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THE ROLE OF INFLAMMATORY MARKERS AND THE MODIFIED SYSTEMIC INFLAMMATORY SCORE IN BETHESDA CATEGORY 3 AND 4 PATIENTS FOR PREDICTION OF MALIGNANCY

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Abstract: Management of Bethesda Category 3 and 4 patients remains a challenge. The modified systemic inflammatory score (mSIS) and other inflammatory parameters are used for prognosis assessment in various cancers. This retrospective study aims to explore prediction strength of the inflammatory parameters in Category 3 and 4 patients. One hundred and twenty three patients had undergone thyroidectomy for Category 3 and 4 fine needle aspiration biopsy (FNAB). The data of inflammatory markers including Neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), albumin to globulin ratio (AGR) and mSIS were evaluated retrospectively. There were no statistically significant difference in inflammatory parameters between benign and malignant patients and none of the inflammatory parameters had predictivity for thyroid cancer. Also in mSIS groups, thyroid cancer incidence were similar (P=0.684). Inflammatory parameters and mSIS were failed to predict thyroid cancer in patients who had category 3 and 4 FNAB.

Keywords: Thyroid cancer, Systemic inflammatory score, Albumin, Inflammation, Neutrophil to lymphocyte ratio, Fine needle aspiration biopsy

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1. Introduction

Thyroid nodules are seen commonly in general population owing to widely use of ultrasonography (USG) (Luo et al., 2012). Fine-needle-aspiration biopsy (FNAB) is an important diagnostic tool for distinciton of malignant or benign thyroid nodules and avoids unnecessary thyroidectomies as well as reduce undesirable complications (Cibas et al., 2008). The Bethesda System was invented to eliminate confusions of interpretation in cytopathological examinations and aimed to use a common terminology in thyroid surgery era. Six categories were recommended by the authors and summarized in Table 1 (Cibas et al., 2017). Management of patients those are included in Category 3 and 4 whose have various malignancy rates remains a challenge for clinicians due to difficulties in decision surgical intervention (Anand et al., 2020).

Cancer related inflammation recently became an attractive research issue by various investigators. Cancer induced inflammation leads to contribute to a microenvironment for tumor cells and peripheral blood cell component distribution is altered in patients with cancer (Mcmillan, 2009; Chechlinska et al., 2010; Park et al., 2016; Huang et al., 2020). Lymphocyte to monocyte ratio (LMR), neutrophil to lymphocyte ratio(NLR) and platelet to lymphocyte ratio (PLR) are the most studied parameters in the literature and have been shown a significant prognostic marker in serious numbers of articles (Schwartz et al., 2020; Xia et al., 2020; Zhou et al., 2020). Recent studies revealed that albumin (ALB) and globulin (GLB) levels are not only useful indicators of nutritional status of the patients, but also can be a prognostic factors in various cancer types due to being a part of systemic inflammation process (Suh et al., 2014; Deng et al., 2016).

Systemic inflammation score (SIS) has been developed to predict prognosis of various cancer types including colorectal cancers, gastric cancers and urinary system cancers (Chang et al., 2015; Watt et al., 2017; Hara et al., 2020). That scoring system based on basic preoperative blood parameters including albumin levels and lymphocyte to monocyte ratio (LMR). Shortly after development of SIS, Lin et al proposed a modified systemic inflammation score (mSIS) system in gastric cancer patients and various studies had been published including other types of cancer (Kanda et al., 2019; Lin et al., 2019; Ataş et al., 2021).

The present study aims to evaluate the malignancy prediction strength of blood cell components and mSIS in patients with Bethesda Category 3 and Category 4.

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Table 1. Bethesda Classification

Category	Description
I	Non-diagnostic or unsatisfactory
II	Benign
III	Atypia of undetermined significance or follicular lesion of undetermined significance
IV	Follicular neoplasm or suspicious for a follicular neoplasm
V	Follicular neoplasm or suspicious for a follicular neoplasm
VI	Malignant

2. Material and Methods

One hundred and twenty three patients whom performed thyroidectomy and those had Bethesda Category 3 and 4 FNAB results between 2016 and 2021 were included the study. Systemic inflammatory diseases, hematological disorders, serious liver and renal diseases, cancer history and anti-inflammatory drug use were accepted as exclusion criteria. All the USG guided FNA specimens were obtained by experienced radiologists or endocrinologists. Demographics of patients (Age, sex), preoperative USG and preoperative cytology results, preoperative albumin and globulin levels, albumin to globulin rate (AGR) and CBC results were collected from hospital data management system and evaluated retrospectively. The mSIS was calculated for every patients as described previously (Table 2) and the patients were divided into three mSIS groups. This study was conducted with the permission of Local ethics board.

Table 2. Modified systemic inflammatory score

mSIS	Definiton
mSIS : 0	Albumin ≥4.0 g/dl and LMR ≥3.4
mSIS : 1	Albumin <4.0 g/dl or LMR< 3.4
mSIS : 2	Albumin <4.0g/dl and LMR<3.4

mSIS= modified systemic inflammatory score, LMR= lymphocyte to monocyte ratio.

2.1. Statistical Analysis

Statistical analyzes were performed with IBM SPSS software, version 25. Normality of data distribution were assessed with the Kolmogorov Smirnov test and either Student-t Test or Mann Whitney-U test were used according to the normality test for analyzing continuous variables. Categorical variables were analyzed with Chi-square tests. A P value of < 0.05 was accepted as statistically significant in all tests (Önder, 2018).

3. Results

Totally 123 patients were included the study and 34 of 123 (27.6%) patients had diagnosed thyroid cancer (TC) after their final histopathological examination. All of the patients diagnosed TC had papillary thyroid cancer (PTC) and of these, 12 patients had papillary microcarcinoma subtype. Total thyroidectomy was performed in majority of the cases (110 of 123, 89.4%) and there were no 30-day mortality. Patients' characteristics were summarized in Table 3. There was no significant difference between benign and malignant group in terms of age, sex and nodules size (P=0.568, P=0.274 and P=0.242 respectively).

Table 3. Patient characteristics and comparisons of benign and malignant patients

	Bening	Malignant	Total	P
Age (years)	47.66 (SD:12.65)	46.24 (SD:13.60)	47.27 (SD:12.88)	0.568 *
Sex (%)				
Male	18	4	22	0.274¥
Female	71	30	101	
	89	34	123	
Nodul size** (mm)	24.02 (SD:11.03)	23.68 (SD:16.99)	23.93 (SD:12.88)	0.242 *
Operation				
Total thyroidectomy	79	31	110	0.697¥
Subtotal thyroidectomy	10	3	13	
Totally	89	34	123	
Lymphocyte (/µL)	2.21 (SD:0.59)	2.09(SD:0.59)	2.17(0.59)	0.318 ±
Monocyte (/µL)	0.50 (SD:0.16)	0.64 (SD:1.01)	0.54(SD:0.54)	0.601 *
LMR	4.77 (SD:1.66)	4.72 (SD:1.96)	4.75 (SD:1.74)	0.897 ±
AGR	1.416 (SD:0.29)	1.506 (SD:0.26)	1.441 (SD:0.29)	0.101*
NLR	2.194 (SD:1.38)	2.197 (SD:0.88)	2.194 (SD:1.26)	0.645*

*=Mann-Whitney U test, ¥= Chi-square test , ±= Student t test, **= The biggest nodule diameter in patients with multinodular goiter, SD= standart deviation , LMR= lymphocyte to monocyte ratio, AGR= albumin to globulin ratio, NLR= neutrophil to lymphocyte ratio.

Inflammatory markers including LMR, AGR did not show statistically significant difference between the groups (P=0.101 and P=0.897, respectively). When the patients were disturbed according to the mSIS value, 103 patients were in mSIS-0 group, 16 patients were in mSIS-1 group and remaining 4 patients were in mSIS-2 group, malignancy rates did not showed significant difference between the groups (Table 4).

Table 4. Relationship between mSIS groups and pathology results after surgery

	mSIS 0	mSIS 1	mSIS 2	Total	P
Benign	73	13	3	89	
Malignant	30	3	1	34	0.684*
Total	103	16	4	123	

*= Chi-square test.

4. Discussion

Novel proposals usually make a great stir in surgical era especially when they are easy applicable. The idea of to diagnose cancer through simple routine laboratory tests with a little amount of blood samples is worthy of investigation for many researchers. Some inflammatory markers including lymphocyte to monocyte ratio, neutrophil to lymphocyte ratio, albumin to globulin ratio were described previously , however, majority of these studies aimed to evaluate only the prognostic significant of the aforementioned markers in different cancer types (Stotz et al., 2014; Jia et al., 2015; Gu et al., 2016; Hsueh et al., 2017; Tan et al., 2018; Song et al., 2021; Tezuka et al., 2021; Atsumi et al., 2021; Castineiras et al., 2021; Mariani et al., 2022). There were a only a few studies had been published about association between systemic inflammatory markers and prediction of cancer diagnosis (Kocer et al., 2015; Li et al., 2017; Ataş et al., 2021) .

Based on LMR and albumin levels, the mSIS index were invented and like other parameters mentioned above is also used for prognosis prediction. To date only one study had been reported in the literature that evaluated the relationship between thyroid cancer and mSIS (Ataş et al., 2021). In that study authors suggested that higher mSIS was associated with TC development risk in Bethesda Category 3 and 4 patients. Although statistically significance difference was reported, low specificity, sensitivity and predictivity values were also reported by the authors. In contrast to Atas et al (2021), we did not found any significant difference between the mSIS groups in terms of TC incidence.

Inflammation and TC association was well studied, and most of the manuscripts revealed that inflammation elements were likely to inhibit tumorogenesis and regulate the cellular homeostasis (Liotti et al., 2012; Galdiero et al., 2018; Ferrari et al., 2019). Unlikely to previous reporting, we could not able to show an association between inflammatory markers and TC diagnosis. We think, there are some possible reasons for this discordance as follows: firstly, there could be some undetected points in the preoperative period, those had effected the inflammatory markers. Second; changes in the cancer tissue microenvironment due to tumor cells did not reflect in the peripheral systemic blood circulation. Third; other factors in the tumor development might influenced the results.

Similar to our findings a recent meta-analysis of 6283 patients, Liu et al showed that preoperative NLR values were not significantly different between patients with TC and those with benign histology (Liu et al., 2016). Also Yaylacı et al. (2016) evaluate the hematological parameters in patients with TC and benign nodular goitre, and they had concluded that the hematological parameters were not helpful. To the best of our knowledge, our study is the second in the literature to explore the thyroid malignancy prediction strength of mSIS and contrary results were found with previous report by Ataş et al. (2016).

This study has some limitations. This is a retrospective study with a relatively small number of patients. Number of patients in groups were not equal and sample size were small, which could cause limited statistical power.

5. Conclusion

In conclusion, the power of mSIS and other systemic inflammatory parameters need further well designed validation studies which include large number of patients. With having low sensibility and specificity rates in previous studies, the use of these parameters should be considered carefully in clinical practice.

Author Contributions

Concept: S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%), Design: S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%), Supervision: S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%), Data collection and/or processing: S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%), Data analysis and/or interpretation: S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%), Literature search: S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%), Writing: S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%), Critical review: S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%), Submission and revision S.O. (25%), Ö.F.B. (25%), A.C.S. (25%) and A.B.Ç. (25%). All authors reviewed and approved final version of the manuscript.

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Approval/Informed Consent

Samsun Training and Research Hospital local ethics committee. Protocol number: GOKA/2021/12/7.

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