The Predictive Values of Preoperative Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Renal Mass; A Retrospective Study

Nötrofil Lenfosit Oranı ve Trombosit Lenfosit Oranının Renal Kitleli Hastalarda Öngörücü Düzeyi; Retrospektif Çalışma

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ABSTRACT

OBJECTIVE: Neutrophil to lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR) are easily accessible inflammatory parameters. Here, we aimed to analyze the coherence of these two markers for the predictive value of both malignancy in patients with a kidney mass and histologic grade for those with RCC.

MATERIAL and METHODS: A total 65 patients who had a kidney mass (median age 58, IQR (interquartile range) 47, 68) and underwent either radical or partial nephrectomy were included in this retrospective study. The NLR and PLR were derived from the complete blood cell count results in the preoperative period. Patients were divided into two groups as benign and malignant. Also patients diagnosed with RCC were further analyzed according to the Fuhrman histologic grading.

RESULTS: Univariate regression analysis showed that logaritmic transformed neutrophil to lympocyte ratio (LnNLR) [1.125, 95%CI (1.00, 31.26) p=0.04] levels were significantly associated with RCC. However, logaritmic transformed platelet to lympocyte ratio (LnPLR) levels did not show any significant association [5.32, 95% CI (0.46, 60.8) p=0.17]. After adjusting the analysis for age and gender, only LnNLR levels [1.14, 95% CI (1.01, 1.30) p=0.03] were still associated with RCC. NLR levels showed sequential increase from low grade to high grade according to the Fuhrman grading system among RCC patients.

CONCLUSION: Higher NLR levels were significantly associated with a malignant kidney mass and high-grade RCC.

KEY WORDS: Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio, Renal cell carcinoma, Fuhrman Grade

ÖZ

AMAÇ: Nötrofil lenfosit oranı (NLR) ve platelet lenfosit oranı (PLR) kolay ulaşılabilen inflamatuvar parametrelerdir. Çalışmada renal kitlesi olan hastalarda her iki markerında hem malignite açısından öngörücü özelliklerini hem de renal hücreli karsinom (RHK) saptanan hastalarda histoloji grade ile ilişkisini değerlendirmeyi hedefledik.

GEREÇ ve YÖNTEMLER: 65 hasta (ortalama yaş 58, IQR 47, 68) retrospektif olarak incelendi. NLR ve PLR değerleri preoperatif tam kan sayımından hesaplandı. Hastalar bening ve maling olarak iki gruba ayrıldı. Ayrıca RCC olan hastalar Fuhrman histolojik gradelemesine göre ileri analize alındı.

BULGULAR: Tekli regresyon analizinde LnNLR [1.125, %95 CI (1.00, 31.26) p=0.04] RHK ile ilişkili saptandı. Fakat, LnPLR anlamlı ilişki [5.32, %95 CI (0.46, 60.8) p=0.17] göstermedi. Yaş ve cinsiyete göre ayarlanmış çoklu regresyon analizinde sadece LnNLR [1.14, %95 CI (1.01, 1.30) p=0.03]'nin RHK ile anlamlı ilişkisi devam ettiği görüldü. RHK hastalarında NLR düzeyleri Fuhrman histoloji gradelemesi ile paralel değişim gösterdi.

SONUÇ: Yüksek NLR düzeyleri malign böbrek kitleleri ve yüksek gradeli RHK ile anlamlı ilişki göstermektedir.

ANAHTAR SÖZCÜKLER: Nötrofil lenfosit oranı, Platelet lenfosit oranı, Renal hücreli karsinom, Fuhrman Grade

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INTRODUCTION

Renal cell carcinoma (RCC) represents 2-3% among all type of malignancies in adults and constitutes more than 90% of primary kidney tumors with the development of metastatic disease (1). Although pronounced developments have been made in surgical, medical and target therapies, the long-term survival remains insufficient due to its common recurrence, distant metastasis and weak response to treatment (2). Although postoperative histological determination is the main factor for predicting the prognosis, there are still markers needed both to predict the malignant potential for the patients who have a preoperative renal mass determined by diagnostic imaging techniques and to predict the prognosis for the patients diagnosed with a malignant kidney mass.

Chronic inflammation has an imperative role in the development of cancer (3). There is an increasing number of reports concluding that systemic hematologic markers such as the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are well predictive for either malignancy presence or prognosis of the malignancy in various cancer types including RCC (4-7). These two markers are simple, easily accessible in the clinical stage and inexpensive. In this retrospective study, we aimed to investigate the coherence of these two markers for their predictive value regarding both the presence of malignancy in patients with a kidney mass and the histological grade for those with RCC.

MATERIALS and METHODS

Study Population

A total of 71 subjects screened and found to have a renal mass by either ultrasound or computed tomography underwent partial or radical nephrectomy between October 2012 and July 2018 at Yuksek Ihtisas University Faculty of Medicine Koru Ankara Hospital Department of Urology and 65 of these patients were included in the retrospective analyses. Exclusion criteria included patients with active infectious or inflammatory disease (i.e. active connective tissue disorder, HIV, any other proven infections), diabetes, or any active coronary artery disease, and patients with inadequate medical records. None of the patients had received anticancer therapy before the operation. Patients under 18 years old were also excluded to ensure homogeneity of the population. Among the 71 subjects, 4 patients were excluded as they were younger than 18 years and 2 patients because of a diabetes diagnosis.

The Institutional Review Board of Yuksek Ihtisas University Faculty of Medicine Koru Ankara hospital approved the study protocol.

Clinical and Laboratory Analyses

The NLR was calculated using the neutrophil and lymphocyte counts from the complete blood count (CBC) obtained before surgery and PLR was calculated as platelet count divided by lymphocyte count from the same CBC results. All surgeries were performed by the same surgical team.

Statistical Analyses

Descriptive statistics were expressed as mean ± SD or median (IQR) for continuous variables and as frequencies and percentage for categorical variables. The comparison of variables between two groups were performed according to normality, using either the t-test or Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. For Fuhrman categories analysis, we used one-way ANOVA to compare the NLR and PLR values in each grade. Logistic regression analyses were used to evaluate the possible association between NLR, PLR and malignancy presence. All leukocyte, neutrophil, lymphocyte, platelet, NLR and PLR values were log-transformed to reach the normal distribution and the transformed values were used in the regression analysis. Since BMI values were not present for all patients, multivariate analyses were adjusted by age and gender. Independent variables were not placed in the model for possible interaction. All tests were two-sided. Differences were considered to be statistically significant if the p value was < 0.05. Statistical analysis was carried out using SPSS, version 25.0.

RESULTS

A total of 65 patients who underwent either radical or partial nephrectomy between October 2012 and July 2018 were retrospectively analyzed. Basic characteristics of the study patients are depicted in Table I. The median age was 58 (IQR; 47, 68) years, with male predominance [48 males (73.8%), 17 females (26.2%)]. After determination of a renal mass by computed tomography, 24 of these patients had undergone partial nephrectomy and 41 radical nephrectomy surgery. Among the 65 patients, pathology specimens after either radical or partial nephrectomy revealed that 49 (75%) patients had RCC, 6 (9%) had an angiomyolipoma, 6 (9%) had an oncocytoma, and 4 (7%) patients had other benign lesions (Table I).

The median leukocyte level was 8800 (6750, 10785)/μL, median neutrophil level 5870 (4220, 8435)/μL, median lymphocyte level 1800 (1255, 2485)/μL, median platelet level 251000 (209000, 332000)/μL, median NLR 3.2 (2.0, 5.6) while PLR was 143 (102, 212) (Table I).

We also compared all characteristics among the study subgroups assigned as benign and malignant. The comparison analysis is depicted in Table II. Although both NLR and PLR values were higher in the RCC group, the differences were not statistically significant (p=0.26 for NLR and p=0.23 for PLR) (Table II).

Association Between NLR, PLR and RCC diagnosis

Univariate logistic regression analysis showed that LnNLR [1.125, 95%CI (1.00, 31.26) p=0.04] levels were statistically significantly associated with RCC pathology. Although LnPLR

levels was found to be predictive with a 5.3 beta coefficient, the association did not reach statistical significance [5.32, 95% CI (0.46, 60.8) p=0.17]. Although being male gender seemed to be a risk factor for an RCC diagnosis, the association was not statistically significant [2.36, 95% CI (0.69, 8.09) p=0.17]. (Table III).

In multivariate analyses conducted after adjusting the analysis for age and gender, only Ln NLR levels [1.14, 95% CI (1.01, 1.30) p=0.03] were still statistically significantly associated with an RCC diagnosis. All results are summarized in Table III. Among 65 RCC patients, we were able to access histological grade (Fuhrman grade) in 45 patients. When the NLR and PLR values were checked in 4 categories, the NLR levels showed a sequential increase from low grade to high grade but with no statistical significance (Figure 1); however PLR showed no changes (Figure 1).

Table I: Basic characteristics of the study patients.

Variables	n=65
Age (years, median, IQR)	58 (47, 68)
Gender (n,%)	
Female	17 (26.2%)
Male	48 (73.8%)
Surgery Type (n, %)	
Radical Nephrectomy	41 (63.1%)
Partial Nephrectomy	24 (36.9%)
Pathology (n)	
Renal Cell Carcinoma	49 (75%)
Angiomyolipoma	6 (9%)
Oncocytoma	6 (9%)
Other (benign)	4 (7%)
Inflammatory Parameters	
White Blood Cell (/μL, median; IQR)	8800 (6750, 10785)
Neutrophil (/μL, median;IQR)	5870 (4220, 8435)
Lymphocyte (/μL, median;IQR)	1800 (1255, 2485)
Platelet (/μL, median; IQR)	251000 (209000, 332000)
NLR (median; IQR)	3.2 (2.0, 5.6)
PLR (median; IQR)	143 (102, 212)

NLR: Neutrophil to lymphocyte ratio, **PLR:** Platelet to lymphocyte ratio.

DISCUSSION

The predictive markers of RCC are known as tumor size, TNM classification, Fuhrman nuclear grade in pathology, histological type, vascular invasion, symptomatology of the patient and physical condition of the patient (8). Increasing evidence suggests that systemic inflammation has a substantial role in the development and progression of cancer (3). Laboratory reflection of the systemic inflammation includes increase or decrease of the acute phase reactants such as fibrinogen, ferritin, albumin, and transferrin, an increase in C-reactive protein, and changes in neutrophil and lymphocyte levels derived from peripheral blood. The strong association between inflammation and development and progression of cancer has driven investigators to find easily accessible and inexpensive markers that can provide results quickly to predict malignancy (9).

The neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are acceptable, inexpensive, easily accessible markers in clinical use and have been studied in many different types of solid organ tumors regarding their predictive value for both the development and prognosis of cancer (10-12). Most of the previous studies have been designed to determine the predictive values of these markers for both metastasis status and mortality related to cancer.

The association between renal cell carcinoma and NLR values has been previously analyzed. Ohno et al. reported that preoperative NLR values were predictive for both prognosis

Table II: Comparison of characteristics between patients with benign and malignant lesions.

Variables	Benign (n= 16)	RCC (n=49)	P
Age (years, median, IQR)	52(38, 70)	60 (51, 68)	0.22
Gender (n,%)			
Female	6 (40%)	11 (22%)	
Male	9 (60%)	39 (78%)	0.14
Inflammatory Parameters			
White Blood Cell (/μL, median; IQR)	9800 (6300, 14000)	8705 (6880, 10660)	0.47
Neutrophil (/μL, median;IQR)	6200 (4060, 12700)	5835 (4220, 8052)	0.18
Lymphocyte (/μL, median;IQR)	1500 (1000, 2400)	1925 (1257, 2675)	0.81
Platelet (/μL, median; IQR)	251000(229000,369000)	249000 (198000,332000)	0.48
NLR (median; IQR)	3.09 (2.04, 5.19)	3.38 (2.06, 12)	0.26
PLR (median; IQR)	138 (103, 193)	181 (102, 242)	0.23

RCC: Renal cell carcinoma, **NLR:** Neutrophil to lymphocyte ratio, **PLR:** Platelet to lymphocyte ratio.

and disease relapse in RCC patients (13). Similarly, Keskin et al conducted another study and declared a close association between NLR values and histological subtypes of RCC. They also reported that high NLR values were predictive for cancer-related mortality (14). Pichler et al. have reported from a large cohort database that preoperative NLR values were only associated with mortality in non-metastatic RCC patients (15). In contrast, Jagdev et al did not find any relation between NLR and prognosis in RCC patients (16).

Table III: Associations Between diagnosis of RCC and inflammatory parameters (Univariate and Multivariate Logistic Regression Analyses).

	Univariate		Multivariate*	
	B (95% CI)	**p**	**B (95% CI)**	**p**
Age (years, mean±SD)	**0.96 (0.92, 1.01)**	**0.18**	-	
Gender (male)	**2.36 (0.69, 8.09)**	**0.17**	-	
Ln-Leukocyte (/µL, median, IQR)	7.23 (0.25, 207.8) 5.56	0.24	15.2 (0.38, 598.1)	0.14
Ln-Neutrophil (/µL, median, IQR)	(0.42, 72.5)	0.19	8.40 (0.59, 151.0)	0.11
Ln-Lymphocyte (/µL, median, IQR)	0.20 (0.01, 3.03)	0.24	0.15 (0.009, 2.75)	0.204
Ln-Platelet (/µL, median, IQR)	2.9 (0.46, 186.3)	0.61	0.81 (0.008, 83.05)	0.93
Ln-NLR (median, IQR)	1.12 (1.00, 1.26)	**0.04**	1.14 (1.01, 1.30)	**0.03**
Ln-PLR (median , IQR)	5.32 (0.46, 60.8)	0.17	4.48 (0.33, 60.9)	0.25

*age and gender adjusted multivariate analyses.

RCC: Renal cell carcinoma, **NLR:** Neutrophil to lymphocyte ratio, **PLR:** Platelet to lymphocyte ratio, **LN:** Log transformation

Fuhrman Grade for RCC					
	1	**2**	**3**	**4**	**p**
NLR	2.08 (1.3, 4.6)	2.7 (1.7, 4.4)	3.9 (2.1, 5.6)	5.1 (2.2, 9.2)	0.56
PLR	124 (70, 174)	123 (102, 157)	179 (98, 223)	111 (89, 226)	0.63

RCC; renal cell carcinoma, NLR; neutrophil to lymphocyte ratio, PLR; platelet to lymphocyte ratio
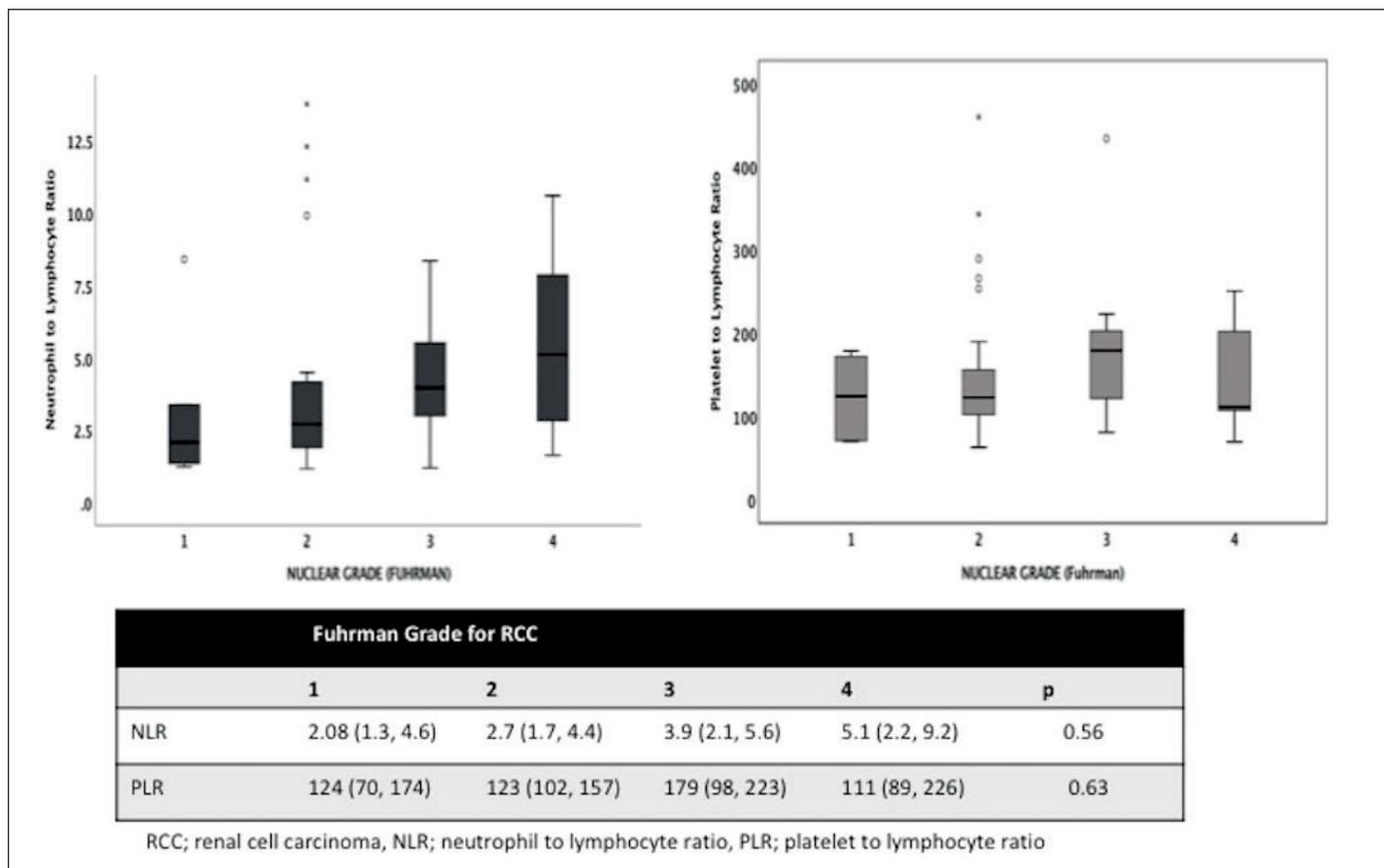
Figure 1: NLR and LR values according to the Nuclear Grade among the RCC patients.

The other simple inflammation-based parameter is PLR, which is also obtainable from the complete blood count. Many studies have revealed that higher pretreatment levels of PLR is associated with poor prognosis in several types of solid cancer (17-19)

In our study, we have performed the analyses regarding the potential predictive value for the presence of malignancy of both NLR and PLR in patients with a renal mass. Sixteen patients who had a benign pathology such as oncocytoma, angiomyolipoma or other types and 49 patients with RCC were compared in terms of the NLR and PLR levels obtained in the preoperative period. Our comparison showed that although the levels of both NLR and PLR were high in RCC patients, the differences did not reach statistical significance and this can be explained in part with the small sample size of our data. However, the univariate logistic regression analysis showed that high levels of NLR were statistically significantly associated with the presence of malignancy. We also have performed multivariate analysis by adjusting the widely known predictive factors for RCC as age and gender and found that NLR values were still significantly associated with RCC pathology. Since we were lacking information regarding the body mass index (BMI) values of most of the patients, we were unable to add BMI to multivariate analysis as a confounder. However, PLR values did not reveal any significant association with malignancy in both univariate and multivariate analysis.

Fuhrman histological grading is a well known marker for the calculation of tumor prognosis in RCC patients. In our study, we have also evaluated the levels of both NLR and PLR in each grade and found that preoperative NLR values showed a sequential increase in each increasing grade; however, PLR did not show any parallel changes. This result has also led us to conclude that preoperative NLR levels might also be favorable marker for the prediction of disease prognosis in RCC patients. Most of our patients had the clear cell type of RCC and we were therefore unable to perform suitable comparison for both inflammatory markers in each RCC subtype.

The evidence indicates that higher PLR levels reflect increased platelet dependent tumor growth (pro-tumor reaction) and decreased lymphocyte mediated anti-tumor immune response, and both have been attributed to progression and poor outcome in tumors (11,20-22). The inflammatory pathways at the tissue level and its reflection in clinical laboratory results might not always be correlated. The lack of power of the relation between PLR and prediction of malignancy or histological status in our study might indicate that neutrophils instead of platelets have a more significant role in the development and progression of malignancy. This issue should be further clarified with studies performing simultaneous blood and specimen evaluation.

We have several limitations in our report including the retrospective design, which might limit the causality interpretation of our results. The small sample size might also blind the statistical association of the markers with endpoints. We also did not include metastatic patients in our analysis, to ensure homogeneity of the population. However, exclusion of the other comorbidities such as active infection, diabetes, coronary disease might have led us to present cleaner results regarding the association between these inflammatory parameters and RCC.

In conclusion, our study confirms that higher NLR levels are an indicator of the presence of RCC and its histological prognosis. We were unable to demonstrate statistical significance regarding the association with PLR levels. Further large scale, follow-up studies are needed to validate these results with certain cut-off levels of these inflammatory parameters.

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CONFLICT OF INTEREST

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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