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Clinicopathological Characteristics of Diffuse Large B-Cell Lymphoma Not Otherwise Specified in Dr. Hasan Sadikin General Hospital Bandung from 2018 to 2023

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ABSTRACT

Introduction
Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS), is the most common group of non-Hodgkin malignant lymphoma globally, representing 25%-40% of adult lymphoma cases. According to the cell of origin(COO), DLBCL NOS is classified into DLBCL germinal center B-cell like(GCB) and DLBCL non-germinal center B-cell like(non-GCB). Since the COO affects the prognosis of DLBCL NOS, this examination is important. Hans algorithm is the most frequently used to distinguish the GCB from non-GCB. This study aims to describe clinicopathological characteristics of DLBCL NOS at Dr. Hasan Sadikin General Hospital Bandung, 2018-2023.

Methods
The subjects of this retrospective descriptive study were DLBCL GCB and non-GCB patients based on Hans algorithm by IHC examination of CD10, BCL6, and MUM1 who received R-CHOP therapy at Dr. Hasan Sadikin General Hospital from 2018 to 2023. All data contained age, gender, B-symptoms, primary tumor location, stage, total International Prognostic Index (IPI) score, and immunochemotherapy status.

Results
A total of 55 patients diagnosed with DLBCL NOS were collected in this study. 50 patients(90.9%) were classified as DLBCL non-GCB and 5 patients(9.1%) were classified as DLBCL GCB. The average age was 62 years, predominantly males(52.7%), extranodal disease(54.5%), no B symptoms(76.4%), and early stage(83.7%). 52 patients(94.6%) had a total IPI score of 0-1, 3 patients(5.4%) had a total IPI score of 2. 21 patients(38.2%) had a response, 13 patients(23.6%) had non-response, and 21 patients(38.2%) are still ongoing to R-CHOP therapy.

Conclusion
DLBCL NOS at Dr. Hasan Sadikin General Hospital from 2018-2023 mainly occurred in men with an average 62 years old and extranodal disease without B-symptoms. DLBCL non-GCB was predominant than GCB. Both DLBCL Non-GCB and GCB were mostly diagnosed at early stage, IPI low-risk group, and had response status to R-CHOP therapy similar to those are still ongoing to R-CHOP therapy.

Keywords: DLBCL NOS, Hans algorithm, DLBCL GCB, DLBCL non-GCB

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INTRODUCTION

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) is a non-Hodgkin malignant lymphoma (NHML) with a diffuse growth pattern consisting of medium to large B cells and large nuclei or larger than macrophage's nuclei or more than twice of the size of small lymphocyte's nuclei.[1] Based on the Global Burden of Cancer Study (GLOBOCAN) in 2022, NHML was 10th place of malignancy in the world with an incidence of 553.389 cases and 7th place of malignancy in Indonesia. The incidence of NHML in Indonesia was about 16.175 cases with more than 50% of the cases were death.[2] Data of cancer registration period 2008-2014 at the Dr. Hasan Sadikin General Hospital Bandung as a tertiary hospital in West Java, Indonesia reported that were 2.980 cases of lymphoma.[3]

DLBCL NOS is the most common of NHML subtype in the world, representing 25%-40% of all adult lymphoma cases.[1,4,5] DLBCL NOS in Indonesia is also the most common of NHML cases, representing 68.2% of all lymphoma cases.[6] DLBCL NOS can occur in all age groups, predominantly occur in the male elderly about 60-80 years old.[1,7] The clinical manifestations of DLBCL are solitary or multiple lymphadenopathy with rapid mass growth, around 30% of patients have B symptoms such as fever >38^0 Celsius in the last 1 month, 10% weight loss in the last 6 months and excessive night sweats in the last 1 month. Majority of the patients have nodal disease at first diagnosed while 30-40% of patients have extranodal disease at first diagnosed. The most common extranodal sites are the gastrointestinal tract, head and neck region, bone, liver, kidney and adrenal glands.[1,3]

Risk factors for DLBCL NOS include genetic abnormalities, immune system dys-regulation, viral exposure, and occupational toxic chemicals exposure. DLBCL can occur de novo, as well as transformation from indolent B-cell lymphomas such as small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, and nodular lymphocyte pre-dominant Hodgkin lymphoma (NLPHL).[1] Based on immunophenotyping, Hans' algorithm divides DLBCL into GCB and non-GCB subtypes by immunohistochemical examination of CD10, BCL6, and multiple myeloma 1 (MUM1). DLBCL patients are classified as GCB subtype if show immunoexpression CD10 (+) or (-), BCL6 (+) and MUM1 (-), while DLBCL patients are classified as non-GCB subtype if show immunoexpression CD10 (-), BCL6 (+) or (-) and MUM1 (+).[8] Some studies results showed positive prognosis of expression those markers. Negative expression of CD10 cases in DLBCL have worse event-free survival than positive expression of CD10 cases and also negative expression of BLC-6 cases in DLBCL have worse overall survival than positive expression of BCL-6. Additionally, over-expression BCL-6 in DLBCL have positive effect on event-free survival.[9] Positive expression of MUM1 cases in DLBCL was associated with inferior prognosis and also MUM1 with cut-off $\geq$ 50% was able to estimate the incidence of death or R-CHOP therapy failure in 24 months.[10] Generally DLBCL GCB have better prognosis than DLBCL non-GCB with a 5-years overall survival (60% versus 35%).[8]

Since February 2006 until now the immunochemotherapy regimen of DLBCL consisted of rituximab cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine) and prednisone (R-CHOP) has been the standard therapy for DLBCL. The 5-years progression-free and overall survival rates of DLBCL NOS are around 70% after R-CHOP therapy but this can vary depending on subtype and stage.[1,3] The 5-years relative survival rate of DLBCL NOS is 73% for localized stage, 72% for regional stage and 55% for metastatic stage. The International Prognostic Index (IPI) can be used to help determine the prognosis of DLBCL. The IPI depends on five prognostic factors such as age, stage, extranodal involvement, performance status, and serum lactate dehydrogenase (LDH) levels. Each prognostic factor is assigned a value of 1 and the total of IPI scores divides patient into four risk groups. IPI score of 0-1 represents low risk group with a 5-years survival rate of 73%, IPI score of 2 represents low-intermediate risk group with a 5-years survival rate of 51%, IPI score of 3 is high-intermediate risk group with a 5-years survival rate of 43% and IPI score of 4-5 is high risk group with a 5-years survival rate of 26%.[3,11]

Given the difference between the clinicopathological characteristics and prognosis of each subtype and the limited available data DLBCL in Indonesia, we aimed to report the clinicopathological characteristics of DLBCL GCB and DLBCL non-GCB at Dr. Hasan Sadikin General Hospital from 2018-2023.

METHODS

This study was a retrospective descriptive study. All data were obtained from

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secondary data from medical records. The samples in this study were DLBCL patients who had been diagnosed as DLBCL NOS based on histopathology (cells morphology) from biopsy and surgery which showed a diffuse growth pattern of medium to large B cells, large nuclei and immunohistochemistry examinations which expressed positive diffuse on CD20 marker and high proliferation on Ki67 marker and no other examinations (FISH, Next-Generation Sequencing), at the Department of Anatomic Pathology of Padjadjaran University, Hasan Sadikin General Hospital from 2018 to 2023. The number of patients enrolled in this study were 55 patients. Demographic status including age of diagnosis which categorized into <60 years old and ≥60 years old, gender and clinical data including primary tumor location which categorized into nodal and extranodal disease, B symptoms which consist of fever >38^0 Celsius in the past 1 month with persistent or recurrent pattern with unknown origin, 10% weight loss in the past 6 months, excessive night sweats in the past 1 month, tumor staging based on Ann Arbor staging which divided into the early stages (stage I-II) and advanced stages (stage III-IV), COO subtypes based on Hans algorithm with immunohistochemistry examination of CD10, BCL6 and MUM1, total IPI score and R-CHOP status were collected based on secondary data from medical records and evaluation of *CT-scan* examination which divided into response, non-response and still ongoing therapy.

Statistical analysis was performed using statistical analysis software SPSS version 26. This study has obtained ethical approval from the Health Research Ethics Committee of Padjadjaran University with number 346/UN6.KEP/EC/2024.

RESULTS

Descriptive Statistics

In this study, we included 55 DLBCL patients treated with R-CHOP regimen of immunochemotherapy at Dr. Hasan Sadikin General hospital, with predominant of male patients 53%. The average patient's age was 62 years old (*M*=62.0 years old, *SD*=14.9 years old) and more often had a primary extranodal disease 54.5%. The location of extranodal tumors in these patients include tonsil, nasal cavity, nasopharynx, maxillary sinus, parotid, proximal tibia, colon, ileum, bladder, while the location of nodal tumors were found in colli, axillary, inguinal, mediastinum lymph node which can be soliter or multiple nodes. Mostly patients had no B symptoms 76.4%, only 1.8% patient had fever, 18% patients had weight loss, and 3.6% patients had both fever and weight loss. 55 patients in Dr. Hasan Sadikin General hospital were mostly diagnosed at an early stage 83.6%. 5 patients (9.1%) had GCB subtype and 50 patients (90.9%) had non-GCB subtype. 31 patients (56.4%) had a total IPI score of 0, 21 patients (38.2%) had a total IPI score of 1 and 3 patients (5.4%) had a total IPI score of 2. 21 patients (38.2%) had a response status to R-CHOP therapy, 13 patients (23.6%) had non-response status to R-CHOP and 21 patients (38.2%) are still ongoing to R-CHOP therapy. Additionally, the characteristics of the patients in detail can be seen in Table 1.

Table 1. DLBCL NOS patient's characteristics.

Variable	N = 55	
	N	%
Age		
Mean ± Std	62.0 ± 14.9	
<60 years old	36	65.5
≥60 years old	19	34.5
Gender		
Male	29	52.7
Female	26	47.3
B Symptoms		
Yes	13	23.6
No	42	76.4
Primary Tumour Location		
Nodal	25	45.5
Extra nodal	30	54.5
Stage		
Stage I	18	32.7
Stage II	28	51.0
Stage III	8	14.5
Stage IV	1	1.8
Cell of origin		
DLBCL GCB	5	9.1
DLBCL non-GCB	50	90.9
IPI Score		
0	31	56.4
1	21	38.2
2	3	5.4
3	0	0
4	0	0
5	0	0
R-CHOP status		
Response	21	38.2
No Response	13	23.6
Ongoing	21	38.2

Among DLBCL GCB subtype patients in this study, all of the patients were males, 80% patients were diagnosed at age younger than 60 years old. There were 20% patients who had B symptom, 60% had nodal disease and 60% were present at an early stage. On the other hand, among DLBCL non-GCB subtype, 52% patients were female, 64% patients were diagnosed at less than 60 years old, 24% had B symptoms, 56% had extra nodal disease,

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86% were present at early stage. Both patients of DLBCL GCB and non-GCB, mostly had total IPI score 0 and had response status to R-CHOP therapy similar to those are still ongoing to R-CHOP therapy. Additionally, the detail of DLBCL GCB and DLBCL non-GCB patients can be seen in Table 2.

Table 2. DLBCL GCB subtype and DLBCL non-GCB subtype patient's characteristics.

Variable	Cell of origin subtype	
	GCB (n=5) n (%)	Non-GCB (n=50) n (%)
Age		
Mean ± Std	46.8±11.8	55.55±13.1
<60 years old	4 (80%)	32 (64%)
≥60 years old	1 (20%)	18 (36%)
Gender		
Male	5 (100%)	24 (48%)
Female	0 (0%)	26 (52%)
B Symptoms		
Yes	1 (20%)	12 (24%)
No	4 (80%)	38 (76%)
Primary tumor location		
Nodal	3 (60%)	22 (44%)
Extra nodal	2 (40%)	28 (56%)
Stage		
Early (Stage I-II)	3 (60%)	43 (86%)
Advance (Stage III-IV)	2 (40%)	7 (14%)
IPI Score		
0	4 (80%)	27 (54%)
1	0 (0%)	21 (42%)
2	1 (20%)	2 (4%)
3	0 (0%)	0 (0%)
4	0 (0%)	0 (0%)
5	0 (0%)	0 (0%)
R-CHOP Status		
Response	2 (40%)	19 (38%)
No Response	1 (20%)	12 (24%)
Ongoing	2 (20%)	19 (38%)

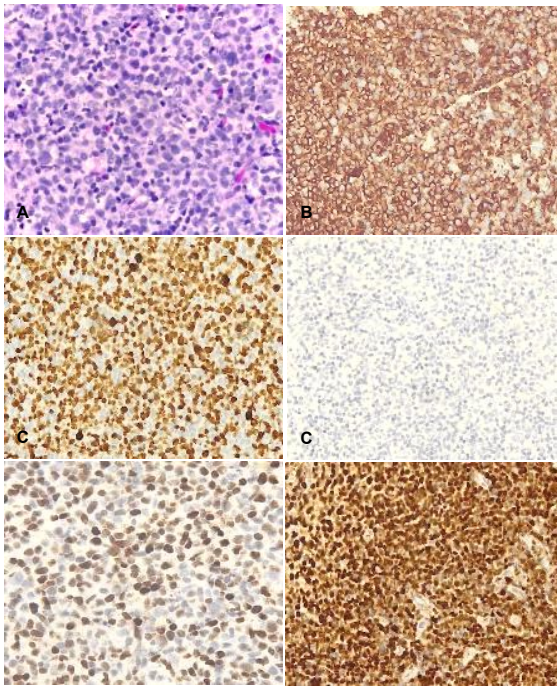

Figure 1. DLBCL GCB subtype. A. DLBCL 400 times magnification with hematoxylin and eosin examination. B. CD20 showed diffuse positivity. C. Ki67 showed high proliferation. D. CD10 showed positive. E. BCL6 showed positive. F. MUM1 showed negative.

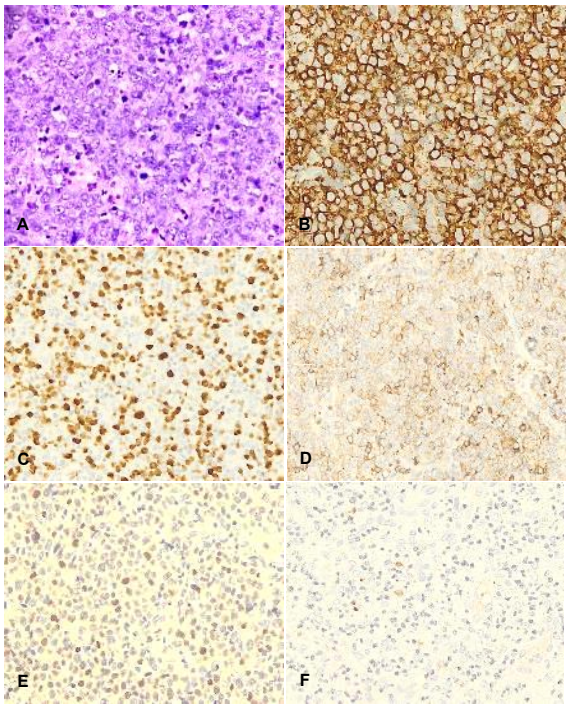

Figure 2. DLBCL Non-GCB subtype. A. DLBCL 400 times magnification with hematoxylin and eosin examination. B. CD20 showed diffuse positivity. C. Ki67 showed high proliferation. D. CD10 showed negative. E. BCL6 showed positive. F. MUM1 showed positive.

DISCUSSION

Statistic data from the National Cancer Institute showed that the rate of new cases of DLBCL per 100.000 persons per year in the world is more frequently occurred in men (6.6/100,000 persons) than in women (4.6/100,000 persons). DLBCL NOS occurs in men slightly more often than in women.[12] This study found that out of 55 DLBCL NOS patients is more frequently affected men (52.7%) than women. A recent study showed that during young age (15-45 years old), DLBCL is more common in men 2-5 times, while a higher age (>65 years old), the sex difference in incidence is nearly eradicated.[13] Some studies suspect that the estrogen and progesterone hormones provide some level of protection from lymphoid tumour cells growth and the other reference said that men are larger than women and attained body height is associated with elevated

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cancer risk assumingly by increased mutational load trough a higher number of stem cell divisions and or growth hormone exposure in childhood.[14] Study in Sweden showed that the men incidence of DLBCL both ABC subtype (Activated B-cell like) and GCB subtype is higher than women and found 1293 genes to be differentially expressed between men and women. The differences are likely due to estrogen effects. That study identified NR4A and MUC5B genes in DLBCL ABC subtype being under estrogen control, with tumour suppressing NR4A genes being induced and tumour stimulating MUC5B being repressed. The estrogen prevents the suppressor function of NR4A gene and the pro-oncogenic activity of MUC5B gene.[15] Both epidemiological data and experimental results support protective function of estrogen.

The average age in this study is 62 years old, with a range of 25-86 years old. DLBCL NOS can occur at any age but develops more frequently in the elderly population.[1] The median age at diagnosis of DLBCL NOS is in the mid-60 years old, 30% of patients are older than 75 years old.[16] Previous study in East Java, Indonesia showed that 54% patients of DLBCL were in the age range of 51-60 years old and 20% patients were >60 years old.[17] This study is also line with epidemiological study in Cairo, Egypt showed that 88.2% patients of DLBCL were in <60 years old group and 11.8% patients were >60 years old.[18] Both the GCB and non-GCB DLBCL subtype in this study were more diagnosed at the age of less than 60 years old.

Clinical manifestation of DLBCL patient is enlarging lymph node or mass at single or multiple sites rapidly. Patients may be found asymptomatic, but B symptoms such as fever, weight loss and night sweats may also appear in some patients.[1] This study revealed that B symptoms were positive in 23.6% of the patients. It is in line with study that conducted by Hassan et al showed that 29.5% patients were positive B symptoms.[18] Systemic B symptoms are seen in around 30% of DLBCL patients, which is lower than in Hodgkin's lymphoma, where B symptoms are present in up 70% of patients. In NHL, the significance of B symptoms for prognosis is less evidence, but they are signs of advance disease.[19] Majority of patients in this study had extranodal disease (54.5%), with the most common extranodal sites were tonsil. The previous study reported both GCB and non-GCB DLBCL subtype were located in extranodal 70%, the most common extranodal sites were tonsil which is in line with this study.[20]

Based on Ann Arbor stage, approximately 50% of DLBCL patients present with early stage.[1] In the present study, both GCB and non-GCB DLBCL patients who diagnosed at early stage were higher (83.7%) than who diagnosed at advanced stage. The previous study stated that 60% of DLBCL patients had an early stage at the time of diagnosis, as well as study in China which reported that 64.8% of patients both nodal DLBCL and extranodal DLBCL had an early stage at the time of diagnosis.[20,21] Another study also showed that extranodal DLBCL patients had early stage at the time of diagnosis (69.3%).[22] Most of the patients presented with early stage which could be attributed to the fact that the patients may present earlier with localizing symptoms.

DLBCL non-GCB subtype (90.9%) is more common than DLBCL GCB subtype at Dr. Hasan Sadikin General Hospital. This study in line with the epidemiological DLBCL study reported that 70.5% patients were DLBCL non-GCB subtype.[21] Another study reported that 58.5% of DLBCL patients were DLBCL ABC subtype followed by 41.5% patients of DLBCL GCB subtype.[23] Studies conducted in Asian countries reported that GCB subtype to be significantly less frequent than the ABC subtype. On the other hand, study in Egypt, according to Hans algorithm, 30 cases (57.7%) were classified as DLBCL GCB subtype and 22 cases (42.3%) were classified as DLBCL non-GCB subtype, as well as studies conducted in Western countries reported that GCB subtype is higher than ABC subtype. The variation of frequency between DLBCL GCB subtype and non-GCB subtype might be depends on geographical location, genetic, demographic factors that have involving role in lymphoma genesis.[22,23,24] Some factors that may influence to the difference of the incidence between DLBCL GCB and non-GCB in Asian and Western countries are low incidence of translocation (14;18) in Asian DLBCL which in line with low incidence of GCB subtypes, the number of Epstein-Barr virus (EBV)-related infections in Asian countries is more predominant which can influence the COO subtype, and EBV-related infections have been known to be capable of activating canonical NF-kB which is the main pathway of DLBCL non-GCB.[25]

The majority of DLBCL GCB and non-GCB patients in this study were low risk group

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with the total IPI score 0-1 (94.6%) followed by low-intermediate risk group with the total IPI score 2 (5.4%). In DLBCL GCB, there was only 1 patient (20%) who belonged to the low-intermediate risk group. These patient was 61 year old male in stage III with stable disease to R-CHOP therapy. On the other hand among DLBCL non-GCB patients, 2 patients (4%) were low-intermediate risk group. Both of the patients were female, 70 and 72 years old, stage III with one of them having complete response to R-CHOP therapy and the other having non-response to R-CHOP therapy. In this study 94.6% of patients with IPI low risk group, there were of 20 patients (38.5%) had a response status to R-CHOP therapy consisting of 17 patients (32.7%) had a complete response and 3 patients (5.8%) had a partial response. The clinicopathological analysis study revealed that IPI score was a significant predictors of overall survival and event-free survival.[26] The retrospective study reported a significant correlation between IPI risk group and the therapy response correlating the better therapy response to the IPI low risk group with complete response 59%.[27] The other study also reported that mostly patients of DLBCL NOS were low risk group 52,3%. IPI low risk group in that study showed better therapy response with 52.3% patients achieved complete response which in line with this study.[18]

In this present study, 38.2% patients had a response status to R-CHOP therapy and 23.6% patients had non-response status to R-CHOP therapy. In the DLBCL GCB subtype, 40% patients had complete responses to R-CHOP therapy, 20% patient did not respond with stable disease and the remaining 40% patients were still on therapy so further follow-up is needed. In the DLBCL non-GCB subtype, 32% patients had complete responses to R-CHOP therapy, 6% patients had partial responses, 24% patients did not respond to R-CHOP therapy with 4% patients had stable disease and 6% patients had progressive disease, and the remaining 38% patients were still on therapy. In this study, the percentage of DLBCL GCB patients who responded to R-CHOP therapy was more than non-GCB patients although the difference in the number of patients. This study also stated that both GCB and non GCB patients were diagnosed at an early stage so that they responded to RCHOP therapy. According to the previous studies, DLBCL GCB subtype has higher proliferation and higher apoptotic index than non-GCB subtype which causes highly expression of CD10 and BCL6 markers in GCB subtype. Thus, DLBCL GCB patients had better response to the therapy than non-GCB patients which made DLBCL GCB had better prognosis than non-GCB. On the other hand, DLBCL non-GCB subtype have more mutations than GCB subtype such as BCL6, INK4, PRDM1, TNFAIP3, SPIB, CARD11, MYD88, MYC / BCL2, NFKB, CD79A, CD79B, CREBBP, E300, MLL2, MEF2B, MEF2B, TBL1, NOTCH1, NOTCH2, BRAF and TP53 genes mutations. This correlates with the poorer response to standard therapy and the poorer prognosis of non-GCB patients compared to GCB patients.[20,28] In contrast to the study by Baliko et all which stated that there was no difference in the 5-years survival between DLBCL GCB and non-GCB subtypes.[26] On this research is a retrospective descriptive study, not prospective study that proves only clinicopathological descriptive data, not association and causation. Additionally, several patients were still ongoing to R-CHOP therapy. It might not be conclusive enough to establish the R-CHOP status so further follow-up was needed.

CONCLUSION

DLBCL NOS at Dr. Hasan Sadikin General Hospital from 2018-2023 mainly occurred in men with average age of 62 years old and extranodal disease without B symptoms. DLBCL non-GCB subtype is more common than DLBCL GCB subtype. Both DLBCL Non-GCB and DLBCL GCB were mostly diagnosed at an early stage, IPI low risk group and have a response status to R-CHOP therapy similar to those are still ongoing to R-CHOP therapy.

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