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The role of inflammatory parameters in the management of cases with atypia of undetermined significance / follicular lesions of undetermined significance

Önemi belirsiz atipi / önemi belirsiz foliküler lezyon vakalarının yönetiminde inflamatuar parametrelerin rolü

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ABSTRACT

AIM: This study aimed to evaluate the potential of hematologic parameters and markers such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) to predict the risk of malignancy in patients whose biopsy results were classified as Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS).

MATERIAL AND METHOD: A total of 188 patients who underwent thyroidectomy at a General Surgery clinic were included in the study. Hematological parameters, including neutrophil count, platelet count, lymphocyte count, monocyte count, and mean platelet volume (MPV) were collected from the hospital database. NLR, PLR, MLR, SII, and SIRI were calculated. Statistical analyses were performed using SPSS v25.

RESULTS: 38 patient (20.21%) were male and 150 patients (79.79 %) were female. The mean age was 48.6 (range 23-79, standard deviation (SD) ± 12.41years). Histopathological examination of the thyroidectomy specimens revealed benign findings in 102 patients (54.3%) and malignant findings in 86 patients (45.7%). The mean age of the malignant group was 45.6, while that of the benign group was 51.1 (p = 0.02). The median tumor size was 17 mm in the malignant group and 21 mm in the benign group (p =0.042). Mean neutrophil count were 4.29 ± 1.0 × 109/L in the benign group and 4.69 ± 1.9 × 109/L in malignant group, respectively (p = 0.031). NLR values were calculated as 1.89 for the benign group and 1.99 for the malignant group (p = 0.045). SII values were higher in the malignant group, with a median value of 584.11× 109/L in the malignant group, median value were 504.63× 109/L in the benign group (p=0.037).

Multivariate logistic regression analysis revealed that both age (odds ratio (OR) = 0.964; 95% confidence interval (CI)= (0.939 – 0.989); p = 0.05) and neutrophil count (odds ratio (OR) = 1.598; 95% confidence interval (CI)= (1.118 – 2.285); p = 0.01) had a significant impact on the differentiation between benign and malignant thyroid nodules.

CONCLUSION: Age and neutrophil count were identified as independent risk factors for malignant thyroid nodules. Among patients with Bethesda Category III thyroid nodules, those under 59.5 years of age and with a neutrophil count above 4.16 x 10^9/L have an increased risk for thyroid malignancy.

Platelet count, monocyte count, MPV and inflammatory parameters, such as PLR, MLR, and SIRI, were insufficient for detecting malignancy in Bethesda III nodules. In this group, young age, small nodule size, high neutrophil count, NLR, and SII were identified as risk factors for malignancy. The Thyroid Imaging Reporting and Data System (TI-RADS) characteristics of nodules should also be considered in the management of these patients.

Keywords: Bethesda reporting system, Atypia of undetermined significance/ follicular lesions of undetermined significance nodules, Thyroid cancer, biomarker

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ÖZET

AMAÇ: Bu çalışma, biyopsi sonucu Önemi Belirsiz Atipi/Önemi Belirsiz Foliküler Lezyon (ÖBA/ÖBFL) olarak sınıflandırılan hastalarda hematolojik parametreler ve nötrofil-lenfosit oranı (NLO), platelet-lenfosit oranı (PLO), monosit-lenfosit oranı (MLO), sistemik immün-inflamasyon indeksi (Sİİ), sistemik inflamasyon yanıt indeksi (SİYİ) gibi ve belirteçlerin malignite riskini öngörü potansiyelini değerlendirmeyi amaçladı.

GEREÇ VE YÖNTEM: Bir Genel Cerrahi kliniğinde tiroidektomi yapılan toplam 188 hasta çalışmaya dahil edildi. Nötrofil sayısı, trombosit sayısı, lenfosit sayısı, monosit sayısı ve ortalama platelet hacmi (OPH) gibi hematolojik parametreler hastane veri tabanından toplandı. NLO, PLO, MLO, Sİİ ve SİYİ hesaplandı. İstatistiksel analizler SPSS v25 kullanılarak yapıldı.

BULGULAR: 38 hasta (%20,21) erkek ve 150 hasta (%79,79) kadındı. Ortalama yaş 48.6 (dağılım 23-79, SD ± 12,41 yıl) idi. Tiroidektomi örneklerinin histopatolojik incelemesinde 102 hastada (%54,3) benign, 86 hastada (%45,7) malign bulgular saptandı. Malign grubun yaş ortalaması 45,6 iken, benign grubun yaş ortalaması 51,1 idi (p = 0,02). Ortanca tümör boyutu malign grupta 17 mm, benign grupta ise 21 mm idi (p =0,042). Ortalama nötrofil sayısı sırasıyla benign grupta 4,29 ± 1,0 × 109/L ve malign grupta 4,69 ± 1,9 × 109/L idi (p = 0,031). NLO değerleri benign grup için 1.89 ve malign grup için 1,99 olarak hesaplanmıştır (p = 0.045). Sİİ değerleri malign grupta daha yüksek saptanmıştır, malign grupta medyan değer 584,11×109/L iken, benign grupta medyan değer 504,63×109/L'dir (p=0,037).

Çok değişkenli lojistik regresyon analizi, hem yaşın (odds oranı (OR) = 0,964; %95 güven aralığı (CI)= (0,939- 0,989); p = 0,05) hem de nötrofil sayısının OR = 1,598; %95 CI= (1,118- 2,285); p = 0,01) benign ve malign tiroid nodülleri arasındaki ayrım üzerinde önemli bir etkisi olduğunu göstermiştir.

SONUÇ: Yaş ve nötrofil sayısı malign tiroid nodülleri için bağımsız risk faktörleri olarak belirlenmiştir. Bethesda Kategori III tiroid nodülü olan hastalar arasında, 59,5 yaşın altında ve nötrofil sayısı 4,16 x 10^9/L'nin üzerinde olanlar tiroid malignitesi için artmış riske sahiptir.

Trombosit sayısı, monosit sayısı ve PLO, MLO ve SİYİ gibi enflamatuar parametreler Bethesda III nodüllerinde maligniteyi tespit etmek için yetersiz bulunmuştur. Bu grupta genç yaş, küçük nodül boyutu, yüksek nötrofil sayısı, NLO ve Sİİ malignite için risk faktörleri olarak tanımlanmıştır. Bu hastaların yönetiminde nodüllerin The Thyroid Imaging Reporting and Data System (TI-RADS) özellikleri de göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Bethesda raporlama sistemi, Önemi belirsiz atipi/önemi belirsiz foliküler lezyonlar, nodüller, Tiroid kanseri, biyobelirteç

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INTRODUCTION

Thyroid nodules are common in adults, and population-based screening studies have revealed that approximately 5% of adults have been identified with clinically palpable nodules.[1] In contrast, the detection rate of nodules on ultrasound scans reaches 68%.[2] The risk of malignancy in these nodules ranges from 7% to 15%, depending on various risk factors.1 However, the majority of nodules detected incidentally during radiological examinations are benign.[3] Currently, ultrasound-guided fine-needle aspiration biopsy (FNAB) is the most effective and practical diagnostic test for determining the malignancy status of nodules.[4]

The 2017 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is used as a standard classification system for interpreting and reporting the results of thyroid FNAB cytology.[4] Based on this classification, the thyroid nodules were categorized into six groups. Among these categories, the Bethesda III category, Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS) nodules, demonstrate a heterogeneous nature with variable malignancy rates. According to the 2017 Bethesda data, the malignancy rate of AUS/FLUS nodules varies between 10% and 30%.4 However, it is important to emphasize that this ratio can exhibit substantial variations, as certain centers have reported rates ranging from 37.8% to 83.3% in their findings.[5–8]

A clear association has been established between inflammation and tumor development in recent years. The interaction between systemic inflammation and local immune responses has been shown to play a role in the initiation, development, and progression of various types of malignancies.[9] Thyroid cancer, like other cancer types, is influenced by and modulates inflammation.[10] Inflammatory parameters can serve as valuable markers for predicting cancer development and can be readily acquired through routine blood tests.
In recent years, numerous inflammatory markers such as C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) have been used for the prediction and prognosis of various cancers, including thyroid cancer.[11–14]
The systemic immune-inflammation index (SII), an inflammatory parameter, is a novel metric derived from the counts of peripheral lymphocytes, neutrophils, and platelets. This index has demonstrated prognostic utility in various cancers, including esophageal squamous cell carcinoma, hepatocellular carcinoma, colorectal carcinoma, small cell carcinoma, wherein elevated values have been linked to poor prognoses. Although research indicates the potential of SII as a valuable marker in thyroid cancer, its widespread utilization remains uncommon.[15–20]
The systemic inflammation response index (SIRI), introduced by Qi et al. in 2016, has been proposed as an autonomous prognostic indicator for disease progression and survival in cases of metastatic pancreatic cancer.[21] Since then, SIRI has been applied in survival research in various cancer types.[22] Although there is research showing the use of SIRI in the differentiation of subacute thyroiditis from Graves' disease, no study has shown its use in the prediction of thyroid cancer.[23]
The management of Bethesda III thyroid nodules poses a significant challenge due to their indeterminate nature and borderline cellularity. The utilization of inflammatory markers in Bethesda III nodules could prove beneficial for assessing the malignancy risk of thyroid nodules. Therefore, in this study, we aimed to evaluate the potential of hematological parameters and markers, such as NLR, PLR, MLR, SII, and SIRI, to indicate malignancy risk in cases categorized as AUS/FLUS.

MATERIAL AND METHOD

The data of 292 patients with AUS/FLUS detected by thyroid fine needle biopsy between January 2014 and January 2023 in Ankara Training and Research Hospital were retrospectively collected from the hospital database.

Patients who did not undergo thyroidectomy (n=60), whose treatment was continued in other centers, and whose data could not be reached (n=24) were excluded from the study. In addition, patients with a previous history of malignancy (n=3), systemic disease (n=1), Diabetes Mellitus (n=13), use of drugs affecting platelet function (n=2), and immunosuppressant drugs (n=1) were not included in the study.
Finally, 188 patients who underwent thyroidectomy at the General Surgery clinic were included in the study. The features of thyroid nodules on preoperative ultrasonography were classified according to the American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS). Parameters such as thyroid-stimulating hormone (TSH) and free thyroxine (fT4) levels, neutrophil count, lymphocyte count, thrombocyte count, and mean platelet volume (MPV) were obtained from preoperative blood tests.

NLR was calculated by dividing the neutrophil count by the lymphocyte count, PLR was calculated by dividing the platelet count by the lymphocyte count, and MLR was calculated by dividing the monocyte count by the lymphocyte count.

SII and SIRI were calculated using the following formulas: SII = (Platelet count × Neutrophil count)/lymphocyte count; SIRI = neutrophil count × monocyte count / lymphocyte count.
In addition to these parameters, the histopathological findings of the thyroidectomy specimens were also acquired from the hospital database.
This study was approved by the Ankara Training and Research Hospital Ethics Committee (decision no: E-22-888, date 16.02.2022)

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (IBM Corp., Armonk, NY), and statistical significance was set at $p<0.05$. The Kolmogorov-Smirnov test was used to analyze the normal distribution of the data. Statistical differences between the groups were evaluated using the Independent Sample T-test for normally distributed continuous variables. For data that did not have a normal distribution, the Mann–Whitney U test was preferred. Categorical variables were compared using the Chi-Square test. Univariate and multivariate logistic regression analyses were conducted to assess and identify the factors influencing malignant thyroid nodules and ascertain the predictors of malignancy. The diagnostic capability of age and neutrophil level was evaluated using receiver operating characteristic (ROC) analysis.

RESULTS

A total of 188 patients who had undergone thyroidectomy were enrolled in the final analysis. Among the patients, 38 (20.21%) were male and 150 (79.79 %) were female. The mean age was 48.6 (range 23-79, SD ± 12.41years).
The demographic, radiological, and histopathological characteristics of the patients are shown in Table 1.
A total of 168 patients diagnosed with AUS/FLUS following fine-needle aspiration biopsy (FNAB) underwent bilateral total thyroidectomy, while an additional 20 patients underwent lobectomy. Histopathological examination of thyroidectomy specimens revealed benign findings in 102 patients (54.3%) and malignant findings in 86 patients (45.7%).
In the benign group, nodular hyperplasia was diagnosed in 34% (n = 64) of all patients with AUS/FLUS, 6.4 % (n = 12) had follicular adenoma, 11.2 % (n = 21) had lymphocytic thyroiditis, and 2.7% (n = 5).
In the malignant group, papillary carcinoma (24) was diagnosed in 14.9% (n = 28) of the patients, papillary microcarcinoma (PMC) in 29.3% (n = 55), and follicular carcinoma (FC) in 1.6% (n = 3)
Among the 86 malignant cases, a significant proportion were observed in TI-RADS 3 (n=37, 43%) and TI-RADS 4 (n=43, 50%) ultrasonographic features

Table 1. The demographic, radiological, and histopathological characteristics of the patients

Variables			Patients
n (%)			188
Sex	Female, n (%)		150 (79.79)
	Male, n (%)		38 (20.21)
Age, mean ± SD, years			48.6 ±12.41
ACR-TIRADS score and histopathologic results of AUS/FLUS nodule *n* (%)			
	Benign	Malign	Total
ACR- TIRADS 1	2 (1.1)	0 (0)	2 (1.1)
ACR- TIRADS 2	29 (15.4)	1 (0.5)	30 (16)
ACR- TIRADS 3	51 (27.1)	37 (19.7)	88 (46.8)
ACR- TIRADS 4	20 (10.6)	43 (22.9)	63 (33.5)
ACR- TIRADS 5	0 (0)	5 (5.8)	5 (2.7)
The final histopathologic results of AUS/FLUS nodules, *n* (%)			
Benign pathologies, 102 (54.3)	Nodular hyperplasia		64 (34)
	Follicular adenoma		12 (6.4)
	Lymphocytic Thyroiditis		21 (11.2)
	Hurthle cell adenoma		5 (2.7)
Malignant pathologies, 86 (45.7)	Papillary carcinoma		28 (14.9)
	Papillary microcarcinoma		55 (29.3)
	Follicular carcinoma		3 (1.6)

SD standard deviation; *ACR- TIRADS* American College of Radiology Thyroid Imaging Reporting and Data System; *AUS/FLUS* atypia/follicular lesion of undetermined significance.

Based on the pathological findings, the mean age of the patients with malignancies was lower. The mean age of the malignant group was 45.6, while that of the benign group was 51.1 (p = 0.02). There were no statistically significant differences in terms of gender (p = 0.385).

This study revealed that the thyroid nodule size was smaller in the malignant group. Specifically, the median tumor size was 17 mm in the malignant group and 21 mm in the benign group (p=0.042). Lymphocytic thyroiditis was identified in a combined total of 76 patient samples, with 39 and 37 cases in the malignant and benign groups, respectively. The subsequent statistical analysis revealed that the presence of lymphocytic thyroiditis had no significant impact on the outcomes (p = 0.505).

In the analysis of blood parameters, we observed no statistically significant differences in fT3 levels, TSH levels, lymphocyte counts, platelet counts, monocyte counts, MPV, and PLR between the malignant and benign groups.

The neutrophil count, NLR and SII were elevated in the malignant group. Specifically, the neutrophil count exhibited values of 4.29 ± 1.0 × 109/L and 4.69 ± 1.9 × 109/L in the benign and malignant groups, respectively (p = 0.031). Similarly, the NLR values were calculated as 1.89 for the benign group and 1.99 for the malignant group (p = 0.045). In addition, the SII values were higher in the malignant group, with a median value of 584.11× 109/L in the malignant group, median value were 504.63× 109/L in the benign group (p=0.037).

Table 2. Comparison of the clinical characteristics of benign and malignant thyroid nodules

Variables	Benign group (*n* = 102)	Malign group (*n* =86)	*p*
n (%)	102 (54.3)	86 (45.7)	
Age, mean ± SD, years	51.1 ± 12.69	45.6 ± 11.45	**0.02***
Sex, Female, n (%)	79 (77.5)	71 (82.6)	0.385
Male, n (%)	23 (22.5)	15 (17.4)	
Nodule size, median (range), mm	21 (6 -75)	17 (5 – 60)	**0.042***
Presence of thyroiditis on the thyroid tissue, n (%)			0.505
Present	39 (38.2)	37 (43)	
Absent	63 (61.8)	49 (57)	
TSH, median (range), mIU/L	1.43 (0.0 1 – 9.96)	1.34 (0.01 – 5.49)	0.838
fT4, median (range), ng/dL	1.10 (0.37 – 47.4)	1.09 (0.44 – 14.16)	0.671
Neutrophil count, mean ± SD, 10^9/L	4.29 ± 1.25	4.69 ± 1.25	**0.031***
Lymphocyte count, median (range), 10^9/L	2.3 (1.11 – 4.42)	2.28 (1.07 – 4.79)	0.976
Platelet count, median (range), 10^9/L	274.5 (100 – 639)	280 (134 – 618)	0.545
Monocyte count, median (range), 10^9/L	0.54 (0.27 – 1.03)	0.5 (0.2 -1.1)	0.092
MPV, mean ± SD, fL	9.81 ± 1.14	10.0 ± 1.18	0.257
NLR, median (range)	1.89 (0.86 – 4.46)	1.99 (0.79 – 5.09)	**0.045***
PLR, median (range)	119.62 (37.04 – 285.91)	120.11 (69.45 – 290.65)	0.813
MLR, median (range)	0.25 (0.09 – 0.46)	0.22 (0.09 – 0.63)	0.09
SII, median (range), 10^9/L	504.63 (123.33 – 1663.17)	584.11 (222.86 – 1776.52)	**0.037***
SIRI, median (range)	1.04 (0.27 – 2.88)	1.08 (0.25 -3.18)	0.673

TSH thyroid-stimulating hormone; *fT4* free thyroxine; *MPV* mean platelet volume; *NLR* neutrophil-lymphocyte ratio; *PLR* platelet -lymphocyte ratio; *MLR* monocyte-lymphocyte ratio; *SII* systemic immune-inflammation index; *SIRI* Systemic Inflammation Response Index; * Statistically significant.

Malignant and benign thyroid nodules were used as dependent variables, while sex, age, nodule size, presence of thyroiditis in the thyroid tissue, TSH, fT4, neutrophil count, platelet count, lymphocyte count, monocyte count, MPV, NLR, PLR, MLR, SII, and SIRI were used as independent variables in the univariate logistic regression analysis

Table 3. Results of univariate and multivariate logistic regression analyses, with postoperative diagnosis of thyroid malignancy as the dependent variable.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex	0.726 (0.351 – 1.499)	0.386	N/A	N/A
Age	0.963 (0.940 – 0.988)	**0.003***	0.964 (0.939 – 0.989)	**0.05***
Nodule size	0.983 (0.963 – 1.005)	0.127	N/A	N/A
Presence of thyroiditis on the thyroid tissue	1.220 (0.680 – 2.189)	0.505	N/A	N/A
TSH	0.951 (0.782 – 1.153)	0.610	N/A	N/A
fT4	0.967 (0.865 – 1.080)	0.546	NA	N/A
Neutrophil count	1.293 (1.021 – 1.637)	**0.033 ***	1.598 (1.118 – 2.285)	**0.010***
Lymphocyte count	1.014 (0.997 - 1.005)	0.947	N/A	N/A
Platelet count	1.001 (1.000–1.007)	0.653	N/A	N/A
Monocyte count	0.197 (0.034 – 1.139)	0.070	0.054 (0.006 – 0.447)	0.09
Mean platelet volume	1.156 (0.900 – 1.485)	0.256	N/A	N/A
NLR	1.430 (0.970 – 2.078)	0.071	0.870 (0.517 – 1.462)	0.598
PLR	1.002 (0.995 – 1.008)	0.630	N/A	N/A
MLR	0.061 (0.002 – 2.284)	0.130	N/A	N/A
SII	1.001 (1.000–1.002)	0.191	N/A	N/A
SIRI	1.079 (0.629 – 1.848)	0.783	N/A	N/A

OR odds ratio; *CI* confidence interval; *N/A* no value is available; *TSH* thyroid-stimulating hormone; *fT4* free thyroxine; *MPV* mean platelet volume; *NLR* neutrophil-lymphocyte ratio; *PLR* platelet -lymphocyte ratio; *MLR* monocyte-lymphocyte ratio; *SII* systemic immune-inflammation index; *SIRI* Systemic Inflammation Response Index; * Statistically significant.

A multivariate logistic regression analysis was performed to exclude the influence of confounding factors. The results of the multivariate logistic regression analysis revealed that both age (odds ratio (OR) = 0.964; 95% confidence interval (CI)= (0.939 – 0.989); p = 0.05) and neutrophil count (odds ratio (OR) = 1.598; 95% confidence interval (CI)= (1.118 – 2.285); p = 0.01) had a significant impact on the differentiation between benign and malignant thyroid nodules (Table 3). Thus, both age and neutrophiles were identified as independent influencing factors for the detection of malignant thyroid nodules.

The diagnostic capability of age and neutrophil level was assessed through receiver operating characteristic (ROC) analysis, including determination of the cutoff point. In addition, metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated

Table 4. ROC curve analysis of age and neutrophil count as independent influencing factors

Variables	AUC	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P value
Age	0.624	0.544 – 0.703	59.5 years	93	29	52.6	83.3	**0.03***
Neutrophil count	0.584	0.503 – 0.665	4.16 x 10^9/L	65.1	49	52.8	63.4	**0.047***

ROC receiver operating characteristic; *AUC* the area under the curve; *CI* confidence interval; *PPV* positive predictive value; *NPV* negative predictive value; * Statistically significant

AUC values for age were 0.624 (p=0.03, 95% CI 0.544 – 0.703) and for neutrophil count were 0.584 (p=0.047, 95% CI 0.503 – 0.665). The cutoff values for age and neutrophil count were set at 59.5 years (sensitivity 93.0%, specificity 29%) and 4.16 x 109/L (sensitivity 65.1%, specificity 49%) (Table 4 and Figure 1).

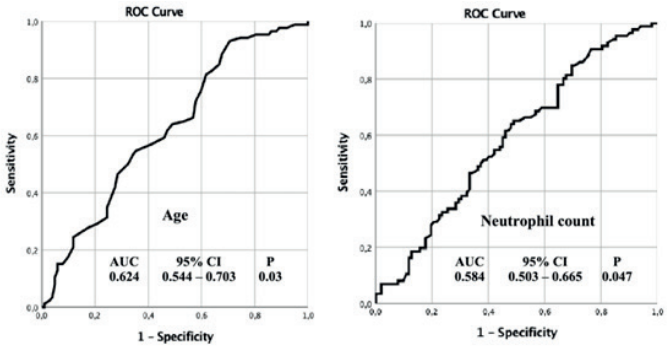

Figure 1. ROC curve analysis of age and neutrophil count as independent influencing factors for the prediction of thyroid cancer. AUC the area under the curve; CI confidence interval;

The findings of our study revealed risk of malignancy increased in patients with thyroid nodules classified as the Bethesda III category who are under 59.5 years of age and exhibit neutrophil counts above 4.16 x 109/L.

DISCUSSION

The worldwide incidence of thyroid cancer has increased over the past several decades.[24–26] Nodules are a common clinical problem in thyroid pathologies. Approximately 5–13% of thyroid nodules identified incidentally during radiological examinations are malignant.[4, 24] Therefore, it is important to differentiate benign from malignant nodules. Ultrasound-guided FNAB is a crucial preoperative diagnostic technique for investigating thyroid nodules. FNAB has an adequacy state rate of 70% to 94%, a sensitivity of approximately 61.8%-98.4% and a specificity of approximately 71.4%-100%.27-29 Cytopathological examination reports of the biopsy material obtained from FNAB were standardized according to the Bethesda System. Bethesda category III represents a heterogeneous group in terms of cytopathological features of lesions. It refers to cytological samples that are challenging to categorize as benign or malignant.[30]
Because of these features, the AUS/FLUS category has reported varying rates of malignancy among different centers. Although postoperative histopathology reports 10-30% malignancy in this patient category, according to the Bethesda System, some centers report higher rates of malignancy.[4–8] According to the ATA guidelines, the rates of malignancy vary between 6 and 48%.1 In this study, among 188 patients, 86 (45.7%) had malignant tumors.
The approach to nodules with a cytopathological diagnosis of AUS/FLUS remains a clinical problem. The recommended options for the management of patients in this category include repeat FNAB, surgery, and follow-up. However, additional tests are needed to determine the right method for these recommendations.
It is known that inflammation contributes to the formation and development of tumors. Also, malignant tumors themselves can stimulate the production of inflammatory markers.[31] CBC parameters and the measurement of some inflammatory biomarkers may be useful in the detection of thyroid malignancies as alternative management choices. Numerous studies have demonstrated that systemic inflammation contributes to cancer development.[9, 11–13] Several studies have explored the correlation between thyroid cancer and inflammation.[10, 14, 19, 20, 32, 33] Peripheral blood SII, SIRI, PLR, and NLR are considered new inflammatory markers and have been reported to be independent prognostic markers in many cancer types.[11, 12, 16, 21, 34]
Very few studies have investigated the predictive properties of inflammatory parameters in terms of thyroid cancer in patients with FNAB cytopathological results of AUS/FLUS. Bostan et al. investigated the predictive values of NLR, PLR, and MPV for thyroid cancer in patients in the Bethesda III category.[35] In our study, we assessed the efficacy of hematological parameters, including neutrophil count, platelet count, lymphocyte count, monocyte count, MPV, and systemic inflammatory biomarkers, such as NLR, PLR, MLR, SII, and SIRI, in predicting the risk of malignancy among nodules Bethesda III category.
Many studies have investigated the efficacy of the NLR in differentiating between malignant and benign thyroid pathologies.[14, 32, 33, 36, 37]. However, these studies were not conducted according to the Bethesda classification. Bostan et al. reported that a high NLR in patients with AUS/FLUS is useful in predicting malignancy. In their study, the cutoff point was designated as 2.24, and the accuracy of NLR in distinguishing malignancy from the benign condition was 0.65 in ROC analysis (AUC 0.665; specificity, 0.808; sensitivity, 0.492).35 In our investigation, the NLR was higher in the malignant group (p=0.045); however, it did not emerge as a predictive factor according to logistic regression analysis. In the present study and the Bostan et al. study, NLR demonstrated limited predictive ability when used as a biomarker among individuals presenting with AUS/FLUS nodules. However, they emphasized that rigorous follow-up is required in cases with an NLR values of 2.24 and above.
The predictive value of PLR and MPV in relation to thyroid malignancy remains controversial. Ozmen et al. and Manatakis et al. reported that PLR and Baldane et al. reported that MPV were beneficial in detecting thyroid cancer.[14, 36, 38] In contrast, Machairas et al. and Bostan et al. showed that PLR and MPV are not significant indicators for differentiating thyroid malignancies.[35, 39] Our study also demonstrated that PLR and MPV were not effective in distinguishing thyroid malignancies.
Currently, no studies have specifically investigated the predictive value of SII and SIRI in patients with Bethesda III malignant thyroid nodules. The results of our study indicate that the SII could prove valuable (p=0.037), while the SIRI demonstrated limited utility (p=0.067), in distinguishing between benign and malignant Bethesda III nodules.
Furthermore, we observed a higher rate of malignancy in young patients with Bethesda III nodules. Similar to our study, the studies conducted by Bostan et al. and Ogmen et al. also identified Bethesda III malignant nodules in young patients.[35, 40]
In addition to age, high neutrophil count was found to be a factor influencing the detection of malignancy in our study. ROC curve analysis performed and cutoff values were calculated. AUC values for age and neutrophil count were 0.624 (p=0.03, 95% CI 0.544 – 0.703) and 0.584 (p=0.047, 95% CI 0.503 – 0.665) respectively. Although we determined these cutoff values in our study, the AUC values were low. This means that our test had low performance.
This study has some limitations, as it was a retrospective study with a limited sample size. Larger prospective studies are needed to establish the potential utility of these parameters.

CONCLUSION

Our study concluded that CBC parameters, such as, platelet count, monocyte count, and inflammatory parameters, such as, PLR, MLR, and SIRI, were insufficient for detecting malignancy in Bethesda III nodules. However, age and neutrophil count were identified as independent risk factors for malignant thyroid nodules. The findings of our study revealed that among patients with Bethesda Category III thyroid nodules, those under 59.5 years of age and with a neutrophil count above 4.16 x 109/L have an increased risk for thyroid malignancy.
Our recommendation for further management of Bethesda III category patients is that if the patient is young, nodule size is small, and neutrophil count, NLR and SII are high, they should be evaluated for malignancy. In our study ultrasonographic findings of malignant patients were mostly characterized by TI-RADS 3 and 4 features (93%). Ultrasonographic features of nodules are also important and must be considered in the management of patients in the Bethesda III ca-

tegory.
In this group, if the patient is young, the nodule size is small, and the neutrophil count, NLR, and SII are high, caution should be exercised regarding malignancy.

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