Research

The effect of neutrophil-lymphocyte ratio on neck nodule size in nasopharyngeal carcinoma chemotherapy

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is a cancer of the head and neck, that ranks as the 4th most malignant cancer in Indonesia. The prognosis of NPC patients is determined from the clinical stage based on the Tumor, Nodule, Metastatic (TNM) classification system. These prognosis factors are not entirely reliable for predicting treatment outcomes. The Neutrophil Lymphocyte Ratio (NLR) represents an index of pro-tumor and anti-tumor activity, that can be used to predict the outcome of neoadjuvant chemotherapy and the patient's well-being as assessed by Karnofsky status, Body Mass Index (BMI), and neck nodule size (NNS). **Purpose:** To study the effect of NLR on Karnofsky status, BMI, and NNS in WHO type III NPC patients who underwent 3 cycles of neoadjuvant chemotherapy. **Method:** Analytical observational research with a cohort-retrospective approach on WHO type III NPC subjects who underwent platinum-based regimen neoadjuvant chemotherapy. NLR pre-chemotherapy was analyzed for its effect on Karnofsky status, BMI, and NNS. **Result:** NLR had no significant effect on Karnofsky status pre- and post-chemotherapy, BMI pre- and post-chemotherapy, NNS pre-chemotherapy, changes in Karnofsky status and BMI pre-and post-chemotherapy, but had significant effect on the size of neck nodules post-chemotherapy, and changes in the size of neck nodules. **Conclusion:** NLR has no significant effect on Karnofsky status, on BMI pre- and post-chemotherapy, and neck nodule size pre-chemotherapy. However, NLR had a significant effect on neck nodule size post-chemotherapy and neck nodule size changes.

Keywords: nasopharyngeal carcinoma, Neutrophil Lymphocyte Ratio, Karnofsky status, Body Mass Index, neck nodule size (NNS)

ABSTRAK

Latar belakang: *Karsinoma Nasofaring (KNF) merupakan keganasan dalam bidang THT yang menempati urutan ke-4 keganasan di Indonesia. Prognosis pasien KNF terutama ditentukan dari stadium klinis berdasarkan sistem klasifikasi Tumor, Nodul, Metastasis (TNM) yang tidak sepenuhnya dapat diandalkan untuk memprediksi hasil pengobatan. Sedangkan Ratio Netrofil-Limfosit (RNL) mempresentasikan indeks aktivitas protumor dan antitumor sehingga dapat digunakan sebagai pelengkap stadium klinis untuk memprediksi hasil kemoterapi neoadjuvan dan kesejahteraan subjek melalui status Karnofsky, Index Massa Tubuh (IMT) dan ukuran nodul leher.* ***Tujuan:*** *Mempelajari efek Rasio Netrofil-Limfosit (RNL), Index Massa Tubuh (IMT), dan ukuran nodul leher pada subjek dengan KNF WHO tipe III yang telah menjalani 3 siklus kemoterapi neoadjuvan.* ***Metode:*** *Penelitian observasional analitik dengan pendekatan kohort-retrospektif menggunakan data rekam medis penderita KNF tipe III* WHO *yang menjalani kemoterapi neoadjuvan menggunakan regimen berbasis platinum. RNL sebelum kemoterapi dianalisis pengaruhnya terhadap status Karnofsky, IMT dan ukuran nodul leher.* ***Hasil:*** *RNL berpengaruh tidak signifikan terhadap status Karnofsky sebelum dan sesudah kemoterapi, IMT sebelum dan sesudah kemoterapi, ukuran nodul leher sebelum kemoterapi, perubahan status Karnofsky, perubahan IMT, namun berpengaruh signifikan terhadap ukuran nodul leher sesudah kemoterapi dan perubahan ukuran nodul leher.* ***Kesimpulan:*** *RNL berpengaruh tidak signifikan terhadap status Karnofsky, IMT sebelum dan sesudah kemoterapi, ukuran nodul leher sebelum* *kemoterapi, namun berpengaruh signifikan terhadap ukuran nodul leher sesudah kemoterapi dan perubahan ukuran nodul leher sebelum kemoterapi, namun berpengaruh signifikan terhadap ukuran nodul leher sesudah kemoterapi dan perubahan ukuran nodul leher.*

Kata kunci: *karsinoma nasofaring, Rasio Netrofil-Limfosit, status Karnofsky, Index Massa Tubuh, ukuran nodul*

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a cancer of the head and neck that ranks as the 4th most malignant cases after breast, cervical, and lung cancers in Indonesia. New NPC cases occur 61,000 in men and 26,000 in women, and there are 51,000 deaths due to NPC (36,000 in men, and 15,000 in women) every year.[1]

The prognosis of NPC patients is determined mainly from the clinical stage. It is based on the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM (Tumor, Nodule, Metastasic) staging system. However, this system is not entirely reliable for predicting the outcome of treatment. Patients with the same clinical stage often exhibit different post-therapy clinical conditions. It indicates that the clinical stage is not accurate enough to predict the well-being of NPC patients.[2,3] Complete blood count including the number of neutrophils and lymphocytes, is one of the simplest and most commonly performed tests, especially before and after treatment for NPC patients. Research conducted by Luo et al.[4] showed that the Neutrophil Lymphocyte Ratio (NLR) is a more stable indicator. It did not change significantly by the influence of age or gender compared to the platelet-to-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and systemic immune inflammation index (SIII). NLR is used as a marker of subclinical inflammation and also represents pro-tumor and anti-tumor activity indices.[5]

Chemotherapy for NPC is conducted with various considerations, including the stage of the disease and the functional status of the patient described by performance status. The patient's condition could be higly highly diverse. Thus, it is important to assess the patient's performance status to provide an overview of therapy readiness and prognosis. The most commonly used assessments of performance status are the Karnofsky Status and the Eastern Cooperative Oncology Group (ECOG) WHO Scale. Patients with head and neck cancer including NPC, often experience malnutrition. Takenaka et al., cited by Hilda et.al[6] examined the nutritional status and its relationship with chemotherapy or radiotherapy through Body Mass Index (BMI). The results showed that the 5-year survival rates for the underweight, normal, and overweight groups were 32.2%, 62.7%, and 73.5%, respectively. Some researches were inquisitive to determine the relationship between nutritional status through BMI and survival rates of NPC patients. Yet, the results are still inconsistent.

Based on the above data, the authors were interested to learn further the effect of NLR on Karnofsky status, BMI, and neck nodule size (NNS) in WHO type III NPC patients who underwent 3 cycles of neoadjuvant chemotherapy. It could be used as a complement to the TNM staging system in predicting the response of neoadjuvant chemotherapy in NPC patients.

METHOD

This was an analytic observational study with a cohort-retrospective design. In this research, an assessment of the neutrophil-lymphocyte ratio (NLR), body mass index (BMI), as well as the recording of Karnofsky status and NNS was carried out. From the results of the examination, the effect of NLR on Karnofsky status, BMI, and NNS was analyzed in NPC WHO type III patients who underwent neoadjuvant chemotherapy for 3 cycles. This research had been approved by the ethical commission of Dr. Saiful Anwar General Hospital. The inclusion criteria of this research were NPC WHO type III patients who had not received radiotherapy, had underwent 3 cycles of neoadjuvant chemotherapy, and WHO type III NPC patients who had completed medical record data according to research variables. While the exclusion criteria from this study were signs and symptoms of active infection, diagnosed diabetes mellitus, HIV/AIDS, kidney failure, hematological disorders, pneumonia, TB, patients who received corticosteroid therapy within a month, and antibiotics within a week before taking the blood sample. The research data were analyzed using Statistical Product and Service Solution (SPSS) software with a 95% confidence degree, = 0.05, significant if $p < 0.05$. To prove that NLR before chemotherapy affects Karnofsky status, BMI, and NNS in NPC WHO type III patients undergoing neoadjuvant chemotherapy, a linear regression test was performed.

RESULT

Table 1. General characteristic

General characteristic (N=26)	Total	%
Gender		
Male	18	69.23
Female	8	30.77
Age group		
11-20 years old	2	7.69
21-30 years old	2	7.69
31-40 years old	2	7.69
41-50 years old	7	26.92
51-60 years old	6	23.08
61-70 years old	6	23.08
71-80 years old	1	3.85
Average of age ± SD (year)	49.23 ± 15.70	
Stadium:		
II	2	7.69
III	4	15.38
IVA	18	69.23
IVB	2	7.69

Table 2. Clinical characteristic

Variable	N	Minimum	Maximum	Mean ± sd
NLR	26	1.91	32.46	7.36 ± 6.49
Karnofsky pre	26	70.00	100.00	83.85 ± 8.98
IMT pre	26	14.88	36.63	20.15 ± 5.00
Neck Nodule Size (cm) pre	26	1.00	14.00	6.04 ± 3.56
Karnofsky post	26	70.00	90.00	87.69 ± 5.87
IMT post	26	13.01	39.54	20.49 ± 5.52
Neck Nodule Size (cm) post	26	0.00	12.00	3.17 ± 3.42
Karnofsky change	26	-20.00	10.00	-3.85 ± 7.52
BMI change	26	-4.71	4.11	-0.34 ± 2.14
Neck Nodule Size (cm) change	26	-3.00	11.50	2.87 ± 3.14

The clinical characteristics of the research subjects included NLR values before neoadjuvant chemotherapy, Karnofsky status, BMI, and NNS before and after cycle III neoadjuvant chemotherapy. There were also changes in Karnofsky status, BMI, and NNS in NPC patients who underwent neoadjuvant chemotherapy for three cycles. The mean NLR before neoadjuvant chemotherapy was 7.36 ± 6.49. The lowest NLR value was 1.91 and the highest was 32.46. The mean Karnofsky Status before neoadjuvant chemotherapy was 83.85 ± 8.98. The lowest Karnofsky status was 70 and the highest was 100. The mean Karnofsky status after neoadjuvant chemotherapy was 87.69 ± 5.87; the lowest Karnofsky status 70 and the highest 90. The mean change in Karnofsky status -3.85 ± 7.52. The mean BMI before neoadjuvant chemotherapy was 20.15 ± 5.00. The lowest BMI value was 14.88 and the highest was 36.63. The mean BMI after neoadjuvant chemotherapy was 20.49 ± 5.52; with the lowest BMI of 13.01 and the highest of 39.54. The mean change in BMI was -0.34 ± 2.14. The mean NNS before neoadjuvant chemotherapy was 6.04 ± 3.56. The lowest NNS was 1 cm and the highest was 14 cm. The mean neck nodule size after neoadjuvant chemotherapy was 3.17 ± 3.42; the lowest neck nodule size being 0 cm (no neck nodule was found on physical examination) and the highest being 12 cm. Mean size change of neck nodules was 2.87 ± 3.14.

In the linear regression test, the results obtained R (coefficient of determination) of 0.041. It meant that 4.1% of NLR variables affected Karnofsky status before neoadjuvant chemotherapy. The results of linear regression testing of the effect of NLR on Karnofsky status have a p-value of 0.322. In the variable NLR with BMI, the results obtained R (coefficient of determination) of 0.136. This meant that 13.6% of the NLR variable affected BMI before neoadjuvant chemotherapy, and the results of linear regression testing the effect of NLR on BMI before chemotherapy had a p-value of 0.064. The NLR variable on the size of the neck nodule resulted in an R (coefficient of determination) of 0.007. It meant that 0.7% of the NLR variable affects the size of the neck nodule before chemotherapy, the results of linear regression testing the effect of NLR on the size of the neck nodule had a p-value of 0.679.

The test results after chemotherapy cycle III showed the effect of NLR on Karnofsky status, the R (coefficient of determination) was 0.033. It meant that 3.3% of the NLR variables affected Karnofsky status after neoadjuvant chemotherapy. The results of the linear regression test of the effect of NLR on Karnofsky status had a p-value of 0.374. In the variable NLR to BMI, the result of R (coefficient of determination) was 0.076. It meant that 7.6% of NLR variables affected BMI after neoadjuvant chemotherapy. The results of linear regression testing the effect of NLR on BMI had a p-value of 0.173. In the NLR variable on the size of the neck nodule, the results obtained R (coefficient of determination) was 0.291. It meant that 29.1% of the NLR variables affected the size of the neck nodules after neoadjuvant chemotherapy, the results of linear regression testing the effect of NLR on the size of the neck nodules after chemotherapy had a p-value of 0.004.

The results of testing the effect of NLR on changes in Karnofsky status, BMI, and NNS were as follows: in the NLR test for changes in Karnofsky status, the R (coefficient of determination) was 0.147. It meant that 14.7% of the NLR variable affected the change in Karnofsky status. The results of the linear regression test of the effect of NLR on the change in Karnofsky's Status had a p-value of 0.053. The variable NLR to changes in BMI obtained results R (coefficient of determination) of 0.023. It meant that 2.3% of the NLR variable affected changes in BMI, the results of linear regression testing the effect of NLR on changes in BMI had a p-value of 0.459. The variable NLR to changes in NNS results obtained R (coefficient of determination) of 0.241. It meant that 24.1% of NLR variables affected changes in NNS, the results of linear regression testing the effect of NLR on changes in NNS had a p-value of 0.011.

Table 3. Results of NLR regression model toward Karnofsky status, BMI, and neck nodule size before cycle III neoadjuvants chemotherapy

	Coefficient (B)	t	p	R	R^2
NLR→Karnofsky	-0.280	-1.012	0.322	0.202	0.041
NLR→BMI	-0.284	-1.942	0.064	0.369	0.136
NLR→ NNS	0.047	0.419	0.679	0.085	0.007

Table 4. Results of NLR regression model toward Karnofsky status, BMI, and neck nodule size after cycle III neoadjuvants chemotherapy

	Coefficient (B)	T	p	R	R^2
NLR→Karnofsky	0.164	0.905	0.374	0.182	0.033
NLR→IMT	-0.234	-1.403	0.173	0.275	0.076
NLR→NNS	0.284	3.138	0.004	0.539	0.291

Table 5. Results of the NLR regression model on changes in Karnofsky status, BMI, and neck nodule size

	Coefficient (B)	t	p	R	R^2
NLR→Karnofsky	-0.444	-2.032	0.053	0.383	0.147
NLR→IMT	-0.050	-0.752	0.459	0.152	0.023
NLR→ NNS	-0.238	-2.764	0.011	0.491	0.241

DISCUSSION

NLR before chemotherapy had no significant effect on Karnofsky status before and after neoadjuvant chemotherapy, as well as on its changes. Research by Zhang et al.[7] reported that increased NLR was associated with decreased Karnofsky status, low forearm circumference, low handgrip strength, reduced food intake, and anorexia in cancer patients with cachexia. This research found that NLR had no significant effect on Karnofsky status before neoadjuvant chemotherapy. This could be due to the possibility that most of the subjects in this study had not experienced cachexia. This assumption was supported by the mean BMI before neoadjuvant chemotherapy in this research of 20.15 ± 5.00. It meant that most of the subjects in this research had a normal BMI before neoadjuvant chemotherapy.

Systemic inflammatory response plays a role in decreasing the quality of life in patients with advanced cancer. Systemic effects of the inflammatory response have major effects on appetite, fatigue, and the patient's functional role. NLR affects Karnofsky status indirectly by increasing the stage of the disease, causing more severe symptoms in NPC. The symptoms that the patient complains about depend on the extent of the tumor. In addition to the increase in NLR, other inflammatory mediators that are thought to be the cause of the decreased performance status and quality of life of advanced cancer patients are IL-1, TNF-α, and IL-6 through Janus Kinase/signal transducer and transcriptional activator (JAK/STAT pathway). These cytokines can affect the neuroendocrine control of appetite leading to anorexia. Cytokines produced by tumors can cause a reduction in muscle mass, fatigue, and impaired physical activity which ultimately affects the patient's quality of life.[8]

Karnofsky status is often used in clinical practice because it is simple, easy, efficient and it is one of the assessments that has been confirmed as a good predictor to assess the quality of life of cancer patients. However, the concept of quality of life is very broad, apart from being taken from physical functions, it is also taken from social functions and emotional functions.[9] The patient's quality of life is complexly affected by a person's health condition, psychological state, level of independence, social relationships, and the environment.[10]

NLR before chemotherapy had no significant effect on BMI before and after neoadjuvant chemotherapy, nor on changes in BMI. In some cancers, NLR was significantly increased in advanced stage (stage III and IV) patients with cachexia compared to patients without cachexia, suggesting a cachexia-driven inflammatory response. Although cachexia may mediate increased systemic inflammation, systemic inflammation is more likely to contribute to cachexia. Consistent with the latter theory, changes in body weight are inversely related to NLR in patients with non-small cell lung cancer, colon cancer, and advanced prostate cancer. Chronic or ongoing inflammation can lead to decreased immune function and nutritional status.[11] Previous studies found that performance status and nutritional status as determined by BMI were found to be closely related to disease stage. Performance status and nutritional status are generally low in patients with advanced disease. Tumor location and stage can directly interfere with the oral intake of patients with head and neck cancer and low-performance status may increase the risk of nutritional deficiencies. Quoted from Hilda et al.[6], the research conducted by Boezetti et al., also confirmed the relationship between primary tumor location and performance status (ECOG) with nutritional risk scores. Changes in BMI in cancer patients receiving neoadjuvant chemotherapy can be influenced by several factors, namely: the occurrence of side effects of nausea and vomiting, drug use, nutritional intake aimed at minimizing side effects of therapy, and the duration of administration of neoadjuvant therapy, because the length of time chemotherapy can also be administered the side effects. Many things could cause a decrease in the intake of energy and macro substances (energy, protein, fat, and carbohydrates) in cancer patients. Some of them are due to an increase in catabolism, medical therapies that can reduce appetite such as chemotherapy and radiation as well as a lack of motivation and good support, from within oneself and the environment.[12]

NLR had no significant effect on NNS before neoadjuvant chemotherapy. The results of this research were in line with the retrospective study conducted by Pan et al.[13], on 251 stage II NPC patients undergoing treatment at Guangxi University Hospital between January 2007-December 2014 found that NLR 2.92 was an independent prognostic biomarker of NPC stage II. NLR was not correlated with neck nodules (N status) but positively correlated with primary tumor (T status). In contrast to the study of stage III/IV A, B NPC patients conducted by Chua et al.[14], who had a high NLR ($\geq$ 3.0) was associated with advanced T status, N status, overall stage, and high EBV DNA titers before therapy. Research conducted by Setakornnukur et al.[15], after stratifying by NPC stage, NLR showed a statistically significant difference in effect between NLR in the NPC stage IVA group, but no significant effect was observed in stage II and III. This phenomenon could be explained through the "cancer superiority" theory explaining that the tumor microenvironment is constantly changing during tumor cell formation and development of precancerous cells, invasive tumors, and tumor metastases. Therefore, NLR can have different effects in different stages of NPC. In this research, no stratification according to the stage was performed to see the effect of NLR on NNS. This might be one of the causes of obtaining different results compared to the results of previous studies. Furthermore, neutrophils have both pro-tumor and anti-tumor roles. The development and progression of malignant cells are a multifactorial influenced process involving the interaction of host cells and tumor cells. The precise role of neutrophils in the tumor microenvironment is controversial. There is a belief that tumor-associated neutrophils appeared to contribute to tumor growth, angiogenesis, and immune tolerance. The interaction between immune cells and tumor cells in the microenvironment allows tumor cells to mediate growth factors and immune tolerance through tumor-associated neutrophils (TANs). Tumor cells have been shown to secrete cytokines, attract neutrophils, and contribute to basement membrane destruction and invasion of tumor cells into surrounding tissues. Factors inhibiting macrophage migration, stimulate TANs to release proteases in the tumor microenvironment facilitating invasion and metastasis to cervical lymph nodes. On the other hand, neutrophils are required for an effective T-cell recruitment process and associated cytotoxic effects on tumors.[16] Studies on TANs had reported conflicting results on the role of TANs in early-stage cancer, with some studies reporting that TANs were associated with a good prognosis in early-stage colorectal cancer, while other studies had shown TANs to be associated with a poorer prognosis in early-stage colorectal cancer, melanoma, and cervical squamous cell carcinoma. However, in late-stage cancer, most studies have found TANs to be associated with a poorer prognosis.[15,16]

Interestingly, the findings in this study revealed that NLR had a significant effect on NNS after neoadjuvant chemotherapy and on changes in neck nodule size. Several studies had explored the relationship between pre-treatment NLR and post-treatment outcomes in cancer patients.[2,16,17] However, there were no studies that specifically explored the effect of NLR on changes in neck nodule size in NPC patients undergoing neoadjuvant chemotherapy. The effect of NLR on changes in neck nodule size in this research might be due to the conditions under which neoadjuvant chemotherapy was administered effectively. 5-FU belongs to a type of chemotherapy drug that can inhibit cell replication at certain phases of the cell cycle (works by inhibiting DNA synthesis in the S phase); while Cisplatin can inhibit cell division in all phases including the G0, G1, and G2 phases. This drug has a mechanism of cross-linking to DNA, thereby preventing replication. Cisplatin has been shown to reduce tumor size, reduce the possibility of micrometastasis and increase tumor sensitivity to radiation. Cisplatin works systemically so that not only cancer cells are affected, but healthy cells throughout the body are also affected by Cisplatin. The impact is the formation of free radicals which, if in excess, are toxic, damaging normal cells in the body, including bone marrow cells, resulting in suppression of the hemopoietic system..[18] Cisplatin can cause increased reactive oxygen species (ROS) production in the body. The accumulation of ROS will release cytochrome-c from the mitochondria through the activation of c-Jun-N-terminal kinase (JNK) and p38MAPK. Furthermore, Cytochrome-c activates caspase-8, -9, and 3 (intrinsic pathway apoptosis), causing apoptosis in cells, i.e. hematopoietic cells, resulting in a decrease in the hematopoietic system. Changes in the hematopoietic system are embryonic blood cell death within a few weeks after exposure to Cisplatin and have different sensitivities. Red blood cells are the most sensitive, followed by white blood cells and megakaryocytes. The most sensitive leukocytes were lymphocytes, followed by neutrophils and other granulocytes, while the less sensitive blood cells were platelets. The decrease in the hematopoietic system due to Cisplatin is related to the dose given. Administration of cisplatin in the repetition of therapy for the next series will make an increase in Cisplatin accumulatively.[18,19] Administration of chemotherapy with an optimal dose and the right duration will be able to maintain a low NLR value, whereas a low NLR during neoadjuvant chemotherapy will provide a better response to therapy.[20] Research conducted by Efranto et al.[21], showed that there was a reduction or reduction in the size of the neck nodules in patients with Cisplatin and 5-FU neoadjuvan chemotherapy with significant results. This was corroborated by several researches reported that neoadjuvant chemotherapy had a higher potential for reducing distant metastatic failure, especially in patients with extensive nodules. The research by Al-Amro et al., cited by Efranto et al.[21], assessed the effectiveness of neoadjuvant chemotherapy Cisplatin and Epirubicin followed by Cisplatin chemotherapy along with radiotherapy in 110 patients with advanced NPC showed complete remission and partial remission achieved in 87 subjects (79%) and 23 subjects (21%) respectively.

In conclusion, NLR has no significant effect on Karnofsky's status, BMI before and after neoadjuvant chemotherapy, size of neck nodules before neoadjuvant chemotherapy, and changes. Yet, it has a significant effect on the size of neck nodules after neoadjuvant chemotherapy and changes in neck nodule size.

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