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Predictive role of neutrophil-lymphocyte and platelet-lymphocyte ratios in thyroid nodules with cytological diagnosis of "undetermined significance" and "suspicious for malignancy"

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Abstract

Objective: To evaluate the predictive role of complete blood count (CBC) parameters in thyroid cytological diagnosis in patients with the diagnosis of undetermined significance (AUS) and suspicious for malignancy (SM) in hematological inflammatory parameters.

Methods: The preoperative CBC of 127 patients who underwent total thyroidectomy were retrospectively evaluated. While 52 patients were defined as AUS (Group 1), 75 patients were defined as SM (Group 2) in thyroid fine-needle aspiration cytology. Both groups were divided into benign and malignant sub-groups according to histopathological diagnosis of thyroidectomy specimens. In each group, the preoperative hematologic parameters (leukocyte, neutrophil, lymphocyte, platelet, neutrophil/lymphocyte ratio 'NLR', platelet/lymphocyte ratio, 'PLR') were compared with respect to malignancy, tumor size, stage and multicentericity of cancer.

Results: The statistical analysis showed that there was no significant difference in comparison of hematological parameters in benign and malignant groups.

Conclusion: Our study showed that there was no role of NLR and PLR in the cytological diagnosis of AUS and SM to predict malignancy. There was also no correlation of hematological parameters to tumor size, multicentricity, and central lymph node metastasis.

Keywords: Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, thyroid, fine-needle aspiration biopsy, undetermined significance, suspicious for malignancy.

Özet: Sitolojik tanısı "önemi belirlenememiş" ve "malignite kuşkusu" olan tiroid nodüllerinde nötrofil-lenfosit ve trombosit-lenfosit oranlarının prediktif rolü

Amaç: Önemi belirlenememiş tanısı alan ve hematolojik enflamatuar parametreleri malignite kuşkusu taşıyan tiroid hastalarının sitolojik tanısında tam kan sayımı (TKS) parametrelerinin prediktif rolünü değerlendirmek.

Yöntem: Total tiroidektomi geçirmiş 127 hastanın preoperatif TKS'leri retrospektif olarak değerlendirildi. İnce iğne aspirasyon sitolojisinde hastaların 52'si önemi belirlenememiş (ÖB, Grup 1) ve 75'i malignite kuşkusu (MK, Grup 2) olarak tanımlandı. Her iki grup, tiroidektomi numunesinin histopatolojik tanısına göre benign ve malign alt gruplara ayrıldı. Her bir grupta preoperatif hematolojik parametreler (lökosit, nötrofil, lenfosit, trombosit, nötrofil/lenfosit oranı 'NLO', trombosit /lenfosit oranı 'TLO') malignite, tümör büyüklüğü, evresi ve kanserin çok merkezli olması açısından karşılaştırıldı.

Bulgular: İstatistiksel analiz benign ve malign gruplarda hematolojik parametrelerin karşılaştırmasında önemli bir farklılık olmadığını gösterdi.

Sonuç: Çalışmamız maligniteyi öngörmede NLO ve TLO'nun sitolojik ÖB ve MK tanısında herhangi bir rolünün olmadığını göstermiştir. Hematolojik parametreler tümör büyüklüğü, çok merkezlilik ve santral lenf nodülü metastazı ile de korele değildir.

Anahtar sözcükler: Nötrofil-lenfosit oranı, trombosit-lenfosit oranı, tiroit, ince iğne aspirasyon biyopsisi, belirlenememiş önem, malignite kuşkusu.

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Thyroid cancer is the most common malignancy of the endocrine system, and the incidence of thyroid cancer is increasing more rapidly than any other cancer.[1,2] Over the past few decades, there has been a dramatic increase worldwide in the number of people diagnosed with thyroid cancer and died of the disease.[2] This rise is attributable to the improved detection methods due to more sensitive diagnostic procedures. Most patients with thyroid cancer do not have any symptoms; typically, they present with a thyroid nodule discovered incidentally during a routine physical examination or on an imaging testing. The thyroid nodule refers to an abnormal growth of thyroid cells that forms a lump within the thyroid gland and majority of thyroid nodules are benign.[3] In the adult population, the incidence of thyroid nodules is 19–67% by high-resolution ultrasound examination. The incidence is relatively higher in women and the elderly, but just 5–15% of the nodules contain thyroid cancer.[4]

Fine-needle aspiration (FNA), as being the gold standard diagnostic method, can rule out cancer. Therefore, the use of FNA for cytopathologic evaluation helps to avoid unnecessary surgery. According to the result of FNA, 60–70% of thyroid nodules are benign, 4–10% are malignant. However, 20–30% of FNA are reported as "atypia of undetermined significance" (AUS), "suspicious for malignancy" (SM) or "nondiagnostic". For an accurate diagnosis, surgery is performed in 80% of these group of nodules and just 6–30% came out as malignant.[3] The group of FNA with the diagnosis of follicular neoplasm usually undergo a surgical procedure.

In the "suspicious" group of cytological diagnosis, further differentiating factors are needed. Various molecular markers have been examined to improve the sensitivity and specificity of FNA cytology, and some of them are being used as test panels in the clinical practice.[5,6] The neutrophil–lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) which are known markers of the systemic inflammatory response, have been associated with progression and survival in most cancers.[7,8] Therefore, we evaluated retrospectively the laboratory tests of our patients who underwent thyroid surgery. Preoperative complete blood counts values were used to predict malignancy rate of thyroid nodules defined as AUS or SM in FNA cytology.

Materials and Methods

The study protocol was approved by our Institutional Review Board. We performed a retrospective analysis, enrolling the preoperative documents of patients who underwent total thyroidectomy with the cytological diagnosis of AUS or SM between January 2010 and June 2014.

We evaluated preoperative hematological parameters; leukocyte, neutrophil, lymphocyte, platelet counts, and NLR and PLR values. The patients were divided into two groups; AUS patients as Group 1, SM patients as Group 2. Groups 1 and 2 were also divided into benign and malignant subgroups on postoperative pathological results. We also analyzed if the size of the tumor, multi-centricity, lymph node metastasis were correlated to NLR and PLR. Leukocytosis or thrombocytosis was not included in the analysis.

Other exclusion criteria were the presence of hematologic disorders, any kinds of infectious disease, patients with elevated thyroid antibodies or impaired thyroid function tests, recurrent disease, previous or accompanying other malignancies.

Statistical analysis

Data analysis was performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA) statistical package software. For the evaluation of study data, Pearson's chi-square, Fisher χ^2 or Yates χ^2 tests were used along with descriptive statistical methods (frequency, percentage, mean, standard deviation). The suitability of the normal distribution of the data was evaluated with Kolmogorov-Smirnov test. Independent samples t-test and one-way ANOVA were used for evaluation of quantitative data with a normal distribution. For the data that were not normally distributed Mann-Whitney U test and Kruskal-Wallis test were used. The p-value <0.05 was regarded as statistically significant.

Results

A total of 127 (F/M: 107/20) patients were enrolled in the study. The overall mean age was 47.17 years, and there was no statistical difference in mean ages of sexes. Fifty-two (F/M: 41/11) patients with the diagnosis of AUS and 75 (F/M: 66/9) patients with the diagnosis of SM were derived from the database. The postoperative histopathological examination of 60 patients was diagnosed as benign goiter, 37 patients with micropapillary carcinoma (PMTC) and 30 patients with papillary thyroid carcinoma (PTC). There was no correlation between the sex and the possibility of malignancy.

There were no statistical differences in the preoperative values of NLR and PLR in predicting malignancy (Table 1). When we analyzed the tumor size, there was no significant correlation found relevant to PMTC and PTC groups (Table 1). The data in Tables 2 and 3 show that no statistical differences were found when comparing NLR and PLR to stage, multicentricity of cancer and central lymph node metastases.

Table 1. The comparison of hematological parameters in benign and malignant groups including PMTC and PTC in all patients.

Parameters	Benign (n=60)	Malignant (n=67)	p^1	PMTC (n=19)	PTC (n=48)	p^2
Wbc	8±2.3	8±2.3	0.7	7.7±2.2	8.1±2.4	0.8
Neu	5±2.2	5±4.5	0.9	4.7±1.7	5.1±2.3	0.9
Lym	2.2±0.9	2.02±0.7	0.7	2.2±1.4	2.1±0.6	0.7
NLR	2.6±2.2	2.6±2.33	0.3	2.4±1.5	2.7±2.6	0.7
Plt	258.2±57.7	254.3±59.4	0.4	256.2±70	247.9±58.3	0.6
PLR	130.9±52.5	124.5±45.5	0.4	127.3±41.7	123.4±47.2	0.6

p^1: comparison of the hematologic parameters of benign group with malignant group' (Mann-Whitney U test), p^2: comparison of the hematologic parameters between benign, PMTC and PTC groups (Kruskal-Wallis test)

In Group 1, 52 (female/male: 41/11) patients with the diagnosis of AUS were identified from the database. The mean age was 50.5±14.4 years and there was no statistical difference in mean age between sexes. There was no significant correlation of the hematological parameters to malignancy and tumor size (Table 4). Due to the low numbers in sub-groups, it was not possible to compare NLR and PLR to stage and multicentricity of cancer.

In Group 2, we evaluated 75 (female/male: 66/9) patients with the diagnosis of SM-derived from the database. The mean age was 44.8±12.3 years, and there was no statistical difference in age between sexes. No correlation was found between sex and the possibility of malignancy. There was no statistical difference in the preoperative hematological parameters between the benign and malignant groups. According to tumor size, there was no significant difference of the hematologic parameters as well (Table 5). Stage of cancer, lymph node metastasis, and multicentricity analysis were not done due to low numbers in the sub-groups.

Table 2. Distributions of hematological parameters of malignant group by stage (Mann-Whitney test).

All groups	Stage 1 (n=53)	Stage 2–4 (n=9)	p
Wbc	7.9±2.3	8.3±2.7	0.7
Neu	5.0±2.2	5.1±2.1	0.9
Lym	2.1±0.7	2.3±0.7	0.5
NLR	2.7±2.6	2.2±1.1	0.6
Plt	250.6±60.9	248.1±67.2	0.8
PLR	127±46.3	112.5±36.5	0.3

Discussion

After an association between cancer and inflammation has been discovered, markers of the systemic inflammatory response have been used to predict relapse and survival in patients with various cancers.[9,10] Chronic irritation such as exposure to smoking and subsequent inflammation may predispose to cancer.[11] Chronic infection with hepatitis viruses causing carcinoma is a well-known fact. The inflammatory component is present in the microenvironment of tumors due to both cytokines being released from either tumor or the host immune system.[12] The resulting production of free radicals such as reactive oxygen intermediates and reactive nitrogen intermediates lead to oxidative damage and DNA mutations.[12] Cancer-related inflammation causes suppression of antitumor immunity

Table 3. Distributions of hematological parameters of malignant group by multicentricity and lymph node metastases (Mann-Whitney test).

	Unifocal disease (n=52)	Multifocal disease (n=9)	p	Lymph node metastases		
				Negative (n=12)	Positive (n=5)	p
Wbc	81±2.4	7.7±2.1	0.6	8.6±2.6	8.7±1.8	0.2
Neu	5.1±2.3	4.5±1,1	0.6	5.1±2.31	5.3±1.6	0.6
Lym	2.1±0.7	2.3 ±1.2	0.9	2.5±1	2.3±0.4	0.9
NLR	2.7±2.6	2.1±0.7	0.8	2.2±1	2.2±0.7	0.6
Plt	253.8±61.92	221.7±58.7	0.1	252±62.6	261.8±26.7	0.7
PLR	128.6±48.6	102.8±46.8	0.2	110.7±43	113.2±20.7	0.5

Table 4. The comparison of hematological parameters with respect to tumor size in Group 1.

Group 1	Benign (n=30)	Malignant (n=22)	p^1	PMTC (n=13)	PTC (n=9)	p^2
Wbc	8.3±2.8	7.5±2.3	0.3	7.6±2.6	7.4±1.9	0.9
Neu	5.4±2.8	4.8±2.5	0.4	4.9±3.0	4.6±1.5	0.6
Lym	2.1±0.9	2.0±0.6	0.7	2.1±0.7	2.0±0.4	0.8
NLR	3.1±2.8	2.9±3.6	0.8	3.4±4.6	2.2±0.6	0.5
Plt	253.7±64.5	237.3±64.4	0.3	244.5±74.9	226.8±47.6	0.9
PLR	139.3±51.1	125.4±51.2	0.3	133.6±63.1	113.6±25.4	0.7

p^1: comparison of the hematologic parameters of benign group and malignant groups' (Mann-Whitney U test), p^2: comparison of the hematologic parameters between benign, PMTC and PTC groups (Kruskal-Wallis test)

by recruiting T cells and activating chemokines, which results in tumor growth and metastasis.[13]

The mechanism of interaction between cancer and neutro¬philia and leukocytosis remains unclear; however, experimental data indicates that activated neutrophils may directly and indirectly stimulate tumor growth.[14] Also, low lymphocyte counts have been associated with generalized suppression of the immune systems of patients with cancer.[15] Impaired or ineffective innate cellular immunity against malignancy causes lymphopenia. Therefore, NLR elevation which facilitates tumor growth due to the imbalanced inflammatory state can be used as a possible indicator of underlying malignancy in benign neoplastic tumors.[15] NLR is an indicative of the balance between pro-tumoral inflammatory state and anti-tumoral immune state.

The combination of neutrophil lymphocyte ratio and platelet-lymphocyte ratio (CNP) was accounted for a predictor of postoperative survival in patients with esophageal squamous cell carcinoma, and CNP was associated with tumor length, depth of invasion and nodal metastasis.[13] In patients with nasopharyngeal carcinoma, NLR was significantly associated with overall survival and progression-free survival.[16] Hemoglobin, NLR and platelet count in patients with nasopharyngeal carcinoma are found useful to predict long-term mortality.[17] Another study suggests that high pretreatment NLR is significantly associated with poor disease-specific survival in oral cancer patients undergoing preoperative chemoradiotherapy.[18]

The results of studies suggested that high NLR was a negative indicator for breast cancer.[19] In the retrospective analysis of two hundred eighty-one colorectal cancer patients, high pre-treatment NLR was found to predict a shorter survival.[20] Higher PLR was also associated with higher mortality in breast cancer patients.[21] In another study, the preoperative value of PLR was a significant independent prognostic marker in patients with resected pancreatic adenocarcinoma.[22]

NLRs were found to be elevated in patients with PMTC and PTC in a pilot study.[13] In another study, although there was no difference in NLR between patients having benign and malignant thyroid nodules, larger tumor size had the higher NLR tertile.[23] However, in our study, the preoperative values of NLR or PLRs had no predictive role in malignancy status or size of tumors. Further studies with larger groups are needed to confirm these results.

Table 5. The comparison of hematological parameters with respect to tumor size in Group 2.

Group 2	Malign (n=45)	Benign (n=30)	p^1	PMTC (n=24)	PTC (n=21)	p^2
Wbc	8.3±2.4	7.6±2.3	0.2	8.0±2.2	8.7±2.7	0.6
Neu	5.2±2.1	4.6±1.7	0.2	4.9±1.8	5.5±2.5	0.6
Lym	2.3±0.9	2.5±0.9	0.3	2.3±1.0	2.3±0.7	0.9
NLR	2.5±1.5	2.1±1.5	0.2	2.5±1.7	2.5±1.4	0.9
Plt	256.6±59.4	262.9±50.8	0.6	261.7±67.6	253.3±50.2	0.7
PLR	124.1±43.1	122.6±53.5	0.8	130.4±48.2	118.1±37.9	0.5

p^1: comparison of the hematologic parameters of benign group to malignant group (Mann-Whitney U test), p^2: comparison of the hematologic parameters between benign, PMTC and PTC groups (Kruskal-Wallis Test)

One of our study's limitations was that we did not analyze the postoperative values of hematologic parameters and did not compare them with preoperative ones. Our aim was to explore a cost-effective preoperative test for a more accurate diagnosis of a thyroid nodule with a cytological diagnosis of AUS or SM. Thyroid cancer still has unsolved mysteries and secrets. Although FNA of a thyroid nodule is the gold standard test for the preoperative assessment, molecular markers or modern imaging techniques are needed to improve thyroid nodule diagnosis and distinguish benign from malignancy to avoid unnecessary surgery.

As a conclusion, we consider that preoperative NLRs and PLRs in AUS and SM groups can not be considered as a predictive diagnostic marker of malignancy. However, further studies with larger groups may reveal different results.

Conflict of Interest: No conflicts declared.

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