

The influence of GCB and Non-GCB subtypes based on the Hans algorithm on 2 Year event-free survival in diffuse large B-cell lymphoma patients who received RCHOP therapy

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Abstract

Background: Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma. Based on the Hans algorithm, DLBCL is divided into two main subtypes, namely Germinal Center B-Cell-like (GCB) and non-GCB. GCB has a better prognosis than non-GCB subtypes.

Aim: To compare the effect of these subtypes on the 2-year event-free survival (EFS) of DLBCL patients who received RCHOP therapy.

Methods: This research is a retrospective cohort study sourced from patient medical record data from Dr. Cipto Mangunkusumo (RSCM) who was registered from January 2014-March 2021. We collected demographic data, clinical examination results, complete hematology laboratories, lactate dehydrogenase (LDH), radiological examinations and events for 2 years. Survival analysis was performed using the Kaplan-Meier curve, cox-regression test was performed to assess the hazard ratio. Nominal variables will be compared using the Chi-Square test or Fisher's Exact test, while numerical variables will be subjected to an independent T-Test or Kruskal-Wallis test.

Results: Our study found 108 DLBCL patients with 33 GCB subtype patients (30.6%), median age 53 years (range 18–88 years), 60 (55.6%) were at stage I or II, and 89 (82%) patients had extranodal lesions 0-1. Event-free survival in the GCB subtype was 54.5% and in the non-GCB subtype group was 42.7%. The mean EFS for the GCB subtype was 19.6 months (95% CI, 17.38-21.82) and for the non-GCB subtype 18.6 months (95% CI, 17.21-20.01). The hazard ratio for GCB subtype was 0.749 (95% CI: 0.416-1.349, $p = 0.336$).

Conclusion: DLBCL patients with the GCB subtype have better 2-year EFS and a longer mean EFS time compared to non-GCB. The GCB subtype was protective against the event, although it was not statistically significant.

Keywords: DLBCL, GCB, non-GCB, RCHOP, survival

Abstrak

Latar Belakang: Diffuse large B-cell lymphoma (DLBCL) merupakan sub tipe tersering dari non-Hodgkin's lymphoma. Berdasarkan algoritma Hans, DLBCL dibagi menjadi dua sub tipe utama, yaitu Germinal Center B-Cell-like (GCB) dan non-GCB. Sub tipe GCB memiliki prognosis yang lebih baik dibandingkan dengan sub tipe non-GCB.

Tujuan: Membandingkan pengaruh kedua sub tipe tersebut terhadap event-free survival (EFS) 2 tahun pada pasien DLBCL yang mendapatkan terapi RCHOP.

Metode: Penelitian ini merupakan studi kohort retrospektif yang bersumber dari data rekam medis pasien di RSUPN Dr. Cipto Mangunkusumo (RSCM) yang terdaftar pada periode Januari 2014 hingga Maret 2021. Data yang dikumpulkan meliputi data demografis, hasil pemeriksaan klinis, laboratorium hematologi lengkap, LDH, pemeriksaan radiologis, dan kejadian selama 2 tahun. Analisis kesintasan hidup dilakukan menggunakan kurva Kaplan-Meier, dan uji regresi Cox digunakan untuk menilai hazard ratio. Variabel nominal dibandingkan menggunakan uji Chi-Square atau uji Fisher's Exact, sementara variabel numerik dianalisis dengan uji T independen atau uji Kruskal-Wallis.

Hasil: Penelitian ini melibatkan 108 pasien DLBCL, dengan 33 pasien (30,6%) memiliki sub tipe GCB. Median usia adalah 53 tahun (rentang 18–88 tahun), sebanyak 60 pasien (55,6%) berada pada stadium I atau II, dan 89 pasien (82%) memiliki lesi ektranodal 0–1. Event-free survival 2 tahun pada sub tipe GCB adalah 54,5%, sedangkan pada kelompok non-GCB adalah 42,7%. Rerata EFS pada sub tipe GCB adalah 19,6 bulan (CI 95%: 17,38–21,82), sedangkan pada sub tipe non-GCB adalah 18,6 bulan (CI 95%: 17,21–20,01). Hazard ratio untuk sub tipe GCB adalah 0,749 (CI 95%: 0,416–1,349; $p = 0,336$).

Kesimpulan: Pasien DLBCL dengan sub tipe GCB memiliki EFS 2 tahun yang lebih baik dan rerata waktu EFS yang lebih panjang dibandingkan dengan sub tipe non-GCB. Sub tipe GCB bersifat protektif terhadap kejadian, meskipun secara statistik tidak bermakna.

Kata kunci: DLBCL, GCB, kesintasan hidup, non-GCB, RCHOP

Background

Diffuse Large B-Cell Lymphoma is the most common subtype of non-Hodgkin's lymphoma (LNH) accounting for 30-40% of all LNH cases. In 2020, there were 77,240 new DLBCL cases in the United States and it is projected to increase 11% in 5 years.¹⁻³ DLBCL has two main subtypes, namely Germinal Center B-Cell-like (GCB) and Activated B-Cell-like (ABC), where the GCB subtype has a better prognosis than ABC (3-year survival without progression 75% vs 40-50%).² The division of subtypes is basically done by making gene expression profiles, but the high cost means that this method cannot be carried out in daily clinical care. Classification of DLBCL subtypes in daily practice is carried out using the Hans algorithm, namely the use of immunohistochemistry, such as CD10, BCL6 and MUM1. Classification using the Hans algorithm has accuracy in terms of prognostic and therapeutic response that is equivalent to gene expression profiling methods.⁴

The main therapy for DLBCL is the RCHOP immunotherapy regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) with a cure rate of 60-70%. However, in 30-40% of cases DLBCL does not respond to this regimen and makes the prognosis worse.⁵ In this study, we wanted to assess how the GCB and non-GCB subtypes based on the Hans algorithm influence 2-year EFS of DLBCL patients who received RCHOP therapy.

Methods

This study used a retrospective cohort design and was conducted at the Cipto Mangunkusumo National Central General Hospital (RSUPN Cipto Mangunkusumo). This study received ethical clearance from Ethical Committee FKUI-RSUPN dr. Cipto Mangunkusumo with reference number KET-133/UN2.F1/ETIK/PPM.00.02/2023.

Data retrieved from medical records of patients who received treatment at the RSCM Hematology Oncology Medical Polyclinic from January 2014 to March 2021. Data taken includes patient identity, age, gender, DLBCL stage, extranodal involvement, tumor size (bulky or not), performance status (ECOG), complete

hematology laboratory examination results, LDH, date and cycle of RCHOP chemotherapy. Event recorded includes disease-related death, relapse (recurrence) and refractory (progression of the disease, and failure in treatment in the form of partial response or stable disease) requiring second-line therapy is carried out when evaluating the response to treatment. Response evaluation was conducted after 3-4 R-CHOP cycle using imaging, after 6-8 times R-CHOP with or without radiotherapy using imaging, and surveillance evaluation of patients who have completed RCHOP for 2 years.

Statistical analysis was carried out using SPSS 20 software (IBM). Analysis is used to see the relationship between dependent and independent variables, and comparison of group outcomes. The level of significance used is $\alpha = 0.05$. Comparison of numerical variables that are normally distributed, hypothesis testing is carried out using the independent T test, while comparison of numerical variables that are not normally distributed, hypothesis testing is carried out using the Mann-Whitney test. Hypothesis testing of nominal variables is carried out using the Chi-Square test. Variables are said to be statistically significantly related if a p value < 0.05 is found. The statistical test used to determine EFS is the Kaplan Meier Curve and Cox-regression analysis to obtain the Hazard Ratio (HR) value with a 95% confidence interval.

Result

Medical records and histopathology data from the FKUI/RSCM Anatomical Pathology Laboratory found 156 patients who met the inclusion criteria. 48 patients were excluded, with details of 7 patients having primary DLBCL of the central nervous system, 3 patients having a history of HIV, and 38 patients not having paraffin blocks. Based on Hans' algorithm, 33 research subjects (30.6%) had the GCB subtype. 56 research subjects (52%) were men with a median age of 53 years (range 18–88 years). 89 subjects (82%) of the study had 0-1 extranodal lesions and 60 (55.6%) subjects according to Ann Arbor were classified as stage I-II. 58 subjects (53.7%) experienced an event. Data regarding patient demographics, laboratory parameters, and immunohistochemical examination results are presented in table 1.

Table 1. Clinical and Molecular Characteristics of Research Subjects

Variable	GCB (n = 33)	Non-GCB (n = 75)
Hb, mean ± SD	11.19 ± 2.1	11.55 ± 2.16
Leukocyte, mean ± SD	6.5524 ± 1.25	6.854 ± 1.789
Thrombocyte, mean ± SD	386.36 ± 74.7	354.92 ± 128.71
Neutrophil, mean ± SD	65.74 ± 16.37	66.98 ± 13.187
Lymphocyte, median ± IQR	18.2 ± 12.45	17.4 ± 10.90
Monocyte, median ± IQR	10.00 ± 6.00	11.00 ± 5.00
IPI Score (n=99)		
Low IPI	21 (72.4%)	4 (77.15%)
High IPI	8 (27.6%)	16 (22.85%)
Ann Arbor Stadium		
Ann Arbor I and II	15 (54.55 %)	45 (60%)
Ann Arbor III and IV	18 (45.45%)	30 (40%)
Ekstranodal Involvement		
0-1	23 (69.67%)	56 (74.66%)
>1	10 (30.33%)	19 (25.34%)
LDH (n=99)		
LDH ≤1x Upper Normal Limit	6 (20.68%)	12 (15%)
LDH >1x Upper Normal Limit	23 (79.32%)	58 (85%)
Event		
No Event	18 (54.5%)	32 (42.7%)
Event/Mortality	15 (45.5%)	43 (57.3%)
Sex		
Man	19 (57.57%)	37 (49.33%)
Woman	14 (42.43%)	38 (50.67%)
Age		
≥ 60 Years	12 (36.36%)	28 (37.33%)
Usia <60 Years	21 (63.64%)	47 (63.67%)

In the EFS analysis, it was found that 18 subjects with GCB subtype DLBCL (54.5%) did not experience an event, while 32 subjects with non-GCB subtype DLBCL (42.7%) did not experience an event. Analysis using cox regression (table 2) found a hazard ratio of 0.749 (95% CI: 0.416-1.349, p = 0.336). In the EFS analysis using the Kaplan-Meier method (figure 1), the average EFS of subjects with the GCB subtype

reached 19.6 months (95% CI, 17.38-21.82) and the non-GCB subtype 18.6 months (95% CI, 17.21-20.01).

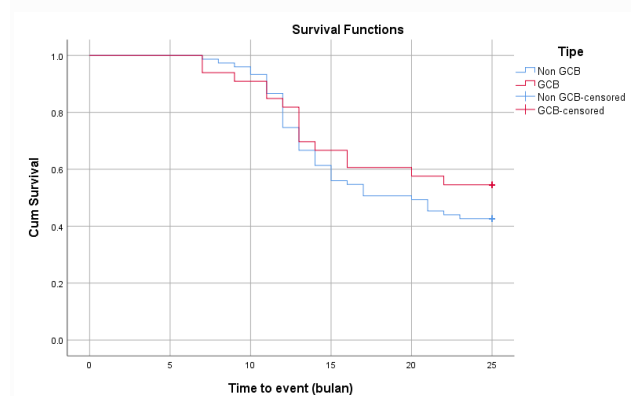


Figure 1. Kaplan-Meier EFS curve for GCB and non-GCB subtypes

Discussion

In this study, it was found that 52% of DLBCL patients were male. This is in accordance with similar studies in Indonesia and abroad which show that the majority of DLBCL patients are male.⁶⁻⁸ The median age of the subjects in this study was 53 years, in line with the research of Reksodiputro et al and the observational research of Huang et al from Fujian.^{8,9} However, the median age is younger than the median age of patients from Western countries and other Asian countries, such as Japan and Korea, which show a higher median age, namely 64 years.¹⁰ This difference occurs because the incidence of Non-Hodgkin's Lymphoma is influenced by race and genetics, lifestyle, Epstein-Barr virus (EBV) infection, and occupational history.¹¹ Meta-analysis showed that a higher proportion of EBV-positive DLBCL was found in the East Asian and Southeast Asian populations (7.2%) compared to the world population (4%).¹² This study found that only 27% of subjects had extranodal manifestations which is in accordance with the research of Blansky et al where extranodal DLBCL was found in 22.2-28.7% of cases.⁶ The majority of DLBCL cases found (55.6%) were at stages I-II. These findings are in accordance with Castillo's study where DLBCL patients of Asian descent were more commonly found in stages I and II (51%). This is not in accordance with data showing that only 30% of DLBCL cases are found at stages I and II. The high rate of finding DLBCL cases in this study can be associated with the use of positron emission tomography (PET) in DLBCL detection.^{2,10}

In this study, it was found that low IPI scores were found more frequently in non-GCB types than GCB (77.15% vs 72.4%), although it was not statistically significant ($p=0.617$). This is different from the study conducted by Patrascu et al where IPI was found low was found to be significantly higher in the GCB group.¹³ Differences in inclusion and exclusion criteria in each study can explain the differences that occurred. The non-GCB group was found to be more common during Ann-Arbor stages I and II than the GCB group, although it was not significant (60% vs 54.55%, $p=0.161$). This is different from the research of Istiadi et al which showed that the Ann-Arbor type I and II groups were more frequently found at the time of diagnosis of the GCB type. This difference can be explained by the difference in location, where this research was carried out at RSUPN Cipto Mangunkusumo which is the national reference for Indonesia, indicating that DLBCL patients who were referred were in an advanced stage.¹⁴ GCB patients were diagnosed extranodally >1 in 30.33% of cases, which was higher than in the non-GCB 25.34%. These data were not statistically significant and similar results were found in previous studies where DLBCL lineages had no effect on nodal or extranodal phenotypes.¹⁵

During the 2-year follow-up period, 58 patients experienced events (53.7%) in the form of disease-related death, relapse (recurrence) and refractory (progression of the disease, and failure in treatment in the form of partial response or stable disease) requiring second-line therapy. These data are similar to the results of other studies which state that recurrence or treatment failure occurs in 40-50% of patients.^{16,17} The event free survival rate in the GCB subtype according to the Hans algorithm is higher than in the non-GCB subtype (54.5% vs 42.7%). Other studies have shown similarly that GCB is superior in EFS, whether determined by CD10 (GCB vs Non-GCB, 51% vs 47%, $p=0.89$), Bcl-6 (GCB vs Non-GCB, 57% vs 35%, $p=0.013$), or MUM1 (GCB vs Non-GCB, 62% vs 31%, $p=0.003$).¹⁸ This is also supported by the low hazard ratio (0.749, IK95% 0.416-1.349), although it is not statistically significant. The use of the Hans algorithm in determining prognosis was also found to be similar in other studies where the GCB subtype group had overall survival (54.9% vs 42.3%, $p<0.001$) and EFS (67.3% vs 43.3%, $p<0.001$) better than the non-GCB subtype group.¹⁹ The overall EFS in this study (46.3%) was similar to the EFS studied in the systematic review, namely ranging from 38.7% - 97.3%. When compared with several other studies, this study found a lower EFS.

The differences that occur between previous studies and this study can be explained by differences in the frequency of administration of immunochemotherapy regimens. The inclusion and exclusion criteria used in each study are also different, for example some studies only included patients aged 18-60 years. Other studies only examined elderly patients aged ≥ 65 years. Several other studies also only examined patients with tumor sizes <7.5 cm.²⁰

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Conflict of Interests

No conflict of interest arises during this study conception and implementation. This research was funded privately by corresponding author (FS).

References

1. Kanas G, Ge W, Quek RGW, Keeven K, Nersesyan K, Jon E. Arnason. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe: population-level projections for 2020–2025. *Leuk Lymphoma*. 2022 Jan 2;63(1):54–63.
2. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. Longo DL, editor. *N Engl J Med*. 2021 Mar 4;384(9):842–58.
3. Susanibar-Adaniya S, Barta SK. 2021 Update on Diffuse large B cell lymphoma: A review of current data and potential applications on risk stratification and management. *Am J Hematol*. 2021;96(5):617–29.
4. Choi WWL, Weisenburger DD, Greiner TC, Piris MA, Banham AH, Delabie J, et al. A New Immunostain Algorithm Classifies Diffuse Large B-Cell Lymphoma into Molecular Subtypes with High Accuracy. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2009 Sep 1;15(17):5494–502.
5. Vodicka P, Klener P, Trneny M. Diffuse Large B-Cell Lymphoma (DLBCL): Early Patient Management and Emerging Treatment Options. *OncoTargets Ther*. 2022 Dec 6;15:1481–501.
6. Blansky D, Fazzari M, Mantzaris I, Rohan T, Hosgood HD. Racial and ethnic differences in diffuse large B-cell lymphoma survival among an underserved, urban population. *Leuk Lymphoma*. 2021 Mar;62(3):581–9.
7. Yang X, Laliberté F, Germain G, Raut M, Duh MS, Sen SS, et al. Real-World Characteristics, Treatment Patterns, Health Care Resource Use, and Costs of Patients with Diffuse Large B-Cell Lymphoma in the U.S. *The Oncologist*. 2021 May;26(5):e817–26.
8. Reksodiputro H, Irawan C, Hardjolukito E. | Reksodiputro. *Indones J Cancer [Internet]*. 2011 Oct

- 1 [cited 2023 Jul 4];5(3). Available from: <https://www.indonesianjournalofcancer.or.id/e-journal/index.php/ijoc/article/view/171>
9. Huang H, Fan L, Fu D, Lin Q, Shen J. Clinical characteristics and outcomes of patients with diffuse large B cell lymphoma treated with R-CHOP-like or CHOP-like regimens: an 8-year experience from a single center. *Ann Palliat Med*. 2020 Jul;9(4):1442452–1441452.
 10. Castillo JJ, Sinclair N, Beltrán BE, Song MK, Ilic I, Leppa S, et al. Similar outcomes in Asian and Western patients with diffuse large B-cell lymphoma treated with R-CHOP. *Leuk Res*. 2013 Apr 1;37(4):386–91.
 11. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-Hodgkin lymphoma. *The Lancet*. 2017 Jul;390(10091):298–310.
 12. Wong Y, Meehan MT, Burrows SR, Doolan DL, Miles JJ. Estimating the global burden of Epstein–Barr virus-related cancers. *J Cancer Res Clin Oncol*. 2022 Jan;148(1):31–46.
 13. Patrascu AM, Streba L, Patrascu Ș, Nacea J, Mogoanta L, Rotaru I. Correlation between Immunohistochemical Subtype and Clinicopathological Features in Patients with Diffuse Large B-cell Lymphoma. *Curr Health Sci J*. 2017;43(3):253–7.
 14. Istiadi H, Sadhana U, Puspasari D, Miranti IP, Karlowee V, Listiana DE, et al. Role of Cell-Origin Profiling Using Immunohistochemistry to Predict the Survival of Patients with Diffuse Large B-Cell Lymphoma in Indonesia. *Yonago Acta Med*. 2021 May 20;64(2):200–6.
 15. Salles G, De Jong D, Xie W, Rosenwald A, Chhanabhai M, Gaulard P, et al. Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium. *Blood*. 2011 Jun 30;117(26):7070–8.
 16. Thieblemont C, Gisselbrecht C. Second-line treatment paradigms for diffuse large B-cell lymphomas. *Curr Oncol Rep*. 2009 Sep;11(5):386–93.
 17. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol Off J Am Soc Clin Oncol*. 2010 Sep 20;28(27):4184–90.
 18. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004 Jan 1;103(1):275–82.
 19. Cho MC, Chung Y, Jang S, Park CJ, Chi HS, Huh J, et al. Prognostic impact of germinal center B-cell-like and non-germinal center B-cell-like subtypes of bone marrow involvement in patients with diffuse large B-cell lymphoma treated with R-CHOP. *Medicine (Baltimore)*. 2018 Nov 9;97(45):e13046.
 20. Zhu J, Yang Y, Tao J, Wang SL, Chen B, Dai JR, et al. Association of progression-free or event-free survival with overall survival in diffuse large B-cell lymphoma after immunochemotherapy: a systematic review. *Leukemia*. 2020;34(10):2576–91.

