Survival Rate of Patients with Diffuse Large B-Cell Lymphoma in the Head and Neck

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ABSTRACT
Diffuse large B-cell lymphoma (DLBCL) is a subtype of aggressive non-Hodgkin lymphoma (NHL). Diffuse Large B-cell lymphoma is a subtype of lymphoma most often found in the head and neck region. Overall survival could be used in assessing the effectiveness of therapies that may affect prognosis and survival. This study aimed to determine the survival rate of patients with DLBCL in the head and neck. This study used a retrospective cohort design, data was taken from the cancer registry between January 2014 and December 2019 at Hasan Sadikin Hospital Bandung and traced the history of survival. The analysis was using Kaplan-meier and all data were analyzed using Statistical Package for the Social Sciences (SPSS) application. The results showed that 148 patients with DLBCL obtained 76 patients (51.4%) male and 72 patients (48.6%) female. About 79 patients (53.4%) were Stage I, 108 patients (73%) ECOG 0. The mean lactate dehydrogenase (LDH) level was 253.76 and 32.48 U/mL Cancer antigen 125 (Ca-125). The 130 patients (87.8%) underwent chemotherapy and 18 (12.2%) chemoradiation. Median survival in DLBCL were 3 year (2.448-3.552, 95% CI). as many as 50% of subjects had died within 3 years. Age, education, stage, ECOG, LDH, IPI, Ca-125, and comorbid had a significant effect in 3-years survival rate of DLBCL patients.

Keywords: *Cancer antigen 125, Diffuse large B-cell lymphoma, Head and Neck, Lactate dehydrogenase, Survival rate.*

1. INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma originating from the germinal center. It represents a heterogeneous group of diseases with variable outcomes differentially characterized by clinical features, cell of origin (COO), molecular features, and frequently recurring mutations [1]. The incidence of NHL in the world is approximately 5–10 times greater than that of Hodgkin Lymphoma (HL), depending more on regional differences [2]. Of the total lymphoma cases 80% originate from B cells and 20% from T cells. The American Cancer Society estimates 77.240 new cases, increasing by 3-4% each year and 5.5% death rates period 2013-2017 [3]. In 2012, this malignancy is included in one of the 10 malignancies with the most frequent incidents in the world [4]. Reksodiputro [5] reported Diffuse Large B Cell Lymphomas (69%) as the most type of B Cells Non-Hodgkin Lymphoma in this multicentre study in Indonesia most group were: male (55.5%) whith median of age of 51 years old. Permana

et al, [6] 2019 found 31 cases DLBCL in the head and neck region who came to the Oncology division ORLHNS Department of Dr. Hasan Sadikin Hospital Bandung, with an average age of 55 years. The study subjects consisted of 48.4% male and 51.6% female, 87% of the subjects were stage I-II, and 13% were stage III-IV.

B-cell lymphomas are found in approximately 90% of all NHL and DLBCL is a subtype of lymphoma that is most often found in the head and neck region. The two most common histologic subtypes are follicular lymphoma and the more aggressive DLBCL [7]. Patients with aggressive NHL have the characteristics of tumours with rapid growth, size, and more striking symptoms but have a high sensitivity to chemotherapy modalities or a combination of radiotherapy [8].

Survival is the percentage of individuals living in a group with a particular disease in a specified period. Overall survival can be calculated at a one-year, three-year, five-year, or 10-year rate to assess the effectiveness of therapy that may affect prognosis and survival rates [9]. Prognostic factors are independent predictors of the survival of LNH sufferers, including IPI (International Prognostic Index) score, LDH level, age, and stage [10]. The percentage of DLBCL patients with increased LDH serum levels which is relatively low, range 10.2-37% [11]. There was an increase in the expression of serum Ca 125 levels in advanced LNH patients (stage 3 or 4) than in the early stages (stage 1 or 2). Diffuse large B-cell lymphoma patients with high LDH and Ca-125 levels have worse prognostic factors at diagnosis, higher relapse rates, and worse life expectancy [12]. This study aims to determine the survival rate of patients with DLBCL in the head and neck.

2. METHOD

This study is a retrospective cohort design. Data were taken from the medical records of all patient of DLBCL in head and neck suffers at Dr. Hasan Sadikin Hospital, Bandung. The inclusion criteria were all DLBCL in head and neck patients who came to Dr Hasan Sadikin Bandung Hospital from January 2014 to December 2019. This study has been approved by the Ethics Committee of Universitas Padjadjaran. The ethical approval number is No: 995/UN6.KEP/EC/2020. The exclusion criteria were patients with dubious histological features (grey-zone lymphoma), missing data, and loss of patients to follow up.

The outcome assessed was one, three, and five years survival, which defined the survival time of LNH sufferers from the first diagnosis to death during 1,3, and 5 years of observation due to any cause. If the patient is still alive at the end of the study and the patient who dropped out before the end of the study will be included in censored. Descriptive data about the characteristics of the subject is presented in the form of a table. The survival analysis used Kaplan Meier. The survival data are presented in the form of tables and survival curves. All data were analyzed using SPSS-22 software.

3. RESULTS AND DISCUSSION

3.1 Results

All the 148 subjects were diagnosed with DLBCL according to the inclusion and exclusion criteria, 76 patients (51.4%) male and 72 (48.6%) females. The mean age was 54.28±13.997, with the youngest 8 years old and the oldest 85 years old. Most of the patients had stage I 79 patients (53.4%), ECOG-PS score 0 (73.0%) and mean LDH level 253.76± 227.7, with the IPI score 0–1 was the highest (77.0%). Mean value of Ca-125 serum levels in 148 subjects was 32.48 U/mL (S.D 37.59) shown in Table 1.

Table 1. Description of Sample

Variable	N=148
Age	
Mean±Std	54.28±13.997
Median	57.0
Range (min-max)	8.00-85.00
Sex	
Male	76(51.4%)
Female	72(48.6%)
Education	
Elementary school	43(29.1%)
Junior high school	36(24.3%)
Senior high school	53(35.8%)
Bachelor/Diploma	16(10.8%)
Stage	
1	79(53.4%)
2	46(31.1%)
3	17(11.5%)
4	6(4.1%)
ECOG Performance Status Score	
0	108(73.0%)
1	20(13.5%)
2	17(11.5%)
3	3(2.0%)

Variable	N=148
LDH	
Mean±Std	253.76±227.700
Median	180.00
Range (min-max)	82.00-1377.00
IPI Score	
0-1	114(77.0%)
2	26(17.6%)
3	6(4.1%)
4	2(1.4%)
Ca-125 serum	
Mean±Std	32.48±37.590
Median	22.45
Range (min-max)	1.90-245.00
Therapy	
Chemotherapy	130(87.8%)
Chemoradiation	18(12.2%)
Comorbid	
None	125(84.5%)
Hypertension	19(12.8%)
Hypertension dan Chronic Kidney Disease (CKD)	1(0.7%)
Hypertension and Diabetes Mellitus (DM)	2(1.4%)
Hypertension, DM and CKD	1(0.7%)

Of the 148 study subjects, there were almost 90% alive patients. For 5 years, the percentage of life and died patients was almost the same. In table 2 showed there was a decrease in the number of patients who were alive in 5 years.

Table 2. Patient Outcome Overview

Variable	N=148
1-year Outcome	
Life	128(86.5%)
Death	20(13.5%)
3-year Outcome	
Life	100(67.6%)
Death	48(32.4%)
5-year Outcome	
Life	77(52.0%)
Death	71(48.0%)

Comparison of the characteristics of subjects at 1 year of survival found that the mean age in the live group was 51.80±12,879 years, 63 male (49.2%) and 65 female (50.8%). In the death group, the mean age was 70.10±10,115 years, male 13 (65.0%) and female 7 (35.0%). The level of education in the most living group was senior high school 52 (40.6%) and elementary school 12 (60.0%) in the group died. Based on the statistical test, p value were age 0.0001, education 0.004, and sex p = 0.189. Meanwhile, the clinical characteristics of patients based on the stage, ECOG, LDH, IPI score, Ca-125, and comorbid were $p<0.05$, so there is a significant difference in the proportion of the group of patients who lived and died (survival 1 year).

At 3 years of survival, the mean age in the live group was 48.29 ± 11,928 years, male 46 (46%) and female 54 (54%). In the died group, the mean age was 66.75 ± 8,826 years, male 30 (62.5%) and 18 (37.5%) female. The education level in the most live groups was senior high school 50 (50%) and elementary school 26 (54.2%) in the dead group. Based on statistical tests, the p value for age, education, stage, ECOG, LDH, IPI, Ca-125, and comorbid were $p <0.05$, so gender and therapy $p>0.05$.

Table 3. Multivariate Analysis with Binary Logistic Regression in DLBCL patients

		B	df	p	OR	CI 95%	
						Lower	Upper
EARLY MODEL	Age	0.719	1	0.165	2.052	0.744	5.657
	Sex	-6.413	1	0.144	0.002	0.000	8.912
	Education	6.458	1	0.151	637.837	0.094	4307215.328
	Stage	-2.592	1	0.232	0.075	0.001	5.270
	ECOG	5.732	1	0.124	308.715	0.206	461761.029
	LDH	0.003	1	0.424	1.003	0.996	1.010
	IPI Score	-0.422	1	0.772	0.656	0.038	11.317
	Ca-125 level	0.123	1	0.085	1.131	0.983	1.301
	Comorbid	3.114	1	0.226	22.500	0.145	3492.150
FINAL MODEL	Age	0.276	1	0.027**	1.318	1.032	1.682
	Education	1.743	1	0.082	5.712	0.800	40.804
	ECOG	2.454	1	0.007**	11.636	1.930	70.146
	Ca-125 level	0.052	1	0.003**	1.054	1.018	1.090

From the multivariate analysis, statistically only the variables age, ECOG score and Ca-125 serum levels had a strong correlation in predicting 1 year survival. (Table 3)

Table 4. Mean and median survival time in DLBCL patients

Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
3.085	.186	2.720	3.449	3.000	.282	2.448	3.552

Estimation is limited to the largest survival time if it is censored.

Table 4 shows the median survival for all subjects was 3 years, meaning that 50% of subjects had died within 3 years.

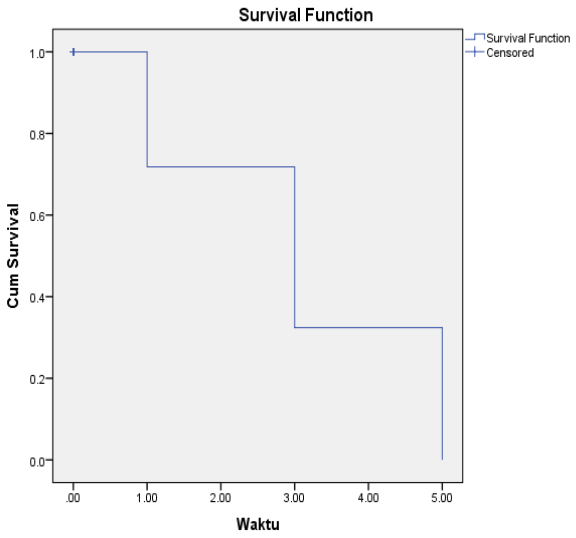

Figure 1. Survival curves of DLBCL patient in the head and neck

3.2 Discussion

Non-Hodgkin Lymphoma can come from B lymphocytes, T lymphocytes, or Natural Killer (NK) cells. Several studies were reported that NHL from the B cell type had a higher incidence than T cell type, with NHL type DLBCL being the most prevalent.13

In this study, DLBCL patients were found to be more male (51.4%) than female (48.6%). This is similar to the Reksodiputro study,5 male (55.5%) and female (44.5%) of NHL sufferers in Indonesian hematology centers. Paramartha and Rena, 13 male (54%) and 46% female. Male is at greater risk of NHL due to smoking habits, occupational factors, environmental and pesticide exposure. In Indonesia, farmers, forest workers and agricultural workers are mostly men.14

Our results showed that the mean age was 54.28 years, with a median of 57.0 (range, 8-85). This study did not differ significantly from the previous studies. Shi et al,15 reported median age of 57 (range, 7-85) years for 1.085 patients with DLBCL in China. Similarly, Peng et al,16 reported an age range of 2–90 years and median age of 64.5 years among 1.929 patients from National Cancer Database (NCDB) clinical oncology in USA. In a study in Netherlands, Issa et al,17 included 23.527 patients with an age range of 15–103 years (mean, 15 years). The age range and median age in a study of 88 patients with NHL by Paramartha and Rena,13 was 17–77 and 50.5 years, respectively. Similarly, a 164-patient reported by Reksodiputro,5indicated a median age of 51 years.

By level of education, elementary and junior high school education gained as much as 53.4%. The knowledge level of the patient to disease and economic problems are all factors that influence the survival.18 Following our findings, Paoli et al,19 described that the DLBCL stage is directly proportional to the ECOG performance status. It was found that the most DLBCL stages were stage 1 (53.4%) and the highest ECOG score of 0 (73%).

Patients with elevated serum LDH at initial diagnosis had a lower survival rate than those with normal LDH levels. Lactate Dehydrogenase has become a component of the International Prognostic Index (IPI), a clinical tool for predicting the prognosis of patients with aggressive NHL. Elevated LDH during or after active treatment can indicate poor treatment outcomes and recurrence/progression of DLBCL disease.20 Our findings that normal LDH and IPI score 0-1 (77%).

Of the 148 total patients, mean Ca-125 serum level was 32.48 U/ml, SD 37.59. From the data, 117 patients (79.1%) had Ca-125 levels below 35 U/ml, 31 (20.9%) Ca-125 serum levels exceeded the cut-off ≥35 U/ml and 31 subjects diagnosed with advanced DLBCL. These results are consistent with Garg and Goyal,21 that serum Ca-125 levels will increase beyond the cut-off ≥35 U/ml in advanced stage. The presence of comorbid will increase the risk of death in patients. It is proven in this study that 15.5% of the outcome of DLBCL patients died both at 1 and 3 years of survival.

Chemotherapy is the most important therapeutic modality, especially for lymphoma with an aggressive phenotype such as B cell lymphoma. The most commonly used chemotherapy regimen for DLCBL is Cyclophasphamide Doxorubicin Vincristine Prednisone (CHOP) in combination with rituximab.22 In this study, 130 patients with DLBCL received chemotherapy (87.8%) and 18 patients (12.2%) with chemoradiation therapy.

Several prognostic factors were independent predictors of LNH patient survival, including IPI score, LDH level, age, and stage.23 Multivariate statistical analysis in this study obtained $p < 0.05$ at age, ECOG score, and Ca-125, which means a significant relationship in predicting outcome. The median survival for all subjects was 3 years, meaning that 50% of subjects had died within 3 years. The survival B cells type of NHL was significantly better than T cell types

and one of the independent predictors of NHL patient survival. Histopathologic of follicular type B cells was reported to have a tendency to grow slowly and an average survival of 1, 3, and 5 years respectively according to 87%, 78.3%, and 60.9%.11 Ninkovic and Lambert [24] reported the 5-year relative survival of DLBCL was 56.7% in UK. Issa et al [17] found increase 5-year survival rate was 58% in Netherlands period 2005-2010. Shi et al, [15] reported the 5-year overall survival rate and progression-free survival rate for DLBCL patients were 62.5% and 54.2%.

The primary site of lymphoma, either the lymph node or different extranodal territories are important in determining the clinical features, treatment options, and outcomes of NHL [15]. Another thing that affects the survival of LNH sufferers is the intolerance of side effects and the toxicity of chemotherapy regimens, especially LNH with very aggressive in addition to growing quickly has a poor response to chemotherapy, so it has a poor prognosis [25]. With the existence of an accurate prediction of survival, it can be a consideration for doctors in determining the therapeutic modality to be chosen, whether to do curative or palliative therapy.

Limitations of this study were using a retrospective analysis such as missing information, the long time follow-up, and the homogeneity of selected patients influenced the results. In this study, the authors did not conduct direct interviews and check the actual condition of the subject. Future studies suggest evaluating the effect of each chemotherapy regimen and other therapeutic modalities as well as how much comorbid influence on the survival of DLBCL patients.

4. CONCLUSION

3-year Overall survival rate for DLBCL patients was 50%. Age, education, stage, ECOG, LDH, IPI, Ca-125, and comorbid had significant effect in 3-years survival rate of DLBCL patients.

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