

# A comparison of the platelet index, neutrophil-lymphocyte and platelet-lymphocyte ratios of patients with differentiated thyroid cancer and nodular hyperplasia

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## Abstract

**Aim:** In our study, it was aimed to determine the usability of the inexpensive, fast and easily accessible platelet index, NLR (Neutrophil to Lymphocyte ratio) and PLR (Platelet to Lymphocyte ratio) as predictive values in patients with differentiated thyroid cancer and nodular hyperplasia.

**Materials and Methods:** The data of 454 patients operated due to differentiated thyroid cancers and nodular hyperplasia at our clinic between 2010 and 2020 and a control group consisting of 120 healthy individuals were retrospectively examined. The data of the patients and the control group were statistically analyzed.

**Results:** The study included a total of 574 participants including 314 patients who received differentiated thyroid cancer surgery, 140 patients who received surgery due to thyroid nodular hyperplasia and a control group consisting of 120 healthy individuals. There was no significant difference among the groups in terms of age. There was a dominance of the female sex among the groups, but the difference was insignificant. There was no significant difference among the groups in terms of their MPV, PLR or NLR values. However, the PDW (Platelet Distribution Width) values were significantly higher among the differentiated thyroid cancer patients.

**Conclusion:** In our study, we observed that the MPV, PLR and NLR values varied, but the differences were not statistically significant. The PDW values were significantly high. Considering the current literature, we concluded that, among the existing parameters, NLR is a more reliable constant value at the stage of diagnosis.

**Keywords:** Differentiated thyroid cancer; goiter; neutrophil-lymphocyte and platelet-lymphocyte ratios; platelet index; thyroid neoplasm

## INTRODUCTION

With the increase in diagnostic imaging, thyroid nodules have become a prevalent clinical problem. Epidemiological studies have shown the incidence of palpable thyroid nodules in iodine-sufficient regions as 5% in women and 1% in men (1). However, with the increasing number of high-resolution imaging techniques, the rates of detecting thyroid nodules have increased substantially (1-4). The clinical significance of thyroid nodules is based on the necessity of excluding thyroid cancer that emerges in 7-15% of cases depending on age, sex, history of exposure to radiation, family history and other factors (1,2,5,6). Differentiated thyroid cancers (DTC) including papillary and follicular cancers constitute the vast majority (>90%) of all thyroid cancers (1,2,7,8). In the last decades, the

increase in the incidence of especially thyroid cancer has been detected as higher than 200%, and most of this increase has been attributed to papillary thyroid cancer (1,2,7,8). In examinations, the diagnosis of papillary carcinoma <1 cm has increased by more than 50% in the last 3 decades (9).

The greatest difficulty faced by doctors taking part in thyroid surgery is balancing the therapeutic approaches of patients with low-risk thyroid cancers and benign thyroid nodules. For this reason, the diagnosis and pathology of patients with thyroid masses become prominent. Physical examination, family history, ultrasonography and fine needle aspiration biopsy are current and indispensable diagnosis tools. Although ultrasonography provides us with clues about the nature of the mass, fine needle

Received: 11.03.2021 Accepted: 10.05.2021 Available online: 19.08.2021

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aspiration cytology has a key role. However, depending on the centers where it is performed, fine needle aspiration cytology provides information at a rate of 70-97% (4,6,8). The management of patients becomes even more difficult especially in uncertain definitions in fine needle aspiration cytology.

Especially recently, there are several studies focusing on the tumor and systemic immune response relationship. Here, the main hypothesis is founded on being able to obtain predictive and/or survey-related information via the relationship of inflammation to the tumor. In this context, the focus has been especially on studies on platelet indices, neutrophil and lymphocyte values. Many publications have shown that measuring the systemic immune response in the physiopathology of head and neck tumors and cancers is useful for the diagnosis and prognosis (10-12).

In our study, we investigated the role of preoperative platelet indices and NLR (Neutrophil/lymphocyte) and PLR (Platelet/lymphocyte) values in predicting the type (benign/malignant) of the neoplasm in patients receiving thyroid surgery at our clinic and their usability as an assistive instrument in thyroid nodules that are difficult to manage through this role.

## MATERIALS and METHODS

The data of patients who received thyroidectomy due to differentiated thyroid cancers and thyroid nodular hyperplasia (goiter) between 2010 and 2020 at our clinic were retrospectively collected. Additionally, a control group was formed with healthy individuals. The study included patients whose data and follow-ups were complete. Patients with complete data and follow-up were included in the study. Exclusion criteria from the study: Patients with incomplete data, those receiving surgery other than modified or radical mastoidectomy, those with hematological disorders, cardiac disorders, autoimmune diseases, inflammatory or infective diseases,

endocrinology diseases or malignancies, those with liver and kidney diseases and those who were receiving medication affecting the coagulation cascade were excluded from the study.

The blood samples of the patients were collected a week before the surgery. Three ml of blood was collected in EDTA vacuum tubes (lavender caps), and the samples were processed within 30 minutes by using a Sysmex XN-1000 automated hematology analyzer (Sysmex, Kobe, Japan).

The data of the study were analyzed by using the SPSS "Statistical Package for the Social Sciences (IBM SPSS22.0)" program. Mean, median, standard deviation, minimum and maximum values were calculated. As the variables did not satisfy normal distribution according to the results of the Kolmogorov-Smirnov test ( $p < 0.05$ ), non-parametric statistical tests were used. Kruskal-Wallis test was used to compare more than two groups. Mann-Whitney U test was used to compare two groups. In the statistical comparison, the alpha error rate was considered significant at  $p < 0.05$ . Approval for the study was obtained from the Scientific Research and Publication Ethics Committee of Inonu University (Decision No: 2020/650).

## RESULTS

The study included 574 participants in total, and these participants were divided into five groups. The first group included Thyroid Papillary Microcarcinoma patients ( $n_1=172$ ), the second group included Thyroid Papillary Carcinoma patients ( $n_2=117$ ), the third group included Thyroid Follicular Carcinoma patients ( $n_3=25$ ), the fourth group included Thyroid Nodular Hyperplasia patients ( $n_4=140$ ), and the fifth group was the control group of healthy individuals ( $n_5=120$ ). There was no statistically significant difference among the groups based on age. In terms of sex, there was a dominance of the female participants, but the difference was not statistically significant. The demographic data of the participants are shown in Table 1.

Table 1. Demographic data of the study

	Sex		Age	p
	Male n(%)	Female n(%)	Mean±Std.Deviation	
Thyroid Papillary Microcarcinoma Group (n1)	25 14.6%	147 85.4%	45.9477±12.74320	P=0.531  Chi-Squared= 3.163
Thyroid Papillary carcinoma group (n2)	9 7.7%	108 92.3%	45.0948±12.81642	
Thyroid Follicular carcinoma group (n3)	2 8%	23 92%	44.5600±14.30058	
Thyroid Nodular Hyperplasia group (n4)	41 46.7%	99 53.3%	46.1857±14.82783	
Control group (n5)	56 46.7%	64 53.3%	51.4417±20.49792	

$p < 0.05$ \*\* was considered statistically significant

Table 2. Hematological parameters and platelet indices

Hematological Parameters and Platelet Indices	GROUP	Thyroid Papillary Microcarcinoma Group n1=172	Thyroid Papillary Carcinoma Group n2=117	Thyroid Follicular Carcinoma Group n3=25	Thyroid Nodular Hyperplasia group n4=140	Control Group n5=120	Test Values
MPV (Mean Platelet Volume)	Mean±Std. Deviation	9.9890±1.41741	10.1034±1.22197	10.0560±1.55163	10.3029±0.95510	10.4925±1.05314	Chi-Squared =6.446 p=0.168
PDW (Platelet Distribution Width)	Mean±Std. Deviation	13.3657±2.68836	13.0816±2.32900	13.3840±2.98617	12.2800±1.98857	12.5150±2.49953	Chi-squared=18.071 p=0.001**
PLT/MPV	Mean±Std. Deviation	27.9279±9.06891	28.5525±8.51941	29.5777±9.87016	26.8790±7.64193	26.3567±6.84992	Chi-squared=6.624 p=0.157
NLR (Neutrophil-Lymphocyte Ratio)	Mean± Std. Deviation	1.8613±0.82859	1.8616±0.85034	2.1175±0.76613	1.9699±2.12569	1.9689±1.54979	Chi-squared=5.013 p=0.286
PLR (Platelet-Lymphocyte Ratio)	Mean±Std. Deviation	119.9556±44.00749	120.5106±38.01853	136.5148±47.20787	116.1049±50.70438	119.7490±45.15337	Chi-squared=7.936 p=0.094

p&lt;0.05\*\* was considered statistically significant

In our study, there was no significant difference among the groups in terms of their MPV, NLR and other parameters (PLR, PLT/MPV). There was a significant difference between the patient groups and the control group in terms of the PDW values (Table 2).

Considering the MPV values among the groups in our study, these values were low in the differentiated thyroid cancer groups, minimally low in the thyroid nodular hyperplasia group and maximum in the control group. However, the differences were not statistically significant ( $p=0.168$ ) (Table 2).

In our study, the NLR values were low in the differentiated papillary thyroid cancer cases, minimal and very close to the control group in the thyroid nodular hyperplasia cases and the highest in the follicular thyroid carcinoma cases. However, the differences were not statistically significant ( $p=0.286$ ) (Table 2).

In the study, the PLR values were high in the differentiated thyroid cancer cases and low in the thyroid nodular hyperplasia cases. However, the differences were not statistically significant ( $p=0.094$ ) (Table 2).

In terms of the PDW values in our study, there was a significant difference between the papillary microcarcinoma group ( $n_1$ ) and the control group ( $n_5$ ). The mean PDW value was  $13.3657 \pm 2.68836$  in the papillary microcarcinoma group and  $12.5150 \pm 2.49953$  in the control group ( $p=0.02$ ). There was no significant difference in terms of the PDW values between the papillary microcarcinoma group ( $n_1$ ) and the papillary carcinoma group ( $n_2$ ) ( $p=0.66$ ). The mean PDW value was  $13.3657 \pm 2.68836$  in the papillary microcarcinoma group and  $12.2800 \pm 1.98857$  in the thyroid nodular hyperplasia group. There was a significant difference in terms of the PDW values between the papillary microcarcinoma group ( $n_2$ ) and the thyroid nodular hyperplasia group ( $n_4$ ) ( $p=0.001$ ). There was no significant difference in terms of the PDW values between the papillary microcarcinoma group ( $n_1$ ) and the follicular thyroid cancer group ( $n_3$ ) ( $p=0.873$ ). The mean PDW value was calculated as  $12.5150 \pm 2.49953$  in the control group and  $13.0816 \pm 2.32900$  in the papillary cancer group. There was a significant difference between the control group and the papillary carcinoma group ( $n_2$ ) in terms of the PDW values ( $p=0.014$ ). There was no significant difference in terms of the PDW values between the control group ( $n_5$ ) and the thyroid nodular hyperplasia group ( $n_4$ ) ( $p=0.96$ ). There was also no significant difference in terms of the PDW values between the control group ( $n_5$ ) and the follicular thyroid cancer group ( $n_3$ ) ( $p=0.157$ ). The mean PDW value was calculated as  $13.0816 \pm 2.32900$  in the papillary carcinoma group and  $12.2800 \pm 1.98857$  in the thyroid nodular hyperplasia group. There was a significant difference in terms of the PDW values between the papillary carcinoma group ( $n_2$ ) and the thyroid nodular hyperplasia group ( $n_4$ ) ( $p=0.006$ ). No significant difference could be found in terms of the PDW values between the papillary carcinoma group ( $n_2$ ) and the follicular cancer group ( $n_3$ ) ( $p=0.985$ ). There was also no difference in

terms of the PDW values between the thyroid nodular hyperplasia group ( $n_4$ ) and the follicular cancer group ( $n_3$ ) ( $p=0.193$ ).

## DISCUSSION

The thyroid gland histologically consists of two main types of parenchymal cells as follicular cells and parafollicular cells. Most thyroid masses develop from follicular cells. While most masses are in a benign character, they are in the form of a part of solitary or multinodular goiter. On the other hand, considering risk factors, 7-15% of these masses show a malignant character (1,2,8,9,13). While differentiated thyroid carcinomas (papillary and follicular) develop from follicular cells, mainly medullary thyroid cancer develops from parafollicular cells. Differentiated thyroid cancers constitute 90-95% of thyroid malignancies (1,2,5,8,9,13). In general, the 5-year survival rate of differentiated thyroid cancers is >90%-95% as reported in various publications (8,13). Among thyroid cancers, 85% are PTC, and 12% are Follicular Thyroid Carcinoma (FTC) (13). In the last decades, the increase in especially the incidence of thyroid cancer has been determined as >200%, and most of this increase was in papillary thyroid cancer (1,2,7,8). In examinations, the diagnosis of <1 cm papillary carcinoma has increased by more than 50% in the last 3 decades (9). In general, the 5-year survival rate in differentiated thyroid cancers is > 95%, and the 1-year survival rate is around 98% (1,2,8,9,13).

Thyroid cancers have a broad spectrum from silent tumors with low mortality rates to aggressive malignant tumors like anaplastic thyroid cancers. This is why making a preoperative diagnosis becomes crucially important in terms of planning an appropriate treatment. Physical examination, family history, ultrasonography and fine needle aspiration biopsy are current and indispensable diagnostic tools. In physical examination and family history, especially the history of exposure to radiation becomes prominent (1,2,8,9,13). Although ultrasonography provides us with clues about the nature of the mass, fine needle aspiration cytology has a key role. However, depending on the centers where it is performed, fine needle aspiration cytology provides information at the rate of 70-97% (4,6,8). In the 2015 update of the ATA guidelines, if there are no high and/or moderate risk factors in USG, FNA is not recommended for thyroid nodules 1 cm or smaller than 1.5 cm (1,13). Fine needle aspiration biopsy results are categorized according to the BETHESDA system (1,2,5,8,13). Especially uncertain definitions in fine needle aspiration cytology make the management of patients even more difficult.

After the relationship between inflammation and cancer had been mentioned by Rudolf Virchow, studies on this topic have intensified. The relationship between tumor cells and stroma provides information about the onset, progression and even prognosis of the disease (14). At the stages of onset and development, tumors firstly draw inflammatory cells towards the microenvironment. They control the activities of other cells through these

cells for tumor growth. They achieve this control over various mediators secreted from cell groups such as lymphocytes, neutrophils, monocytes and macrophages. In this context, the focus has been especially on studies regarding the platelet indices, neutrophil and lymphocyte values. It has been reported that the role of neutrophils takes place through neutrophil extracellular traps (NETs) in the pathophysiology of tumors and cancer (15,16). NETs are extracellular DNA clusters related to cytotoxic enzymes that are produced by neutrophils to catch and eliminate microorganisms (16). On the one hand, the precise role of neutrophils in tumor microenvironments is still debated, while on the other hand, tumor-associated neutrophils (TANs) appear to contribute the progression, angiogenesis and immunity tolerance of tumors. Additionally, TAN is stimulated to release proteases in tumor microenvironments that make invasion and nodal metastasis easier (17). All these changes in the immune response lead to an increase in the neutrophil counts, and therefore, NLR. Increased NLR reported in various malignancies in the medical literature supports the aforementioned pathophysiological mechanisms (10).

Lymphocytes are a significant component of the immune system, and with their antitumor property, they play a main role in the pathophysiology of cancer. Lymphocyte dominance provides us with information that the prognosis will be better (18). In contrast, in tumor pathophysiology, lymphopenia is accompanied by poor prognosis (19). Wee et al. reported that lymphopenia is strongly related to increased serum IL-6 levels and the TNF- $\alpha$  receptor and reflects cancer-related immunosuppression (20). In our study, although the NLR value was found high in the differentiated thyroid cancer patient groups, the difference was not statistically significant. The NLR values increased in the follicular thyroid cancers, but they were found to be lower in comparison to the control group in other differentiated thyroid cancers. It has been suggested in the literature that NLR can be used in evaluating response to treatment (21), staging, and treatment planning (22). On the contrary, it has been argued that NLR is insufficient in distinguishing benign and malignant thyroid diseases, so it is not suitable for use as a predictive value (23-25). In our study, it was observed that the NLR levels increased in the differentiated thyroid cancer cases, but they were reduced/close to normal values in papillary/micropapillary carcinomas. It was seen that our results were compatible with a part of results reported in the literature. In this context, considering the lymphovascular invasion/metastasis potential of follicular thyroid cancers, it was thought that they could lead to a higher systemic immune response.

Proinflammatory factors, chemokines, growth factors and platelets have a significant role that may cause cancer development on the basis of inflammation (26,27). Platelet (PLT) count, platelet distribution width (PDW) and mean platelet volume (MPV) are known as the platelet indices. Their low costs and high repeatability rates increase the usability of PLT and the platelet indices

(27). Platelets facilitate production and secretion of the vascular endothelial growth factor (VEGF) that plays a role in tumor angiogenesis and inflammation (28). Larger platelets are more active than smaller ones, and MPV shows platelet function. Considering the MPV values in our study, the MPV values in the differentiated thyroid cancer cases were found to be lower in comparison to the control group. This situation may have been related to the faster metabolism and rapidly changing platelet pool in the pathophysiology of cancer. Along with those who stated that MPV is insufficient in distinguishing thyroid benign and malignant masses in the literature (24,27,29), some have argued that it can be used as an inexpensive and easily obtainable biomarker to differentiate thyroid benign and malignant masses (26,30).

The platelet distribution width is the standard deviation of the log-converted data of platelets, and higher levels show that abnormally large and small platelets are in circulation. In comparison to MPV, PDW is a more reliable marker in predicting the hypo-productive or hyper-destructive etiology of thrombocytopenia (31). In our study, the PDW values in the differentiated thyroid cancer cases were significantly higher than those in the control group. It was considered that this situation was a statistical reflection of the reduced MPV levels and fast-changing platelet pool. Contrary to the authors in the literature that PDW values are low and significant in thyroid differentiated cancers (24,27,29), some authors find the PDW value high and significant in differentiated thyroid cancers (30). Based on lymphocytes, the platelet-lymphocyte ratio (PLR) was studied to be used as an inflammatory marker (32). In our study, there was no significant difference among the groups in terms of the PLR values. Kutlutürk et al. could not find a significant difference in PLR values between the hormonal phases of papillary thyroid carcinoma (32). Ari et al. found PLR levels to be high in thyroid carcinomas and inflammatory thyroid events, but they stated that these levels were not significant in distinguishing thyroid carcinoma and inflammation (23). Yıldız et al. While detecting significantly higher PLR values in patients with papillary thyroid carcinoma compared to patients with nodular goiter (29), Machairas et al. low, but did not detect any significant difference (25).

## CONCLUSION

Our study may be criticized due to its retrospective design. It included the analysis of differentiated thyroid cancers and lesions for a 10-year period. When the results of our study are compared to the literature:

- MPV values are affected by many factors, and there are conflicting results in the literature. Therefore, it is not suitable to use MPV values in the fields of diagnosis and follow-up.
- PDW values were found to be significantly higher among the patient groups in our study. However, as they reflect the existing platelet pool volumetrically, one needs to be very careful while assessing their results. PDW values are

a more standardized form of MPV values, and they are also affected by factors that affect MPV.

•NLR values were found high in some differentiated thyroid cancers in our study. This result was partly compatible with the literature. NLR levels are a useful marker in terms of assessing diagnosis and/or treatment especially after the values they create a systemic response in the pathophysiology of cancer.

•In the current literature, it is seen that NLR levels are useful parameters that reflect systemic immune response as they reflect lymphocyte and neutrophil values that play a role in the pathophysiology of cancer.

*Acknowledgements: For his contribution during data collection, thank you to Dr. Emrah Gunduz, Dr. Hatice Celik, and Dr. Muhammed Jurat*

*Conflict of Interest: The authors declare that they have no competing interest.*

*Financial Disclosure: There are no financial supports.*

*Ethical Approval: Approval for the study was obtained from the Scientific Research and Publication Ethics Committee of Inonu University (Decision No: 2020/650).*

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