Cross-sectional Study

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Prognostic significance of the preoperative platelet-lymphocyte ratio in nonmetastatic renal cell carcinoma: cross-sectional study

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Introduction: The prognostic significance of the platelet-lymphocyte ratio (PLR) in nonmetastatic renal cell carcinoma (RCC) is controversial, although it has been established as a prognostic factor in several cancers.
Objective: The objective of our study was to evaluate the prognostic significance of the PLR in patients with nonmetastatic RCC.
Patients and methods: The authors performed a retrospective analysis of patients with nonmetastatic RCC who were operated between 2004 and 2020. Five years recurrence-free survival and metastasis-free survival were calculated. The prognostic significance of the preoperative PLR was assessed. The Kaplan–Meier method was utilized to graphically display survivor functions. Univariate and multivariate Cox's proportional hazards regression models were utilized to analyze the association between PLR and oncological outcomes. Differences were considered significant if $P < 0.05$.
Results: Two hundred and two patients were included. The mean follow-up was 56.8 ± 3 months. Patients with a higher PLR had larger tumors ($P = 0.02$), higher ASA score ($P = 0.001$), symptomatic forms ($P = 0.01$), and more frequent tumor necrosis ($P = 0.02$). Recurrence-free survival and metastasis-free survival rates were significantly lower in patients with high PLR than in those with low ratios (each $P < 0.005$). Multivariate analysis identified PLR as an independent predictor of recurrence-free survival ($P = 0.002$) and metastasis-free survival ($P < 0.001$).
Conclusion: A higher PLR was associated with aggressive renal cancer. In addition, the PLR was a significant prognostic factor for both recurrence-free survival and metastasis-free survival in patients with nonmetastatic RCC.

Keywords: lymphocyte, nonmetastatic, platelets, prognosis, renal cell carcinoma

Introduction

Kidney cancer accounts for 2–3% of adult cancers and is the third most common urologic cancer after bladder tumors and prostate cancer. Renal cell carcinoma (RCC) itself accounts for 90–95% of malignant tumors of the kidney[1,2].

The platelet-lymphocyte ratio (PLR) is an easily measured and inexpensive marker of inflammation. A number of malignancies have been linked to the PLR[3]. The synthesis of inflammatory cytokines triggered by the tumor microenvironment alters acute phase reactants and hematological components, including serum platelets and lymphocyte counts.

HIGHLIGHTS

- The platelet-lymphocyte ratio (PLR) is an easily measured and inexpensive marker of inflammation.
- The prognostic significance of the PLR in the renal cancer is still controversial.
- A high preoperative PLR is an independent adverse prognostic factor on survival after curative surgery.

The prognostic significance of PLR in the renal cancer is still controversial. The objective of our study was to evaluate the prognostic significance of preoperative PLR in patients with nonmetastatic RCC.

Patients and methods

It was a retrospective, observational study conducted in a tertiary care center. Institutional Review Board approval was obtained (CEBM.EPS.HR/16/2022). Our data has been reported in line with the strengthening the reporting of cohort, cross-sectional and case-control studies in surgery (STROCSS) criteria[4]. In this study, the authors confirmed that all methods were carried out under the relevant guidelines and regulations (Helsinki Declaration) under the number research registry 8493.

We conducted an observational, analytical study collecting all patients who had a diagnosis of kidney cancer and who underwent surgical intervention from January 2004 to December 2020. None of the patients had a history of other types of malignant tumor,

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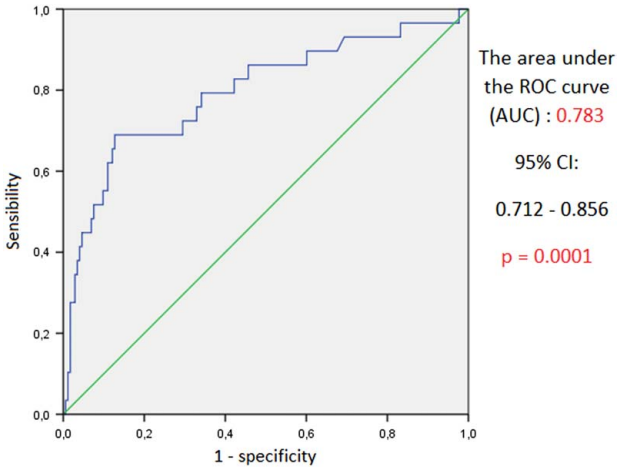

Figure 1. ROC curve analysis for five-year CSS of the PLR.

lymph node metastasis or distant metastasis, upper urinary tract urothelial carcinomas, secondary renal metastases, benign renal tumors (oncocytoma, angiomyolipoma). We also excluded, from this study all patients with missing survival data or who died from another pathology. For each case, the following data were noted: epidemiological data, hospitalization data, radiological assessment data, treatment, results of histopathological examination of surgical specimens, postoperative patient follow-up, and survival. Cancer-specific survival was defined as the duration from the date of diagnosis until death due to the renal cancer. Our oncological surveillance routinely includes abdominal/chest imaging within 6 months of surgery and subsequently every 6–12 months[1].

We used to predict survival in nonmetastatic RCC: the University of California Los Angeles integrated staging system (UISS)[5], ASSURE model[6], the Stage, Size, Grade, and Necrosis (SSIGN) Score[7].

An analysis of all these data was performed using IBM SPSS Statistics 25 software. Thus, we obtained means, percentages, and the distribution of each of the studied parameters. The comparison was made with the Student's *t*-test and χ^2, the differences were considered significant if $P < 0.05$. The ROC curve represents the evolution of sensitivity and specificity for the different threshold values. The search for risk factors for recurrence was performed by calculating the odds ratio. Five years recurrence-free and metastasis-free survival curves were performed with the Kaplan–Meier method and survival curve comparisons with the Log-Rank test. Multivariate analysis was performed according to the Cox model, taking into account all factors measured in univariate analysis that had a significance level below 0.05 ($P < 0.05$). Cox regression was performed to determine factors independently associated with recurrence-free and metastasis-free survival. Multivariate analysis measured the association by the Hazard Ratio and its 95% CI.

Results

Two hundred and two patients were included in our study. The median age of the patients was 59.5 (27–86) years. The sex ratio was 2/1. About 61% of the patients were hypertensive. Diabetes was present in 39.1% of the patients. A metabolic syndrome was found in 38.1% of cases. The most frequent finding was back pain in 90.1% of cases. The renal tumor was on the right side in 112 cases (55.5%). The mean preoperative hemoglobin level was 12.4 ± 1.8 g/dl. The mean preoperative glomerular filtration rate (GFR), calculated with the MDRD formula, was 82 ± 22 ml/min/1.73m². The mean operative time was 149.73 ± 37.41 min. Intraoperative bleeding was less than 300 ml in 81.7% of cases. Sixty-eight patients had conservative treatment (33.7%).

Table 1

Clinical characteristics in patients with renal cell cancer according to platelet/Lymphocyte ratio

	Platelet-lymphocyte ratio (PLR)		
	PLR < 195	**PLR ≥ 195**	***P***
Number of patients (*n*, %)	107 (52.97)	95 (47.02)	0.1
Age (Years), median (Range)	57.21 (36–86)	59.23 (27–85)	0.6
Gender (*n*, %)			
Male	74 (36.63)	55 (27.22)	0.8
Female	33 (16.33)	40 (19.80)	
ASA Score (*n*, %)			
ASA1 - 2	94 (46.53)	74 (36.63)	**0.001**
ASA3 - 4	13 (1)	21 (10.39)	
Diabetes (*n*, %)	41 (20.29)	39 (19.30)	0.26
Chronic hypertension (*n*, %)	54 (26.73)	69 (34.15)	0.51
Symptoms (*n*, %)			
Lumbar pain	59 (29.2)	87 (43.06)	
Hematuria	16 (7.92)	18 (8.91)	**0.01**
paraneoplastic syndrome	1 (0.49)	2 (1)	
Tumor size (mm), median (Range)	54.98 (10–120)	62.67 ± 33.24 (12–150)	**0.02**
Tumor location (*n*, %)			
Upper pole	48 (23.76)	41 (20.29)	0.68
Low pole	39 (19.30)	31 (15.34)	
Mid- renal	20 (9.90)	23 (11.38)	
Preoperative GFR (ml/min/1,73m²)			
GFR ≥ 60	94 (46.53)	67 (33.16)	
30 ≤ GFR ≤ 59	10 (4.95)	18 (8.91)	0.25
GFR < 30	3 (1.48)	10 (4.95)	
Mean Hemoglobin (g/dl), ± SD	12.68 ± 4.26	11.89 ± 3.98	0.6
MeanPlatelets count (x10³/mm³), ± SD	293 ± 85	345 ± 42	0.72
MeanLymphocytes count(/mm³), ± SD	1700 ± 230	1400 ± 150	0.13
Pathological stage (*n*, %)			
T1	46 (22.77)	39 (19.3)	
T2	41 (20.29)	37 (18.31)	0.4
T3	16 (7.92)	8 (3.96)	
T4	4 (1.98)	11 (5.44)	
Histology (*n*, %)			
Clear cell carcinoma	87 (43.06)	44 (21.78)	
Papillary carcinoma	8 (3.96)	32 (15.84)	0.53
Chromophobe carcinoma	11 (5.44)	15 (7.42)	
Others	1 (0.49)	4 (1.98)	
Surgical Treatment (*n*, %)			
Radical nephrectomy	68 (33.66)	66 (32.67)	0.2
Partial nephrectomy	39 (19.3)	29 (14.35)	
Tumor grade (Furhman) (*n*, %)			
1–2	63 (31.18)	103 (51)	0.6
3–4	15 (7.42)	21 (10.39)	
Tumors necrosis (*n*, %)	2 (1)	7 (3.46)	**0.02**
Lymphovascular invasion(*n*, %)	4 (1.98)	6 (2.97)	0.3
Sarcomatoid (*n*, %)	2 (0.99)	4 (1.98)	0.1
Mean Follow-up (months), ± SD	56 ± 8	52 ± 6	0.42

Table 2

The survival rates without recurrence and without metastases according to the different prognostic models

Prognostic model	Recurrence-free survival (%)	Metastasis-free survival (%)
UISS		
Low-risk	81.8	88.6
Intermediate risk	68.9	71.2
High-risk	20.5	16.8
SSIGN		
Low-risk	75.2	82.1
Intermediate risk	60.9	72.9
High-risk	29.1	32.8
ASSURE		
Low-risk	84.6	85.5
Intermediate risk	77.9	79.9
High-risk	21.8	18.4
Platelet-lymphocyte ratio		
<195	91.2	90.6
≥ 195	72.7	71.8

ROC curve analysis indicated that the area under the ROC curve of PLR for predicting five-year cancer-specific survival was 0.783 (Fig. 1). It identified an optimal cutoff value for baseline PLR of 195. As a result, 107 patients (52.97%) had PLR <195 and 95 (47.02%) had PLR ≥ 195. Demographic and baseline characteristics of the total patient population by PLR cutoff are summarized in Table 1. Patients with a higher PLR had larger tumors ($P=0.02$), higher ASA score ($P=0.001$), symptomatic forms ($P=0.01$), and more frequent tumor necrosis ($P=0.02$).

Of the 202 patients with nonmetastatic RCC, according to SSIGN, 63, 4.5, and 32.5% of patients were in the low-, intermediate-, and high-risk categories, respectively. According to the UISS prognostic model, 34.7, 54.5, and 10.9% of patients were in the low, intermediate, and high-risk categories, respectively. According to the ASSURE model, 65, 22, and 13% of patients were in the low, intermediate, and high-risk categories, respectively. Five-year recurrence-free and metastasis-free survival rates are summarized in Table 2. Univariate and multivariate analysis of predictors factors of five-year recurrence-free and metastasis-free survival is summarized in Table 3 and Table 4. Metastasis-free survival was better in patients with low PLR (Log-Rank; $P=0.01$) (Fig. 2), as was recurrence-free survival (Log-Rank; $P=0.02$)(Fig. 3).

Discussion

This is a study to evaluate the prognostic significance of preoperative PLR in nonmetastatic renal cancer. The present study

Table 3

Predictors of recurrence-free and metastasis-free survival: univariate analysis

	Recurrence-free survival			Metastasis-free survival		
	Hazard ratio	CI (95%)	*P*	Hazard ratio	CI (95%)	*P*
Age (Years)						
≥ 60	0.985	0.429–1.569	0.48	4.69	1.59–21.26	**0.02**
<60	0.645	0.689–1.225		1.68	1.9–4.26	
Sex						
Male	0.908	0.597–1,381	0.67	1.27	0.87–3.88	0.1
Female	1.215	0.463–3.190		1.13	0.7–1.7	
Hypertension						
Yes	1.87	0.598–7.269	0.3	1.4	0.77–7.25	0.69
No	1.59	0.265–9.43		1.08	0.46–5.68	
Diabetes						
Yes	1.76	0,129–7.598	0.1	1.89	0.879–3.269	0.43
No	1.1	0.546–7.411		1.15	0.9–2.78	
Tumor size (cm)						
≥ 5	10.25	4.289–31.97	**0.001**	6.26	1.59–28.26	**0.04**
<5	5.68	1.95–11.26		4.55	1.76–19.56	
Chirurgical treatment						
Radical nephrectomy	0.945	0.622–1.436	0.8	1.44	0.669–7.588	0.5
Partial nephrectomy	1.128	0.429–2.968		1.08	0.546–5.369	
Histology						
Clear Cell Carcinoma	0.878	0.159–5.2	0.06	1	0.498–5.269	0.08
Others	0.967	0.453–4.289		0.879	0.888–2.223	
PLR						
≥ 195	4.56	1.15–18.98	**0.01**	7.46	1.11–16.39	**0.001**
<195	3.2	1.752–8.29		3.38	1.2–12.6	
Sarcomatoid						
Yes	4.22	1.489–15.66	$<$**0.0001**	5.88	2.789–11.22	$<$**0.001**
No	1.26	2.758–4.369		4.31	1.293–8.999	
Tumorsnecrosis						
Yes	8.29	4.68–36.369	**0.002**	0.988	0.759–4.369	0.07
No	2.25	1.58–21.25		0.799	0.88–2.38	

Table 4

Predictors of recurrence-free and metastasis-free survival: multivariate analysis.

	Recurrence-free survival			Metastasis-free survival		
	Hazard ratio	CI (95%)	*P*	Hazard ratio	CI (95%)	*P*
Age ≥60 years	–	–	–	1.16	0.72–4.94	0.6
Tumor size ≥5 cm	6.75	1.48–21.89	**0.002**	1.36	1.002–5.49	0.8
PLR ≥195	7.59	4.12–22.64	**0.01**	3.87	1.32–26.29	**0.02**
Sarcomatoid	2.24	1.77–13.78	**0.04**	3.23	1.91–7.56	**0.001**
Tumors necrosis	1.68	0.69–4.37	0.08	–	–	–

showed that patients with high PLR were associated with a higher risk of overall mortality.

Many studies have suggested that the systemic inflammatory response plays an important role in cancer development and progression[3]. Biomarkers of systemic inflammation can be classified into two panels: the blood count (neutrophils, monocytes, lymphocytes, and platelets) and a panel of specific serum proteins (albumin, C-reactive protein, and fibrinogen)[8]. These indicators have been shown to be related to the prognosis of patients with various cancers, including kidney cancer[9,10]. PLR has become an important parameter in the prognostic model of patients with nonmetastatic kidney cancer due to its advantageous properties such as low cost and easy access in clinical settings[11]. Indeed, an elevated PLR reflects an increase in the platelet's dependent inflammatory response and a decrease in the lymphocyte-mediated antitumor immune response[12]. Thus, platelets would also contribute to the growth and spread of cancers. Indeed, it has been shown that platelets are able to promote different processes essential to the growth and progression of cancers such as angiogenesis angiogenesis, lymphangiogenesis, or the metastatic process[13]. It has also been shown that like platelet-derived microparticles may also play an important role in the

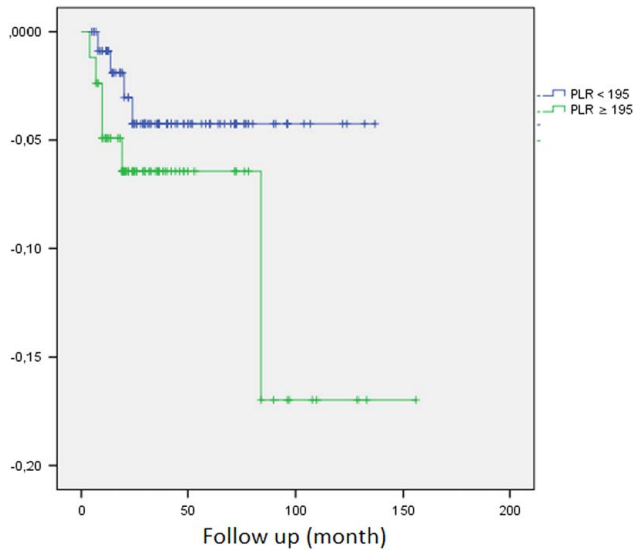

Figure 2. Kaplan–Meier curves for five-year metastasis-free survival of patients classified by the PLR.

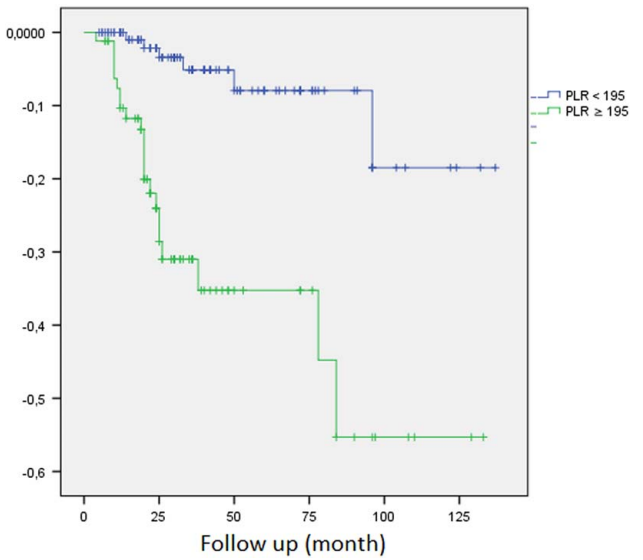

Figure 3. Kaplan–Meier curves for five-year recurrence-free survival in patients classified by the PLR.

proliferation of cancer cells, interactions between cancer cell interactions, metastatic progression, angiogenesis, and inflammation[13]. In contrast, lymphocytes are associated with antitumor immunity, and lymphopenia reflects the immune response dependent on impaired lymphocytes. Several studies have highlighted the importance of lymphocytes and demonstrated that increasing tumor infiltration with lymphocytes showed a better prognosis in cancer patients[14]. Numerous research studies have investigated the relationship between PLR and oncologic prognosis. In a recent meta-analysis, four studies evaluated the relationship between higher PLR and progression free survival[15]. All the studies have relatively consistent results that higher PLR was associated with poor progression free survival[15]. Overall, a higher PLR (cutoff >195) is associated with poor outcomes in RCC[15–17]. Correa[6] did not integrate biological data into their prognostic model at all, the PLR remains an indicator that is still accessible, available, and inexpensive that can help guide patient management or follow-up. Levin showed that PLR is a robust prognostic marker in nonmetastatic RCC that clearly outperforms other inflammatory indexes in those who had undergone nephrectomy. However, its prognostic effect was limited in the low-risk category of RCC (stage pT1a; $P<0.001$ vs. $P=0.571$)[18].

Indeed, the indication for surgery in elderly patients with localized renal tumors may be reconsidered in the case of a low PLR. In this case, a less severe treatment can be discussed: percutaneous treatment (radiofrequency or cryotherapy) or even active surveillance. Postoperatively, the subsequent oncological follow-up should be close in the case of a high PLR because of the increased risk of locoregional or distant recurrence. This study has some weaknesses, in particular the retrospective nature of the study and the relatively long inclusion period, which leads to a bias related to the evolution of management over the period, as well as the quality of the collection of the oldest data.

Conclusion

This study evaluated the prognostic significance of preoperative PLR in nonmetastatic kidney cancer. A high preoperative PLR is an independent adverse prognostic factor on survival after curative surgery. Nevertheless, there is currently no recommendation on the use of this ratio for the follow-up of nonmetastatic kidney cancer. Further studies are needed to verify the current results and validate the inclusion of the PLR in nomograms for nonmetastatic kidney cancer.

Ethical approval

Institutional Review Board approval was obtained (CEBM. EPS.HR/16/2022). The authors confirmed that all methods were carried out under the relevant guidelines and regulations (Helsinki Declaration) under the number research registry 8493.

Consent

Written informed consent for publication has been acquired from the patients.

Sources of funding

We have any financial sources for our research.

Author contribution

Y.O. and K.C.: concept of study; K.C.: data collection; Y.O. and K.C.: results discussion; Y.O.: manuscript writing; Y.N.: paper revision; Y.O., K.C., and Y.N.: final approval of the version to be published.

Conflicts of interest disclosure

All authors disclose any conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: NA.
2. Unique Identifying number or registration ID: 8493.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): NA.

Guarantor

Dr Ouanes Yassine is the guarantor of the study and accept full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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