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Original Article

The Relationship between Neutrophil on Lymphocyte Ratio with Clinical Stage of Nasopharyngeal Carcinoma Patients

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ABSTRACT

Introduction: *The general objective of this study was to determine the relationship between the ratio of neutrophils to lymphocytes and the clinical stage in patients with nasopharyngeal carcinoma. While the specific goal is to know the characteristics of patients with nasopharyngeal carcinoma. Knowing the description of peripheral neutrophil levels in patients with nasopharyngeal carcinoma. Knowing the description of peripheral lymphocyte levels in patients with nasopharyngeal carcinoma. Knowing the picture of NLR at the clinical stage of patients with nasopharyngeal carcinoma.* ***Methods:*** *The target population in this study were all patients with nasopharyngeal carcinoma. The affordable population is all patients with nasopharyngeal carcinoma who are undergoing treatment at. RSUP. Dr Wahidin Sudirohusodo for the period July 2018 to July 2019..* ***Results:*** *Based on statistical analysis of the data, this study did not find a significant relationship between the neutrophil-lymphocyte ratio and the clinical stage of nasopharyngeal carcinoma (P = 0.252), even after correcting for sex. Statistical tests were used to see whether or not there was a relationship. between these two variables is the Kruskal-Wallis test, which was chosen because it is a non-parametric comparative test for variables with more than two categories.*

Conclusions: *Based on statistical analysis of the data, this study did not find a significant relationship between the neutrophil-lymphocyte ratio and the clinical stage of nasopharyngeal carcinoma (P = 0.252), even after correcting for sex.*

1. INTRODUCTION

Nasopharyngeal carcinoma is a malignancy / malignant tumor that forms in the nasopharyngeal tissue (located behind the nasal cavity directly under the base of the skull). Various studies suggest that nasopharyngeal carcinoma is associated with Epstein-Barr Virus (EBV) and several other factors (such as environmental, genetic, cigarette smoke, firewood smoke, and wood dust).

Nasopharyngeal carcinoma is one of the reported carcinomas with an incidence of less than 1 case per 100,000 population, but the highest incidence was reported in South China, which was 50 cases per 100,000 population (mainly in Guan Dong Province). Globally, about 65,000 cases of nasopharyngeal carcinoma are reported annually and more than 80% are from South China and Southeast Asia. -25 cases per 100,000 population.[3.6]

Many experts state that the systemic inflammatory response has a close relationship with carcinomas, including nasopharyngeal carcinoma. The inflammatory response is said to have an important role in the mechanism of carcinogenesis, namely the early stages, growth, and development of malignancy.[7,8] Neutrophils and lymphocytes have a role in the inflammatory response mechanism, where neutrophils can release substances that can harm the host, namely stimulating tumor growth. or have the potential to give a poor prognosis for tumors.9,10 Meanwhile, lymphocytes, through the adaptive and innate immune systems, can act as anti-tumors or have the ability to eliminate tumors.[11]

Various studies believe that the Neutrophil Lymphocyte Ratio (NLR) or the ratio of neutrophils to lymphocytes is an inflammatory marker that can be an independent prognostic and is associated with the inflammatory response at various stages of carcinogenesis (including initiation, invasion, progression, and metastasis) and life expectancy of patients with various types of malignancy. . An increase in NLR has been shown to be associated with an adverse outcome for several carcinomas, of which nasopharyngeal carcinoma is one of them.

Kartika (2019) reported that there was a significant relationship between NLR and the clinical stage of nasopharyngeal carcinoma, where the higher the NLR, the higher the clinical stage, and vice versa.15 Takenaka (2017) in a meta-analysis of 9 studies (5,397 patients) reported that although half of the studies reported insignificant results, the combined Hazard Ratio (HR) showed significant overall survival/OS/survival in general, disease-specific survival/DSS/disease-specific survival, progression-free survival/PFS, and poorer distant metastatic-free survival/DMFS is associated with an increase in NLR.16 Then, Ye (2016) reported that high NLR was associated with distant metastases in patients with nasopharyngeal carcinoma.14 These data made researchers interested in conducting a study entitled “The Relationship between

Neutrophil to Lymphocyte Ratio with Clinical Stage in Nasopharyngeal Carcinoma Patients at RSUP Dr. Wahidin Sudirohusodo Period July 2018 - July 2019.

2. METHODS

The target population in this study were all patients with nasopharyngeal carcinoma. The affordable population is all patients with nasopharyngeal carcinoma who are undergoing treatment at. RSUP. Dr Wahidin Sudirohusodo for the period July 2018 to July 2019. The research sample includes the entire affordable population that meets the inclusion and exclusion criteria. The sampling method in this research is using the total sampling technique. Of the 33 research subjects included in the study, it was found that most of the research subjects were male, and the rest were female. This study is an analytical observational study with a cross-sectional approach, which is the best way to get the prevalence of a condition. Data analysis was carried out, namely univariate and bivariate data analysis. Univariate analysis was carried out descriptively of each variable with a frequency distribution table accompanied by an explanation.

3. MAIN HEADING OF THE ANALYSIS OR RESULTS

3.1. RESULTS

3.1.1. Characteristics of Research Subjects

The population studied in this study were all patients with nasopharyngeal carcinoma who were treated at RSUP Dr. Wahidin Sudirohusodo, Makassar, South Sulawesi in July 2018 to July 2019 through. This study succeeded in obtaining 33 research subjects through the *total sampling* method , where the data were completely obtained through the patient's medical record in the form of secondary data.

Table 3.1. Proportion of Gender in Research Subjects

Gender	Frequency (n)	Percentage (%)
Man	20	60.6
Woman	13	39.4
Total	33	100.0

Based on the data obtained, information was obtained that 60.6% of the research subjects were male, while the remaining 39.4% were female (see Table 3.1). Based on the age distribution, it was found that the subjects in this study had an average age of 46.61 ± 14.63 years (see Table 3.2). The age range of the study population was 55 years (15 to 70 years).

Table 3.2. Age Distribution on Research Subjects

Parameter	Age (Years)
Mean ± Standard Deviation	46.61 ± 14.63

Median	45.00
Mode	18*
Range (Min. – Max.)	55 (15 – 70)

* There are several modes, the smallest mode is shown

3.1.2. Neutrophil-Lymphocyte Ratio

The neutrophil-lymphocyte ratio (neutrophil- to-lymphocyte ratio/NLR) in this study is the result of a calculation obtained by dividing the value of the percentage of neutrophils by the value of the percentage of lymphocytes examined from the same sample. The variables of neutrophil count, lymphocyte count, and neutrophil-lymphocyte ratio were assessed on a numerical scale. The distribution of these three variables can be seen in Table 3.3. This study found that the average NLR value in this study was 10.28 ± 14.31. After testing the normality of the data on these three variables, it was found that these three variables were not normally distributed (see Table 3.4). The conclusion of this normality test was taken using the Shapiro-Wilk test because the number of samples in this study was relatively small (n = 33).

Table 3.3. Distribution of Neutrophil Count, Lymphocyte Count, and Neutrophil-Lymphocyte Ratio

Variable	Average ± SD	median	Range (Min. – Max.)
Neutrophil Count (10^3/µL)	9.58±8.28	7.04	35.80 (1.71 – 37.51)
Lymphocyte Count (10^3/µL)	1.53±0.91	1.44	4.51 (0.26 – 4.77)
Neutrophil-Lymphocyte Ratio	10.28 ± 14.31	5.09	72.83 (0.72 – 73.55)

Table 3.4. Normality test

Variable	P value	
	Kolmogorov-Smirnov	Shapiro-Wilk
Neutrophil Count	0.001	< 0.001
Lymphocyte Count	0.168	0.004
Neutrophil-Lymphocyte Ratio	< 0.001	< 0.001

3.1.3. Nasopharyngeal Carcinoma Clinical Stage

Based on the data obtained from the medical records of the research subjects, it was found that most of the patients with nasopharyngeal carcinoma were at stage IVA, as many as 13 subjects (39.4%). This proportion was followed by stage II and stage III both having 7 subjects (21.2%), and stage IVB as many as 6 subjects (18.2%). This study did not find any patients with nasopharyngeal

carcinoma who were still in stage I. In more detail, the proportion of nasopharyngeal carcinoma stages found in this study can be seen in Table 3.5. The staging of nasopharyngeal carcinoma used in this study uses the latest classification from the AJCC eighth edition in 2018.

Table 3.5. Nasopharyngeal Carcinoma Stage Proportion

Stadium	Frequency (n)	Percentage (%)
I	0	0
II	7	21.2
III	7	21.2
IV A	13	39.4
IV B	6	18.2
Total	33	100.0

The proportion of each nasopharyngeal carcinoma stage parameter, namely T (tumor), N (node) and M (distant metastases) in this study can be seen in Table 3.6. From this study, it can be obtained data that the most staging parameters of nasopharyngeal carcinoma in research subjects are T2 and T4, respectively 9 subjects (27.3%) for tumor parameters, N2 as many as 11 subjects (33.3%) for node parameters, and M0 for 27 subjects (81.8%) for distant metastases.

Table 3.6. Proportion of Nasopharyngeal Carcinoma Stage Parameters

Variable	Frequency (n)	Percentage (%)
T (tumor)		
1	7	21.2
2	9	27.3
3	8	24.2
4	9	27.3
N (Node)		
0	7	21.2
1	6	18.2
2	11	33.3
3	9	27.3
M (Distant Metastases)		
0	27	81.8

1	6	18.2
Total	33	100.0

3.1.4. Relationship between Neutrophil-Lymphocyte Ratio with Clinical Stage of Nasopharyngeal Carcinoma

The relationship between the neutrophil-lymphocyte ratio and the clinical stage of nasopharyngeal carcinoma was performed on a tabular basis and statistically to see a trend and/or a statistically significant relationship between the two variables. The tabular analysis which can be seen in Table 3.7 shows that the highest mean neutrophil-lymphocyte ratio was found at stage IVA (14.15 ± 20.32) and the lowest at stage III (5.85 ± 5.04). The neutrophil-lymphocyte ratio is a numerical variable that is not normally distributed, so a comparative bivariate analysis was performed using a non-parametric test, namely the Kruskal-Wallis test. From this test, it was found that there was no significant relationship between the neutrophil-lymphocyte ratio and the stage of nasopharyngeal carcinoma (P = 0.497).

Table 3.7. Relationship Between Neutrophil-Lymphocyte Ratio and Clinical Stage of Nasopharyngeal Carcinoma (Kruskal-Wallis Test)

Nasopharyngeal Carcinoma Stage	n	Neutrophil-Lymphocyte Ratio (10^3/µL)			P value (Statistic test)
		Average ± SD	median	Range (Min. – Max.)	
I	0	-	-	-	0.497 (*Kruskal-Wallis Test*)
II	7	8.12±9.99	2.67	23.54 (0.74 – 24.28)	
III	7	5.85±5.04	3.34	14.75 (0.72 – 15.47)	
IVA	13	14.15 ± 20.32	6.11	71.78 (1.77 – 73.55)	
IVB	6	9.59±9.83	5.49	25.24 (1.94 – 27.19)	

After merging the variable categories of nasopharyngeal carcinoma stage IVA and IVB into a single stage category IV, the Kruskal-Wallis test was performed again and there was no significant relationship between the neutrophil-lymphocyte ratio and the stage of nasopharyngeal carcinoma (P = 0.356). The merging of categories was carried out one step further, namely by combining the categories of nasopharyngeal carcinoma stages I, II, and III into stage I-III categories. This modified variable was then tested using the Mann-Whitney test (see Table 3.8), but found that there was no significant relationship between the neutrophil-lymphocyte ratio and the stage of nasopharyngeal carcinoma (P = 0.252). A significant relationship between the neutrophil-lymphocyte ratio and the stage of nasopharyngeal carcinoma was not found even though it was corrected for sex (P = 0.791 for males and P = 0.217 for females).

Table 3.8. Relationship Between Neutrophil-Lymphocyte Ratio with Clinical Stage of Nasopharyngeal Carcinoma (Mann-Whitney Test)

Nasopharyngeal Carcinoma Stage	n	Neutrophil-Lymphocyte Ratio (10^3/µL)			P value (Statistic test)
		Average ± SD	median	Range (Min. – Max.)	
Beginning (I-II)	7	8.12±9.99	2.67	23.54 (0.74 – 24.28)	0.252 (*Mann-Whitney Test*)
Continue (III-IV)	26	10.86±15.38	5.84	72.83 (0.72 – 73.55)	

A more detailed analysis was also carried out on the parameters of clinical staging of nasopharyngeal carcinoma, namely the T (tumor), N (nodal), and M (distant metastases) components. Analysis of these three parameters found that there was no significant relationship between the neutrophil-lymphocyte ratio and the clinical stage parameters of nasopharyngeal carcinoma, with P = 0.133 for the T parameter, P = 0.414 for the N parameter, and P = 0.963 for the M parameter.

4. DISCUSSIONS

Based on statistical analysis of the data, no significant relationship was found between the neutrophil-lymphocyte ratio variable and the clinical stage of nasopharyngeal carcinoma (P = 0.497). The statistical test used to see whether or not there is a relationship between these two variables is the Kruskal-Wallis test, which was chosen because it is a non-parametric comparative test for variables with more than two categories.

This study seeks to find out the possibility of a statistically significant relationship between these two variables by combining the categories of the clinical stage variables of nasopharyngeal carcinoma.) and advanced stages (III-IV). However, after combining and performing statistical tests with non-parametric comparative tests for variables with two categories (Mann-Whitney test), no significant relationship was found between the neutrophil-lymphocyte ratio and the clinical stage of nasopharyngeal carcinoma (P = 0.252). Even after correction for both sexes, there was still no significant relationship between the neutrophil-lymphocyte ratio and the clinical stage of nasopharyngeal carcinoma, with P values of 0.791 for males and 0.217 for females.

Further analysis was carried out on the parameters of the clinical staging determinants of nasopharyngeal carcinoma, namely the T (tumor), N (nodal), and M (distant metastases) components. Analysis of these three parameters found that there was no significant relationship between the neutrophil-lymphocyte ratio and the clinical stage parameters of nasopharyngeal carcinoma, with P = 0.133 for the T parameter, P = 0.414 for the N parameter, and P = 0.963 for the M parameter.

The results of this study are not in accordance with the hypothesis, namely that the neutrophil-lymphocyte ratio can be used as a biological marker (biomarker) to determine the level of disease progression which is characterized by the clinical stage of nasopharyngeal carcinoma. The relationship between neutrophil-lymphocyte ratio and malignancy was proposed by Sambasivaiah K, et al in 2005 in India, where the study

found that the value of the neutrophil-lymphocyte ratio was found to be higher in cancer at an advanced stage compared to an early stage. However, this study used all cancer patients regardless of the location of the malignancy, where only 2.8% of the study subjects were patients with head and neck malignancies. 45

Another study conducted by Kartika, et al in 2019 in Bandung, Indonesia also found a relationship between the value of the neutrophil-lymphocyte ratio and the clinical stage of squamous cell cancer in the head and neck, where the higher the neutrophil-lymphocyte ratio value, the higher the clinical stage. of his violence. However, this difference could be due to the non-specificity of the location of the malignancy studied by the study, where only 4.3% of the study group had nasopharyngeal carcinoma. 46

Although the two studies suggesting an association between the neutrophil-lymphocyte ratio and clinical stage of malignancy did not specifically examine nasopharyngeal carcinoma, the possibility that this relationship exists is significant still cannot be ruled out with certainty, because theoretically the host response to increased cancer progression should be cause a systemic inflammatory reaction that can be seen by increasing the value of the neutrophil-lymphocyte ratio. However, the absence of this finding in this study could be due to the relatively small sample size in this study which did not allow this study to be generalized to a larger population. 47

Another possibility why no relationship was found between the neutrophil-lymphocyte ratio and the clinical stage of nasopharyngeal carcinoma is that in a specific malignancy, in this case nasopharyngeal carcinoma, the neutrophil-lymphocyte ratio does not directly describe disease progression, but rather describes the prognostic value of the malignancy. Research conducted by Yin J, et al in 2017 and Yao JJ, et al in 2019 suggested the same thing, namely that a high neutrophil-lymphocyte ratio value in nasopharyngeal carcinoma before treatment describes a worse prognosis and survival compared to the neutrophil ratio value. -low lymphocytes. 48.49

5. CONCLUSION

Based on statistical analysis of the data, this study did not find a significant relationship between the neutrophil-lymphocyte ratio and the clinical stage of nasopharyngeal carcinoma (P = 0.252), even after correcting for sex. Statistical tests were used to see whether or not there was a relationship. between these two variables is the Kruskal-Wallis test, which was chosen because it is a non-parametric comparative test for variables with more than two categories.

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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.