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Evaluation of the Prognostic Value of Preoperative Neutrophil-to-lymphocyte Ratio in Renal Cell Carcinoma

Renal Hücreli Kanserlerde Preoperatif Nötrofil Lenfosit Oranının Prognostik Belirteç Olarak Değerlendirilmesi

İsmail Basmacı, Serdar Çelik, Ertuğrul Şefik, Erhan Aydın, Serkan Yarımoğlu, İbrahim Halil Bozkurt, Tansu Değirmenci

Bozyaka Training and Research Hospital, Clinic of Urology, İzmir, Turkiye

What's known on the subject? and What does the study add?

Neutrophil/lymphocyte ratio (NLR) has been investigated as a prognostic marker in many cancers. In this article we aimed to investigate the prognostic value of NLR in renal cell carcinoma.

Abstract

Objective: To investigate the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in renal cell carcinoma (RCC).
Materials and Methods: Preoperative NLR value in 125 patients who underwent surgical treatment for renal tumor between January 2012 and September 2017 and and received the pathological diagnosis of RCC, was evaluated. The patients were initially divided into two groups as patients with and without metastases at the time of diagnosis.
Subsequently, the patients were divided into two groups according to the pathological stage. In the first group, patients with localized RCC (pT1 and pT2) were evaluated and in the other group, those with advanced RCC (pT3 and pT4) were evaluated, and then, these two groups were compared.
Results: The mean NLR was higher in group with metastasis than in group without metastasis at the time of diagnosis (4.4±2.8 and 2.9±1.6, respectively; p=0.029). When a NLR of 3.1 was taken as the cut-off value; it was observed that the NRL value in 7 of 8 patients with metastasis at diagnosis was above 3.1. (p=0.002, OR=14.6). Overall survival was 59.8±2.7 months and 49±4.5 months in patients with a NLR of <3.1 and >3.1, respectively (p=0.045).
Conclusion: We assume that preoperative NLR can be evaluated as a prognostic marker for overall survival in patients with RCC.
Keywords: Renal cell carcinoma, Neutrophil-to-lymphocyteratio, Prognostic marker

Öz

Amaç: Renal hücreli kanserlerde (RHK) prognostik belirteç olarak nötrofil lenfosit oranının (NLO) etkinliğini araştırmak.
Gereç ve Yöntem: Ocak 2012 - Eylül 2017 tarihleri arasında böbrek tümörü nedeniyle cerrahi tedavi uygulanan ve RHK patolojisi olan 125 hastanın preoperatif NLO'su değerlendirildi. Hastalar ilk tanı anında metastaz olanlar ve olmayanlar olarak iki gruba ayrıldı. Ardından hastalar patolojik T evresine göre iki gruba ayrıldı. İlk grupta T1 ve T2 evreli lokalize hastalar, diğer grupta T3 ve T4 evreli invaziv hastalar değerlendirilerek veriler bu iki grup arasında karşılaştırılarak incelendi.
Bulgular: NLO tanı anında metastazı olan grupta, metastazı olmayan gruba oranla daha yüksekti (sırasıyla 4,4±2,8 ve 2,9±1,6; p=0,029). NLO=3,1 değeri sınır değer olarak alındığında tanı anında metastatik olan 8 hastanın 7'sinin değeri 3,1'in üzerinde olduğu gözlendi (p=0,002, OR=14,6). NLO <3,1 olan hastalarda genel sağkalım 59,8±2,7 ay iken NLO >3,1 olan hastalarda 49±4,5 ay olarak saptandı (p=0,045).
Sonuç: Bu çalışmada preoperatif NLO, RHK hastalarında genel sağkalım açısından prognostik belirteç olarak değerlendirilebileceği gösterilmiştir.
Anahtar Kelimeler: Renal hücreli kanser, Nötrofil lenfosit oranı, Prognostik belirteç

Correspondence: İsmail Basmacı MD, Bozyaka Training and Research Hospital, Clinic of Urology, İzmir, Turkiye
E-mail: ibasmaci@yahoo.com **ORCID-ID:** orcid.org/0000-0001-5012-6590
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Introduction

Renal cell carcinoma (RCC) represents 2-3% of all cancers, and is the most common genitourinary malignancy after prostate and bladder cancer (1). As a result of the increased widespread use of computed tomography (CT) and ultrasonography (USG), the frequency of incidental identification of early stage tumors has increased (2,3). Nearly 8% of patients with localized disease, who undergo partial or radical nephrectomy, develop metastatic disease during follow-up (4). A variety of models based on clinicopathological findings, such as TNM stage and Fuhrmann nuclear grade have been developed to estimate the outcomes for RCC patients to determine postoperative risks and to develop individualized treatments (5,6). Other well-known prognostic factors are lymphocyte infiltration and histological subtype. However, not all of these prognostic factors are reliable (7). In clinical practice, a prognostic factor will have a great potential if it is easily evaluated, cheap and can be used in routine practice.

Many studies have shown the role of local and systemic inflammation in the development of cancer metastasis (8). Due to this effect, neutrophil-to-lymphocyte ratio (NLR) has been assessed as an independent prognostic factor for inflammation and many cancer types (9). A high NLR has been defined as a prognostic factor for poor overall survival, disease-free survival and progression-free survival in cancer patients (9). Our aim in this study was to assess the prognostic value of preoperative NLR in predicting survival and tumor recurrence in RCC patients.

Materials and Methods

Records of 153 patients, who underwent surgical treatment due to kidney tumors at our clinic from January 2012 to September 2017, were retrospectively analyzed in accordance with the ethical principles of the Helsinki Declaration. Twenty-eight patients, including 10 with benign results, 8 with urothelial carcinoma, 1 with lymphoma and 9 with missing data, were excluded from the study. The remaining 125 patients were included in the study.

Demographic data (age and sex), preoperative radiological findings (presence of invasion and metastasis at the time of diagnosis), preoperative laboratory data (serum neutrophil and lymphocyte levels and neutrophil/lymphocyte ratio), operation data, operation side, pathologic data (pathologic T stage, tumor size, Fuhrmann nuclear grade, tumor histology) and postoperative follow-up data (follow-up imaging) were investigated. All patients were assessed preoperatively with thoracic, abdominal and pelvic CT. According to the pathologic T stage determined by the 2010 TNM classification system, cellular evaluation was made using the Fuhrmann grading system (10,11). Preoperative full blood count was evaluated 1 day before the operation with no blood transfusion, no active infection or fever. Preoperative NLR was calculated by dividing neutrophil count by lymphocyte count.

For patient follow-up, the kidney tumor follow-up protocol stated in the EAU 2010 guidelines was used (12). Accordingly, low-risk patients (pT1a, pT1b) underwent USG and chest X-ray once every 6 months in the first postoperative year and once a year after that. Intermediate-risk patients had thoracic and abdominal CT at 6 months, 2 and 5 years postoperatively and annual USG and chest x-ray at 1, 3, 4 and 5 years postoperatively. High-risk patients underwent thoracic and abdominal CT every 6 months in the first year and every year afterwards. Mortality data for patients were obtained from the Turkish Statistical Institute database and the hospital database. The patients were last assessed in October 2017. Overall survival was calculated as the duration in months from the date of operation until death due to any cause. Presence of metastasis at the time of diagnosis was identified with preoperative radiological investigation and patients with metastasis after surgical treatment were referred to medical oncology. Patients without preoperative clinical metastasis were assessed according to radiological evaluation results for recurrence and metastasis presence during follow-up.

The patients were initially divided into two groups as those with and without metastasis according to the presence of clinical metastasis at the time of diagnosis. All data were compared between the groups. Then patients were further divided into two groups according to pathologic T stage. The first group included patients with pT1 and pT2 stage localized RCC and the other group pT3 and pT4 stage invasive RCC. The data in these two groups were compared and investigated.

Statistical Analysis

Continuous data from the demographic information of patients were analyzed descriptively, while categorical data were analyzed according to frequency and proportion. Firstly, patients with and without metastasis at the time of diagnosis were compared. Then, the pT1 and pT2 patients were compared with pT3 and pT4 patients. In the comparisons the Mann-Whitney U test, binary logistic regression analysis and Pearson's chi-square test were used. Survival analysis was done using the Kaplan-Meier method. All data were analyzed with the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, Ill) software program. Data were given as mean ± SD. A p value of less than 0.05 was considered statistically significant.

Results

The data on demographic characterstics, preoperative radiological and clinical findings, pathological findings and follow-up data for the 125 patients [79 (63.2%) male and 46

(36.8%) female] included in the study are shown in Table 1. The median follow-up duration was 24.6 (0.03-68.6) months and the mean age of the patients was 58.6±12.3 years. The mean tumor size was 5.6±3.3 cm, and when patients were assessed in terms of histologic subtypes, 88 (70.4%) had clear-cell RCC, 19 (15.2%) had papillary RCC and 18 (14.4%) had chromophobe RCC. The mean overall survival was 56.2±2.4 months, with 21 patients (16.8%) exitus during follow-up.

When the patients were initially evaluated in two groups according to clinical metastasis status at the time of diagnosis, it was found that 117 patients did not have metastasis and 8 patients had metastasis and these two groups were compared. Comparative results for the data in both groups are given in Table 2. The mean Fuhrmann nuclear grade was 2.2±0.6 in the non-metastasis group and 3±0.5 in the metastasis group (p<0.001). NLR was higher in the metastasis group compared

Table 1. Demographic, pathological and laboratory data of patients

		n=125	Percentage (%)
Age (years) (mean ± SD)		58.56±12.349	
Sex	Male	79	63.2
	Female	46	36.8
Site of surgery	Right	57	45.6
	Left	68	54.4
NLR (mean ± SD)		2.96511±1.753766	
Tumor size (cm) (mean ± SD)		5.620±3.2781	
Pathological subtype of RCC	CCRCC	88	70.4
	PRCC	19	15.2
	CRCC	18	14.4
Fuhrmann grade	1	9	7.2
	2	85	68
	3	26	20.8
	4	5	4
Microscopic surgical margin status	Negative	118	94.4
	Positive	7	5.6
Tumor stage according to the TNM classification (Pt)	T1a	48	38.4
	T1b	33	26.4
	T2a	13	10.4
	T2b	7	5.6
	T3a	20	16.0
	T3b	3	2.4
	T4	1	0.8
Lymph node according to the TNM classification (N)	N0	122	97.6
	N1	3	2.4
Metastasis according to the TNM classification (M)	M0	117	93.6
	M1	8	6.4
TNM stage	1	81	64.8
	2	19	15.2
	3	24	19.2
	4	1	0.8
Overall survival	Alive	117	83.2
	Deceased	8	16.8
Duration of follow-up (months), median (min-max)	-	24.6 (0.03-68,6)	-
Overall survival (months) (mean ±SD)	-	56.2±2.4	-

NLR: Neutrophil/lymphocyte ratio, CCRCC: Clear cell renal cell carcinoma, PRCC: Papillary renal cell carcinoma, CRCC; Chromophobe renal cell carcinoma, SD: Standart deviation, RCC: Renal cell carcinoma, TNM: Tumor, node, metastases

to the non-metastasis group (4.4±2.8 and 2.9±1.6, respectively, p=0.029). Multivariate analysis also revealed a significant difference in NLR between the groups (p=0.035). Receiver operating characteristics curve analysis identified that the sensitivity and specificity of the NLR cut-off value of 3.1 were 87.5% and 67.5%, respectively (AUC=0.731, p=0.029). When a NLR of 3.1 was taken as a cut-off value, the NLR value in 7 of 8 patients with metastasis at the time of diagnosis was observed to be above 3.1 (p=0.002, OR=14.6). However, this value did not show a significant correlation with T stage, Fuhrman nuclear grade, lymph node (LN) involvement, surgical margin positivity, local recurrence and development of metastasis during follow-up. In the group without metastasis, there were 19 patients with invasive disease (pT3-4) (16%), while in the metastasis group 6 patients had invasive disease (75%) (p<0.001). The number of patients with LN metastasis was 1 in the non-metastasis group (0.8%) and 2 in the clinical metastasis group (25%) (p=0.01). The number of patients with positive surgical margins in the non-metastasis and metastasis groups were 4 (3.4%) and 3 (37.5%), respectively (p<0.001). The mean survival duration in the non-metastasis group was longer compared to that in the metastasis group (58.4±2.3 months and 18.5±4.5 months, respectively, p<0.001). During follow-up, 16 patients in the non-metastasis group (13.6%) and 5 patients in the metastasis group (62.5%) were exitus (p<0.001). There were no significant differences for other statistical data.

According to pathological stage, there were 100 patients with pT1-2 and 25 patients with pT3-4. Comparative results for data in the two groups are given in Table 3. Fuhrmann nuclear grade was lower in the pT1-2 group compared to the pT3-4 group

Table 2. Comparison of demographic, pathological and laboratory data of metastatic and non-metastatic patients at the time of diagnosis

			Group of patients without metastasis (n=117)	Group of patients with metastasis (n=8)	p
Age (years) (mean ± SD)			58.54±12.57	58.88±9.12	0.984†
Sex (n)	Male		72	7	0.141•
	Female		45	1	
Site of surgery	Right		54	3	0.634•
	Left		63	5	
NLR (mean ± SD)			2.87±1.63	4.41±2.80	0.029†
Tumor size (cm) (mean ± SD)			5.337±3.0651	9.763±3.7025	<0.001†
Pathological subtype of RCC		CCRCC	83	5	0.727•
PRCC		17	2		
CRCC		17	1		
pT		T1a	48	0	<0.001•
T1b		33	0		
T2a		11	2		
T2b		6	1		
T3a		17	3		
T3b		2	1		
T4		0	1		
pN		N0	116	6	0.01
N1		1	2		
Microscopic surgical margin status		Negatif	113	5	<0.001•
Pozitif		4	3		
Duration of follow up (months), median (min-max)			26.5 (0.03-68.6)	13.7 (1.9-39.8)	0.050†
Overall survey (month) (mean ± SD)			58.4±2.3	18.5±4.5	<0,001*
Overall survival		Alive	101	3	<0.001•
Deceased		16	5		

†Mann-Whitney U test, •chi-square test, *Kaplan-Meier survival analysis
NLR: Neutrophil/lymphocyte ratio, CCRCC: Clear cell renal cell carcinoma, PRCC: Papillary renal cell carcinoma, CRCC; Chromophobe renal cell carcinoma, SD: Standart deviation, RCC: Renal cell carcinoma

(2.1±0.5 and 2.7±0.8, respectively, p<0.001). The mean tumor size was 5.2±3.1 cm in the pT1-2 group and 7.5±3.2 cm in the pT3-4 group (p<0.001). NLR was higher in the pT3-4 group compared to the pT1-2 group (3.8±2.6 and 2.8±1.4, respectively) and multivariate analysis also showed a significant difference in NLR between the groups (p=0.035). While LN metastasis was not observed in patients in the pT1-2 group LN metastasis was present in 3 patients (13.6%) in the pT3-4 group. The number of patients with clinical metastasis on preoperative assessment was 2 (2%) and 6 (24%) in the pT1-2 and pT3-4 groups, respectively (p<0.001). The number of patients with positive surgical margins was 3 (3%) in the pT1-2 group and 4 (25%) in the pT3-4 group (p=0.011). On follow-up, the time to recurrence was longer in the pT1-2 group compared to that in the pT3-4 group (63.4±1.9 months and 28.7±3.1 months, respectively, p<0.001). The mean overall survival was longer in the pT1-2 group than in the pT3-4 group (62.8±1.9 months and 26±3.1 months, respectively; p<0.001). During follow-up, 8 patients in the pT1-2 group (8%) and 13 patients in the pT3-4 group (54.1%) were exitus (p<0.001). There were no significant differences identified for other statistical data. According to the NLR cut-off value of 3.1, the patients were divided into two groups as NLR <3.1 and >3.1. There was no significant difference observed in recurrence-free survival between the two groups (Figure 1, NLR <3.1 - 60.8±2.6 months, NLR >3.1 - 56.5±3.9 months, p=0.409). However, when

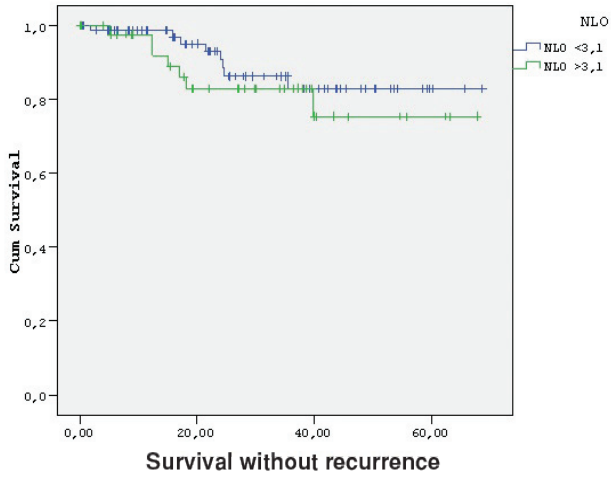

Figure 1. Kaplan-Meier survival plot for relapse-free survival and analysis result

Table 3. Comparison of demographic, pathological and laboratory data of pT1-2 and pT3-4 patients

			pT1-2 (n=100)	pT3-4 (n=25)	p
Age (years) (mean ± SD)			58.19±12.42	60.04±12.17	0.509†
Sex (n)	Male		62	17	0.578•
	Female		38	8	
Site of surgery	Right		45	12	0.788•
	Left		55	13	
NLR (mean ± SD)			2.77±1.43	3.76±2.57	0.071†
Tumor size (cm) (mean ± SD)			5.16±3.14	7.47±3.23	<0.001†
Pathological subtype of RCC		CCRCC	68	20	0.470•
PRCC		16	3		
CRCC		16	2		
pN		N0	100	22	0.007•
N1		0	3		
Metastasis according to TNM classification (M)		M0	98	19	<0.001•
M1		2	6		
Microscopic surgical margin status		Negative	97	21	0.011•
Positive		3	4		
Duration of follow-up (months), median (min-max)			27.9 (0.03-68.63)	17 (0.2-39.9)	0.003†
Time to recurrence (months) (mean ± SD)			63.4±1.9	28.7±3.1	<0.001*
Overall survival (months) (mean ± SD)			62.8±1.9	26±3.1	<0.001*
Overall survival		Alive	92	12	<0.001•
Deceased		8	13		

†Mann-Whitney U test, •chi-square test, *Kaplan-Meier survival analysis
NLR: Neutrophil/lymphocyte ratio, CCRCC: Clear cell renal cell carcinoma, PRCC: Papillary renal cell carcinoma, CRCC; Chromophobe renal cell carcinoma, SD: Standart deviation, RCC: Renal cell carcinoma, TNM: Tumor, node, metastases

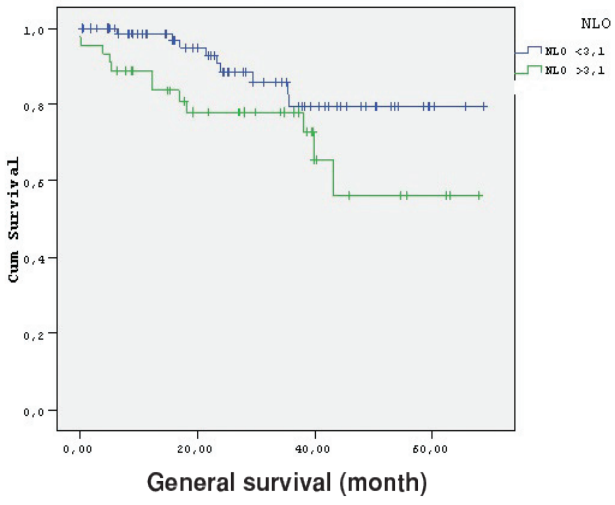

Figure 2. Kaplan-Meier survival plot for OS and analysis result

overall survival was assessed, this value was 59.8±2.7 months for patients with a NLR <3.1 and 49±4.5 months for patients with a NLR >3.1 (Figure 2, p=0.045).

Discussion

In recent years, many laboratory markers and risk scores associated with these markers have been defined to predict prognosis for RCC patients. Of these, the Leibovich prognosis score, the Mayo clinic stage, size, grade and necrosis score, and ULCA integrated staging system to assess metastasis-free survival and additional immunohistochemical evaluation of biological markers and genomic assessments for RCC follow-up in the postoperative period to assess cancer-free survival are recommended to predict prognosis (13,14,15,16). As a result, we assessed preoperative and postoperative data forming the basis of scoring in our study. In line with this, when we examined our results, NLR in the group with metastasis at the time of diagnosis was identified to be significantly higher compared to that in the group without metastasis. When the patients were grouped according to pathologic stage, NLR was significantly higher in the pT3-4 group than in the pT1-2 group.

Inflammation in the microenvironment of the tumor plays an important role in angiogenesis, proliferation and tumor invasion. Additionally, the intrinsic effect of inflammation is required to inactivate tumor suppressor genes and for oncogene activation (8). High percentage of neutrophil values is associated with chemokines, growth factors and proteases associated with angiogenesis. These neutrophil-associated factors help tumor cells to invade extracellular matrix and vascular wall and development of metastasis (17). Low lymphocyte values are a marker of reduced cellular immune response. Cytokine release preventing tumor distribution and development and cytotoxic cell death occurs due to lymphocytes (18).

The prognostic value of NLR in predicting recurrence was first investigated by Ohno et al. (19) in a study including 192 patients with non-metastatic RCC. This study revealed that patients with a NLR >2.7 had worse recurrence-free survival. A study by Tanaka et al. (20) in 2014 found that a high NLR value (>3 threshold value) was associated with advanced T stage, lymphovascular invasion, LN involvement and poor cancer-specific survival. Similarly, in a review of 15 studies, Boissier et al. (21) observed that a NLR <3 predicted reduced recurrence risk, with better overall survival and disease-free survival in patients with localized RCC than in those with metastatic and locally advanced RCC. In our study, NLR was higher in the group with metastasis at the time of diagnosis compared to the group without metastasis. In multivariate analysis, NLR was found to be an independent factor for metastasis. When a NLR of 3.1 was accepted as a cutoff value, there was no significant difference in recurrence-free survival, but overall survival was longer in patients with a NLR <3.1.

Study Limitations

Limitations of the study include the retrospective nature of the study and the low number of patients (especially in the metastasis group).

Conclusion

This study shows that preoperative NLR may be considered a prognostic factor in terms of general survival in RCC patients.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Ç., İ.B., T.D., S.Y., Design: İ.B., Data Collection and/or Processing: İ.H.B., S.Ç., İ.B., E.Ş., S.Y., E.A., Analysis and/or Interpretation: S.Ç., İ.B., E.Ş., E.A., Literature Research: S.Ç., İ.B., T.D., S.Y., Writing: İ.B.

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