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Correlation of neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR) with r-chop therapy response in diffuse large B-cell lymphoma (DLBCL) patients

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ABSTRACT

Background: The exploration of simple, cost-effective, and low-risk prognostic markers, such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) as predictive factors for survival in diffuse large B-cell lymphoma (DLBCL) patients receiving R-CHOP therapy has become increasingly important due to the variability in results seen in prior studies.

Methods: This observational cross-sectional study analyzed NLR, LMR, and PLR as predictors of survival in DLBCL patients treated with R-CHOP. Data was collected from DLBCL patients from June 2017 to June 2022. All statistical analyses were performed using R version 4.2.3 using pROC package for receiver-operating characteristic curves analyses. Univariate and multivariate logistic regression analyses were performed to assess predictors' association with overall survival (OS).

Results: There were 112 DLBCL patients receiving R-CHOP, 87 were classified as surviving, while 25 were not. Univariate logistic regression analyses revealed significant associations between overall survival (OS) and IPI scores ($p < 0.001$). Conversely, gender, response to R-CHOP therapy, and hematologic indicators of NLR > 2.0, PLR > 213.4, and LMR > 1.1 did not show significant associations with OS. Multivariable logistic regression analysis using backward selection identified LMR ($p = 0.036$; 0.24 (95%CI: 0.05 to 0.84) as independent predictors for OS in DLBCL patients.

Conclusions: Our study revealed several fundamental risk factors, including extranodal involvement, ECOG performance status, LDH, and LMR, were independently associated with 2-year mortality in DLBCL patients before initiating R-CHOP therapy. However, due to the limitations of this study, further research with larger sample sizes is warranted.

Keywords: lymphoma, non-hodgkin lymphoma, international prognostic index, prognostic marker, lymphocyte-to-monocyte ratio

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) stands as the predominant variant among non-Hodgkin lymphomas (NHL), comprising approximately 30-40% of B-cell NHL cases [1]. Its occurrence escalates with advancing age, typically manifesting with a diagnosis occurring around the seventh decade of life. Nevertheless, DLBCL may manifest across all age groups, with a marginal male predilection [2]. Various risk factors contribute to its pathogenesis, encompassing genetic predispositions, infectious agents, and environmental influences. A significant advancement in DLBCL treatment involves incorporating rituximab into the combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) [3]. Previous studies have demonstrated that this novel combined approach yields greater survival benefits for DLBCL patients. However, over 30% of DLBCL patients remain refractory to initial therapy or experience relapse as a consequence [4].

The international prognostic index (IPI) is widely employed for predicting outcomes in aggressive lymphoma patients and selecting optimal therapeutic interventions. Furthermore, numerous efforts have been undertaken to enhance the predictive capacity of the IPI [5]. Nonetheless, these models still exhibit limitations in identifying patients who may not derive benefit from R-CHOP therapy. Evidence suggests that certain DLBCL patients fail to achieve significant survival benefits from R-CHOP therapy [6]. Hence, there is an urgent need for easily accessible and effective prognostic markers. Several studies have demonstrated the association between pretreatment neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) with the therapeutic response to R-CHOP in patients with DLBCL [7-9].

Abnormal inflammatory reactions and immune status affect the pathobiology of lymphoma, thus influencing treatment outcomes for lymphoma patients [10]. Absolute lymphocyte counts have been found to predict clinical outcomes in DLBCL. Additionally, neutrophils play a crucial role in the innate immune defense against infectious diseases, where the NLR comprehensively reflects the inflammatory and immune status in cancer patients and has been shown to be a significant predictor of survival in patients with various types of cancer such as laryngeal carcinoma, esophageal cancer, renal cell carcinoma, and gallbladder carcinoma [11, 12]. Besides NLR, markers such as the LMR and PLR are currently being seriously investigated for their association with survival in hematological malignancies. In this study, we aim to comprehensively analyze the relationship between the NLR, LMR, PLR prior to treatment as predictors of survival in DLBCL patients treated with R-CHOP.

METHODS

Study Design

This was an observational analytical study with a cross-sectional design to analyze the role of NLR, LMR, and PLR prior to treatment as predictors of survival in DLBCL patients treated with R-CHOP. This research took DLBCL patients from June 2017 to June 2022 in the Oncology Outpatient Clinic, Dr. Soetomo Hospital, Surabaya, Indonesia. This research had been approved by the local ethics committee (IRB number: 1051/LOE/301.4.2/IX/2022). Informed consent was taken from the patients if they agreed to be part of the study sample.

Patients Characteristics

Samples included in this study should fulfill the following inclusion criteria:

(1) aged > 18 years and

(2) patients with DLBCL who underwent a minimum of 4 cycles of R-CHOP therapy.

Patients with infectious diseases, chronic inflammation or autoimmune, and coexisting malignancies diseases were excluded. A physical and history examination were carried out before taking blood. Retrieved baseline characteristics included gender, age, B symptoms, Ann Arbor stage, ECOG performance, extranodal involvement, LDH and IPI scores.

Data Analysis

All statistical analyses were performed using R version 4.2.3 using pROC package for receiver-operating characteristic (ROC) curve analyses. Patients were divided into two groups based on the overall survival (OS) outcomes. The baseline characteristics are presented in tabular form and analyzed descriptively. For hematologic indicators (NLR, PLR, and LMR), we determined the cut-off value based on the Youden index of the ROC curve. Shapiro-Wilk normality test was employed to evaluate the distribution of the continuous variables. To compare differences between groups, a non-parametric test for variables without normal distribution was performed. We also calculated the odds ratio for each variable to evaluate the risk factors for the OS outcomes in DLBCL patients receiving RCHOP through univariate and multivariate logistic regression analysis.

The area under the curve (AUC) with 95% confidence interval (CI), sensitivity, and specificity were calculated and compared with one another. The cut-off value was determined by the Youden index. Statistical significance was defined as a p-value less than 0.05.

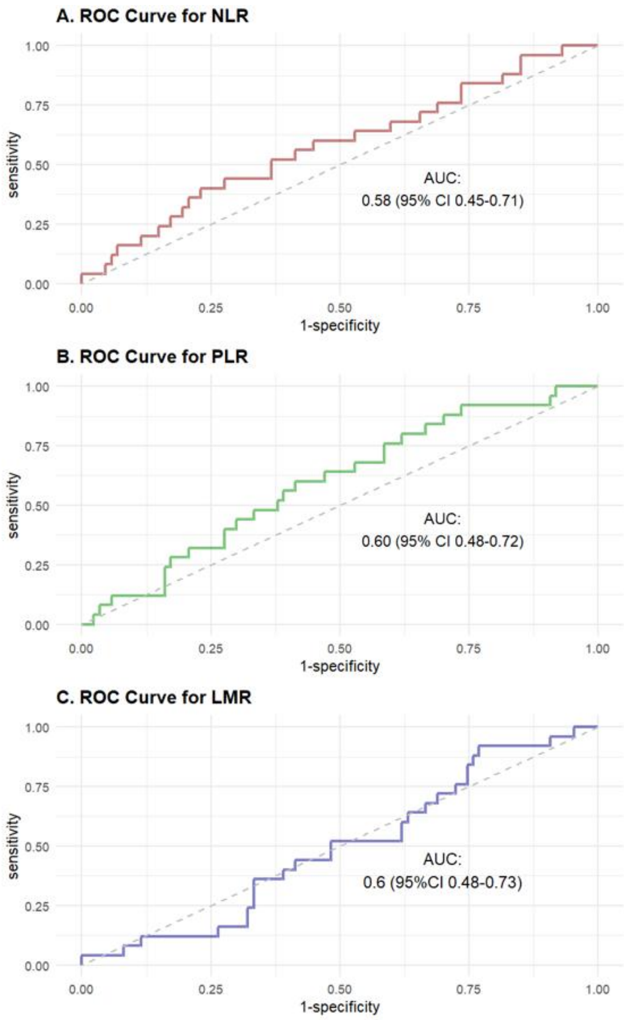

Figure 1. The ROC curve for NLR (panel A), PLR (panel B), and LMR (panel C) in predicting the overall survival of DLBCL patients who received R-CHOP (Source: Authors' own elaboration)

RESULTS

Cut-Off Value

We determined, by the Youden index of the ROC curve analysis, an optimal cut-off value of 2.0, 213.4, and 1.1 for NLR, PLR, and LMR, respectively (**Figure 1**). These cut-off values

Table 1. Univariate logistic regression of clinical characteristics of DLBCL patients between surviving (n = 87) and non-surviving (n = 25) groups

	Variables	Surviving (n = 87)	Non-surviving (n = 25)	p-value	OR (95% CI)
Gender	Male	52	19	0.143	2.13 (0.81 to 6.33)
	Female	35	6		
Age	≤60	64	13	0.044*	2.56 (1.02 to 6.48)
	> 60	23	12		
B symptoms	Yes	61	23	0.040*	4.90 (1.33 to 31.94)
	No	26	2		
Ann Arbor stage	I/II	50	6	0.005*	4.28 (1.63 to 12.73)
	III/IV	37	19		
ECOG performance status	0-1	51	9	0.049*	2.52 (1.02 to 6.55)
	2-4	36	16		
Extranodal involvement	0-1	80	13	0.004*	5.38 (1.72 to 17.38)
	≥ 2	7	12		
LDH	Low	33	3	0.022*	4.48 (1.41 to 19.97)
	High	54	22		
IPI scores	0-1 (low risk)	40	1	< 0.001*	3.20 (1.94 to 5.80)
	2 (low-intermediate risk)	19	4		
	3 (high-intermediate risk)	21	11		
	4-5 (high risk)	7	9		
NLR	Low (≤ 2)	20	10	0.095	0.448 (0.175 to 1.170)
	High (> 2)	67	15		
PLR	Low (≤ 213.4)	36	15	0.103	0.471 (0.185 to 1.153)
	High (> 213.4)	51	10		
LMR	Low (≤ 1.1)	59	21	0.123	0.401 (0.109 to 1.176)
	High (> 1.1)	28	4		

were used to discriminate between low and high values of each parameter. The AUC curve for the NLR was 0.58 (95%CI 0.45 to 0.71), the PLR was 0.60 (95%CI 0.48 to 0.72), and the LMR was 0.6 (95%CI 0.48 to 0.73).

Univariate Logistic Regression Analysis

There were 112 DLBCL patients receiving R-CHOP, and they were classified into surviving (n = 87) and not surviving group (n = 25). Binary univariate logistic regression analyses showed a significant association between OS and age (p = 0.044), B-symptoms (p = 0.040), Ann Arbor stage (p = 0.005), ECOG performance status (p = 0.049), extranodal involvement (p = 0.004), LDH (p = 0.022), and IPI scores (p < 0.001) on the contrary to the other clinical characteristics of gender (p = 0.143), response to R-CHOP therapy (p = 0.538) and the hematologic indicators of NLR > 2.0 (p = 0.095), PLR > 213.4 (p = 0.103), and LMR > 1.1 (p = 0.123) (**Table 1**).

Multivariable Logistic Regression Analysis

Using backward selection of the predictors in the multivariable logistic regression model, extranodal involvement (p = 0.010; OR = 5.38 (95%CI: 1.53 to 20.92)), ECOG performance status (p = 0.044; OR = 2.96 (95%CI 1.06 to 8.93)), LDH (p = 0.016; OR = 6.23 (95%CI: 1.62 to 34.66)), and LMR (p = 0.036; OR = 0.24 (95%CI: 0.05 to 0.84)) were found to be the independent predictors for OS in DLBCL patients. The final model is presented in **Table 2**.

Table 2. Adjusted OR for predictors of OS at admission prior to receiving R-CHOP

Predictors	Adjusted OR (95% CI)	p-value
Gender	2.05 (0.66 to 7.04)	0.229
Extranodal involvement	5.38 (1.53 to 20.92)	0.010*
ECOG performance status	2.96 (1.06 to 8.93)	0.044*
LDH	6.23 (1.62 to 34.66)	0.016*
LMR	0.24 (0.05 to 0.84)	0.036*

DISCUSSION

The number of lymphocytes in peripheral blood is considered an indicator of immunity [13]. Lymphocytes play a vital part in monitoring immunity and shielding against tumors. The NLR serves as a comprehensive indicator of both inflammation and immune health in cancer patients, proving to be a significant predictor of survival across various cancer types [11]. Consequently, there is ongoing discussion surrounding prognostic markers like the NLR, LMR, and PLR, with a particular focus on their potential correlation with survival rates in hematological malignancies.

In this study, owing to non-normal data distribution and the presence of extreme outliers in the NLR, PLR, and LMR parameters, the continuous data were transformed into binary variables for logistic regression according to cutoff values obtained from ROC curve analysis. Analysis of the AUC curves revealed that baseline NLR, PLR, and LMR had poor diagnostic performance in predicting 2-year mortality. This study also found that 2-year mortality outcome in DLBCL patients who received R-CHOP treatment was associated with the baseline IPI score and its components of age over 60 years, Ann Arbor stage, ECOG performance status, extranodal involvement, and elevated LDH. Additionally, the presence of B symptoms was associated with 2-year mortality, whereas gender and baseline NLR, PLR, and LMR were not. We also obtained a multivariable model following backward selection of the predictors where extranodal involvement, ECOG performance status, LDH, and LMR were identified as independent predictors of 2-year mortality for DLBCL patients who received R-CHOP. Despite gender and LMR showing non-significance in the univariate analysis, they were included in the final model. A p-value cutoff of < 0.15 was chosen for variable inclusion, diverging from the conventional p < 0.05 threshold [14]. After incorporating all variables, a backward selection process was used to refine the model, summarized in **Table 2**.

The IPI has long been a significant and widely recognized system for predicting the risk associated with DLBCL [5]. However, in the past decade, the integration of rituximab into standard chemotherapy regimens has greatly improved treatment strategies and outcomes for DLBCL [15]. This development has sparked ongoing debate regarding the relevance of IPI in the rituximab era, prompting concentrated efforts to validate its prognostic value. In this study, we found that the five classical IPI factors remain suitable as prognostic indicators for survival outcomes in the rituximab era. This is supported by clinical trials involving 1,062 patients treated with three different rituximab-based chemoimmunotherapy regimens [16]. Rituximab resulted in remarkable but inconclusive improvements in survival outcomes within each IPI category. Therefore, the classical IPI factors can still be utilized to predict survival outcomes in the rituximab era [17].

Previous studies have suggested that NLR correlates with poor OS as well as worse PFS [11]. Lymphocytes play a crucial role in innate cellular immunity and are important in destroying residual malignant cells. It is widely believed that tumor-infiltrating lymphocytes (TILs) are associated with better clinical outcomes in cancer [18]. Conversely, neutrophils may reflect the presence of tumor-associated macrophages and circulating monocytes, which contribute to host antitumor immunity and promote tumor angiogenesis [19]. From our hypothesis, NLR might be a good index reflecting the balance between inflammation and immunoreaction in cancer. However, lymphoma is a cancer of lymphocytes where the host's innate immunity has been destroyed, and the number of TILs may be reduced in lymphoma patients [20]. Therefore, we assume that it may be difficult for NLR to reflect the outcomes of lymphoid malignancies.

To contextualize these findings, recent meta-analyses and previous studies (2025-2026) have further explored the role of systemic inflammatory indices NLR as dynamic biomarkers rather than static predictors of outcome. These studies emphasize that temporal changes in NLR during chemotherapy cycles may better capture treatment response and immune reconstitution compared to baseline values alone. In hematologic malignancies, the prognostic performance of NLR appears more heterogeneous than in solid tumors, highlighting disease-specific immune microenvironment differences [21, 22]. However, lymphoma is a cancer of lymphocytes where the host's innate immunity has been destroyed, and the number of TILs may be reduced in lymphoma patients [20]. Therefore, we assume that it may be difficult for NLR to reflect the outcomes of lymphoid malignancies.

Patients diagnosed with DLBCL who exhibit a low LMR and an elevated PLR demonstrate significantly poorer OS [23]. Lymphocytes play a pivotal role in orchestrating tumor immunological surveillance and defense mechanisms by inhibiting tumor cell proliferation and growth [24]. Consequently, LMR serves as a potential indicator of the pro-tumor and anti-tumor responses elicited in the context of inflammation. In the rituximab era, accumulating evidence further suggests that LMR may also serve as a surrogate marker for monocyte-driven immunosuppression within the tumor microenvironment [25]. High monocyte counts have been associated with increased differentiation into tumor-associated macrophages, which promote immune evasion and resistance to immunochemotherapy [26]. Recent retrospective studies published in 2025 have demonstrated that combining LMR with established clinical indices, such as the IPI, improves risk stratification accuracy in DLBCL patients receiving R-CHOP-based regimens [27]. Moreover, integrating LMR with lymphocyte and monocyte count indices may offer a more concise assessment of the host's pro-tumor and anti-tumor capacities [28]. Conversely, an increase in platelet counts and/or a decrease in lymphocyte counts can result in a high PLR. Activated platelets are involved in both early and advanced stages of tumor angiogenesis [29]. Additionally, platelets release transforming growth factor-β1, which, together with the direct interaction of platelets and tumor cells, activates epithelial-mesenchymal transition related pathways and subsequently induces metastasis [30]. However, it is imperative to note that in the present study, the results from univariate logistic regression analysis did not identify LMR and PLR as significant predictors of survival among DLBCL patients undergoing R-CHOP chemotherapy. Nonetheless, a cautious interpretation of these findings is warranted due to the potential influence of confounding factors.

Limitations

Due to several limitations, findings in this study should be interpreted cautiously. Firstly, the study had a shorter follow-up time of two years, whereas many studies in the literature have a longer follow-up time, ideally 5 years or more. This shorter follow-up period might have led to an underestimation of the findings. Secondly, the NLR, PLR, and LMR variables were transformed into binary variables instead of keeping the data continuous due to extreme outliers and non-normal distribution. Additionally, different populations may have different cut-off values for differentiating between low and high values of these parameters. Thirdly, the multivariable model used to predict 2-year mortality has not externally been validated in other populations. Therefore, the diagnostic performance of the model has yet to be confirmed further.

CONCLUSIONS

We found that several baseline risk factors, including extranodal involvement, ECOG performance status, LDH, and LMR, were independently associated with 2-year mortality among DLBCL patients before receiving R-CHOP treatment. However, regarding the limitations of this study, further research involving larger populations is necessary.

Author contributions: PNAA, SUYB, & IDGU: writing–original draft and formal analysis; **PNAA & SUYB:** conceptualization; **PNAA, IDGU, IAW, & NRP:** methodology and data curation; **SUYB:** supervision; & **IAW, NRP, & DSB:** writing–review & editing. All authors have agreed with the results and conclusions.

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AI statement: The authors stated that AI-based tools were used to correct grammar and spelling.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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