ORIGINAL ARTICLE

Assessment of inflammatory parameters as predictive markers for malignancy in thyroid nodules: a study on the correlation with Bethesda classification

Evaluación de los parámetros inflamatorios como marcadores predictivos de malignidad en nódulos tiroideos: un estudio sobre su correlación con la clasificación de Bethesda

Mustafa C. Şenoymak[1], Süleyman Baş[2], Murat Yeniçeri[3], Kadem Arslan[2], Erdinç Yaman[2], Hasan H. Çoban[2], Dilek Yavuzer[4], and Alpaslan Tanoğlu[5]*

[1]Department of Endocrinology and Metabolism, University of Health Sciences, Sultan Abdulhamid Han Training and Research Hospital; [2]Department of Internal Medicine, University of Health Sciences, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital; [3]Department of Rheumatology, University of Health Sciences, Bakırkoy Dr. Sadi Konuk Training and Research Hospital; [4]Department of Pathology, University of Health Sciences, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital; [5]Department of Internal Medicine, Bahçeşehir University, Faculty of Medicine Istanbul, Turkey

Abstract

Objective: *The study aimed to assess the predictive significance of inflammatory parameters as potential markers for malignancy in individuals with thyroid nodules.* **Method:** *Nine hundred and ninety-one patients with thyroid nodules who had undergone thyroid fine-needle aspiration biopsy were included and classified according to the Bethesda system. Neutrophil lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) values obtained from hemogram parameters were determined for each patient. The study examined the correlation between the Bethesda classification and NLR/SII levels. In addition, a comparison was made between the inflammatory parameters of the benign and malignant Bethesda groups.* **Results:** *Five hundred and seventy-three patients were classified as Bethesda 2 (benign), 34 as Bethesda 6 (malignant). A correlation was observed between the Bethesda classification and NLR and SII levels (r: 0.230, $p < 0.001$; r: 0.207 $p < 0.001$, respectively). NLR and SII values were significantly higher in the malignant group ($p < 0.001$). The cutoff value for SII in predicting benign and malignant thyroid nodules was 489.86 × 10^3/mm^3 with a sensitivity of 88.2% and a specificity of 63.7%. The cutoff value for NLR for the same prediction was 2.06 with a sensitivity of 82.4% and a specificity of 83.4%.* **Conclusions:** *The findings of this study indicate that SII and NLR may be valuable prognostic markers for predicting the malignancy of thyroid nodules.*

Keywords:*Thyroid nodüle. Thyroid cancer. Fine needle aspiration biopsy. Systemic immune-inflammation index.*

Resumen

Objetivo: *Evaluar parámetros inflamatorios como posibles marcadores de malignidad en individuos con nódulos tiroideos.* **Método:** *Se incluyeron 991 pacientes con nódulos tiroideos que se sometieron a biopsia por aspiración con aguja fina y se clasificaron según el sistema de Bethesda. Se determinaron los valores de la relación neutrófilo-linfocito (NLR) y el índice de inflamación inmunitaria sistémica (SII). El estudio exploró la correlación entre la clasificación de Bethesda y los valores de NLR/SII, y comparó los parámetros inflamatorios de los grupos benignos y malignos de Bethesda.* **Resultados:** *Se clasificaron 573 pacientes como Bethesda 2 (benigno) y 34 como Bethesda 6 (maligno). Se observó una correlación entre la*

***Correspondence:**
Mustafa C. Şenoymak
E-mail: senoymak@gmail.com

Date of reception: 20-07-2023
Date of acceptance: 23-08-2023
DOI: 10.24875/CIRU.23000370

Cir Cir. 2024;92(3):347-353
Contents available at PubMed
www.cirugiaycirujanos.com

clasificación de Bethesda y los valores de NLR y SII (r: 0.230; r: 0.207). Los valores de NLR y SII fueron mayores en el grupo maligno (p < 0.001). El valor de corte para SII en la predicción de nódulos tiroideos benignos y malignos fue de 489.86 × 10³/mm³, con una sensibilidad del 88.2% y una especificidad del 63.7%; para NLR fue de 2.06, con una sensibilidad del 82.4% y una especificidad del 83.4%. **Conclusiones:** *El SII y el NLR pueden ser valiosos marcadores pronósticos para predecir la malignidad de los nódulos tiroideos.*

Palabras clave: *Nódulo tiroideo. Cáncer de tiroides. Biopsia por aspiración con aguja fina. Índice de inflamación inmunitaria sistémica.*

Introduction

Thyroid nodules are a frequently encountered clinical finding, with prevalence estimates of up to 60% in certain populations[1]. Despite the majority of nodules being benign, a significant proportion of them, ranging from 5% to 15%, is malignant[2]. The most accurate diagnostic procedure for evaluating the malignancy of thyroid nodules is performing a thyroid fine-needle aspiration biopsy (FNAB) on nodules that are considered to be at high risk[3]. The Bethesda System, which categorizes thyroid nodules into six categories based on the cytological findings of FNAB, is the standard reporting system used to classify the results of thyroid FNAB[4]. However, there is still significant overlap between benign and malignant nodules, leading to the need for additional practical and non-invasive markers to improve diagnostic accuracy and prevent unnecessary surgeries.

In recent years, the hematological parameters have gained attention as potential markers to enhance the diagnosis and prognosis of various inflammatory conditions, including cancers[5-12]. Systemic immune-inflammation index (SII) is a composite index based on the absolute counts of neutrophils, lymphocytes, and platelets and has been found to be associated with the prognosis of several cancers. In a previous study, it was observed that the SII of patients with differentiated thyroid cancer was significantly higher when compared to a control group (6). Similarly, in a recent study, it has been reported that elevated neutrophil–lymphocyte ratio (NLR) values in patients with nodules can predict malignancy[11]. However, there is insufficient and conflicting data about predicting value of NLR and SII in malign thyroid nodules.

The aim of this study was to assess the predictive significance of inflammatory parameters, specifically NLR and SII, as potential markers for malignancy in individuals with thyroid nodules. By evaluating the correlation between inflammatory parameters and the Bethesda classification, this investigation aimed to contribute to the existing knowledge and potentially enhance the diagnostic accuracy and risk assessment of thyroid nodules.

Methods

This study was conducted in compliance with the principles of the Helsinki Declaration and with the approval of Sancaktepe Sehit Prof Dr Ilhan Varank Training and Research Hospital Ethics Committee, with a number of 2022/137.

Patients included in this study were 18 years of age or older who underwent thyroid FNAB at Sancaktepe Sehit Professor Doctor Ilhan Varank Training and Research Hospital between March 2018 and October 2022. Only patients with available data, including demographic information, laboratory parameters, and cytological results were included in this study. Exclusion criteria for this study were pre-defined to include patients with unavailable medical data, active infection, chronic infection (tuberculosis, hepatitis B, C etc.), acquired immunodeficiency syndrome, non-thyroid malignancy, autoimmune rheumatologic or hematologic disease, advanced liver or kidney failure, dysregulated diabetes mellitus, systemic infiltrative diseases (sarcoidiosis, hemochromatosis etc.) history of head-and-neck radiation, thyroid surgery or primary thyroid disease, pregnancy, or the use of medications that could potentially alter complete blood count parameters.

An automated hematology analyzer, Mindray-BC6800, was used to measure the hemogram parameters. The cytology results and laboratory data of eligible patients were retrieved from the medical information system. NLR was calculated with the formules: neutrophil count/lymphocyte count (9). SII was calculated with the formula: neutrophil count X platelet count/lymphocyte count (7). Patients were

grouped according to their Bethesda classification of thyroid nodules, and SII, NLR, and other parameters were evaluated for each group[4]. This classification reports the results as non-diagnostic (Bethesda Category 1), benign (Bethesda Category 2), atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda Category 3), follicular neoplasm or suspicious for a follicular neoplasm (Bethesda Category 4), suspicious for malignancy (Bethesda Category 5) or malignant (Bethesda Category 6).

The parameters of patients with benign cytology (Bethesda 2) and malignant cytology (Bethesda 6) were compared. In addition, the correlation between inflammatory parameters and the Bethesda classification was examined.

Statistical analysis

IBM Corporation Statistical Package for the Social Sciences, version 23.0, was used for all data analyses. The normal distribution of the data between groups was assessed using the Kolmogorov–Smirnov test. Descriptive statistics, including percentages and either mean ± standard deviation or median interquartile range, were used to summarize the data based on the normality of the distribution. The statistical analysis involved comparing the distributions of continuous variables between two independent groups using the Mann–Whitney U test, while the Chi-square test was used for qualitative data. Spearman correlation analysis was used to evaluate the relationships between quantitative variables. The receiver operating characteristic (ROC) curve was used to evaluate the predictive performance of neutrophil, lymphocyte, and SII for malignant thyroid nodules and to determine their optimal cutoff values, sensitivity, and specificity. The statistical significance level was established at a $p < 0.05$.

Results

The total number of patients enrolled in the study was 991. Seven hundred and ninety-six of them were female and 195 were male. The median age of the patients was 53 years. Among the 991 patients, the distribution according to the Bethesda classification was as follows: 126 (12.7%) were classified as Bethesda 1, 573 (57.8%) as Bethesda 2, 202 (20.4%) as Bethesda 3, 28 (2.8%) as Bethesda 4, 28 (2.8%) as Bethesda 5, and 34 (3.4%) as Bethesda 6. The distribution of patients according to FNAB cytology results and inflammatory parameters is presented in table 1. In a retrospective analysis of patients, it was found that all individuals classified as Bethesda 5 and 6 underwent thyroidectomy. Among the 28 patients with Bethesda 5, 24 (85%) had a histopathological diagnosis of differentiated thyroid carcinoma, and similarly, all Bethesda 6 patients had a histopathological diagnosis of differentiated thyroid carcinoma.

The details of the comparison between malignant and benign groups are summarized in table 2. Lymphocyte levels were found to be significantly higher in the benign group compared to the malignant group ($p < 0.001$). Neutrophil, NLR, and SII values were significantly higher in the malignant group compared to the benign group ($p < 0.001$). In addition, the pairwise comparison of the Bethesda groups based on SII and NLR are shown in table 3. Significant differences were observed between 1 and 3, 1 and 5, 1 and 6, 2 and 3, 2 and 5, 3 and 6, and 4 and 6.

The area under the curve (AUC) in the ROC curve drawn for the SII variable of patients with malignant thyroid nodules is 0.822 and its standard error is 0.34. The area under the ROC curve was statistically significant ($p < 0.001$). The cutoff value for SII was found to be $489.86 \times 10^3/mm^3$. The sensitivity of this value is 88.2%, and the specificity is 63.7%. The ROC curve analysis for the NLR variable in patients with malignant thyroid nodules showed an AUC of 0.848 with a standard error of 0.41, indicating statistically significant diagnostic accuracy ($p < 0.001$). The optimal cutoff value for NLR was determined to be 2.06 with a sensitivity of 82.4% and specificity of 83.4%, as demonstrated by figure 1.

A statistically significant positive correlation was identified between the Bethesda classification and the values of NLR and SII, as evidenced by correlation coefficients of 0.230 ($p < 0.001$) and 0.207 ($p < 0.001$), respectively. This association was consistently observed across the range of Bethesda categories. Notably, on excluding cases with non-diagnostic cytology (Bethesda 1), a discernible pattern emerged: a consistent rise in NLR and SII values coincided with an increase in the Bethesda classification. This trend is visually elucidated through figure 2, depicting the correlation of NLR values, and figure 3, illustrating the association of SII values with the Bethesda classification.

Table 1. Inflammatory parameters and cytological results of study participants

Total patients (n = 991%)	NLR	SII	p-value
Bethesda 1 (126, 12.7)	1.86 (1.23-2.55)*	450 (325.41-657.13)*	p1 < 0.001† p2 < 0.001†
Bethesda 2 (573, 57.8)	1.72 (1.43-1.94)*	437.81 (350.87-552.87)*	
Bethesda 3 (202, 20.4)	2.22 (1.56-2.46)‡	561.25 (397.51-704.56)*	
Bethesda 4 (28, 2.8)	2.80 (0.88-2.89)*	576.49 (223.95-773.12)*	
Bethesda 5 (28, 2.8)	3.04 (2.30-3.24)*	746.41 (267.32-881.20)*	
Bethesda 6 (34, 3.4)	3.18 (1.90-3.47)*	665.62 (533.25-921.67)*	

*Median (IQR). †Kruskal–Wallis Test. NLR: neutrophil–lymphocyte ratio; SII: systemic immune-inflammation index; p1: NLR comparison between groups; p2: SII comparison between groups.

Table 2. Demographic characteristics and hemogram parameters of study groups

Parameters	Benign nodule group (n = 573)	Malignant nodules group (n = 34)	p-value
Gender (male/female)	117 (95.1%) / 456 (94.2%)	6 (4.9%) / 28 (5.8%)	0.696*
Age (years)	54 (45-62)†	51.29 ± 16.26‡	0.198§
Leukocyte ($\times10^3/mm^3$)	6.99 (5.97-8.12)†	7.26 ± 1.22‡	0.335§
Neutrophil ($\times10^3/mm^3$)	3.94 (3.33-4.74)†	4.91 ± 1.11‡	< 0.001§¶
Lymphocyte ($\times10^3/mm^3$)	2.35 (1.96-2.74)†	1.77 ± 0.54‡	< 0.001§¶
Platelet ($\times10^3/mm^3$)	259 (222.50-300)†	258.67 ± 50.98‡	0.660§
Hemoglobin (gr/dL)	13.30 (12.40-14.20)†	13.30 ± 1.83‡	0.976§
NLR	1.72 (1.43-1.94)†	3.18 (2.07-3.59)†	< 0.001§¶
SII ($\times10^3/mm^3$)	437.81 (350.46-552.87)†	665.62 (533.25-921.67)†	< 0.001§¶
TSH (mIU/L)	1.37 (0.78-2.28)†	1.00 (0.50-2.18)†	0.118§
Free T4 (ng/dL)	1.12 (1.00-1.29)†	1.08 ± 0.20‡	0.207§
Free T3 (ng/L)	3.06 (2.69-3.37)†	2.88 ± 0.46‡	0.125§

*Chi-square test. †Median (IQR).‡Mean±SD. §Mann–Whitney U test. ²p < 0.05. SII: systemic ımmune-ınflammation ındex; NLR: neutrophil–lymphocyte ratio; TSH: thyroid stimulating hormone.

Discussion

To the best of our knowledge, this study is the first to investigate the correlation between Bethesda classification and inflammatory parameters, making it a pioneering study in this field. In addition, it encompasses one of the largest cohorts of patients with thyroid nodules, allowing for a comprehensive analysis of inflammatory parameters and enhancing the robustness and generalizability of the findings. The inclusion of all patients who underwent FNAB provides substantial and reliable data for evaluating the association between these parameters and thyroid nodules, significantly contributing to the current understanding in the field. Our results showed that SII and NLR values were significantly higher in patients with malignant nodules compared to patients with benign nodules and the ROC analysis revealed that they had moderate discriminatory powers in the diagnosis of malignant thyroid nodules. Furthermore, there was a positive correlation between Bethesda classification and SII and NLR.

The current research on the correlation between SII and thyroid nodules is limited. Our results are in line with earlier studies that have found a connection between increased SII levels and the presence of malignant thyroid nodules. Deng et al. conducted

Table 3. Pairwise comparison of Bethesda groups based on SII and NLR

Bethesda groups	P* (NLO)	P* (SIII)
1 and 2	0.182	0.407
1 and 3	0.005†	**0.003†**
1 and 4	0.561	0.613
1 and 5	**0.033†**	**0.045†**
1 and 6	**<0.001†**	**< 0.001†**
2 and 3	**<0.001†**	**<0.001†**
2 and 4	0.126	0.253
2 and 5	**0.003†**	**0.009†**
2 and 6	**<0.001†**	**< 0.001†**
3 and 4	0.166	0.617
3 and 5	**0.019†**	0.142
3 and 6	**< 0.001†**	**0.001†**
4 and 5	0.088	0.174
4 and 6	**0.009†**	0.021†
5 and 6	**0.029†**	0.572

*Mann–Whitney U test. †Those in bold were statistically significant (p < 0.05). SII: systemic immune- inflammation index; NLR: neutrophil–lymphocyte ratio.

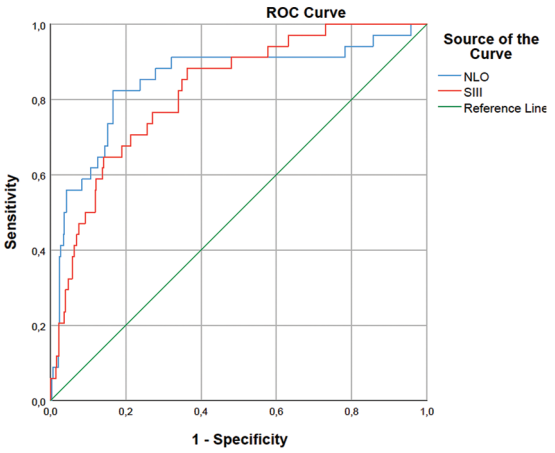

Figure 1. Receiver operating characteristic curve of systemic immune-inflammation index and neutrophil–lymphocyte ratio.

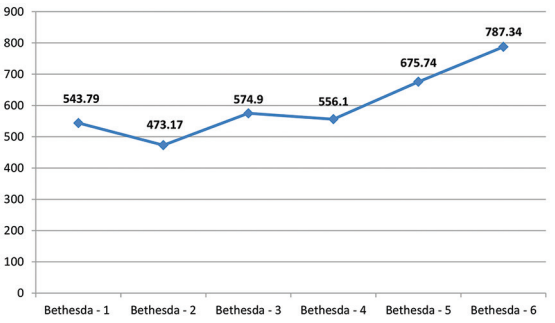

Figure 2. The relationship between Bethesda classification and SII. SII: systemic immune-inflammation index r: 0.207; p < 0.001.

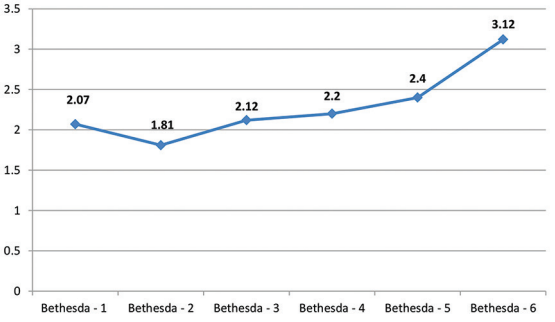

Figure 3: The relationship between Bethesda classification and NLR. NLR: neutrophil–lymphocyte ratio r: 0.230; p < 0.001.

a study on 514 patients classified as TIRADS 3 based on ultrasound evaluation and found that patients with malignant nodules had higher SII values compared to those with benign nodules[13]. In this study, it was found that SII is an independent risk factor for determining malignancy, and a cutoff value of 545.63 × 10^9/L was determined for distinguishing between malignant and benign nodules. In contrast to the previous study, our study included not only patients with TIRADS 3 nodules but all patients who underwent biopsy, resulting in a larger sample size. In another recent study, the SII values of 93 patients with differentiated thyroid carcinoma and 33 control subjects were compared, and the SII values of patients with thyroid cancer were found to be significantly higher[6]. In this study, SII was not found to be associated with histological type, lymphovascular, perineural, or capsule invasion. On the contrary, Zhang et al. found in their study that SII could be an important parameter for determining central lymph node metastasis in differentiated thyroid cancer[8].

The association between NLR and thyroid nodules has been extensively studied. According to a study conducted in Turkey, it has been suggested that preoperative high NLR levels in patients with thyroid nodules could serve as an indicator of possible malignancy[11]. Similarly, in a research by Koçer et al., it was found that NLR values were higher in patients

with thyroid carcinoma compared to those with multinodular goiter. Similar to our study findings, the cutoff value of NLR for distinguishing between malignant and benign nodules was found to be 1.91 with 89% sensitivity and 54.5% specificity in this study[12]. A meta-analysis including nine studies and 3081 patients with differentiated thyroid carcinomas revealed that preoperative NLR is an important biomarker associated with tumor growth, metastasis, and prognosis[10].

The underlying mechanisms linking SII and thyroid malignancy are not fully understood, but conjecture suggests that chronic inflammation might play a role in the initiation and advancement of cancer[14,15]. Inflammation plays a critical role in many pathogenic stages of carcinogenesis, including genomic instability, induction of cell proliferation, suppression of apoptosis, and increase in neovascularization[16]. It has been reported that inflammation is not only a risk factor for tumor formation and development but also that inflammatory cytokines are secreted in tumor tissue[17]. The key cells of inflammation, neutrophils, have been associated with tumor development. Through chemokines and interleukins, neutrophils are recruited and infiltrate the tumor tissue, contributing to tumor proliferation[18]. When the inflammatory cascade is initiated, there is an increase in platelet count and function. Platelets are known to secrete platelet-derived growth factors, which create a favorable microenvironment for tumor development by building extracellular matrix[19]. Lymphocytes play a critical role in fighting tumor cells, especially CD8 T cells, which have cytotoxic effects on malignant cells. Research has established a correlation between cancer incidence and lymphocyte count, with studies indicating that decreased overall survival and progression-free survival are linked to lymphopenia in malignancies[20].

Several limitations should be acknowledged in relation to this study. First, the study focused on a cross-sectional analysis, lacking longitudinal data that would provide insights into the predictive value and stability of the inflammatory parameters over time. Moreover, it was relied on cytological results. Cytology results can occasionally yield false-negative or false-positive outcomes, which could have influenced the accuracy of our findings. In addition, The Bethesda classification system itself is subject to inter-observer and intra-observer variability, which may impact the accuracy of malignancy prediction. Finally, the study primarily focused on a limited set of inflammatory parameters, neglecting other potential markers that could have provided a more comprehensive understanding of their relationship with the Bethesda classification.

Conclusion

Our study demonstrates that SII and NLR can be useful and non-invasive markers in predicting malignancy in thyroid nodules as it provides an easily measurable, inexpensive, and non-invasive method for clinical practice.

Funding

The authors declare no funding was received.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects: The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent: The authors have obtained the approval of the Ethics Committee for the analysis and publication of clinical data obtained routinely. The informed consent of the patients was not required because it was a retrospective observational study.

References

1. Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clin Endocrinol Metab. 2008;22:901-11.
2. Hegedüs L. Clinical practice. The thyroid nodule. N Engl J Med. 2004;351:1764-71.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1-133.
4. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The bethesda system for reporting thyroid cytopathology: a meta-analysis. Acta Cytol. 2012;56:333-9.
5. Ji Y, Wang H. Prognostic prediction of systemic immune-inflammation index for patients with gynecological and breast cancers: a meta-analysis. World J Surg Oncol. 2020;18:197.
6. Kars A, Sahin A, Kılıc K, Sakat MS, Bilen A. Systemic immune inflammation index in differentiated thyroid cancers. Acta Otorhinolaryngol Ital. 2022;42:150-4.
7. Ye Z, Hu T, Wang J, Xiao R, Liao X, Liu M, et al. Systemic immune-inflammation index as a potential biomarker of cardiovascular diseases: a systematic review and meta-analysis. Front Cardiovasc Med. 2022;9:933913.

8. Zhang Z, Xia F, Wang W, Huang Y, Li X. The systemic immune-inflammation index-based model is an effective biomarker on predicting central lymph node metastasis in clinically nodal-negative papillary thyroid carcinoma. Gland Surg. 2021;10:1368-73.
9. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the ımmune system and diseases. Int J Mol Sci. 2022;23:3636.
10. Feng J, Wang Y, Shan G, Gao L. Clinical and prognostic value of neutrophil-lymphocyte ratio for patients with thyroid cancer: a meta-analysis. Medicine. 2020;99:e19686.
11. Sit M, Aktas G, Erkol H, Yaman S, Keyif F, Savli H. Neutrophil to lymphocyte ratio is useful in differentiation of malign and benign thyroid nodules. P R Health Sci J. 2019;38:60-3.
12. Kocer D, Karakukcu C, Karaman H, Gokay F, Bayram F. May the neutrophil/lymphocyte ratio be a predictor in the differentiation of different thyroid disorders? Asian Pac J Cancer Prev. 2015;16:3875-9.
13. Deng Y, Zhang J, Zou G, Li S, Gong Z, Yue G, et al. Peripheral blood ınflammatory markers can predict benign and malignant thyroid nodules. Int J Endocrinol. 2022;2022:2319660.
14. Guarino V, Castellone MD, Avilla E, Melillo RM. Thyroid cancer and inflammation. Mol Cell Endocrinol. 2010;321:94-102.
15. Fugazzola L, Colombo C, Perrino M, Muzza M. Papillary thyroid carcinoma and ınflammation. Front Endocrinol (Lausanne). 2011;2:88.
16. Liotti F, Visciano C, Melillo RM. Inflammation in thyroid oncogenesis. Am J Cancer Res. 2012;2:286-97.
17. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6:149-63.
18. Jaillon S, Ponzetta A, Di Mitri D, Santoni A, Bonecchi R, Mantovani A. Neutrophil diversity and plasticity in tumour progression and therapy. Nat Rev Cancer. 2020;20:485-503.
19. Gkolfinopoulos S, Jones RL, Constantinidou A. The emerging role of platelets in the formation of the micrometastatic niche: current evidence and future perspectives. Front Oncol. 2020;10:374.
20. Ménétrier-Caux C, Ray-Coquard I, Blay JY, Caux C. Lymphopenia in cancer patients and its effects on response to ımmunotherapy: an opportunity for combination with Cytokines? J İmmunother Cancer. 2019;7:85.