POSTOPERATIVE HIGH NEUTROPHIL-LYMPHOCYTE RATIO PREDICTS SURVIVAL IN RENAL CELL CARCINOMA

Yüksek Nötrofil- Lenfosit Oranının Renal Hücreli Karsinomda Preoperatif ve Postoperatif Dönemde Sağkalıma Etkisi

Alper SONKAYA[1]

[1]*Umraniye Training and Research Hospital. Umraniye, İSTANBUL, TÜRKİYE*

ABSTRACT	ÖZ

Objective: The neutrophil-lymphocyte ratio (NLR) has been used as a marker of systemic inflammatory response and various studies confirmed it affects overall survival in renal cell carcinom (RCC). Most studies used NLR as a poor prognostic factor when assesed preoperatively. The aim of our study is to demonstrate the postoperative NLR as a poor prognostic factor.

Material and Methods: We reviewed 135 patients with RCC who were treated and followed in Kocaeli Univercity Medical Oncology Department between 2003 and 2014. Overall survival and progression free survival were assesed by using Kaplan-Maier method and prognostic significance of NLR and other independent factors were assesed by using cox regression models.

Results: Univariate and multivariate analyses showed that T stage (HR:1.86; 95% Cl:1.2-2.5 p:0.003), hemoglobin count (HR:0.51; 95% Cl:0.34-0.76 p:0.001) and NLR (HR: 2.6; 95% Cl:1.1-5.5 p:0.017) as independent prognostic factors for overall survival.

Conclusion: An increased NLR even after partial or radical nephrectomy can be a prognostic marker for RCC. In addition to recent studies which found preoperative NLR is a poor prognostic factor in RCC, we found postoperative NLR has a significance in overall survival.

Amaç: Nötrofil-lenfosit oranı (NLO) sistemik inflamatuar yanıtı gösteren belirteçlerden biridir ve birçok çalışma renal hücreli karsinomda (RHK) genel sağkalımı etkilediğini ispatlamıştır. Yapılmış çalışmalarda NLO genellikle nefrektomi öncesi bakılmış ve kötü prognostik faktör olarak değerlendirilmiştir. Bu çalışmada postoperatif NLO'nun prognostik önemini göstermeyi amaçladık.

Gereç ve Yöntemler: 2003 ile 2014 tarihleri arasında Kocaeli Üniversitesi Medikal Onkoloji kliniğinde takip ve tedavi olan 135 hasta geriye dönük olarak incelendi. Genel sağkalım ve progresyonsuz sağkalım Kaplan-Maier metoduyla NLO ve diğer bağımsız değişkenlerin prognostik önemi cox regresyon modeliyle hesaplandı.

Bulgular: Univariete ve multivariete analizlerde T evresi (HR:1.86; %95 Cl:1.2-2.5 p:0.003), hemoglobin seviyesi (HR:0.51; %95 Cl:0.34-0.76 p:0.001) ve preoperatif NLO (HR:2.6; %95 Cl:1.1-5.5 p:0.017) RHK hastalarında genel sağkalımı etkileyen bağımsız faktörler olarak görüldü.

Sonuç: Parsiyel ya da radikal nefrektomi yapılmış RHK hastalarında artmış NLO oranı prognostik belirteç olarak kullanılabilir. Geçmiş çalışmalarda preoperatif NLO yüksekliğinin öneminin vurgulanmasına ek olarak çalışmamızla postoperatif NLO seviyesinin önemi gösterilmiştir.

Keywords: Neutrophil lymphocyte ratio, renal cell carcinom, survival

Anahtar Kelimeler: Nötrofil lenfosit oranı, renal hücreli karsinom, sağkalım

INTRODUCTION

Renal cell carcinomas (RCC) are responsible for 80 to 85 percent of primary renal neoplasms. The insidence varies from region to region (1). It is more common in men compared with women (2). Only 17 percent present with metastatic disease, 62 percent present with localized disease and the rest present with regional disease (3). RCC recurs in 10% to 20% of patients after curative surgery (4). Many factors and models have been used to predict the patients prognosis (5). Tumor size, pathologic Tumour-Node-Metastasis (pTNM) stage, histologic subtype, disease related symptoms, performance status and Fuhrman grade were used in these models. C-reactive protein, neutrophil or platelet count which correlates with systemic inflammation has been shown as a prognostic factor in different cancer types. Various studies have shown that high NLR is a poor prognostic factor such as in pancreatic, colorectal, lung, breast cancers (6-9). An increased neutrophil-lymphocyte ratio (NLR) has been proposed as a marker to predict the prognosis of RCC patients and many studies found preoperative NLR as a poor prognostic marker in RCC (10-14). We hypothesize that a high NLR is associated with poor prognosis even its assesed postoperative.

MATERIALS AND METHODS

In this retrospective analysis, we reviewed 135 patients with RCC who were treated and followed in Kocaeli University Medical Oncology Department between 2003 and 2014. All patients were diagnosed via pathology. All clinicopathological data were retrieved from medical reports of department of medical oncology. Pathologic T stages were reviewed according to seventh edition of the TNM classification system (15). The blood samples were taken at the time of admission to medical oncology department whether the patients were operated or not. The cut off value for

neutrophil-lymphocyte ratio as a poor prognostic factor was determined as above 3. NLR>3 was determined as high NLR and NLR<3 was determined as low NLR. The neutrophil count more than 10×10^3 was defined as high neutrophil count and platelet (PLT) count more than 400×10^3 was defined as high PLT. The cut off value for LDH was the upper limit of our laboratory and determined as high and low according to this limit.

RESULTS

Of the 135 patients followed at our institution between 2003 and 2014 whose NLR was available, the mean age was 58.9±11.7 years. The mean overall survival is 29.9 months and the maximum follow up period was 130 months. A total of 107 patients underwent radical nephrectomy and 7 patients underwent partial nephrectomy, 21 patients didn't go operation. 97 (71%) patients were male and 38 (28%) were female. In this follow up 62 patients are alive and 73 patients are exitus, 27 (20%) patients were stage 1, 37 (27%) patients were stage 2, 25 (18%) patients were stage 3 and 42 (31%) were stage 4 at the time of admission to medical oncology department. In analyses 112 (63%) patients had clear cell histologic subtype, 85 (63%) patients had high NLR and 42 (31%) patients had low NLR, 46 patients had distant metastasis at the time of diagnosis and 45 patients became metastatic in the follow up period. High NLR was statistically correlated with size and stage and the presence of distance metastasis status.

In this study we performed univariable and multivariable analyses to investigate which parameters are associated with overall survival. After univariate analyses we found high neutrophil (p=0.018), high platelet (p=0.005), high NLR (p=0.001), high LDH (p=0.017), low hemoglobulin (p=0.001), large tumor size (p=0.001) and pathological T stage (p=0.001)

affect overall survival. Factors remained independently associated with overall survival on multivariate analyses included age, tumor size, LDH score, NLR and pathologic T stage, we found T stage (HR:1.86; 95% Cl:1.2-2.5 p=0.003), hemoglobin count (HR:0.51; 95% Cl:0.34-0.76) and postoperative NLR (HR:2.6; 95% Cl:1.1-5.5 p:0.017) (Figure 1). There was no significant correlation between disease free survival and NLR. Neutrophil count and platelet count have correlation with overall survival, p=0.014 and p=0.013 respectively (Table 1). We could not demonstrate correlation between calcium level and overall survival.

Table 1. Univariate and multivariate analysis of different parameters on overall survival

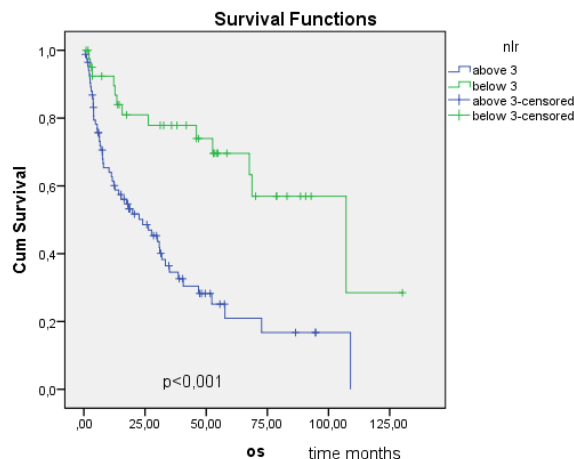|	Univariate analysis		Multivariate analysis	
	HR (95% Cl)	*p*	HR (95% Cl)	*p*
Age at admission	0.93	0.776	1.00	0.467
Tumor size	1.1	0.006	1.00	0.969
LDH score	0.53	0.019	0.56	0.156
NLR	3.3	0.001	2.67	0.017
Hemoglobulin	0.58	0.001	0.51	0.001
T stage	1.82	0.001	1.86	0.003
Platelet	0.37	0.005	1.16	0.762

Figure 1. Kaplan-Meier curves for RCC patients overall survival groups categorised by the NLR. OS: overall survival

DISCUSSION

In this study we reviewed 135 patients with RCC and found that many parameters affect the survival of RCC patients. The most common used prognostic model for RCC patients is Memorial Sloan-Kettering Cancer Centre (MSKCC) model (16). The parameters in MSKCC are Karnofsky performance status, hemoglobin level, corrected calcium level, serum LDH level and operation status. In our study we confirmed that low hemoglobin, high LDH and low performance status are associated with poor prognosis when we define overall survival as primary end point. We could not demonstrate corrected calcium level as a prognostic marker. We think this discordance between two studies depends on the evaluation times of the patients; we assesed most of the patients after nephrectomy and probably most patients with high calcium levels had anti hypercalcemic treatment before admission to the medical oncology department. Viers et al, demonstrated preoperative high NLR predicts poor prognosis among patients with M_0 clear cell RCC who underwent radical nephrectomy (17).

In our study 107 patients underwent radical nephrectomy and 7 patients underwent partial nephrectomy, in this nephrectomized patients we found a statistically significant association between overall survival and NLR (p=0.001). Heng et al demonstrated that thrombocytosis is an independent prognostic factor in patients with RCC treated with VEGF targeted therapy (18). We demonstrated high platelet count is an independent poor prognostic factor in RCC patients. This could be explained with the association between thrombocytosis and tumor cells invasion and metastasis capacity (19). In our study 42 (31%) patients had neutrophilia and 29 of these had distance metastasis in the follow up period, we found a negative correlation between neutrophilia and overall survival. Pichler et al demonstrated preoperative NLR as a prognostic factor in non- metastatic RCC (20). In the light of that study we hypothesized that NLR is a prognostic factor in RCC when assesed preoperatively or post operatively and established a statistically meaningful relation between NLR and overall survival. In our analyse we found correlation between tumor size and NLR independently from T stage. Despite the relation between overall survival and NLR, we could not demonstrate a statistically meaningful relation between disease free survival and NLR. We think this is the major weakness of our study cause we were not avaible to state the comorbidities. We know from recent studies that high NLR is associated with many chronic deadly diseases. Another limitation of our study is its retrospective data collecting design and low patient volume.

In conclusion, we think high NLR even after partial or radical nephrectomy can be a prognostic marker for RCC, but this hypothesis needs confirmation of other independent studies in the future.

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