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ORIGINAL ARTICLE

Can Simple Parameters such as Neutrophil-to-Lymphocyte Ratio and Neutrophil Count Predict the Nature of Adrenal Masses?

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SUMMARY

Background: **The immune system responds to many diseases by triggering an inflammatory response, which in turn produces changes in the formulation of blood elements in the circulation. Certain parameters derived from the complete blood count, mainly the neutrophil/lymphocyte ratio (NLR), have been used as biomarkers in the diagnosis and prognosis of solid tumors.**
Methods: **A total of 66 patients who underwent surgery for adrenal lesions were analyzed. Complete blood count-derived parameters obtained preoperatively were studied according to the nature of the definitive pathology report.**
Results: **As a result of ROC analysis, neutrophil and NLR parameters were found to be significant diagnostic biomarkers in differentiating benign from malignant lesions (AUC = 0.853 (0.760 - 0.947); $p < 0.001$, AUC = 0.702 (0.557 - 0.848); $p = 0.025$, respectively). Other blood parameters were similar between the groups ($p > 0.05$). The discrimination power of NLR was significantly more successful than neutrophil count. The cutoff point for the NLR was found to be 4.36. Concerning tumor diameters of all study groups, the malignant group was found to be statistically different from the others ($p < 0.001$). A positive significant correlation was observed between tumor diameter and NLR ($r = 0.435$, $p < 0.001$).**
Conclusions: **The systemic inflammatory response to adrenal lesions may be evaluated by means of NLR, an elevated NLR value in combination with a large lesion may be predictive of malignancy rather than benignity.**
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KEY WORDS

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INTRODUCTION

Patients with adrenal masses are often encountered incidentally during imaging and they are present in up to 4% of computed tomography scans [1]. When a lesion measures more than 1 cm is discovered then it is called incidentaloma. Although most adrenal incidentalomas are benign non-functional adenomas; however, hormonal and radiological evaluation is often indicated to exclude an asymptomatic functioning adrenal tumor or malignancy. The main point in these patients with an adrenal incidentaloma is to rule out early malignancy

and to diagnose hormonally functional tumors. In addition to a detailed history with a careful physical examination, adrenal hormonal evaluation and imaging other than CT scan may also be required. Among these advanced imaging tests are the chemical shift MRI, positron emission tomography (PET) scan, and metaiodobenzylguanidine (MIBG) scan. Ambiguous cases may even require fine-needle aspiration biopsy (FNAB).

The role of the immune response in relation with tumor progression has been a topic of continual discussion and research. The main response of the immune system to inflammatory diseases and even various malignancies including gastrointestinal cancers and breast cancer is by initiating a local then a systemic inflammatory response [2-5]. This response commences with the activation of leukocytes leading to the initiation of several inflammatory cascades provoking numerous changes leading to the secretion and mobilization of various growth factors and interleukins.

In recent years, many studies have focused on the role of white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet distribution width (PDW), mean platelet volume (MPV), red cell distribution width (RDW), platelet count (PLT), lymphocyte (L) and neutrophil (N) values in the diagnosis of many maladies. NLR was shown to be a good independent biomarker in inflammatory conditions such as acute cholecystitis, diverticulitis, and inflammatory bowel disease, as well as being a prognostic and diagnostic indicator in malignancies [6-9].

This study's aim is to retrospectively interpret the adrenal masses by using complete blood count (CBC) derived parameters to discriminate benign from malignant lesions as first glance markers. Moreover, we intended to find a correlation between the size of the lesion, the nature of the lesion, and these simple CBC derived parameters.

MATERIALS AND METHODS

The study was designed to retrospectively evaluate consecutive cases of adrenalectomy performed in a single academic tertiary referral center. Ethical committee approval for this study was obtained from the Local Research Ethics Committee registered under the number 19-KAEK-268. The patients were recruited after the review of the electronic database using relevant ICD-10 codes. The search was limited to the time span between January 2010 and January 2020. The demographic and clinical data including patient age, gender, location of the lesion, the diameter of the lesion, biochemical tests, surgical technique, preoperative diagnosis, the postoperative pathology report, diagnostic tool, length of hospital stay, and morbidities were retrieved by reviewing patient electronic medical files. The data of this study were collected and analyzed in March 2020. The diagnosis of adrenal mass was made based on clinical presentation, physical examination, biochemical studies, or incidentally during radiological examinations for a different purpose on computed tomography CT, magnetic resonance imaging MRI or during PET-CT. Hemoglobin, PDW, RDW, MPV, neutrophil, lymphocyte, NLR, WBC, and platelet counts were retrieved from a complete blood count test conducted as a routine test at admission to the hospital for every patient with an adrenal mass. NLR is obtained by dividing the neutrophil-to-lymphocyte counts or percentages.

Statistical analyses

Statistical analysis of the data collected in our study was carried out with the SPSS (SPSS Inc., Chicago, IL, USA) program. Descriptive statistics of continuous variables obtained by measurement were reported using median (min-max) with mean ± standard deviation depending on the normal distribution of the data. Categorical variables were presented as numbers (n) and percent (%). The normal distribution of the data was tested with the Shapiro-Wilk test. Comparison of patients' age, length of stay, tumor diameter, complete blood count parameters, and neutrophil-to-lymphocyte ratio (NLR) values between benign and malignant groups were performed using the *t*-test in independent groups and Mann-Whitney U test in non-normally distributed data. In the subgroups of benign pathologies, NLR comparison was performed with the Kruskal-Wallis test since parametric test assumptions were not provided. The correlation between tumor diameter and NLR was investigated by the Pearson's test. Benign and malignant ratio comparisons between tumor diameter (< 4 cm and ≥ 4 cm) groups were performed with Fisher's exact test. Whether neutrophil count and NLR values could be diagnostic and prognostic markers in benign and malignant diagnosis was statistically investigated using ROC (Receiver Operating Characteristic) analysis method. ROC plots and area under the curve (AUC) and 95% confidence intervals of this area were calculated. For AUC in the analysis; 0.9 - 1: excellent, 0.8 - 0.9: good, 0.7 - 0.8: medium, 0.6 - 0.7: weak, and 0.5 - 0.6: unsuccessful. The Youden index (maximum sensitivity and specificity) was used to determine the best cutoff point in ROC analysis. Sensitivity, specificity, positive-negative predictive values, and likelihood ratio (+) values were calculated using the cutoff points determined after the ROC analysis to determine the discrimination power of the parameters that can be used in the diagnosis of benign and malignant lesions. The statistical significance level was accepted as $p < 0.05$.

RESULTS

A total of 66 consecutive cases, 53 patients with benign and 13 patients with malignant pathologies were included in this study. The distribution of the pathologies is as follows: Cushing syndrome: 35, aldosteronoma: 9, pheochromocytoma: 5, adrenal cortical hyperplasia: 2, myelolipoma: 1, adrenal cyst: 1, adrenocortical carcino-

Table 1. Comparison of the patients' ages, length of hospital stay, and tumor diameters among the research groups.

	Groups	n	Mean ± SD median (min - max)	p-value
Age	**malignant**	**13**	**62.15 ± 12.16**	**0.104 [a]**
	benign	**53**	**56.74 ± 10.21**	
Length of hospital stay	**malignant**	**13**	**11.15 ± 7.31 7 (3 - 23)**	**0.006 [b]**
	benign	**53**	**5.85 ± 3.24 5 (2 - 17)**	
Tumor diameter	**malignant**	**13**	**5.88 ± 2.56 5.5 (2.5 - 13)**	**< 0.001 [b]**
	benign	**53**	**2.75 ± 0.82 2.6 (1.8 - 5.8)**	

[a] - Independent samples *t*-test, [b] - Mann-Whitney U test, SD - standard deviation.

Table 2. Comparison of patients' complete blood count parameters and NLR values among the research groups.

	Groups	n	Mean ± SD	Median (min - max)	p-value
Hb	**malignant**	**13**	**11.4 ± 2.03**	**10.7 (8 - 15.1)**	**0.103 [a]**
	benign	**53**	**12.27 ± 1.62**	**12.4 (9.2 - 16.4)**	
PDW	**malignant**	**13**	**13.42 ± 4.51**	**14.6 (4.5 - 18.2)**	**0.853 [a]**
	benign	**53**	**13.69 ± 4.84**	**12.8 (0.30 - 24.77)**	
Neutrophil	**malignant**	**13**	**40.85 ± 27.69**	**43.2 (5.8 - 88.7)**	**0.024 [b]**
	benign	**53**	**24.07 ± 24.39**	**10.58 (3.3 - 76.5)**	
Lymphocytes	**malignant**	**13**	**5.76 ± 4.18**	**5.8 (0.8 - 12.9)**	**0.669 [b]**
	benign	**53**	**9.35 ± 10.97**	**3.33 (0.9 - 42.6)**	
NLR	**malignant**	**13**	**8.04 ± 3.83**	**7.3 (3.22 - 16.96)**	**< 0.001 [b]**
	benign	**53**	**3.89 ± 3.25**	**2.64 (0.96 - 14.88)**	
MPV	**malignant**	**13**	**9.76 ± 2.73**	**10.4 (6.52 - 15.8)**	**0.663 [b]**
	benign	**53**	**9.54 ± 2.34**	**9 (6.53 - 19.4)**	
WBC	**malignant**	**13**	**10.83 ± 3.77**	**11.4 (4.78 - 17.10)**	**0.411 [b]**
	benign	**53**	**9.82 ± 3.33**	**8.93 (2.8 - 18.88)**	
Platelet	**malignant**	**13**	**320.6 ± 169.6**	**236 (162 - 754)**	**0.923 [b]**
	benign	**53**	**285.2 ± 90**	**264.4 (110 - 547)**	
NLR	**A**	**9**	**2.17 ± 0.99**	**1.78 (1.15 - 3.68)**	**0.053 [c]**
	CS	**34**	**4.19 ± 3.77**	**2.46 (0.96 - 14.88)**	
	P	**5**	**4.85 ± 1.09**	**5.23 (3.13 - 5.80)**	
	other	**5**	**3.96 ± 2.82**	**2.83 (1.14 - 8.27)**	

[a] - Independent samples *t*-test, [b] - Mann-Whitney U test, [c] - Kruskal-Wallis test, SD - standard deviation.
NLR - Neutrophil-to-Lymphocytes ratio, Hb - Hemoglobin, PDW - Platelet Distribution Width, MPV - Mean Platelet Volume, WBC - White Blood Cell, A - Aldosteronoma, CS - Cushing Syndrome, P - Pheochromocytoma, Other - Adrenal Cyst, Myelolipoma, and Benign Adrenocortical Hyperplasia.

ma: 10, and metastasis: 3. female patients account for 69.7% of the total study number. The female-male ratios were similar between the groups (p = 0.190), where 73.6% (n = 39) of the benign group were female and 26.4% (n = 14) were male, 53.8% (n = 7) of the malignant group were female and 46.2% (n = 6) were

Table 3. ROC (Receiver Operating Characteristic) analysis results for neutrophil count and NLR values and sensitivity, specificity, positive-negative predictive values and likelihood ratio (+) values.

	NLR	Neutrophil
AUC (95% CI)	0.853 (0.760 - 0.947)	0.702 (0.557 - 0.848)
p-value	< 0.001	0.025
Cutoff	4.36	10.16
Sensitivity	0.923 (0.621 - 0.996)	0.923 (0.621 - 0.996)
Specificity	0.698 (0.555 - 0.813)	0.472 (0.335 - 0.612)
PPV	0.429 (0.250 - 0.626)	0.3 (0.171 - 0.467)
NPV	0.974 (0.846 - 0.999)	0.961 (0.784 - 0.998)
LR +	3.06 (1.97- 4.74)	1.75 (1.30 - 2.36)

NLR - Neutrophil-to-Lymphocytes ratio, AUC - Area Under the ROC Curve, CI - Confidence Interval, PPV - Positive Predictive Values, NPV - Negative Predictive Values, LR - Likelihood Ratio.

Table 4. Comparison of benign/malignant ratios according to tumor diameter groups.

			Groups		Total	p-value
			benign	malignant		
Tumor diameter	< 4	n	49	3	52	< 0.001 *
		%	94.2%	5.8%	100%	
	≥ 4	n	4	10	14	
		%	28.6%	71.4%	100%	
Total		n	53	13	66	
		%	80.3%	19.7%	100%	

*** - Fisher's exact test.**

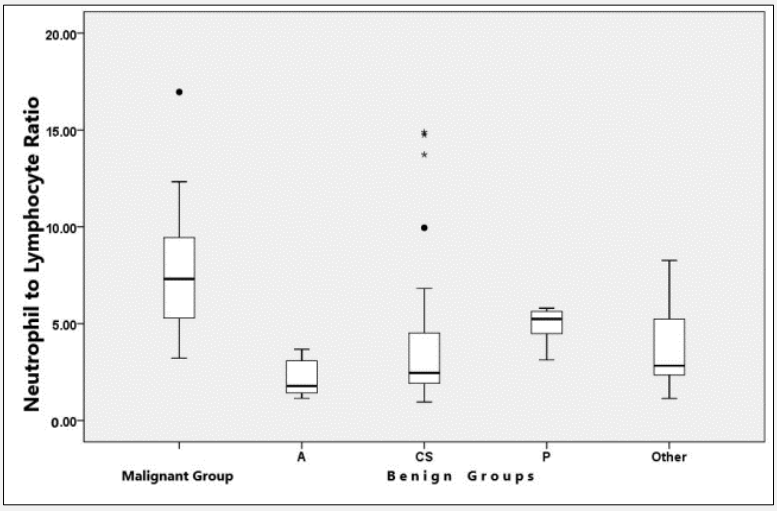

Figure 1. Boxplot showing comparison of Neutrophil-to-Lymphocyte ratios between malignant and benign groups.

Footnote: A - Aldosteronoma, CS - Cushing Syndrome, P - Pheochromocytoma, Other - Adrenal Cyst, Myelolipoma, and Benign Adreno-cortical Hyperplasia.

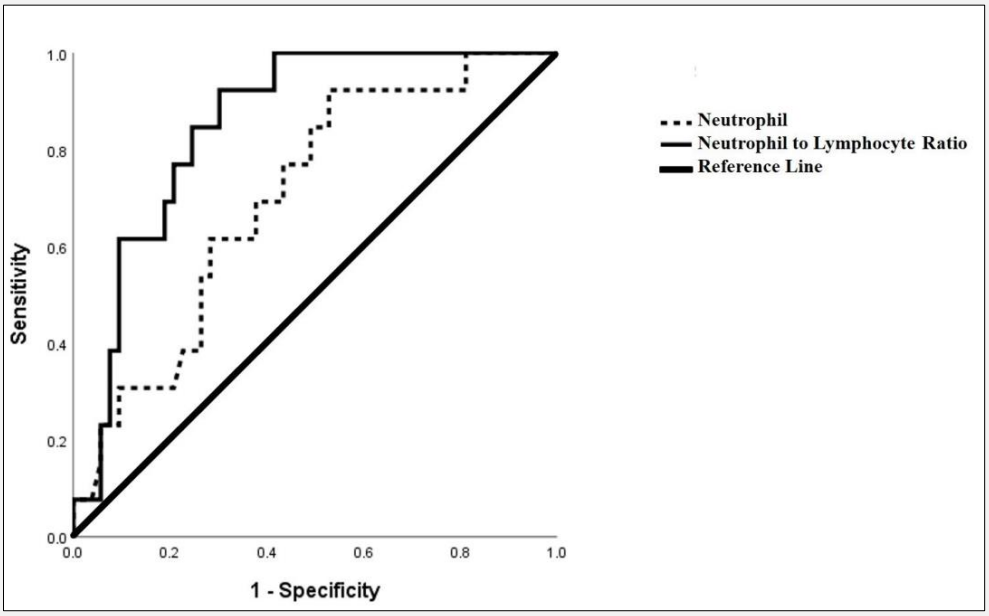

Figure 2. ROC (Receiver Operating Characteristic) curves for Neutrophil count and Neutrophil-to-Lymphocyte ratios.

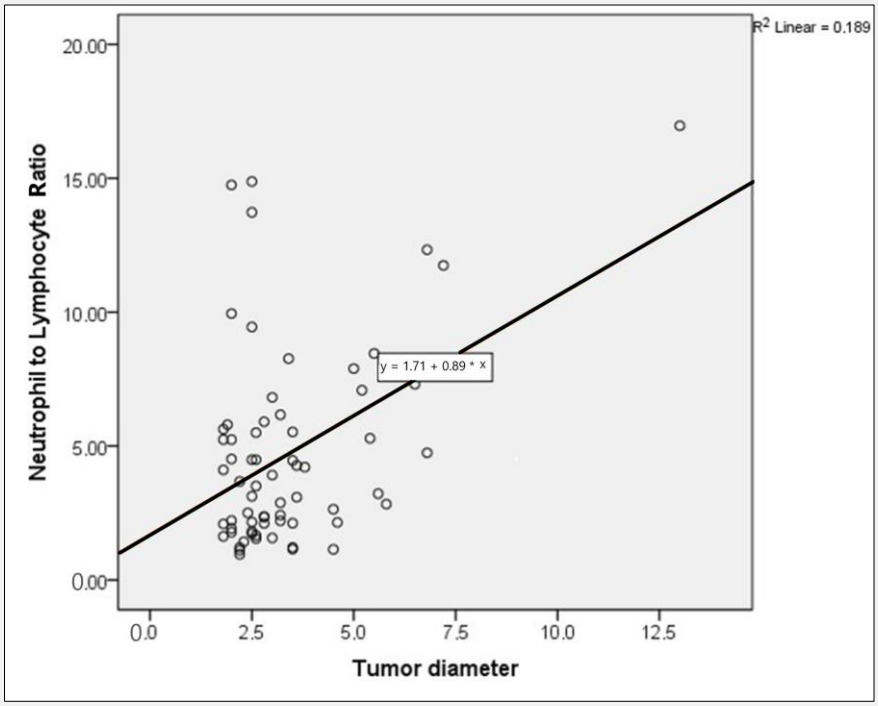

Figure 3. Scatter plot with regression curve for the correlation between Neutrophil-to-Lymphocyte ratios and tumor diameters.

male. The mean age of the patients in the study was 57.8 ± 10.74. The mean age of the benign group was 56.74 ± 10.21, and the mean age of the malignant group was 62.15 ± 12.16. The mean ages between the research groups were not statistically different ($p = 0.104$, Table 1). The mean hospitalization time of all patients was 6.89 ± 4.78. The duration of hospitalization of the malignant group was 5.85 ± 3.24 (median (min-max): 5 (2 - 17)) statistically significantly higher than the hospitalization period of the 11.15 ± 7.31 (7 (3 - 23)) benign group ($p = 0.006$, Table 1). The tumor diameter mean of the whole group was 3.37 ± 1.83. The tumor diameter of the malignant group was 5.88 ± 2.56 (5.5 (2.5 - 13)) statistically significantly larger than the tumor diameter of the benign group ($p < 0.001$, Table 1). Comparison of patients' ages, length of stay, and tumor diameters between the study groups are shown in Table 1. The localization of the lesion was 42.4% on the right and 57.6% on the left side. Total morbidity was seen in 5 (7.6%) patients. Laparoscopic surgery was performed in 63.6% and open surgery in 36.4% of patients.

The comparisons of the patient's complete blood count parameters and NLR values are presented in Table 2. Neutrophil and NLR values were found statistically different between benign and malignant groups ($p = 0.024$, $p < 0.001$, Table 2). Other blood parameters were similar between the groups ($p > 0.05$, Table 2). Among the subgroups of the benign group, NLR values were not significantly different, but were close to the limit of significance ($p = 0.053$). The comparison of NLR values in malignant, benign, and benign subgroups is also shown in Figure 1.

ROC (Receiver Operating Characteristic) analysis results of neutrophil counts and NLR values along with sensitivity, specificity, positive-negative predictive values, and likelihood ratio (+) values are presented in Table 3. Besides, the ROC curve is shown in Figure 2. As a result of ROC analysis, neutrophil and NLR parameters were found to be significant diagnostic biomarkers in differentiating benign from malignant lesions (AUC = 0.853 (0.760 - 0.947); $p < 0.001$, AUC = 0.702 (0.557 - 0.848); $p = 0.025$, respectively, Table 3). The discrimination power of the NLR ratio was significantly more successful than neutrophil count (Figure 2). The cutoff point for NLR was found to be 4.36. Classification success for this cutoff point; sensitivity was 92.3% (62.1% - 99.6%) and specificity was 69.8% (55.5% - 81.3%) (Table 3).

A positive significant correlation was observed between tumor diameter and NLR ($r = 0.435$, $p < 0.001$, Figure 3).

Concerning tumor diameters of all study groups, the malignant group was found to be statistically different from the others ($p < 0.001$). The group with a tumor diameter of 4 cm and above was found to have a malignant pathology in 71.4% of the cases, whereas, this ratio is only 5.8% in case of a tumor diameter of less than 4 cm (Table 4).

In the group with a tumor diameter of 4 or more, the AUC value was found to be significant as 1 after the second ROC analysis to determine the benign malignant diagnosis discrimination power of NLR ($p = 0.005$). The sensitivity and specificity values for the cut point 3.03 value determined for NLR were 100%. There were 14 patients with a tumor diameter of 4 and larger, and all 10 patients with an NLR value greater than 3.03 were malignant, and 4 patients with less than 3.03 were benign.

DISCUSSION

Simple blood tests such as CBC-derived parameters have been frequently used as prognostic markers for several illnesses, including inflammatory diseases [10] and malignancies [11]. The rationale behind the use of these markers is to unveil the reflection of the changes that occur in the circulating blood elements as the result of the immune system's response to the underlying disease. The most widely used parameter is NLR. This biomarker is used as a prognostic factor for HCC [12], ovarian [13], vulvar [14], and adrenocortical cancers (ACC) [15].

In the current study, we initially evaluated hemoglobin, PDW, RDW, MPV, neutrophil, lymphocyte, NLR, WBC, and platelet counts in relation to the nature of the lesions, whether benign or malignant, according to the definitive pathology report. Among these parameters NLR and neutrophil counts were the only possible biomarkers that showed statistically significant differences. However, neither NLR nor neutrophil count showed any significant difference between the benign subgroups which included aldosteronoma, Cushing syndrome, pheochromocytoma, and others (adrenal cyst, myelolipoma and benign adrenal hyperplasia).

During radiologic imaging, the detection of a tumor larger than 4 cm is a well-known ominous sign of malignancy with a sensitivity of 81% [16]. In this way, a tumor size of 4 cm and greater is set as the cutoff point to differentiate malignant from benign lesions, knowing that lesions smaller than 5 cm can still be malignant in up to 16% of the cases [17], and larger lesions can still be benign. In the present study, a significant difference was found between the malignant and benign groups according to tumor size. In fact, the group with a tumor size of more than or equal to 4 cm had malignant pathology of 71.4% of the cases compared to 5.8% when the tumor measures less than 4 cm. This is compatible with many studies. A report from the National Italian Study Group showed that 4 cm as a cutoff point had a 93% sensitivity of detecting adrenocortical carcinoma [18,19]. Similarly, the Mayo Clinic group found that in their study group all the adrenal carcinomas were between 4 and 6 cm in diameter [20].

Of note, the tumor size, as well as the hospital stay, were found to be significantly larger in the malignant group when compared to the benign group; however, the age, gender of the patient, and tumor size did not

differ between the two groups.

Bagante et al. showed that NLR and possibly PLR can be used as prognostic factors for patients with ACC demonstrating that a NLR value of greater than 5 is associated with recurrence as well as worse outcomes such as readmission and postoperative complications. Moreover, in our study the ROC analysis showed that the NLR and neutrophil count was found to be of significant importance in differentiating malignant from a benign lesion, with NLR having higher significance. The cutoff point for NLR was found to be 4.36 with a sensitivity and specificity of 92.3% and 69.8% respectively. Similar NLR values and even lower counts have been reported to be of significant importance for instance in the diagnosis of prostate cancer [21].

Our data strongly suggest that a positive significant correlation was observed between tumor diameter and NLR, this implies that NLR and tumor size when taken together may help stratify the pre-operative diagnosis of patients with an adrenal mass. Interestingly, in our report when the tumor size is greater or equal to 4 cm is further stratified according to NLR by using ROC analysis for the second time to differentiate malignant from benign pathologies, a significant relationship was found, where a NLR value of 3.03 or higher in patients with tumor size greater than or equal to 4 cm showed specificity and sensitivity of 100%. This conclusive finding may be attributed to the relatively small sample size due to the rarity of adrenal malignant tumors which account for 1 - 2 patients per million [22] and may also be coincidental. Similarly, the multivariate analysis of a study conducted by Mochizuki et al. showed that the combination of NLR and the size of the tumor were found to be independent predictors of malignant adrenal disease [23].

A limitation to our work is the study design itself, being retrospective in profile, thus it could be vulnerable to bias. The sample size, especially concerning the number of malignant lesions, is another limiting factor and this is due to the scarcity of the disease. Nevertheless, it is worth mentioning that this work confirms the results of some other studies showing that NLR can be used as a diagnostic factor in combination with the tumor size in diagnosing adrenal masses.

CONCLUSION

In patients with adrenal masses, simple blood parameters such as neutrophil count and especially NLR may play an important role in presumably predicting the nature of the lesion at the first glance prior to extensive work-up. In addition, NLR when combined with tumor size can be even more accurate in foretelling the possible pathology whether benign or malignant.

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None.

Statement of Ethics:
Ethical committee approval for this study was obtained from the Local Research Ethics Committee registered under the number 19-KAEK-268. All methods were performed in accordance with the relevant guidelines and regulations of the institution. All patients provided written informed consent.

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Declaration of Interest:
I confirm on behalf of the other authors that there is no conflict of interest to declare.

Data Availability Statement:
The data sets generated during the current study are available from the corresponding author upon request.

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