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Original Article

Comparison of Platelet-Lymphocyte Ratio Before and After Chemotherapy in Histopathology Type of Nasopharyngeal Carcinoma

Aksimitayani[1], Abdul Kadir[1], Muhammad Fadjar Perkasa[1], Abdul Qadar Punagi[1]

[1]*Department of Otorhinolaryngology - Head and Neck Surgery, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia*

Corresponding Author:
Name: Aksmitayani, MD
Email: aksmitayani@gmail.com

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ABSTRACT

Introduction: *Nasopharyngeal carcinoma (NPC) is a non-lymphomatous squamous cell carcinoma in the nasopharyngeal epithelial layer which can be classified into three categories with different prognosis based on histopathological examination. This study aimed to compare platelet-lymphocyte ratio (PLR) in NPC patients before and after chemotherapy based on histopathological type.* ***Method:*** *this cohort study recorded data from medical records. The histopathological type, chemotherapy regimen, clinical stage, and PLR of NPC patients were recorded and compared before and after therapy using paired T-test and Wilcoxon test. The prognostic strength of PLR and the value of the cut-off point was determined by looking at the Area Under Curve (AUC) value using the Receiver Operating Characteristic (ROC) curve method.* ***Results:*** *A total of 44 NPC patients received chemotherapy for three cycles, including 21 patients with NPC type-2 and 23 patients with NPC type-3. There were significant differences in the average PLR before and after undergoing three cycles of chemotherapy in WHO type III NPC (p=0.023). At the same time, there were no statistically significant differences in WHO type II (p=0.131). The prognostic ability of pre-chemotherapy PLR in assessing disease progression in WHO type II was good (AUC=0.763) with 100.0% sensitivity and 73.68%*

specificity. In WHO type III NPC, the prognostic ability of PLR was very good (AUC 0.881) with 100% sensitivity value and 76.19% specificity. ***Conclusion:*** *A significant PLR decrease was obtained after the 3rd cycle of chemotherapy in WHO type III NPC following Docetaxel-cisplatin regimen but not in WHO type II. This is probably due to the use of a cisplatin therapy regimen that is more responsive to WHO type III NPC. In addition, examining PLR value before undergoing chemotherapy can be a predictor in assessing disease progression in WHO type III NPC patients.*

1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a non-lymphomatous squamous cell carcinoma in the nasopharyngeal epithelial layer. In 2018, Globocan reported 129,079 new cases of NPC worldwide, of which 72,987 resulted in death. There were 17,992 new cases in Indonesia, where the number of deaths reached 11,204 cases.[1] The incidence depends on the variation of race and geographic area. NPC is generally sensitive to radiotherapy; besides that, chemotherapy is one of the treatment options in patients. At an advanced stage, it is necessary to combine cancer therapy modalities, both platinum-based chemotherapy combined with radiotherapy (chemoradiotherapy). Based on the National Comprehensive Cancer Network (NCCN) guidelines in 2018, patients with stage 2 and above can be given chemotherapy either as adjuvant chemotherapy, neoadjuvant chemotherapy, or concurrent chemotherapy [2,3].

Based on the type of histopathology obtained from biopsy examination, WHO classifies NPC into several subtypes: Type I or keratinized squamous cell carcinoma; nonkeratinized nasopharyngeal carcinoma which is further classified into differentiated (WHO type II) and undifferentiated (WHO type III), and basaloid squamous cell carcinoma. Studies show that WHO type III is the most common.[4] Classifying NPC based on histopathological type is essential because it will affect the management approach and prognosis. Unfortunately, no biological markers can predict chemotherapy prognosis and it is imperative to combine 2 or 3 such markers to get an excellent diagnostic value [5].

A previous study suggested that platelet-lymphocyte ratio (PLR) can be used to predict the survival rate of NPC patients, where an increase in PLR was associated with poor survival. A high PLR was associated with lymph nodes stage (N) in NPC patients [6]. Research by Kong Yew et al. in 2017 showed a significant difference of neutrophil-lymphocyte ratio (NLR) between NPC patients who experienced recurrence and non-recurrence; treatment failure was significantly higher in the group of patients with high NLR.[7] Increased NLR and PLR were associated with poor survival in NPC patients.[8] There is a relationship between NLR, lymphocyte-monocyte ratio (MLR), and PLR with the development and metastatic nasopharyngeal carcinoma[9], where higher PLR is associated with worse prognosis.[10] However, the association of PLR in patients with different NPC histologic subtypes is still unclear.

Therefore, our aims of study were to compare the PLR of NPC patients receiving chemotherapy with different histologic subtypes and determine the prognostic value of PLR in assessing the therapeutic response to disease progression based on histopathological type.

2. METHODS

Study Design

This cohort study was conducted at the otorhinolaryngology, head neck outpatient clinic and inpatient ward of Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia from May–December 2020. Ethical approval was obtained from Hasanuddin University Ethics Committee (No:424/UN4.6.4.5.31/PP36/2020). Written informed consent was obtained from all participants.

Samples

The inclusion criteria of samples were patients in between 25-60 years, undergoing inpatient treatment, diagnosed with NPC with histopathology, and undergoing chemotherapy for at least three cycles. Treatment response was based on WHO criteria and classified into complete response, partial response, no response, and progressive disease. The exclusion criteria were pregnancy, distant metastases at the time of initial diagnosis, presence of other primary tumors, presence of autoimmune disorders (SLE and HIV), underwent previous chemotherapy treatment, and relapsed patients. The histopathological type, clinical stadium, routine blood tests, and therapeutic response of patients before and after chemotherapy were collected from the medical records.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics version 24 for Windows. Normality test was done using Shapiro-Wilk with a significance level of <0.05 (Alpha = 5%). The Paired-T test and Wilcoxon test were used to see the significance of the difference between NLR and LMR values on the therapeutic response in NPC patients receiving chemotherapy. Finally, to determine the prognostic strength of PLR and the value of the cut-off point by looking at the Area Under Curve (AUC) value using the Receiver Operating Characteristic (ROC) curve method.

3. RESULTS

Characteristics of Subjects

This study was conducted on 21 patients with WHO type II and 23 patients with WHO type III NPC who had received chemotherapy at dr. Wahidin Sudirohusodo Hospital from May to December 2020. Table 1 shows that the average age of the study subjects was 54.04±7.28 years in WHO type II and 47.82±11.14 years in WHO type III NPC. The majority of the research subjects were male (32 subjects, 72.7%). Most of the research subjects were stage III and IV (16 subjects, 36.4%). The most common chemotherapy regimen obtained by research subjects was paclitaxel-cisplatin regimen (24 subjects, 54.5%). As many as 31 people (70.5%) showed no response to chemotherapy.

Table 1. Distribution & sample characteristics based on WHO classification of NPC type

Variable	WHO type II (n = 21)	WHO type III (n = 23)	Total (n = 44)
Age (year)			
20-30	0 (0.0%)	1 (4.3%)	1 (2.3%)
31-40	1 (4.8%)	2 (8.7%)	3 (6.8%)
41-50	5 (23.8%)	11 (47.8%)	16 (36.4%)
>50	15 (71.4%)	9 (39.1%)	24 (54.5%)
Gender			
Man	15 (71.4%)	17 (73.9%)	32 (72.7%)
Woman	6 (28.6%)	6 (26.1%)	12 (27.3%)
WHO Stage			
I	0 (0.0%)	2 (8.7%)	2 (4.5%)
II	5 (23.8%)	5 (21.7%)	10 (22.7%)
III	7 (33.3%)	9 (39.2%)	16 (36.4%)
IV	9 (42.9%)	7 (30.4%)	16 (36.4%)
Chemotherapy Regimen			
Docetaxel-Carboplatin	3 (14.3%)	7 (30.4%)	10 (22.7%)
Docetaxel-Cisplatin	1 (4.8%)	0 (0.0%)	1 (2.3%)
Paclitaxel-Carboplatin	7 (33.3%)	2 (8.7%)	9 (20.5%)
Paclitaxel-Cisplatin	10 (47.6%)	14 (60.9%)	24 (54.5%)
Therapy Response			
Complete response	0 (0.0%)	0 (0.0%)	0 (0.0%)
Partial response	4 (19.0%)	5 (21.7%)	9 (20.5%)
No response	15 (71.5%)	16 (69.6%)	31 (70.5%)
Progressive disease	2 (9.5%)	2 (8.7%)	4 (9.0%)

Comparison of laboratory markers before and after chemotherapy three cycles

Table 2 shows significant differences in the mean of platelets and lymphocytes number ($p<0.05$) before and after chemotherapy in WHO type II patients. In WHO type III patients, there were significant differences in the mean of platelets, lymphocytes, and leukocytes ($p<0.05$) before and after therapy. Figure 1 shows a significant decrease in the mean PLR in WHO type III NPC patients ($p<0.05$), while there was no difference in the decrease in the mean PLR in WHO type II patients ($p>0.05$).

Table 2. Comparison of laboratory markers before and after three cycles of chemotherapy in nasopharyngeal carcinoma (NPC) patients by histopathological type

Variable	Chemotherapy cycle		P-value
	Pre	Post	
WHO type II			
Platelet	335.23±116.06	268.28±70.52	****0.025**
Lymphocytes	22.86±12.24	31.13±16.24	****0.021**
leukocyte	10.02±3.84	7.51±3.67	**0.079
PLR	179.61±76.64	155.19±68.80	**0.131

WHO type III			
Platelet	378.60±81.39	290.95±87.02	*0.000
Lymphocytes	18.80±10.40	31.92±15.41	**0.002
leukocyte	10.35±3.10	7.04±3.86	**0.007
PLR	257.89±192.25	195.95±153.96	**0.023

P-values were calculated using the *Paired-T test and the **Wilcoxon test.

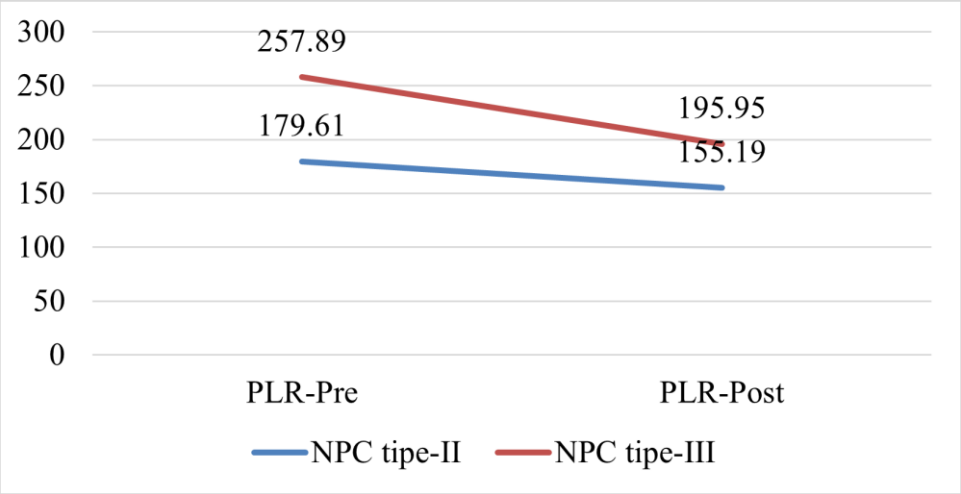

Figure 1. Comparison of average platelet-lymphocyte ratio (PLR) pre- and post-chemotherapy in NPC based on histopathology type classification

Platelet-lymphocytes ratio (PLR) before and after three-cycle chemotherapy based on stage, type, and therapy response

Table 3 shows the mean PLR in WHO type II and III NPC patients based on stage, chemotherapy regimen, and response to therapy which showed significant differences before and after three cycles of chemotherapy ($p<0.05$). WHO type II participants who received Paclitaxel-cisplatin regimen showed a significant increase in PLR difference ($p<0.05$) after three cycles of chemotherapy which suggested that the use of Paclitaxel-cisplatin chemotherapy regimen in WHO type II is not better than WHO type III NPC.

Table 3. Comparison of PLR before and after chemotherapy three cycles based on stage, type, and response therapy in nasopharyngeal carcinoma patients (NPC)

Variable	Platelet-lymphocyte Ratio		P-value
	Pre-Chemotherapy cycles	Post- Chemotherapy cycles	
WHO Type II			
Stage			
I	-	-	-
II	189.66±46.49	146.54±84.09	**0.005
III	158.95±52.03	182.28±42.03	*0.000
IV	190.09±104.94	138.93±77.37	**0.000
Chemotherapy Regimen			
Docetaxel-Carboplatin	192.92±70.17	134.43±63.53	*0.002
Docetaxel-cisplatin	219.27	121.32	**0.180

Paclitaxel-Carboplatin	216.46±101.15	164.84±92.96	****0.001**
Paclitaxel-cisplatin	145.86±50.80	158.05±59.23	***0.000**
Therapy Response			
Complete response	-	-	-
Partial response	202.67±73.85	153.32±84.71	***0.000**
No response	167.77±81.60	154.59±70.43	****0.000**
Progressive disease	222.25±4.21	163.40±59.51	**0.068
WHO Type III			
Stage			
I	558.20±607.10	413.08±508.33	**0.068
II	289.70±191.78	179.31±109.42	****0.005**
III	213.42±75.52	205.59±95.49	***0.000**
IV	206.56±70.93	133.39±55.28	****0.001**
Chemotherapy Regimen			
Docetaxel-Carboplatin	224.31±66.49	138.02±63.61	****0.001**
Docetaxel-cisplatin	-	-	-
Paclitaxel-Carboplatin	227.14±62.40	97.78±55.79	**0.068
Paclitaxel-cisplatin	279.08±242.85	238.94±180.91	****0.000**
Therapy Response			
Complete response	-	-	-
Partial response	232.21±86.61	220.36±129.74	***0.000**
No response	220.02±122.36	152.31±76.71	****0.000**
Progressive disease	625.10±512.48	484.00±408.03	**0.068

P-values were calculated using the *Paired-T test and the **Wilcoxon test.

Cut Off Value, Sensitivity, and Specificity of PLR as Prognostics for Progressive disease to therapy

The receiver operating characteristic (ROC) curve is used to estimate the outcome in type II and III NPC patients (Figure 2). The area under the curve (AUC) in WHO type II was 0.763, with the sensitivity and specificity values being maximized with a PLR cut-off of 210.69 (sensitivity = 100.0; specificity = 73.68). Moreover, in WHO type III NPC, the area under the curve (AUC) was 0.881, with the sensitivity and specificity values being maximized by the PLR cut-off (sensitivity = 100.0; specificity = 76.19). This result shows that pre-chemotherapy PLR of >210.69 and >251.80 in type II and WHO type III NPC patients, respectively, are associated with poor outcome (Table 4).

Table 4. Characteristics of ROC in PLR in predicting prognosis in NPC histopathological type

PLR	Cut-off	AUC	Sensitivity	Specificity	95% CI	P-value
WHO type II	210.69	0.763	100.0	73.68	0.530-0.919	**0.009**
WHO type III	251.80	0.881	100.0	76.19	0.678-0.977	**0.003**

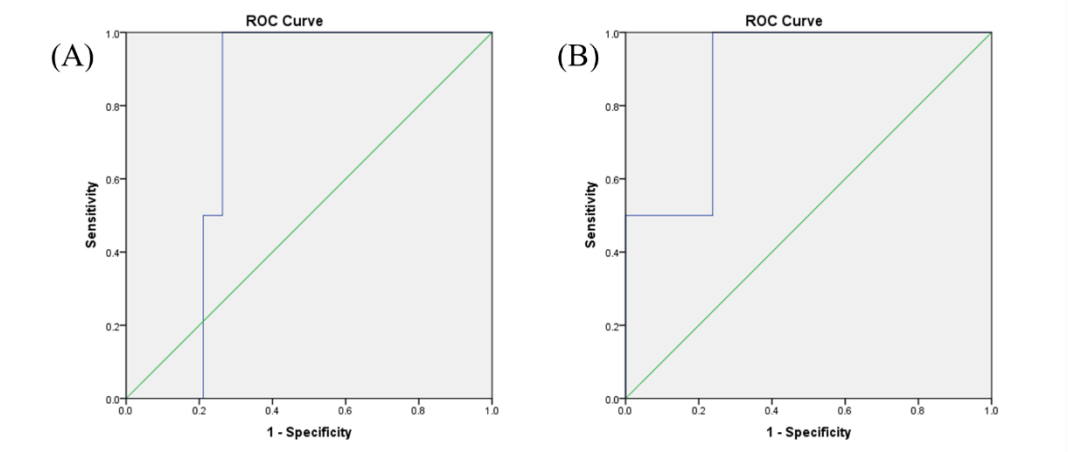

Figure 2. Receiver operating characteristic (ROC) curve for PLR (Platelet-lymphocyte ratio) values in WHO type II (A) and WHO type III (B).

4. DISCUSSIONS

In this study, we investigated the prognostic effect of PLR in WHO type II and WHO type III NPC patients receiving chemotherapy. The data on the characteristics of the research subjects showed that of the 44 study subjects, the average age was 54.04±7.28 years for WHO type II and 47.82±11.14 years for WHO type III NPC. It has been suggested that a mutation in DNA repair mechanism and the decrease in body's immune system at the age of more than 40 years lead to a higher incidence of malignancy in such age group.[11] In addition, NPC is more common in men than women because men tend to smoke and consume alcohol more than women [12].

Our study shows that there was a significant amount of type II and WHO type III patients with advanced stages (stages III and IV). The prognosis of NPC is strongly influenced by early diagnosis and treatment, considering that the 5-year survival rate in patients with stage III is 38.4% and 16.4% in patients with stage IV.[13] In addition, the response to therapy patients was found to be high in both type II and III NPC. Still, the percentage of no-response therapy was higher in WHO type II. It is hypothesized that patients with WHO type II and type III NPC were more likely to experience resistance to chemotherapy and increased relapse compared to WHO type III NPC. The presence of gene mutations in type II causes the cisplatin regimen to be insensitive to cancer cells [14].

Platelet levels of patients with type I and WHO type III NPC were higher before chemotherapy. Thrombocytosis in NPC patients is thought to be due to the influence of proinflammatory cytokines. Epstein Barr virus infection in NPC epithelial cells causes overexpression of interleukin-6 (IL-6).[15] Thrombocytosis causes resistance to chemotherapy and increased aggressiveness of the cancer cells. Fluctuations in platelet count during treatment is associated with the role of platelets in the prediction of tumor recurrence and evaluation of therapy.[16,17]

In addition, the number of lymphocytes in WHO type III NPC patients was significantly lower after therapy. This might occur as lymphocytes play a role in destroying tumor cells and inhibiting metastasis. Cellular antitumor immune responses can be activated by lymphocytic infiltration. In fact, in response to chemotherapy, T

lymphocytes can be chronically activated to enhance cancer cell apoptosis by presenting tumor-associated antigens to immune cells [18]. Cytotoxic lymphocytes play a fundamental role in cell-mediated immunological destruction. Lymphocytes in the circulation secrete several cytokines that affect the histopathological type of NPC [19].

Our results showed a significant difference in the mean PLR before and after therapy in WHO type III NPC patients. The measurement before chemotherapy was higher than after three cyles of chemotherapy with Docetaxel-Carboplatin and paclitaxel-cisplatin therapy regimen. However, there was no significant PLR difference in WHO type II patients before and after three cycles of chemotherapy. This might be due to an increased overexpression of the ERCC1 gene (excision repair cross-complementation group 1) as this gene conveys lower response to treatment and causes resistance to cisplatin.[14] Another study stated that patients with WHO type II experienced more relapses than WHO type III NPC [20].

One of the side effects of the paclitaxel-cisplatin regimen in this case was a decrease in the production of hematopoietic cells due to bone marrow suppression. Paclitaxel causes bone marrow suppression by strongly binding to the microtubules of bone marrow cells. This prevents depolymerization and damages mitochondrial and nuclear DNA of bone marrow cells which leads to increased Bax, Bak, Bim, Bok, and Bad and decreased Bcl-2 and Bclx expression which subsequently leads to inhibition of mitosis then cell apoptosis.[21,22] On the other hand, cisplatin binds to the DNA of bone marrow cells and causes DNA damage during replication through intrastrand crosslinked DNA due to contributions ROS, cytochrome-c, JNK, p38MAPK, caspase which decrease the number of cells, including platelets [22,23].

In our study, the cut-off point for the platelet-lymphocyte ratio in assessing the objective response to disease progression was 210.69 which has a sensitivity and specificity of 100.0% and 73.68%, respectively. This is supported by a meta-analysis conducted by Berdash et al. which concluded that PLR can be used as a predictor of NPC progression.[24] Platelet lymphocyte ratio reflects complex interactions between systemic inflammatory responses and tumor micro-environments. High PLR generally result in relative thrombophilia and lymphopenia. Infiltration of tumor lymphocytes has been shown to improve prognosis and response to treatment. Infiltration of Th17 lymphocyte cells in cancer cells increases MIF expression (macrophage migration inhibitory factor), where high MIF level is associated with improved treatment outcomes. Based on this, it can be known that low lymphocyte count hampers the ability of the body to produce a robust immune response. High PLR is an estimate of the relationship between tumors, inflammatory responses, and cancer cell interactions to the immune response [25].

Platelet lymphocyte ratio reflects the inverse effect of platelets and lymphocytes on the progression and metastasis of cancer cells because platelets cause angiogenesis, migration, and metastasis of cancer cells through the release of growth factors that influence treatment response. In addition, PLR can reflect the body's immune condition in fighting cancer cells [26,27].

Currently, no literatures have shown consistent results for PLR cut-off differences in each histopathological type. Biological response mechanisms are different in each type of NPC type. A previous study found that the expression of excision protein was

significantly higher in WHO type II than WHO type III NPC. The platelet at the PLR examination count in WHO type III was higher than in WHO type II [28].

5. CONCLUSION

The PLR after the third cycle of chemotherapy in WHO type III was lower compared WHO type II. A PLR of >251.80 before chemotherapy in WHO type III NPC patients is associated with a more progressive disease with a sensitivity value of 100.0% and specificity of 76.19%.

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Conflict of Interest Statement:

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.