



Evaluation of Serum Neutrophil to Lymphocyte Ratio in the Results of Thyroid Fine Needle Aspiration; Can It Discriminate a Clinical Benefit for the Atypia of Undetermined Significance?

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ABSTRACT

Background Thyroid biopsy results are evaluated according to The Bethesda System for reporting thyroid cytopathology worldwide. The most ambiguous result from these categories is the Bethesda-III which is defined as “atypia of undetermined significance” (AUS). Neutrophil to lymphocyte ratio (NLR) is still evaluated in thyroid disorders and malignancy. The purpose of this study was to evaluate the NLR results in Bethesda categories and whether the NLR can discriminate a clinical benefit for the AUS category.

Material and Methods In this retrospective study, 1771 patients who had fine needle aspiration biopsy were examined. Demographic characteristics, NLR, Bethesda scores, operation rates and postoperative histopathological results were recorded.

Results The categories were; Bethesda-I for 298 (16.8%), Bethesda-II for 1320 (74.5%), Bethesda-III for 60 (3.4%), Bethesda-IV for 27 (1.5%), Bethesda-V for 36 (2%), Bethesda-VI for 30 (1.7%) results respectively. The mean NLR was 2.68. There was no statistically significant difference between groups in terms of NLR ($p=0.250$). Overall, 226 (12.76%) patients were underwent thyroidectomy. The AUS group was found by 3.4%, operation rate was 21.66% and malignancy rate was 23.07%. There was a statistically significant difference between Bethesda scores and malignancy rates ($p<0.001$). There was no statistically significant difference between the postoperative results in terms of NLR ($p=0.973$).

Conclusions The NLR does not differ according to the Bethesda categories neither the postoperative histopathological results. It is not a predictive parameter for the benign or malignant differentiation. We think that NLR cannot discriminate a clinical benefit for the surgery decision in the follow-up of the AUS category.

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Introduction

Thyroid nodule is a frequent problem in the clinical practice. While the detection rate of the nodule by the palpation is about 4% due to the inability to recognize the small ones, this rate is up to 68% by the thyroid ultrasonography (USG).¹ Malignancy rate in thyroid nodule is about 5-10% that is why a careful examination is required.¹ The gold standard diagnostic method for the thyroid nodule is fine-needle aspiration biopsy (FNAB) and cytopathologic evaluation. The Bethesda System for reporting thyroid cytopathology (TBSRTC) has been used increasingly since 2007 to classify thyroid nodules and this system broadly classifies thyroid nodules into six categories stratified by risk of malignancy.² In these categories, atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) category is still the most ambiguous and it is not benign neither malignant.

This category introduce the suspicious, atypical cytological or architectural features, but do not diagnose follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN), suspicious for malignancy (SM) status.

Systemic inflammatory response was found to be related to cancer pathophysiology in recent years.³⁻⁵ Neutrophil to lymphocyte ratio (NLR) is an indicator of systemic inflammatory response and has been associated with the pathogenesis, development, progression, metastasis and even respond to treatment in solid tumors especially.⁶⁻⁸ Many studies evaluating NLR in terms of thyroid malignancy give dissimilar results.⁹⁻¹³ On the other hand, the value of NLR in the benign or malignant differentiation in the AUS category is not clear.

The aim of this study is to examine the FNAB results, to compare the Bethesda categories in terms of NLR, to evaluate the pathology results in patients who underwent thyroidectomy, and to see whether NLR is effective in the benign-malignant differentiation in the AUS category.

Material and Methods

Study Design

This study is a retrospective-cohort study. The results of the patients with thyroid nodule who were admitted to Education and Research Hospital of Medicine Faculty of University Ordu and Ordu State Hospital between May 2018 and December 2019 were evaluated. Demographic information and medical histories related to disease were obtained from patient files. This study was approved by the Ethics Committee of the Medicine Faculty of University Ordu (Number 2018-111).

Patient Selection

Patients older than 18 years old with thyroid nodule and normal thyroid function tests, without any diagnosed thyroid disease were included in the study. Any systemic disease, malignancy and drug use were also in exclusion criteria.

Data Collection

Age, gender, hemogram parameters, FNAB and postoperative histopathological results were analyzed.

Laboratory and Pathological Parameters

Hemogram parameters taken before FNAB were evaluated. White blood cell count (WBC), neutrophil count (N), lymphocyte count (L), were obtained from the complete blood count report. NLR was calculated as the neutrophil count divided by the lymphocyte count.

FNAB and post-surgery specimens were evaluated by the same pathologists in our hospital. According to TBSRTC, the results of FNAB were divided into six groups: I- Nondiagnostic (ND), II- Benign, III- AUS/FLUS, IV- FN/SFN, V- SM, and VI- Malignancy.

Statistical Analysis

Analysis of data used the Statistical Package for the Social Sciences 22 (SPSS, Inc, Chicago IL, USA). Continuous variables were expressed as descriptive statistics; mean, standard deviation, minimum and maximum values. Categorical variables were expressed as number and percentage. Mann-Whitney U test was used for continuous

variables. Chi-square test was used to determine the relationship between categorical variables. P values of <0.05 were considered statistically.

Results

In this study, 1771 patients were analyzed. Mean age was 54.12±13 years old. As 1,465 (82.72%) of the patients were female, 306 (17.28%) were males. The categories were; Bethesda-I for 298 (16.8%), Bethesda-II for 1,320 (74.5%), Bethesda-III for 60 (3.4%), Bethesda-IV for 27 (1.5%), Bethesda-V for 36 (2%), Bethesda-VI for 30 (1.7%) patients respectively. There was no difference in term of gender but a significantly statistical difference in term of age between the groups ($p=0.026$). Descriptive parameters are given in Table 1. The mean NLR value was 2.68 (0.59-16.80); 3.12 (0.69-15.7) for males and 2.59 (0.59-16.80) for females. The median value of NLR was found to be 2.11.

There was no statistically significant difference between Bethesda groups in terms of NLR ($p>0.05$) (Table 2).

It was detected that 226 (12.76%) patients were underwent thyroidectomy during the follow-up period.

These patients were 33 (11.07%) of 298 in Bethesda-I, 87 (6.59%) of 1,320 in Bethesda-II, 13 (21.66%) of 60 in Bethesda-III, and all of the Bethesda-IV, Bethesda-V, Bethesda-VI groups. The postoperative histopathological results were found benign in 133 patients and malign in 93. No significant difference was found between the benign and malign results in terms of NLR. Postoperative histopathological results were given in Table 3.

The malignancy rates in patients with thyroidectomy were 12.5% in Bethesda-I, 26.43% in Bethesda-II, 23.07% in Bethesda-III, 40.74% in Bethesda-IV, 61.1% in Bethesda-V, and 93.3% in Bethesda-VI groups. There was a statistically significant difference between Bethesda scores and malignancy rates ($p<0.001$). No statistically significant difference was found between the patients with thyroidectomy in Bethesda groups in terms of NLR (Table 4).

Discussion

In this study, 1,465 (82.7%) of 1,771 patients with thyroid nodule were female and 306 (17.3%) were males. According to TBSRTC, the results were in benign (Bethesda-II) category for 1,097 (74,93%)

Table 1. Demographic characteristics of the groups

Variables	Bethesda-I (n=298)	Bethesda-II (n=1320)	Bethesda-III (n=60)	Bethesda-IV (n=27)	Bethesda-V (n=36)	Bethesda-VI (n=30)	P value
Age (mean±sd) (range)	54.33±13.4 (23-91)	54.15±13.1 (21-95)	56.32±14.0 (27-86)	52.70±17.2 (24-84)	55.78±14.9 (16-88)	45.97±14.9 (15-77)	0.026
Gender							
Female	235	1098	49	25	33	25	0.165
Male	63	222	11	2	3	5	

sd: standart deviation, $p<0.05$ is considered to be significant

Table 2. NLR values of the groups

Variables	Bethesda-I (n=298)	Bethesda-II (n=1320)	Bethesda-III (n=60)	Bethesda-IV (n=27)	Bethesda-V (n=36)	Bethesda-VI (n=30)	P value
NLR (mean±sd) (range)	2.69±1.70 (0.67-11.9)	2.71±1.78 (0.59-16.8)	2.47±1.78 (0.74-9.14)	2.28±0.91 (1.17-4.40)	2.29±1.61 (0.70-8.90)	2.80±1.63 (0.72-6.70)	0.250

sd: standart deviation, $p<0.05$ is considered to be significant, NLR: Neutrophil to lymphocyte ratio

Table 3. Postoperative histopathological results according to Bethesda Scores

Pathology Results	Bethesda-I (n=33)	Bethesda-II (n=87)	Bethesda-III (n=13)	Bethesda-IV (n=27)	Bethesda-V (n=36)	Bethesda-VI (n=30)	Total N=226
Benign							
Multinodular goiter	11	18	2	6	3	-	43
Colloidal nodule	2	2	1	1	3	-	9
Nodular hyperplasia	9	33	4	3	2	-	51
Follicular adenoma	6	2	1	1	2	1	13
Hashimoto's thyroiditis	-	1	-	1	1	-	3
Lymphocytic thyroiditis	-	4	1	1	1	-	7
Adenomatous hyperplasia	-	3	-	1	1	-	5
Diffuse hyperplasia	-	-	-	1	1	-	2
Granulomatous thyroiditis	-	1	-	1	-	1	3
Malign							
Papillary cancer	4	20	2	7	16	24	70
Hurtle cell neoplasia	-	1	1	2	4	-	8
Oncocytic cell nodule	1	1	1	2	1	-	6
Mucoepidermoid carcinoma	-	-	-	-	1	2	3
Medullary carcinoma	-	1	-	-	-	2	3
Total	33	87	13	27	36	30	226

women and 222 (72.07%) men. It is known that thyroid nodules are approximately 4 times more common and benign in women than men.¹ We found similar results in this study. Although the Bethesda-VI age was significantly lower than the other groups, it was compatible with the ages at which thyroid cancer was seen and was not in the primary aim of our study.

In this study, no significant difference was found between Bethesda groups in terms of NLR. Many studies of the NLR in the thyroid diseases are mostly on its evaluation in benign-malign differentiation and offers contrasting results. In the study of Kocer *et al.*⁹, NLR was significantly higher in the papillary thyroid cancer group than the multinodular goiters group. Similarly, Çadırcı *et al.*¹⁰ reported a significant difference in NLR between the differentiated thyroid cancer and healthy groups. In another study, mean NLR of

malign nodule group was significantly higher than both those in benign nodule that therefore it was suggested that elevated NLR may be an indicator of underlying malign nodular disease in preoperative period.¹¹ In contrast, Yaylaci *et al.*¹² reported that NLR was not different in patients with benign nodular goiter and papillary thyroid cancer. In a meta-analysis conducted by Liu *et al.*¹³, it was concluded that the benign nodules and the differentiated thyroid cancers did not differ in terms of NLR.

In the Bethesda-VI category 30 results were detected but the malignant results increased to 93 cases according to the postoperative pathology results. Thus, malignancy rate was found to be 5.24% in this study. This rate is similar to the expected rate in the population as 5-10%. Also, malignancy rates in patients with thyroidectomy were similar to those stated in TBSRTC only it

Table 4. NLR values of those operated on according to Bethesda groups

Variables	Bethesda-I (n=33)	Bethesda-II (n=87)	Bethesda-III (n=13)	Bethesda-IV (n=27)	Bethesda-V (n=36)	Bethesda-VI (n=30)	P value
NLR (mean±sd) (range)	2.61±1.75 (0.70-7.65)	2.553±1.40 (0.84-8.91)	2.49±1.20 (1.12-5.30)	2.29±0.97 (1.19-4.40)	2.58±1.25 (1.38-5.60)	2.91±1.76 (0.72-6.70)	0.973

sd: standart deviation, p<0.05 is considered to be significant, NLR: Neutrophil to lymphocyte ratio

was found to be higher in the group Bethesda-II (26.43%).¹⁴ We can think that the operation was decided according to the other malignancy criteria by the follow up although the FNAB result was benign. In this study 60 (3.4%) patients were detected as Bethesda-III. However, more recent studies have shown that the incidence of the Bethesda-III category was to be high as 10-12%.¹⁵⁻¹⁶ Essentially, AUS/FLUS implies an intermediate histologic grade between the benign and malignant grades. Therefore, it is the most undecided FNAB result about the malignancy diagnosis. In our study, 13 (21.6%) patients underwent surgery in AUS category and malignancy rate was detected as 23,07%. In the study by Eriwo *et al.*¹⁷, malignancy rate was found to be 29.8% in AUS category. Ryu *et al.*¹⁸ reported this rate as 35.3% and Mileva *et al.*¹⁹ reported as 36.1%. We think that the fallibility of the ratio may occur due to the different experiences and competencies of pathology and radiology specialists.

In this study, we found ten benign and only three malign histopathological results in patients with thyroidectomy in the AUS group. NLR comparison between these groups could not be made due to the low number of patients. In a study of the patients who underwent thyroidectomy with AUS and SM categories, a comparison was made between benign and malignant groups in terms of NLR and no significant difference was found.²⁰ On the other hand, some studies have shown that the other criteria are much important than the NLR as well as the pathological results in the malignancy diagnosis and surgical decision of the AUS category. In the study of Ryu *et al.*¹⁸, the increase in age was found to be parallel with the increase in the risk of thyroid malignancy in the patients with Bethesda-III category by the follow-up. In the study of Remonti *et al.*²¹ it was reported that microcalcification and central

vascularization provides by 96% the malignancy diagnosis in Bethesda-III category.

There are some studies in which the NLR was evaluated in the thyroid malignancy based on thyroiditis. Kocer *et al.*⁹ reported that there was no difference in NLR between papillary thyroid cancer groups with and without lymphocytic thyroiditis on the basis. Similarly, in the study of Eroglu *et al.*²², NLR was evaluated in nodular hyperplasia, thyroiditis, papillary ca and papillary ca with thyroiditis. No statistical difference was found between the groups in terms of NLR. Ari *et al.*²³ found that the mean NLR was significantly higher in the thyroiditis group and non-significantly higher in the papillary cancer group than in the healthy group. However, no significant difference was found between the thyroiditis and papillary cancer groups. In our study, postoperative histopathological results revealed 3 granulomatous and 3 Hashimoto thyroiditis and 7 lymphocytic thyroiditis. In the AUS group, there was only one lymphocytic thyroiditis. Unfortunately, the low number of thyroiditis was insufficient for us to compare the effect of thyroiditis on NLR in this study.

We recognize certain limitations to our study. Firstly and major limitation was the retrospective design and relatively small simple size in AUS category. Secondly, the number of patients in the groups was heterogeneous, which may have statistically negatively affected our results. Thirdly, it was limited to a certain geographical region; therefore, the results may not be generalizable. Despite these limitations, there is an advantage of this study such as there are a limited number of studies in the literature that examine the relationship between the AUS category and NLR, but this relationship is not clear yet. We hope that it can make a concept for the future studies.

Conclusions

In conclusion, the present study showed that NLR does not differ according to Bethesda categories.

Additionally, the patients who underwent thyroidectomy also did not show any difference in NLR from those who did not. Moreover, there was no difference in NLR between benign and malignant postoperative histopathologic results. We think that it is not possible to say that NLR has a predictive role in making the decision of follow-up or surgery in the AUS category.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: OO; Study Design: OO, HC; Supervision: OO; Materials: OO, HC, CA, MCA; Data Collection and/or Processing: OO, HC, CA, MCA; Statistical Analysis and/or Data Interpretation: CA; Literature Review: OO; Manuscript Preparation: OO; and Critical Review: OO, HC, CA.

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