

Evaluation and Clinical Significance of Hemogram Parameters in Adrenal Incidentaloma Cases

Adrenal Incidentaloma Olgularında Hemogram Parametrelerinin Değerlendirilmesi ve Klinik Önemi

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Abstract

Objective	Adrenal incidentaloma (AI) are randomly detected masses in magnetic resonance imaging (MRI) or computed tomography (CT) scans taken for different reasons. Although AI is not generally known as an inflammatory clinical condition, its proinflammatory properties have been demonstrated. In this study, we aimed to investigate the relationship between AI and neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) and its clinical significance.
Materials and Methods	A total of 178 patients who were followed up in the Endocrinology clinic due to AI between January 2018 and December 2019 were retrospectively screened and analyzed.
Results	The median of NLR and PLR (IQR; 25%-75%) values were 2.21 (1.61; 1.58-3.2) and 112.56 (57.31; 87.81-145.12), respectively. According to tumor locations, median NLR (IQR; 25% -75%) values were 2.24 (1.72; 1.52-3.22) in right-sided AIs, 2.08 (1.14; 1.63-2.77) in left-sided AIs and 2.49 (2.61;1.52-4.13) in bilateral AIs, and no statistically significant difference was found (p=0.172). Likewise, the PLR median (IQR; 25%-75%) was 116.18 (61.1; 88.25-149.35) in right-sided AIs, 102.87 (52.76; 85.01-137.77) in left-sided AIs and 126.88 (66.7; 95.06-161.76) in bilateral, with no statistically significant difference (p=0.158). There was no statistically significant difference in NLR and PLR in regard of functionality (p=0.357 and p=0.174, respectively). In addition, NLR and PLR results were compared according to presence of hypertension (HT) and no difference was found (p=0.10 for NLR, p=0.32 for PLR). Of the factors examined in relation to hemogram parameters, only tumor size had a positive but low correlation with NLR (r=0.199, p=0.01).
Conclusion	In this study, we found that NLR and PLR did not increase statistically significantly in AI patients. However, there was a positive correlation between tumor size and NLR. It is concluded that although inflammatory hemogram parameters are inexpensive and easily accessible in general, there is no clinical significance in AI patients.
Keywords	Adrenal incidentaloma; Neutrophil to Lymphocyte Ratio; Platelet to Lymphocyte Ratio

Öz

Amaç	Adrenal insidentaloma (AI), manyetik rezonans görüntüleme (MRI) veya bilgisayarlı tomografi (BT) taramalarında farklı nedenlerle rastgele saptanan kitlelerdir. AI inflamatuvar bir klinik durum değildir fakat proinflatuvar özellikleri gösterilmiştir. Biz bu çalışmada AI ile nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR) arasındaki ilişkiyi ve bu oranların klinik önemini ortaya koymaya çalıştık.
Gereç ve Yöntemler	Ocak 2018 - Aralık 2019 tarihleri arasında AI nedeniyle Endokrinoloji kliniğinde takip ettiğimiz toplam 178 hasta retrospektif olarak tarandı.
Bulgular	NLR ve PLR medyan (IQR; % 25-75) değerleri sırasıyla 2.21 (1.61; 1.58-3.2) ve 112.56 (57.31; 87.81-145.12) idi. Tümör yerleşimlerine göre; NLR medyan (IQR; % 25-75) değerleri: sağ taraflı 2.24 (1.72; 1.52-3.22), sol taraflı 2.08 (1.14; 1.63-2.77) ve bilateral 2.49 (2.61; 1.52-4.13) olarak saptandı ve istatistiksel olarak anlamlı bir fark bulunmadı (p = 0.172). Benzer şekilde, PLR medyan (IQR; % 25-75) değerleri: sağ taraflı 116.18 (61.1; 88.25-149.35), sol taraflı 102.87 (52.76; 85.01-137.77) ve bilateral 126.88 (66.7; 95.06-161.76) olarak saptandı ve istatistiksel olarak anlamlı bir fark bulunmadı (p = 0.158). Fonksiyonel AI'lar ve non-fonksiyonel AI'lar karşılaştırıldığında NLR ve PLR açısından istatistiksel olarak anlamlı bir fark yoktu (sırasıyla p = 0.357 ve p = 0.174). Ek olarak, NLR ve PLR sonuçları hipertansiyon (HT) varlığına göre karşılaştırıldı ve fark bulunmadı (NLR için p = 0.10, PLR için p = 0.32). Hemogram parametreleriyle ilişkili olarak incelenen faktörlerden sadece tümör büyüklüğü NLR ile düşük fakat pozitif korelasyon gösterdi (r = 0.199, p = 0,01).
Sonuç	Bu çalışmada AI hastalarında NLR ve PLR'nin istatistiksel olarak anlamlı bir şekilde artmadığını saptadık. Ancak tümör boyutu ile NLR arasında pozitif korelasyon olduğu tespit edilmiştir. Genel olarak inflamatuvar hemogram parametrelerinin ucuz ve kolay ulaşılabilir olmasına rağmen AI hastalarında klinik bir öneminin olmadığı sonucuna varılmıştır.
Anahtar Kelimeler	Adrenal insidentaloma; Nötrofil / Lenfosit Oranı; Trombosit / Lenfosit Oranı

INTRODUCTION

Adrenal incidentaloma (AI) are randomly detected masses in magnetic resonance imaging (MRI) or computed tomography (CT) scans taken for different reasons. Its prevalence differs in distinct risk populations and generally varies between 0.4-10%.¹⁻³ The tumors are located bilaterally in 10-15% of cases with adrenal incidentaloma.⁴⁻⁵ Most of the cases are benign and only 0.7-5% are malignant.⁶⁻¹⁰ While this distinction is generally made according to imaging features, sometimes it can be diagnosed pathologically after surgery. While most adrenal incidentalomas are non-functional, 10 to 15 percent produce excess hormones, most of which are cortisol.⁶⁻⁷

Complete blood cells such as neutrophils, lymphocytes and platelets are an important part of the immune system and have been used in the evaluation of infection and inflammation for a very long time. The high neutrophil lymphocyte rate is caused by increased absolute neutrophil count and/or decreased absolute lymphocyte count. While neutrophils are part of the natural immune system, lymphocytes are part of the adaptive immune system. Neutrophil activation abnormalities have been previously investigated in many autoimmune diseases and in various acute and chronic inflammatory conditions. Adaptive immune system abnormalities leading to decreased lymphocyte count have been investigated in the pathogenesis of many autoimmune diseases. The net result of both conditions is an increased neutrophil-lymphocyte ratio.^{11,12} Platelets, on the other hand, are the cellular part of the natural hemostasis process. However, recent studies have shown that these cells also play a role in immune response. Platelets may secrete some cytokines during the inflammatory process, contributing to an increase in the number of immune cells, causing tissue destruction.¹³ In recent years, NLR and PLR have become increasingly used as predictive markers of acute and chronic inflammation.¹⁴⁻¹⁶ In addition, these markers have been used in many cancers and their effects on survival, prognosis and morbidity have been investigated.¹⁴⁻¹⁹ The prognostic significance of NLR in adrenocor-

tical cancer (ACC) has been investigated and correlated with poor prognosis.²⁰⁻²¹ However, we did not find an article in the literature where these markers were investigated in the functional distinction of adrenal incidentaloma.

In this study, we observed that neither NLR nor PLR results increased in AI patients.

Although adrenal incidentalomas are not generally an inflammatory condition, in this study, it was aimed to show the relationship of these tumors with NLR and PLE, which are cheap and easily accessible markers.

MATERIALS and METHODS

A total of 196 adrenal incidentaloma patients diagnosed between January 2018 and December 2019 at our institute were retrospectively analyzed and 178 (3 malignant diseases and 175 benign diseases) who met the inclusion criteria were included in the study. Acute and chronic inflammations, infectious conditions, and the presence of non-adrenal malignancy have been screened in all patients and positive ones were excluded from the study. In addition, patients under the age of 18 were excluded from the study. Three patients with malignancy and four patients with pheochromocytoma had a history of adrenalectomy and all these patients had pathologic confirmation. The demographic data and the functional laboratory evaluation results of all patients were recorded. NLR was calculated from the hemogram parameters that were examined when performing routine functional evaluation when tumor was detected in the adrenal gland. The hemogram parameters of the patients with adrenalectomy were obtained in the preoperative period. In accordance with previous reports, we set the cut-off value of 5 and of 190 as the threshold for defining an elevated NLR and PLR, respectively.²²

Our research is a cross-sectional type descriptive research. Local ethics committee approval (Ref. No.: 71522473/050.01.04/41) was obtained from the Sakarya University Ethics Committee. (11.02.2020)

Statistical Analysis

Data analysis was performed by using SPSS-22 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z). The variables were investigated using visual (histograms, probability plot) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. We performed analyses to describe and summarize the distributions of variables. Continuous variables were reported as the median and interquartile range (IQR) and as whole number and percentages for categorical variables. We use the Mann-Whitney U test or Kruskal-Wallis test to compare continuous nonparametric variables. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using Spearman test. The longest diameter of the larger of the lesions in both adrenal glands was taken for the tumor size value used when conducting correlation analysis. The statistically significant two tailed p-value was considered as <0.05.

RESULTS

One hundred seventeen (65.7%) of the patients included in the study were female and 61 (34.3%) were male (F/M=1.91). The average age was 59.0±11.4 years. Three cases were malignant, one of which was anaplastic pleomorphic sarcoma, one was adrenocortical cancer and one was lung cancer metastasis. Four patients had pathologically confirmed pheochromocytoma. The remaining 171 patients were followed up as benign adrenal adenoma. According to localization, 58 cases were right-sided, 81 cases were left-sided, and 39 cases were bilaterally located. Descriptive statistics were summarized in table 1. Functionally, 146 (82%) patients were nonfunctional, while the remaining 32(18%) patients were functional [cushing:27(15.2%), primary aldosteronism:1(0.6%), and pheochromocytoma:4(2.2%)]. Baseline characteristics according to the functionality of the tumor were summarized in table 2.

Table-1. Summary of the baseline demographic data, clinical findings and laboratory results of the patients.

		Mean ±Std deviation	Median (IQR)	Frequency (Percent)
Age (years)		59.0 ± 11.4		
Tumor size (mm)	right	22.8 ± 10.85		
	left	21.50 ± 8.17		
Body-mass index (kg/m ²)	female	33.84 ± 6.73		
	male	29.61 ± 5.06		
Gender	female			117(65.7%)
	male			61(34.3%)
Tumor localization	right			58 (32.6%)
	left			81 (45.5%)
	bilateral			39 (21.9%)
The functionality of the tumor	nonfunctional			146 (82%)
	cushing			27 (15.2%)
	primary aldosteronism			1 (0.6%)
	pheochromocytoma			4 (2.2%)
Histological character	benign			175 (98.4%)
	malign			3 (1.6%)
NLR			2.21 (1.58-3.2)	
PLR			112.56 (87.81-145.12)	

NLR:Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio

Table 2. Clinical and demographic characteristics of the patients according to the functionality of the tumor.

	Non-functional* (n=146)	Cushing* (n=27)	Primary aldosteronism* (n=1)	Pheochromocytoma* (n=4)
Age	58.8 ± 11.3	62.8 ± 8.4	33.0	45.8 ± 19.4
Gender (F/M, %)	66.4/33.6	66.7/33.3	0/100	50/50
Body-mass index	32.76 ± 6.23	28.89 ± 7.47	25.2	27.90 ± 6.65
Hypertension (yes, %)	52.5	81.5	100	75
diabetes mellitus (yes, %)	25.9	28.1	0	25

* The data for continuous variables were expressed as mean ± SD or as ranges.

The median of NLR and PLR (IQR; 25%-75%) values were below the levels of 5 for NLR and 190 for PLR, which we take as reference. These values were 2.21 (1.61; 1.58-3.2) and 112.56 (57.31; 87.81-145.12), respectively (table 1). According to tumor locations, median NLR (IQR; 25%-75%) values were 2.24 (1.72; 1.52-3.22) in right-sided, 2.08 (1.14; 1.63-2.77) in left-sided and 2.49 (2.61;1.52-4.13) in bilateral, and no statistically significant difference was found (p=0.172). Likewise, the PLR median (IQR; 25%-75%) was 116.18(61.1; 88.25-149.35) in right-sided, 102.87 (52.76; 85.01-137.77) in left-sided and 126.88 (66.7; 95.06-161.76) in bilateral, with no statistically significant difference (p=0.158). There was no statistically significant difference in terms of NLR and PLR even when grouped functionally (p=0.357 and p=0.174, respectively). These findings were summarized in table 3. In addition, NLR and PLR results were compared according to presence of hypertension (HT) and no difference was found (p=0.10 for NLR, p=0.32 for PLR).

Table 3. Summary of the differences between NLR and PLR results according to the localization and functionality of the tumor

		NLR Median (IQR;25%-75%)	PLR Median (IQR;25%-75%)
Tumor	Right	2.24 (1.72; 1.52-3.22)	116.18 (61.1; 88.25-149.35)
	Left	2.08 (1.14; 1.63-2.77)	102.87 (52.76; 85.01-137.77)
	Bilateral	2.49 (2.61;1.52-4.13)	126.88 (66.7; 95.06-161.76)
p value		0.172	0.158
The functionality of the tumor	Nonfunctional	2.14 (1.45; 1.57-3.02)	110.32 (58.72; 85.63-144.35)
	Functional	2.42 (1.84; 1.60-3.44)	122.09 (32.37; 93.18-155.56)
p value		0.357	0.174
NLR:Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio			

While a positive correlation was detected between NLR and PLR (r=0.544, p<0,001), a positive correlation was found between the cortisol response to 1 mg dexamethasone suppression test (DST) and tumor size (r=0.300, p<0,001). Of the factors examined in relation to hemogram parameters, only tumor size had a low but positive correlation with NLR (r=0.199, p=0,01). Correlation analysis results were summarized in table 4.

Table 4. Summary of correlation analysis (Spearman test) results between NLR, PLR, tumor size and cortisol response to 1 mg (DST).

		NLR	PLR	Tumor Size	Cortisol response to 1 mg (DST)
NLR	Correlation coefficient	1	0.544	0.199	0.061
	p value	-	<0.0001	0.01	0.458
PLR	Correlation coefficient	0.544	1	0.096	0.097
	p value		-	0.22	0.234
Tumor size	Correlation coefficient	0.199	0.096	1	0.300
	p value	0.01	0.22	-	<0.0001
Cortisol response to 1 mg (DST)	Correlation coefficient	0.061	0.097	0.300	1
	p value	0.458	0.234	<0.0001	-
NLR:Neutrophil to Lymphocyte Ratio; PLR:Platelet to Lymphocyte Ratio; DST:Dexamethasone Suppression Test					

DISCUSSION

In this study, we determined that NLR and PLR values in adrenal incidentaloma cases were not higher than normal reference range. In fact, the elevation of NLR and PLR has been documented in many studies, both in malignant diseases and in acute and chronic inflammatory conditions.¹⁴⁻¹⁹ Although adrenal incidentalomas are not generally an inflammatory clinical condition, proinflammatory cytokines such as tumor necrosis factor- α (TNF α), interleukin-6 (IL6) and monocyte chemoattractant protein-1 (MCP1) have been shown to increase in nonfunctional tumors.²³⁻²⁵ However, there are not many studies in the literature investigating the relationship between functional adrenal incidentalomas and inflammatory markers. Of these, several studies have shown that these markers are partially

elevated. Clinical researches on Cushing's syndrome can be given as an example.²⁶⁻²⁷ The reason for the result determined in this study may be that the inflammatory condition is mild in adrenal incidentaloma or the studies mentioned above have been done with a small number of patients.

A positive relationship is known between functional adrenal tumors such as Cushing's syndrome, primary aldosteronism and pheochromocytoma, and cardiovascular risk factors such as hypertension.²⁸ Some studies have investigated the relationship between hypertension and NLR and PLR. In these studies, NLR and PLR have been shown to be associated with an increase in both dipper and non-dipper pattern systolic blood pressure.²⁹⁻³¹ Unfortunately, we did not include ambulatory blood pressure monitoring in our study protocol. However, in our study, NLR and PLR results were not different in either regarding of functionality or in the presence of HT.

Subclinical Cushing's syndrome causes increased cardiovascular morbidity and mortality.³² Inflammation plays an important role in the development mechanisms of cardiovascular diseases.²⁷ In the current study, a moderately positive correlation was found between cortisol response to 1 mg DST and tumor size. However, although there was no correlation between these hemogram parameters and cortisol results, a low positive correlation was found between tumor size and NLR. This may be due to extreme values caused by malignant diseases associated with large tumor size. Because adrenocortical cancer, the primary tumor of adrenal glands, has been positively associated with increased NLR.^{17,18}

In addition to endocrine malignancies such as thyroid cancer, a wide range of malignancies and NLR and PLR relationships have been investigated³³⁻³⁸. So much so that the results obtained in some cancers have claimed that NLR is more valuable than the commonly used inflammation marker such as CRP.¹⁸ In our study, higher values were de-

tected in malignant cases. However, since the number of malignant cases was very low, we thought that it was not correct to generalize this with this study.

Although it is accepted that the selection of threshold values is quite appropriate due to the similarity of the study conducted by Bagente F. et al, in which PLR and NLR threshold values are taken as reference, it should be kept in mind that NLR and PLR do not have a definite threshold value in the study, and different threshold values are observed in different populations and diseases.

Limitations of the study: This is a single-center study with relatively few cases. Since we designed it as a retrospective study, we could not compare with the healthy control group. Therefore, we considered the recommendations of reference studies for the threshold value. In addition, we did not consider all the accompanying diseases of the patients. Some of these may be conditions that affect the inflammatory state.

CONCLUSION

In this study, we found that NLR and PLR did not increase in patients with adrenal incidentaloma. However, there was a positive correlation between tumor size and NLR. It is concluded that although inflammatory hemogram parameters are inexpensive and easily accessible in general, there is no clinical significance in AI patients.

Ethics Committee Approval

Sakarya University Ethics Committee. (11.02.2020)
(Ref. No.: 71522473/050.01.04/41)

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