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The Association of BCL2 Expression with Proliferation Index Ki67 and Clinicopathology Aspect of Diffuse Large B-Cell Lymphoma

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ABSTRACT

Background
Diffuse Large B-cell Lymphoma (DLBCL) is the most common lymphoma. It has various histological patterns, grades, and poses challenges in therapy and prognosis The prognosis of DLBCL is determined by several factors, including immunophenotyping and genetics involving the BCL2 protein This study aims to determine the correlation between BCL2 expression and clinicopathological factors including age, gender, histopathological variants, and proliferation index Ki67 in DLBCL.

Methods
This study was an analytical observational study with a *cross-sectional* study involving 50 cases of DLBCL at Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar. BCL2 expression was evaluated by immunohistochemical staining and its expression was classified into positive and negative. A chi-square test was done to analyze the relationship between BCL2 expression with age, gender, morphology variant, and proliferation index Ki67 of DLBCL. Significance was determined at $p<0.05$.

Result
In this study, a total of 25 (75.8%) out of 33 cases of male patients had positive BCL2 expression, in contrast to female patient samples who showed more negative BCL2 examples. A total of 27 cases (69.2%) of all cases with high Ki67 index proliferation showed BCL2 positive. Bivariate analysis showed a significant relationship between gender ($p=0.005$) and Ki67 proliferation index ($p=0.047$) with BCL2 expression. There was no significant association between BCL2 expression with age and morphology variant.

Conclusion
There is a significant association between BCL2 with Ki67 expression and the clinicopathological aspect of gender in DLBCL. It provides additional prognostic information in conjunction with other clinicopathological parameters. It also can be considered to use Ki67 as one of the indicators of prognosis factors in DLBCL cases and considered as a substitute for BCL2 as one of the markers of DLBCL progressivity at Prof. Dr.I.G.N.G Ngoerah Hospital.

Keywords: diffuse large B-cell lymphoma, BCL2, Ki67

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INTRODUCTION

Large B-cell Non-Hodgkin Lymphoma (NHL) with the entity Diffuse Large B-cell Lymphoma (DLBCL) is the most common type of lymphoma, accounting for 80-85% of all cases. Patients usually came with major complaints single or multiple tumors, whether nodal or extranodal. DLBCL is an aggressive disease with heterogeneous characteristics, in terms of histology, genetics, morphology, and prognosis.[1]

In Indonesia, the NHL is the seventh most common cancer. The most common type of NHL in Asia, including Indonesia was DLBCL. [2] Approximately 64% of patients with DLBCL are found at an advanced stage of disease. Recent national epidemiology data on DLBCL is still very limited. The incidence of DLBCL peaks in the sixth decade, with a median age of 60-70 years. About 40% of cases are found in patients over 70 years of age.[1]

DLBCL has several morphology variants, including centroblastic, immunoblastic, anaplastic, and other variants. Each variant shows different morphology and biologic behavior. Some studies have found that immunoblastic variants have a poor prognostic effect on DLBCL. However, other studies have found different results. There are still many conflicts reported regarding the association of the morphological variants with prognosis in DLBCL.[3]

Currently, the therapeutic option of using the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) has become the first-line standard of care for DLBCL. However, 20% to 50% of DLBCL patients experience relapse or are refractory to first-line and are eligible for second-line and subsequent treatment. Unfortunately, once patients reach the third line regiment, few treatments are available and overall survival is less than 7 months.[4]

Various clinical, histopathological, molecular, and genetic factors have been associated with the prognosis of DLBCL patients. Clinical markers associated with the prognosis of DLBCL according to the International Prognostic Index (IPI) include age (cut off > 60 years), poor performance status at diagnosis, Eastern Cooperative Oncology Group (ECOG) ≥ 2, advanced tumor stage (Ann Arbor stage III-IV), high LDH levels and involvement of one extranodal gland. [4] The International Prognostic Index (IPI) has been used to predict the prognosis of DLBCL patients, but it still cannot fully explain the differences in treatment outcomes and relapse in DLBCL patients.[1] This certainly increases interest in finding and learning more about biomarkers that can identify the success of therapy and the possibility of relapse in DLBCL patients.

One of the biomarkers that is used to determine the prognosis of DLBCL is the Ki67 proliferation index. Examination of the Ki67 proliferation index by immunohistochemical method has been routinely performed and included as a basic panel in the diagnosis of DLBCL. An increase in Ki67 of more than 30% is said to be a high proliferation rate and is strongly associated with poor overall survival in DLBCL. However, several studies that examined the relationship between Ki67 and outcome in DLBCL still found contradictory and inconclusive results.[5–8]

Another biomarker that influences the prognosis of DLBCL is the B-cell lymphoma 2 (BCL2) protein. This protein plays a role in the regulation of apoptosis or programmed cell death, located in the inner mitochondrial membrane. BCL2 is an anti-apoptotic protein where cell oncogene activation is associated with an increase in the number of anti-apoptotic protein groups (BCL2, BCLXL, and MCL1). In DLBCL, BCL2 is expressed in 40-70% of cases. The co-expression of BCL2 and MYC proteins assessed by immunohistochemical examination known as "double expresser" is found in about 30% of DLBCL cases and is associated with poor prognosis when compared to DLBCL cases that do not express both proteins.[3,4]

BCL2 has a different function from Ki67. BCL2 is a protein that acts to inhibit the process of programmed cell death, which can result in the accumulation of damaged cells. On the other hand, BCL2 also has an antiproliferative effect on the G0/G1 phase cell cycle. [9] The existence of mutations and amplification in the gene encoding BCL2 cause high expression of BCL2 in DLBCL patients. Ki67 is a non-histone nuclear protein, which is synthesized in the early phase of the cell cycle and used to assess cell proliferation activity. Both BCL2 and Ki67 have often been used to assess the prognosis of DLBCL patients, but the assessment is mostly done separately with controversial results. In a

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study conducted by Rahimi et al, it was found that there was no significant relationship between BCL and Ki67 with the prognosis of DLBCL patients. A significant relationship was found between BCL2 and Ki67 where an increase in BCL2 expression was followed by an increase in Ki67 proliferation index in DLBCL.[10]

Research that correlates the combination of Ki67 and BCL2 cell proliferation levels with the prognosis of DLBCL patients was conducted by Tang et al. This study evaluated the prognostic value of the combination of BCL2 and Ki67 expression and found that DLBCL patients with BCL2/Ki67 coexpression showed poor survival.[11]

In the era of national health insurance, it will certainly be difficult to conduct various molecular examinations related to prognosis in DLBCL cases due to cost-efficiency constraints. For this reason, there is a need for research that links the prognosis of DLBCL with various clinical and pathology examinations that are routinely done and used as a standard for the diagnosis of lymphoma in Indonesia, especially in Bali, such as the association between clinical factors with the proliferation markers Ki67 and BCL2.

METHODS

This research was a cross-sectional analytical study. The study was performed at the Anatomical Pathology Laboratory of Prof. Dr. I.G.N.G Ngoerah Hospital from May 2023 to January 2024. The study population was all DLBCL cases. The target population was DLBCL cases whose tissues were examined at the Anatomical Pathology Laboratory of Prof. Dr. I.G.N.G Ngoerah Hospital during the period 1 January 2017 to 31 December 2022. Samples were selected using the total sampling method using the unpaired two-proportion sample formula. According to the minimal sample size, 50 cases were included in this study. The clinical data set included age at diagnosis, gender, and histopathological diagnosis were collected from the hospital management information system.

Inclusion criteria were DLCBL cases that had been diagnosed histopathologically and immunohistochemically with clinical data in the form of complete age and gender. Histopathological diagnosis involved centroblastic and immunoblastic types of DLBCL. Researchers want to assess the association of BCL2 expression with clinicopathological factors including age, gender, morphological variants, and Ki67 proliferation index in DLBCL.

BCL2 expression was evaluated by immunohistochemical staining with Leica mouse monoclonal antibody PA-0117 (1:200 dilution) using an Automatic Leica Bond-Max immunostainer. Immunostaining was done in formalin-fixed paraffin-embedded (FFPE) tissue retrieved from the archive at the Anatomical Pathology Laboratory of Prof. Dr. I.G.N.G. Ngoerah Hospital. Interpretation of BCL2 expression using a binocular light microscope Leica DM500 was conducted by the researcher and two pathologists. BCL2 expression was assessed in the tumor cell membrane, using a quantitative method by calculating the percentage of positive stained tumor cells using a microscope with low power magnification (40x). The BCL2 positivity score was divided into 0-4% (score 1), 5-25% (score 2), 26-50% (score 3), 51-75% (score 4), and >75% (score 5). [12] Then the scores were grouped into BCL2 negative for scores 1 to 3 and BCL2 positive for scores 4 and 5.

Ki67 proliferation index data was obtained from IHK examination data which was recorded on SIMARS RSUP Prof Dr. I.G.N.G Ngoerah. The Ki67 score was assessed as follows: 0-4% (score 1), 5-25% (score 2), 26-50% (score 3), 51-75% (score 4), 76-90% (score 5), and > 90% (score 6). [13] The scores were then grouped into 2 groups, which are the low proliferation index group for scores 1 and 2; and the high proliferation index group for scores 3 to 6. Data was processed using the Statistical Package for the Social Sciences (SPSS) 27.0 for Windows. Data were analyzed using Pearson's Chi-square method to analyze the relationship between BCL2 expression and age, gender, morphology variants, and Ki67 index. Spearman correlation test was then performed to assess variables that were significantly correlated. The significance value was determined at $p < 0.05$.

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RESULT

The patient's age ranges from 7-75 years old, with a mean age of 54.86 ± 2.437 years with an age. A total of 32 people (64%) with age < 60 years, and 18 people (36%) with age ≥ 60 years. Male gender was more dominant than female with 33 cases (66%) and 17 cases (34%) were female. DLBCL morphological variants were found in 39 cases (78%) including centroblastic variants and 11 cases (22%) were immunoblastic variants. For the Ki67 proliferation index, it was found that more DLBCL showed a high proliferation rate, which was 39 cases (78%), and the rest with low proliferation rate, which was 11 cases (22%). BCL2 expression was found positive in 31 cases (62%) and negative in 19 (38%) cases. All clinicopathological characteristics are summarized in Table 1.

Table 1. Subject Characteristics.

Parameter	Total	Percentage (%)
Age (years old)		
≥60	18	36
<60	32	64
Gender		
Male	33	66
Female	17	34
Morphology variant		
Centroblastiv	39	78
Imunoblastic	11	22
Ki67 expression		
Low	36	22
High	31	78
BCL2 expression		
Negative	19	38
Positive	31	62

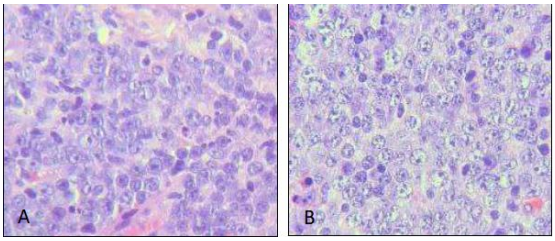


Figure 1A-B. DLBCL morphology variant. A. Imunoblastic variant. B. Centroblastic variant.

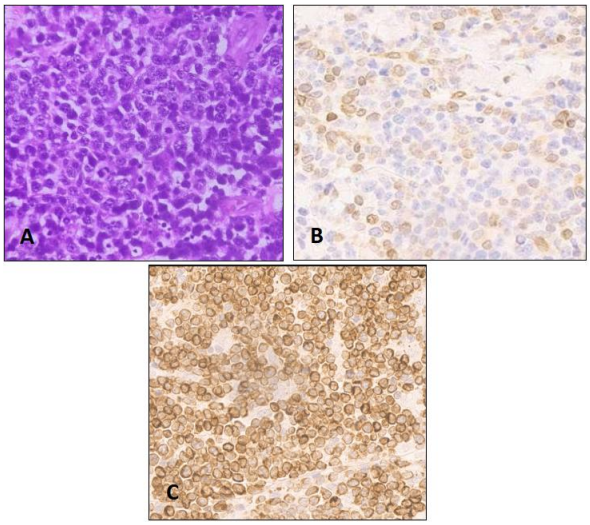


Figure 2A-C. A. DLBCL histopathology (HE, 400 times). B. BCL2 expression negative (score 2). C. BCL2 expression positive (score 5) (IHC BCL2,.400 times)

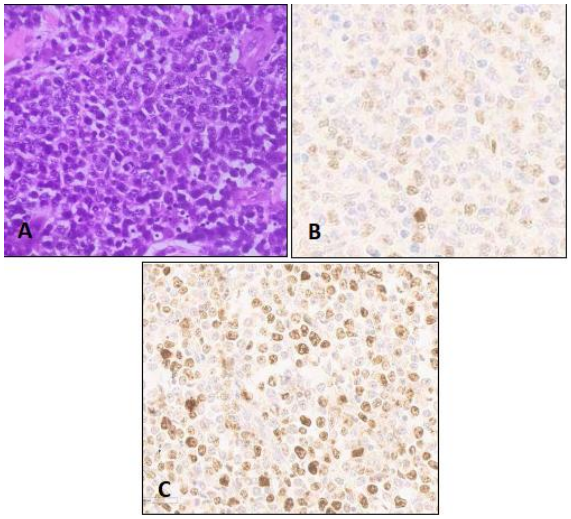


Figure 3. A. DLBCL histopathology (HE, 400 times). B. Ki672 expression low proliferation index (score 2). C. Ki67 expression high proliferation index (score 5) (IHC Ki67, 400 times)

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In the patients with age ≥60 and <60 years old there were more cases with BCL2 positive, respectively 13 (72.2 %) cases and 18 (56.3%) cases. A total of 25 (75.8%) out of 33 cases of male patients had positive BCL2 expression, in contrast to female patient samples who showed more negative BCL2 examples (p = 0.005). In cases with positive BCL2 expression, 25 cases (80.64%) showed centroblast morphology variants and 6 cases (19.35%) showed immunoblast morphological variants. In cases with negative BCL2 expression, 14 cases (73.68%) showed centroblast morphology variants and 5 cases (26.31%) showed immunoblast morphological variants. Chi-square analysis showed there is no significant relationship between BCL2 expression and morphological variants (p = 0.564). A total of 27 cases (69.2%) from 39 cases with high Ki67 index proliferation showed BCL2 positive, in contrast with 7 (63.6%) from 11 patients with low Ki67 proliferation index showing negative BCL2 expression. Chi-square analysis showed a significant relationship between the Ki67 proliferation index and BCL2 expression (p = 0.047). Overall, there was a significant association between gender and Ki67 proliferation index with BCL2 expression, but no significant association between age and morphology variant with BCL2 expression as shown in Table 2.

Table 2. The association between BCL2 expression with age, sex, morphology variant, and Ki67 proliferation index.

Variable	BCL2 expression		Total	*p-value*
	Positive	Negative		
Age (years old)				0.264
≥60	13 (72.2%)	5 (27.8%)	18	
<60	18 (62%)	14 (43.8%)	32	
Gender				0.005
Male	25 (75.8%)	8 (24.2%)	33	
Female	6 (35.3%)	11 (64.7%)	17	
Morphology variant				0.564
Centroblast	25 (64.1%)	14 (35.9%)	39	
Imunoblast	6 (54.5%)	5 (45.5%)	11	
Ki67 proliferation index				0.047
High	27 (69.2%)	12 (30.8%)	39	
Low	4 (36.4%)	7 (63.6%)	11	

p-value <0.05

Furthermore, the Spearman correlation test was conducted to assess the strength of the correlation between the Ki67 proliferation index and BCL2 expression. The test found a positive correlation with a significance level of 0.047 (p<0.05).

Table 3. Correlation test results between Ki67 proliferation index and BCL2 expression.

Variable	Median	Koefisien r	p
Ki67 (%)	75 (2-95)	0.391	0.047
BCL2 (%)	75 (0-100)		

p-value < 0.05

DISCUSSION

Lymphomas are a heterogeneous group of disorders with wide morphology, geographical, and clinical spectrum variations. The most common type of them is Diffuse Large B-cell Lymphoma (DLBCL). Various clinical, histopathological, molecular, and genetic factors have been associated with the prognosis of DLBCL patients but have not completely explained relapse or poor response to therapy.

The prognosis of DLBCL is based on the clinical features of The International Prognostic Index (IPI), including poor performance status at diagnosis (Eastern Cooperative Oncology Group/ECOG ≥ 2), age, advanced tumor stage (Ann Arbor stage III-IV), high LDH levels and involvement of one extranodal gland. Other factors affecting prognosis include tumor size (≥ 10 cm), gender, vitamin D deficiency, low body mass index, serum IgM elevation, lymphocyte/ monocyte count, and concordance of bone marrow results. Some immunohistochemical markers such as the Ki67 index, which is associated with tumor cell proliferation, are also often associated with age, clinical variables, and cell of origin (COO).[1,3,14,15]

In this study, it was found that most DLBCL cases were at the age of <60 years

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(64%). The youngest DLBCL patient was 7 years old and the oldest was 92 years old. Previous research conducted in Indonesia also found the same thing, where DLBCL was mostly found at the age of 45 to 64 years.[16] Most cases in this study were found in men (66%). This finding is in line with the literature that DLBCL is more common in men than women. [3,17] Meta-analysis research conducted by Yildirim, et al also found that DLBCL cases were more common in men than women. [18] The relationship between BCL2 expression and gender was found significant in our study (p=0.007). DLBCL does occur more in males than females. Gender factors are prognostic in DLBCL, including data on better survival for women receiving rituximab-based therapy. [18] The impact of gender on the outcome of patients with DLBCL has been discussed controversially. From nonrandomized comparisons, it appears that the negative impact of male gender is more pronounced in DLBCL patients treated with R-CHOP–like chemotherapy than with chemotherapy alone. Rituximab clearances between males and females drift apart with increasing age, elderly females have a highly significantly slower rituximab clearance (and hence higher serum levels and longer exposure times) compared with elderly males. [18,19]

In this study, there was no significant association between BCL2 expression with age and morphology variant. Elderly has an unfavorable prognostic factor that correlates with lower survival in DLBCL.[20] BCL2 has a role as an anti-apoptotic. There is a tendency for the apoptosis index to increase with age, which may be related to the role of human growth factor (hGH) controlled by insulin-like growth factor 1 (IGF-1).[21] Several studies have shown that IGF-1 can prevent apoptosis and the concentration of IGF-1 in the blood decreases with age.[22]

Positive BCL2 expression is dominated by centroblastic morphological variants, but no significant relationship was revealed between BCL2 expression and DLBCL morphological variants (p=0.405). The centroblastic morphology variant is the most common in DLBCL and is characterized by medium to large lymphoid cells with vesicular nuclei containing fine chromatin. There are 2-4 nucleoli near to nuclear membrane and little basophilic cytoplasm. Some recent studies have associated the morphological variant with IGH/MYC rearrangement, and not with BCL2 or BCL6 rearrangement. [13] A study conducted by Grange et al. (2004) stated that there was no significant relationship between BCL2 expression and immunoblast or centroblast morphological variants in primary cutaneous large B-cell lymphomas.[23] This is in line with the results obtained in this study.

A total of 27 (69.2%) DLBCL cases with a high Ki67 proliferation index had positive BCL2 expression, while 12 cases (30.8%) had negative expression. Of the 11 DLBCL cases with low proliferation index, 7 cases (63.6%) had negative BCL2 expression and 4 cases (36.4%) had positive expression. Ki67 immunohistochemistry is a marker of cell proliferation that is assessed based on the percentage of cell nuclei stained. Many studies have confirmed the diagnostic and prognostic role of the Ki67 index in cancer. On the one hand, a high Ki67 index signifies the aggressive nature of the tumor and hence a poor prognosis; alternatively, a high proliferation index also leads to a better response to chemotherapy in many tumors. Ki67 is involved in cell proliferation and BCL2 is involved as anti-apoptosis, both of which play important roles in determining tumor growth and prognosis.[24] In theory, Ki67 is a marker of active cell proliferation in both normal and tumor cell populations, especially in dividing cells/mitosis. Ki67 protein will be expressed in all active phases of the cell cycle: at the end of G1 phase, S phase, G2 phase, and peak at M phase. However, Ki67 will disappear rapidly after cell division and is not expressed in G0 phase. Low So during the cell cycle, Ki67 expression may vary. [7,25] This is probably why Ki67 expression was found in the DLBCL case above. An increase in Ki67 of more than 30% is considered a high level of proliferation and is strongly associated with poor overall survival in DLBCL. However, several studies that examined the relationship between Ki67 and outcome in DLBCL still found contradictory and inconclusive results. [26,27] We believe it may be based partly on the different threshold values used to define high vs. low Ki67 expression status and interobserver variability in interpreting expression.

In theory, BCL2 has a different function from Ki67. BCL2 is a protein that acts to inhibit the process of programmed cell death so that it

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can result in the accumulation of damaged cells. On the other hand, BCL2 also has an antiproliferative effect on the G0/G1 phase cell of BCL2 in DLBCL patients. [9] Ki67 is a nonhistone nuclear protein, which is synthesized in the early phase of the cell cycle and used to assess cell proliferation activity. Both BCL2 and Ki67 have been frequently used to assess the prognosis of DLBCL patients, but the assessment is mostly done separately with controversial results. In a study conducted by Rahimi, et al, it was found that there was no significant relationship between BCL2 and Ki67 with the prognosis of DLBCL patients. A significant relationship was found between BCL2 and Ki67 where an increase in BCL2 expression was followed by an increase in Ki67 proliferation index in DLBCL. This finding in line with the results obtained in this study, where a significant positive correlation was found between the high proliferation index of Ki67 and positive expression of BCL2, which means that an increase in Ki67 proliferation index is in line with an increase in BCL2 expression. Tang et al. reported a study linking the combination of Ki67 and BCL2 cell proliferation levels with the prognosis of DLBCL patients. This study evaluated the prognostic value of the combination of BCL2 and Ki67 expression and found that DLBCL patients with BCL2/Ki67 coexpression showed poor survival.[11]

BCL2 is topographically restricted to proliferating cells and patients who have a longer lifespan with impaired apoptosis. In studies related to oral squamous cell carcinoma (OSCC), there is a positive correlation between BCL2 and Ki67 expression. This suggests that although BCL2 is overexpressed in the early stages of OSCC, the expression is affected by the proliferation potential induced by Ki67. Moreover, this study suggests that this correlation between Ki67 and BCL2 is directly related to the improvement of histological grade. Nevertheless, considering the gaps and inconsistencies in the literature, future studies with large samples are needed to validate the hypothesis.[28]

CONCLUSION

Based on the results of this research, it can be concluded that there is a significant relationship between BCL2 with Ki67 expression and the clinicopathological aspect of gender in DLBCL. The positive correlation between a high Ki67 proliferation index and BCL2 expression, whereas a high cell proliferation index can be in line with and followed by increased BCL2 expression in DLBCL. The positive correlation between Ki67 proliferation index and BCL2, it can be considered to use Ki67 as one of the indicators of prognosis factors in DLBCL cases and considered as a substitute for BCL2 as one of the markers of DLBCL progressivity at Prof. Dr. I.G.N.G Ngoerah Hospital.

Further research that links the combination of BCL2/Ki67 expression with survival rate in DLBCL is needed with larger samples and multicentre and involving various related fields of science to further strengthen the results of this study so that they can be applied to clinical practice guidelines for DLBCL cases.

Research Ethics

This research has received approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Udayana with no. 849/UN14.2.2.VII.14/LT/2023.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this research.

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