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Research Article

Which Preoperative Inflammation Markers are More Valuable Prognostic Markers in Renal Cell Cancer Patients who Have Undergone Nephrectomy?

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Abstract

Objectives: This retrospective study evaluated the prognostic significance of inflammation markers (IMs) in patients with renal cell cancer (RCC) who had undergone nephrectomy.

Methods: A total of 118 patients—39 (33.1%) were female, and 79 (66.9%) were male—were included in the study. All medical records were reviewed retrospectively. The cut-off values for the IMs (c-reactive protein (CRP), CRP/albumin ratio (CAR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic immune-inflammatory index (neutrophils × platelets)/lymphocytes) (SIII)) were defined by receiver operating characteristic (ROC) analysis. Overall survival (OS) and disease-free survival (DFS) were plotted using the Kaplan–Meier method and compared using the log-rank test. Cox regression analysis was performed for univariate and multivariate analyses, and hazard ratios (HRs) with 95% confidence intervals (CIs) were used to quantify the indices for estimating survival.

Results: An optimal CAR cut-off value of 8 was defined according to the ROC analysis. The area under the curve for CAR (0.755) for OS and DFS was greater than that for CRP, NLR, PLR, and SIII. Multivariate analysis demonstrated that CAR is an independent prognostic factor for OS ($p<0.001$) in patients with RCC who have undergone nephrectomy.

Conclusion: The findings of the present study suggest that preoperative CAR might be an independent prognostic marker for patients with RCC who have undergone nephrectomy and might have value compared with other established inflammation-based prognostic scores. The prognostic value of this novel inflammation-based prognostic score needs to be verified in patients with other types of cancer.

Keywords: C-Reactive protein to albumin ratio, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, prognostic score, renal cell cancer

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Renal cell carcinoma (RCC) constitutes 80–85% of primary renal cancers.[1] Although the 5-year survival rate in RCC patients has increased from 34% to 73%, its incidence has risen rapidly. This survival is thought to be due to early diagnosis and the development of curative surgical techniques.[2] Determining prognostic factors is very important to improve survival. Many factors determine the prognosis of RCC patients who undergo nephrectomy: age, gender, performance status, symptoms, histology type, Fuhrman grade, TNM stage, T stage, N stage, M stage, tumor necrosis, and

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perinephritic fatty tissue invasion.[3] Also, there is increasing data that a systemic inflammatory response is associated with poor outcomes in patients suffering from various types of cancer.[4] Several standard inflammation-based prognostic scores, including neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), have been reported to have prognostic value in patients with RCC.[5]

The C-reactive protein (CRP) to albumin (Alb) ratio (CAR) has also been reported as a novel inflammation-based prognostic marker in multiple types of tumor, including hepatocellular carcinoma, colorectal cancer, esophageal cancer, renal cancer, pancreatic cancer, non-small cell lung cancer, and esophagogastric junction and gastric cancer.[6–14] Also, it has been evaluated and demonstrated as a poor prognostic marker in patients with RCC.[15–18] However, most of these studies included only small study populations and their conclusions remain inconclusive.

In the present study, we investigated the prognostic value of CAR in patients with RCC who had undergone nephrectomy. We also evaluated CRP, NLR, PLR, and SIII in these patients and compared them with CAR.

Methods

Patients

In this cross-sectional, retrospective study, archive records between January 2011 and July 2018 for all RCC patients who underwent nephrectomy in Bezmialam Vakif University Hospital were used. Patients who were not in follow-up, whose pathology report could not be obtained, who could not endure a nephrectomy, and who showed other inflammatory conditions were not included. Patients with initial nephrectomy, whose pathology reports could be accessed, were included.

We used the 2017 AJCC staging system (8th Edition) for pathological TNM staging. In addition to this, pathological nodal parameters included nodal involvement and extra-nodal extension. The Fuhrman nuclear grading (FG) system was used for grading in pathological staging. The characteristics affecting prognoses—such as the presence of a sarcomatoid component and the presence of fat invasion—were recorded. Hematuria and flank pain symptoms were classified as local; respiratory, gastrointestinal, fatigue, night sweats, fever, and weight loss were classified as systemic symptoms. Recurrence type (local or distant) was recorded.

Follow-up schedules were applied, referring to the NCCN Clinical Practice Guidelines. Follow-up CT and chest X-rays were performed to detect any findings suspected of disease progression every 3 months in the first 2 years. After that, patients were followed up every 6 months. The duration of the follow-up was calculated from the day of surgery to the day of death or the last visit.

Data from 179 patients were examined. Thirteen patients were lost to follow-up. Forty-eight patients who showed other inflammatory conditions were excluded. In total, 118 patients with RCC met the requirements for inclusion and were evaluated.

Inflammation-based prognostic scores and other variables

Values for NLR, PLR, SIII, and CAR were calculated. Blood samples were obtained before the initial treatment to measure levels of CRP (mg/dL), albumin (g/L), and hemoglobin (Hb). Also, white blood cell (WBC), neutrophil, lymphocyte, and platelet (Plt) counts were determined. NLR, PLR, and SIII were defined as absolute neutrophil count and platelet counts, respectively, divided by the total lymphocyte count.

Ethics

This study was approved by the institutional review board of the hospital and was performed in compliance with all principles of the Helsinki Declaration. As the data were retrospective in nature and analyzed anonymously, informed consent was not obtained from the patients.

Statistical Analysis

Statistical analysis was carried out using SPSS for Windows, Version 24.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the median and range or the mean±SD. The normality test was performed using Kolmogorov–Smirnov analysis. In cases where normal distribution was not available, the Mann–Whitney U test was performed to compare continuous variables between the two groups. The Pearson χ^2 test or Fisher exact test was used to comparing qualitative variables. Receiver operating characteristic (ROC) curves were plotted with sensitivity (true-positive fraction) on the y-axis and 1−specificity (false-positive fraction) on the x-axis. ROC curves were plotted for CRP, CAR, NLR, PLR, and SIII values to predict overall survival. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Cox regression analysis was performed for univariate and multivariate analyses, and hazard ratios (HRs) with 95% confidence intervals (CIs) were used to quantify the indices estimating the survival. A two-sided p-value of <0.05 was deemed statistically significant.

Results

Patient Characteristics

The clinicopathological characteristics of the patients are shown in Table 1. A total of 118 patients with RCC were iden-

Table 1. Demographic features and tumor characteristics of the patients

Gender, %	
Female	39/118 (33.1)
Male	79/118 (66.9)
Age (Mean±SD)	56.4±12.7
Tumor size (Mean±SD)	7.0±4.2
Local symptom, %	
Present	116/118 (98.3)
Absent	2/118 (1.7)
Systemic symptoms, %	
Present	67/118 (56.8)
Absent	51/118 (43.2)
ECOG, %	
0	46/118 (39)
1	72/118 (61)
Stage, %	
T1-3N0	14/118 (11.9)
T1-3NX	79/118 (66.9)
T1-3N1	14/118 (11.9)
T1-3NXM1	11/118 (9.3)
Fuhrman Grade, %	
1	3/118 (2.5)
2	44/118 (37.3)
3	57/118 (48.3)
4	14/118 (11.3)
Type of surgery, %	
Radical	61/118 (51.7)
Partial	57/118 (48.3)
Tumor localization, %	
Right	63/118 (53.4)
Left	55/118 (46.6)
Histology, %	
Clear cell	107/118 (90.7)
Non-clear cell	11/118 (9.3)
Sarcomatoid component, %	
Present	11/118 (9.3)
Absent	107/26 (90.7)

tified on our institutional database. Seventy-nine (66.9%) patients were male, and thirty-nine (33.1%) patients were female. The median age of the patients was 58.43±12.68 years. Eastern Cooperative Oncology Group Performance Score (ECOG PS) was 0–1 at the time of diagnosis. On admission, 116 (98.3%) patients had local symptoms, and 67 (56.8%) patients had systemic symptoms. Radical nephrectomy was performed in 61 patients (51.7%), and partial nephrectomy was performed in 57 patients (48.3%). Tumor localization was the right kidney in 63 (53.4%) patients and the left kidney in 55 (46.6%) patients; 90.7% (107/118) of the patients had clear cell histology, and 9.3% (11/118) had non-clear cell histology. Eleven (9.3%) patients were metastatic at the time of diagnosis, 14 (11.9%) were staged as T1-3N1M0, 79 (66.9%) as T1-3NXM0, and 14 (11.9%) as T1-3N0M0. FG 1 patient rate was 2.5% (3/118), FG 2 patient rate was 37.3% (44/118), FG 3 patient rate was 48.3% (57/118), and FG 4 patient rate was 11.9% (14/118). Also, a sarcomatoid component was detected in 11 (9.3%) patients.

ROC Analysis

Patients' inflammation parameters (CRP, NLR, PLR, SIII, and CAR values) were recorded. ROC analysis was performed to determine the optimal prognostic value of each parameter. Accordingly, CRP: 30 mg/dL, NLR: 2.3, PLR: 192, SIII: 1371, and CAR: 8 were determined as cut-off values for predicting OS based on the areas under the curve (AUC) in the ROC analysis (CRP: 0.691, p=0.005 (sensitivity: 50%, specificity: 83%); NLR: 0.70, p=0.001 (sensitivity: 86%, specificity: 50%); PLR: 0.729, p<0.001 (sensitivity: 57%, specificity: 81%); SIII: 0.698, p=0.002 (sensitivity: 50%, specificity: 79%); CAR: 0.755, p=0.001 (sensitivity: 67%, specificity: 84%)) (Table 2).

Overall Survival

There were 118 patients who underwent radical or partial nephrectomy. The median follow-up time from nephrectomy was 55 months. Median overall survival (OS) was not achieved in all patients. The 3-year and 5-year OS rates for all 118 patients were 86% and 75%, respectively.

Table 2. Receiver operating characteristic parameters of positive prognostic factors for overall survival in renal cell carcinoma

Variable	AUC ((95%) CI)	Sensitivity, %	Spesifity, %	Cut-of value	p
CRP	0.691	50	83	30 mg/dl	0.005
CAR	0.755	67	84	8	0.001
NLR	0.700	86	50	2.3	0.001
PLR	0.729	57	81	192	<0.001
SIII	0.698	50	79	1371	0.002

CRP: c-reactive protein, CAR: c-reactive protein/albumin ratio, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SIII: systemic immune inflammatory index.

The patients were divided into two groups, with CRP ≤30 mg/dL and CRP >30 mg/dL. The median OS was unreachable in the first group and 61 months in the second group. OS was significantly worse in patients with preoperative CRP levels above 30 mg/dL (95% CI: 23–99 months, p<0.001) (Fig. 1). The patients were divided into two groups, with NLR ≤2.3 and >2.3. Median OS was not achieved in the first group, and 89 months in the second group. Preoperative NLR higher than 2.3 was found to be associated with worse prognosis (95% CI: 51–127 months, p=0.002) (Fig. 2). The patients were divided into two groups, with PLR ≤192 and >192. Median OS was not achieved in the first group, and 62 months in the second group. Preoperative PLR greater than 192 was associated with a significantly poorer prognosis (95% CI: 51–73 months, p<0.001) (Fig. 3). The patients were divided into two groups, with SIII ≤1371 and >1371. Median OS was not achieved in the first group, and 89 months in the second group. SIII greater than 1371 was associated with a significantly poorer prognosis (p<0.001) (Fig. 4). The patients were divided into two groups, with CAR ≤8 and >8. Median OS was not reached in the first group, and 55 months in the second group. At the time of diagnosis, survival was significantly worse in patients with CAR >8 (95% CI: 23–88 months, p<0.001) (Fig. 5).

Cox Regression Analysis for Overall Survival

We performed univariate and multivariate analyses to assess predictive value for OS in all patients (Table 3).

Univariate Cox Regression Analysis

Univariate analysis identified several variables significantly associated with OS: sex (male; HR: 2.73 (1.03–7.23), p=0.043), systemic symptoms (HR: 0.27 (0.10–0.73), p=0.009), partial nephrectomy (HR: 4.56 (1.83–11.37), p=0.001), non-clear cell histology (HR: 5.21 (2.18–12.47), p<0.001), the presence of fat invasion (HR: 2.98 (1.37–6.50), p=0.006), and the presence of a sarcomatoid component (HR: 7.83 (3.17–19.32), p<0.001). However, primary tumor

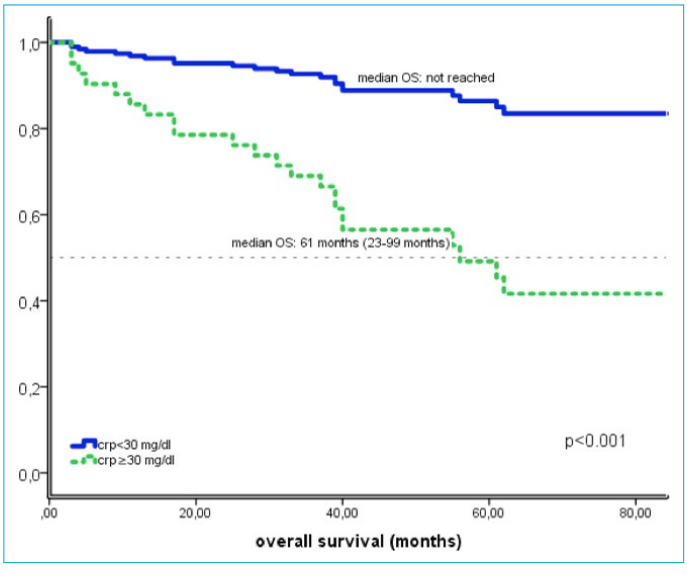

Figure 1. Kaplan-Meier curves according to CRP (<30 mg/dl and ≥30 mg/dl) of overall survival.

crp: c-reactive protein; OS: overall survival; CI: confidence interval.

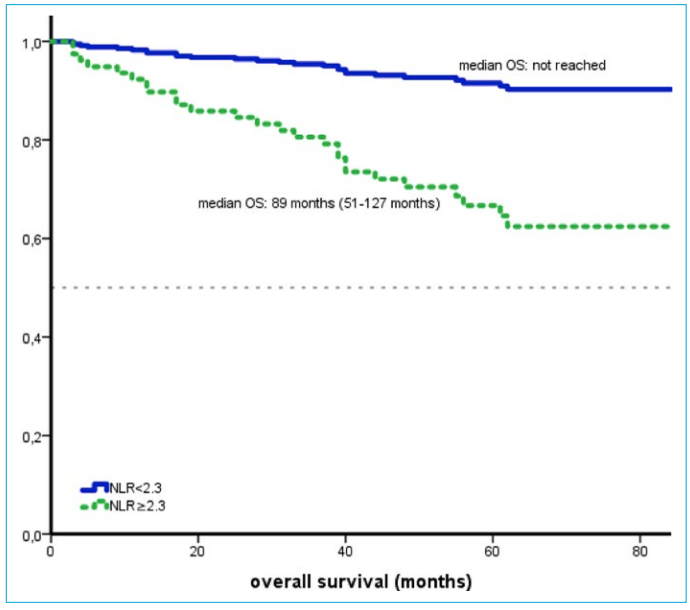

Figure 2. Kaplan-Meier curves according to N/L ratio(<2.3 and ≥2.3) of overall survival.

N: neutrophil; L: lymphocyte; OS: overall survival; CI: confidence interval; NLR: Neutrophil lymphocyte ratio.

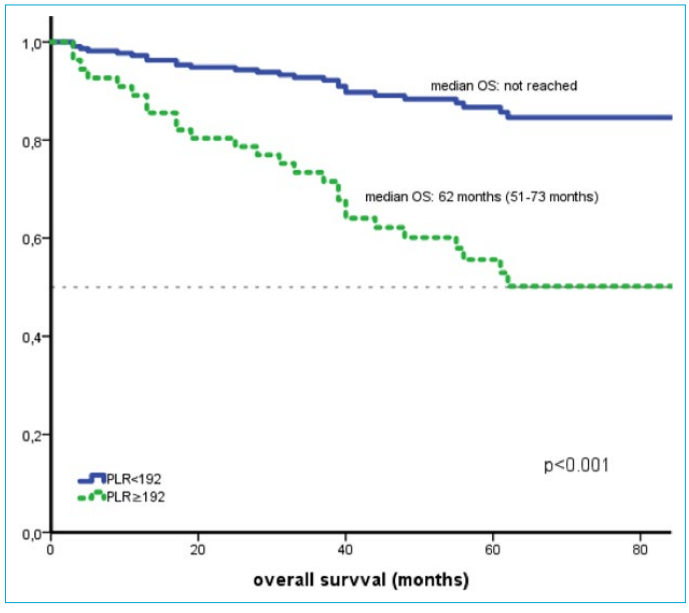

Figure 3. Kaplan-Meier curves according to Plt/L ratio (<192 and ≥192) of overall survival.

Plt: platelet; L: lymphocyte; OS: overall survival; CI: confidence interval; PLR: Platelet lymphocyte ratio.

location was not associated with OS (HR: 0.55 (0.25–1.24), p=0.151). In addition, the immune parameters CRP level >30 mg/dL (HR: 4.84 (2.11–11.10), p<0.001), NLR >2.3 (HR: 4.60 (1.59–13.30), p=0.005), PLR >192 (HR: 4.11 (1.91–8.87), p<0.001), SIII level >1371 (HR: 3.62 (1.70–7.72), p=0.001), and CAR >8 (HR: 10.39 (3.53–30.57), p<0.001) were found to be significantly associated with increased risk of death.

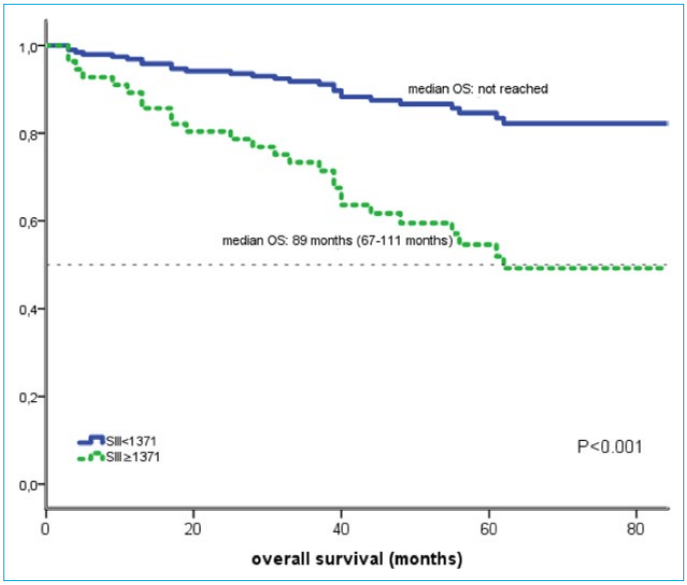

Figure 4. Kaplan-Meier curves according to SIII (<1371 and ≥1371) of overall survival.

SIII: systemic immune inflammation index; OS: overall survival; CI: confidence interval.

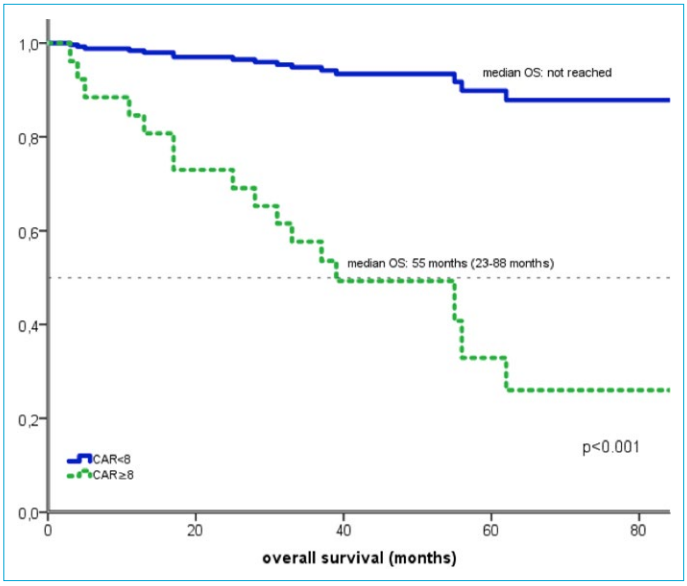

Figure 5. Kaplan-Meier curves according to crp/albumin ratio (<8 and ≥8) of overall survival.

crp: c-reactive protein; OS: overall survival; CI: confidence interval; CAR: c-reactive protein albumin ratio.

Multivariate Cox Regression Analysis

In multivariate Cox regression analysis, CAR (HR: 8.88 (2.74–28.77), p<0.001), PLR (HR: 6.15 (2.00–18.93), p=0.002), and male sex (HR: 6.09 (1.33–27.97), p=0.020) were associated with an increased risk of death. Among the immune parameters, high-level CAR was the most valuable negative prognostic factor. In second place, high-level PLR was found to be a negative prognostic factor. There was no prognostic significance of other immune factors.

Discussion

In the present study, we assessed the prognostic value of preoperative CRP, CAR, PLR, NLR, and SIII in patients with RCC who had undergone nephrectomy. In our study, preoperative CAR was shown to the best prognostic index for patients with RCC who undergo nephrectomy, compared with several other inflammation-based scores, including CRP, NLR, PLR, and SIII. The results consistently showed that increased CAR is significantly associated with a shorter OS and serves as an independent prognostic factor for patients with RCC after surgery. Also, increased PLR is significantly associated with a shorter OS. While CAR and PLR are independent risk factors for OS, CRP, NLR, and SIII are not reliable prognostic factors for patients with RCC.

In a study by Motzer et al.,[19] when determining prognostic factors in metastatic RCC patients, inflammatory markers such as neutrophils and platelets were not part of the International Metastatic RCC Database Consortium (IMDC) prognostic criteria. However, in 2009, Heng et al.[20] showed that neutrophil and platelet values besides the classic IMDC prognostic factors are important prognostic factors for metastatic RCC patients using anti-vascular endothelial growth factor (VEGF) drugs. Also, many studies have shown the relationship between inflammation and cancer, and the relationship between increased inflammation and poor survival has been demonstrated in many types of cancer.[4] Inflammatory parameters such as CRP, NLR, PLR, and SIII were the leading markers evaluated in the studies.[5] Recently, many studies comparing the ratio of CRP and albumin to other common inflammatory markers have been performed. Increased CAR is associated with poor prognosis in many types of cancer, including RCC, and many studies have shown it to be more valuable than conventional inflammatory markers.[6–14] One of these assessed RCC patients who had undergone nephrectomy.[15]

Zou et al.[16] showed that increased preoperative CAR is associated with worse survival in non-metastatic RCC patients who have undergone nephrectomy. Gao et al. also demonstrated the prognostic significance of CAR in papillary RCC patients who have undergone nephrectomy.

Table 3. Prognostic factors of overall mortality

	Univariate analysis HR (95% CI)	p	Multivariate analysis HR (95% CI)	p
Gender				
Female	Reference	0.043	Reference	0.020
Male	2.73 (1.03-7.23)		6.09 (1.33-27.97)	
Systemic symptoms				
Absent	Reference	0.009		
Present	0.27 (0.10-0.73)			
Type of surgery				
Radical nephrectomy	Reference	0.001		
Partial nephrectomy	4.56 (1.83-11.37)			
Tumor localization				
Left	Reference	0.151		
Right	0.55 (0.25-1.24)			
Histology				
Clear cell	Reference			
Non-clear cell	5.21 (2.18-12.47)	<0.001		
Perinephritic fatty tissue invasion				
Absent	Reference	0.006		
Present	2.98 (1.37-6.50)			
Sarcomatoid component				
Absent	Reference	<0.001		
Present	7.83 (3.17-19.32)			
CRP				
<30	Reference	<0.001		
≥30	4.84 (2.11-11.10)			
NLR				
<2.3	Reference	0.005		
≥2.3	4.60 (1.59-13.30)			
PLR				
<192	Reference	<0.001	Reference	0.002
≥192	4.11 (1.91-8.87)		6.15 (2.00-18.93)	
SIII				
<1371	Reference	0.001		
≥1371	3.62 (1.70-7.72)			
CAR				
<8	Reference	<0.001	Reference	<0.001
>8	10.39 (3.53-30.57)		8.88 (2.74-28.77)	

Gao et al.'s[17] study showed the importance of CAR, even for different histological subtypes. In addition to these two studies, Konishi et al.[18] demonstrated that CAR is also a useful parameter in demonstrating treatment-related drug resistance in metastatic RCC patients. According to this, in patients with high CAR values, the early progression of tyrosine kinase inhibitor drug therapies is seen. In our study, which evaluated 118 RCC patients who had undergone nephrectomy in a single center, an increase in CAR was also associated with poor prognosis, following these studies.

Systemic inflammation has also been shown to be associated with reactive thrombocytosis in many cancer types.[21] Thrombocytosis develops in 10–57% of cancer patients.[22] This is thought to be associated with IL-6 and VEGF.[23] VEGF is an essential parameter in both the pathophysiology and treatment of RCC patients. Considering the relationship between VEGF and thrombocytosis, thrombocytosis may be a predictor of poor prognosis by showing tumor burden. Based on this, it was thought that PLR might be associated with prognosis in RCC patients who have undergone nephrectomy. Still, the increase in preoperative PLR value could not be associated with worse survival in non-metastatic RCC

patients. In contrast, an increase in NLR value has been associated with poor survival.[24,25] In our study, unlike these studies, we demonstrated that preoperative PLR is associated with poor prognosis in RCC patients who have undergone nephrectomy, but NLR is not associated with survival.

In our study, we also compared AUC values for systemic inflammatory biomarkers to predict OS. We demonstrated that CAR is a more reliable OS marker in RCC patients who have undergone nephrectomy compared with CRP, NLR, PLR, and SIII. Based on all these results, we think that CAR is a reliable, easily calculated, and cost-effective biomarker that can be used to predict prognosis in non-metastatic RCC patients. Also, adjuvant and neoadjuvant therapies are not yet fully defined and may help to identify patients who will benefit more from these therapies in the future.

Another issue is the CAR cut-off value. Although many studies have demonstrated the importance of CAR in operated RCC patients, the cut-off value is not yet clear. In other studies, the cut-off value for CAR was 0.073 (15), 0.094 (17), and 0.05 (18), respectively. In the first step, although the CAR cut-off value of 8 in our study seems to be very different from these other studies, this is due to calculation of the laboratory CRP and albumin values in mg/dL. When standardized according to other studies, the actual cut-off value is 0.08. This shows that further studies are needed to determine a specific cut-off value.

The limitations in this study are its retrospective design and the relatively small number of patients. Multi-institutional and prospective randomized controlled trials are required to confirm our preliminary findings.

Conclusion

In summary, we demonstrated that increased preoperative CAR and PLR is associated with shorter survival in non-metastatic RCC patients who have undergone nephrectomy. Since CAR can be measured preoperatively, this system should be incorporated in routine diagnosis for risk stratification and treatment decision-making for operable RCC patients.

Disclosures

Ethics Committee Approval: The Ethics Committee of Bezmialem Vakif University provided the ethics committee approval for this study (01/04, 07.01.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – T.D., M.B.; Design – T.D., M.B.; Supervision – T.D., M.B.; Materials – T.D., M.B.; Data collection &/or processing – T.D., M.B.; Analysis and/or interpretation – T.D., M.B.; Literature search – T.D.; Writing – T.D., M.B.; Critical review – T.D.

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