Prognostic Values of Hemoglobin and Red Blood Cell Distribution Width to Overall Survival in Non-Hodgkin Lymphoma

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ABSTRACT

Background. After the Rituximab era, baseline International Prognostic Index (IPI) is not sufficient for the initial risk stratification of patients with Non-Hodgkin lymphoma (NHL). Low hemoglobin (Hb) levels and high red blood cell distribution width (RDW) baseline are known to be associated with poor outcomes and overall survival in malignancy. This study aimed to evaluate the prognostic value of Hb and RDW to overall survival in NHL patients who undergoing chemotherapy at Dr. Sardjito Hospital.
Method. A retrospective cohort study in NHL from patients' medical records diagnosed from 2014 to 2018 and undergoing chemotherapy at Dr. Sardjito Hospital. The prognostic influence of clinical factors including Hb and RDW on 3 years of overall survival were studied by using Kaplan-Meier curves and univariate Cox regression tests. To evaluate the independent prognostic relevance of basic characteristics data (age, gender, BMI, performance status, Ann Arbor stage, extranodal involvement), Hb, and RDW, multivariate Cox proportional hazards regression was applied.
Results. From 292 NHL patients included, the median Hb was 12.7 g/dL and the median RDW was 14.2%. The mean survival time was 31.13 months, 38 patients (13%) died during the 3 years of follow-up. The most common causes of death were sepsis (68.4%) and 12 patients (4.1%) died within <30 days of chemotherapy. Based on Cox regression univariate analysis, patients with lower Hb levels (<10 gr/dL) had a 3-year overall survival lower than Hb>10 gr/dL (71% vs. 87%, CI 95%, p=0.014), with Hazard Ratio 2.49 (p=0.02). Patients with higher RDW>15.5 levels had lower overall survival than patients with RDW<15.5 levels (77.5% vs. 91.1%, CI 95%, p=0.002), and Hazard Ratio 2.78 (p=0.02). Based on multivariate analysis, performance status (OR=2.589, CI 95%, 1.225-5.471, p=0.013) and RDW (OR=2.292, CI 95%, 1.106-4.48, p=0.026) are independent predictor factors of 3-year overall survival.
Conclusion. NHL patients with lower Hb and higher RDW levels have lower 3-year overall survival.

Keywords: *Hemoglobin, RDW, Non-Hodgkin Lymphoma, prognostic value, overall survival*

ABSTRAK

Latar Belakang. *Kemampuan skor* International Prognostic Index *(IPI) sebagai prediktor prognosis Limfoma Non- Hodgkin (LNH) menjadi menurun setelah era rituksimab, sehingga penelitian tentang prediktor prognosis LNH masih terus dilakukan. Kadar hemoglobin (Hb) rendah dan* red blood cell distribution width *(RDW) tinggi pada awal diagnosis diketahui berhubungan dengan*

kesintasan hidup yang rendah pada pasien keganasan. Penelitian ini bertujuan untuk mengetahui nilai prognostik kadar Hb dan RDW terhadap kesintasan hidup pasien LNH yang menjalani kemoterapi di RSUP Dr. Sardjito.
Metode Penelitian. *Penelitian kohort retrospektif berdasarkan data rekam medis pasien LNH yang terdiagnosis sejak tahun 2014-2018 dan menjalani kemoterapi di RSUP Dr. Sardjito. Hubungan antara kadar Hb dan RDW terhadap kesintasan hidup dianalisis menggunakan metode Kaplan-Meier dan* Cox regression test. *Untuk menentukan faktor prediktor independen terhadap kesintasan hidup 3 tahun dilakukan analisa multivariat* cox regression *terhadap data karakteristik dasar (umur, jenis kelamin, indeks masa tubuh, status performa, stadium Ann Arbor, dan keterlibatan ekstranodal), Hb, dan RDW.*
Hasil Penelitian. *Dari 292 pasien LNH, didapatkan median Hb 12.7 g/dL dan RDW 14.2%. Rerata kesintasan hidup 31.13 bulan, dengan pasien meninggal selama periode* follow-up *3 tahun sebanyak 38 pasien (13%). Sebab kematian terbanyak adalah sepsis (68,4%) dan 12 pasien (4.1%) meninggal dalam waktu <30 hari setelah kemoterapi. Berdasarkan analisis univariat* Cox Regression*, pasien dengan kadar Hb<10 gr/dL memiliki kesintasan hidup 3 tahun lebih rendah dibandingkan pasien dengan kadar Hb>10 gr/dL (71% vs 87%, CI 95%, p=0.014), dengan* Hazard Ratio *2.49 (p = 0.02). Pasien dengan kadar RDW>15.5 memiliki kesintasan hidup yang lebih rendah dibandingkan pasien dengan kadar RDW<15.5 (77.5% vs 91.1%, CI 95%, p=0.002),* Hazard Ratio *2,78 (p = 0.02). Berdasarkan analisa multivariat, status performa (OR=2.589, CI 95%, 1.225-5.471, p=0.013) dan RDW (OR=2.292, CI 95%, 1.106-4.748, p=0.026) merupakan faktor prediktor independen terhadap kesintasan hidup 3 tahun.*
Kesimpulan. *Pasien LNH dengan kadar Hb rendah dan kadar RDW tinggi memiliki kesintasan hidup yang lebih rendah.*

Kata Kunci: Limfoma Non-Hodgkin, Hemoglobin, RDW, kesintasan hidup

INTRODUCTION

Non-Hodgkin Lymphoma (NHL) is the most common type of lymphoid malignancy and accounts for about 62.4% of all lymphoid cases.[1] NHL, a heterogeneous disease, can be subdivided into several types according to different manifestations and molecular characteristics using the WHO classification. Even though the survival rate has been improved by immunochemotherapy advances in the last two decades, 30-40% of NHL patients experience relapse or refractory disease.[2] In the 1990s, several prognostic score systems have been established and applied to predict the survival of patients with NHL. The International Prognostic Index (IPI) is a well-established prognostic index system that stratified NHL patients into four risk groups: low, low-intermediate, high-intermediate, and high with a 5-years survival of each group was 73%, 51%, 43%, and 26%, respectively.[2,3] The IPI has been widely used in clinical applications and is the standard practical prognostic tool for NHL patients. However, it was established before the immunochemotherapy era, which has dramatically increased the survival rate. According to various studies, the IPI system failed to identify a high-risk group after immunochemotherapy.[2]

Based on 3 major studies, the MabThera International Trial (MInT), the *Groupe d'Etude des Lymphomes de l'Adult* (GELA study), and the Rituximab with CHOP over 60 years (RICOVER-60 trial), the addition of Rituximab to CHOP standard chemotherapy can improve the prognosis of NHL patients, without increasing its toxic effects.[4]

Several studies of other prognosis evaluation systems have been developed for more precise evaluation of NHL patients, ranging from simple laboratory and clinical parameters, modern radiological examinations, to molecular examinations, along with the improvement of NHL survival which is getting better after the rituximab era.[2]

Low baseline hemoglobin (Hb) levels are one of the predictors of poor prognosis, chemotherapy failure, and poor clinical stages in NHL patients.[1] Red cell distribution width (RDW) is routinely examined with the complete blood count (CBC) test that shows the heterogeneity in erythrocyte size.[5] Recent studies have reported high RDW levels and increased mortality in malignancy, particularly lung cancer and multiple myeloma.[5,6] The mechanism underlying those associations of RDW with survival or disease progression has not been elucidated, but high levels of RDW are thought to be provoked by chronic inflammation, poor nutritional status, oxidative stress, and age-associated disease via changes in erythropoiesis.[6] Therefore, this study aimed to determine the prognostic value of Hb and RDW levels to the overall survival of NHL, especially at RSUP Dr. Sardjito.

METHODS

This is a retrospective cohort study using data from the medical records of NHL patients who were first diagnosed in 2014-2018 and received standard chemotherapy at RSUP Dr. Sardjito. This research was begun at the time ethical clearance was published, from May 2021 to December 2021. The research was done in the Medical Records Division and Tulip Division of Dr. Sardjito Hospital, Yogyakarta. The inclusion criteria were patients who were diagnosed with NHL for the first time at Dr. Sardjito Hospital, Yogyakarta between 2014 and 2018, aged >18 years, and received standard therapy. The exclusion criteria were subjects with incomplete data, who did not undergo therapy, and with severe anemia due to acute bleeding.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 23 and consisted of determining the cut-off value using the ROC curve, univariate analysis, multivariate Cox regression, and survival test using the Kaplan-Meier method. This study was approved by the Medical and Health Research Ethics Commission, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada (FKKMK UGM) and was permitted by the Director of Dr. Sardjito Hospital Yogyakarta.

Table 1. Patient characteristics (n=292)

Variable	n (%)
Sex	
Male	**168 (58.5%)**
Female	124 (42.5%)
Age	56 years (49-64 years)
<60 years	**196 (67%)**
≥60 years	96 (33%)
Body mass index (BMI)	21.19 kg/m^2 (18.73 – 23.59 kg/m^2)
Underweight	55 (19.2%)
Normal	**237 (80.8%)**
Eastern Cooperative Oncology Group (ECOG) Performance Status	
0-1	**247 (87.6%)**
≥2	45 (12.4%)
Extranodal involvement	
Single	**256 (88%)**
Multiple	36 (12%)
Ann-Arbor clinical staging	
I-II	**221 (75.4%)**
III-IV	71 (24.6%)
Lactate dehydrogenase (LDH)	
Normal	62 (42.8%)
High	**83 (57.2%)**
International Prognostic Index (IPI) Score	
0-1	**258 (88.4%)**
≥2	34 (11.6%)
Non-Hodgkin Lymphoma subtype	
Diffuse Large B-cell Lymphoma (DLBCL)	**138 (47.26%)**
Small to intermediate B-cell Lymphoma	108 (36.98%)
T-Cell Lymphoma	23 (7.87%)
Follicular Lymphoma	10 (3.42%)
Anaplastic Large Cell Lymphoma	3 (1.02%)
Small Lymphocytic Lymphoma	1 (0.34%)
NOS	9 (3.08%)
Haemoglobin (Hb)	12.7 g/dL (11.4 – 13.7g/dL)
Hb ≥ 10 g/dL	**268 (91.8%)**
Hb < 10 g/dL	24 (8.2%)
Red cell distribution width (RDW)	14.2% (13%-16%)
Normal	**235 (80.5%)**
High	57 (19.5%)
Chemotherapy regiment	
RCHOP	**197 (67.5%)**
RCEOP	39 (13.4%)
RCOP	7 (2.4%)
CHOP	33 (11.3%)
CEOP	15 (5.1%)
COP	1 (0.3%)
Three years-survival	
Alive	**254 (87%)**
Dead	38 (13%)
Mean survival time	32.3 months

NOS: not otherwise specified; RCHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; RCEOP: Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone; RCOP: Rituximab, Cyclophosphamide, Vincristine, Prednisone; CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; CEOP: Cyclophosphamide, Etoposide, Prednisolone, Vincristine; COP: Cyclophosphamide, Vincristine, Prednisone.

RESULTS

The total number of eligible patients at Dr. Sardjito Hospital with NHL was 497. Those who met the inclusion criteria were 313 patients, 21 subjects were excluded due to loss of follow-up, and the total number of subjects included for analysis was 292.

Based on the characteristics data in Table 1, from 292 NHL patients, 168 (58.5%) the subjects were males, 196 (67%) patients were <60 years, 237 (80,8%) patients with normal bidy mass index (BMI), 247 (87.6%) patients with good performance status (ECOG 0-1), 221 (75.4%) patients with early-stage (stage I-II), 138 (47.26%) patients with subtype DLBCL, and 256 (88%) patients with single extra nodal involvement.

From the baseline laboratory data, the median haemoglobin (Hb) was 12.7 g/dL (11.4 - 13.7 g/dL), 268 (91.8%) patients with normal Hb (≥ 10 g/dL). The median of red cell distribution width (RDW) was 14.2% (13% - 16%), with 235 (80.5%) patients with normal RDW levels. Of 145 patients who were examined for baseline lactate dehydrogenase (LDH), 83 (57.2%) were patients with high LDH. Based on the chemotherapy regimen, 197 (67.5%) patients received standard chemotherapy with the RCHOP regimen. Other standard chemotherapy regimens used were the RCEOP regimen (n=39; 13.4%), the RCOP regimen (n=7; 2.4%), the CHOP regimen (n=33; 11.3%), the CEOP regimen (n=15; 5.1%), and the COP regimen (n=1; 0.3%).

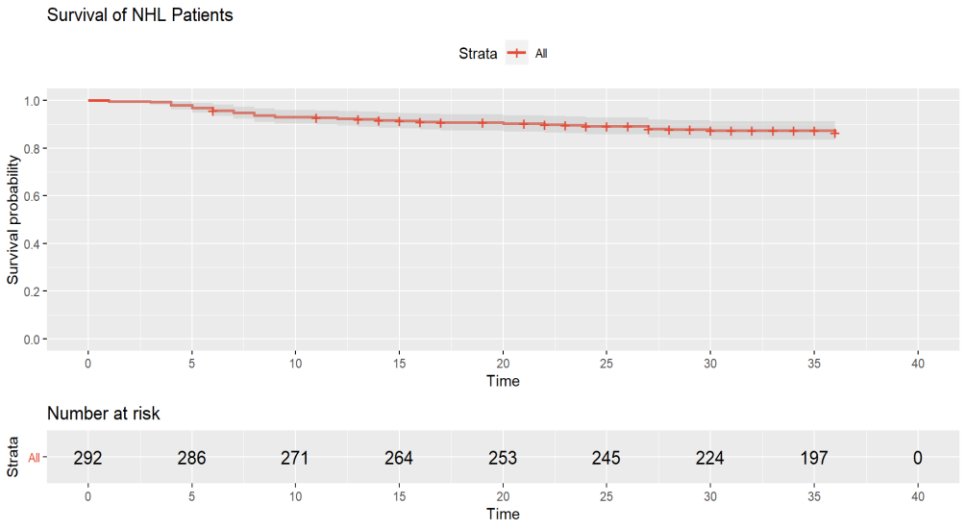

Figure 1. Three Years Overall Survival (OS) of NHL Patients

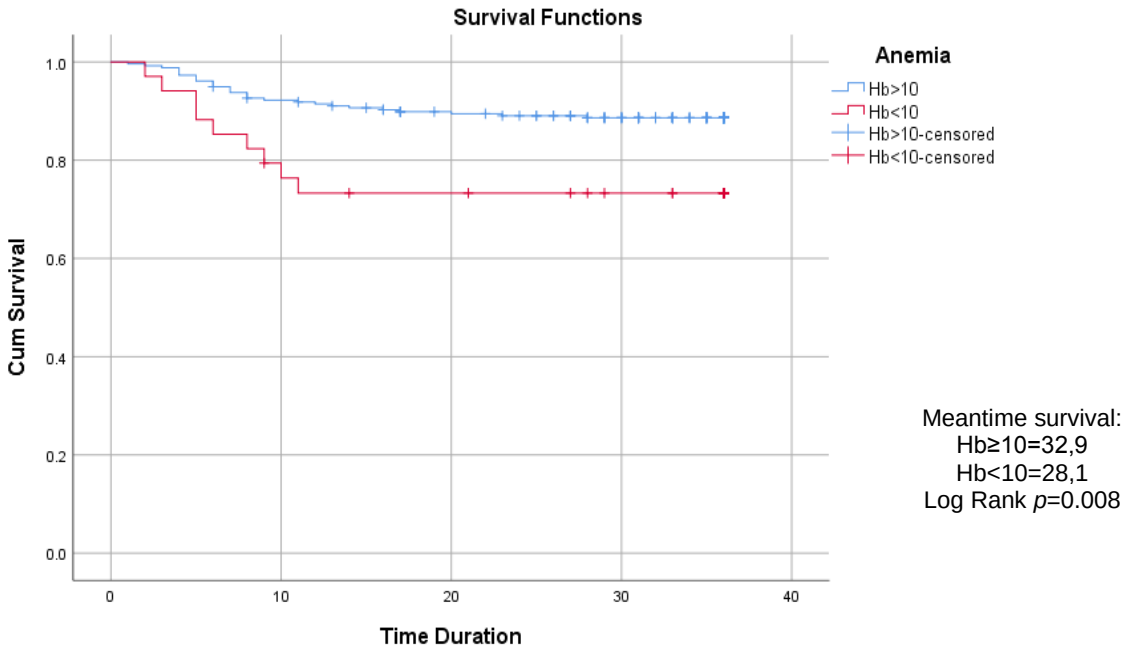

Figure 2. Kaplan-Meier Analysis for 3-year Overall Survival According to Baseline Hb (<10 and ε 10 g/dL) in NHL patients (n=292)

Figure 1 shows the 3-year overall survival (OS) of NHL patients at Dr. Sardjito Hospital was 87%, with a mean survival of time 32.3 months. Based on Kaplan-Meier's survival analysis (Figure 2), after follow-up for 3 years, NHL patients with lower Hb (Hb < 10 g/dL) had lower 3-year OS compared to NHL patients with higher Hb (Hb ε 10 g/dL). The 3-year OS of the subjects with Hb ε 10 mg/dl was higher than subjects with Hb < 10 mg/dl (88.8% vs 73.5%; *p*=0.008). Based on the Cox Regression analysis (Table 2) the Hazard ratio (HR) was 2,631 (*p*=0.011).

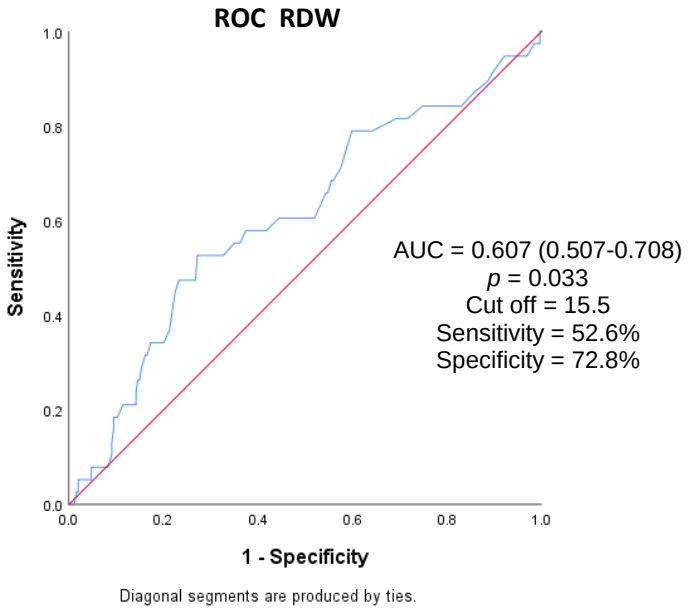

Figure 3. Receiver operating characteristic (ROC) analysis of red cell distribution width (RDW)

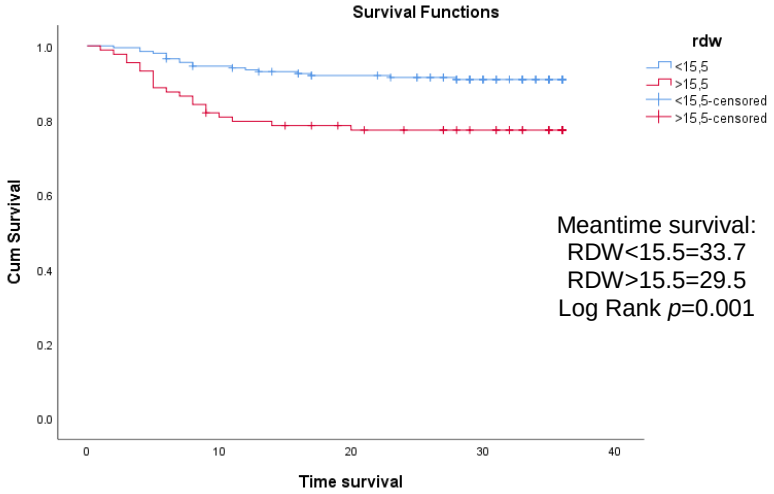

Figure 4. Kaplan-Meier Analysis for 3-year Overall Survival according to baseline RDW (normal < 15,5% and elevated > 15,5%) in NHL patients (n=292)

Table 3. Cox Regression Analysis for 3-year Overall Survival according to Baseline RDW

		Status						
		Alive		Dead		*p*	HR	CI 95%
		n	%	n	%			
RDW	<15.5	185	91.1%	18	8.9%	0.002	2.78	1.47-5.26
	>15.5	69	77.5%	20	22.5%			

RDW: red cell distribution width, HR: hazard ratio, CI: confidence interval

The univariate Cox Regression analysis (Table 4) showed that prognostic factors for 3-year OS of NHL patients were high ECOG performance status (≥2, p=0.004) and advanced ann arbor clinical stage (stage III-IV, p=0.020). Meanwhile, no statistically significant differences in 3-year OS of NHL patients were observed for other variables, including age, BMI, subtype histopathology, and extranodal involvement (p>0.05).The multivariate Cox Regression analysis (Table 5), including variables that had a p-value of <0.05 in the univariate analysis, showed that higher RDW (>15.5%, OR=2.292, 95% CI, 1.106-4.748, p=0.026) and high ECOG performance status (≥2, OR=2.589, 95% CI, 1.225-5.471, p=0.013) were found to be an independent prognostic factor of 3-year OS in NHL patients.

Table 4. Univariate Analysis for 3-year Overall Survival in Patients with NHL

		3-years OS						
		Alive		Dead		*p*	HR	CI 95%
		n	%	n	%			
Age	<60 years	196	87.2%	25	12.8%	0.995	0.99	0.50-1.99
	≥60 years	96	87.5%	13	12.5%			
ECOG Performance Status	0-1	247	89.5%	26	10.5%	**0.004***	**2.96**	**1.43-6.14**
	≥2	45	71.4%	12	28.6%			
Body mass index	Underweight	55	90.9%	5	9.1%	0.306	1.64	0.64-4.19
	Normal	237	85.7%	33	14.3%			
Subtype	Non-DLBCL	154	85.1%	23	14.9%	0.370	1.35	0.70-2.58
	DLBCL	138	89.1%	15	10.9%			
Ann Arbor clinical stage	I-II	221	89.9%	23	10.1%	**0.020***	**2.19**	**1.13-4.21**
	III-IV	71	78.9%	15	21.1%			
Extra nodal involvement	*Single*	256	88.7%	29	11.3%	0.052	2.17	0.99-4.76
	Multiple	36	77.1%	9	22.9%			

* p<0.05. ECOG: Eastern Cooperative Oncology Group, OS: overall survival, HR: hazard ratio, CI: confidence interval

Table 5. Multivariate Analysis for 3-year Overall Survival in Patients with NHL

			95,0% CI	
	p	OR	Lower	Upper
Haemoglobin	0.258	1.617	0.703	3.717
RDW	**0.026***	**2.292**	**1.106**	**4.748**
ECOG Performance Status	**0.013***	**2.589**	**1.225**	**5.471**
Ann Arbor clinical stage	0.159	1.671	0.818	3.413

RDW: red cell distribution width, ECOG: Eastern Cooperative Oncology Group, OR: odd ratio, CI: confidence interval

DISCUSSION

In this study, the patient characteristics are similar to the patient characteristics of a multicentre study on the epidemiology and survival of NHL patients in Indonesia published in 2015. In those studies, the following patient characteristics were obtained: the median age of the patient was 51 years, most of the patients were male (55.5%), stage II (35.4%), performance status 0-1 (77.7%), the most common type of histopathology was DLBCL (68.2%), extranodal involvement <2 (100%), and IPI score 2 (36%).[7] Characteristics of NHL patients at RSUP Dr. Sardjito are generally similar to national characteristics. In this study, the largest proportion of histology types was DLBCL (47.26%), according to global data of 30-40%.[2]

With similar patient characteristics to national characteristics, the 3-year OS of NHL patients at Dr. Sardjito Hospital in this study was better. The 3-year OS of NHL patients in the previous study was 36.4% with a median survival time was 8 months.[7] Meanwhile, the OS of 3-year NHL patients in this study was 87%, with a median follow-up was 31.3 months. Similar to the results of a multicentre retrospective study by Shi *et al.*, in 314 DLBCL patients, 3-year OS was 75.7% with a median follow-up was 30.3 months.[2] The better 3-year OS of NHL patients in this study compared with the previous national multicentre study in 2015, showed the benefit and the development of immunochemotherapy in the NHL coupled with the better accessibility to chemotherapy. In this study, 83.3% of patients received standard chemotherapy with a Rituximab-based regimen. The administration of a standard Rituximab-based chemotherapy regimen, namely R-CHOP, remains the mainstay of therapy and can achieve long-term disease control in nearly 90% of patients presenting with limited-stage and in up to 60% of those presenting with advanced stages.[8]

The prevalence of anemia in lymphoproliferative diseases and malignancy is quite high. The results of this study showed NHL patients with normal Hb (≥ 10 g/dL) had a better 3-year OS (87%) than NHL patients with lower

Hb (<10 g/Dl, 71%) and were statistically significant (p=0.014), with HR 2.49 (p=0.02). These results are similar to previous studies, which showed that lower Hb levels in NHL patients before therapy were significantly associated with a poor prognosis.[1,9–11] Hb is an easy, inexpensive, and reproducible laboratory parameter. Therefore, Hb levels should be able to be combined in the established prognostic index.[11]

Because the Hb level included in this study was observed naïve to treatments, hence the most possible pathogenesis was due to the progression of the NHL disease itself. Inflammation has been recognized to play a massive role in the development of lymphoma. The pathogenesis of anemia in lymphoma is suggested to be related to inflammation in B-cell NHL patients, which causes excessive cytokine production, abnormal iron reserve utilization, cell infiltration in the bone marrow, autoimmune hemolytic, and impaired erythropoietin synthesis.[12] Inhibition effects of interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) on erythropoietin production have been shown to interfere with the erythroid progenitor response to erythropoietin in vivo studies. Increased IL-6 is specifically considered to be the role factor causing anemia in DLBCL patients and high serum IL-6 levels are indicators of poor prognosis in DLBCL patients.[11,13] Pro-inflammatory cytokines also interfere with iron metabolism. Hepcidin is the main regulator of iron metabolism and a mediator of inflammatory causes of anemia. Pro-inflammatory cytokines cause an increase in hepcidin, which causes iron retention in macrophages so that the amount of iron available for erythropoiesis decreases. This pathogenesis plays a role in chronic disease anemia, including anemia in malignancy.[12,13]

According to ROC analysis, the area under the curve (AUC) for RDW was 0.607 (95% CI, 0.507-0.708, p=0.033) optimal cut-off value was 15.5%, with 52.6% sensitivity and 72.8% specificity. From the results of the AUC curve, the ability of the RDW cut-point 15.5% to discriminate was 0.607. Based on the reference, the ideal AUC value is >0.7. An AUC value of $0.6<AUC\leq0.7$ falls into the category of sufficient or acceptable. Especially when used for diagnostic tools, the higher the AUC, of course, the better. However, it is often found that several diagnostic tools with the same AUC value can produce different performances, influenced by their sensitivity and specificity values.[14] In this study, the RDW specificity value was 72.8%, so RDW was more specific but insensitive in discrimination NHL patients who had better a 3-year OS.

The cut-off value of RDW is similar to the previous study by Perisa *et al.* From the study of Perisa *et al.*, the 5-year OS of DLBCL patients with

RDW >15% was lower (36.6% vs. 79.4%, p<0.001, log-rank test) and from the results of the Cox regression analysis, it was showed that RDW >15% was an independent prognostic factor against survival (HR 3.654, 95% CI).[5] In this study, NHL patients with higher RDW (>15.5%) also had lower OS (77.5% vs 91.1%, p=0.002), and from univariate cox regression analysis obtained HR = 2.78 (CI 95%, 1.47-5.26, p=0.002). The results of this study are consistent with similar studies by Perisa *et al.*, Zhou *et al.*, and Li *et al.*, which showed that higher RDW levels in NHL patients were significantly associated with poor prognosis. Higher RDW is significantly associated with more frequent B-symptoms (p=0.001), higher IPI scores (p=0.032), more extranodal involvement (p=0.035), and lower ECOG performance status (p=0.031). Higher RDW has a lower survival (53.6% vs. 83.6%, p<0.001), with OR = 0.345 (p<0.001).[5,10,15]

Based on the studies by Ai *et al.*, 7 trials with 1031 patients suffering from hematological malignancies were included in the meta-analysis, and the results indicated that increased pretreatment RDW predicted poor overall survival (HR = 2.35, 95% CI 1.70–3.24), poor progress-free survival (HR = 2.44, 95% CI 1.70–3.49) and poor event-free survival (EFS) (HR = 3.15, 95% CI 1.59–6.25). Furthermore, similar results were observed in subgroup analysis stratified by cancer type, such as multiple myeloma, and diffuse large B cell lymphoma.[16]

RDW has been used as one of the indicators of the inflammatory response in malignant patients. Inflammation and malnutrition are known to be associated with increased RDW. Oxidative stress conditions, inflammation, erythrocyte fragmentation, insufficient nutrient intake, hypertension, dyslipidemia, and impaired erythropoietin function will cause an increase in RDW. Several studies have shown an association of increased RDW with an increase in inflammatory indicators such as IL-6, LED, hs-CRP, transferrin, tumor necrosis factor, leucocytes, neutrophils, fibrinogens, and anemia. Some studies have also shown an association of RDW with levels of erythropoietin, albumin, iron, folic acid, and vitamin B12.[5,10,16] High levels of RDW reflect an ongoing inflammatory process in the body that interferes with erythrocyte maturation. This inflammatory process also affects the production of the hormone erythropoietin, causes deficiencies in some nutrients such as iron, vitamin B12, and folic acid, and triggers oxidative stress processes. Inflammation disrupts the process of erythropoiesis and interferes with the maturation of erythrocytes by changing the cell membranes of erythrocytes. The role of inflammation in the development of lymphoma has been widely

known. Lymphoma progressivity is influenced by interactions of tumor cells and non-neoplastic cells, as well as interactions with the environment around tumor cells.[15]

Based on univariate analysis, the classical variables that are significantly associated with 3 years OS were ECOG performance status and ann arbor clinical stage. Poor performance status and advanced clinical stage have lower 3-year OS. From the multivariate analysis, only RDW and ECOG performance status are consistent as independent prognostic predictors of 3-year OS in NHL patients. Other classical variables such as age, sex, BMI, Ann Arborr stage, histopathological type, and extranodal involvement have no significant differences in 3-year OS. These results are similar to Zhou *et al.* studies, from the multivariate analysis, only RDW is consistent as an independent predictor of survival. The variables of age, gender, B symptoms, performance status, LDH, stage, IPI score, extranodal involvement, and histopathology type were not significantly associated with poor survival. [15] The development of immunochemotherapy after the Rituximab era, was able to overcome the constraints of classical factors such as old age, less BMI, and advanced stage.

Based on cohort research by the Tromsø Study conducted in 1994-1995 through to the end of follow-up on December 31, 2010, with a total sample of 25,383 patients, there was an association between high RDW and increased risk of regional and distal metastasis at the time of diagnosis in men and women of post-menopausal age. In men, a 1% increase in RDW was associated with a 21% increased risk of regional cancer spread (HR 1.21, 95% CI 1.11-1.33) and a 19% increased risk of distal metastasis (HR 1.19, 95% CI 1.06-1.33).[17] Those cohort studies indicate that anemia, and iron deficiency in particular, is probably not the underlying link between high RDW and cancer risk. Those studies suggest that mechanisms other than anemia and iron deficiency without anemia, such as worsened health conditions with subsequent low-grade inflammation, may link high RDW to cancer risk.[17]

Based on the MabThera International Trial (MInT), the addition of Rituximab to CHOP standard chemotherapy by 6 cycles can improve the prognosis of DLBCL patients without being accompanied by an increase in toxic effects. Administration of a combination chemotherapy regimen of Rituximab and CHOP 6 cycles in young DLBCL patients with a good prognosis was able to increase event-free survival (EFS) 3 years by up to 20% compared to the group with CHOP 6 cycle chemotherapy without Rituximab (79% [95% CI 75–83] vs 59%[54–64], log-rank p<0·0001), and increased survival of 3 years to 9% (93%[90–95] vs 84% [80–88], log-rank

p=0·0001).[18] After being followed for up to 6 years, EFS in the group of patients who got Rituximab was 18.5% higher than the group without Rituximab (74.3% vs 55.8%, CI 95%, log-rank p<0.001).[4]

Similarly, in elderly lymphoma patients (60-80 years), based on research by *the Groupe d'Etude des Lymphomes de l'Adult* (GELA study), the addition of rituximab-CD20 monoclonal antibodies, to CHOP chemotherapy increases the complete-response rate, EFS and survival of lymphoma patients, as well as decreases the risk of failure and mortality of therapy. The complete-response rate of the group of elderly patients given chemotherapy with the CHOP and rituximab (R-CHOP) regimens was higher than that of the CHOP group alone (76% vs. 63%, p = 0.005). EFS and 2-year survival are also better (57% vs 38%, p <0.001, and 70% vs 57%, p=0.007)).[19] After being followed for 10 years, the survival of 10 years in the group of patients who got rituximab was 15% higher than the group of patients without rituximab (43% vs. 28%, p<0.001), with a median survival time of 7 years 9 months in the group with rituximab and 37 months in the group without rituximab.[20] Even based on the study of Rituximab with CHOP over 60 years (RICOVER-60 trial), the addition of rituximab in the group of elderly patients with lymphoma can decrease the incidence of metastasis in the central nervous system (6.9% vs 4.1%, RR 0.58, 95% CI, p=0.046).[21] Those studies indicated that being elderly is not a significant obstacle to the administration of chemotherapy in lymphoma patients. Therefore, until now, research on NHL prognostic predictors, ranging from simple laboratory and clinical parameters, and modern radiological examinations, to molecular examinations continues to develop, along with the improvement of NHL survival that has improved after the rituximab era.[2]

Since our study was retrospective, the limitations were no option due to the inadequateness of data. This study also came from a single care center that is prone to a referral bias. In addition, the assessment of the survival was also influenced by the incidence of loss to follow-up.

In this study, Hb and RDW levels were examined at the beginning of treatment, during the patient's follow-up, many factors could affect Hb and RDW values. Other comorbid factors that can affect Hb and RDW levels have also not been studied, for example, anemia conditions due to chronic diseases such as cirrhosis.

CONCLUSION

NHL patients with lower Hb levels and higher RDW levels had poor 3-year overall survival. Hb and RDW are prognostic factors in NHL patients. Further studies are expected to be

carried out with a prospective cohort design as the clinical development can be followed and the disruptive variables can be precisely controlled. In addition, subsequent studies can combine Hb and RDW levels in an established prognostic index score (R-IPI or NCCN-IPI) to improve sensitivity and specificity in patient stratification to predict the survival and determination of therapy.

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