

FFPE tissue sections of 3 µm thickness of all DLBCL cases were placed on poly-L-lysine-coated slides, and subsequently, the slides were prepared and heated for 60 minutes in a steamer. Next, we performed deparaffinization, rinsing the slides with running tap water. Subsequently, we incubated in blocking solutions (0.5% H2O2 in methanol) to inactivate endogenous peroxidase, and then the slides were rewashed using running tap water. Pretreatment using the Antigen Retrieval Procedure in a decloaking chamber with Tris EDTA (pH 9.0) at 96 °C was performed for each tissue slide. The slides were then cooled down for 45 minutes at room temperature and were rinsed using phosphate buffer saline (PBS) (pH 7.4). Slides were drained, and 2–3 drops of Blocking Background Sniper (Starr Trek Universal HRP Detection Kit System, Biocare®) were applied. Afterward, the slides were incubated for 5–10

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minutes, and the Blocking Background Sniper agent was discarded.

Next, the slides were incubated overnight at 40 °C using rabbit anti-human MYC primary monoclonal antibody (clone Y69, Eptiomics, Burlingame, CA, USA) at a 1:200 dilution. The slides were then rinsed using PBS (pH 7.4) and incubated for 5–10 minutes. Drops of secondary antibodies (Trekkie Universal Link, Starr Trek Universal HRP Detection Kit System, Biocare®) were applied. Then, the slides were washed using PBS (pH 7.4) and incubated with Trekavidin-HRP (Starr Trek Universal HRP Detection Kit System, Biocare®) at room temperature. Next, diaminobenzidine (DAB) chromogen was used, followed by counterstaining. The slides were then gradually dehydrated, cover-slipped with aqueous mounting media, and reviewed under light microscopes.

Positive c-MYC protein expression was determined exclusively for dark-brown homogenous nuclear staining areas. We categorized the results as IHC positive (well-stained nuclear) and negative (poor-stained nuclear) staining. The areas with IHC-positive staining were identified at 40x magnification in all slides. Those areas' five most representative sites were photographed randomly at high magnification (400x) using a camera-equipped microscope (Leica ICC 50HD®). The photographs were evaluated and scored further using the Image J image processing and analysis program downloaded from the National Institutes of Health website. The same image of each case was reviewed by two independent observers (SHF and HE), blinded to all clinical, histological, and immunohistochemical results. Each observer evaluated and scored every case individually and kept the score for themselves. At the end of the study, both observers revealed their scores, and kappa analysis was performed to reduce inter-observer bias. Any difference in scores was considered a discrepancy. They were reevaluated and resolved by reviewing the photomicrograph simultaneously. The average of the two concordant scores was taken as the final score.

Assessment of the results of the c-MYC immuno-histochemical review was carried out by identifying the tumour area that is well drained and then photographing it. As many as five places with 40X objective lens magnification using a Leica ICC 50 HD microscope equipped with a camera. Photos processed using the ImageJ® program. The results were reported with the percentage of cells, and the number of cells extracted was calculated until a minimum of 1000 tumour cells were reached in 2 to 5 large fields of view. The assessment of the positivity of the c-Myc review is marked by brown at the core. The intensity of the review, both weak and strong, is still calculated as positive. Positive values are listed as percentages using the formula X/total. tumour cells (≥ 1000) x 100%, where X is the number of positive tumour cells. As there was no generally accepted cut-off of c-MYC expression detected by IHC, we determined 60.4% as the cut-off point, which was established based on the receiver operating characteristic (ROC) curve with 85% sensitivity and specificity (area = 0.865; 95% CI 0.746–0.984; p = 0.000). A score less than 60.4% was considered a low c-MYC expression, while ≥ 60.4% was regarded as a high c-MYC expression.

Statistical analysis

Pearson's chi-square test or Fisher's exact test was used to evaluate differences between the examined variables. $p < 0.05$ were considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software program version 20.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

We reviewed 1.200 cases of B-cell lymphoma, with 453 diagnostic DLBCL cases divided into 83 GCB and 252 non-GCB cases. At first, random sampling was performed. We decided to use consecutive sampling as there were many technical difficulties in retrieving data and tissue blocks for further IHC assay. Cases with incomplete immunohistochemistry staining, inadequate paraffin blocks, and/or those with unrecognized subtypes were excluded. Forty DLBCL cases were collected. We divided them into two groups of GCB and non-GCB subtypes, and each group included 20 cases.

Patient characteristics and c-MYC expression

There were 23 men and 17 women (ratio of 1.35: 1) in this study. Characteristics associated with c-MYC expression are presented in **Table 1**. Most patients were ≥ 50 years old (24–67, median = 53 years old). Extranodal lymphoma occurred more frequently than nodal lymphoma (70% vs. 30%), which included the Waldeyer ring area, sinonasal area, and gastrointestinal organs. High c-MYC expression was mostly found in centroblastic variants that demonstrated diffuse proliferation of large lymphoid cells with scant, amphophilic to basophilic cytoplasm, vesicular nuclei, and prominent nucleoli.

Table 2 shows that higher c-MYC expression was dominantly found in GCB subtypes rather than in non-GCB subtypes (n = 17, 42.5% vs. n = 3, 7.5%; $p < 0.001$). Compared to GCB patients, non-GCB subtype patients were younger (50,9 years old vs. 52 years old). We found no discrepancy between high and low c-MYC expression in terms of age, gender, and site. However, we concluded there was a significant difference among the morphologic features (**Table 1**). High c-MYC expression showed positive staining for CD10, BCL6, MUM1, and Ki67, respectively. According to Hans' criteria, 17 (42%) cases were categorized as GCB subtypes and 3 (7.5%) cases as non-GCB subtypes. Significant findings were found when CD10 and Ki67 staining were applied ($p < 0.05$). Relevant data can be found in **Table 2**.

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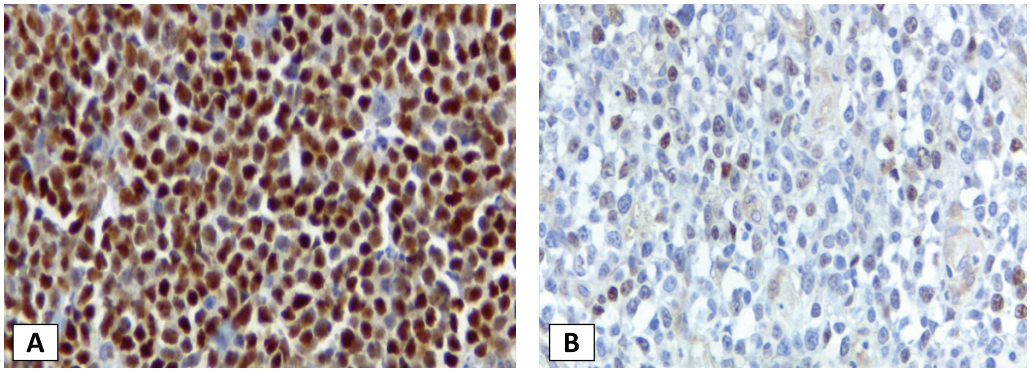

Figure 1. Representative immunohistochemistry (IHC) cases of high and low c-MYC protein expression. c-MYC protein expression was exclusively in brown nuclei (400x). (A) The high c-MYC protein expression (≥ 60.4% c-MYC-positive tumor cells); (B) The low c-MYC protein expression (< 60.4% c-MYC-positive tumor cells)

Table 1. Baseline characteristics of DLBCL patients as related to c-MYC expression

Variable	DLBCL				Total (n = 40)	%	p
	GCB subtype (n = 20)		Non-GCB subtype (n = 20)				
	High* c-MYC	Low* c-MYC	High* c-MYC	Low* c-MYC			
Age (years old)							
< 50	7	1	-	9	17	42.5	0.500
≥ 50	10	2	3	8	23	57.5	
Gender							
Male	10	2	1	10	23	57.5	0.500
Female	7	1	2	7	17	42.5	
Sites							
Nodal	4	1	1	6	12	30.0	0.366
Extranodal	13	2	2	11	28	70.0	
Morphology							
Centroblastic	11	2	-	3	16	40.0	0.004
Immunoblastic	4	-	2	11	17	42.5	
Anaplastic	2	1	1	3	7	17.5	

*c-MYC cut-off was determined at 60.4%. High c-MYC expression was indicated with a score of ≥ 60.4%, while low c-MYC expression was considered when the score was less than 60.4%.

Table 2. Immunotype profile as related to c-MYC protein expression in DLBCL patients (n = 40)

Characteristics	High c-MYC		Low c-MYC		p
	n	%	n	%	
Hans criteria					
GCB	17	42.5	3	7.5	0.000[a]
Non GCB	3	7.5	17	42.5	
CD10					
Positive	17	42.5	2	5.0	0.000[a]
Negative	3	7.5	18	45.0	
BCL6					
Positive	16	40.0	16	40.0	0.653[b]
Negative	4	10.0	4	10.0	
MUM1					
Positive	18	45.0	18	45.0	0.698[b]
Negative	2	5.0	2	5.0	
Ki67					
High	16	40.0	10	25.0	0.047[a]
Low	4	10.0	10	25.0	

a: Chi-square test, b: Fisher test

Table 3. Immuno-expression of c-MYC between GCB and non-CGB DLBCL

DLBCL	c-MYC expression				p
	High	Low	High	Low	
	n	%	n	%	
GCB	17	42.5	3	7.5	< 0.001
Non-GCB	3	7.5	17	42.5	
Total	20	50	20	50	

Two independent observers (SFH and HE) observed all cases. No significant inter-observer results were obtained using an unpaired t-test (p = 0.000), and good inter-observer agreement was shown by kappa analysis (kappa = 0.952). We revealed their scores, and a kappa analysis was performed to reduce inter-observer bias. Any difference in scores was considered as discrepant. Such cases were reevaluated simultaneously by the two observers. The average of the two concordant scores was taken as the final score.

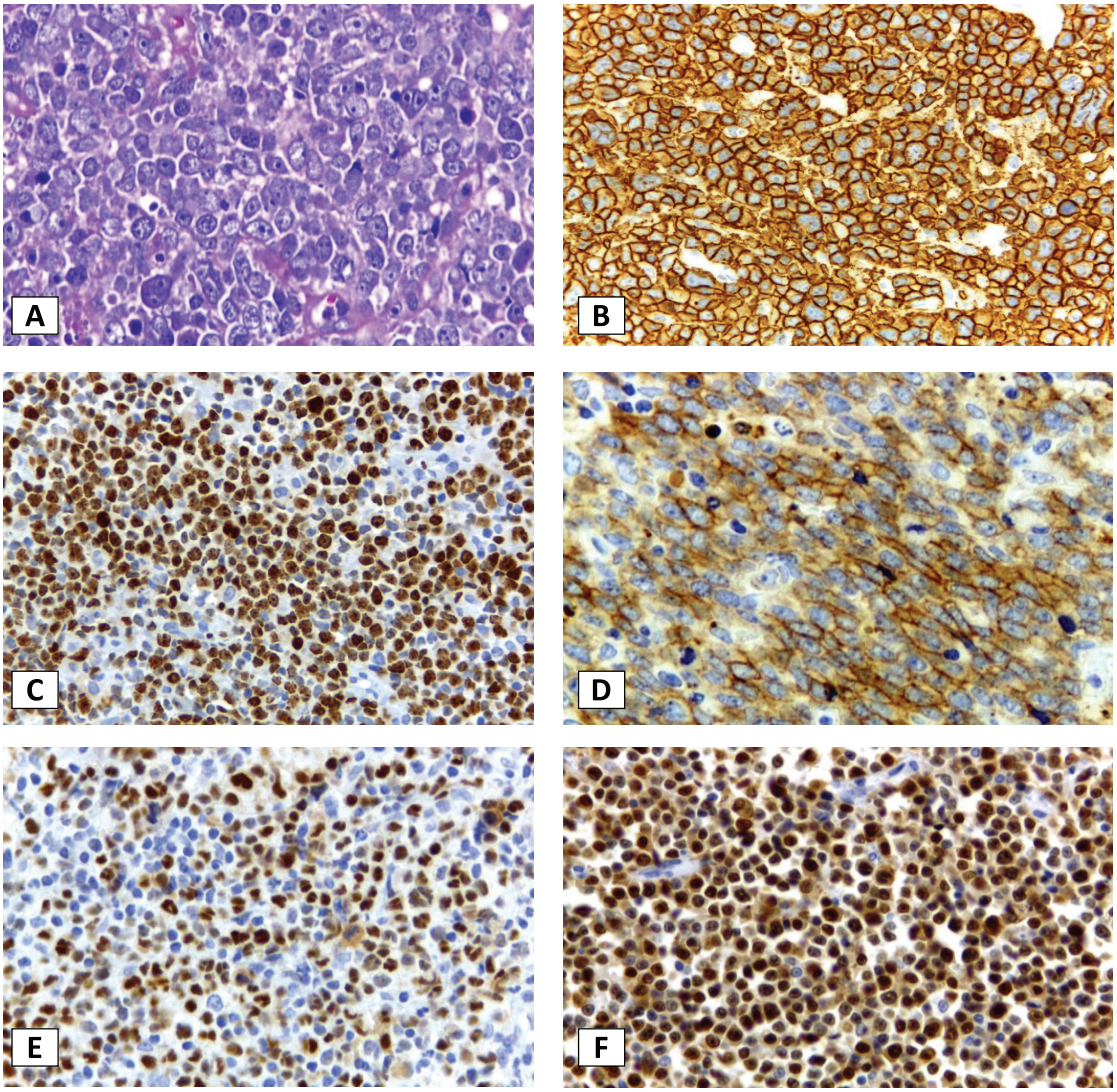

Figure 2. Representative IHC cases of immunophenotype profile in DLBCL patients.
(A) Centroblastic variant, the tumor cell shows a typical appearance (H&E, 400x), IHC DLBCL;
(B) CD20 staining, positive in the cell membrane (400x);
(C) Ki67 staining, positive in brown nuclear (400x);
(D) CD10 staining, positive in the cell membrane (400x);
(E) BCL6 staining, positive in nuclear (400x);
(F) MUM1 staining, positive in nuclear (400x).

DISCUSSION

A personalized treatment regimen for patients with cancer, particularly lymphoma, is more favorable and may become the main goal in the near future. Lymphoma sub-typing can make a great difference in therapy selection as there is unique heterogeneity and biological characteristics. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL); however, there is a lack of data about its prevalence or incidence [1,13,16–18].

Most of our patients were over 50 years old (median: 53 years old, 24–67 years). One study showed that DLBCL patients have a range of ages between 19 and 88 years, with a median age of 57 years. Another study showed it was found mostly in the 7th decade.1–4 As the aging process may cause DNA mutation, it is logical to hypothesize that the tumor incidence certainly increases with the aging process.

Extranodal lymphoma occurred more commonly than nodal lymphoma in our study (70% vs. 30%) since LNH

cases more commonly have an extranodal site in the gastrointestinal organ, Waldeyer ring area, tonsil, sinonasal, adenoid, spleen, bone marrow, and thymus [16]. Our study described similar results. Extranodal lymphoma can be found more frequently since lymphocytes also circulate in blood vessels and systemic circulation. Moreover, other experts assumed that it may be related to the migration process associated with chemokines and receptors in the tumor microenvironment or lymphoid cell homing and ligands of the endothelial veins [4,14,17].

Most cases of GCB subtype in our study had the centroblastic variant, while the non-GCB subtype had the immunoblastic variant, which is consistent with the results of another study. There was a significant difference in the morphologic features. It may because of the oncogenetic pathway of the GCB subtype that's derived from B cell migrating from the light zone containing a lot of centrocytes to the dark zone with numerous numbers of centroblast; while the non-GCB subtype is derived from the end of B cell differentiation in the light zone of germinal center before it differentiates into plasmablastic [1,4,9,13–19].

There is no definite standard procedure to asses c-MYC expression. De Silva & Klein [20] suggest a c-MYC cut-off point between 30% and 80%, with a median of 55%. In our study, we used our cut-off of 60.4% because DLBCL characteristics in the Indonesian population may be different from those in Asian or Western countries [3].

We found that high c-MYC expression was more common in the GCB subtype than in the non-GCB subtype (17 cases, 42.5% vs. 3 cases,7.5%). A previous study explained in their study that high c-MYC expression was found in 29-47% of DLBCL patients [20]. c-MYC gene is regulated in the light zone of the germinal center (GC), and then it subsequently re-enters the dark zone of GC, which is the same location as the GCB subtype [5-9]. Some experts have confirmed that B-cell activation with high MYC expression in the germinal center consistently involves T-cell activation and the microenvironment in the light zone of the GC. The role of activated-induced cytidine deaminase (AID), which also facilitates the process of chromosomal breaks in the MYC locus during the process of somatic hypermutation (SHM) and class switch recombination (CSR), may be related to genomic instability. All of the above mechanisms are hypothesized to cause higher MYC expression in GC, which is thus more commonly found in the GCB subtype of DLBCL.

The underlying DLBCL pathogenesis and biologic mechanisms of c-MYC associated with its immunophenotype profile are very complex. As a nuclear transcription factor, c-MYC plays an important role as it is correlated to multiple genes, signaling pathways, and regulatory processes in B cells, including the transcriptional repressors BCL6 and IRF4/MUM1. It is assumed that BCL6 and MUM1 could be involved in c-MYC deregulation in GC [21].

Interestingly, our study found both subtypes express high MUM1, which plays a role as the master regulator of plasma cells (non-germinal center). It is predominantly visible in the light zone of GC. The MUM1 cells (+) are more centrally located in the light zone and have plasma cell-like cytoplasm. Tsuboi et al. [22] described that the proportion of MUM1 is approximately 75% of all DLBCL. This phenomenon might be related to the findings that some B cells may undergo Class Switch Recombination (CSR) and activated-induced cytidine deaminase (AID) without accompanying somatic hypermutation (SHM) of variable regions in the IgH gene, and they are considered to account for aberrant MUM1 expression in the germinal center (GC) [2,22].

The number of DLBCL samples that can be used is limited, and clinical data (such as ethnic origin, disease history, and therapy response) are not as readily available. These limitations make it difficult to determine the relationship between biological behavior and the clinical picture of DLBCL patients in Indonesia, which is important information for future research on patient therapy and its results.

CONCLUSION

Our study has demonstrated that higher c-MYC expression is found more frequently in GCB subtypes. c-MYC expression may serve as marker for predicting survival in DLBCL patients both with GCB and non-GCB subtypes; however, further studies with larger sample sizes and longer follow-up periods are required.

DECLARATIONS

Competing Interest

The author(s) declare no competing interest in this study.

Ethical approval and consent to participate

The study has been approved by the Ethical Committee, Health Research Ethics Committee, and Institutional Review Board (IRB) at the Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo National General Hospital, Jakarta, by Ethical Clearance Number 340/UN2. F1/ETIK/2016

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