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Araştırma

Platelet-to-Lymphocyte Ratio is an Independent Prognostic Factor in Clinically Non-Metastatic Renal Cell Carcinoma

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ABSTRACT

Objective: *We aimed to investigate the prognostic significance of the preoperative platelet-to-lymphocyte ratio (PLR) in a cohort of clinically non-metastatic renal cell carcinoma (RCC).*

Material and Methods: *We evaluated a retrospective analysis of 298 patients who underwent radical or partial nephrectomy for RCC between 2006 and 2015. The optimal cutoff value for the PLR was calculated using receiver operating curce (ROC) analysis. The prognostic value of PLR was determined by Kaplan-Meier curve, univariable and multivariable Cox regression models.*

Results: *The optimal cut-off level was 200 (AUC=0.715; sensitivity, 52.4%; specificity, 90.6%) for PLR by ROC curve analysis and elevated PLR was significantly correlated with worse cancer-specific survival (CSS). Multivariable analysis showed that elevated PLR was an independent risk factor for CSS (HR, 3.460; 95% CI, 1.691-7.081; p=0.001). A high PLR was also significantly correlated with aggressive tumor behaviors. Subgroup analysis revealed significant associations of the elevated PLR on CSS for both clear cell and non-clear cell RCC types (p<0.001).*

Conclusion: *The PLR is an independent prognostic factor for CSS after treatment with curative intent for clinically localized clear cell and non-clear cell RCC. PLR may provide a significant adjunct for clinical trial design and risk stratifying patients for localized RCC.*

Keywords: *lymphocytes, platelets, prognosis, renal cell carcinoma, survival*

ÖZ

Klinik Non-Metastatik Renal Hücreli Kanserde Trombosit/Lenfosit Oranı Bağımsız Prognostik Bir Faktördür

Amaç: *Operasyon öncesi trombosit/lenfosit oranı (TLO)'nın klinik non-metastatik renal hücreli kanser (RHK)'de prognostik öneminin araştırılması planlandı.*

Gereç ve Yöntem: *RHK nedeniyle 2006 ve 2015 yılları arasında radikal veya parsiyel nefrektomi geçiren 298 hastanın retrospektif analizi yapıldı. TLO için optimal kestirim değeri "receiver operating curve" (ROC) analizi ile hesaplandı. TLO'nun prognostik önemi; Kaplan-Meier eğrileri, tek değişkenli ve çok değişkenli Cox regresyon modelleri ile değerlendirildi.*

Bulgular: *TLO için ROC analizi ile optimal kestirim noktası 200 (AUC=0.715; sensitivite, %52,4; spesifite, %90,6) idi ve yükselen TLO daha kötü kanser spesifik sağkalım (KSS) ile anlamlı olarak ilişkili bulundu. Çok değişkenli analiz ile yükselen TLO'nun KSS için bağımsız bir risk faktörü olduğu gösterildi (HR, 3,460; 95% CI, 1,691-7.081; p=0,001). Ayrıca yüksek TLO'nun agresif tümör davranışı ile anlamlı ilişkisi olduğu gösterildi. Altgrup analizine göre yükselen TLO'nun hem clear cell hem de non-clear cell RHK'de KSS ile anlamlı ilişkisi saptandı.*

Sonuç: *Klinik lokalize clear cell ve non-clear cell RHK'de küratif amaçlı yapılan tedaviler sonrası TLO, KSS için bağımsız prognostik bir faktördür. TLO, lokalize RHK ile ilişkili klinik çalışmaların dizaynında ve risk sınıflamasında anlamlı bir katkı sağlayabilir.*

Anahtar kelimeler: *lenfositler, prognoz, renal hücreli kanser, survi, trombositler*

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 3% of all malignancies and clear cell RCC is the most prevalent type of RCC [(1)]. After curative treatment for RCC disease recurs in 10% - 20% of patients [(3)]. Stratification

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of patients considering their risk of recurrence is important to discuss the treatment options and describe further follow-up [3]. Several prognostic parameters have been assessed in RCC and these include tumor stage, histologic type and Fuhrman grade [1,4]. Novel molecular markers have been evaluated to improve the prognostic parameters' predictive correctness; nevertheless, none of them is recommended for daily practice due to limited accessibility and high costs. It is important to investigate useful prognostic markers for the prognosis of RCC patients.

The systemic inflammatory response in cancer patients plays an important role in disease progression and RCC is considered to be an immunological inflammatory malignancy [5]. Markers of inflammation such as C-reactive protein (CRP), erythrocyte sedimentation rate, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have gained prognostic value in patients with several malignancies [6-8]. Recent studies have demonstrated hematologic prognostic systems to predict prognosis in RCC patients [9,10]; however, their role in localized disease is less clear.

Preoperative measurements of lymphocytes, neutrophils and thrombocytesrepresent easily measured and inexpensive routine values. The PLRis associated with poor prognosis in several diseases [11-17]. There is argument that platelets might preserve circulating tumoral cells from destruction by the immune mechanism and facilitate adhesion of tumoral cells to the endothelium by the configuration of tumor thrombus [18]. In addition, lymphocytes affect the course of immune surveillance and lymphopenia is a representative marker of poor immune response [19]. A combined index using lymphocytes and platelets might be a potent prognostic marker for localized RCC. Nevertheless, data regarding the prognostic significance of the PLR in localized RCC are scarce.The aim of this study was to evaluate the effect of pre-surgical PLR on cancer-specific survival (CSS) in non-metastatic clear cell and non-clear cell RCC patients.

MATERIAL and METHODS

In this retrospective study, the medical records of 412 patients who underwent radical or partial nephrectomyfor clinically localized RCC at our department between 2006 and 2015 were reviewed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration. The study was approved by the internal review board (No. 2016/558) and informed consents were obtained from eligible patients.

The database include information on the demographics, preoperative laboratory parameters, pathological findings and survival of patients. Medical data were evaluated for age, gender, white blood cell (WBC) count within 7 days prior to surgery, follow-up time and cause of death. The complete blood counts were obtained by a hematology analyzer (Coulter Gen-S Hematology Analyzer, Beckman Coulter Corp, Hialeah, Florida). Pathological data included T, N and M stage according to 2010 TNM classification, tumor size, Fuhrman grade [20], presence of renal vein invasion, vena caval invasion, Gerota fascia invasion, renal pelvic invasion, tumor necrosis, and lymph node status. The pathological assessment was performed by experienced pathologist.

Patients with distant metastasis (n=42) prior to treatment were excluded from the study for CSS analysis purposes. Patients with relevant pathologies affecting systemic inflammatory response (n=30), prior pre-surgical or post-surgical chemotherapy, radiotherapy or immunotherapy (n=22),hematologic disease (n=12), and mixed type RCC or familial RCC (n=8) were also excluded from the study. Finally, 298 patients were analyzed.

Postoperatively, every 6 month, all patients were assessed for the first two years and annually thereafter. The outcome measure of this study was CSS, calculated from the time ofsurgery to the time of RCC related death.

The data was analyzed with Statistical Package for Social Sciences (SPSS) version 22 (IBM Co., Armonk, NY, USA). Cancer-specific survivalwas estimated by Kaplan-Meier method with differences evaluated by log-rank test. The optimal cut-off value of PLR was detected using receiver operating curve analysis according to the maximum sensitivity and specificity. Backward stepwise multivariable Cox

proportion analysis was performed to detect the effect of potential confounders such as age, tumor stage, Fuhrman grade, and other pathological variables on CSS. Comparison between categorical variables was performed using the chi-square test. Correlations were considered statistically significant at a $p<0.05$ level.

RESULTS

The clinicopathological characteristics of the entire study population are listed in Table 1. The final cohort included 183 male (61.4%) and 115 female (38.6%). Median age at surgery was 61 years (22-86). Partial and radical nephrectomy was performed in 118 (39.6%) and 180 (60.4%), respectively. The mean follow-up period was 37.8±22.3 months (17-54) and during follow-up period, overall, 70 patients (23.4%) died from all causes and 46 patients (15.4%) died from cancer specific causes.

Based on the 7th TNM classification, distribution of tumor stage (I-II and III-IV) in this study was 224 (75.16%) and 74 (24.83%), respectively. Accor-

Table 1. Clinicopathological characteristics of patients.

Characteristics	Min-Max	Median	Mean±s.d./n-%
Age	22-86	61	61.5±13.2
Sex			
Male			183-61.4%
Female			115-38.6%
Histology			
Clear cell			210-70.5%
Non clear cell			88-29.5%
T Stage			
I-II			224-75.16%
III-IV			74-24.83%
Fuhrman Grade			
I			58-19.5%
II			116-38.9%
III			90-30.2%
IV			34-11.4%
Tumor size (cm)	1.2-17.0	5.0	5.6±2.9
Platelet count$X10^3$ (mm^3)	116-856	257	286.6±133.3
Lymphocyte count (mm^3)	0.5-5.8	1.9	2.0±0.8
Neutrophil count (mm^3)	1.5-17.0	4.8	5.5±2.8
NLR[a]	0.9-22.3	2.6	3.1±2.5
PLR[b]	40.0-570.7	130.0	157.7±92.4

[a]: *NLR neutrophil-to-lymphocyte ratio*
[b]: *PLR platelet-to-lymphocyte ratio*

Table 2. Univariate and multivariate Cox regression models of clinicopathological characteristics for the prediction of cancer specific survival.

	Univariate Model			Multivariate Model		
	HR[a]	% 95 CI	P	HR	% 95 CI	p
Age	1.008	0.98 - 1.04	0.640			
Sex	5.992	1.40 - 25.73	0.016			
Histology (clear cell vs. non clear cell)	0.490	0.21 - 1.16	0.106			
Fuhrman Grade (G3-4 vs. G1-2)	3.546	2.03 - 6.20	0.0001	2.63	1.54-4.60	0.0001
Urea	0.992	0.96 - 1.03	0.671			
Calcium	1.571	0.71 - 3.49	0.268			
Creatine	1.120	0.60 - 2.08	0.719			
Hemoglobin	0.761	0.61 - 0.95	0.015			
Eozinophile	1.711	0.08 - 36.38	0.731			
Basophile	1.097	0.03 - 44.85	0.961			
Monocyte	1.990	0.74 - 5.33	0.171			
Platelet	1.004	1.00 - 1.01	0.0001			
Neutrophile	1.144	1.01 - 1.29	0.028			
Lymphocyte	0.383	0.18 - 0.80	0.011			
NLR[b]	1.095	1.01 - 1.19	0.037			
PLR[c] (≤200 vs. >200)	5.14	2.63 - 10.10	0.0001	3.460	1.691-7.081	0.001
Tumor size (<7 vs. ≥7 cm)	3.33	1.70 - 6.53	0.0001	2.568	1.28-5.14	0.008
Renal vein invasion	4.966	1.44 - 17.09	0.011			
Renal capsule infiltration	3.557	1.38 - 9.18	0.009			
Renal sinüs involvement	4.836	2.04 - 11.49	0.0001			
Adrenal gland involvement	6.332	1.47 - 27.32	0.013			
Gerota fascia invasion	35.738	3.99 - 319.8	0.001			
Lymph node involvement	13.970	4.62 - 42.22	0.0001	3.281	1.09-9.9	0.005
Angiolymphatic invasion	10.066	3.99 - 25.42	0.0001			
Renal pelvis involvement	2.957	1.08 - 8.09	0.035			
Tumor necrosis	1.673	0.61 - 4.57	0.315			

[a]:*HR hazard ratio*
[b]:*NLR neutrophil-to-lymphocyte ratio*
[c]:*PLR platelet-to-lymphocyte ratio*

ding to histological type, the number of clear cell and non clear cell RCC were 210 (70.5%) and 88 (29.5%), respectively. Nuclear grading according to the Fuhrman classification was G1 in 58 (19.5%), G2 in 116 (38.9%), G3 in 90 (30.2%), and G4 in 34 (11.4%).

Associations of variables and CSS were evaluated by univariable analysis. The results showed that sex, tumor size, Fuhrman grade, renal vein invasion, renal capsule infiltration, renal sinus involvement, renal pelvis involvement, angiolymphatic invasion, lymph node involvement, adrenal gland involvement, Gerota fascia invasion, hemoglobin, platelet, lymphocyte and neutrophil counts, NLR, and PLR were prognostic factors of CSS. Multivariable analysis indicated that PLR (HR, 3.460; 95% CI, 1.691-7.081; p=0.001) can independently predict CSS, together with tumor size, Fuhrman grade and lymph node involvement (Table 2).

The mean platelet count was 286±133.3, the mean lymphocyte count was 2.0±0.8, and the the mean PLR was 157.7±92.4. Using the criteria referred above, we detected a cut-off value of 200 (AUC=0.715; sensitivity, 52.4%; specificity, 90.6%) in the ROC curvefor the PLR to be optimal to differentiate between patients' CSS that prompted us to select 200 as the optimal cut-off value for all statistical analysis to discriminate between low (≤200, n=250) and high (>200, n=48) PLR (Figure 1). Three-year and 5-year CSS probabilities were 91.1% and 86.6% in the PLR ≤ 200 group and 50.2% and 42.5% in the PLR > 200 group, respectively (log rank p value <0.001).

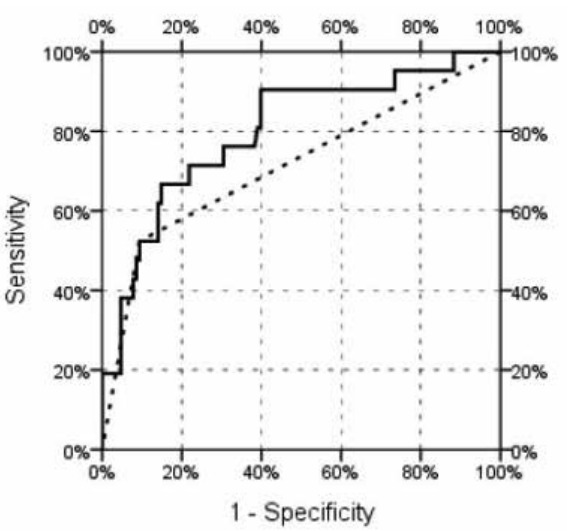

Figure 1. ROC analysis. The area under curve (AUC) for PLR was 0.715 (95% CI 0.578-0.852). The optimal cut-off value based on CSS was 200 for PLR (52.4% sensitivity and 90.6% specificity) by ROC curve analysis

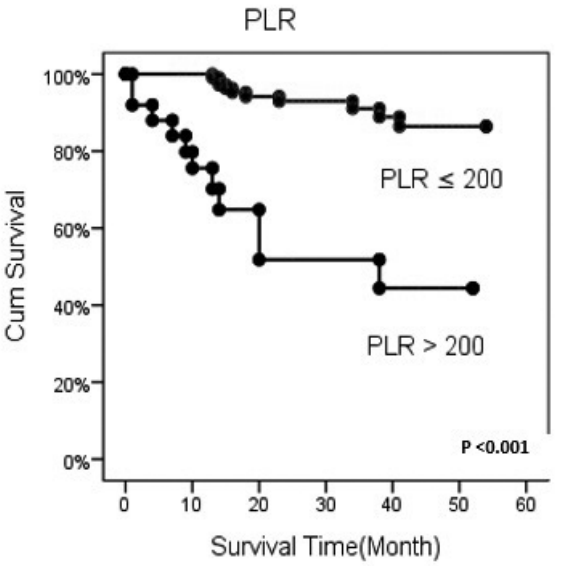

Figure 2. Kaplan-Meier curves for cancer specific survival in 298 patients with localized RCC according to platelet-to-lymphocyte ratio

Table 3. Association of the high platelet-to-lymphocyte ratio with clear cell and non-clear cell RCC types on cancer-specific survival.

	HR[a]	% 95 CI	p
Hystologic Type			
Non-Clear Cell - PLR[b]	1.009	1.004 - 1.014	0.001
Clear cell - PLR	1.010	1.006 - 1.015	0.000

[a]: HR hazard ratio
[b]: PLR platelet-to-lymphocyte ratio

Table 4. Association of platelet-to-lymphocyte ratio with pathological parameters.

	PLRa ≤ 200 n=250		PLR >200 n=48		
	n	%	n	%	p
Renal vein invasion	12	4.8%	4	8.3%	0.522
Renal capsule infiltration	22	8.8%	12	25.0%	0.030
Renal sinüs involvement	48	19.2%	20	41.6%	0.025
Adrenal gland involvement	4	1.6%	2	4.1%	0.438
Gerota fascia invasion	0	0.0%	2	4.1%	0.168
Lymph node involvement	2	0.8%	6	12.5%	0.015
Angiolymphatic invasion	22	8.8%	18	37.5%	0.001
Renal pelvis involvement	14	5.6%	16	33.3%	0.001
Tumor necrosis	32	12.8%	18	37.5%	0.005

[a]: PLR platelet-to-lymphocyte ratio

Figure 2 shows the Kaplan-Meier curves for CSS. It displays that a high PLR is a consistent factor for poor prognosis in localized RCC patients ($p<0.001$). Subgroup analysis revealed significant correlations of the high PLR value on CSS for both clear cell and non-clear cell RCC types ($p<0.001$) (Table 3).

A high PLR value significantly associated with renal capsule infiltration, renal sinus involvement, renal pelvis involvement, angiolymphatic invasion, tumor necrosis, and lymph node involvement (Table 4).

DISCUSSION

In this study, we studied the prognostic value of preoperative measurements of systemic inflammatory response in patients undergoing curative treatment for clear cell and non-clear cell RCC. Our study shows that PLR is an independent prognostic factor after treatment for localized clear cell and nonclear cell RCC. We also found that high PLR was associated with renal capsule infiltration, renal sinus involvement, renal pelvis involvement, angiolymphatic invasion, tumor necrosis, and lymph node involvement. Although serum hemoglobin, platelet count, lymphocyte count, neutrophil count, and NLR were significant markers in univariable model, they were not independently associated with survival in the multivariable analysis.

To the best of our knowledge, this study is the first study of PLR focused on localized clear cell RCC, together with non-clear cell RCC. Fox et al. [21] reported that the prognostic role of PLR was indicated in patients with advanced RCC. In non-metastatic disease, the prognostic significance of NLR and lymphocyte to monocyte ratio in patients after treatment were reported in many studies [22,23]. Lee et al. [24] evaluated pretreatment PLR in patients with localized clear cell RCC. In their study, authors were not able to identify the PLR as an independent prognostic factor. However, our study demonstrate that PLR is an independent prognostic factor for localized clear cell and nonclear cell RCC. Lucca et al. [25] also analyzed the prognostic role of the PLR and reported that PLR was a significant prognostic factor in patients with localized clear cell RCC. The optimal cut point for the PLR was found 145 in their study. In our study, we found that the optimal cut-off for PLR is 200 with 52.4% sensitivity and 90.6% specificity. Since our findings may be particular to our cohort, additional external validation is essential.

As easily and cheaplymeasured routine inflammatory markers, they can serve asa helpful addition to standard prognostic indicators, such as TNM stage, Fuhrman grade and tumor size. The association between cancer and systemic inflammation has been hypothesized in the last few decades. The inflammatory response in patients with malignancy plays an important role in cancer progression. Grimes et al. [26] reported a systematic review of the prognostic role of inflammation in patients with localized RCC undergoing nephrectomy, recently. In their systematic review, they showed that elevated NLR to be associated with a poorer prognosis and they stated that evidence for PLR is minimal in this issue. Turkmen et al. [27] found a positive correlation of PLR, NLR and interleukin-6, tumor necrosis factor-α. They also reported that PLR was better than NLR at predicting inflammation. In our study, an elevated pre-surgical PLR was significantly associated with poor CSS; however, NLR is not independently associated with survival in the multivariable analysis. Our findings indicate that patients with an elevated PLR may benefit from more frequent follow-up protocols and more comprehensive treatment approaches.

Inflammation is open to induce protumorigenic microenvironment changes. The causes why PLR might be of prognostic relation in patients with RCC remain speculative in this section. One theory, thrombocytosis in malignancy may increase tumorigenesis by platelet derived growth factor, vascular endothelial growth factor and thrombospondin [28,29]. According to another theory, platelets may protect circulating tumor cells from demolition by the immune system. Moreover, platelets facilitate adhesion of circulating tumor cells to the endothelium [18]. Second, lymphopenia is a surrogate indicator of poor immune response.The decreased lymphocytes also plays a role in inflammatory response to tumor biology. Menges et al. [30] reported that a decrease in CD +4 T lymphocyte can lead lymphocyte mediated immune reaction to malignancy.

Limitations of our study comprise the retrospective data evaluation with a relatively small population size. Second, no details was available concerning

performance status and further inflammatory markers such as CRP and procalcitonin. Third, only the effect of PLR on CSS was assessed, but not on disease-free or recurrence-free survival. Despite these limitations, our findings suggest an important prognostic role of the PLR for patients with localized clear cell and non-clear cell RCC. However, further studies are required to confirm the relationship between PLR and prognosis in RCC patients.

CONCLUSION

Our study suggests that PLR is an independent prognostic factor for CSS after surgery in patients with clinically localized clear cell and non-clear cell RCC. PLR may provide a significant complement for clinical trial design and risk stratifying patients undergoing curative treatment for localized RCC.

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Conflict of interest
The authors declare no conflict of interest.

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