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Neutrophil to iymphocyte ratio: Does it really differentiate between papillary thyroid carcinomas and multinodular goiter

Nötrofil lenfosit oranı: Papiller tiroit kanserini multinodüler guatrdan gerçekten ayırt eder mi?

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ABSTRACT

Aim: The aim of this study is to reveal the value of preoperative neutrophil lymphocyte ratio in differential diagnosis between papillary thyroid carcinoma, papillary thyroid microcarcinoma and benign multinodular goiter.

Materials and methods: Patients with papillary thyroid carcinoma, papillary thyroid microcarcinoma, and multinodular goiter whose histopathological diagnosis was confirmed by postoperative pathology reports were included in the study.

Results: The TSH levels were statistically significantly different among the groups ($p < 0.001$). The intergroup comparison revealed that the TSH levels were significantly lower in the multinodular goiter group compared to the papillary thyroid carcinoma and papillary thyroid microcarcinoma groups ($p < 0.001$, p0.001). The mean neutrophil count was 4.98 ± 1.19 in the papillary thyroid carcinoma group, 4.68 ± 1.33 in the papillary thyroid microcarcinoma group, and 4.59 ± 1.40 in the multinodular goiter group. The neutrophil counts of the groups were found to be significantly different ($p = 0.013$). The papillary thyroid carcinoma group had a significantly higher neutrophil count than the multinodular goiter group. The mean Neutrophil lymphocyte ratio value was 2.20 ± 0.71 in the papillary thyroid carcinoma group and 2.02 ± 0.92 in the multinodular goiter group. Neutrophil lymphocyte ratio values were significantly higher in the the papillary thyroid carcinoma group ($p = 0.006$).

Conclucion: We believe that increased neutrophil lymphocyte ratio may be an indicator of underlying malignant disease in patients with thyroid nodules in the preoperative period.

Keywords: Neutrophil lymphocyte ratio, papillary thyroid carcinoma, multinodular goiter.

ÖZ

Amaç: *Bu çalışmanın amacı, preoperatif nötrofil lenfosit oranının papiller tiroit karsinomu, papiller tiroit mikrokarsinomu ve benign multinodüler guatr arasında ayırıcı tanıdaki değerini ortaya koymaktır.*

Metod: *Çalışmaya, total tiroidektomi uygulanan ve histopatolojik tanıları postoperatif patoloji raporları ile doğrulanan papiller tiroit karsinomu, papiller tiroit mikrokarsinomu ve multinodüler guatr hastaları dahil edildi.*

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Bulgular: *Ortalama TSH düzeyi papiller tiroit karsinomu grubunda 1.85 ± 1.18 mIU / L, papiller tiroit mikrokarsinomu grubunda 1.78 ± 1.04 mIU / L ve multinodüler guatr grubunda 1.15 ± 0.91 mIU / L idi. TSH düzeyleri gruplar arasında istatistiksel olarak anlamlı farklıydı (p <0,001). Gruplar arası karşılaştırma, multinodüler guatr grubunda TSH seviyelerinin papiller tiroit karsinomu ve papiller tiroit mikrokarsinomu gruplarına kıyasla önemli ölçüde daha düşük olduğunu ortaya çıkardı (p <0.001, p0.001). Ortalama nötrofil sayısı papiller tiroit karsinomu grubunda 4,98 ± 1,19, papiller tiroit mikrokarsinomu grubunda 4,68 ± 1,33 ve multinodüler guatr grubunda 4,59 ± 1,40 idi. Grupların nötrofil sayıları anlamlı olarak farklı bulundu (p = 0,013). Papiller tiroit karsinomu grubu, multinodüler guatr grubuna göre önemli ölçüde daha yüksek nötrofil sayısına sahipti Ortalama nötrofil lenfosit oranı, papiller tiroit karsinomu grubunda 2.20 ± 0.71 ve multinodüler guatr grubunda 2.02 ± 0.92 idi. Nötrofil lenfosit oranı papiller tiroit karsinomu grubunda anlamlı olarak yüksekti (p = 0,006).*

Sonuç: *Ameliyat öncesi dönemde tiroit nodülü olan hastalarda nötrofil lenfosit oranı artışının altta yatan kötü huylu hastalığın bir göstergesi olabileceğine inanıyoruz.*

Anahtar Sözcükler: *Nötrofil lenfosit oranı, papiller tiroit karsinomu, multinodüler guatr.*

INTRODUCTION

Thyroid nodules are a very common condition detected in at least 4% of the population by physical examination and in more than 50% of the population by ultrasound in non-iodine-deficient countries (1, 2). While the overall prevalence of thyroid nodules is increasing, only 5 to 10% of these nodules are malignant (3). This brings forth the requirement to assess thyroid nodules in terms of malignancy (2).

Papillary thyroid carcinomas (PTC) account for 1% of all malignancies and 70-80% of all thyroid cancers (4). They are 3 times more common in women. Age is an important prognostic factor, and according to the TNM staging system, the cut-off age is 45 years (5). Papillary thyroid microcarcinomas (PTMC) are defined as thyroid carcinomas smaller than 1 cm (6) and generally have an excellent prognosis, with reported mortality rates of up to 0.5% (7).

Inflammation plays a critical role in many aspects of cancer, including tumor development, progression, clinical presentation, and prognosis (8). Tumor-host interaction can have a significant impact on patient outcomes. However, this effect is often not taken into consideration in current prognostic systems. It is assumed that the interaction between cancer and inflammation is complex and is based on different physiological processes in cancer tissue such as various inflammatory cells, mediators, and signalling pathways (9).

White blood cells actively participate in the inflammation process. Neutrophils are the important effectors of inflammatory response, and blood neutrophils have long been considered as markers of the systemic inflammatory response (10). For numerous types of cancer, lymphocytopenia indicates a general state of immune deficiency, and suppressed immune function negatively affects survival. Recently, neutrophil-lymphocyte ratio (NLR) has emerged as a simple and valid marker of the systemic inflammatory response (11). It has been demonstrated that hematological components of the systemic inflammatory response, especially the neutrophil-lymphocyte ratio (NLR), have a prognostic value in various cancers (12). Elevated NLR has been shown to be an independent predictive factor for poor cancer prognosis (13). Similar to neutrophils and leukocytes, the angiogenic, metastatic and proteolytic activities of platelets in inflammation and their metabolic role in cancer pathogenesis are unquestionable (14). In the literature, elevated platelet levels are associated with an increased risk of recurrence and metastasis risk in advanced cancers, and various tumours (15). Moreover, the thyroid stimulating hormone (TSH) is a growth factor for thyroid cancer, and the reduction of serum TSH levels with exogenous thyroid hormone administration is closely associated with reduced recurrence and mortality in patients with thyroid cancer (16).

Thyroid cancer is closely associated with inflammation (9). Seretis et al. first reported that preoperative NLR was significantly increased in patients with papillary thyroid microcarcinoma or thyroid cancer (17). However, Liu et al. and Kim et al. found that there was no difference in NLR values among patients with benign or malignant thyroid nodules in the general population (18-19).

The aim of this study was to evaluate the potential relationship in PTC, PTMC, and benign multinodular goiter (MNG) patients in terms of preoperative NLR values.

MATERIALS AND METHODS

The study included papillary thyroid carcinoma (PTC), papillary thyroid microcarcinoma (PTMC), or benign multinodular goiter (MNG) patients aged > 18 years who underwent total thyroidectomy between January 2015 and May 2020 and whose histopathological diagnoses were confirmed by evaluating the postoperative pathology reports. This study is retrospective, and it was granted ethical approval by the local ethics committee and all participants gave signed informed consent form. Ethical approval number: KAEK/Date:24.06.2020 Decision number: 103. University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey. The exclusion criteria were as follows: having non-papillary thyroid carcinomas, admission for recurrence, having known hematological disorders, history of malignancy, active infection, chronic drug use (steroids, etc.), having diabetes mellitus or other chronic inflammatory diseases such as rheumatoid arthritis, malignancy, or pregnancy, and having a white blood cell count (reference range 4–10 × 10^9/L) or thyroid stimulating hormone (TSH) level (reference range 0.27–4.2 mIU/L) out of the reference range. Patients with a history of active and previous thyroiditis determined by physical examination and past imaging findings were also excluded from the study.

The demographic characteristics (age, gender, etc.) of the patients were recorded. TSH values were measured at least 1 week prior to the operation. Evaluating complete blood count test one day before the operation, neutrophil and lymphocyte counts were determined. The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count.

All patients were preoperatively diagnosed by a fine-needle aspiration biopsy (FNAB); however, the definitive diagnosis was determined by the pathological examination of thyroidectomy specimens. Patients whose FNAB results were reported as benign but pathological examination revealed incidental micropapillary carcinoma were excluded from the study. The patients were divided into 3 groups according to the postoperative pathology reports as papillary thyroid carcinoma (PTC) (tumor size > 1 cm), papillary thyroid microcarcinoma (PTMC) (tumor size < 1 cm), and benign multinodular goiter (MNG). Tumor size was determined as the size of the largest lesion measured during the histopathological examination.

Statistical method

The categorical variables were presented as frequencies and percentages and the continuous variables were expressed as means and standard deviation. The normality of the variables was tested with the Shapiro-Wilk test. Non-normally distributed data were analyzed using the Kruskal-Wallis test, and Bonferroni-corrected Dunn's test was used for post hoc analysis. The chi-square test was used to compare categorical variables. The ROC curve was used to determine the optimum cut-off value of the NLR values as well as to establish the point of highest sensitivity and specificity. Data were analyzed using the Statistical Package for the Social Sciences for Windows version 22.0 (SPSS Inc., Chicago, Illinois, USA) and a p-value of < 0.05 was considered statistically significant.

RESULTS

The study included a total of 622 patients. Since 9 patients operated with the pre-diagnosis of multinodular goiter was found to have incidental micropapillary carcinoma, they were excluded from the study, and the final analysis was performed on 613 subjects. The mean age of the subjects was 48.48 ± 12.43 years, and the female-to-male ratio was 508/105. The demographic characteristics and hematological data are presented in (Table-1).

The mean TSH level was 1.85 ± 1.18 in the PTC group, 1.78 ± 1.04 in the PTMC group, and 1.15 ± 0.91 in the MNG group. The TSH levels were significantly different among the groups ($p < 0.001$). The intergroup comparison revealed that the TSH levels were significantly lower in the MNG group compared to the PTC and PTMC groups ($p < 0.001$, p0.001). There was not significant difference between the PTC and PTMC groups in terms of TSH values.

The mean neutrophil count was 4.98 ± 1.19 in the PTC group, 4.68 ± 1.33 in the PTMC group, and 4.59 ± 1.40 in the MNG group. The neutrophil counts of the groups were found to be significantly different ($p = 0.013$). The PTC group

had a significantly higher neutrophil count than the MNG group (p = 0.01).

The NLR values were significantly different among the study groups (p = 0.006) (Table-2). The mean NLR value was 2.20 ± 0.71 in the PTC group and 2.02 ± 0.92 in the MNG group, and the NLR values were significantly higher in the PTC group (p = 0.006). The NLR values were not statistically different between the PTC and PTMC groups, as well as between the PTMC and MNG groups (p = 0.569 and p = 0.521, respectively).

ROC analysis was performed for NLR in predicting malignancy (Figure-1). Accuracy rate and the optimum cut-off value were 0.573 and 1.56, respectively. NLR was found to be 82.1 % sensitive and 33.3 % specific in predicting malignancy (Table-3). The lymphocyte and platelet count of the groups were not statistically different.

Table-1. Demographic characteristics and haematological data of patients.

	PTC (n = 102) Mean ± SD	**PTMC (n = 94) Mean ± SD**	**MNG (n = 417) Mean ± SD**	**p**
Age	44.50 ± 11.06	47.97 ± 13.28	49.57 ± 12.37	**0.001**
Gender				
Female [n (%)]	84 (82.4%)	83 (88.3%)	341 (81.8%)	
Male [n (%)]	18 (17.6%)	11 (11.7%)	76 (18.2%)	0.313
TSH (mIU/L)	1.85 ± 1.18	1.78 ± 1.04	1.15 ± 0.91	**< 0.001**
Neutrophil (10^3/µL)	4.98 ± 1.19	4.68 ± 1.33	4.59 ± 1.40	**0.013**
Lymphocytes (10^3/µL)	2.38 ± 0.63	2.39 ± 0.87	2.44 ± 0.70	0.354
Platelets (10^3/µL)	289.73 ± 58.39	271.35 ± 56.91	280.72 ± 64.94	0.066
NLR	2.20 ± 0.71	2.17 ± 0.96	2.02 ± 0.92	**0.006**

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Table-2. Mean NLR Levels.

	PTC (n = 102) Mean ± SD	**PTMC (n = 94) Mean ± SD**	**MNG (n = 417) Mean ± SD**	**p**
NLR value	2.20 ± 0.71 [a,b]	2.02 ± 0.92 [a,c]	2.17±0.96 [b,c]	**0.006**

[a] p=0,569 group PTC vs. group PTMC

[b] p=0,006 group PTC vs. group MNG

[c] p=0,521 group PTMC vs. group MNG

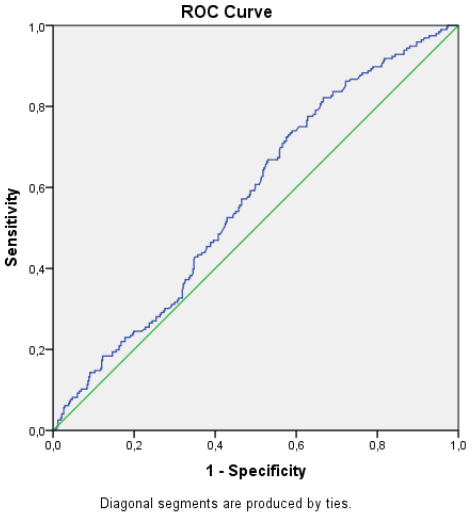

Figure-1. Roc analysis.

DISCUSSION

Age is an important prognostic factor for PTC and is used for PTC staging systems (5, 18). Seretis et al. reported that elderly PTC patients had significantly higher NLR values (17). Although the mean age was significantly higher in the MNG group in our study, we believe that the increased NLR values of the PTC group give more reliable results, regardless of age.

Inflammation plays a critical role in many aspects of cancer, including tumor development, progression, clinical presentation, and prognosis (8). It is evident that carcinogenesis itself increases chronic inflammation, which in turn allows inflammatory markers to be a possible indicator of survival and cancer-related complications (20). Cancers have been shown to

secrete myeloid growth factors (such as granulocyte colony-stimulating factor, IL-1, IL-6, and tumor necrosis factor-alpha), which may result in tumor-related leucocytosis and neutrophilia (21). Neutrophilia is believed to occur due to the paraneoplastic activity of the primary tumor or its production of granulocyte colony-stimulating factor (22). There is strong evidence suggesting that the tumor microenvironment contains inflammatory cells such as macrophages, neutrophils, lymphocytes, and dendritic cells, which play a role in the development of tumours (23). Contrary to studies suggesting that the increased neutrophil count is associated with a negative prognosis (24), Liu J. et al did not find a significant difference between PTC and nodular goiter groups in terms of neutrophil counts (18). Our results indicate that neutrophil counts were significantly higher in the PTC group compared to the MNG group.

Romano F et al found that patients with pancreatic ductal adenocarcinoma had more significant lymphocytopenia before and after surgery compared to patients with gastric and colorectal carcinoma, and although lymphocytopenia has often been associated with immune suppression in cancer patients, they concluded that the degree of immunosuppression may vary between different tumour types (25). Neutrophilia and/or lymphopenia are considered the indicators of increased NLR and inflammation. Systemic inflammation has been associated with neutrophilia and lymphocytopenia, which inevitably lead to increased NLR values (2). It has been demonstrated that hematological components of the systemic inflammatory response, especially the neutrophil-lymphocyte ratio (NLR), have a prognostic value in various cancers (11). In our study, there was no significant difference between the lymphocyte numbers of the study groups; yet, the neutrophil count was significantly higher in the PTC group compared to the MNG group, and it was considered that this increased NLR might be due to neutrophilia.

An increased NLR reflects an increased reaction associated with increased tumor-specific immunity. Also, it is obvious that NLR is an affordable and inexpensive prognostic biomarker that can be used to clinically assess human cancers. In the literaturei it has been reported that NLR can be used to predict survival in cancer patients (12). In a meta-analysis including 40559 patients with various solid tumors, Templeton et al demonstrated that NLR was correlated with poor overall survival (26). There are many publications reporting that NLR is associated with thyroid malignancies, as well as other types of cancer (2, 17-19, 27, 28). In their pilot study, Seretis C et al. retrospectively investigated the association between NLR and papillary thyroid carcinoma and found that preoperative NLR was significantly higher in patients with PTMC and PTC [17]. Similarly, Kocer D et al concluded that NLR may be a potential indicator that may provide an insight to the differentiation between benign and malignant thyroid disorders (27). A study by Gong W et al. showed that high NLR values in patients with papillary tumors were positively correlated with advanced stage disease, size of tumors, lymph node metastasis, and multifocality (28). In contrast, Liu J et al. evaluated 843 thyroid patients (including 321 PTC patients, 83 thyroid adenoma patients, and 439 nodular goiter patients) and did not find a significant difference between the NLR values of the three groups (18). In their study on 1066 women, Kim SM et al. found that there was no difference between the NLR findings of patients with benign or malignant thyroid nodules in the general population (19). Although there are different results in the literature, the PTC patients in our study were found to have significantly higher NLR values.

Liu CL et al evaluated 159 patients with malignant and 318 patients with benign thyroid nodules and reported that tumor size was correlated with NLR in patients with thyroid cancer (29). In contrast, we did not find a statistical difference between the PTC and PTMC groups in our study.

TSH is a growth factor for thyroid cancer, and the reduction of serum TSH levels with exogenous thyroid hormone administration is associated with reduced recurrence and mortality in patients with thyroid cancer (16). Therefore, it is likely that the high prevalence of thyroid malignancy in patients with elevated serum TSH concentrations is due to the trophic effect of TSH on thyroid tissue, which promotes neoplasia and carcinogenesis. Jin J et al. investigated the value of serum thyroid stimulating hormone (TSH) levels in predicting malignancy among 653 patients with nodular thyroid disease and demonstrated that higher serum TSH levels were associated with a higher risk of malignancy in patients with nodular thyroid disease (30). Similarly, Kim D et al reported that

patients with PTC had higher TSH levels than those with benign thyroid nodules (31). In our study, the TSH levels were significantly higher in the PTC and PTMC groups compared to the MNG group; our results suggest that TSH stimulation may play a role in thyroid oncogenesis. Further understanding of the relationship between serum TSH and thyroid cancer can play an important role in describing thyroid cancer pathogenesis.

Although it has been reported that the release of proinflammatory mediators such as IL-1, IL-2, and IL-6 from tumor cells can lead to megakaryocytic thrombosis (32). we did not find a significant difference between the platelet counts of the PTC and PTMC patients.

The limitations of this study include its retrospective design, being a single-center study, and not comparing the NLR values of thyroidectomy patients with those of healthy controls.

CONCLUSION

The primary result of this study is that patients with papillary thyroid carcinoma has higher NLR values than patients with benign nodules. NLR can be used to differentiate between benign thyroid lesions and PTC. It should be kept in mind that NLR alone is not a predictive factor but can provide an opinion. We are of the opinion that increased preoperative NLR in patients with thyroid nodules may be an indicator of underlying malignancy. There is a need for larger prospective clinical studies.

Conflict of interest

We declare that we have no conflict of interest.

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