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Original Article

# Difference of Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymphocyte Ratio, and Platelet-to-Lymphocyte Ratio in Patients with Non-Hodgkin and Hodgkin Lymphoma

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## Abstract

**Background:** Malignancy and inflammation are strongly connected. The inflammatory processes play a significant part in the development of lymphoma. Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) can be used as potential biomarkers of inflammation in lymphoma. This study aimed to discover the differences between NLR, MLR, and PLR in patients diagnosed with non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL).

**Methods:** This study employed a retrospective design using data from the lymphoma registry at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia from 2020 to 2023. Sampling was carried out consecutively. Hematological data of patients with NHL and HL before chemotherapy were collected. The variance between the two groups was examined utilizing the Mann-Whitney U test.

**Results:** In total, 122 data of patients were included, consisting of 75% NHL patients and 25% HL patients with a median age of 54 years (IQR 43–62). The overall NLR, MLR, and PLR tended to be lower in nHL than in HL patients although the differences were not statistically significant; with NLR 2.7 (0.7–12.2) vs. 3.2 (1.1–10.8) p=0.287, MLR 0.36 (0.04–1.86) vs. 0.46 (0.09–1.78) p=0.150, and PLR was 160.6 (20.2–1533.3) vs. 211.2 (50.6–1156.3) p=0.189, for NHL and HL, respectively.

**Conclusions:** The lower values of NLR, MLR, and PLR in NHL indicate lower systemic inflammatory status in NHL than HL patients. Further studies are needed to evaluate dynamic changes of these biomarkers during treatment..

**Keywords:** Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, non-Hodgkin lymphoma, Hodgkin lymphoma

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## Introduction

Complete blood count is a basic hematology examination that is extensively used in daily clinical practice. This examination encompasses the number of leucocytes, erythrocytes, and platelets. Several research studies have investigated the distribution of various types of white blood cells in various medical conditions.[1–3] The involvement of inflammatory process has been recognized to be significant in the development of lymphoma.[3] Additionally, the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have emerged as potential biomarkers capable of indicating the presence of inflammation and can be used to estimate the process and level of inflammation, among others in patients with lymphoma.

Non-Hodgkin's lymphoma (NHL) is the dominant form of hematological cancer worldwide, including various groups of B and T-cell proliferative disorders. It can be distinguished from Hodgkin's lymphoma by its distinct clinical appearances, the absenteeism of Reed-Sternberg cells, and the lack of Cd15 and Cd30 discoloration in histological

**Table 1 Age and Gender of Patients with Hodgin and Non-Hodgin Lypmphoma**

| Variable | Total (n=122) | HL (n=30) | NHL (n=92) | p-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 52 ± 15 | 42 ± 17 | 55 ± 14 | <0.001* |
| Gender; n (%) | | | | |
| Male | 72 (59.0) | 15 (50.0) | 57 (62.0) | 0.248** |
| Female | 50 (41.0) | 15 (50.0) | 35 (38.0) | |

Note: HL= Hodgin lymphoma; NHL= non-Hodgin lymphoma, *=analyzed using t-test, **= analyzed using Chi-square

examination. More than 40 major subtypes have been identified, and the most common are indolent follicular lymphoma and aggressive diffuse large B-cell lymphoma. These subtypes are correlated with specific genetic mutations and risk factors.[4]

In 2020, the global burden of NHL was 16,125 current events, and 9,024 NHL deaths were reported. In addition, an estimated 1,188 new incidents and 363 deaths of HL were diagnosed globally.[5] The five-year prevalence of NHL was 15.78/100,000 population and 1.34/100,000 population in HL. Due to the large burden of the diseases, prediction is needed for disease prevention and early treatment.[5] Therefore, this study aimed to measure the distinction between NLR, MLR, and PLR as inflammation biomarkers in non-Hodgkin's and Hodgkin's lymphoma.

## Methods

This study used retrospective design conducted at Dr. Hasan Sadikin Hospital, Bandung, Indonesia using the lymphoma registry data of this hospital from 2020 to 2023 as the main data. The study had a permit from the Ethics Committee of the Dr. Hasan Sadikin General Hospital with reference number LB 02.01/X.6.5/41/2023.

Complete blood count tests of NHL and HL patients before chemotherapy were reviewed and collected consecutively. The inclusion criteria were all patients aged 19–81 years diagnosed with NHL and HL and underwent chemotherapy. The independent variables were NLR, MLR, PLR, whereas the dependent variables were non-Hodgkin lymphoma and Hodgkin lymphoma.

Data were presented in the form of mean±standard deviation (SD) for normally distributed data and median (range) for non-normally distributed data. Qualitative variables were offered as numbers and percentages. Comparison of non-normally distributed quantitative variables was performed using the Mann-Whitney U test. The chi-square test was utilized to analyze qualitative variables. Statistical significant was set at p-value ≤ 0.05. Data analysis was performed using STATA 13 statistical software.

## Results

In total, hematological data from 122 lymphoma patients were retrieved, consisting of 75% NHL patients and 25% HL patients. The overall mean±SD age was 52±15 years. The mean±SD age in the HL group was lower than in the NHL group (42±17 vs 55±14) as

**Table 2 Comparison of Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Platelet-to-Lymphocyte Ratio (PLR) in Patients with Hodgin and non-Hodgin Lymphoma**

| Variable | Total (n=122) | HL (n=30) | NHL (n=92) | p-value |
|---|---|---|---|---|
| Lymphocyte | 1702.5 (315–9154) | 1597.5 (320–5028) | 1746 (315–9154) | 0.684[b] |
| Neutrophil | 47812 (1575–22185) | 4817 (2340–22185) | 4763 (1575–17165) | 0.784[b] |
| Monocyte | 691.5 (112–2366) | 727.5 (142–2366) | 668.5 (112–1928) | 0.316[b] |
| Platelet | 328221 ± 109318 | 354167 ± 117397 | 319761 ± 105847 | 0.135[a] |
| Leucocyte | 7440 (1340–29580) | 7885 (3210–29580) | 7405 (1340–24100) | 0.764[b] |
| NLR | 2.9 (0.7–12.2) | 3.2 (1.1–10.8) | 2.7 (0.7–12.2) | 0.287[b] |
| MLR | 0.36 (0.04–1.86) | 0.46 (0.09–1.78) | 0.36 (0.04–1.86) | 0.150[b] |
| PLR | 177.3 (20.2–1533.3) | 211.2 (50.6–1156.3) | 160.6 (20.2–1533.3) | 0.189[b] |

Note: HL= Hodgin lymphoma; NHL= non-Hodgin lymphoma, [a]mean±SD, [b]median (min-max), [c]n (%), [a]analyzed using t-test, [b]Mann whitney, [c]Chi-square

depicted in Table 1.

The comparison of NLR, MLR and PLR between HL and NHL groups was shown in Table 2. Lymphocytes were slightly lower in the HL group compared to the NHL group, but not significantly different (median: 1597.5 vs 1746, p=0.684). Meanwhile, neutrophils, monocytes, platelets, leucocytes were slightly higher in the HL group than NHL, but not significantly different (p>0.05).

The median NLR in the HL group was 3.2 (range: 1.1–10.8), while in the NHL group was 2.7 (range: 0.7–12.2), statistically showing insignificant difference (p=0.287) as well as the median MLR and PLR in the HL and NHL groups showed statistically insignificant differences (p=0.150 and p=0.189), with the median MLR in the HL group being 0.46 (range: 0.09–1.78), while in the NHL group it was 0.36 (range: 0.04–1.86), the median PLR in the HL group was 211.2 (range: 50.6–1156.3), while in the NHL group it was 160.6 (range: 20.2–1533.3) (Table 2).

## Discussion

In this study, the lymphocytes are slightly lower in the HL group than in the NHL group. Meanwhile, neutrophils, monocytes, platelets, leucocytes are slightly higher in the HL group than NHL group but not significantly different. The ratio of neutrophil over lymphocytes is influenced by many conditions including age, chronic disease, cancer of solid organs, hematologic malignancy, anemia, and stress. The normal range of NLR is between 1–2, values higher than 3.0 and below 0.7 in adults are pathological. This ratio has also been associated with tumor progression, as it has been known as a prognostic marker in myeloma, lymphoma, and solid tumors.[2,6–7]

The ratio of monocytes to lymphocytes reflects a balance characterized by an elevation in monocytes and a reduction in lymphocytes. This can arise due to an inflammatory response prompted by tumor growth. Patients with solid tumors or hematological malignancies have exhibited elevated peripheral monocyte counts.[8] According to the reports, the count of monocytes in the bloodstream indicates the presence of tumor-associated macrophages (TAMs) inside the tumor micro milieu and holds promise as a potential biomarker. These mechanisms could corroborate the findings of this study.[9]

Neutrophils are an important marker of inflammatory response. Neutrophils increase in response to inflammation in cancer. While platelets increase along with neutrophils, there is a suppression of lymphocytes responsible for the immune response.[9]

Hodgkin's lymphoma, a malignant disease originating from lymphocytes, has been the subject of extensive research for many years and continues to be a topic of interest. Recently, significant progress has been made in improving treatment outcomes for Hodgkin's lymphoma and particularly in reducing long-term side effects. Response to treatment is considered a favourable prognostic factor in Hodgkin lymphoma. Additionally, certain pre-treatment factors such as advanced stage B symptoms, bulky disease, extra-nodal extension, male gender, high erythrocyte sedimentation rate, anemia, leukocytosis, and specific serum markers are widely recognized as prognostic factors in Hodgkin lymphoma.[10]

Hodgkin lymphoma is associated with various hematological irregularities, including anemia, low platelet count (thrombocytopenia), high or low neutrophil count (neutrophilia or neutropenia), increased eosinophils (eosinophilia), and reduced lymphocyte count (lymphopenia).[11]

Computed tomography (CT), Fluorodeoxyglucose (FDG), and positron emission tomography (PET) are recommended for evaluation. PET is interpreted using standar criteria developed in Deauville, France. In 2014 the Lugano classification introduced an updated lymphoma staging system by incorporating FDG, PET, and CT into the standard staging process. However, universal acceptance of the Lugano staging system is still pending.[12]

A study examining the prognostic significance of the NLR in Hodgkin's lymphoma established a threshold NLR value of 4.23 to expect the treatment outcome. An elevated NLR was linked to a lower therapeutic response rate. The sensitivity and specificity of this measurement were appraised at 60% and 65%, respectively.[13]

A study conducted in Italy compared NLR values between Hodgkin lymphoma patients and healthy individuals, revealing higher NLR values in the patient group (5.0 vs. 1.6). Higher NLR correlated with advanced stage of the disease, increased neutrophil count, reduced lymphocyte count, and elevated levels of systemic inflammation markers. Progression-free survival (PFS) at 60 months was observed to be 86.6% for patients with NLR values greater than or equal to 6, compared to 70.1% for those with NLR values less than 6. The study suggested that NLR can predict PFS

in Hodgkin lymphoma patients regardless of stage at diagnosis. Further studies are proposed to incorporate PET scan results along with NLR and LMR values which may form a novel prognostic system for Hodgkin lymphoma.[14]

Risk stratification has become increasingly crucial in the era of de-escalation therapy for early-stage Hodgkin lymphoma. Identifying patients at high risk for relapse and therefore unsuitable for de-escalation of treatment is of utmost importance. Although PET is commonly used, it is considered insufficient for this purpose. In a retrospective analysis, NLR and PLR were found to be correlated with poorer freedom from progression (FFP). Furthermore, there was a correlation between pre-treatment factors such as bulky disease, B symptoms, stage II disease, and higher NLR and PLR values. Neither NLR nor PLR has been proved to be effective in predicting relapse.[15]

A meta-analysis study examined the prognostic significance of LMR in Hodgkin lymphoma and included eight retrospective studies observed that low LMR was related to inferior overall survival (OS) and progression-free survival (PFS), possibly attributable to the more aggressive nature of Hodgkin lymphoma or reduced tolerance to treatment. This finding aligns with the established prognostic significance of lymphopenia in Hodgkin lymphoma, further emphasizing the importance of LMR to be a prognostic factor.[16]

Diffuse large B-cell lymphoma (DLBCL) is the predominant form of non-Hodgkin lymphoma in adults, representing 30–58% of cases. Staging for DLBCL follows the system of Ann Arbor. The international prognostic index (IPI) is widely used in diagnosing DLBCL. The score of IPI is determined by considering several factors, including the patient's age, presence of extra-nodal disease sites, serum lactate dehydrogenase level, staging of diseases, and the Eastern Cooperative Oncology Group (ECOG) performance score.[17]

Follicular lymphoma (FL) is a predominant type of indolent NHL in Western countries. It is a diverse illness characterized by a varied prognosis. The approach to managing FL depends on individual patient factors and characteristics of the illness. Treatment is typically initiated for most patients within 3–4 years of diagnosis. Several risk stratification tools are accessible to aid in determining appropriate management strategies.[18]

The prognostic significance of NLR in FL has less supporting evidence compared to DLBCL. In a retrospective cohort study conducted in Hongkong, in 88 FL patients, both LMR and NLR can be potential prognostic factors. The optimal cut-off values were 3.20 and 2.18 for LMR and NLR. A higher LMR at diagnosis was linked to improved progression-free survival, while an elevated NLR at relapse was associated with poorer post-progression survival. The study suggests that incorporating LMR and NLR values, in addition to Follicular Lymphoma International Prognostic Index (FLIPI), could provide reliable prognostic information for FL patients.[19]

A previous study found that AMC values of 580 or higher, NLR values of 2.43 or higher, and PLR values of 120.85 or higher were associated with a negative prognosis for the 5-year progression-free survival. Thus, NLR was not identified as an independent risk factor for both progression-free survival (PFS) and overall survival (OS).[20]

In contrast, another study has presented different findings, stating that neither the counts of neutrophils, lymphocytes, or platelets nor their corresponding ratios were indicative of overall survival (OS). Interestingly, the only factor that exhibited a correlation with OS was the pre-treatment hemoglobin level. The presence of anemia was associated with a poorer prognosis.[21]

Primary cutaneous T-cell lymphoma (PCTCL) is a diverse category of NHL that makes up approximately two-thirds of all cutaneous lymphomas. Among the various subtypes of cutaneous T-cell lymphoma (CTCL), the most prevalent is mycosis fungoides (MF), constituting more than half of all PCTCL cases.[22] During its initial phases, the condition typically exhibits a slow-growing nature, exerting minimal impact on the patient's overall life expectancy. However, a subsection of patients who experience accelerated disease progression and the dissemination of T cells beyond the skin exists. It is imperative to identify individuals at a heightened risk of rapid progression to provide appropriate management and care.[23]

In Turkey, there was no notable distinction observed in terms of demand therapy, time to therapy initiation, staging, or time to progression between patients with NLR ≥ 2 and those with an NLR < 2.[24] A prospective study examining screening tests in individuals diagnosed with early-stage mycosis fungoides revealed that no significant variation was identified in NLR values across different staging groups, suggesting that NLR might only serve as a prognostic marker in patients with progressive disease rather than early-

stage patients.[25]

In another study, a novel index of prognostic for Peripheral T-cell lymphoma unspecified was developed, which incorporated NLR, level of serum lactate dehydrogenase, and albumin. The primary objective of this index was to predict the response to initial chemotherapy. The study assessed the time to treatment failure rate (TTF) one-year post-diagnosis. Patients with a score of 0 (no adverse factors) had a TTF of 71.4%, while those with a score of 1 (1 adverse factor) had a TTF of 31.8%. Patients with a score of 2 (2-3 adverse factors) had the lowest TTF at 4.5%. The prognostic capacity of this model was found to be superior to the previously used prognostic index. Scores of 1 and 2 responded well to chemotherapy and should be considered as strong candidates for stem cell transplantation. Additionally, a lower absolute lymphocyte ratio count to absolute monocyte count ALC/AMC <2 was associated with shorter PFS and OS.[26]

A Chinese study examining the prognostic significance of derived neutrophil-to-lymphocyte ratio (dNLR) in 33 individuals with extra-nodal natural killer/T-cell lymphoma (ENKTL) revealed that patients with a dNLR of 3.6 or higher showed shorter PFS and OS than those with a dNLR below 3.6. Additionally, a small absolute lymphocyte count was identified as an unfavorable prognostic indicator.[27] Another study examining the correlation between the parameter of inflammation (LMR, NLR, and PLR) in T-lymphoblastic lymphoma (T-LBL) found that patients with LMR of 3.3 or higher and PLR of 200 or higher had inferior PFS and OS rates.[28]

The exact reasons underlying the prognostic value of NLR and MLR are still uncertain. However, extensive studies, including meta-analysis, have consistently shown the prognostic significance of PLR in DLBCL. PLR has emerged as a potential noninvasive biomarker for identifying patients with poor prognosis and aggressive disease characteristics in DLBCL.[29]

The significance of NLR and MLR has been widely established in various hematologic disorders, including NHL and HL. Assessment of the clinical implications of NLR and MLR can enhance existing prognostic indexes, leading to a more accurate prognosis for individuals with hematologic malignancies.

The retrospective design could be one of the limitations of this study as it may introduce certain biases in the data analysis. Additionally, the sample size was small, which may limit the generalizability of the findings. Furthermore, due to the inadequate duration of monitoring, it was not feasible to accurately predict the progression of the inflammation process.

In conclusion, this study assesses the clinical effectiveness of newly introduced markers, namely NLR, PLR, and MLR, for their prognostic value in NHL and HL patients. The system of immunity and the role of inflammation in NHL and HL have been the subjects of extensive research, drawing significant interest from the scientific community over the years. Although not statistically significant, NLR, MLR, and PLR tend to be lower in NHL than HL. These markers are simple tools to assess inflammatory parameters that might associated with the prognosis of malignant hematology.

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