PLATELET TO LYMPHOCYTES RATIO IN THE CLINICAL STAGE OF NASOPHARYNGEAL CARCINOMA

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is an undifferentiated form of squamous cell carcinoma arising from the epithelium of the nasopharynx and is the most common head and neck cancer in Southeast Asia. Inflammation has been shown to have a significant influence on tumor growth in humans. Platelet to lymphocyte ratio (PLR) is an inflammation-based test that is simple and inexpensive to obtain, and it has the potential to be used in the evaluation of NPC as a tumor development assessment. **Objective:** In nasopharyngeal carcinoma, PLR is expected to be a tumor progression marker. The goal of this study is to assess PLR levels in NPC patients. **Method:** This was a case-control study that used data from the Nasopharyngeal Cancer Register System of the Indonesian Association of Ear, Nose, and Throat Head and Neck Surgeons' Head and Neck Surgical Oncology Study Group (PERHATI-KL). The inclusion criteria were met by 383 patients in total. **Result:** T1 has the lowest average in the T classification (238.7), while T4 has the highest average (258.8). The average PLR value increases in the N classification, from N0 to N3, from 220.5 to 285.5. Classification M has the same results, with M1 having a higher average (353.9) compared to M0 (245.7). Similar results were found in the staging group, wherein stage I (108.6) and stage IVB (340.4), higher staging corresponded to higher mean PLR values. **Conclusion:** The highest PLR value is in T4, N3, and M1 classification. The clinical stage with the highest PLR value is IVB.

Keywords: Nasopharyngeal carcinoma, Head and neck cancer, Platelet to Lymphocyte Ratio,

Background

Nasopharyngeal carcinoma (NPC), previously known as lymphoepithelioma, is an undifferentiated form of squamous cell carcinoma arising from the epithelium of the nasopharynx. Tumor predilection is commonly seen in Rosenmüller's fossa, then invades adjacent anatomical spaces or organs.[1-3]

After larynx, thyroid, and oral cavity, nasopharyngeal carcinoma is the fourth most frequent head and neck cancer. In 2020, the global incidence of Nasopharyngeal Carcinoma (NPC) is expected to be 133,354 (0.7%) new cases, with a prevalence of 5 cases per 100,000 population per year. Asian countries accounted for 85.2% of NPC. The prevalence of NPC in Indonesia is 6.2/100,000. NPC is the most common head and neck cancer in Otorhinolaryngology Head and Neck Surgery Department, Dr. Hasan Sadikin (RSHS) Bandung with 921 (35.20%) new cases from 2013 to 2018.[4-7]

The gold standard for diagnosing NPC is a nasopharyngeal mass biopsy. The masses may infiltrate the tissues surrounding the nasopharynx, towards the base of the skull or palate, the nasal cavity, or the oropharynx. Unilateral trismus, pain, otitis media, otalgia, tinnitus, nasal obstruction, epistaxis, hearing loss, and cranial nerve palsies are all symptoms of a primary tumor. Cervical lymphadenopathy is a common manifestation of NPC that eventually leads to hospitalization. Imaging is required to diagnose cases involving the submucosa, like a Computed Tomography Scan (CT-scan) or a magnetic Resonance Imaging (MRI).[8]

Tumor inflammation can promote tumor growth and angiogenesis, and it has been identified as a factor in tumor development in human. Studies have revealed that platelets produce inflammatory cytokines and chemokines might promote the growth of tumors is one of many proposed pathways for how PLR has prognostic relevance. By secreting vascular endothelial growth factors and encouraging tumor cell migration to other organs, platelets support tumor angiogenesis and stromal development. Through the inhibition of tumor cell proliferation and induction of cell death, lymphocytes contribute significantly to the immunological anticancer response. The anti-tumor immune response includes tumor-infiltrating lymphocytes, which also take a role in various stages of tumor formation. Therefore, PLR may represent a compromise between tumor-promoting functions and anti-tumor immune reactions in NPC.[9-13]

The PLR test has the potential to be employed in the evaluation of NPC as a means of monitoring tumor growth. Consequently, the purpose of this study is to measure PLR levels in NPC patients.

METHOD

This research was carried out at Dr. Hasan Sadikin Bandung General Hospital. Data was collected from the Nasopharyngeal Cancer Register System for the Oncology Head and Neck Surgery Study Group, Indonesian Otorhinolaryngology Head and Neck Surgery Society (PERHATI-KL) from 2016 to 2020.

The inclusion criteria for this study were patients with nasopharyngeal carcinoma diagnoses, no prior cancer treatment, and full medical record data. The exclusion criteria were primary malignancy elsewhere, residual or recurrent NPC, and a history of diabetes mellitus or cardiovascular disease.

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Results

Three hundred and eighty three of the 542 participants met the inclusion requirements. The subjects were divided into 246 males (64.2%) and 137 females (35.8%). The average subjects' age was between 40 and 49 years old (29.5%), with the youngest subject being 13 and the oldest being 84. In 135 cases (35.2%), the main tumor categorization with the highest frequency was T2 (35,7%2. Classification N3 had 42% of all lymph node metastases. Ninety percent of the patients (90,1%) lacked distant metastases. Stage IVA comprised the majority of the 223 participants in this study (58.2%).

Table 1. Subject characteristics

Characteristics	Subject (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

Table 2 shows that T1 (238,7) has the lowest average value in the T classification while T4 has the greatest average value (258,8). In contrast, the average PLR value in the N classification increases with stage, from N0 to N3, from 220,5 to 285,5. Similar results can be seen in the M classification, where individuals with M1 have higher average values (353,9) than those with M0 (245,7). Similar results were found in the staging group, where in stage I (108.6) and stage IVB (340.4), higher staging corresponded to higher mean PLR values.

Table 2. Platelet to lymphocyte ratio based on TNM classification

Characteristic	Subject (n=383)	%	PLR Mean
Primary Tumor (T)			
T1	62	16,2	238,7
T2	135	35,2	265,6
T3	117	30,5	253,9
T4	69	18,0	258,8
Lymph Node Metastasis (N)			
N0	70	18,3	220,5
N1	70	18,3	224,6
N2	82	21,4	257,3
N3	161	42,0	285,5
Distant Metastasis (M)			
M0	345	90,1	245,7
M1	38	9,9	353,9
Staging Group			
I	9	2,3	108,6
II	42	11,0	202,4
III	73	19,1	219,6
IVA	223	58,2	271,0
IVB	36	9,4	340,4

Discussion

With an incidence of 85.2% across Asia, particularly East and Southeast Asia, NPC ranks fourth among head and neck cancers. After China, Indonesia has the second-highest number of NPC cases. Risk factors like gender, ethnicity, and family history which cannot be modified, as well as modifiable risks such as dietary pattern, has an important role in NPC.[14-16]

As economic growth and development over the past ten years have witnessed a move from traditional Chinese diet patterns to Western diet patterns, NPC incidence in Hong Kong, Taiwan, and Singapore has decreased. This demonstrates that dietary habits have a significant impact on NPC cases. Asian eating habits such as salted fish, smoked meat, aged vegetables, preserved vegetables, and herbal tea consumption can all increase the risk of NPC. The early consumption of salted fish has been linked to an increase in childhood cases of NPC in South China. In the Chinese population, eating salted fish throughout childhood raised the incidence of NPC, but this did not happen in adolescents or adults.[15]

There were 1.8 times as many male as female participants in this study. Males were more likely to develop NPC cases than females, according to the WHO, and the ratio of male to female NPC cases in Southeast Asia was 3:1. The risk of NPC increased 6 times in smokers and 3.5 times in alcoholic drinkers, and 19 times when these two lifestyle variables were present.[17]

According to research by Li et al., male NPC patients who smoked were 70:1 more likely to do so than women who drank alcohol. According to research by Long et al, smoking increases a woman's risk of developing NPC later in life to the same extent as it increases a man's risk. Tobacco smoke inhaled into the nasopharynx contains components that can activate EBV. [18,19]

Gender influences NPC patient survival, as Zhong-Li et al discovered that female NPC patients have a higher 10-year survival rate than male NPC patients. The estrogen hormone protects women from NPC, so the survival rate of female NPC patients decrease after menopause, though the mechanism is still unknown. NPC is linked to the X chromosome on chromosome 6, which carries the Human Leucocyte Antigen (HLA), making men more susceptible to the disease. [17, 19]

According to Chang et al., the highest incidence of NPC is between the ages 40 and to late 50s. The findings of this study confirmed this, with the age groups of 40-49 years having the highest percentage (40.2%) and 50-59 years having the second-highest percentage (25.5%). Two factors that contribute to this are smoking and eating salted fish from a young age. Furthermore, those who have smoked for more than ten years are at a higher risk of developing NPC. The viral load of EBV DNA is a biomarker that can be used as an initial screening for NPC. According to Gihbid et al., EBV DNA plasma levels in patients above 30 years old are 4 times higher than in patients under 30 years.[17-23]

The genetic factors of the patient are important in the development of NPC. The ends of DNA chains that contain proteins that protect DNA from damage are known as telomeres. Telomere length in NPC patients was 3 times shorter than normal, indicating that telomere shortening is involved in tumor development. Telomere shortening is caused by the aging process and is associated with male gender.[22]

Lymphocytes play an important role in the immune system because they influence the immune response to infectious microorganisms and other foreign substances. The specific lymphocyte response functions to attack microorganisms, protect against tumors, and cause tissue rejection after organ transplantation. T lymphocytes are the most common immunocompetent cells, and there are three types: T-helper (Th), T-cytotoxic (Tc), and T-regulator (Treg). Immune cells develop from pluripotent stem cells, which then differentiate through two pathways: the lymphoid pathway, which produces lymphocytes and their subsets, and the myeloid pathway, which produces phagocytic cells and other cells. Anti-tumor immune cells, particularly lymphocytes known as Tumor-Infiltrating Lymphocytes, infiltrate the tumor microenvironment (TILs). Inflammation in solid tumors causes many leukocytes to infiltrate the tumor, including lymphocytes, neutrophils, eosinophils, basophils, monocytes/macrophages, dendritic cells, and NKCs. Lymphocytes are important in the antitumor immune response because they inhibit tumor cell proliferation and induce cell death. Tumor-infiltrating lymphocytes have been linked to a favorable prognosis in a variety of solid cancers. T cells were found to produce a lot of CD4+ and CD8+ when nasopharyngeal biopsy preparations from NPC patients were examined.[23, 24]

Tumor antigen-containing cells will express their antigens alongside MHC class I molecules to form complexes via T lymphocyte receptors (TCR) and CD8+ T lymphocytes. Tc lymphocytes will form when CD8+ T lymphocytes become active as effectors. Tumor cells that express tumor antigens with MHC class II molecules can be recognized and form complexes with CD4+ T lymphocytes formed active CD4+ T lymphocytes (Th lymphocytes). The lymphocytes secrete interferon-gamma (IFN) and tumor necrosis factor-alpha (TNF). Both of these lymphokines will stimulate tumor cells to increase of MHC class I molecules, enhancing Tc lymphocyte cytotoxicity.[25,26]

The PLR value represents the balance between the platelet count's tumor growth activity and the lymphocyte count's suppression of tumor progression. Inflammation can stimulate thrombopoiesis and megakaryopoiesis. Increased peripheral blood platelets can be an indirect indicator of tumor activity because tumor cells release mediators such as GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), IL-1, G-CSF (Granulocyte-Colony-Stimulating Factor), and IL -6. A high number of peripheral blood lymphocytes, on the other hand, is an indicator of tumor suppression because tumor cell antigens recognized by the immune system will activate Th lymphocytes, which will secrete IFN and TNF to increase lymphocyte production and phagocytosis of tumor cells by NKC.[27]

Conclusion

Based on the TNM classification, this study discovered that the T4, N3, and M1 had the greatest PLR values. The clinical stage with the highest PLR value is IVB.

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