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Evaluation of preoperative neutrophil-lymphocyte ratio in differentiated thyroid carcinoma with lymph node metastasis

Preoperatif nötrofil–lenfosit oranı ile lenf nodu metastazı olan differansiye tiroid karsinomu arasındaki ilişkinin değerlendirilmesi

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Abstract

Aim: Systemic inflammatory response has been shown to play a critical role in all stages of tumor development, progression and metastasis. High neutrophil lymphocyte ratio (NLR) is thought to be an indicator of poor prognosis of tumors. In this study, we investigated the relationship between preoperative NLR and lymph node metastasis of differentiated thyroid carcinoma (DTC).

Methods: The study included a total of 74 patients diagnosed with DTC according to pathology results after thyroid surgery. The NLR was determined by dividing the absolute neutrophil count in the whole blood count by the lymphocyte count. Optimal cut-off value was estimated by means of ROC curve. The study was designed a cross-sectional study.

Results: With a 95% confidence interval, the area under the curve of 0.620 and the likelihood ratio of 3.2, the cut-off value for NLR was found to be 2.59 with 44.4% sensitivity and 86.2% specificity, respectively. There was a significant relationship between the current cut off value and the lymph node metastasis of DTC (P=0.03).

Conclusion: NLR was found to be significantly increased in lymph node-positive differentiated thyroid cancers. The neutrophil to lymphocyte ratio as an inflammation index is inexpensive for patients with differentiated thyroid carcinoma, easily available and easy to obtain from routine blood tests.

Keywords: Neutrophil, Lymphocyte, Thyroid, Carcinoma

Öz

Amaç: Sistemik inflamatuar yanıtın tümör gelişimi, ilerlemesi ve metastazının tüm aşamalarında kritik bir rol oynadığı gösterilmiştir. Yüksek nötrofil lenfosit oranının (NLO), tümörlerin kötü prognozunun bir göstergesi olduğu düşünülmektedir. Bu çalışmada, preoperatif NLO ile diferansiye tiroid karsinomunun (DTC) lenf nodu metastazı arasındaki ilişkiyi araştırdık.

Yöntemler: Çalışmaya tiroid cerrahisi sonrası patoloji sonuçlarına göre DTC tanısı alan toplam 74 hasta alındı. NLO, tam kan sayımındaki mutlak nötrofil sayısının lenfosit sayısına bölünmesiyle belirlenmiştir. En uygun cut-off değeri ROC eğrisi ile tahmin edilmiştir. Çalışma cross-sectional olarak dizayn edildi.

Bulgular: %95 confidence interval ile eğri altında kalan alan 0,620 olan analizde olabilirlik oranı 3,2 olarak hesaplandığında %44,4 sensivite ve %86,2 spesifite ile NLR için cut-off değer 2,59 olduğu saptandı. Mevcut cut-off değeri ile DTC'nin lenf nodu metastazı arasında anlamlı bir ilişki vardı (P=0,03).

Sonuç: NLO lenf nodu pozitif diferansiye tiroid kanserlerinde anlamlı olarak yüksek bulundu. İnflamatuar indeks olarak nötrofil lenfosit oranı, diferansiye tiroid karsinomu olan hastalar için ucuzdur, kolay kullanılabilir ve rutin kan testlerinden elde edilmesi kolaydır.

Anahtar kelimeler: Nötrofil, Lenfosit, Tiroid, Karsinom

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Introduction

Systemic inflammatory response has been shown to play a critical role in all stages of tumor development, progression and metastasis [1]. Many studies to date have shown that elevated inflammatory biomarkers can (such as CRP, TNFα, and IL-6) reliably predict poor prognosis in various malignant neoplasms (esophageal, gastric, pancreas, colonic, ovarian, kidney, and lung) [1-3]. High neutrophil lymphocyte ratio (NLR) is thought to be an indicator of poor prognosis of tumors [2,4]. There are many studies to conclude increased NLR in some types of cancer. A high NLR has been shown to correlate with high recurrence or mortality rates in a wide range of malignant neoplasms [5-7].

Thyroid cancer is the most commonly encountered endocrine tumor. The well-differentiated, slow-growing thyroid malignancies derived from follicular cells are called differentiated thyroid carcinoma (DTC). Within the category of DTC, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are the two subtypes, which are distinguished by their distinct cytological features [8]. Several studies have shown a higher incidence of differentiated thyroid cancers (DTC) in patients with thyroiditis [8]. The formation of thyroid cancers is associated with local and systemic inflammatory responses. Therefore, it is important to investigate the relationship between preoperative NLR and tumor characteristics in patients with DTC, to better understand tumor growth and prognosis of thyroid cancer. The detection of NLR in daily practice is inexpensive to be routinely measured and may be useful to identify high-risk patients [9-10]. In the literature, some authors found a significant relationship between NLR and DTC prognosis [11], while some reported no difference in NLRs among patients with benign or malignant thyroid nodules [12]. Therefore, the relationship between the NLR and the DTC is controversial. In this study, we investigated the relationship between preoperative NLR and lymph node metastasis of differentiated thyroid carcinoma.

Materials and methods

Patient population

This study was conducted between December 2016 and November 2018 in the Department of Endocrinology and Metabolism Diseases and the patients whose medical records were accessible were examined retrospectively. The ethical committee approval was not taken because the study nature was retrospective. Patients diagnosed with differentiated thyroid carcinoma were included according to the pathology results after thyroid surgery. Clinical parameters included age, gender, blood indexes (complete blood count, absolute neutrophil count, absolute lymphocyte count and hemoglobin, etc.), tumor size (largest lesion size measured during histopathological examination), lymph node metastasis, and pathological features. The neutrophil lymphocyte ratio was determined by dividing the absolute neutrophil count in the whole blood count by the lymphocyte count. Patients with conditions known 3 months before the operation and have potential to affect the white blood cell count like chronic medical disease, hematological disorders, past malignancy histories, coronary artery diseases, glucocorticoid use and acute infection were excluded from the study. In addition, no patients with WBC count outside the institutional reference range (4000-10.000 /ml) were allowed to be included in the study.

Statistical analysis

Descriptive statistical methods (percent, mean, median, range, standard deviation) were used to provide the basic features of the data. Data was reported as means or median (standard deviation). The Pearson Chi-Square test was used for comparison of qualitative data. Receiver operating characteristic (ROC) curve was constructed for NLR and the area under the ROC curve (AUC) value with 95% CI was calculated. Optimal cut-off value for NLR was determined. In all comparisons, $P<0.05$ was considered significant. Statistical analyzes were performed using the SPSS 23.0 program (SPSS for Windows, Inc., Chicago, Illinois, USA).

Results

Seventy-four patents with differentiated thyroid cancer were included in the study. The mean age of the patients was 46.1 (12.1) (min: 22, max: 73). While 64 (86.5%) of the patients were female, 10 (13.5%) were male. The mean preoperative basal leukocyte values of the patients were 7.42 (1.47) cells/μL, the mean of basal neutrophil values was 4.34 (1.10) cells/μL and the basal lymphocyte values were 2.31 (0.64) cells/μL (Table-1).

TNM staging of differentiated thyroid cancer cases was performed according to AJCC 7th edition [13]. When differentiated thyroid cancer cases were evaluated, papillary thyroid cancer (PTC) was detected in 69 cases (93.2%) and follicular thyroid cancer was detected in 5 patients (6.8%). When PTC cases were evaluated, 13 cases (41.9%) were in T1a stage, 11 cases (35.5%) were in T1b stage, 5 cases (16.1%) were in T2 stage and 2 cases (6.5%) were in T4a stage. Follicular variant was found in 28 cases (75.7%) in the T1a stage, in 5 cases (13.5%) in the T1b stage, in 3 cases (8.1%) in the T2 stage and in 1 case (2.7%) in the T4a stage. Histopathological results showed that both classical and follicular variant was detected together in 1 case in stage T1b. Minimally invasive follicular thyroid carcinoma was detected in 1 out of 4 cases (25%) with T1a stage and in 3 cases (75%) with T2 stage. One patient with extensive invasive follicular thyroid cancer was found to have T2 stage (Table 2).

Table 1: Demographic characteristics and hematological data of DTC patients

	n	%
Total	74	100
Sex		
Male	10	13.5
Female	64	86.5
Age (years)		
<45 years	33	44.5
≥45 years	41	55.5
	Mean (SD)	Normal range
WBC total (cells/mL)	7420 (1470)	4000–10.000
Neutrophils (cells/mL)	4340 (1100)	2000–8000
Lymphocytes (cells/mL)	2310 (640)	900–5200

DTC: Differentiated thyroid carcinoma, SD: Standard deviation

Table 2: The relationship between the thyroid cancer variants and T stage

Thyroid cancer variants	T1a	T1b	T2	T4a	Total
Papillary thyroid cancer classical variant	13	11	5	2	31
Papillary thyroid cancer follicular variant	28	5	3	1	37
Papillary thyroid cancer classical and follicular variant	0	1	0	0	1
Minimally invasive follicular thyroid carcinoma	1	0	3	0	4
Extensive invasive follicular thyroid cancer	0	0	1	0	1
Total	42	17	11	3	74

When evaluated according to lymph node involvement; 24 patients (77.4%) had N0, 4 patients (12.9%) N1a and 3 (9.7%) had N1b disease. The follicular variant was found to be N0 in 35 cases (94.6%), N1a in 1 (2.7%) and N1b level in 1 (2.7%) case. Histopathological results showed that in 1 patient with N0 disease, both classical and follicular variant were detected together. All of 4 patients with minimally invasive follicular thyroid carcinoma had N0 stage. One patient with diffusely invasive follicular thyroid cancer was in N0 stage (Table 3). Seventy-four patients were found to be in stage M0 in terms of metastasis in TNM staging. In terms of lymph node metastasis, ROC curve analysis was performed to determine the predictive value of neutrophil lymphocyte ratio.

When the likelihood ratio was calculated to be 3.2 in the analysis with 95% confidence interval and area under the curve of 0.620, it was found that the cutoff value for NLR was 2.59 with 44.4% sensitivity and 86.2% specificity (Figure1). There was a significant relationship between the current cut off value and the lymph node metastasis of differentiated thyroid cancer (P=0.03).

Table 3: The relationship between the cut off value of neutrophil lymphocyte ratio and DTC lymph node metastasis

		Stage N			
Cut 0ff		N0	N1a	N1b	Total
<2.59	Count	56	2	3	61
	% of Total	75.7	2.7	4.1	82.4
>2.59	Count	9	3	1	13
	% of Total	12.2	4.1	1.4	17.6
Total	Count	65	5	4	74
	% of Total	87.8	6.8%	5.4	100.0

DTC: Differentiated thyroid carcinoma

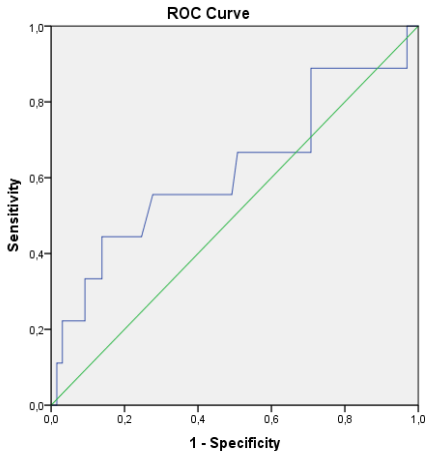

Figure 1: Receiver Operating Characteristic (ROC) Curves for Neutrophil-Lymphocyte

Discussion

Preoperative NLR is an inexpensive, easily accessible and frequently used parameter that reflects the systemic inflammatory response and the status of the immune system. High absolute neutrophil counts and low lymphocyte counts reflect higher inflammatory activity in patients. NLR may have a potentially important function in tumor progression and patient prognosis. In our study, we showed that preoperative NLR correlates positively with lymph node metastasis of differentiated thyroid carcinoma. Inflammatory cytokines (interleukin-1 receptor α, interleukin-6, 7, 8) may contribute to a tumor microenvironment that supports tumor invasion [14]. Neutrophils can inhibit tumor necrosis factor-α secretion (TNF-α) by producing vascular endothelial growth factor (VEGF). This is thought to play a role in tumor development and angiogenesis [15-16]. The reduction in lymphocyte count may reflect reduced specific antitumor immune activity [17]. In a meta-analysis involving patients with various solid tumors (breast, lung, liver, colon, and pancreas), Templeton et al. showed that high NLR is associated with negative overall survival [18]. Histopathological evaluation is accepted as the gold standard in the diagnosis of thyroid tumors. Recently, some laboratory parameters have been used as a marker for differentiation and prognosis of thyroid cancers. Examples include the use of the correlation between neutrophil lymphocyte ratio and tumor diameter, and the use of a neutrophil / lymphocyte ratio as a marker for papillary microcarcinoma screening [3]. Because the specificity of NLR is low, these values can only give an idea. When ROC curve analysis was calculated to define the predictive neutrophil lymphocyte ratio in terms of lymph node metastasis, in our study, 2.59 was found as threshold value with 44.4% sensitivity and 86.2% specificity. The optimal cutting level of the NLR is not yet standardized. Manatakis et al. [19] found a significant difference in the lymph node metastasis of PTCs when they determined the cut off level of NLR as 2.44. Koçer et al. [20] in their study compared the benign and malignant thyroid nodules and cut off value of NLR was suggested as 1.91. An interesting point that has been confirmed in our study is that the NLR values of differentiated thyroid cancer are relatively low compared to other solid tumors. A comprehensive meta-analysis investigating the relationship between NLR and various neoplasms' prognosis (gastrointestinal, gynecological, pulmonary, brain, breast, head and neck), up to 7.7 percent in NLR medians was detected [18].This study showed that high NLR in DTC patients was positively correlated with lymph node metastasis of AJCC TNM stage reflecting the malignancy degree of the tumor with.

In conclusion, preoperative high NLR in DTC patients was positively associated with lymph node metastasis of AJCC-TNM stage reflecting the degree of malignancy of the tumor. This work may give an idea for new therapies that aim to increase the lymphocyte value to reduce NLR and control tumor growth through immune reactions.

The use of single institution data, the retrospective nature and the small sample size are the main constraints of our study. Because of the fact that the non-invasive, encapsulated PTC follicular variant is classified as noninvasive follicular thyroid neoplasm with papillary-like nuclear properties, we think that this retrospective comparison between classical and follicular variants of PTC may possibly be subject to bias and error.

Conclusion

NLR was found to be significantly increased in lymph node positive differentiated cancers. The neutrophil to lymphocyte ratio as an inflammation index is inexpensive for patients with differentiated thyroid carcinoma, easily available and easy to obtain from routine blood tests.

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