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The Predictive Power of Biological Markers for Malignant Thyroid Nodules. Single-Center Experience

Malign Tiroid Nodülleri için Biyolojik Belirteçlerin Prediktif Değeri. Tek Merkez Deneyimi

Recayi Capoglu[1], Zulfu Bayhan[2], Emre Gonullu[2], Murat Coşkun[1], Tarık Harmantepe[2], Furkan Küçük[2], Hakan Demir[1]

[1] Sakarya University Training and Research Hospital, Department of General Surgery, Sakarya, Turkey

[2] Sakarya University Faculty of Medicine, Department of General Surgery, Sakarya, Turkey

ORCID ID: Zulfu Bayhan https://orcid.org/0000-0002-7587-7267, Recayi Çapoğlu https://orcid.org/0000-0003-4438-4301, Emre Gonullu https://orcid.org/0000-0001-6391-4414, Murat Coskun https://orcid.org/0000-0002-6361-913X, Ahmet Tarık Harmantepe https://orcid.org/0000-0003-2888-7646, Furkan Kucuk https://orcid.org/0000-0002-2558-9144, Hakan Demir https://orcid.org/0000-0001-5973-4605

***Sorumlu Yazar / Corresponding Author:** Zulfu Bayhan **e-posta / e-mail:** zulfubayhan@gmail.com

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Abstract

Aim Thyroid nodules are mostly benign. Although it varies by region, 5.4% of nodules in men and 6.5% of nodules in women may be malignant. In rural regions where a radiologist, an endocrine surgeon, a cytologist, and an endocrinologist are not present, difficulties may be experienced in the management of thyroid nodules.

Material and Method This present study aims to determine if it is possible to comment on whether the nodule is malignant by evaluating the biological markers in patients with thyroid nodules.

Results We reviewed retrospectively the data of patients between January 2019 and September 2020 who underwent total thyroidectomy in terms of thyroid ultrasonography results, thyroid fine-needle aspiration biopsy results, neutrophil, platelet, lymphocyte, red blood cell, and mean erythrocyte volume (MCV) values, histopathological examination results of thyroid specimens. Subsequently, we calculated Mentzer index, Systemic immune-inflammatory index, and neutrophil-lymphocyte ratio for each patient.

Conclusion 140 patients were included in the study. 110 (78.6%) of the patients were female and 30 (21.4%) were male. The mean age of the patients was 48 ± 12.5 (20-76). There was no statistically significant difference in Mentzer index, Systemic inflammatory index, and neutrophil-lymphocyte ratios between patients with malignant and benign thyroid nodules.

Keywords Biological markers have limited predictive power in the management of thyroid nodules. Therefore, the use of biomarkers that we have studied in the treatment of thyroid nodules does not seem possible at present.

Özet

Amaç *Tiroid nodülleri çoğunlukla benign özelliktedir. Yerleşim bölgelerine göre değişmekle birlikte erkeklerde nodüllerin % 5,4'ü, kadınlarda ise % 6,5'i malign olabilir. Radyoloji, endokrin cerrahisi, patoloji ve endokrinoloji uzmanlarının bulunmadığı kırsal bölgelerde tiroid nodüllerinin yönetiminde zorluklar yaşanabilir. Çalışmamızda, tiroid nodülü olan hastalarda bazı biyolojik belirteçlerin analizi ve nodülün benign malign ayırımı açısından öneminin belirlemesi amaçlanmaktadır.*

Gereç ve Yöntem *Ocak 2019-Eylül 2020 tarihleri arasında total tiroidektomi yapılan hastaların tiroid ultrasonografi sonuçları, tiroid ince iğne aspirasyon biyopsi sonuçları, tiroidektomi örneklerinin histopatolojik inceleme sonuçları, nötrofil, trombosit, lenfosit, eritrosit sayıları ve ortalama eritrosit hacmi (MCV) değerleri retrospektif olarak gözden geçirildi. Daha sonra her hasta için Mentzer indeksi, Sistemik immün-inflamatuar indeks ve nötrofil-lenfosit oranları hesaplandı*

Bulgular *Çalışmaya 140 hasta dahil edildi. Hastaların 110'u (% 78,6) kadın, 30'u (% 21,4) erkekti. Hastaların yaş ortalaması 48 ± 12.5 (20-76) idi. Mentzer indeksi, Sistemik inflamatuar indeks ve nötrofil-lenfosit oranlarında malign ve benign tiroid nodülleri olan hastalar arasında istatistiksel olarak anlamlı fark yoktu.*

Sonuç *Biyolojik belirteçlerin tiroid nodüllerinin tedavisinde sınırlı prediktif gücü vardır. Bu nedenle tiroid nodüllerinin tedavisinde halihazırda çalıştığımız biyobelirteçlerin kullanımı mümkün görünmemektedir.*

Anahtar Kelimeler *Mentzer Index, Systemic Inflamatuar Index, Neutrophil to Lymphocyte Ratio, Thyroid Nodule, Thyroid Cancer*

INTRODUCTION

Thyroid nodules are present in 19% - 68% of the population and are more common in women and older[1,2]. Additionally, the thyroid nodules are mostly benign. Although it varies by region, 5.4% of nodules in men and 6.5% of nodules in women may be malignant[3]. The incidence rate of malignant thyroid nodules is increasing day by day. It has been reported in various publications that the reason for this situation may be the detection of previously undetected small malignant nodules due to the developments in imaging techniques rather than the increase in the frequency of the disease[4]. Detection of malignant thyroid nodules when they are much smaller in size, determination of new cytological and pathological criteria, performing molecular tests, and current developments in treatment methods enable the management of these nodules in a personalized way, with algorithmic and evidence-based care[5]. For this purpose, national and international guidelines for the follow-up and treatment of thyroid nodules have been determined[6,7]. In centers where a radiologist, an endocrine surgeon, a cytologist, and an endocrinologist are present, the follow-up and treatment of thyroid nodules can be performed accurately according to these guidelines. However, in rural regions where these facilities are not available, difficulties may be experienced in the management of the treatment of thyroid nodules. Patients in these regions can be consulted to central hospitals by specialists. Still, failures may occur in the diagnosis from time to time due to a lack of basic information that should be given about the patient, which may cause physician and patient dissatisfaction due to overtreatment or undertreatment[8].

There are various studies in the literature on the use of biological markers in kidney failure, in inflammatory conditions such as appendicitis, cholecystitis, and cancer diseases to predict the course of the current disease[9-12]. Biological markers may assist specialists working in rural hospitals in the management of thyroid nodules[9,13].

This present study aims to determine if it is possible to comment on whether the nodule is malignant by evaluating the biological markers in patients with thyroid nodules.

MATERIAL and METHODS

The Ethics Committee of the Sakarya University School of Medicine approved the study and data collection on 1st of October 2021 (71522473/050.01.04/64743/437).

We reviewed retrospectively the data of patients who underwent total thyroidectomy in our clinic between January 2019 and September 2020. We included patients over 18 years of age who have not had previous thyroidectomy surgery and patients without a history of hematological disease.

In our clinic, we examine every patient thought to have a thyroid nodule by ultrasonography (US), and we report these USs according to the Thyroid Imaging Reporting & Data System (TIRADS). When we detect a thyroid nodule on the US, we perform a fine needle biopsy (FNB) for nodules extending out of the thyroid tissue, for subcapsular nodules located adjacent to the recurrent laryngeal nerve or trachea, for nodules showing rim calcification, for over 1 cm, solid and hypoechoic nodules, for nodules with suspected malignancy lymph node accompanied, for nodules with suspected malignancy such as irregular borders on ultrasound. These biopsies are reported by pathologists using the BETHESDA classification.

We evaluated the patients' most recent preoperative thyroid ultrasonography (US) and thyroid fine-needle aspiration biopsy (FNAB) results, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), neutrophil, platelet, lymphocyte, red blood cell, mean erythrocyte volume (MCV) values, histopathological examination results of thyroid specimens. We calculated Mentzer index (MI) (MCV/RBC), Systemic immune-inflammatory index (SII) (Plt x neutrophil / lymphocyte), neutrophil-lymphocyte ratios (NLR) for each patient.

Statistical Analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distributions of numerical variables were normal. Accordingly, the independent sample t-test and the Kruskal Wallis test were used to compare the numeric variables between groups. The numeric variables were presented as mean ± standard deviation or median [Q1 – Q3]. Categorical variables were compared by the Chi-Square test. Categorical variables were presented as a count and percentage. A p-value <0.05 was considered significant. Receiver operator characteristic (ROC) curve analysis was used to identify the best cut-off value and assess the performance of the test score for appendicitis. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp.)

RESULTS

140 patients were included in the study. 110 (78.6%) of the patients were female and 30 (21.4%) were male. The mean age of the patients was 48 ± 12.5 (20-76). Histopathological examination of total thyroidectomy specimens of 140 patients included in the study revealed that while 53 patients had malignant nodules (37.9%), 87 patients (62.1%) did not. When the blood parameters were examined, the mean TSH value was 2.14 mU/ml ± 7.32 mU/ml (0.0-76.7), the mean fT3 value was 4.8 pg/ml ± 1.2 pg/ml (2.5-3.6), the mean fT4 value was 12.5 ng/dl ± 3.49 ng /dl (2.4-41.1), mean neutrophil value was 4.2 (10^3/uL) ± 1.5 (10^3/uL) (1.8-14.3), mean lymphocyte value was 2.2 (10^3/uL) ± 0.5 (10^ 3/uL) (0.8-4.1), mean platelet value was 277.1 ± 198.8 (128-2500), mean MCV value was 85.6 fL ± 10.2 fL (29-99.4), mean Rbc value was 4.6 (10^6/uL) ± 0.4 (10^6/uL) (3.6-7.1). Ultrasonographic examination of the patients revealed TIRADS 2 findings in 25 (18%) patients, TIRADS 3 findings in 54 (39%) patients, TIRADS 4 findings in 52 (37%) patients, and TIRADS 5 findings in 9 (6%) patients. Fine needle aspiration biopsy revealed Bethesda 2 findings in 61 (43.5%) patients, Bethesda 3-4 in 13 (9%) patients, Bethesda 5 in 54 (38.5%) patients, and Bethesda 6 in 13 (9%) patients (Table 1,2).

The mean MI was 18.7 ± 3.04 (6.04-25.7), the mean NLR was 2.08 ± 1.2 (0.6-11.5), and the mean SII was 584.2 ± 580.3 (140.8-5643.9) (Table 1,2).

Table 1: Classification of preoperative ultrasonographic examination and fine-needle aspiration biopsies according to postoperative histopathological examination results.

		Malignant	Benign	p Value
Ultrasonography	TI-RADS 1	0 0 (0%)	0 0 (0%)	0.00
	TI-RADS 2	5 (20%)	20 (80%)	
	TI-RADS 3	8 (14.8%)	46 (85.2%)	
	TI-RADS 4	32 (61.5%)	20 (38.5%)	
	TI-RADS 5	9 (100%)	0 (0%)	
Fine Needle Aspiration Cytology				
	Bethesda 1	0 (0%)	0 0 (0%)	0.00
	Bethesda 2	12 (19.7%)	49 (80.3%)	
	Bethesda 3-4	5 (42%)	7 (58%)	
	Bethesda 5	25 (46.3%)	29 (53.7%)	
	Bethesda 6	12 (92.3%)	1 (7.7%)	
TI-RADS: Thyroid Imaging Reporting & Data System				

Table 2: Distribution of patients in terms of gender, age, blood parameters, Metzer index, neutrophil-lymphocyte ratio, and systemic inflammatory indices.

		Malign	Benign	p-Value
Gender	Female	40 (36.4%)	70 (63.6%)	
	Male	13 (43.3%)	17 (56.7%)	
Age		47.1 ± 13.6 (20-76)	49.9 ± 11.7 (21-76)	0.19
Thyroid Stimulating Hormone		1.8 mU/ml ± 2.6 mU/ml (0.0-17)	2.3 mU/ml ± 9.05 mU/ml (0-76.7)	0.05
Free Triiodotironin (fT3)		4.8 pg/ml± 1.4 pg/ml (2.5-13.6)	4.8 pg/ml± 1.1 pg/ml (2.7-12.5)	0.43
Free Tiroksin (fT4)		12.5 ng/dl ± 2.5 ng/dl (5.3-20.3)	12.5 ng/dl ± 3.9 ng/dl (2.4-41.1)	0.66
Neutrophil		4.5 (10^3/uL) ± 1.8 (10^3/uL) (2.28-14.1)	4.07 (10^3/uL) ± 1.3 (10^3/uL) (1.86-8.7)	0.10
Lymphocyte		2.1 (10^3/uL) ± 0.5 (10^3/uL) (0.8-3.3)	2.2 (10^3/uL) ± 0.6 (10^3/uL) (1.2-4.1)	0.98
Red Blood Cell (Rbc)		4.7 (10^6/uL) ± 0.4 (10^6/uL) (3.9-5.7)	4.5 (10^6/uL) ± 0.5 (10^6/uL) (3.6-7.1)	0.07
Platelet (Plt)		305.8 ± 313.9 (128-2500)	259.6 ± 59.3 (147-399)	0.56
Mean Corpuscular Volume (MCV)		85.6 fL ± 10 (29-96)	85.6 fL ± 10.4 (29-99.4)	0.83
Mentzer index		18.3 ± 2.9 (6-23.5)	18.9 ± 3.1 (6.9-25.7)	0.42
Neutrophil Lymphocyte Ratio (NLR)		2.3 ± 1.7 (1-11.5)	1.9 ± 0.8 (0.6-6.9)	0.10
Systemic Immune Inflammatory Index (SII)		715.2 ± 871.4 (224.2-5643.9)	504.5 ± 261.2 (140.8-1732.1)	0.11

According to the results of the histopathological examination, when the patients are categorized according to the presence of benign and malignant disease:

Patients With Malignant Thyroid Nodules

Malignant thyroid nodules were determined in 54 (38%) patients in histopathological examination. Forty (75%) of the patients were female, and 13 (25%) were male. The mean age of the patients was 47.1 ± 13.6 (20-76), mean TSH value was 1.8 mU/ml ± 2.6 mU/ml (0.0-17), mean fT3 value was 4.8 pg/ml ± 1.4 pg/ml (2.5-13.6), mean fT4 value was 12.5 ng/dl ± 2.5 ng/dl (5.3-20.3), mean neutrophil value was 4.5 (10^3/uL) ± 1.8 (10^3/uL) (2.28-14.1), mean lymphocyte value was 2.1 (10^3 /uL) ± 0.5 (10^3/uL) (0.8-3.3), mean Rbc value was 4.7 (10^6/uL) ± 0.4 (10^6/uL) (3.9-5.7), mean plt value was 305.8 ± 313.9 (128-2500), mean MCV value was determined as 85.6 fL ± 10 fL (29-96). US revealed TIRADS 2 findings in 5 (9%) patients, TIRADS 3 findings in 8 (15%) patients, TIRADS 4 findings in 32 (59%) patients, and TIRADS 5 findings in 9 (17%) patients. FNB revealed Bethesda 2.5 in 12 (22.2%) patients, Betheta 3-4 in 5 (9.4%) patients, Bethesda 5 in 25 (46.2%) patients, and Bethesda 6 in 12 (22.2%) patients (Table 1,2).

Mean MI was 18.3 ± 2.9 (6-23.5), mean NLR rate was 2.3 ± 1.7 (1-11.5), mean SII was 715.2 ± 871.4 (224.2-5643.9) (Table 1,2).

Patients With Benign Thyroid Nodules

Benign thyroid nodules were found in 86 (62%) patients in histopathological examination. Seventy (80%) of the patients were female and 17 (20%) were male. The mean age of the patients was 49.9 ± 11.7 (21-76). The mean TSH value of the patients was 2.3 mU/ml± 9.05 mU/ml (0-76.7), the mean fT3 value was 4.8 pg/ml ± 1.1 pg/ml (2.7-12.5), the mean fT4 value was 12.5 ng/dl ± 3.9 ng/dl (2.4-41.1), the mean neutrophil value was 4.07 (10^3/uL) ± 1.3 (10^3/uL) (1.86-8.7), the mean lymphocyte value was 2.2 (10^3/uL) ± 0.6 (10^3/uL)) (1.2-4.1), the mean Rbc value was 4.5 (10^6/uL) ± 0.5 (10^6/uL) (3.6-7.1), the mean Plt value was 259.6 ± 59.3 (147-399), the mean MCV value was 85.6 fL ± 10.4 fL (29-99.4). Ultrasonographic examination of the patients revealed TIRADS 2 findings in 20

(23.2%) patients, TIRADS 3 findings in 46 (54%) patients, and TIRADS 4 findings in 20 (23.2%) patients. Fine needle aspiration biopsy revealed Bethesda 2 in 49 (57%) patients, Betheta 3-4 in 7 (8.1%) patients, Bethesda 5 in 29 (33.7%) patients, and Bethesda 6 in 1 (1.2%) patients (Table 1,2). The mean MI was 18.9 ± 3.1 (6.9-25.7), the mean NLR was 1.9 ± 0.8 (0.6-6.9), the mean SII was 504.5 ± 261.2 (140.8-1732.1) (Table 1.2).

There was no significant difference in terms of age and gender between patients with malignant and benign diseases as a result of histopathological examination (p values 0.19, 0.48, respectively).

Although the rate of TIRADS 2 and 3 diseases in the US examination was higher in patients with benign thyroid nodules than in patients with malignant nodules, the rate of TIRADS 4 and 5 diseases in the US was statistically significantly higher in patients with malignant thyroid nodules (p= 0.00).

Bethesda 2,3,4 disease rate in fine-needle aspiration biopsy was found to be statistically significantly higher in patients with benign thyroid nodules in histopathological examination. Bethesda 5,6 disease rate in fine-needle aspiration biopsy was found to be statistically significantly higher in patients with malign thyroid nodules in histopathological examination. (p=0.00).

We evaluated the preoperative blood parameters of the patients, and no significant difference was found between the groups in terms of TSH, fT3, fT4, neutrophil, lymphocyte, RBC, PLT, MCV, MI, NLR, and SII in patients with malignant disease (respectively p. values: 0.05, 0.43, 0.66, 0.10, 0.98, 0.07, 0.56, 0.83, 0.42, 0.10, 0.11).

In the ROC analysis, it was observed that the MI (AUC: 0.46), NLR (AUC: 0.58), and SII (AUC: 0.57) failed to predict malignancy in thyroid nodules (Figure 1).

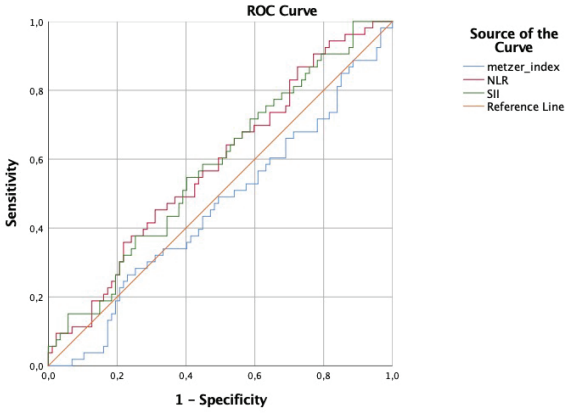

Figure 1: ROC analysis of the power of Mentzer index, Neutrophil Lymphocyte ratio, and Systemic immune-inflammatory index to predict Thyroid malignancy.

DISCUSSION

Since inflammation has a critical role in malignancy, there are studies proposing that NLR may also increase in malignancies in the literature[14–18]. Kocer D. et al. In their study with 232 patients who were operated on for multinodular goiter in 2015, stated that NLR might be used to differentiate malignant and benign thyroid diseases[19]. Song CY et al., in their study with 220 patients in 2021, stated that NLR might be used to predict lymph node metastases in the central neck region in Papillary Thyroid Cancer patients[9]. On the other hand, Ito Y et al. stated that the prognosis would be worse in the presence of distant metastases in PTC and in cases where NLR is >3[20]. In our study, we did not find a statistically significant difference in terms of NLR between patients with benign or malignant thyroid nodules. The reason why the difference between the two groups was not statistically significant may be the fact that NLR is not specific for malignancy; there may be other accompanying inflammatory diseases that may affect the rate of NLR together with the thyroid disease present in the patients. Furthermore, the inflammatory response may be different in each patient.

SII is calculated by multiplying platelet and NLR and also increases in cases of increased inflammation[21]. Various

studies in the literature propose that SII may be used to determine prognosis in patients with malignant disease[22–24]. Zhang et al. stated that SII could be used to predict central lymph node metastasis in PTC patients in their study conducted in 2021 with 406 PTC patients with no clinically detected central neck lymph node metastasis (cN0)[21]. In our study, we did not find a significant difference between patients with benign and malignant disease in terms of SII. Many factors can affect the platelet count, such as spleen diseases, thrombopoietin level, and hematological diseases[25]. Moreover, in addition to these factors that can affect the platelet count, we think that the fact that many factors may affect the neutrophil and lymphocyte counts, as we mentioned above, explains the lack of statistical difference in terms of SII between groups.

The Mentzer index is calculated by dividing the mean erythrocyte volume by the red blood cell, primarily used for the differential diagnosis of iron deficiency anemia and thalassemia[26,27]. Anemia occurs in half of the cancer patients due to many etiological factors[28]. We compared the patients with malignant thyroid nodules and benign thyroid nodules in terms of MI, due to our hypothesis that there may be an increase in the Mentzer index in patients with malignant thyroid nodules. No statistically significant difference was found between the groups. Anemia in cancer patients is mainly due to tumor-related blood loss, increased red blood cell (RBC) destruction, and decreased RBC production. The reason why there was no statistically significant difference between the groups may be the absence of these three etiological factors in thyroid malignancies.

In our study, we found that the rate of detection of malignancy in nodules reported as TIRADS 4 and 5 on the US was much higher than in TIRADS 2 and 3 nodules, consistent with the literature[29]. We observed that nodules reported as high stage according to the Bethesda classification on FNA, in accordance with the literature, were more malignant than the nodules reported as lower Bethesda stage on FNA.

Management of thyroid nodules is specified in current guidelines developed based on recent developments and evidence-based medicine[5]. Diagnosis and treatments performed regardless of these guidelines for various reasons may result in overtreatment or undertreatment (30,31).

Limitations of the study

The study was conducted in a single center and with a small number of patients.

CONCLUSION

Although there are studies proposing that biological markers may be used in the differential diagnosis of thyroid diseases, there are studies in the literature suggesting that these markers have limited predictive power in the management of thyroid nodules, as in our present study. For this reason, it may be recommendable to not manage thyroid nodules in centers where there is no radiologist, surgeon, pathologist experienced in the thyroid, and patients may need to be consulted to centers where these facilities are available. Besides, it should be kept in mind that TIRADS and BETHESDA classifications are still superior to all other methods.

Conflict of Interest

None declared by the authors.

Financial Disclosure

None declared by the authors.

Ethics Comittee Approval

This is study was approved by Sakarya University Ethics Committee (01/10/ 2021: 71522473/050.01.04/64743/437).

Informed Consent

Retrospective study

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Authors contributions:

All authors have read and approved the final manuscript. Concept: R.C, Z.B and E.G, Design: R.C, Z. B, E.G, Data Collection or Processing: E.G, T.H, F.K, M.C, H.D Analysis or Interpretation: R.C, E.G, T.H Literature Search: Z.B, M.C, F.K, H.D, Writing: R.C, Z.B, E.G

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