

## Role of Cell-Origin Profiling Using Immunohistochemistry to Predict the Survival of Patients with Diffuse Large B-Cell Lymphoma in Indonesia

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### ABSTRACT

**Background** Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma in Asia and Indonesia. DLBCL could be further classified according to cell of origin as the germinal center B-cell (GCB) subtype or the non-germinal center B-cell (non-GCB) subtypes; of these, the non-GCB subtype usually has poorer prognosis. The purpose of this study is to determine the relationship between the cell-origin subtype and 3-year overall survival of patients with DLBCL at Kariadi General Hospital Semarang.

**Methods** This research represents an observational analytical study of 36 patients with DLBCL who visited Kariadi General Hospital between January and August 2017. Data on age of diagnosis, tumor location, disease stage, and 3-year overall survival were collected. DLBCL subtype was determined via immunohistochemical examination of CD10, BCL6, and MUM1 protein expression. Data analyses, including the chi squared test and Kaplan-Meier curves, were conducted.

**Results** The study population included 18 patients with GCB-subtype DLBCL and 18 patients with non-GCB-subtype DLBCL. No significant difference ( $P = 0.171$ ) between disease stage and cell-origin subtype was noted between groups. Patients with the non-GCB subtype had a 3-year overall survival that was significantly worse than that of patients with the GCB subtype ( $P = 0.026$ ). Moreover, the 3-year survival rate of patients with the non-GCB subtype of the disease was 38.9% while that of patients with the GCB subtype was 77.8%. Patients with advanced stages of DLBCL also had a 3-year overall survival that was significantly worse than those of patients with early stages of the disease ( $P < 0.001$ ), with the 3-year survival rate of patients with advanced stage was 14.3%.

**Conclusion** Patients with non-GCB-subtype DLBCL or advanced stages of the disease have a lower 3-year overall survival rate and poorer prognosis compared with those with other subtypes or earlier stages of the disease.

**Key words** diffuse; Indonesia; large B-cell; lymphoma; survival rate

Lymphoma, a malignancy arising from lymphoid tissue, can be divided into two main groups: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Over 85% of all lymphoma cases in the world are NHL, and more than 90% of these cases could be classified as mature B cells NHL.<sup>1, 2</sup> In Indonesia, NHL is the seventh most common cancer. The most common type of NHL in Asia, including Indonesia, is diffuse large B-cell lymphoma (DLBCL). Approximately 64% of all patients with DLBCL are found in advanced stages of the disease (Ann Arbor stages III and IV).<sup>1-3</sup>

DLBCL is an aggressive B-cell NHL characterized histologically by a diffuse pattern of malignant lymphoid cells expressing various B cell markers, including CD20, CD79a, CD19, CD22, PAX5, BOB1, and OCT2; the cells also have a high Ki-67 proliferation index.<sup>2-4</sup> DLBCL can be classified into two subtypes according to the molecular profile of the original cells, namely germinal center B-cell type (GCB) and non-germinal center B-cell type (non-GCB), by immunohistochemical examination of CD10, BCL6 and MUM1.<sup>2, 5, 6</sup> In general, GCB-subtype DLBCL has better prognosis and overall survival compared with the non-GCB subtype.<sup>2, 7</sup>

Case data of lymphoid tissue malignancies in Indonesia are neither well developed nor widely available. The accurate diagnosis of DLBCL cases in Indonesia is also complicated by the general lack of immunohistochemical examination. Achieving a complete diagnosis of DLBCL, including its molecular subtype, is very important to support immunotherapy efforts and predict the prognosis of affected patient. This study aims to determine the prevalence of DLBCL patients based on its cell of origin immune-profile and its correlation with clinical features and 3-year overall survival, in Kariadi General Hospital Semarang.

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Received 2020 August 21

Accepted 2021 April 26

Online published 2021 May 20

Abbreviations: DLBCL, Diffuse Large B-Cell Lymphoma; GCB, Germinal Center B-cell; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

## MATERIALS AND METHODS

### Patients and methods

This research represents an observational analytical study with a retrospective cohort design. A total of 36 patients who had been diagnosed with DLBCL based on histopathological and immunohistochemical examinations, including diffuse CD20 and high Ki-67 expression, by the Anatomical Pathology Laboratory of Kariadi General Hospital, Semarang, which is the top referral hospital in Central Java, Indonesia, between January and August 2017 were recruited to this study. The patients were followed-up for 3 years after diagnosis and treatment to determine their 3-year overall survival. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Diponegoro University (Authorization number: 106/EC/FK-RSDK/III/2018).

### Immunohistochemistry examination method

DLBCL specimens from all patients were prepared into paraffin blocks and sectioned into approximately 4  $\mu$ m thick slices by using a microtome. One section each was used for CD10 staining, BCL6 staining, and MUM1 staining. Paraffin sections were deparaffinized using xylene, rehydrated using ethanol and washed in phosphate buffered saline (pH 7.4).

Antigen retrieval using Tris-EDTA buffer (PH 9) was conducted in a microwave for 10 min at 750 W and 15 min at 350 W and slide staining used monoclonal antibodies of CD10, BCL6 and MUM1 (Leica Biosystem, Newcastle, UK) at 1: 100 dilution. All stained slides were examined at 100 $\times$  and 400 $\times$  magnification, and positivity was determined. CD10 expression was considered positive if immunostaining localized in the plasma membrane of malignant lymphoid cells was observed, BCL6 and MUM1 expression were considered positive if immunostaining localized in the nucleus was noted. According to the Hans algorithm, the germinal center B-cell (GCB) subtype was defined as CD10+ or BCL6+ and MUM1-, and all others (CD10- and BCL6- or CD10- and MUM1+) were defined as the non-GCB subtype.<sup>8</sup>

### Statistical methods

The clinical features of the patients, including age of diagnosis (age > 50 years vs. age < 50 years), tumor location (nodal, extra nodal), Ann Arbor tumor stage [early stage (stage I and II) vs. advanced stages (stage III and IV)], and cell-origin subtype based on immunohistochemical examination of CD10, BCL6 and MUM1 were collected. The overall survival of a patient was evaluated in terms of number of months they remained

alive from diagnosis until August 2020. Data analysis was carried out using Statistical Package for Social Sciences (IBM SPSS statistic, version 21, IBM Chicago, IL). Correlations between variables were analyzed using the chi squared test with a significance level of < 0.05, and survival analysis was conducted using Kaplan-Meier curves with the log-rank test.

## RESULTS

### Clinicopathological features of the patients

Thirty-six patient with DLBCL at Kariadi General Hospital were included in this study. Most (52.8%) of the patients were diagnosed at an age of over 50 years, with a median age of diagnosis of 52 years. The majority of the patients had tumors at extra nodal locations (75%). The most common location of extra nodal tumors included the gastrointestinal tract, liver, spleen, kidney, nasal cavity, mediastinum, tonsils, palpebra, conjunctiva, central nervous system, and femur. The most common locations of nodal tumors included the cervical, inguinal, axillary, and submandibular lymph nodes; the tumors could be observed singly or in multiple clusters. In terms of Ann Arbor staging, most of the patients had early-stage DLBCL (61.1%; Table 1).

### Clinicopathological features according to cell-origin subtype

In terms of cell-origin subtype, 18 patients (50%) had the GCB subtype, while 18 patients (50%) had the non-GCB subtype (Fig. 1). Three years after diagnosis and receiving R-CHOP treatment, 15 patients (41.7%) died.

Among the patients with GCB-subtype DLBCL in this study, 55.5% were diagnosed at older than 50 years of age, 72.2% had tumors with extra nodal locations, and 72.2% were at early stages of the disease. Among patients with non-GCB subtype DLBCL, 50% were diagnosed at older than 50 years of age, 77.8% had tumors with an extra nodal location, and 50% were at early stages of the disease. No significant difference and correlation between age of diagnosis, location, and stage with cell-origin subtype of DLBCL was observed (Table 2).

### Overall survival of patients

After 3 years of follow-up, 15 patients died and 21 patients survived. Among the 15 patients who died, 4 had the GCB subtype and 11 had the non-GCB subtype. Therefore, at the end of the follow-up period, 14 patients with GCB-subtype DLBCL survived (77.8%) and 7 patients with non-GCB-subtype DLBCL survived (38.9%). The median survival of non-GCB patients was 6 months.

**Table 1. Clinicopathological features of DLBCL patients (n = 36)**

	Frequency	Percentage
Age of diagnosis	51.83 ± 14.08 years (median: 52 years, min: 22 years, max: 77 years)	
Age category		
< 50 years	17	47.20%
> 50 years	19	52.80%
Location		
Nodal	9	25%
Extra nodal	27	75%
Stage		
Early (I, II)	22	61.10%
Advanced (III, IV)	14	38.90%
Cell-origin subtype		
GCB	18	50%
Non GCB	18	50%
3-year overall survival		
Alive	21	58.30%
Dead	15	41.70%

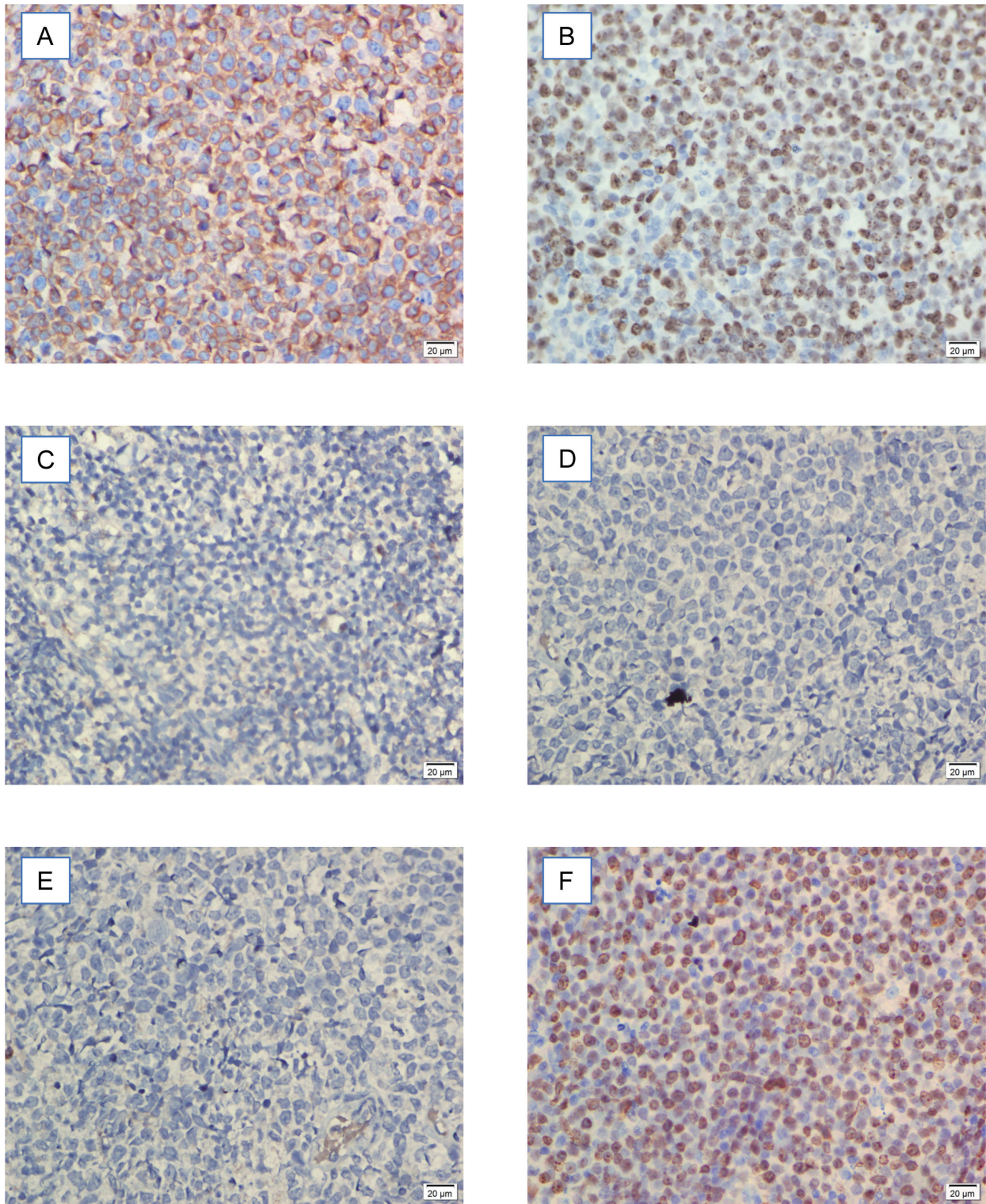
In terms of disease stage, among the 15 patients who died during follow-up, 3 had early-stage DLBCL and 12 had advanced-stage DLBCL. Therefore, 18 patients with early-stage DLBCL survived (86.4%) and 2 patients with advanced-stage DLBCL survived (14.3%) until the end of follow up. The median survival time of patients with advanced-stage DLBCL was 5 months (Fig. 2).

## DISCUSSION

In this study, 36 patients with DLBCL who visited Kariadi General Hospital Semarang between January 2017 and August 2017, were followed-up for the next 3 years to determine their 3-year overall survival and the clinical factors influencing survival, including age at diagnosis, tumor location (nodal/extra nodal), Ann Arbor tumor stage, and cell-origin subtype (GCB/non-GCB) by using immunohistochemical examination. Patients with DLBCL are usually diagnosed at an older age, with a median age in the sixth or seventh decade; however, some patients are diagnosed at a younger age. Several studies conducted in East Asia have reported that the median age of patients with DLBCL at the time of diagnosis is the fifth decade.<sup>9, 10</sup> These previous findings coincide with the result of the present study, where the age of diagnosis of patients with DLBCL is approximately 51 years; the youngest patient was diagnosed at 22 years, and the oldest patient was diagnosed at 77 years. Patients with GCB-subtype DLBCL in this

study were more likely to be diagnosed at age of > 50 years, while those with non-GCB-subtype DLBCL were diagnosed at equal proportions of less than 50 years and more than 50 years. No significant difference between age of diagnosis and cell-origin subtype of DLBCL was noted in this study. This finding is in line with previous studies showing that patients with GCB-subtype DLBCL are more likely to be diagnosed at an older age than non-GCB patients; No significant difference and correlation between age of diagnosis with cell-origin subtype of DLBCL were noted.<sup>11–13</sup>

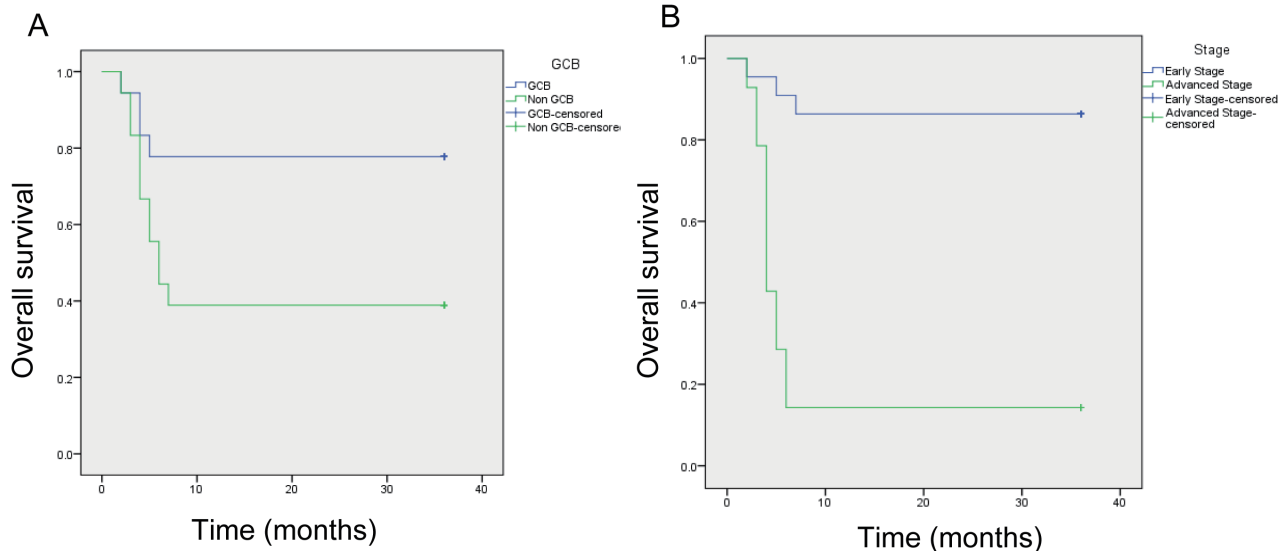
Nearly 50% of the patients with DLBCL were diagnosed with stage I or II (early stage) disease without a PET/CT scan. If a PET/CT scan was added as an examination, the prevalence of stages I and II DLBCL patients may be reduced. While approximately 64% of all DLBCL patients had stage III or IV disease, in other studies in Asia, DLBCL patients (52–60%) were slightly more likely to be classified with stage I or II disease.<sup>14–16</sup> In the present study, most patients with DLBCL at the Kariadi General Hospital had stage I or II (61.1%) disease according to the results of the CT scan of the patient. Approximately 72.2% of the patients with GCB-subtype DLBCL in this study were diagnosed at stage I or II, while 50% of the patients with non-GCB-subtype DLBCL were diagnosed at stage I or II; the rest were diagnosed with stage III or IV disease. Therefore, no significant difference and correlation were found between disease stages and cell-origin subtype. Previous



**Fig. 1.** A: CD10 positivity in GCB (germinal center B-cell) DLBCL (diffuse large B-cell lymphoma). B: BCL6 positivity in GCB DLBCL. C: MUM1 negativity in GCB DLBCL. D: CD10 negativity in non-GCB DLBCL. E: BCL6 negativity in non-GCB DLBCL. F: MUM1 positivity in non-GCB DLBCL. Bar = 20 µm.

**Table 2. Correlation of age of diagnosis, location, and stage with the cell-origin subtype of DLBCL**

	GCB	Non GCB	<i>P</i>
<b>Age of diagnosis</b>			
< 50 years	8 (44.5%)	9 (50%)	0.738
> 50 years	10 (55.5%)	9 (50%)	
<b>Location</b>			
Nodal	5 (27.8%)	4 (22.2%)	0.7
Extra nodal	13 (72.2%)	14 (77.8%)	
<b>Stage</b>			
Early (I, II)	13 (72.2%)	9 (50%)	0.171
Advanced (III, IV)	5 (27.8%)	9 (50%)	



**Fig. 2.** Three-year overall survival of patients with DLBCL. **A:** Based on cell-origin subtype (GCB vs. non-GCB). **B:** Based on clinical stage (early vs. advanced).

studies indicated no significant differences between nodal/extra nodal location and cell-origin subtype of DLBCL.<sup>17–19</sup>

The results showed that the proportions of patients with GCB- and non-GCB-subtype DLBCL at Kariadi General Hospital Semarang are relatively equal (50%); previous studies in Europe and the USA revealed a slightly higher proportion (60%) of patients with GCB subtype DLBCL. Differences in frequency between GCB and non-GCB DLBCL are highly dependent on the geographical location, race, median age of the patient population and methodology used by researchers. However, the proportion of patients with non-GCB subtype DLBCL in Asian countries is generally lower than that of the rest of the world. This difference in

proportion may be closely related to the characteristics of race and geographical location. These previous findings coincide with the result of the present study, where patients with GCB-subtype had a lower proportion (50%).<sup>2, 19, 20</sup>

Survival analysis by the log-rank test indicated that patients with non-GCB subtype DLBCL generally have significantly lower overall survival (38.9%) compared with those with the GCB subtype (77.8%). The median survival time of non-GCB DLBCL patients was 6 months. Patients with advanced-stage DLBCL also showed significantly lower overall survival (14.3%) compared with those with early-stage DLBCL (86.4%). The median survival time of patients with advanced-stage was 5 months (Table 3). Patients with

**Table 3. Overall survival of patients based on cell-origin subtype and disease stage**

	Number of events (% survival)	P
All DLBCL patients (n = 36)	15 (58.3%)	
GCB subtype	4 (77.8%)	0.026
Non-GCB subtype	11 (38.9%)	
All DLBCL patients (n = 36)	15 (58.3%)	
Early (n = 22)	3 (86.4%)	< 0.001
Advanced (n = 14)	12 (14.3%)	

GCB-subtype DLBCL are known to have a better prognosis and higher overall survival and progression free survival than those with the non-GCB subtype. Patients with GCB-subtype DLBCL had a 1-year overall survival rate of 90% and a 2-year survival rate of 74%. By comparison, patients with non-GCB-subtypes DLBCL had a 1-year overall survival rate of 61% and a 2-year survival rate of 46%; these values are generally lower than those obtained for the GCB subtype.<sup>2, 13, 18</sup> The present study obtained similar results, that is, patients with GCB-subtype DLBCL at Kariadi General Hospital have significantly better 2-year overall survival (77.8%) compared with those with the non-GCB subtype (38.9%). The overall survival of patients with GCB-subtype DLBCL is comparable with that of the same group in other studies (77.8% vs. 74%). Among patients with GCB-subtype DLBCL who died in the first year of this study, four had an advanced tumor stage, and 2 showed MUM1 overexpression or was triple-positive for CD10, BCL6 and MUM1. Earlier research demonstrated that patients with GCB-subtype DLBCL and triple positive for CD10, BCL6 and MUM1 have lower overall survival compared with those with classic GCB-subtype DLBCL (i.e., positive CD10, positive BCL6 and negative MUM1).<sup>21, 22</sup>

In this study, patients with non-GCB subtype DLBCL in Semarang had lower overall survival compared with those with non-GCB subtype DLBCL in other studies (38.9% vs. 46%). The difference observed could be due to the large number of patients with non-GCB subtype DLBCL who died in the first year of the study; among the 12 patients who died, 9 (75%) were at an advanced tumor stage. Patients with non-GCB subtypes DLBCL are known to have poor prognosis. The inferior prognosis of non-GCB subtype DLBCL is related to the presence of more mutations in non-GCB subtype DLBCL than in the GCB subtype. In the non-GCB subtype of DLBCL, mutations were found in at least 20 growth regulating genes, including BCL6, INK4, PRDM1, TNFAIP3, SPIB, CARD11, MYD88, MYC, BCL2, NFKB, CD79A, CD79B, CREBBP, E300,

MLL2, MEF2B, MEF2B, TBL1, NOTCH1, NOTCH2, BRAF, and TP53. By comparison, in the GCB subtypes of DLBCL, mutations were found in at least seven growth-regulating genes, namely, BCL2, EZH2, CREBBP, TNFRSF14, GNA13, SGK1, and C-REL.<sup>23–25</sup>

In conclusion, patients with non-GCB subtypes DLBCL have significantly lower 3-year overall survival than those with the GCB subtype (38.9% vs. 77.8%;  $P = 0.026$ ). Patients with advanced stages of the disease also had significantly lower overall survival compared with those at early stages (14.3% vs. 86.4%;  $P < 0.001$ ).

*Acknowledgments:* This study was financially supported by a research grant from the Faculty of Medicine, Diponegoro University, Semarang, Central Java, Indonesia

*The authors declare no conflict of interest.*

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