RESEARCH ARTICLE

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Development of Nomogram for Predicting the Overall Survival of Diffuse Large B-Cell Lymphoma (DLBCL) Patients Based on Clinical Data and Systemic Inflammation Markers

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Abstract

Objective: Diffuse large B-cell lymphoma (DLBCL) is the most prevalent non-Hodgkin lymphoma and an aggressive blood malignancy. Despite the development of prognostic factors for DLBCL across clinical and molecular aspects, the accessibility and affordability can vary, specifically in developing countries. Therefore, this study aimed to examine the systemic immune inflammation index (SII), a predictive factor for DLBCL and generated from basic blood data. The study also established an effective predictive nomogram by integrating clinicopathological factors to predict overall survival (OS). **Methods:** A retrospective analysis was carried out on the laboratory and clinicopathological data of DLBCL patients from January 2012 to December 2020 from the Division of Hematology and Medical Oncology, Department of Internal Medicine, Dr. Sardjito Hospital, Yogyakarta, Indonesia. Cox survival analyses, both univariate and multivariate, were used to find prognostic markers associated with OS. The dynamic nomogram was created using all independent prognostic variables. **Results:** A total of 94 patients were included and based on the Akaike Information Criterion values from multivariate Cox analysis, absolute monocyte count (AMC), platelet count (PLT), platelet-to-lymphocytes ratio (PLR), and SII were independent prognostic factors of OS in DLBCL patients, and are included in the nomogram. The area under the curve in this group was 0.8, while the nomogram's C-index for predicting OS was 0.74. **Conclusion:** This study found that monocyte count, platelet count, PLR, and SII can predict OS in our study population of Indonesian DLBCL. Nomogram created from this findings is a new and potentially effective model for predicting OS.

Keywords: Diffuse large B-cell lymphoma- prognostic factors- overall survival- nomogram

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Introduction

Diffuse Large B-Cell Lymphoma (DLBCL) is the most prevalent histological subtype of non-Hodgkin's lymphoma (NHL). This subtype is a varied group with a range of morphology, immunophenotypes, and biological characteristics [1]. DLBCL represents 25-30% of new NHL cases reported around the world, as reported by previous studies [2, 3]. Standard R-CHOP immunochemotherapy, which includes rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone, can be used to treat the majority of DLBCL cases. A total of 60–70% of DLBCL patients achieve sustained full remission [4], but 30–40% suffer from recurrence or refractory disease [5, 6]. Therefore, careful prognostic evaluation was essential for early diagnosis and effective therapy selection, significantly impacting patients survival.

In patients with DLBCL, three clinical parameter-assisted algorithms forecast overall survival (OS). The International Prognostic Index (IPI), which was first used in 1993, was the most useful instrument throughout the CHOP era and is still in use today [7]. With the introduction of rituximab, identifying high-risk groups using IPI has become challenging. The IPI was updated to the Revised IPI in 2007 [8], to better stratify patients receiving R-CHOP, and the National Comprehensive Cancer Network-IPI [9].

Despite the revision, these systems were not effective in identifying high-risk or relapse/refractory DLBCL patients [10, 11]. Therefore, the development of effective biomarkers to identify aggressive behavior and predict recurrence is crucial to avoid over-medication. Gene expression profiles and molecular genetic markers have recently been used as prognostic indicators for DLBCL survival [12–15], but the high expense shows the need for easily available and reasonably priced criteria for prognosis and therapy recommendations.

The role of systemic inflammatory responses in the

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tumor microenvironment has gained more attention. According to recent research, the lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) are factors that have a major impact on the prognosis of DLBCL patients [16–18]. The relationship between the systemic immune inflammation index (SII) and DLBCL outcomes is rarely investigated, but recent studies showed that a high SII is a poor prognostic indicator in DLBCL [19, 20]. Compared to molecular genetic markers, blood cell-derived biomarkers are more affordable for practical use. Therefore, this study aimed to determine whether inflammatory indices can provide a clinically effective nomogram for predicting the prognosis of DLBCL when paired with other prognostic and clinicopathological markers. This easy-to-use tool visually represents complex formulas to estimate survival probability and enhance predictive accuracy [19, 20].

Materials and Methods

Patients

Clinical and laboratory data from the medical records of DLBCL patients diagnosed and treated at Dr. Sardjito Hospital between January 2012 and December 2020 were extracted for a retrospective analysis. The extraction of data commenced in 2023 after ethical clearance was obtained and eligible candidates were patients who were over sixteen, had a biopsy-based diagnosis, full laboratory, and clinical data, and had conventional treatment with at least four cycles of R-CHOP/R-CEOP. Ethical clearance was obtained from the Ethical Committee of the Faculty of Medicine at Universitas Gadjah Mada with approval number KE/FK/1356/EC/2023.

Data Collection

The data collected in this study included age, lactate dehydrogenase (LDH), number of extranodal sites, Ann Arbor Staging, IPI, percentage of red cell distribution width (RDW), platelet count (PLT), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and absolute monocyte count (AMC). These data were obtained before DLBCL treatment and the SII was calculated by dividing the total amount of platelets by the total number of neutrophils and lymphocytes. In the case of PLR and NLR, the platelet and neutrophil were divided by lymphocyte count, respectively. OS was determined as the time between diagnosis and death, while LMR is the ratio of lymphocytes to monocytes. This study documented 387 patients with a DLBCL diagnosis between 2012 and 2020, as shown in Figure 1. Among these patients, 94 who received at least four cycles of R-CHOP/R-CEOP and had complete IPI met the inclusion criteria for analysis.

Statistical Analyses

Statistical analysis was performed using R for Windows (version 4.2.2 https://cran.r-project.org/bin/windows/base/) and SPSS software (IBM Corporation, USA, version 25). The association between SII and other substantial clinicopathological features was examined using the Chi-square/Fisher's Exact test. To compare the accuracy of each SII/NLR/PLR/LMR index in predicting patient outcomes, the ROC curve was used to calculate the best cut-off values and calculate the area under the curve (AUC). Survival curves were generated using the Kaplan-Meier method to determine OS rates, and comparisons were made with different groups of a variable using the log-rank test.

Univariate and multivariate analyses were conducted using the Cox model to determine prognostic indicators for OS. Based on the model's least Akaike Information Criterion (AIC) value, the optimal subset of covariates was chosen to create a nomogram that forecasts OS. Using the "rms" tool in R software, a nomogram was created based on the results of multivariate analysis using OS endpoints that were 1 to 3 years old. In the primary validation cohort, nomogram accuracy was examined for discriminating using Harrell's C-index, which is the percentage of patient pairings having outcome-consistent prediction [21].

Results

Clinical characteristics of patients

Correlation between SII and clinicopathologic variables

The clinical features of the 94 individuals with confirmed DLBCL who were part of this investigation are shown in Table 1. The female-to-male ratio was 1:1.24, and the average age was 55 years old, with a range of 17 to 80 years. Nine patients (9.58%) had ECOG≥2, while 28 (27.66%) had advanced stages. A total of 49 (52.13%), 27 (28.72%), 15 (15.96%), and 3 (3.19%) patients had low, low-intermediate, high-intermediate, and high IPI scores, respectively. The most popular regimen was R-CHOP (n=83, 88.3%), which was followed by R-CEOP (n=11, 11.7%).

Patients were categorized into two groups according to the SII index cut-off values. Table 1 shows significant differences between the two groups in PLT, ANC, ALC, PLR, NLR, and LMR. However, there were no significant differences in age, ECOG score, extranodal site, LDH, stage, RDW, AMC, and IPI.

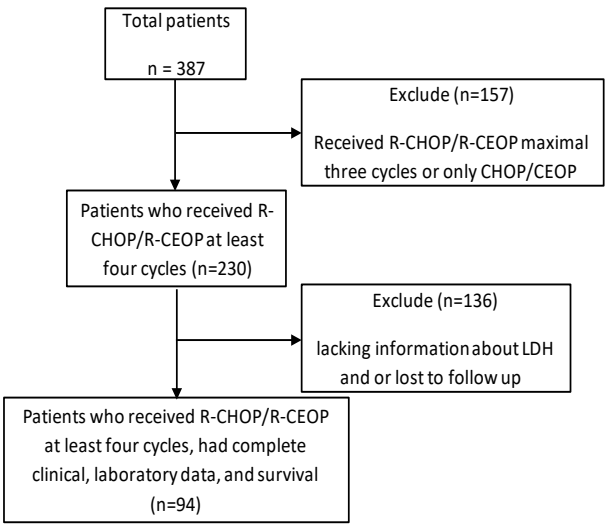

Figure 1. CONSORT Diagram: Flowchart of Patient Data Collection.

Table 1. Relationship between the Clinicopathological of DLBCL Patients and the SII Index

Patient Characteristics	SII Index				p-value
	SII < 1,210.615		SII ≥ 1,210.615		
	n	%	n	%	
Age					
<60	36	38.30	25	26.60	0.8286
≥60	21	22.34	12	12.77	
ECOG score†					
< 2	53	56.38	32	34.04	0.3094
≥ 2	4	4.26	5	5.32	
Sites†					
< 2	51	54.26	33	35.11	1
≥ 2	6	6.38	4	4.26	
LDH					
Normal	21	22.34	7	7.45	0.104
Elevated	36	38.30	30	31.91	
Stage					
I & II	43	45.74	25	26.6	0.5502
III & IV	14	14.89	12	12.77	
RDW (%)					
≤ 14.355	31	32.98	18	19.15	0.7394
> 14.355	26	27.66	19	20.21	
PLT (x 103 / µL)					
< 315.5	37	39.36	8	8.51	9.88E-05
≥ 315.5	20	21.28	29	30.85	
ANC (x 103 / µL)					
< 5.29	43	45.74	8	8.51	9.35E-07
≥ 5.29	14	14.89	29	30.85	
ALC (x 10^3 / µL)					
< 1.59	13	13.83	27	28.72	4.38E-06
≥ 1.59	44	46.81	10	10.64	
AMC (x 10^3 / µL)					
≤ 0.625	30	31.91	22	23.4	0.6612
> 0.625	27	28.72	15	15.96	
IPI†					
Low Risk (0-1)	32	34.04	17	18.09	0.6063
Low-Intermediate Risk (2)	16	17.02	11	11.7	
High-Intermediate Risk (3)	8	8.51	7	7.45	
High Risk (4-5)	1	1.06	2	2.13	
PLR					
< 193.415	49	52.13	8	8.51	1.72E-09
≥ 193.415	8	8.51	29	30.85	
NLR					
< 3.425	50	53.19	5	5.32	4.53E-12
≥ 3.425	7	7.45	32	34.04	
LMR					
< 2.71	12	12.77	24	25.53	5.08E-05
≥ 2.71	45	47.87	13	13.83	

†, Fisher Exact test

Data showed that 40 patients had comorbidities (data not shown), with hypertension being the most common (28 patients), followed by diabetes mellitus (13 patients). Additional comorbidities include nephrolithiasis, congestive heart failure, deep vein thrombosis, pulmonary and extrapulmonary TB, chronic kidney disease, chronic obstructive pulmonary disease, and other cancers. Considering that the majority of patients did not have these conditions, the primary analysis did not specifically assess the impact of the comorbidities on SII and OS. However, previous studies showed that systemic inflammation markers, such as SII, may be influenced by immunocompromising conditions, including diabetes mellitus and tuberculosis. Future studies with bigger sample numbers are required to examine the effect of these comorbidities on SII and OS, thereby providing a better understanding of the relationship.

Receiver operating characteristic (ROC) curve analysis was used to determine the ideal cut-off values for inflammatory indicators in predicting OS. The thresholds that maximize sensitivity and specificity were identified using the Youden Index. According to this study, the best cut-off points for SII, NLR, PLR, and LMR were 1210.625, 3.425, 193.415, and 2.71, respectively (Figure 2A). NLR was 0.63, but the area under the ROC curve (AUC) for SII, PLR, and LMR was 0.68. This result suggests that inflammatory indices might not be enough for prognostic evaluation in this sample.

Univariate and Multivariate Analysis of OS

In this study, the OS rate for the dataset was 71.3% at the final observation time point (32 months), with a 95% confidence interval between 58.0% and 87.7%. Patients in the low, low-intermediate, high-intermediate, and high categories had low OS rates of 72.3% at 32 months, 66.7% at 20 months, 80.0% at 11 months, and 66.7% at 8 months, respectively. Although the analysis aimed to evaluate 5-year OS, survival rates for each IPI category were reported at different time points based on available follow-up data and events in each group, representing the last observed data where patients were at risk.

During the study period from 2012 to 2020, OS rates were provided for each inflammation index. Patients with SII<1210.615 had an OS rate of 87.7%, higher than those with SII≥1210.615 of 47.9% (p=0.0052, Table 2) (Figure 2B). The NLR/PLR/LMR survival curve also shows a similar trend as patients with NLR<3.425 had an OS rate of 84.3%, significantly higher than NLR≥3.425, which was 52.7% (p=0.057, Table 2) (Figure 2C). Furthermore, the PLR<193.415 was associated with an 82.7% OS rate, significantly higher than the 47.2% OS rate observed in patients with PLR≥193.415 (p=0.0034, Table 2) (Figure 2D). The LMR<2.71 had an OS rate of 52.1%, significantly lower than the 81.9% OS rate in patients with LMR≥2.71 (p=0.0045, Table 2) (Figure 2E). As shown in Table 2, ECOG score, SII, PLR, and LMR showed distinct survival curves for each factor within the cohort.

The multivariate Cox proportional hazard model was used to determine if the parameters in Table 3 are reliable predictors. First, a proportional hazard assumption test was carried out, and each factor was found to satisfy the

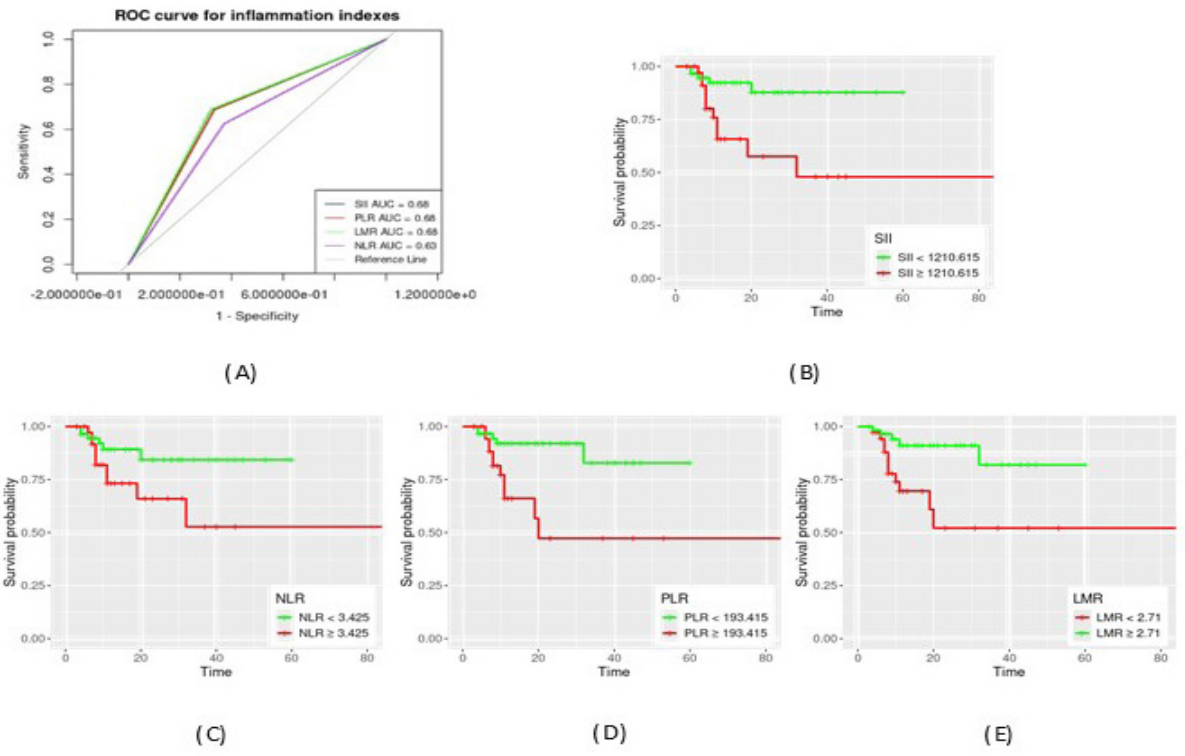

Figure 2. Overall Survival of a Patient with DLBCL Provided by Inflammation Index. (A) Predictive performance of SII versus PLR, NLR, and LMR using ROC curves in the primary cohort. (B) OS with SII <1,210.615 (green) and ≥1,210.615 (red). (C) OS with NLR <3.425 (green) and ≥3.425 (red). (D) OS with PLR <193.415 (green) and ≥193.415 (red). (E) OS with LMR <2.71 (green) and ≥2.71 (red) at diagnosis.

Table 2. Log-Rank Test Showing Survival Curve Differences for Each Factor in the Group

Variable	p-value	Variable	p-value
Age		ALC (x 10^3 / μL)	
<60	0.61	< 1.59	0.066
≥60		≥ 1.59	
ECOG score		AMC (x 10^3 / μL)	
< 2	0.027*	≤ 0.625	0.11
≥ 2		> 0.625	
Sites		IPI	
<2	1	Low Risk	0.55
≥2		Low-Intermediate Risk	
LDH		High-Intermediate Risk	
Normal	0.78	High Risk	
Elevated		SII	
Stage		< 1210.615	0.0052**
I & II	0.34	≥ 1210.615	
III & IV		PLR	
RDW (%)		< 193.415	0.0034**
≤ 14.355	0.65	≥ 193.415	
> 14.355		NLR	
PLT (x 10^3 / μL)		< 3.425	0.057
< 315.5	0.6	≥ 3.425	
≥ 315.5		LMR	
ANC (x 10^3 / μL)		< 2.71	0.0045**
< 5.29	0.12	≥ 2.71	
≥ 5.29			

PH assumption. Furthermore, these factors were compiled and entered into the regression model for estimation. According to univariate analysis, decreased OS was strongly correlated with ECOG > 2, high SII, high PLR, and low LMR, as shown in Table 3. In the multivariate analysis, four clinical and hematological characteristics (AMC, PLT, PLR, and SII) did not violate the PH assumption (p=0.26), resulting in the best Cox model with AIC=107.32 achieved through backward elimination. Hazard ratio forest plots and associated 95% CIs for OS are shown in Figure 3 based on Cox proportional hazards (PH) regression analysis.

In the multivariable model, patients in the category of AMC>0.625×10^3/μL have six times higher risk of death compared to those with AMC≤0.625×10^3/μL (HR: 5.93, CI: 1.7-20.33, p=0.005). However, the risk of death was decreased for patients with PLT of at least 315.5 compared to those with PLT < 315.5 (HR: 0.31, CI: 0.1–0.93, p=0.037). The result also showed that patients with PLR≥193.415 have a five times higher risk of PLR<193.415 to death (HR: 5.30, CI: 1.4-19.73, p=0.013). According to Figure 3, the risk of death was three times higher for patients in the SII category than for those without one (HR: 3.55, CI: 1.0-12.47, p=0.048).

Nomogram Predicting Survival

Nomogram, based on AIC results, predicts 1-, 2-, and 3-year OS for DLBCL using monocytes, platelets, PLR, and SII, as shown in Figure 4. Monocytes have the greatest influence on early DLBCL prognosis, followed by PLR, SII, and PLT. Clinicians can calculate the total score from these variables to obtain specific survival probabilities for up to 3 years. Nomogram estimates 1-, 2-, and 3-year OS by summing points for each variable on a point scale. Furthermore, the prognostic performance of the nomogram and the IPI was assessed by comparing the respective AUC values. The AUC for the nomogram and the IPI in predicting OS was 0.8 and 0.59, respectively (Figure 5). This result suggests the superior predictive ability of the nomogram over the IPI.

Discussion

Table 1 shows the descriptive statistics for patients with DLBCL associated with the SII index. The IPI score serves as the foundation for NHL treatment decisions

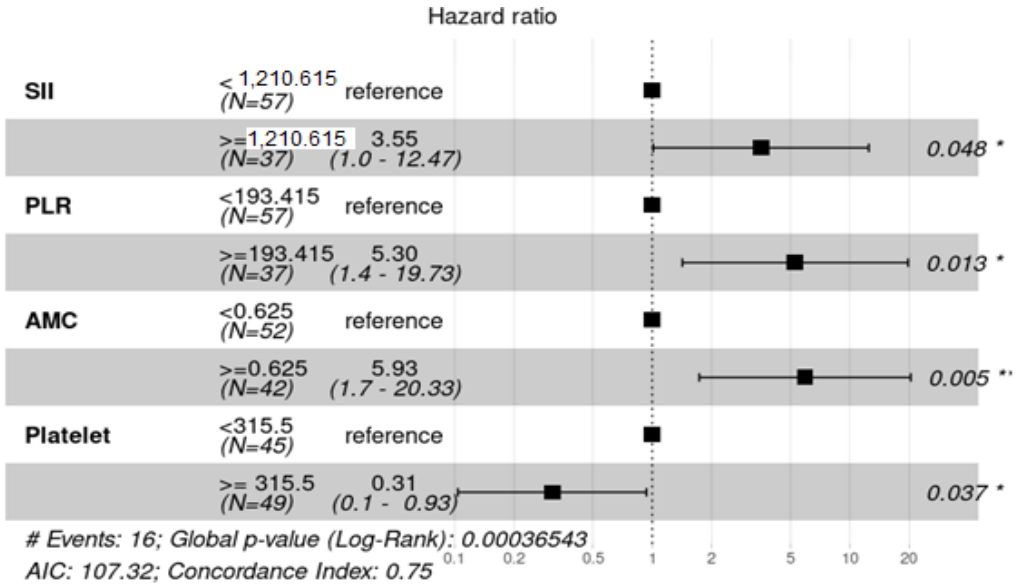

Figure 3. Forest Plot of Hazard Ratios from Multivariable Cox PH Regression Model

Table 3. Univariate and Multivariate Analysis of Prognostic Factors for OS in Patients with Diffuse Large B-cell Lymphoma.

Variable		Univariate Analysis		Multivariate Analysis	
	PH Assumption	HR (95% CI)	p-value	HR (95% CI)	p-value
Age					
<60	0.075	1			
≥60		1.3037 (0.4684-3.629)	0.612		
ECOG score					
< 2	0.5	1			
≥ 2		3.4269 (1.079-10.89)	0.0368*		
Sites					
<2	0.73	1			
≥2		1.003464 (0.2251-4.473)	0.996		
LDH					
Normal	0.59	1			
Elevated		0.8511 (0.2722-2.661)	0.782		
Stage					
I & II	0.75	1			
III & IV		1.6261 (0.5977-4.424)	0.341		
RDW (%)					
≤ 14.355	0.063	1			
> 14.355		1.2622 (0.4647-3.428)	0.648		
PLT (x 10^3 / µL)					
< 315.5	0.32	1		1	
≥ 315.5		0.7668 (0.2825-2.082)	0.602	0.3117 (0.1039-0.9347)	0.03749*
ANC (x 10^3 / µL)					
< 5.29	0.46	1			
≥ 5.29		2.2098 (0.7958-6.136)	0.128		
ALC (x 10^3 / µL)					
< 1.59	0.45	1			
≥ 1.59		0.3963 (0.1428-1.099)	0.0754		
AMC (x 10^3 / µL)					
≤ 0.625	0.95	1	0.116	1	
> 0.625		2.2646 (0.8172-6.276)		5.9301 (1.7298-20.3296)	0.00463**
IPI					
Low Risk	0.2	0.4969 (0.05843-4.227)	0.522		
Low-Intermediate Risk		1.1142 (0.13070-9.498)	0.921		
High-Intermediate Risk		0.6765 (0.06880-6.652)	0.738		
High Risk		1			
SII					
< 1,210.615	0.24	1		1	
≥ 1,210.615		4.0996 (1.409-11.93)	0.00964**	3.5493 (1.0106-12.4651)	0.04810*
PLR					
< 193.415	0.43	1		1	
≥ 193.415		4.3724 (1.498-12.77)	0.00696**	5.2951 (1.4215-19.7252)	0.01299*
NLR					
< 3.425	0.39	1			
≥ 3.425		2.6020 (0.9385-7.214)	0.0661		
LMR					
< 2.71	0.95	1			
≥ 2.71		0.2397 (0.08248-0.6963)	0.00866**		

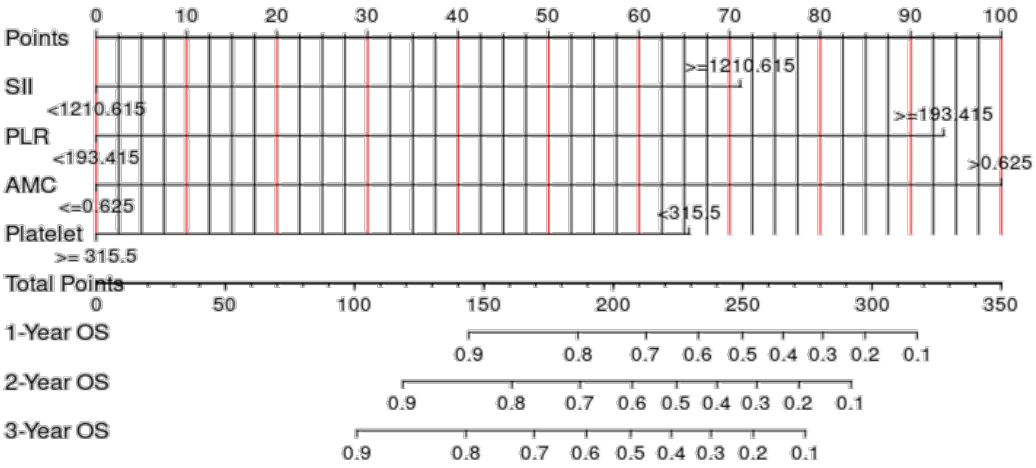

Figure 4. Clinical Nomogram of DLBCL Patients Estimating 1-, 2-, and 3-year Survival based on Prognostic Factors.

and is often used as a guide for prognostic estimation. However, other risk variables were not considered in the method, and the classification was only based on age, ECOG score, extranodal locations, stage, and LDH, which did not accurately reflect the biological heterogeneity of DLBCL patients. Therefore, IPI may not accurately predict OS for current DLBCL patients, specifically those categorized as high-risk [10, 11].

Previous studies have shown the relationship between anemia and poor prognosis in lymphoma patients in Indonesia [22]. Therefore, this study combined clinicopathological to construct an effective survival prognostic model, then a comparison was made between conventional index and SII. The Cox model is suitable for this cohort, meeting the proportional hazards (PH) assumption (p=0.26), as shown in Table 3. Based on the Cox model, a nomogram was formed, containing blood cellular components, such as monocytes, platelets, PLR, and SII. These components represent a proposed simple and visual tool for prognostic prediction of DLBCL patients. Effect size was expressed as a hazard ratio with a 95% confidence interval, as shown in Figure 3.

Several studies have shown a correlation between monocytes and platelets with the prognosis of different forms of cancer. Consequently, this study assessed the prognostic significance of the AMC using a cut-off of $0.625\times10^3/\mu L$ and the result showed that OS of patients below and above this cut-off was 81.9% and 56.6%, respectively. Ths result is also consistent with Tadmor et al. [23] who used a cut-off of $0.63\times10^3/\mu L$, and OS rates of 71% and 59% for patients below and above this threshold, respectively. Other studies have also explored prognostic role of monocytes in DLBCL [24, 25].

Previous results have shown that platelets contribute to the development and spread of cancer [26, 27]. Several clinical observations and laboratory studies suggest that low PLT (thrombocytopenia) in tumors correlates with a poor prognosis, both in non-hematologic and hematologic tumors [28–31]. In this study, platelet levels below 315.5 at diagnosis were considered a poor prognostic predictor of OS for patients. These results are consistent with the report of an earlier study showing that low PLT is a stand-alone risk factor for DLBCL [18, 32].

PLR index is a useful, non-invasive biomarker for poor prognosis and aggressive features in DLBCL patients, but the cut-off value varies [33]. A high PLR upon diagnosis is

Table 4. Detail Scores of All Variables in the Nomogram.

Variable	Nomogram score
SII	
< 1,210.615	0
≥ 1,210.615	71
PLR	
< 193.415	0
≥ 193.415	94
AMC	
≤ 0.625	0
> 0.625	100
PLT	
< 315.5	65
≥ 315.5	0

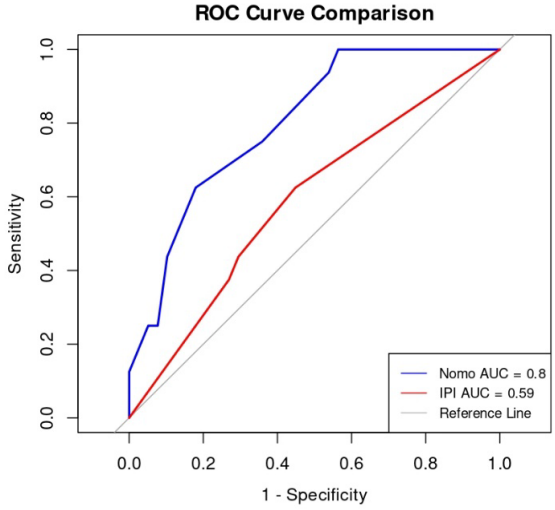

Figure 5. The ROC Curves Comparison between the Nomogram and IPI Score.

an independent predictor of OS in patients with DLBCL, according to a previous study that determined an ideal PLR cut-off value of 270.27 [34]. Additionally, with a rate of 76.7%, a high PLR with a cut-off of 150 was linked to poor survival [35]. A dependable predictor of survival for newly diagnosed DLBCL patients was PLR≥170 [36]. In this cohort, the optimal cut-off for PLR was obtained at 193.415, where values at the upper limit showed adverse OS for patients.

A recent study has shown that the SII index has the potential to be prognostic factor for several cancers, including DLBCL [37]. The SII with a cutoff of 1046 along with IPI has shown accurate prognostic ability compared to IPI to predict OS at 3 and 5 years [19]. Other studies also show that nomogram built based on SII with an optimal cutoff of 1684 has better accuracy and discrimination compared to other prognostic systems, such as IPI or NCCN-IPI [20]. The SII cutoff value in this study was 1210.615 and was identified as one of the potential prognostic parameters (Table 4).

In the last stage, a new prognostic parameter for Indonesian DLBCL patients was presented, useful for individual risk estimation and patients counseling, which can be integrated into advanced prognostic models. Cellular blood components and inflammatory indices can be derived from routine blood cell counts in oncology reports. Due to the simplicity and low cost, these indices provide valuable prognostic information for DLBCL management, facilitating widespread acceptance by clinicians.

Available information suggests that the nomogram in this present study is the first to predict the probability that patients will survive DLBCL for 1 to 3 years from initial diagnosis, assuming death does not occur due to other causes. The nomogram model outperforms the traditional IPI/SII method in terms of discriminatory ability and predictive accuracy. Remarkably, the results of this study showed that the present dynamic nomogram's AUC (0.8) was greater than the IPI's (0.59) (see Figure 5).

One of the study's shortcomings is that the nomogram was created under the presumption that the clinical and laboratory characteristics of the DLBCL patients in this cohort were typical. Second, the database for the dynamic nomogram was generated from a single cancer center, which resulted in a tiny sample size that hasn't been validated with other groups in Indonesia, even if they performed better in the validation cohort. Furthermore, the multivariate analysis's incorporation of covariates did not follow Harrell's rules, which stipulate that there must be at least ten times as many events as covariates. Third, nomogram provides prognosis at diagnosis rather than during evaluation, thereby limiting the utility. Finally, this study did not incorporate any molecular or genetic biomarkers. Despite these drawbacks, nomograms have a predictive impact on DLBCL patients in Indonesia when considered while making clinical practice decisions. These results serve as a foundation for future studies on the prognosis of patients with DLBCL. In addition, this nomogram is expected to stimulate ongoing clinical studies with broader geographic recruitment and increased validation.

Author Contribution Statement

Each author contributed to the conception and execution of the study. SS processed the data prepared by MSH. SS produced the text with input from MSH, FA-K, and G. After discussing the results, all authors gave approval to the finished work.

Acknowledgements

Ethical Declaration

All procedures carried out in studies involving human participants are according to the Ethical Committee of the Faculty of Medicine at Universitas Gadjah Mada in Yogyakarta, Indonesia with approval number KE/FK/1356/EC/2023.

Approval

This study is an important part of the student's approved thesis, which stems from the work of a graduate student.

Conflict of Interest

The authors declare no conflict of interest.

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