

ORIGINAL RESEARCH

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Platelet levels and neutrophil to lymphocyte ratio in thyroid nodules with and without cancer diagnosis**Soycan Mizrak¹, Sirin Kucuk²**¹*Usak University Training and Research Hospital, Medical Biochemistry Laboratory, Usak, Turkey*²*Usak University Training and Research Hospital, Medical Pathology Laboratory, Usak, Turkey*

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Nodular formation of thyroid tissue is a very common endocrinologic pathology. Approximately 5% of thyroid nodules can prove to be cancerous. The usefulness of mean platelet volume (MPV) and neutrophil to lymphocyte ratio (NLR) is determined as an indicator of immunological response and subclinical inflammation in recent years. In this study we evaluate the association of thyroid stimulating hormone (TSH), platelet, mean platelet volume (MPV) and NLR levels between the thyroid nodules that turn into cancer and do not convert. Our study consisted of patients with thyroid nodules that converted to thyroid cancer (n = 100) and didn't convert to thyroid cancer (n = 100). These patients were selected retrospectively using the Hospital Information System. The TSH, NLR, platelet and MPV levels were recorded preoperatively and the difference between them was evaluated statistically with SPSS 21. Differences between groups were examined with using Mann Whitney U Test. P < 0.05 were considered significant. Platelet, TSH and neutrophil values were significantly higher in the nodular group which convert to thyroid cancer (p < 0.05). In addition, the likelihood of being thyroid cancer increased 1.47 times with a unit increase in the NLR variable, and 1.008 times with a unit increase in the platelet variable. High levels of platelet and neutrophil in thyroid cancer may be due to increased cytokine level changes. It can be shown that data obtained from total blood count, which is an easy, inexpensive and reproducible assay, can be used as a marker in predicting prognosis with further studies.

Keywords: Thyroid cancer, neutrophil, lymphocyte, platelet**Introduction**

Nodular thyroid diseases which are seen in 32% of women and 33% of men are among the most common endocrinologic diseases [1]. Half of those thyroid nodules are solitary while the other half are multinodular. We can't decide whether the nodule is benign or malignant without a pathological examination. The clinical importance of thyroid nodules is to exclude the diagnosis of underlying thyroid cancer.

The best test in order to make a diagnosis is fine needle aspiration biopsy (FNAB). However, there are two important problems of fine needle aspiration biopsy. First, inadequate or non-diagnostic results, the second is the indeterminate category of lesions, which constitute 15-30% of all thyroid biopsies. Therefore, there is a need for biomarkers to be used in thyroid tumors, contributing

to predicting the accuracy of FNAB, tumor aggressiveness or behavior. 5-15% of thyroid nodules are proved to be cancerous [2]. Thyroid cancer incidence has rapidly increased during the past few decades due to increases in the incidence of papillary thyroid carcinomas [3]. The relationship between inflammation and cancer has started to be investigated since leucocytes were observed in tumorigenic cells by Rudolf Virchow [4]. The inflammation around neoplastic tissues is characterized by the presence of leukocytes with macrophages, mast cells, and T cells [5]. The neutrophil-lymphocyte ratio (NLR) that is known as a marker of the systemic inflammatory response, has been associated with the progression and the survival of most cancers [6]. Increased NLR levels is a negative prognostic factor for various cancers [7]. The role of platelets is also important in the relationship between cancer and inflammation. Circulating platelets count and production are increased in inflammatory diseases. It is thought that these platelets migrate to the area of inflammation where highly reactive and large platelets are rapidly consumed. Mean platelet volume (MPV) shows platelet activation and platelet function changes. Large platelets are more active than small platelets [8]. NLR and MPV levels analyzed in hemocytometers are useful markers that

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are easily accessible. The present study aimed to evaluate the association of NLR and MPV levels between benign and malignant thyroid nodules.

Materials: The present study was a retrospective study. The Ethical Committee and Institutional Review Board of Usak University Faculty of Medicine, where the study was conducted, approved the study design. For this retrospective study, we reviewed the medical records of 200 patients who have thyroid nodules in our hospital between January 2015 and March 2018. Patients with history of hematological disorders, chronic inflammatory disease or autoimmune disease, acute or chronic infection, other known malignancy were excluded from the study. All patients were divided into two groups. Group 1 (n=100) were patients with thyroid nodules that didn't convert to thyroid cancer, group 2 (n=100) were patients with thyroid nodules that converted to thyroid cancer. We retrospectively analyzed the patient files to obtain data including age, gender, detailed disease history, and preoperative TSH levels, neutrophil, lymphocyte, platelet count and mean platelet volume values. The preoperative data reflect the values measured at the time of examination. TSH assays were performed on a fully automated ADVIA Centaur analyzer (Siemens Healthcare Diagnostics, Munich, Germany). The neutrophil to lymphocyte ratio were calculated by dividing the neutrophil value with the lymphocyte value and mean platelet volume were noted. All of the CBC analyses were performed in the hematology laboratory of our hospital. An automatic blood counter (ABX Pentra 120 DF, Horiba Medical, USA) was used for whole blood counts.

Material and Methods

The results of the study transferred from forms to SPSS 21 computer statistical analysis software and statistical analyses were performed. Mann Whitney U test used for comparison of the groups. The chi-square analysis was applied to examine the relationships between the groups of nominal variables. Logistic Regression Analysis was used to determine the risk factors. Results were expressed as mean $\pm$ standard deviation and a p value of <0.05 was considered statistically significant.

Results

The study included 200 patients diagnosed and followed up with thyroid nodules. These patients were divided into 2 groups. Patients in Group 1 (n = 100) was diagnosed as thyroid nodules and Group 2 (n = 100) consisted of patients who were diagnosed as thyroid nodules and then turned into papillary carcinoma. First,

we evaluated the relationship between groups and gender with chi-square test. There was no statistically significant relationship between groups and genders (Table 1, $p>0.05$). Although not meaningful; 46.7% of males and 50.6% of females had Thyroid cancer.

The data of the patients in the preoperative period were recorded by using the hospital information system. We examined TSH levels, neutrophil, lymphocyte, platelet counts and MPV levels in both groups. The relationship that we have obtained between the groups and the variables is given in Table 2.

There was a statistically significant difference in age between groups ($p < 0.05$). Age values of nodular goiter group were significantly higher.

There was a statistically significant difference between the groups in terms of TSH (U / L) values ($p < 0.05$). TSH (U / L) values of Thyroid cancer group were significantly higher.

There was a statistically significant difference between the groups in terms of Neutrophil values ($p < 0.05$). Neutrophil values of Thyroid cancer group were significantly higher.

There was a statistically significant difference between the groups in terms of PLT values ($p < 0.05$). PLT values of Thyroid cancer group were significantly higher.

There was no statistically significant difference between the groups in terms of other variables ($p > 0.05$).

Logistic Regression analysis was performed to determine the Thyroid cancer status as a dependent variable and as a risk factor (Table 3).

According to the results of logistic regression analysis, a one-year increase in the age variable decreases the probability of being a Thyroid cancer (OR = 0.974). One unit enhances in the NLR variable, increases the probability of being a Thyroid cancer 1.471 times (OR = 1.471). The probability of being one unit enhances in the platelet variable increased by 1,008 times (OR = 1,008).

We can distinguish accurately 63% of patients using age, NLR and PLT variables a new future case of with Nodular Goiter, Thyroid cancer 62% of patients and 62,8%, in general, can accurately distinguish (Table 4).

Table 1. The chi-square test on the relationship between groups and gender

		Grup						The Chi-Square Test	
		Nodular Goiter		Thyroid cancer		Total		Chi-Square	p
		n	%	n	%	n	%		
Gender	Male	16	53.3	14	46.7	30	100.0	0.039	0.692
	Female	84	49.4	86	50.6	170	100.0		
	Total	100	50.0	100	50.0	200	100.0		

Table 2. Mann whitney u test result on the difference between groups and variables

		Grup						The Chi-Square Test	
		n	Mean	Median	Min	Max	ss	z	p
Age	Nodular Goiter	100	50.9	51.0	18.0	81.0	13.3		
	Thyroid cancer	100	46.4	44.5	24.0	77.0	12.4	-2.6	0.009
	Total	200	48.7	48.0	18.0	81.0	13.0		
TSH (U/L)	Nodular Goiter	100	2.20	.90	0.00	33.50	5.63		
	Thyroid cancer	100	2.88	1.45	0.00	51.30	6.37	-3.8	0.0001
	Total	200	2.54	1.30	0.00	51.30	6.01		
Neutrophil	Nodular Goiter	100	4.0	3.9	1.0	7.9	1.5		
	Thyroid cancer	100	4.6	4.4	1.4	9.1	1.4	-2.69	0.007
	Total	200	4.3	4.2	1.0	9.1	1.5		
Lymphocyte	Nodular Goiter	100	2.0	1.9	.8	4.8	.8		
	Thyroid cancer	100	2.1	2.1	.5	4.4	.8	-1.14	0.253
	Total	200	2.1	2.0	.5	4.8	.8		
NLR	Nodular Goiter	100	2.1	1.9	.9	4.1	.7		
	Thyroid cancer	100	2.4	2.2	.9	8.0	1.1	-1.9	0.056
	Total	200	2.2	2.0	.9	8.0	1.0		
Platelet	Nodular Goiter	100	235.0	213.5	139.0	471.0	66.6		
	Thyroid cancer	100	268.5	257.0	129.0	556.0	69.9	-4.05	0.0001
	Total	200	251.8	234.0	129.0	556.0	70.2		
MPV	Nodular Goiter	100	9.0	9.0	6.4	12.0	1.0		
	Thyroid cancer	100	8.8	8.7	7.3	11.4	.9	-1.29	0.194
	Total	200	8.9	8.8	6.4	12.0	1.0		

Table 3. Logistic regression analysis result

	p	OR	95% C.I. for OR	
			Lower	Upper
Age	.026	.974	.951	.997
NLR	.026	1.471	1.047	2.069
Platelet	.002	1.008	1.003	1.012

Table 4. Classification table for thyroid cancer and nodule

Classification Tablea				
		Predicted		
		Group		Percentage Correct
Platelet	Nodular Goiter	63	36	63.6
	Thyroid cancer	38	62	62.0
Overall Percentage				62.8

Discussion

Although the presence of thyroid nodules are common in adults, the occurrence of thyroid cancer is rare. The important point for clinicians is to identify malignant (5–10%) and benign thyroid nodules. After an association between cancer and inflammation was discovered, markers of the systemic inflammatory response have been used to predict relapse and survival in patients with various cancers. Neutrophil and lymphocyte cells are the basis of the inflammatory response. Lymphocytes inhibit the proliferation and metastatic activities of tumor cells through the release of cytokines. Neutrophil-to-lymphocyte (NLR) is an independent risk factor in the diagnosis of tumor development. NLR has recently emerged as a simple and a valid composite marker of systemic inflammatory response [9]. Although it is inexpensive, easily calculated and readily available, its use in the preoperative assessment and postoperative follow-up of malignant thyroid cancer patients remains as a matter of debate. Nevertheless, the NLR is universally available from routine blood tests and does not increase the diagnostic workup cost [10]. On the other hand, the association of higher NLR with aggressive clinical and pathological characteristics may suggest a negative outcome. Oflazoglu et al found that high preoperative NLR and Platelet-to-lymphocyte (PLR) levels correlated with better and disease-free survival at a statistically significant level. Several other studies also showed that high preoperative NLR levels correlated with better, disease-free survival at a statistically significant level [11–13]. Therefore NLR is useful to predict long-term mortality. Seretis et al. [10] indicated that there is a higher neutrophil-to-lymphocyte ratio in patients with thyroid cancer when compared with patients with benign thyroid disorders but found no association between neutrophil-to-lymphocyte ratio levels and multifocality. In contrary to these findings, we have found no correlation between the NLR and the presence of thyroid cancer in our study. The number of neutrophils and lymphocytes increased in the same rate in thyroid cancer patients. In this study, no significant differences between the benign and malignant nodular groups were found in gender distribution. In addition, there was no difference in the NLR value and gender of the patients with benign and malign nodules examined in our study. The meta-analysis of McLeod DSA et al aimed to examine the associations between pretreatment NLR and differentiated Thyroid Cancer (DTC). In parallel to our findings, McLeod's meta-analysis showed that the pretreatment NLR values were not significantly different for patients with DTC to those with benign nodules. [14]. These results suggest that an elevated NLR is neither a sensitive nor a specific indicator of progressing DTC in patients with nodular goiters. However, Kocer et al.'s report suggested that the NLR was a meaningful diagnostic tool for discriminating poorly differentiated thyroid cancer [15]. However the conclusiveness of these results require further validation as they were limited by the heterogeneity of subgroups and the small sample size used in the study.

Neutrophil counts were significantly higher in the papillary thyroid cancer (PTC) group than the multinodular goiter (MNG) group ($p < 0.05$). Lymphocyte counts were significantly higher in the MNG group than the other group ($p < 0.05$) [15]. Several studies reported that inflammation and PTC are associated with each other. There is an increased incidence of PTC in patients with thyroiditis [9]. In Liu et al.'s study, it was noted that the age of the PTC

patients (53.57 ± 13.32 y) appeared older than the age of patients with benign nodules (49.25 ± 13.15 y) as was the case in our study. As reported in several studies, NLR is correlated with thyroid cancer characteristics, such as tumor size, patient's age, and the clinical stage parameters of thyroid cancer. Liu et al. found that the preoperative NLR correlated with DTC tumor size. However, Liu et al. and Kim et al. showed that tumor size, extra thyroidal invasion, and lymph node metastasis was not associated with the NLR value [9, 16]. Bayır O et al reported that preoperative NLRs and PLRs in atypia of undetermined significance and suspicious for malignancy groups can't be considered as a predictive diagnostic marker of malignancy [17].

Platelets are activated by pro-inflammatory cytokines such as IL-1, IL-6, then they release angiogenic growth factors and stimulate the tumor progression. Thrombocytosis is an indicator of inflammation severity. Voutsadakis IA shows that high platelet to lymphocyte ratio is associated with poor prognosis and is used as a diagnostic or predictive instrument in several malignancies [18]. Similar to our findings, in Kocer D et al study, platelet counts were not significantly different between the groups ($p > 0.05$) [15].

The thyroid functions must be examined for any patient with a thyroid nodule. The most useful marker directly reflecting the thyroid functions is the serum thyroid hormone levels or the tissue hormone concentration. The role of TSH as a predictor of thyroid nodule malignancy has been evaluated by several studies conducted during the last few years. In recent meta-analyses, higher serum TSH levels were associated with an increased risk of thyroid cancer [14]. Expression of growth factors, receptors and proto-oncogenes increase with TSH signaling pathway activation. Therefore, TSH is considered to be a major thyroid cell growth factor [19]. For this reason, clinician physicians suppress the TSH levels in treatment of thyroid cancer.

Identification of the prognostic indicators for age, which are biologically different, is very important in deciding an appropriate therapeutic strategy. In our study, age is an important prognostic factor for patients with malignant nodules of thyroid. Significant differences were seen in young age groups in local recurrence. It may be a reflection of the underlying differences in harvested nodes at lymph node dissection or tumor size [20]. But in our study, we could not examine the relationship between the tumor size and the lymph node dissection width and age. Also, in our study, age values of nodular goiter group were found to be significantly higher than the cancer patients. Kim et al. and Liu et al. found that thyroid cancer patients who are older than 45 had significantly higher NLRs. However, it was found that the preoperative NLR was significantly lower in older patients. Consequently, there are only 2 studies where no differences were found in the NLR values between patients that are aged younger and older than 45 [21,16]. The mean TSH level increases with age and a higher TSH level is associated with a higher incidence of thyroid cancer [22].

The limitation of our study was that we did not investigate a correlation between the variables (NLR, PLT, TSH) and clinicopathological parameters of patients, such as lymph node metastasis, grade of differentiation or tumor stage because of its retrospective status.

Conclusion

In conclusion, our results indicate that the neutrophil and platelet counts of patients with thyroid cancer are significantly different than that of patients with benign nodules. An elevated level of these values seems to be a reliable indicator of progressing thyroid cancer in patients with MNG. The Neutrophil and platelet count is universally available from routine blood tests. Since these tests are inexpensive and are easy to analyze, the prognostic significance of benign and malignant nodules is important. Therefore larger, prospective and clinically-supported studies are required to confirm our findings.

Competing interests

The authors declare that they have no competing interests.

Financial Disclosure

The financial support for this study was provided by the investigators themselves.

Ethical approval

Before the study, permissions were obtained from local ethical committee.

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