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Platelet to Lymphocytes Ratio to Predict Nasopharyngeal Carcinoma Progressivity

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Abstract

BACKGROUND: Nasopharyngeal carcinoma (NPC) is a head and neck cancer that arises from the nasopharyngeal epithelium. It is one of the most common malignancies in Southeast Asia. In 2020, there were 133,354 new cases of NPC worldwide, with 113,659 occurring on the Asian continent (85.2%). In Indonesia, the prevalence of NPC is 6.2/100,000 people, with 13,000 new cases each year. NPC was the most frequent head and neck cancer in the Otorhinolaryngology-Head and Neck Surgery Department Dr. Hasan Sadikin Hospital Bandung from 2013 to 2018, with 921 (35.20%) new cases.

AIM: Platelet-to-lymphocyte-ratio (PLR) testing has the potential to be employed as a prognostic marker in the evaluation of NPC. The purpose of this study is to investigate the link between PLR and the clinical stage of NPC.

METHODS: Between 2016 and 2020, a cross-sectional study was conducted on NPC patients at Hasan Sadikin Hospital in Bandung. Patient information was gathered from the registry of the Oncology Head and Neck Surgery Study Group. Three hundred and eighty-three people met the requirements for inclusion.

RESULTS: Lymph node metastases ($p = 0.001$), distant metastases ($p = 0.001$), and clinical stage ($p < 0.001$) are all classified differently by PLR. The platelet to lymphocytes ratio was linked to lymph node metastasis, distant metastases, and clinical stage in a statistically significant ($p < 0.05$). Patients with a PLR >287 have a 3.69 times chance of developing distant metastases, while those with a PLR >160 have a 1.38 times chance of progressing to the advanced stage.

CONCLUSION: PLR is linked to the nasopharyngeal cancer clinical stage. Furthermore, in NPC patients, PLR can predict advanced stage and distant metastases.

Introduction

Nasopharyngeal carcinoma (NPC) is a head and neck cancer that develops from the nasopharyngeal epithelium. It is one of the most common malignancies in Southeast Asia [1], [2], [3].

According to the International Agency for Research on Cancer, there were 133,354 new cases of NPC worldwide in 2020, with 113,659 (85.2%) of them occurring in Asia, particularly East Asia (65,866 cases) and Southeast Asia (36,747 cases). In Indonesia, the prevalence of NPC is 6.2/100,000 people, with around 13,000 new cases each year. NPC was the most frequent head and neck cancer in the Otorhinolaryngology-Head and Neck Surgery Department Dr. Hasan Sadikin Hospital Bandung from 2013 to 2018, with 921 (35.20%) new cases [4], [5], [6], [7].

The NPC is diagnosed by history taking, physical examination, laboratory examination, radiology examination, and nasopharyngeal mass biopsy as the golden standard. Clinical symptoms include nasal congestion, epistaxis, tinnitus, ear fullness, otalgia, diplopia, cranial nerve disorders (nerves III, IV, V, and VI), and a lump in the neck [8].

Inflammation has been identified as a critical element in the development of tumors in humans, and it has been linked to an increased risk of tumor formation and angiogenesis. Inflammatory mediators and cells make up the tumor-associated inflammatory response.

Inflammation-based tests, such as the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein-to-albumin ratio, and platelet-to-lymphocyte-ratio (PLR), have been developed to predict oncological outcomes in a variety of solid tumors [9], [10], [11].

Platelets can create inflammatory cytokines and chemokines, leading to the formation of tumors. TNF-, IL-1 and Interleukin-6 (IL-6) are pro-inflammatory cytokines produced by platelets. IL-6 can stimulate the development of megakaryocytes into platelets and participate in the recruitment of neutrophils, causing the thrombosis cycle to become more active due to the inflammatory process. Interleukin-6 has been proven in several studies to promote increased platelet count in cancer patients by stimulating thrombopoietin synthesis. By generating vascular endothelial growth factors and

aiding inflammatory cell movement, platelets aid tumor angiogenesis, and stromal development. Many types of leukocytes, including lymphocytes, neutrophils, eosinophils, basophils, monocytes/macrophages, dendritic cells, and natural killer cells, infiltrate solid tumors, which show classic indications of inflammation (NKC). T lymphocytes play a crucial role in the immunologic antitumor response by suppressing tumor cell proliferation and promoting cell death. Tumor-infiltrating lymphocytes (TILs) are critical components of the antitumor immune response and play a role in tumor formation at various stages. As a result, in NPC, PLR may indicate a balance between tumor development and antitumor immune response [1], [12], [13].

The PLR has the potential as a prognostic marker that can evaluate NPC. Therefore, this study intends to study the relationship of PLR to the clinical stage of NPC.

Table 1: Demographic characteristics of patients

Characteristic	Total (n = 383)	%
Gender		
Male	246	64.2
Female	137	35.8
Age (year)		
< 20	13	3.4
20–29	30	7.8
30–39	45	11.7
40–49	113	29.5
50–59	108	28.2
60–69	60	15.7
≥ 70	14	3.7
T Classification		
T1	62	16.2
T2	135	35.2
T3	117	30.5
T4	69	18.0
N Classification		
N0	70	18.3
N1	70	18.3
N2	82	21.4
N3	161	42.0
M Classification		
M0	345	90.1
M1	38	9.9
Stage Group		
I	9	2.3
II	42	11.0
III	73	19.1
IVA	223	58.2
IVB	36	9.4

Methods

Between 2016 and 2020, a cross-sectional study of NPC patients at Hasan Sadikin Hospital in Bandung was conducted. Patient information was gathered from the registry of the Oncology Head and Neck Surgery Study Group. Hasan Sadikin Hospital's Ethics Committee gave their approval to this study. Three hundred eighty-three subjects met the following criteria: they were diagnosed with NPC, had not received chemotherapy, radiotherapy, or chemoradiation, and had complete medical records. Patients having initial cancer elsewhere, recurring cancer, diabetes, or cardiovascular disease were excluded from the study.

Statistical analysis

The demographic characteristic of the patient was analyzed using the Kolmogorov–Smirnov test to compare non-paired data. The correlation was analyzed using Spearman. Cutoff value determined using receiver operator characteristic (ROC) curve. Significance was accepted as $p < 0.05$.

Results

According to Table 1, there were 383 patients in this study, 246 (64.2%) men and 137 (35.8%) women. The subjects were mostly in their 40s and 50s (29.5%), with the youngest being 13 and the oldest being 84. The primary tumor was T2 which was 135 (35.2%). The highest number of lymph node metastases was N3 with 161 (42%), and distant metastases were M0 with 345 (90.1%). With 223 subjects, most of the participants in this study were in stage IVA (58.2%), followed by Stage III (19.1%) with 73 participants. The Kolmogorov–Smirnov test revealed that the subjects in this study were not normally distributed, with a $p < 0.001$.

Platelet to lymphocyte ratio has significant differences in lymph node metastases ($p = 0.001$), distant metastases ($p = 0.001$), and clinical stage ($p < 0.001$) classifications, as shown in Table 2. The platelet to lymphocytes ratio was statistically linked to lymph node metastasis, distant metastases, and clinical-stage ($p < 0.05$). Distant metastases had a very low or negligible correlation with PLR, whereas lymph

Table 2: Characteristic relationship with PLR in NPC patients

Characteristic	PLR	Coeff Correlation		
	Median (Range)	p*	r **	p
Gender		0.941	0.023	0.571
Male	209.5 (45–2302)			
Female	204.0 (66–1478)			
Age (year)		0.103	−0.116	0.023
< 20	248.0 (83–1478)			
20–29	215.0 (69–806)			
30–39	212.0 (45–612)			
40–49	213.0 (80–2302)			
50–59	188.0 (52–725)			
60–69	172.5 (87–589)			
≥ 70	258.0 (122–1074)			
T Classification		0.478	0.048	0.345
T1	197.0 (45–1170)			
T2	210.0 (52–1473)			
T3	204.0 (69–2302)			
T4	213. (86–1478)			
N Classification		0.001	0.205	0.001
N0	166.0 (45–1074)			
N1	200.5 (78–588)			
N2	199.0 (80–1478)			
N3	229.0 (52–2302)			
M Classification		0.001	0.161	0.002
M0	202.0 (45–2302)			
M1	206.0 (45–2302)			
Stage group		< 0.001	0.335	< 0.001
I	107.0 (45–153)			
II	136.0 (78–1074)			
III	185.0 (80–617)			
IVA	217.0 (52–2302)			
IVB	307.5 (86–1473)			

PLR: Platelet-to-lymphocyte-ratio, NPC: Nasopharyngeal carcinoma

node metastases (r = 0.205) and prognostic stages (r = 0.335) had low correlations.

The PLR cutoff value was determined through calculations using the ROC curve. With a sensitivity of 57.89% and a specificity of 76.23%, the cutoff value of 287 with p = 0.002 had a sensitivity of 57.89% and 76.23% shown in Figure 1 and Table 3. The relative risk = 3.69 is shown in Table 4. This shows that NPC patients with PLR >287 have a 3.69 times more risk of distant metastases than those with PLR ≤287. Table 5 and Figure 2 show that the PLR cutoff is 160 with p < 0.001, a sensitivity of 77.75%, and a specificity of 68.6%. Patients with PLR values >160 have a 1.38 times more risk of becoming advanced stage NPC patients than those with PLR ≤160 shown in Table 6.

Table 3: PLR cutoff value for distant metastases

Youden Index	Cut off	Sensitivity	Specificity
0.3413	287	57.89	76.23

PLR: Platelet-to-lymphocyte-ratio.

Discussion

Non-modifiable risks such as gender, ethnicity, and family history, as well as modifiable risks such as smoking, childhood consumption of salted fish, nitrosamines in some traditionally processed foods in southern China, and use of traditional herbal medicines in Asian populations, as well as environmental risk factors such as formaldehyde, wood dust, smoke, and chemicals, may all play a role in the pathogenesis of NPC [14].

Table 4: Relationship of PLR with distant metastases in NPC patients

PLR	Distant meta states		p
	M1 (%)	M0 (%)	
> 287	22 (57.9)	82 (23.8)	< 0.001
≤ 287	16 (42.1)	263 (76.2)	

Note: RR (CI 95%) : 3,69 (2,02 – 6,74).

Diet pattern is a factor that affects NPC. Asian dietary trends, such as salted fish, smoked meat, aged vegetables, preserved vegetables, and drinking herbal teas, have been linked to an elevated risk of NPC in several case studies. In South China, the increase in cases of NPC in children is related to the consumption of salted fish at an early age. Research in several Asian countries shows that Asian people consume salted fish or salted vegetables at least once a week [15].

Table 5: PLR cutoff value for clinical stage

Youden Index	Cut Off	Sensitivity	Specificity
0.741	160	77.41	68.63

PLR: Platelet-to-lymphocyte-ratio.

In this study, there were more male subjects than females with a ratio of 1.8: 1. According to the WHO, NPC cases were more common in men; in Southeast Asia, the ratio of NPC cases was 3:1 for men. This is also in line with studies conducted by Hardianti *et al*., who found that NPC cases at Hasan

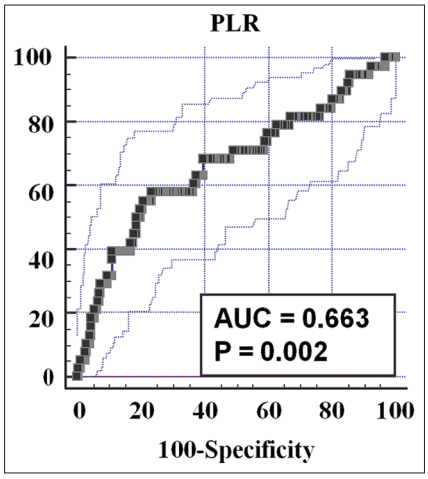

Figure 1: ROC curve for distant metastatic PLR cutoff

Sadikin Hospital were 1.7:1 more common in men. This comparison is influenced by lifestyle factors such as smoking and alcohol drinking, which raises NPC incidence by 5.8 times and 3.6 times, respectively, and by 19 times if both factors are present. The carcinogenic mechanism of tobacco is direct contact of combustion smoke with the nasopharyngeal epithelium. Tobacco also has substances that can activate EBV. Zuo *et al*. suggested that NPC is related to the X chromosome, which causes a person to be more susceptible to NPC because the male X chromosome, namely chromosome 6, has human leucocyte antigen, which is susceptible to NPC. Women have the hormone estrogen as protection from NPC. The survival rate of female NPC patients decreases at postmenopausal age, this is related to high estrogen levels before menopause, but the mechanism still needs further research. The incidence of NPC peaks between the ages of 45 and 59, according to Chang *et al*. The results of this study showed the same thing, with the most cases occurring in the 40–49 year age group (29.5%). This is related to smoking habits and consumption of salted fish since childhood. Furthermore, persons who have smoked for more than 10 years have an increased risk of having

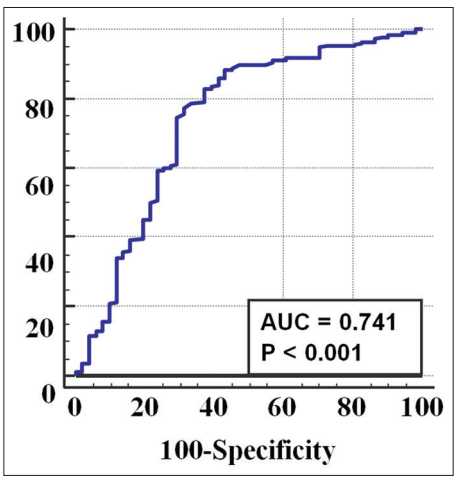

Figure 2: ROC curve for clinical stage PLR cutoff

Table 6: Relationship of PLR with Clinical Stage in NPC patients

PLR	Clinical stage		p
	Advanced	Early	
> 160	257 (77.4%)	16 (31.4%)	< 0.001
≤ 160	75 (22.6%)	35 (68.6%)	

Note: RR (CI 95%) : 1,38 (1,21 – 1,57).

NPC. In the previous decade, many studies have shown that EBV DNA viral load is a sensitive and non-invasive biomarker for monitoring NPC. In the study by Gihbid *et al*., plasma EBV DNA levels were 4 times higher in patients over 30 years old [15], [16], [17], [18], [19], [20].

Genetic factors are also a risk factor for NPC. Patient DNA is one of the essential factors in the pathogenesis of NPC. Telomeres are the ends of the DNA chain that contain proteins to protect the DNA. Telomere length in NPC patients is 3.2 times shorter than in normal tissue; this indicates that telomere shortening is involved in tumor progression. Ko *et al*. studies suggest that telomere shortening is associated with old age and males [21].

There is an infiltration of antitumor immune cells in the tumor microenvironment, especially lymphocytes called TILs. Elevated TIL in various types of cancer is associated with a good prognosis. It was found that the main cytokine components obtained from nasopharyngeal biopsy preparations in NPC patients were CD4+ and CD8+, substances produced by T lymphocytes. Barely *et al*. study found that TIL was associated with an increase in overall survival (OS) in NPC patients. PLR does not describe the activity of suppressing the progression of the primary tumor because the PLR value is derived from the bloodstream, whereas the body's immune response to the tumor occurs in the tumor due to the infiltration of immune cells such as neutrophils, eosinophils, basophils, monocytes/macrophages, dendritic cells, NKC, and lymphocytes [22], [23].

Tumor cells have antigens that will be expressed with MHC Class 1, forming a complex through TCR and CD8 + lymphocytes, which become active as effectors called Tc lymphocytes which function to destroy tumor cells and then become memory cells. A small amount of tumor cell antigen will be expressed with class II MHC. It will form a complex with CD4 + T lymphocytes, causing CD4+ T lymphocytes to become active as Th lymphocytes, producing IFN and TNF, increasing the expression of class I MHC molecules, and improving Tc lymphocytes' cytotoxic function. In addition, the cross-presentation mechanism in which APC presents tumor cell antigens to T lymphocytes will trigger CD4 + Th lymphocytes to stimulate Tc lymphocytes to kill tumor cells [24].

Thrombocytosis is caused by the production of the cytokines IL-1, IL-6, GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), and G-CSF (Granulocyte-Colony-Stimulating Factor), which accelerate thrombopoiesis and megakaryopoiesis in cancer patients. Platelets protect cancer cells by binding P-selectin to the surface of cancer cells, which is mediated by glycoproteins that connect with tumor cells on their membranes. Platelets not only shield cancer cells by forming a physical barrier against NKC, but they also interfere with NKC's detection of cancer cells and increase cancer cell survival by activating TGF and Nuclear factor-kB (NF-kB), two factors that promote cancer cell proliferation. Platelets can transfer "normal" Class I MHC molecules to cancer cells' surfaces, making them indistinguishable from foreign cells and interfering with NKC's cytotoxicity and IFN- production. Platelet-excreting TGF also reduces NKC activity. As a result, cancer cells may reduce the amount of CD8+ T lymphocytes produced or even fail to identify them [25], [26].

The process of metastasis is also influenced by platelets through the attachment of platelets to the surface of the CTC so that it is not recognized by immune cells during circulation and facilitates CTC to adhere to the walls of blood vessels and lymphoid tissue so that metastasis occurs. Because many platelets protect tumor cells from being recognized by the immune system, lymphocytes do not proliferate in blood circulation, and thrombocytosis in NPC patients will promote lymph node metastasis and distant metastases. Platelets are also implicated in the adaptive immune response and development of Th lymphocyte cells, which is a double-edged sword in cancer progression. Platelets aid cancer angiogenesis and are immunosuppressive, stimulating CD8 + T lymphocytes. In preclinical experiments on mice, the thrombocytopenia state reduced cancer metastasis, and in another group, the lymphocytopenia state increased the cancer cell metastasis because lymphocytes are the body's first line of defense in preventing circulating and lymphatic circulating metastases [26], [27], [28], [29].

The many cell types in the tumor micro environment communicate with one another to aid cancer development; for example, systemic inflammation response index (SIRI) and systemic immune-inflammation index (SII), a combination of NLR and monocyte and platelet, were linked to cancer patient prognosis. Neutrophils can increase tumor motility, migration, and invasion by releasing pro-inflammatory cytokines, matrix metalloprotease 9 (MMP9), and VEGF. In contrast to neutrophils, monocytes, and platelets' pro-tumor functions in malignant carcinomas, lymphocytes play an essential part in the antitumor immune response [30], [31].

Kumarasamy *et al*. suggested that PLR and NLR have evidenced potential as prognostic markers for clinical use, particularly in Head and Neck Cancer. Because there is presently no generally validated non-invasive and cheap biomarker that acts as a proxy for tumor burden or treatment response in a malignancy like HNC, especially HPV-negative HNC, this is very relevant. NLR, PLR, SII, and SIRI were found to be strongly linked with poor OS and progression free

survival in NPC patients in a research by Li *et al*. Study by Zeng *et al*., compared SIRI, SII, NLR, and PLR in NPC patients, they found that PLR was optimal predictive indicators for NPC [30], [31], [32].

Conclusion

PLR has a significant association with the clinical stage of nasopharyngeal cancer, according to this study. Furthermore, in NPC patients, PLR can predict advanced stage and distant metastases.

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