



Prognostic Clue in Papillary Thyroid Carcinoma: Neutrophil Lymphocyte Ratio

Papiller Tiroid Karsinomada Tümör Büyüklüğü ve Metastazın Belirticisi Olarak Nötrofil Lenfosit Oranı

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ABSTRACT

Aim: Inflammation plays a critical role in many cancer features such as tumor development and progression. Recently, the neutrophil-lymphocyte ratio (NLR) has been evaluated as a simple and valid systematic marker of inflammatory response. The aim of this study was to investigate the prognostic value of the preoperative neutrophil / lymphocyte ratio.

Material and Methods: In this study, archive files of 259 adult cases were evaluated retrospectively. Kolmogorov Smirnov test, Mann Whitney U Test, Kruskal Wallis and Dunn multiple comparison tests were used in the statistical analysis.

Results: A statistical correlation was found between the neutrophil/lymphocyte ratio and T staging, lymph node and distant metastases ($p<0.001$). As the TNM stage increased, the neutrophil/lymphocyte ratio also increased ($p=0.001$). As a separate subgroup, a statistically significant correlation was found between papillary microcarcinomas and neutrophil/lymphocyte ratio ($p<0.001$). When the neutrophil/lymphocyte cut-off values were taken as $>1,644 >2.0906 >1,644$, the sensitivity to predict papillary thyroid cancers larger than 1 cm, lymph node metastasis and distant metastasis was found to be 85.4%, 73.8%, and 96% respectively.

Conclusion: Neutrophil/lymphocyte ratio is associated with tumor size and presence of metastasis. The neutrophil/lymphocyte ratio may help us predict the size of the tumor, lymph node involvement, and distant metastasis when the right cut-off points are established.

Keywords: Thyroid cancer, neutrophil lymphocyte ratio, carcinogenesis

ÖZ

Amaç: Enflamasyon, tümör gelişimi ve ilerlemesi gibi birçok kanser özelliğinde kritik bir rol oynar. Son zamanlarda, nötrofil lenfosit oranı (NLR), inflamatuvar yanıtın basit ve geçerli bir sistematik belirteci olarak değerlendirilmiştir. Bu çalışmanın amacı ameliyat öncesi nötrofil/lenfosit oranının prognostik değerini araştırmaktır.

Gereç ve Yöntemler: Bu çalışmada 259 erişkin olgunun arşiv dosyaları retrospektif olarak değerlendirildi. İstatistiksel analizde Kolmogorov Smirnov testi, Mann Whitney U Testi, Kruskal Wallis ve Dunn çoklu karşılaştırma testleri kullanıldı.

Bulgular: Nötrofil/lenfosit oranı ile TNM evrelemesi, lenf nodu ve uzak metastazlar arasında istatistiksel korelasyon bulundu ($p<0.001$). TNM evresi arttıkça nötrofil/lenfosit oranı da artışı saptandı ($p=0,001$). Aynı bir alt grup olarak papiller mikrokarsinomlar ile nötrofil/lenfosit oranı arasında istatistiksel olarak anlamlı bir korelasyon bulundu ($p<0,001$). Nötrofil/lenfosit kesim değerleri $>1.644 >2.0906 >1.644$ olarak alındığında 1 cm'den büyük papiller tiroid kanserlerini, lenf nodu metastazı ve uzak metastazı öngörme duyarlılığı %85,4, %73,8 ve %96 olarak bulundu.

Sonuç: Nötrofil/lenfosit oranı tümör boyutu ve metastaz varlığı ile ilişkilidir. Nötrofil/lenfosit oranı, doğru kesme noktaları belirlendiğinde tümörün boyutunu, lenf nodu tutulumunu ve uzak metastazı tahmin edilmesine yardımcı olabilir.

Anahtar Sözcükler: Tiroid kanseri, nötrofil lenfosit oranı, karsinogenez



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INTRODUCTION

Thyroid cancers are commonly well-differentiated tumors originating from follicular cells. Changes in the immune system are observed during tumor development. Ultrasonography (USG), thyroid function tests, and biopsies can be used to distinguish benign from malignant nodules. Rarely are malignant nodules neglected despite the fact that the majority of cases are benign. Localization in a posterior location (which is difficult to reach with a biopsy) and limited experience with pathologic evaluations contribute to the failure of detection (1). Although these obstacles frequently necessitate costly genetic analyses, they also encourage the search for inexpensive and readily accessible alternatives.

Early lesions such as premalignant foci are usually infiltrated by cells such as lymphocytes, macrophages and granulocytes. Leukocytes take part in the inflammatory process (2). This inflammatory state contributes to tumor growth, invasion, angiogenesis, and metastasis (3). Due to the significance of systemic inflammation in tumor growth and progression, the neutrophil-to-lymphocyte ratio (NLR) as an integrated indicator based on peripheral lymphocyte and neutrophil counts has received increased attention. NLR are readily quantifiable, reproducible, and inexpensive inflammatory markers that have been shown to accurately predict outcomes. Neutrophil-lymphocyte ratio is a simple indicator of systemic inflammatory response and plays a role as a prognostic factor in some types of cancer (4).

Thyroid cancer also exhibits a close relationship with inflammation. An increase in the number of neutrophils is an indicator of poor prognosis, as neutrophils indicate tumor development and tumor-related inflammation. While the neutrophil-lymphocyte ratio increases due to an increase in the neutrophil count and/or a decrease in the lymphocyte count, an increase in the neutrophil-lymphocyte ratio creates a protumoral condition and shows a poor prognosis, while a decrease in the neutrophil-lymphocyte ratio creates an antitumoral condition and shows a good prognosis (5).

Numerous investigations on the association between papillary thyroid carcinoma and NLR have been published. Nonetheless, this relationship is still unclear, and it is unknown at what numerical value this relationship becomes significant.

In this study, we sought to examine the association between age, gender, tumor size, lymph node metastasis, distant metastasis, TNM stages, which influence thyroid prognosis, and neutrophil/lymphocyte ratio. In addition, a secondary objective is to determine at what threshold value the presence of malignancy can be meaningful when using NLR.

MATERIAL and METHODS

The study was carried out after the approval of the ethics committee of Gaziantep University Clinical Research Ethics Committee with protocol code 392 and decision no: 14/391.

In this study, archive files of 303 adult patients who were followed up with the diagnosis of well-differentiated thyroid cancer in Gaziantep University Faculty of Medicine, Department of Endocrinology and Metabolic Diseases were retrospectively evaluated.

Inclusion criterias include histopathological diagnosis of well-differentiated papillary thyroid cancer, and absence of active infection before the operation, hematological disease, second primary cancer, use of steroids within three months, operated due to acute myocardial infarction or coronary artery disease, chronic inflammatory diseases such as systemic lupus erythematosus.

Our study included 259 patients with papillary carcinoma of well-differentiated thyroid cancers. Papillary Carcinoma TNM classification was made as stated by the 2017 The American Joint Committee on Cancer. Papillary microcarcinoma was defined as carcinoma of 1 cm or less than 1 cm. Evaluated pathological parameters are: Tumor diameter (cm), lymph node invasion, vascular invasion, distant metastasis, extrathyroidal involvement, multifocal involvement, histopathological reports, PTC subtypes (AJCC 2017) (6).

Statistical Analysis

Kolmogorov Smirnov test was used to check the conformity of continuous variables with normal distribution. The Mann Whitney U Test was used for the comparison of the non-normally distributed variables in 2 independent groups, and the Kruskal Wallis and Dunn multiple comparison tests were used for the comparison of more than 2 independent groups. ROC curve analysis was performed to test the discrimination of the methods. Median (25%-75%) values are given as introductory statistics. SPSS for Windows version 22.0 package program was used for statistical analysis and $P < 0.05$ was considered statistically significant.

After determining true positive, true negative, false positive and false negative values for the entire study group and each subgroup formed, sensitivity, specificity, positive predictive value, negative predictive value values were determined using the formulas given below. Predictive value and accuracy values were calculated.

RESULTS

Clinical and demographic features of patients with papillary thyroid carcinoma are shown in Table 1.

Biochemical and Histopathological features of patients with papillary thyroid carcinoma are shown in Table 2.

A significant difference was observed in terms of NLR values according to TNM classification ($p=0.001$). A statistically significant difference was found between T1a-T3, T1a-T4, T1b-T4, T2-T4 in paired studies. A significant difference was found between the groups in terms of lymph node involvement ($p=0.001$). While the difference between N0-N1a ($p=0.001$) and N0-N1b ($p<0.001$) was statistically significant in paired comparisons, no statistical difference was found between N1a-N1b ($p=0.954$). Comparison of the neutrophil lymphocyte ratio according to the stages was found to be significantly different ($p=0.001$). In paired comparisons, a significant difference was found between stages 1-3 ($p=0.001$) and stages 1-4 ($p<0.001$). Comparison of

the neutrophil lymphocyte ratio according to the stages was found to be significantly different ($p=0.001$). In paired comparisons, a significant difference was found between stages 1-3 ($p=0.001$) and stages 1-4 ($p<0.001$).

For optimum sensitivity and specificity in determining the predictability of the lesion's microcarcinoma to 1 cm neutrophil lymphocyte ratio, the cut-off value was 85.4%, specificity 46.9% (AUC: 0.654, 95%CI: 0.593) when NLR was taken as 1.644 with the Receiver operating characteristic (ROC) - 0.712) (Figure 1).

When the cut-off value of NLR with Receiver operating characteristic (ROC) was accepted as 2.09 for predicting lymph node metastasis, the sensitivity was 73.8%, the specificity was 56.6% (AUC: 0.687 95% CI=0.626-0.743) (Figure 2).

Table 1: Clinical and demographic features of patients with papillary thyroid carcinom.

	Min-Max	Mean \pm SD
Age (Year)	16-82	45.6 \pm 14.2
	n	%
Gender		
Female	201	73.6
Male	58	22.4
Tumor Localization		
Unilateral	164	63.3
Bilateral	95	36.7

*Data are presented as minimum -maximum values with mean \pm Standard Deviation

Table 2: Biochemical and Histopathological features of patients with papillary thyroid carcinom.

	n	%
Tumor Diameter		
\leq 1 microcarcinoma	81	31.3
> 1 cm	178	68.7
	Min-Max	Mean \pm SD
Neutrophil count (10^3 /Microliter)	900-14300	5023 \pm 1727
Lymphocyte count (10^9 /Microliter)	900-5100	2391 \pm 676
Neutrophil lymphocyte ratio	0.64-5.42	2.20 \pm 0.79
Tumor diameter (milimeter)	0.05-9.2	2.09 \pm 1.64

*Data are presented as minimum -maximum values with mean \pm Standard Deviation

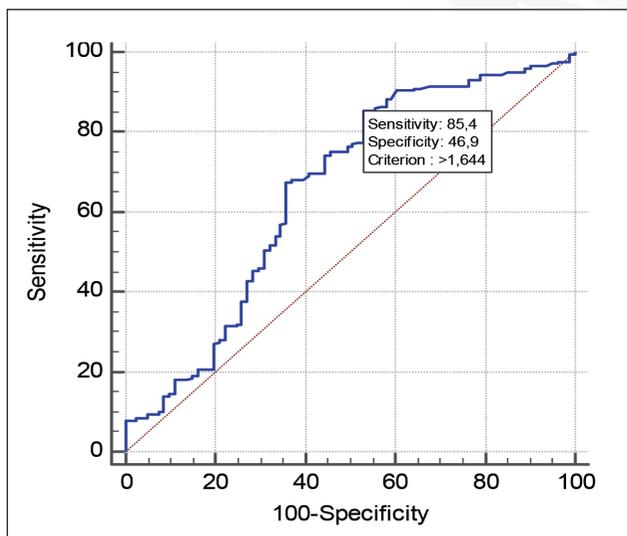


Figure 1: ROC curve of NLR in predicting microcarcinomas.

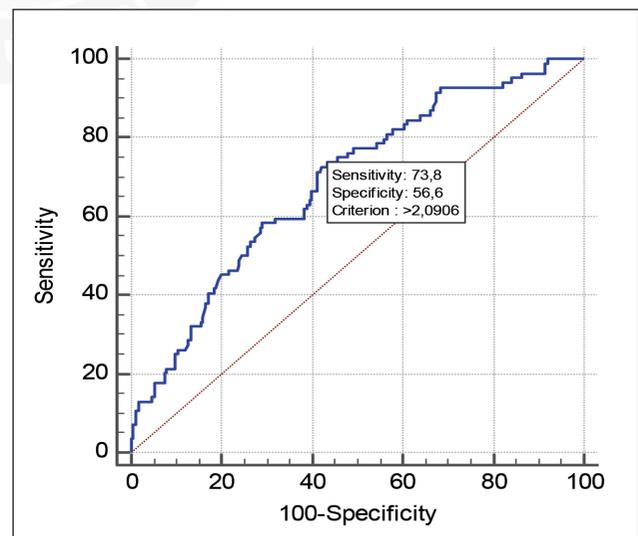


Figure 2: ROC curve of NLR in predicting lymph node metastasis.

Table 3: The predictive ability of NLR for papillary thyroid carcinoma larger than 1 cm, lymph node metastasis, distant metastasis.

Parameters	Sensitivity	Specificity	95% confidence interval
Tumor larger than 1cm*	85.4%	46.9%	0.593- 0.712
Lymph node metastasis**	73.8%	56.6%	0.626 -0.743
Distant metastasis***	96%	26.9%	0.579-0.699

Assuming cut-off values * >1.644 , ** >2.0906 , *** >1.644

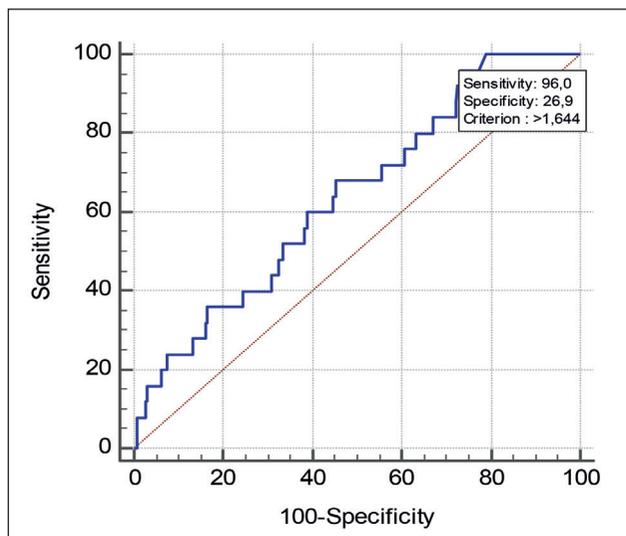


Figure 3: ROC curve of NLR in predicting distant metastasis.

When the Receiver operating characteristic (ROC) cut-off value of NLO was accepted as 1.644 to detect distant metastases, the sensitivity was 96% specificity 26.9% (AUC: 0.641 95% CI=(0.579-0.699)) (Figure 3).

The ability to predict NLR of papillary thyroid carcinoma larger than 1 cm, lymph node metastasis, distant metastasis is shown in Table 3.

DISCUSSION

The inflammatory response plays a role in the development of the tumor and enables us to make predictions about the prognosis of the tumor (7). Neutrophil and lymphocyte cells are the basis of the inflammatory response. Studies conducted by lymphopenia showed that it creates an immune-tolerant microenvironment around the tumor and has a poor prognosis effect (8).

The association of increased NLR with poor prognosis in cancer conditions has been shown in many studies (9-11). In the study of Seretis et al., a significant difference was found when the NLR of patients with incidental papillary thyroid cancer and thyroid cancer was compared with the

NLR of the control group and patients with benign thyroid pathologies. Incidental papillary thyroid cancer and thyroid cancer were detected in patients with NLRs above 2.5 (12).

In the study of Liu et al., a significant correlation was found with tumor size and recurrence according to ATA classification with the increase in NLR. The median NLR with thyroid cancer varied between 1.86 and 3.4 in studies (13). In our study, NLR was found to be 2.20 ± 0.79 . In our study, similar to previous studies, no significant difference was found according to age and gender as being bilateral. In our study, a significant difference was found when the NLR of 81 patients with papillary microcarcinoma (less than 1 cm and 1 cm) and 178 patients with papillary carcinoma larger than 1 cm were compared.

In the study of Liu et al., differentiated thyroid cancers are 1.2 (0.6-2) cm - 1.5(0.5-2.6) cm -2.2(1.1-3.2) cm according to size A significant difference was found when NLRs were compared by grouping them into groups ($p=0.004$) (14). When Cho et al. divided patients with advanced stage 3 or stage 4 thyroid tumors into two classes as high NLR and low NLR (30.4-26.5%, respectively), a significant difference was found (15). Cho et al. no significant difference was found according to distant metastasis in the study of all thyroid cancer patients (15). In our study, a significant difference was found when NLR was compared according to distant metastasis status.

There are many studies showing the relationship between NLR and cancer prognosis (16-18). While the cut-off value was 3.73 in the study of Xia An et al. the cut-off value was found as 3.2 in Aizawa et al.'s T4 gastric cancer (10,19). Determining the ideal NLR value for DTC prognosis is important for clinical applications. Therefore, it seems that current studies try to find the most appropriate value for prognosis by determining NLR threshold values. Although there is no clear data on this subject in the literature, many different cut-off point values have been determined.

There were no studies in the literature regarding the cut-off value in NLR and the predictability of tumor size or lymph node and metastasis in patients with thyroid papillary/carcinoma. In our study, when the cut-off value of NLR for predicting lesions larger than 1 cm was taken as 1.644, the sensitivity was 85.4%, the specificity was 46.9%. When the cut-off value of NLR to predict the presence of lymph node metastasis was accepted as 2.09, the sensitivity was 73.8%, the specificity was 56.6%. When the cut-off value for NLR to predict the presence of distant metastases was accepted as 1.644, the sensitivity was 96%, the specificity was 26.9%.

In summary, we evaluated the relationship between the patients' thyroid papillary carcinoma clinicopathological features and NLR in our study. A significant positive correlation was found between tumor size, lymph node, distant metastasis metastasis and NLR, When the neutrophil/lymphocyte

cut-off values were taken as $> 1,644 > 2.0906 > 1,644$, the sensitivity to predict papillary thyroid cancers larger than 1 cm, lymph node metastasis and distant metastasis was found to be 85.4%, 73.8%, and 96% respectively.

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None

Author Contributions

Study conception and design: **Osman Hakan Demir, Mesut Özkaya**, Data collection: **Zeynel Abidin Sayiner, Osman Hakan Demir**, Analysis and interpretation of results: **Zeynel Abidin Sayiner, Osman Hakan Demir, Mesut Özkaya**, Manuscript preparation: **Zeynel Abidin Sayiner**.

Conflicts of Interest

There is no conflict of interest between the authors.

Financial Support

None.

Ethical Approval

The study was carried out after the approval of the ethics committee of Gaziantep University Clinical Research Ethics Committee with protocol code 392 and decision no: 14/391.

Review Process

Extremely peer-reviewed and accepted.

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