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Relationship Between Tumor Size and Neutrophil–Lymphocyte Ratio in Patients with Papillary Thyroid Carcinoma

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Abstract

Objective: Inflammation plays a very important role in the stages of cancer development. In thyroid cancer, systemic inflammatory markers, such as neutrophil–lymphocyte ratio, may have important potential roles in prognosis. There are conflicting studies concerning the predictive value of neutrophil–lymphocyte ratio in thyroid cancer. In this study, our aim was to evaluate the correlation between clinicopathological features and neutrophil–lymphocyte ratio in patients with papillary thyroid carcinoma.

Methods: In this study, the records of 102 patients diagnosed with papillary thyroid carcinoma who underwent surgical treatment in the General Surgery Clinic of our hospital between March 2013 and March 2021 were retrospectively analyzed.

Results: The median neutrophil–lymphocyte ratio was calculated as 1.84, and the patients were divided into 2 groups as neutrophil–lymphocyte ratio < 1.84 and neutrophil–lymphocyte ratio ≥ 1.84. Age, gender, multifocality, bilaterality, and lymph node metastasis did not statistically significantly differ between the 2 groups. The difference in the extrathyroidal spread was close to statistical significance. There was a statistically significant difference in tumor size between the high and low neutrophil–lymphocyte ratio groups.

Conclusion: We found a positive correlation between neutrophil–lymphocyte ratio and tumor size in patients with papillary thyroid carcinoma. In addition, in the high neutrophil–lymphocyte ratio group, the presence of extrathyroidal spread was close to the significance level.

Keywords: Neutrophil-to-lymphocyte ratio, papillary thyroid carcinoma, thyroid neoplasms, inflammation

Introduction

Cancer occurs as a result of the disruption of a very delicate balance between molecular pathways that stimulate and inhibit cancer development. Significant progress has been made in research in terms of the demonstration of a relationship between cancer and inflammation. Inflammation plays a crucial role in all stages of cancer, including development, progression, and metastasis. Components involved in the inflammatory response produce various growth factors, inflammatory cytokines that contribute to tumor development, and chemokines. The interaction between tumor cells and the inflammatory microenvironment around these cells may have a significant impact on the prognosis of patients.[1-3] Cancer is associated with an increased burden of inflammation.[4,5] Also, neutrophil–lymphocyte ratio (NLR) is associated with inflammatory conditions such as inflammatory bowel disease, diabetes mellitus, cardiac disorders, thyroiditis, irritable bowel disease, and Covid-19 infection.[4,6-12] Chronic inflammation, acquisition and accumulation of genetic alterations, and loss of normal physiological regulation can induce the expression of tumor-associated antigens. These inflammatory responses may paradoxically promote tumorigenesis and inhibit response to therapy.[13]

Pro-inflammatory cytokines are proteins that mediate intercellular communication. Elevation of pro-inflammatory cytokines is considered an indicator of cancer prognosis and the patient's response to the tumor. Therefore, systemic inflammatory biomarkers, such as C-reactive protein (CRP), NLR, platelet–lymphocyte ratio, and albumin concentration may have important potential roles in prognosis.[14]

Thyroid cancer is the most common endocrine system malignancy, accounting for 96% of all endocrine cancers and 3% of all cancers.[15] Although thyroid cancer has been shown to have a close relationship with chronic inflammation, recent studies have published inconsistent results concerning the relationship between inflammation and tumor behavior.[16]

Neutrophil–lymphocyte ratio is an inexpensive and widely available biomarker of the host immune system that can be measured from peripheral blood. It has been suggested that high NLR values are associated with a poor prognosis in solid tumors.[17] In a study, it was reported that NLR value may be used as a potential marker in differentiating benign and malignant thyroid disorders.[18] However, the use of NLR in the preoperative and postoperative evaluation of papillary thyroid carcinoma (PTC) is limited and remains controversial.[19]

In this study, we aimed to evaluate the relationship between NLR and clinicopathological features in patients with PTC.

Material and Method

This study was carried out with the approval of Adıyaman University Non-Interventional Clinical Research Ethics Committee (Date: February 16, 2021, No: 2021/02-23) in accordance with the principles of the Declaration of Helsinki. Since the study was designed as retrospective, informed consent was waived. In this study, the records of 173 patients diagnosed with PTC who underwent surgical treatment in the General Surgery Clinic of our

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hospital between 2013 and 2021 were retrospectively reviewed. Patients with secondary primary tumors, lung and bone metastases, hematological disease, anemia, hyperthyroidism, and a history of myocardial infarction or ischemia in the last 6 months, those with signs of systemic infection, and those with a tumor smaller than 1 cm according to the pathology report were excluded from the study. A total of 102 patients were included in the sample. The demographic characteristics of the patients (age and gender), preoperative complete blood count, neck ultrasonography (in the evaluation of lymph node metastasis), and tumor characteristics obtained from pathology reports (multifocality, bilateral involvement, extrathyroidal spread, lymph node metastasis, and tumor size) were recorded. From the complete blood count analysis, hemoglobin, white blood cell count, and neutrophil and lymphocyte counts were noted. Neutrophil–lymphocyte ratio was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. The patients were divided into 2 groups according to the NLR value being above or below the median value. These 2 groups were compared in terms of demographic and histopathological variables.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 25.0 (IBM SPSS Corp., Armonk, NY, USA). The normality distribution of the data was analyzed with the Kolmogorov–Smirnov test. The Mann–Whitney *U*-test was used in the analysis of numerical data, and the chi-square test was used in the analysis of categorical data. The relationship between tumor size and NLR was evaluated with the linear regression analysis. A *P* value of <.05 was considered statistically significant.

Results

Of the 102 patients, 86 (84.3%) were female and 16 (15.7%) were male. The mean age was 43.72 ± 12.91 (15-69) years. The mean hemoglobin value 13.37 ± 1.69 (9.05-16.71), the mean white blood cell count was 7.75 ± 1.63 (5.26-12.91), the mean neutrophil count was 4.48 ± 1.48 (1.84-8.57), the mean lymphocyte count was 2.33 ± 0.66 (1.08-4.72), and the mean NLR value was 2.10 ± 1.00 (0.83-6.76) (Table 1).

The median NLR was calculated as 1.84, and the patients were divided into 2 groups as NLR < 1.84 and NLR ≥ 1.84. Age, gender, multifocality, bilaterality, and lymph node metastasis variables did not statistically significantly differ between the 2 NLR groups (*P* = .170, *P* = .174, *P* = .695, *P* = .415, and *P* = 1.00, respectively). The difference in extrathyroidal spread was close to the statistical significance level (*P* = .052). There was a statistically significant difference between the high and low NLR groups in relation to tumor size (*P* = .036) (Table 2 and Figure 1). When the relationship between tumor size and NLR was evaluated, Spearman's correlation coefficient was 0.244, which was statistically significant (*P* = .013).

Table 1. Demographic and Hematological Characteristics of Patients with Papillary Thyroid Carcinoma

Variables	Mean ± SD	Minimum-Maximum
Age (years)	43.72 ± 12.91	15-69
Female (n, %)	86, 84.3%	
Male (n, %)	16, 15.7%	
Hemoglobin	13.37 ± 1.69	9.05-16.71
WBC count	7.75 ± 1.63	5.26-12.91
Neutrophil count	4.48 ± 1.48	1.84-8.57
Lymphocyte count	2.33 ± 0.66	1.08-4.72
NLR	2.10 ± 1.00	0.83-6.76

NLR, neutrophil–lymphocyte ratio; SD, standard deviation; WBC, white blood cell.

Discussion

The potential relationship between cancer and chronic inflammation was first proposed more than a century ago by the German pathologist Rudolf Virchow.[19] In fact, pathologists have long recognized that certain tumors are heavily infiltrated by macrophages and lymphocytes both within and around the primary tumor.[20] Today, it is widely accepted that inflammation and cancer are closely related since inflammation has both cancer-inhibiting and cancer-modeling properties.[1,21] In addition, inflammation is considered to play a very important role in tumor development and proliferation by inducing tumor proliferation, angiogenesis, and metastasis through the induction of neutrophils, cytokines, chemokines, and CRP, and reducing patient response to anti-cancer drugs.[21-23] Neutrophils are important mediators of the inflammatory

Table 2. Relationship Between the Clinicopathological Features of Papillary Thyroid Carcinoma and Preoperative Neutrophil–Lymphocyte Ratio

Variables	n (%)	NLR < 1.84	NLR ≥ 1.84	*P*
Age				
<45 years	58 (56.9)	25 (43.1%)	33 (56.9%)	.170
≥45 years	44 (43.1)	25 (56.8%)	19 (43.2%)	
Sex				
Female	86 (84.3)	45 (52.3%)	41 (47.7%)	.174
Male	16 (15.7)	5 (31.3%)	11 (68.8%)	
Multifocality				
Yes	45 (44.1)	21 (46.7%)	24 (53.3%)	.695
No	57 (55.9)	29 (50.9%)	28 (49.1%)	
Bilaterality				
Yes	37 (36.3)	16 (43.2%)	21 (56.8%)	.415
No	65 (63.7)	34 (52.3%)	31 (47.7%)	
Extrathyroidal spread				
Yes	11 (10.8)	2 (18.2%)	4 (81.8%)	.052
No	91 (89.2)	48 (52.7%)	43 (47.3%)	
Lymph node metastasis				
Yes	10 (9.8)	5 (50.0%)	5 (50.0%)	1.00
No	92 (90.2)	45 (48.9%)	47 (51.1%)	
Tumor size (cm)	2.78 ± 1.88	2.26 ± 1.36	3.29 ± 2.17	.036

NLR, neutrophil–lymphocyte ratio.

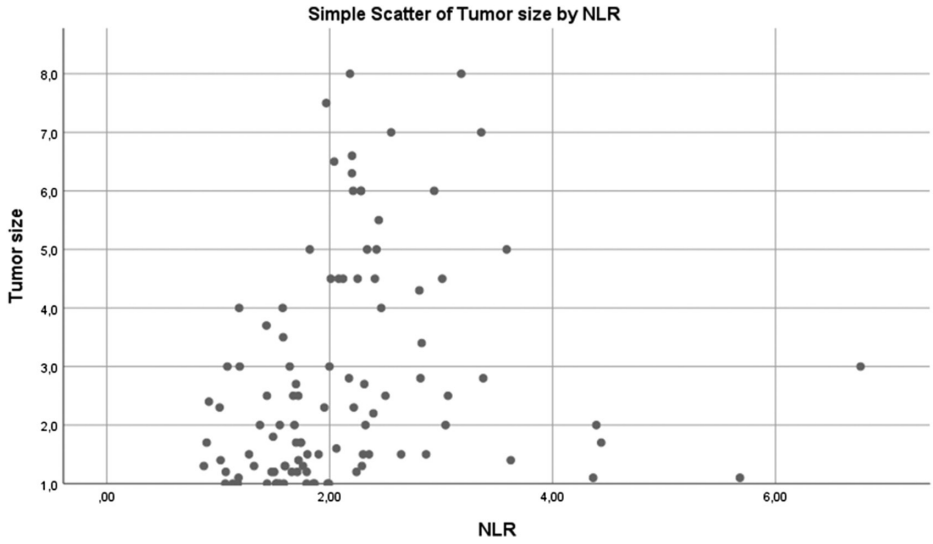

Figure 1. Relationship between the tumor size and neutrophil–lymphocyte ratio.

response and have long been used as a marker of systemic inflammatory response.[19]

Neutrophil–lymphocyte ratio has recently emerged as a simple and valid marker of systemic inflammatory response.[24] Although it is inexpensive, easy to calculate, and simple to obtain, its use in the preoperative evaluation of PTC remains a subject of debate. In this study, we aimed to examine the relationship between the clinicopathological features and NLR in patients with PTC.

Liu et al[25] evaluating 321 patients with PTC, found higher NLR values in the advanced age group (≥45 years) compared to younger patients and argued that this might constitute both a risk and prognostic factor for this cancer for elderly patients. Similarly, in a study conducted with patients with PTC, Lang et al[26] found a statistically significant relationship between increased age and high NLR. In contrast, Kim et al.[27] who evaluated 1066 patients undergoing total thyroidectomy for PTC, reported that the preoperative NLR values were statistically significantly lower in the elderly (≥45 years) group. In a meta-analysis, Feng et al[15] examined preoperative NLR values in patients with PTC and did not find a significant relationship between age and NLR. Our results also did not reveal a statistically significant difference in the preoperative NLR values between the elderly and younger patients (P = .170) (Table 2).

In recent studies, no significant correlation was found between gender and NLR in the comparison of clinicopathological variables and preoperative NLR values in patients with PTC.[1,14] Similarly, in our study, the difference between gender and preoperative NLR was not statistically significant (P = .174) (Table 2).

Manatakis et al[1] and Jiang et al[28] found higher preoperative NLR values in patients with multifocal PTC and noted that the difference between them was statistically significant. On the other hand, Ceylan et al[14] and Kim et al[27] argued that the difference between the NLR values of multifocality was not statistically significant. In our study, multifocality was seen in 46.7% of patients in the low NLR group and 53.3% of those in the high NLR group, and the difference was not statistically significant (P = .695) (Table 2).

In a previous study on PTC, bilaterality was seen in 6% of patients in the low NLR group and 67% of those in the high NLR group, and the difference was reported to be statistically significant.[28] In another study, bilaterality was observed in 65 patients in the high NLR group, whereas it was not present in 140 patients in the low NLR group, and the difference was statistically significant.[1] Lang et al[26] detected no significant difference between the NLR groups according to bilaterality. Similarly, in our study, no significant difference was found in bilaterality between the high and low NLR groups (P = .415) (Table 2).

Lang et al[26] reported that the rate of extrathyroidal spread did not statistically significantly differ between the NLR groups. In contrast, Ceylan et al[14] observed extrathyroidal spread in 11 patients in the high NLR group versus 3 patients in the low NLR group, indicating a statistically significant difference. Similarly, in another study, a significantly higher level of extrathyroidal spread was found in the high NLR group.[1] In the current study, extrathyroidal spread was observed in 2 patients in the low NLR group and 4 patients in the high NLR group, and the difference was close to the statistical significance level (P = .052) (Table 2).

In studies conducted by Lee et al[13] and Manatakis et al[1], lymph node metastasis was found to be statistically significantly higher in the high NLR group. In other studies, no statistically significant relationship was reported between lymph node metastasis and NLR.[14,27,28] In the current study, lymph node metastasis was detected in patients in both NLR groups, and the difference was not statistically significant (P = 1.00) (Table 2).

Manatakis et al[1] compared the tumor size of patients with PTC according to their NLR values and reported no significant difference. On the contrary, in many other studies, there was a statistically significant positive correlation between tumor size and NLR.[14,26,27] In our study, we determined a statistically significant difference between the high and low NLR groups in relation to tumor size (Table 2). We also evaluated the relationship between tumor size and NLR in patients with PTC using linear regression analysis. We calculated Spearman's correlation coefficient as 0.024 and observed a statistically significant positive correlation between tumor diameter and NLR (P = .013).

This study has certain limitations. First, this study was carried out with a limited number of patients and retrospective design. The second limitation to consider is that NLR is not specific to the inflammation process and can be affected by a wide variety of factors. Another limitation is patients with tumors smaller than 1 cm were not included in the sample. Even PTCs that are smaller than 1 cm have the potential to metastasize locally and distantly. Large-volume, prospective, controlled studies are needed to overcome these limitations and obtain clearer results in future.

Conclusion

In this study, we found a positive correlation between NLR and tumor size in patients with PTC. In addition, the presence of extrathyroidal spread in the high NLR group was close to the statistical significance level. In conclusion, NLR, which is a very simple and easily available systemic inflammation marker, can be used as a potential alternative marker in determining prognosis in patients with PTC.

Ethics Committee Approval: This study was carried out with the approval of Adıyaman University Non-Interventional Clinical Research Ethics Committee (Date: February 16, 2021, No: 2021/02-23).

Informed Consent: Informed consent was waived due to the retrospective nature of this study.

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