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Is Modified Systemic Inflammation Score a Predictor of Malignancy in Indeterminate Thyroid Nodules?

Modifiye Sistemik İnflamasyon Skoru İndetermine Tiroid Nodüllerinde Malignitenin Bir Göstergesi midir?

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ABSTRACT Objective: The aim of this study is to evaluate the preoperative diagnostic value of modified systemic inflammation score (mSIS) in predicting the presence of malignancy in patients with indeterminate thyroid nodules. **Material and Methods:** It is a retrospective study. Three hundred and sixty eight patients who underwent thyroid lobectomy were screened. Patients were divided into 3 groups according to modified SIS; mSIS 0 for those were albumin (alb) ≥ 4.0 gr/dL and lymphocyte monocyte ratio (LMR) ≥ 3.4, mSIS 1 for those were alb<4.0 gr/dL or LMR<3.4, mSIS 2 for those were alb<4.0 gr/dL and LMR<3.4. According to the results of the postoperative pathology, the patients were divided into two groups as benign and malignant. **Results:** The malignancy was found in 24 patients in histopathological examination. Ten (41.7%) of these were micropapillary, 8 (33.3%) were papillary, and 6 (25%) were follicular carcinomas. There was no difference between the malignant and benign groups in terms of LMR and albumin values. mSIS 0 had a 65% malignancy rate, mSIS 1 69.2%, and mSIS 2 66.6%. There was no statistically significant difference between the groups. **Conclusion:** MSIS may not be a predictor of malignancy in indeterminate thyroid nodules. Further studies are needed to understand this issue.

ÖZET Amaç: Bu çalışmanın amacı belirsiz tiroid nodülü olan hastalarda malignite varlığını öngörmede modifiye sistemik inflamasyon skorunun (mSIS) preoperatif tanısal değerini araştırmaktır. **Gereç ve Yöntemler:** Retrospektif bir çalışmadır. Tiroid lobektomi yapılan 368 hasta tarandı. Modifiye SIS'e göre hastalar 3 gruba ayrıldı; albümin (alb) ≥ 4,0 gr/dL ve lenfosit monosit oranı (LMR) ≥ 3,4 olanlar mSIS 0, alb <4,0 gr/dL veya LMR <3,4 olanlar mSIS 1, alb <4,0 gr/dL ve LMR<3.4 olanlar mSIS 2. Postoperatif patoloji sonuçlarına göre hastalar benign ve malign olarak iki gruba ayrıldı. **Bulgular:** Histopatolojik incelemede 24 hastada malignite saptandı. Bunların 10'u (%41,7) mikropapiller, 8'i (%33,3) papiller ve 6'sı (%25) foliküler karsinomdu. Malign ve benign gruplar arasında LMR ve albümin değerleri açısından fark yoktu. mSIS 0'da malignite oranı %65, mSIS 1'de %69,2 ve mSIS 2'de %66,6 idi. Gruplar arasında istatistiksel olarak anlamlı fark yoktu. **Sonuç:** MSIS, indetermine tiroid nodüllerinde malignitenin bir göstergesi olmayabilir. Bu konuyu anlamak için daha ileri çalışmalara ihtiyaç vardır.

Keywords: Modified systemic inflammation score; thyroid lobectomy; indeterminate thyroid nodule; Bethesda classification

Anahtar Kelimeler: Modifiye sistemik inflamasyon skoru; tiroid lobektomi; indetermine tiroid nodülü; Bethesda sınıflandırması

Thyroid nodules (TN) are extremely common. While the incidence of TN that may be palpable is nearly 5% in females and 1% in males, this rate approaches 70% in high-resolution ultrasound.[1] Cancer occurs in 7-15% of TN. Cancer risk is affected by variables such as age, gender, family history, and ra-

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diation exposure. The gold standard for assessing the risk of cancer and deciding on surgery is cytological examination after fine needle aspiration. There are 6 categories in the Bethesda System for Reporting Thyroid Cytopathology.[2] Each category has a different probability of thyroid cancer. Cytological examination does not always clearly distinguish benign pathology from malignant pathology. TN with Bethesda category 3 and 4, which constitute around 20% of all TN, have an indeterminate cytology.[3] Atypia of undetermined significance and follicular lesion of undetermined significance (AUS/FLUS) is classified as Bethesda 3 and follicular neoplasm and suspicious for follicular neoplasm (FN/SFN) is classified as Bethesda 4.[2] The risk of cancer is 6-18% and 10-40%, respectively, for Bethesda 3 and Bethesda 4. There is still disagreement on the best approach regarding these 2 groups. Although surgery is an option, follow-up with a repeat biopsy is also another option.[1,2] Therefore, further methods that will assist us in determining the malignancy risk of indeterminate TN might be useful.

Inflammation is well known to increase the risk of occurrence of several forms of cancer, including head and neck cancers, pancreatic cancer, colorectal cancer, ovarian cancers, and prostate cancer.[4] In lymphocytic thyroiditis, the immune system plays a role in the transformation of malignancy.[5,6] Many studies have been carried out focused on whether the prognosis of cancer be able to estimate by measurement of leukocyte fractions in the blood and their ratio to each other, albumin (alb) and C-reactive protein measures. In addition, systemic inflammation score (SIS) have been utilized to predict the prognosis of many types of cancer and thyroid cancer.[7-12] A composite score of the lymphocyte-to-monocyte ratio and serum alb concentration are used to construct the modified systemic inflammation score (mSIS).[13]

This research aims to determine whether the mSIS has any diagnostic significance of identifying malignancy in indeterminate TN.

MATERIAL AND METHODS

Three hundred sixty eight patients who underwent thyroid lobectomy between 2013 and 2021 were retrospectively screened. Thirty-six patients with a solitary nodule and preoperative cytology that is Bethesda cathegory 3 or 4 were included. Ethics committee consent was taken for the study (date: October 20, 2022, no: B.10.1.TKH.4.34.H.GP.0.01/30). The study was carried out in accordance with the Declaration of Helsinki. Consent was taken from the patients.

Those with hematological diseases, liver and kidney diseases, steroid users, systemic inflammatory diseases, those under the age of 18, those with a history of hypothyroidism or hyperthyroidism, those with a history of thyroiditis, and those with a previous diagnosis of cancer were excluded. In addition, those with a nodule larger than 40 mm, those who had radiation exposure to the head-neck area, and those with a a history of thyroid cancer in the family were excluded. According to postoperative pathology, it was grouped as benign and malignant.

Age, gender, body mass index (BMI), preoperative cytology, preoperative thyroid stimulating hormon levels, free T3 levels, and free T4 levels, lymphocyte, monocyte and alb levels of the patients were recorded. The BMI formula was weight (kg)/height squared (m^2). Blood was taken after eight hours of fasting. Lymphocyte monocyte ratio (LMR) was lymphocytes count/monocytes count. Considering the factors that would influence the development of malignancy, the patients were divided into 3 groups according to the mSIS. mSIS 0 was alb was less than 4.0 g/dL and LMR was less than 3.4. mSIS 1 was alb was less than 4.0 g/dL or LMR was less than 3.4. mSIS 2 was alb was less than 4.0 g/dL and LMR was less than 3.4. Then, a statistical analysis was performed on the association between preoperative mSIS and postoperative pathology.

STATISTICAL METHOD

The descriptive data included mean, maximum, median minimum, standard deviation, ratio values, and frequency. Kolmogorov-Simirnov test was used to distribute the variables. Quantitative independent data were analyzed by using independent sample t test and Mann-Whitney U test. Chi-square test was utilised for analysing the qualitative independent data. Fischer test was utilised because the require-

ments of chi-square did not meet. SPSS 28.0 (IBM Corp., Armonk, NY) program was used in the analysis.

RESULTS

A total of 36 patients were included in this study. The mean age was 46.8±13.0 years. There were 27 (75%) females and 9 (25%) males. The BMI of the patients was 27.8±3.42. Bethesda category III TN were 31 (86.1%) whereas Bethesda IV TN were 5 (13.9%). All of the cases underwent lobectomy. As a result of postoperative pathological examination, malignancy was detected in 24 (66%) patients. Ten (41.7%) of these were micropapillary, 8 (33.3%) were papillary, and 6 (25%) were follicular carcinomas. While Bethesda 3 had a malignancy ratio of 70%, Bethesda 4 had a malignancy ratio of 40%. Table 1 presents data with demographic characteristics, pathology, and laboratory.

No difference was observed between the malignant and benign groups in terms of basic variables in the univariate analysis. When the LMR ratio was evaluated, no statistically significant difference was found between the malignant and bening groups. In terms of alb levels, we found no significant differ-

TABLE 1: Demographic, clinical, pathological and laboratory data of patients.

		Minimum-maximum	Median	Median± SD
Age		18.0-71.0	46.5	46.8±13.0
Albumin		3.60-5.10	4.20	4.21±0.35
Lymphocyte		1.04-3.38	2.19	2.18±0.56
Monocyte		0.19-0.78	0.44	0.45±0.14
Lymphocyte /Monocyte		2.76-7.13	5.00	5.06±1.27
		Total	Percentage	
Sex	Female	27	75.0%	
	Male	9	25.0%	
Bethesda Classification	III	31	86.1%	
	IV	5	13.9%	
Postoperative pathology	Benign	12	33.3%	
	Malignant	24	66.7%	
mSIS	0	20	55.6%	
	I	13	36.1%	
	II	3	8.3%	

TABLE 2: The comparison of all demographic, clinical, pathological and laboratory data between the benign and malignant groups.

		Benign Group		Malignant Group		
		MedianSD	Median	Median±SD	Median	p
Age		44.8±13.6	42.0	47.8±12.8	48.5	0.515[t]
Albumin		4.25±0.31	4.20	4.19±0.37	4.20	0.621[t]
Lymphocyte		2.39±0.54	2.36	2.08±0.56	2.14	0.129[t]
Monocyte		0.47±0.14	0.45	0.44±0.14	0.43	0.654[t]
Lymphocyte / Monocyte		5.35±1.22	5.68	4.91±1.29	4.84	0.332[t]
		Total	%	Total	%	p
Sex	Female	7	58.3%	20	83.3%	0.102X^2
	Male	5	41.7%	4	16.7%	
Bethesda Classification	III	9	75.0%	22	91.7%	0.307X^2
	IV	3	25.0%	2	8.3%	
mSIS	0	7	58.3%	13	54.2%	0.813X^2
	I	4	33.3%	9	37.5%	
	II	1	8.3%	2		8.3%

[t]Independent sample t-test/X^2chi square test, SD: Standard deviation.

ence. When the patients in this research were grouped in 3 categories based on mSIS; 20 patients' mSIS was 0, 13 patients' mSIS 1, and 3 patients' mSIS 3. Malignancy was detected in 65% of the mSIS 0 group, 69.2% of the mSIS 1 group, 66.6% of the mSIS 2 group, and there is no statistically significant difference between the groups (Table 2).

DISCUSSION

In the case of cytological diagnosis of indeterminate TN, a difficult decision has to be made between observation and surgery. The order of recommendations of international guidelines for nodules categorized as AUS/FLUS is as follows: first repeat fine-needle aspiration biopsy (FNAB), then molecular studies if available, and finally diagnostic surgery. Although lobectomy is first advised in cases with FN/SFN, total thyroidectomy may be recommended over lobectomy if nodules are in the opposite lobes and there are other characteristics that increase the risk of malignancy, such as a history of thyroid malignancy in family and nodules bigger than 4 cm.[1,2,14] Even though molecular testing is useful, it may not always be available. Then again, repeated FNABs may be very unpleasant and taxing for patients. Additionally, if a completion thyroidectomy is required after a lobectomy due to a potential malignancy, patients will be at risk for additional surgery and anesthesia. In addition to cytological testing, a scoring system that is cheap and with a simple interface and good diagnostic value can be used to predict the cancer risk and support the decision for the surgical treatment.

mSIS comprehensively demonstrates nutritional status and inflammation in cancer patients.[13] Kanda et al. studied 443 patients who received curative surgical excision for esophageal squamous cell carcinoma. According to the mSIS score, they divided the patients into 3 groups. They concluded that the mSIS score is associated with disease-specific mortality risk.[15] Xiong et al. studied 317 patients with esophagogastric junction adenocarcinoma who received surgical treatment. They concluded that there is a strong correlation between overall survival and mSIS scores.[13] mSIS is also associated with prognosis of melanoma, lymphoma, breast cancer, and lung cancer.[16-19]

Inflammation is considered to have a significant influence on the development and prognosis of cancer. Studies that claim a relationship between preoperative mSIS and malignancy have tried to explain this relationship. First, when there is a chronic inflammation, liver synthesis less alb, which can lead to hypoalbuminemia. Alb is regarded in cancer patients as a potential prediction of malnutrition and cachexia. Second, a low lymphocyte count is assumed to be linked to a worse prognosis since lymphocytes are crucial for anticancer immunity. Circulating monocytes, which are different from lymphocytes, develop into macrophages, accelerate the development of malignancy by encouraging tumor progression, angiogenesis, and metastasis.[13,19-22]

There are just a few research on the relationship between biochemical markers and malignancy in TN. Ataş et al. concluded that there is a significant relationship between mSIS and malignancy and so it can be used as a marker for making surgical decisions in their 2 separate studies on indeterminate TN and persistent nondiagnostic TN.[23,24] Li et al. claims that there is a significant relationship between low alb count and high pdw value and thyroid cancer in their study with platelet distribution width and albumin results.[25] Kocer et al. also claims that the N/L ratio could be used as a predictor for TN malignancy in their study examining the relationship between neutrophil/lymphocyte ratio and thyroid cancer.[26] While planning our study, we had some differences from the literature. First of these was exclusion of patients with more than one nodule. Presence of more than one nodule, especially nodules with suspicious ultrasonographic findings in terms of malignancy, may be effective in making a surgical decision regardless of the preoperative FNAB result. In other words, if there is more than one ultrasonographicly suspicious nodule in a patient with indeterminate nodule as a result of FNAB taken from one nodule, the surgeon or endocrinologist may be more willing to prefer diagnostic surgery. Our aim was to evaluate the effect of systemic inflammation score on surgical decision-making regardless of the other factors. Our second difference was that we excluded solitary nodules over 4 cm from the study. The reason for this was that the diagnostic value of FNAB from nodules over 4 cm

was low and the risk of malignancy was increased regardless of the other reasons.

In our study, it was found that more than 50% of the cases were malignant. This rate seems to be higher than the literature, but this rate may not reflect the real risk of cancer in nodules with indeterminate cytology. Since not all indeterminate TN were included in the study, it could not be expected to correctly predict the real risk of malignancy. In our study, the focus was on the predictive effect of mSIS on malignancy in TN with indeterminate cytology. However, unlike the literature, there was no statistically significant difference between the mSIS groups. In other words, no predictive effect of mSIS on malignancy in indeterminate TN was found. These results differ from the limited number of studies in the literature examining the relationship between SIS and TN. We think that limiting our study to patients with solitary nodules smaller than 4 cm unilaterally and undergoing thyroid lobectomy surgery may be effective in obtaining different results. In addition, since there is not enough studies in the literature, it is not possible to make a definitive decision about the predictive effect of mSIS on the risk of malignancy of indeterminate nodules.

This study has some limitations. First, the study was conducted retrospectively on patient files. In addition, since a very specific patient group is focused on, the number of patients is relatively low.

CONCLUSION

mSIS is not a predictor of malignancy in indeterminate TN. Further studies are needed to understand this issue.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Yaşar Kemal Duymaz, Serap Önder;* ***Design:*** *Ahmet Mahmut Tekin, Şamil Şahin;* ***Control/Supervision:*** *Serap Önder, Ahmet Mahmut Tekin;* ***Data Collection and/or Processing:*** *Burak Erkmen, Cumhur Selçuk Topal, Fatih Savran;* ***Analysis and/or Interpretation:*** *Şamil Şahin, Fatih Savran;* ***Literature Review:*** *Burak Erkmen, Cumhur Selçuk Topal;* ***Writing the Article:*** *Yaşar Kemal Duymaz;* ***Critical Review:*** *Serap Önder, Ahmet Mahmut Tekin;* ***References and Fundings:*** *Şamil Şahin, Burak Erkmen;* ***Materials:*** *Fatih Savran, Cumhur Selçuk Topal.*

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