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Original Article

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

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Abstract

Objective: The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are easily accessible inflammatory parameters. In the present study, we aimed to analyze the coherence of these two markers for the predictive value of malignancy in patients with a kidney mass and histologic grade of patients with renal cell carcinoma (RCC).
Materials and Methods: A total of 65 patients with a kidney mass (median age, 58; IQR, 47-68), who underwent either radical or partial nephrectomy, were included into this retrospective study. The NLR and PLR were derived from the complete blood cell count results at the preoperative period. Patients were divided in to two groups: as benign and malign. Also, patients with diagnosed RCC were further analyzed using the Fuhrman histologic grading.
Results: A univariate regression analysis showed that the LnNLR (1.125, 95% confidence interval [CI] [1.00-31.26]; p=0.04) levels were significantly associated with RCC. However, the 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 the LnNLR levels (1.14, 95% CI [1.01-1.30]; p=0.03) were still associated with RCC. The NLR levels showed a sequential increase from the low grade to high grade according to the Fuhrman grading system among RCC patients.
Conclusion: Higher NLR levels were significantly associated with a malign kidney mass and high-grade RCC.
Keywords: Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, renal cell carcinoma, Fuhrman Grade

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INTRODUCTION

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

Chronic inflammation plays a crucial role in the development of cancer (3). There are a growing number of reports concluding that systemic hematologic markers such neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are good predictors of either malignancy presence or malignancy prognosis 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 the predictive value of both the malignancy in

patients who have a kidney mass and the histologic grade for those with RCC.

MATERIALS AND METHODS

Study Population

A total of 71 subjects screened, in whom a renal mass was detected by either ultrasound or computed tomography, underwent partial or radical nephrectomy between October 2012 and July 2018 at the Yuksek Ihtisas University School of Medicine, Koru Ankara Hospital, Department of Urology, and 65 of those were included into the retrospective analyses. Exclusion criteria included patients with an infectious or inflammatory disease (i.e., connective tissue disorder, HIV, any other proven infections), patients with diabetes mellitus, any coronary artery disease, or patients who had no sufficient medical records. Also, none of the patients received anticancer therapy before the surgical procedure. Patients aged <18 years were also excluded for homogeneity of the population. Among 71 subjects, 4 patients were excluded for being <18 years, and 2 patients were excluded due to diabetes mellitus.

The Institutional Review Board of the 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 a complete blood count (CBC) obtained before the surgery, and PLR was calculated as platelets divided by lymphocytes using the same CBC results. All surgeries were performed by the same team.

Statistical Analysis

Descriptive statistics were expressed as the mean±standard deviation (SD) or median (IQR) for continuous variables, and as frequencies and percentage for categorical variables. The comparison of variables between the two groups was performed according to the normality, either the t-test or the Mann-Whitney U test for continuous variables, and chi-squared test for categorical variables. For the Fuhrman categories analysis, we used the one-way analysis of variance to compare the NLR and PLR values in each grade. Logistic regression analyses were used to evaluate the possible association between the NLR, PLR, and malignancy presence. All leukocytes, neutrophils, lymphocytes, platelets, and NLR and PLR values were log-transformed to reach the normal distribution, and transformed values were used in the regression analysis. Since we were not able to obtain body mass index values for all patients, multivariate analyses were adjusted by age and gender. Independent variables were not put together in the model for possible interaction. All tests were two-sided. A p value less than 0.05 was considered statistically significant. The statistical analysis was carried out using the The Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp.; Armonk, NY, USA).

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 study patients are presented in Table 1. The median age was 58 (IQR, 47, 68) years, with male predominance (48 males [73.8%], 17 females [26.2%]). After detecting the renal mass using computed tomography, 24 patients underwent partial, and 41 underwent radical nephrectomy surgeries. Among 65 patients, after either radical or partial nephrectomy, pathology specimens revealed that 49 (75%) patients had RCC, 6 patients had angiomyolipoma (9%), 6 patients had oncocytoma (9%), and 4 patients (7%) had other benign lesions (Table 1).

The median leukocyte level was 8,800 (6,750-10,785)/μL, the median neutrophil level was 5,870 (4,220-8,435)/μL, the median lymphocyte level was 1,800 (1,255-2,485)/μL, the median platelet level was 251,000 (209,000-332,000)/μL, the median NLR was 3.2 (2.0-5.6), and the PLR was 143 (102-212) (Table 1).

We also compared all characteristics among the study subgroups assigned as benign and malign. The comparison analysis is presented in Table 2. Although both the 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 2).

Table 1. Basic characteristics of study population

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 cells (/μL, median; IQR)	8,800 (6,750-10,785)
Neutrophils (/μL, median; IQR)	5,870 (4,220-8,435)
Lymphocytes (/μL, median; IQR)	1,800 (1,255-2,485)
Platelets (/μL, median; IQR)	251,000 (209,000-332,000)
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

Table 2. Comparison of Characteristics between Patients with Benign and Malign Lesions

Variables	Benign (n=16)	RCC (n=49)	P-value
Age (years, median, IQR)	52 (38-70)	60 (51-68)	0.22
Gender (n,%)			
Female	6 (40%)	11 (22%)	0.14
Male	9 (60%)	39 (78%)	
Inflammatory Parameters			
White blood cells (/µL, median; IQR)	9,800 (6,300-14,000)	8,705 (6,880-10,660)	0.47
Neutrophils (/µL, median; IQR)	6,200 (4,060-12,700)	5,835 (4,220-8,052)	0.18
Lymphocytes (/µL, median; IQR)	1,500 (1,000-2,400)	1,925 (1,257-2,675)	0.81
Platelets (/µL, median; IQR)	251,000 (229,000-369,000)	249,000 (198,000-332,000)	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

Table 3. Association between the RCC Diagnosis 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-Leukocytes (/µL, median, IQR)	7.23 (0.25-207.8)	0.24	15.2 (0.38-598.1)	0.14
Ln-Neutrophils (/µL, median, IQR)	5.56 (0.42-72.5)	0.19	8.40 (0.59-151.0)	0.11
Ln-Lymphocytes (/µL, median, IQR)	0.20 (0.01-3.03)	0.24	0.15 (0.009-2.75)	0.204
Ln-Platelets (/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; SD: standard deviation; CI: confidence interval

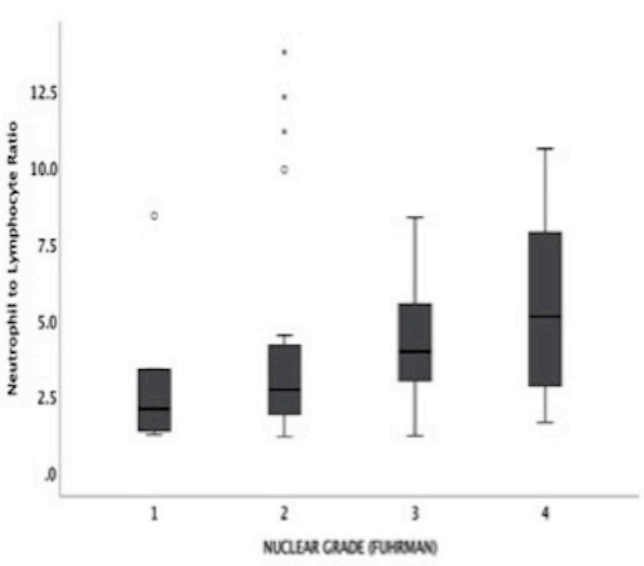
Association between NLR, PLR, and RCC Diagnosis

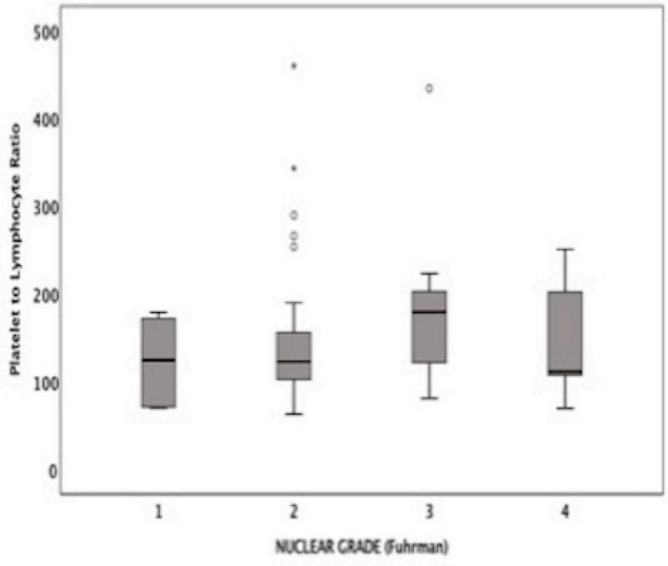
A univariate logistic regression analysis showed that the LnNLR (1.125, 95%CI [1.00-31.26]; p=0.04) levels were statistically significantly associated with the RCC pathology. Although the ln-PLR levels showed to be predictive with the 5.3 beta coefficient, the association did not reach statistically significance (5.32, 95%CI [0.46-60.8]; p=0.17). Although the male gender seems to be a risk factor for being diagnosed with RCC, the association was not statistically significant (2.36, 95% CI [0.69-8.09]; p=0.17) (Table 3).

In multivariate analyses, after adjusting the analysis for age and gender, only the LnNLR levels [1.14, 95%CI (1.01-1.30); p=0.03] were still statistically significantly associated with the RCC diagnosis. All results are summarized in Table 3. Among 65 patients with RCC, we reached 45 of those, histological grade (Fuhrman grade), and when we checked the NLR and PLR values among 4 categories, the NLR levels showed a sequential increase from the low grade to the high grade but did not show any statistically significance (Figure 1); however, the PLR showed no rationale changes (Figure 1).

DISCUSSION

The predictive markers of RCC are the 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 plays a substantial role in the develop-





	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 PLR values according to the nuclear grades in patients with RCC.

ment and progression of cancer (3). The laboratory reflection of the systemic inflammation includes an increase or decrease of the acute phase reactants such as fibrinogen, ferritin, albumin, transferrin, increase of C-reactive protein, and changes in the neutrophil and lymphocyte levels derived from peripheral blood. The strong association between inflammation and the development and progression of cancer has driven the researchers to find easily accessible, inexpensive, and fast markers for to predict malignancy (9).

The NLR and PLR are acceptable, inexpensive, easily accessible markers in clinical use and have been studied in many different type of solid organ tumors regarding the predictive value for both cancer development and prognosis (10-12). Most of the previous studies have been designed to predict values of those markers for both the metastasis status and and cancer related mortality.

Of those, the association between the RCC and NLR values has been previously analyzed. Ohno et al. (13) reported that the preoperative NLR values were predictive for both the prognosis and disease relapse in patients with RCC. Similarly, Keskin et al. (14) performed another study that claimed that there was a close association between the NLR values and histological subtypes of RCC. They also reported that high NLR values were predictive for cancer-related mortality. Pichler et al. (15) reported, examining a large cohort database, that preoperative NLR values were only associated with mortality in patients with non-metastatic RCC. On contrary, Jagdev et al. (16) did not find any relation between the NLR and prognosis in patients with RCC.

The other simple inflammation-based parameter is PLR, which is also obtainable from a CBC. Many studies disclosed that higher pretreatment levels of PLR were associated with a poor prognosis in several types of solid cancer (17-19).

In our study, we have performed the analyses regarding the possible prediction value for the presence of malignancy of both NLR and PLR in patients with a renal mass. Sixteen patients who had benign pathology such as oncocytoma, angiomyolipoma, and other type and 49 patients with RCC were compared in terms of the NLR and PLR levels obtained at the preoperative period. Our comparison showed that although both levels of NLR and PLR were high in patients with RCC, the differences did not reach the statistical significance, which can be explained in part with a small data sample size. However, the univariate logistic regression analysis showed that high levels of NLR were statistically significantly associated with the presence of malignancy. We also performed a multivariate analysis

by adjusting the widely known predictive factors for RCC such as age and gender, and we found that the NLR values were still significantly associated with the RCC pathology. Since we were lacking the information regarding the BMI values of most of the patients, we were not able to add BMI to the multivariate analysis as cofounder. However, in both the univariate and multivariate analysis, the PLR values did not reveal any significant association with malignancy.

The Fuhrman histological grading is a well-known marker for the calculation of tumor prognosis in patients with RCC. In our study, we 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 also led us to conclude that preoperative NLR levels might also be a favorable marker for the prediction of disease prognosis in patients with RCC. Most of our patients had a clear cell type of RCC; hence, we were not able to perform a suitable comparison for both inflammatory markers in each RCC subtype.

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

Our study had several limitations, including its retrospective design, which might have limited our results' causality interpretation. Also, the small sample size may hide the statistical association of the markers with endpoints. We also did not include metastatic patients in our analysis, to yield the homogeneity of the population. However, the exclusion of other comorbidities such as infection, diabetes mellitus, and coronary artery disease might lead us to the present clearer results regarding the association between these inflammatory parameters and RCC.

CONCLUSION

Overall, our study confirms that higher NLR levels indicate the presence of RCC and its histological prognosis. We were not able to detect statistical significance regarding the association with PLR levels. Further large scale, follow-up studies are needed to validate these results with certain cutoff levels of these inflammatory parameters.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of Yuksek Ihtisas University Faculty of Medicine, Koru Ankara Hospital.

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Conflict of Interest: The authors have no conflict of interest to declare.

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