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Atak et al.

Predictive Role of Neutrophil to Lymphocyte Ratio in Differentiation of Different Thyroid Pathologies

Farklı Tiroid Patolojilerinin Ayrımında Nötrofil Lenfosit Oranının Prediktif Rolü

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Abstract
The neutrophil/lymphocyte ratio (NLR) and platelete/ lymphocyte ratio (PLR) is a simple marker of systemic inflamatory response. The aim of this study was to examine the relationship of NLR and PLR with thyroid cancer and different benign thyroidal pathologies such as multi nodular goiter and thyroiditis. 331 patients who underwent thyroidectomy in general surgery department of our hospital between 2015 and 2017 were evaluated. Laboratory findings, demographic characteristics and pathology reports of patients were retrospectively reviewed. Patients were devided into four groups according to pathological reports. 241 of 331 patients were diagnosed with MNG (MNG Group), 17 were thyroiditis (T group), 49 were thyroid carcinomas (TK Group) and 24 were thyroid carcinoma with thyroiditis (T-TK Group). Patients were also devided into two groups according to precence of malignancy as benign (n=258) and malign (n=73). NLR and PLR values of groups were compared. 292 (88.2%) of paitents were female and 39 (11.8%) were male with a mean age was 50.52±12.08 years. There was no statistically significant difference between four groups in terms of NLR and PLR values (p>0.05). However, according to presence of malignancy, NLR values of malignant group was found to be statistically higher than the NLR values of benign group (p=0.039; p<0.05). There were no difference between two groups according to PLR values (p>0.05). In our study, there was no relationship between different thyroid pathologies and NLR and PLR. There is a need for prospective, randomized, large series of studies on the subject.
Keywords: Goiter, Neutrophil/Lymphocyte Ratio, Thyroid Carcinomas

Öz
Nörtofil lenfosit oranı (NLO) ve platelet lenfosit oranı (PLO) sistemik enflamatuar yanıtın basit bir göstergesidir ve bazı hastalıklarda prognostik olduğu gösterilmiştir. Bu çalışma NLO ve PLO ile tiroid kanseri ve tiroidin multinodüler guatr ve tiroidit gibi diğer benign hastalıkları arasındaki ilişkiyi ortaya koymak amacı ile gerçekleştirildi. Hastanemiz genel cerrahi kliniğinde 2015-2017 yılları arasında tiroidektomi ameliyatı olan 331 hasta değerlendirildi. Hastaların laboratuar bulguları, demografik özellikleri ve patoloji raporları geriye dönük olarak incelendi. Patoloji raporlarına göre hastalar 4 gruba ayrıldı. 331 hastanın 241'ine MNG (MNG Grup), 17'sine tiroidit (T Grup), 49'una tiroid karsinomu (TK Grup), 24'üne ise tiroidit ile birlikte tiroid karsinomu (T-TK Grup) teşhisi konuldu. Hastalar ayrıca malignite varlığına göre göre benign (n=258) ve malign (n=73) olarak 2 gruba ayrıldı. Grupların NLO ve PLO değerleri karşılaştırıldı. Hastaların 292'si kadın (%88.2), 39'u erkek (%11.8) olup ortalama yaş 50.52±12.08 idi. Dört grup arasında NLO ve PLO değeri açısından istatistiksel olarak anlamlı fark saptanmadı (p>0.05). Bununla birlikte malignite varlığına göre malign grubun NLO değeri, benign grubun NLO değerine göre istatistiksel olarak anlamlı düzeyde yüksek saptandı (p=0.039; p<0.05). Malignite varlığına göre grupların PLO ölçümleri arasında istatistiksel olarak anlamlı farklılık saptanmadı (p>0.05). Bizim çalışmamızda farklı tiroid patolojileri ile NLO ve PLO arasında ilişki saptanmadı. Konu ile ilgili prospektif, randomize geniş serili çalışmalara ihtiyaç duyulmaktadır.
Anahtar Kelimeler: Guatr, Tiroid Karsinomu, Nötrofil/Lenfosit Oranı

Introduction

The thyroid nodule is a common pathology seen in approximately 4-7% of the adult population (1). Thyroid nodules may be single or multiple. Although multinodular goiter (MNG) is known to be a benign pathology, it has a low risk of malignancy (2). Recent studies have suggested that the incidence of malignancy in the patients with MNG approaches that of the patients with a solitary thyroid nodule alone (3). Thyroiditis is another commonly seen pathology of the thyroid gland. There are different types of thyroiditis such as lymphocytic thyroiditis, Hashimoto's thyroiditis, and subacute thyroiditis. The close association between lymphocytic thyroiditis and thyroid cancer has been demonstrated with studies performed (4). Thyroid cancer is the most common type of cancer of the endocrine system. A more rapid increase is seen in the incidence of thyroid cancer compared to the other types of cancers. Since 1975 to the present time, the incidence rate of thyroid cancer has increased 3-fold (5), however, the survival rate is about 97% in the patients with well-differentiated thyroid cancer (6).

The immune system has an important role in the control and prevention of progression of many diseases. In recent years, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) obtained by dividing absolute neutrophil counts and absolute platelet counts to absolute lymphocyte counts respectively are used as a marker of the systemic inflammatory condition and it has been shown that it was correlated with prognosis in many cardiovascular diseases and malignancies (7,8).

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There is relatively little literature available on the correlation of NLR with thyroid diseases compared to other diseases. This study was performed to be able to demonstrate whether NLR and PLR were predictive in the discrimination of different thyroid disorders or not.

Material and Method

Three hundred and thirty-one patients undergoing thyroid surgery due to nodular goiter, multinodular goiter, toxic goiter, thyroid carcinoma or suspected thyroid carcinoma in general surgery department of our hospital between April 2015 and March 2017 were evaluated. The surgery and possible complications were explained to all of the patients in detail and a written informed consent form was received from all of them. The study was planned according to the Declaration of Helsinki. Routine laboratory findings, demographic characteristics and pathology reports of the patients were retrospectively evaluated before surgery.

The patients were divided into 4 groups according to pathology reports as follows: MNG Group, Thyroiditis Group (T Group), Thyroid Carcinoma Group (TC Group), Thyroiditis together with Thyroid Carcinoma Group (T-TC Group). Additionally, the patients were divided into 2 groups as benign (n=258) and malignant (n=73) according to the presence of malignancy. Serum neutrophil, lymphocyte, and platelet values were determined within 15 days before the surgery. NLR was obtained by dividing absolute neutrophil counts to absolute lymphocyte counts and PLR was obtained by dividing absolute platelet counts to absolute lymphocyte counts. NLR and PLR values of the groups were compared.

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for the statistical analysis. During the evaluation of the study data, regarding the comparisons of descriptive statistical methods (mean, standard deviation, median, and frequency, ratio, minimum and maximum) as well as quantitative data, Mann Whitney U test was used for the intergroup comparisons of parameters without normal distribution. The Kruskal-Wallis was used for comparing three or more groups without normal distribution. Fisher's exact test was used for comparison of qualitative data. Diagnostic screening tests (sensitivity, specificity, PPV, NPV) and ROC Curve analysis were used for determination of cut-off point for the parameters. Significance was evaluated at a level of $p<0.05$.

Results

Three hundred and thirty-one patients were included in the study. Eighty-eight point two percent of the patients (n=292) were females, 11.8% of them

(n=39) were males and the mean age was 50.52 ± 12.08 years (Table 1). Unilateral total thyroidectomy, near-total thyroidectomy and bilateral total thyroidectomy surgeries, were performed in 34, 2 and 234 patients, respectively. According to pathology reports, 241, 7 and 49 of 331 patients were diagnosed with MNG, thyroid carcinoma, and thyroiditis with thyroid carcinoma. Among thyroiditis, lymphocytic thyroiditis, Hashimoto's thyroiditis, nonspecific thyroiditis, and subacute thyroiditis were determined in 8 (2.4%), 6 (1.8%), 2 (0.6%) patients, and 1 (0.3%) patient, respectively. Twenty-nine (8.8%) and 20 (6%) of forty-nine patients with thyroid carcinoma comprised of papillary and follicular carcinoma, and papillary microcarcinoma (Table 2).

Table 1. Demographic characteristics of patients

Age (year)	Gender			
	Female		Male	
Min-Max (Median) Mean±SD	n	%	n	%
24–78 (50) 50.52±12.08	292	88.2	39	11.8

Table 2. Distribution of variables related to disease

		n	%
Operation	Hemithyroidectomy	34	10.3
	Near-Total Thyroidectomy	2	0.6
	Total Thyroidectomy	295	89.1
Diagnosis	Thyroidectomy	17	5.1
	Hashimato Thyroiditis	6	1.8
	Lymphocytic Thyroiditis	8	2.4
	Nonspesific Thyroiditis	2	0.6
	Subacute Granulomatous Thyroiditis	1	0.3
	Multinodulary Goiter	241	72.8
	Thyroid Carcinoma	49	14.8
	Papillary+Foliculary Carcinoma	29	8.8
	Papillary Microcarcinoma	20	6.0
	Thyroid Carcinoma + Thyroiditis	24	7.3
	PMC + Lymphocytic Thyroiditis	7	2.1
	PMC + Nonspesific Thyroiditis	2	0.6
	TC + Hashimato Thyroiditis	2	0.6
	TC + Lymphocytic Thyroiditis	8	2.4
	TC+ Nonspesific Thyroiditis	5	1.5

PMC: Papillary Microcarcinoma, TC: Thyroid Carcinoma

Although the NLR value was determined to be higher in TC and T-TC groups compared to the other groups, no statistically significant difference was found between groups (P=0.169). The PLR value was determined to be higher in thyroiditis group compared to the other groups, but no statistically significant difference was found between groups regarding the PLR value (p=0.627) (Table 3). However, according to the presence of malignancy, the NLR value of malignant group was determined to be statistically significantly higher compared to the NLR value of benign group (p=0.039; p<0.05). No statistically significant difference was determined between PLR measurements of groups according to the presence of malignancy (p>0.05)

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(Table 4). The cut-off point was determined to be 1.77 for NLR according to malignancy. The sensitivity, specificity, positive predictive value, and negative predictive value for 1.77 cut-off value of NLR were 64.38%, 53.49%, 28.1 and 84.1; respectively (Table 5).

The area under the curve in ROC curve obtained and standard error was determined to be 57.9% and 3.6%, respectively (Figure 1).

Table 3. Evaluation of NLO and PLO measurements according to diagnosis

			Diagnosis			Test Value
		Nodulary Goitre	Thyroiditis	Thyroid carcinoma	Thyroiditis+ Thyroid carcinoma	*p*
	n	241	17	49	24	
NLR	Min-Max (Median)	0.5-4.3 (1.71)	1.05-3.7 (1.76)	1.02-4.7 (1.97)	1.08-3.17 (2.01)	χ^2:5.038
	Mean±SD	1.88±0.72	1.99±0.68	2.11±0.83	2.00±0.60	*c0.169*
PLR	Min-Max (Median)	35.3-286.7 (121.3)	86.4-273.3 (121)	49.7-281.3 (118.1)	98.3-179.3 (116.3)	χ^2:1.743
	Mean±SD	124.12±38.97	140.87±54.34	130.94±47.17	129.70±27.52	*c0.627*

Table 4. Evaluation of NLR and PLR measurements according to malignancy

		Malignancy		Test value
		Benign (n=258)	Malign (n=73)	*p*
NLR	Min-Max(Median)	0.5-4.3(1.71)	1.02-4.7(1.97)	Z:-2.067
	Mean±SD	1.88±0.71	2.07±0.76	*a0.039**
PLR	Min-Max(Median)	35.3-286.7(121.2)	49.7-281.3(117.3)	Z:-0.925
	Mean±SD	125.22±40.24	130.53±41.54	*a0.355*

Table 5. Diagnostic screening tests for NLO and ROC curve analysis

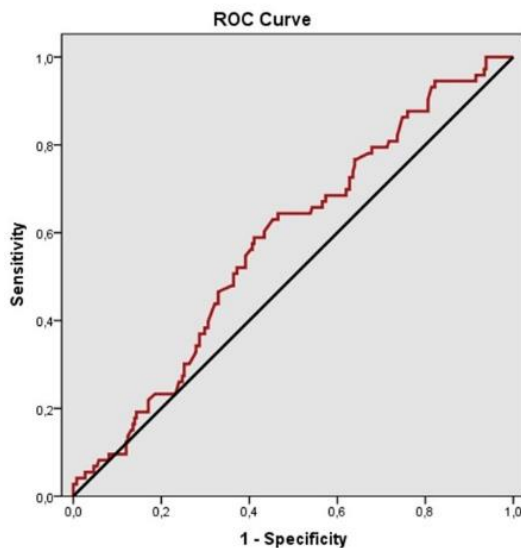|		Diagnostic Scan				ROC Curve		
	Cut off	Sensitivity	Specifity	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	*p*
NLR	≥*1.77*	64.38	53.49	28.10	84.10	**0.579**	0.508-0.650	*0.039**

Figure 1. ROC curve. ROC curve showing the sensitivity and specificity of neutrophil to lymphocyte ratio

Discussion

In our study, we aimed to demonstrate whether NLR and PLR were predictive of the discrimination of four different thyroid pathologies or not and we concluded two results. First, we determined no statistically significant difference between different thyroid pathologies regarding the NLR and PLR value. Second, we found that the NLR value was significantly higher in malignant group compared to the benign group.

NLR is a simple method obtained from neutrophil and lymphocyte counts and evaluating systemic inflammation. Neutrophils are activated after injury and destruction of tissues and they release some enzymes such as acid phosphatase, elastase, and myeloperoxidase. Some changes occur in the ratio of circulating lymphocytes during the systemic inflammatory response. Relative lymphopenia accompanies neutrophilia. The ratio of these two subgroups is used as an inflammatory marker in the clinical practice of intensive care unit (9). NLR was also used for the prediction of development of bacteremia in patients with community-acquired infection and it was shown in a study performed that elevated NLR was more sensitive than elevated white blood cell counts in patients with suspected appendicitis (10). NLR is known to be a predictor of prognosis in also cardiovascular disease. After the use of relative lymphopenia as a prognostic factor in coronary artery disease and chronic heart failure, NLR was also begun to be used in these diseases. Elevated NLR was shown to be a marker of poor prognosis in

patients undergoing cardiovascular intervention. It has been demonstrated that mortality was increased in acute coronary syndrome as NLR increased (10,11).

After a demonstration of the correlation between cancer and inflammation, systemic inflammatory markers were begun to be used for the survival of many cancer types (12). Many studies showed that NLR has correlated with prognosis in breast, colorectal, stomach, pancreas, hepatocellular and renal carcinoma. It is known that neutrophils increase tumor cell proliferation, angiogenesis, and distant metastasis and lymphocytes play a crucial role in the immune response to tumor cells. When considered from this point of view, it is estimated that NLR is correlated with prognosis (13,14).

In addition to their primary functions for providing hemostasis, platelets cause migration of the cells into the injured region, abundant secretion of proinflammatory cytokines and consequently occurrence of a proinflammatory environment in lesion area by interacting with endothelial cells, progenitor cells and leukocytes (monocytes, neutrophils, dendritic cells, T- cells). In recent years, it has been reported that also mean platelet volume reflected platelet function and platelet activation function and it could be an inflammatory marker in different chronic diseases. Besides, as elevated NLR also elevated PLR was shown to be associated with mortality in cardiac diseases (8,15,16). Also, in their previous study performed in end-stage renal disease patients, Türkmen et al. suggested that PLR showed a better correlation with proinflammatory cytokines such as IL-6 and TNF-alpha and therefore PLR was a better inflammatory marker than NLR (8). The combination of NLR and PLR was used for predicting postoperative survival in esophageal squamous cell carcinoma and this combination was shown to be associated with tumor length, depth of invasion, and nodal metastasis (17).

Liu et al. (18) demonstrated that preoperatively elevated NLR was associated with increased tumor size and high risk of recurrence in patients with differentiated thyroid cancer. In a similar study, Seretis et al. (19) reported that especially elevated NLR greater than 2.5 was associated with thyroid cancer.

In our study, NLR was found to be higher in TC and T-TC groups compared to the other groups, but the difference was not statistically significant. We consider that a small number of patients can cause this result. However, NLR was found to be higher in the malignant group compared to the benign group. This may occur due to increased neutrophil count and/or decreased lymphocyte count. Decreased lymphocyte count in cancer patients may be associated with a myelosuppression secondary to bone marrow suppression or generalized infection. Neutrophilia may have occurred in response to the production of ectopic myeloid growth factors which

are a part of paraneoplastic syndromes or with a high degree of probability cancer associated inflammation developing secondary to tissue injury and cytokine release (20).

In conclusion, since the gold standard method in evaluation of thyroid diseases is a histopathological investigation and NLR is not specific, this test should not be taken into consideration as a diagnostic test alone. The NLR value can only provide an idea. Differently, from the other non-invasive markers, NLR is a cheap and easily applicable method. Although NLR has a very limited value in the diagnosis of thyroid cancer, due to a possible correlation between systemic inflammatory response and tumor formation in the thyroid gland, it seems to be noteworthy to demonstrate the subject more clearly with prospectively designed studies.

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