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Original Article

Elevated preoperative inflammatory ratios (NLR/PLR) predict adverse pathology and poor surgical outcomes in metastatic renal cell carcinoma: a retrospective analysis

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Abstract: Objective: To clarify the clinical utility of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in metastatic renal cell carcinoma (mRCC). Methods: We enrolled 240 RCC patients, including 100 primary RCC (pRCC) and 140 mRCC cases. Peripheral venous blood was sampled for NLR and PLR quantification. NLR/PLR correlations with clinicopathological features and their impacts on surgical outcomes were discussed. Results: We determined significant NLR and PLR elevations in mRCC versus pRCC cases. NLR had an area under the curve (AUC) of 0.710 while PLR exhibited an AUC of 0.716 in diagnosing mRCC. PLR correlated intimately with clinical staging and Fuhrman grading, while NLR was additionally linked to the metastatic site. In clinical stage discrimination, the AUC was 0.679 for NLR and 0.634 for PLR, with corresponding AUC of 0.656 and 0.612 in Fuhrman grade diagnosis. Additionally, the postoperative prognosis of mRCC patients was significantly and independently influenced by clinical staging, Fuhrman grading, NLR, and PLR. Conclusion: NLR and PLR, showing up-regulated expression in mRCC, correlate intimately with advanced clinical staging and higher Fuhrman grading. Clinical stage III-IV, Fuhrman grade (3-4), elevated NLR (≥2.76), and high PLR (≥166.50) are predictors of unfavorable surgical outcomes in mRCC.

Keywords: Peripheral blood inflammatory biomarkers, metastatic renal cell carcinoma, pathological features, surgical outcomes, NLR, PLR

Introduction

Being a urogenital malignancy, kidney cancer is etiologically linked to tobacco smoking, obesity, hypertension, and chronic kidney disease [1]. Renal cell carcinoma (RCC) is dominant among all kidney cancers (~90%), with the clear cell subtype being most prevalent, carrying high metastasis and recurrence risks [2, 3]. RCC shows a male predisposition, with a ~40% mortality risk and 30% metastasis/recurrence rate. Moreover, metastatic RCC (mRCC) patients exhibit a 5-year survival rate as low as 10% [4-6]. Radical and partial nephrectomies are the current mainstays for mRCC, procedures that improve patient overall survival to some extent [7]. Yet, around 20% of the cases experience disease progression post-surgery [8]. Hence, it is pressing to identify determinants associated with mRCC progression and prognosis to enable timely intervention and survival extension.

Systemic inflammation has been increasingly implicated in tumorigenesis and progression, possibly exerting an influence on tumor metastasis and relapse [9, 10]. This has resulted in an increasing interest in various peripheral blood (PB) inflammatory parameters for their potential to predict pathological features and prognosis in cancer patients. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), for instance, have been validated as prognostic indicators in colorectal cancer [11]. In operable pancreatic ductal adenocarcinoma, they correlate with infiltration depth, lymph node metastasis, clinical stage, and lymphovascular invasion [12]. Additionally, preoperative NLR and PLR help predict prognosis in cell RCC with spinal metastases [13]. Teishima et al. further reported NLR's role as a prognostic predictor for mRCC patients with extrapulmonary metastases undergoing targeted therapy, aiding in forecasting progression-free sur-

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vival (PFS) [13, 14]. A meta-analysis by Zhou et al. [15] also linked elevated PLR to poorer prognosis in RCC patients [15].

This study analyzes the associations of PB inflammatory parameters (NLR and PLR) with pathological features in mRCC patients and evaluates their influence on postoperative results, given the scant evidence in this area. We expect the findings to aid in advancing the preoperative profiling and prognostication for mRCC patients, ultimately facilitating more personalized treatment strategies.

Methods

Patient information

Patient eligibility criteria: 1. Age: 18-85 years; 2. A preoperative kidney cancer diagnosis by computed tomography (CT) or magnetic resonance imaging (MRI); 3. Surgical treatment (radical/partial/cytoreductive nephrectomy) in the Urology Department of our hospital; 4. A complete blood count test report one week preceding surgery. Exclusion criteria: 1. Additional malignancies or severe infections; 2. Prior corticosteroid therapy, radiotherapy, chemotherapy, or heparin therapy; 3. Myelodysplastic syndromes or chronic myeloid leukemia; 4. Diseases potentially affecting hematological parameters (e.g., acute/chronic infections, acute hemorrhage, hemolysis).

This retrospective study was conducted using data from patients who underwent surgery at the Guizhou Provincial People's Hospital between January, 2021 and December, 2023. All patients had a RCC diagnosis confirmed pathologically. Metastatic status was assessed by postoperative imaging and pathological reports. Specifically, classification as primary RCC (pRCC) or mRCC was based on postsurgical histopathology, with pRCC patients exhibiting no evidence of metastasis [16]. The Fuhrman grade [17] was assessed for all cases. A total of 240 patients were included in this study, comprising patients of 100 pRCC and 140 mRCC. Peripheral venous blood reports were collected to determine NLR and PLR levels. The analysis of patients' baseline data such as age, sex, pathological type, clinical staging, Fuhrman grading, metastatic site, and surgical method revealed no notable intergroup differences ($P>0.05$), indicating clinical comparability. The hospital's ethics committee approved the study protocol.

Statistical analysis

The NLR and PLR were calculated according to neutrophil, lymphocyte, and platelet counts for comparative analysis and optimal cut-offs of NLR and PLR were determined by the receiver operating characteristic (ROC) curves of the subjects, based on which grouping (high and low expression groups) was performed. The patients were followed up for one year, mainly through post-operative review, outpatient visits, telephone follow-up, etc., to record their post-operative condition, tumor recurrence and metastasis, and survival status. During the follow-up, the occurrence of postoperative serious adverse events, tumor recurrence, metastasis, or death was regarded as a poor prognosis; otherwise, it was regarded as a good prognosis.

In this study, a blinding method was implemented for the outcome assessors. Specifically, the researchers responsible for collecting and determining patients' prognostic endpoints (tumor metastasis, surgical outcomes, etc.) did not participate in the initial data extraction process, and were completely unaware of the patients' group allocation (pRCC or mRCC groups). They only classified the follow-up data based on the established objective criteria (e.g., imaging reports, death certificates). Additionally, the researchers conducting the statistical analysis also remained blinded to the grouping.

SPSS23.0 was used for data analysis. After testing of measurement data for normal distribution, the data (e.g., age, PLR) conforming to a normal distribution are represented as ($\bar{x}\pm sd$), and the comparison between groups adopts a t test; those that do not conform to a normal distribution are represented by medians, and the differences between groups are compared using a nonparametric test. The number of cases (percentage) (n [%]) is used to represent the counting data (gender, pathological type, etc.), and a χ^2 test is used for comparison between groups. To evaluate the predictive value of NLR and PLR for clinical stage and Fuhrman grade in mRCC patients, optimal cut-off values were determined using ROC curve analysis. To identify predictors of surgical prognosis in mRCC patients, univariate screening followed by multivariate modelling were employed. $P<0.05$ is the statistical threshold.

Table 1. Comparison of general data between mRCC and pRCC patients

Factors	n	pRCC (n=100)	mRCC (n=140)	Z/χ^2	P
Mean age (years)	240	54.50 (52.25, 66.00)	61.00 (53.00, 69.00)	-1.594	0.111
Age (years old)				2.824	0.093
<60	119	56 (56.00)	63 (45.00)		
≥60	121	44 (44.00)	77 (55.00)		
Sex				1.710	0.191
Male	183	72 (72.00)	111 (79.29)		
Female	57	28 (28.00)	29 (20.71)		
Pathological type				1.189	0.276
Clear cell renal cell carcinoma	195	78 (78.00)	117 (83.57)		
Others	45	22 (22.00)	23 (16.43)		
Clinical staging				0.488	0.485
I-II	190	77 (77.00)	113 (80.71)		
III-IV	50	23 (23.00)	27 (19.29)		
Fuhrman grading				0.075	0.784
Grade 1-2	156	66 (66.00)	90 (64.29)		
Grade 3-4	84	34 (34.00)	50 (35.71)		
Metastatic site				-	-
Bone	55	-	55 (39.29)		
Lungs	47	-	47 (33.57)		
Others	38	-	38 (27.14)		
Surgical method				3.434	0.064
Partial nephrectomy	38	21 (21.00)	17 (12.14)		
Radical nephrectomy	202	79 (79.00)	123 (87.86)		

Note: mRCC, metastatic renal cell carcinoma; pRCC, primary renal cell carcinoma.

Results

Comparison of general data between mRCC and pRCC patients

The general data of mRCC and pRCC patients, such as mean age, age, sex, pathological type, clinical staging, Fuhrman grading, metastatic site, and surgical method, were not significantly different after comparative analysis (P>0.05, **Table 1**).

NLR and PLR levels in peripheral venous blood samples of RCC patients in the two groups

mRCC patients showed statistically higher levels of NLR and PLR in PB samples than pRCC patients (P<0.05, **Figure 1**).

ROC analysis of the efficiency of NLR and PLR in screening mRCC

The ROC analysis data showed that the AUC of NLR screening for mRCC was 0.710 (95% CI: 0.644-0.776), the optimal cut-off value was 2.755, the sensitivity was 60.00%, and the specificity was 72.00%. The AUC of PLR in screening mRCC was 0.716 (95% CI: 0.652-0.780), with an optimal cutoff of 166.500, a sensitivity of 63.57%, and a specificity of 73.00% (**Table 2** and **Figure 2**).

Correlation of NLR and PLR with pathological characteristics of mRCC patients

According to the optimal cut-offs analyzed above, mRCC patients were grouped into high or low NLR and PLR groups, respectively, with 84 cases and 56 cases included in NLR high and low expression groups, as well as 89 and 51 cases in PLR high and low expression groups, respectively.

NLR was found to be little linked to age, sex, pathological type, and surgery method (P> 0.05), but was strongly associated with clinical staging, Fuhrman grading, and metastasis site of mRCC patients (P<0.05, **Table 3**).

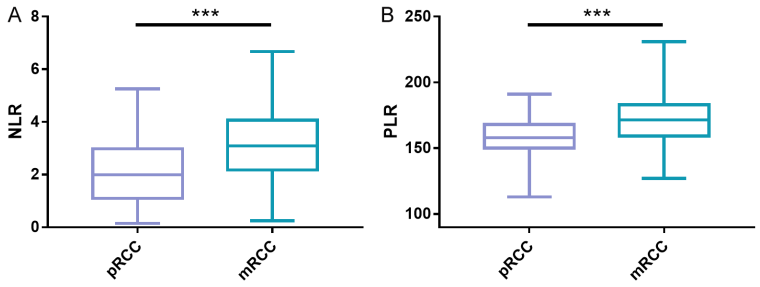

Figure 1. NLR and PLR levels in peripheral venous blood samples of RCC patients in the two groups. A. mRCC patients showed statistically higher NLR levels in peripheral venous blood samples than pRCC patients. B. The level of PLR in peripheral venous blood samples was significantly higher in mRCC patients. Note: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; RCC, renal cell carcinoma; mRCC, metastatic renal cell carcinoma; pRCC, primary renal cell carcinoma. ***P<0.001 vs. pRCC.

As for PLR, it had no close connection with age, sex, pathological type, metastatic site, and surgical method (P>0.05), but had a strong association with clinical staging and Fuhrman grading in mRCC patients (P<0.05, **Table 4**).

Predictive potential of NLR and PLR for clinical stage and Fuhrman grade in mRCC

ROC curve analysis quantified the predictive capacity of NLR and PLR for clinical stage and Fuhrman grade in mRCC (**Tables 5**, **6** and **Figure 3**). For clinical stage discrimination, the AUC was 0.679 (95% CI: 0.578-0.780) for NLR and 0.656 (95% CI: 0.563-0.748) for PLR, with sensitivities of 88.89% and 80.00%, and specificities of 46.90% and 51.11%, respectively. Regarding Fuhrman grade prediction, the AUC for NLR was 0.634 (95% CI: 0.526-0.742; sensitivity: 85.19%; specificity: 41.59%), while PLR achieved an AUC of 0.612 (95% CI: 0.517-0.708; sensitivity: 78.00%; specificity: 44.44%).

Determinants of postoperative prognosis in mRCC patients

We followed all 140 patients with mRCC for one year. 26 of them had a favorable prognosis, and the remaining 114 cases had unfavorable outcomes. In assessing determinants of surgical prognosis for mRCC, clinical stage, Fuhrman grade, NLR, and PLR emerged as significant independent factors upon both univariate and multivariate analyses (P<0.05). Other examined variables, including age, sex, pathological type, metastatic site, and surgical technique, demonstrated no significant prognostic value (P>0.05). Refer to **Tables 7**, **8** for comprehensive data.

Discussion

Although RCC accounts for only 3 percent of adult malignancies, nearly 70,000 cases were diagnosed in the United States alone in 2018, with about 20,000 associated deaths [18, 19]. At present, the relevant research on the diagnosis and treatment of mRCC is still ongoing and optimized [20], and this study is conducted to provide a more valuable reference for the management of mRCC patients.

In this study, NLR and PLR levels in PB samples were significantly higher in mRCC patients than those in pRCC patients, suggesting that NLR and PLR may mediate the occurrence and development of mRCC and have certain metastasis prediction potential in mRCC. Then, the AUCs of NLR and PLR in screening mRCC were determined to be 0.710 and 0.716, respectively, suggesting that both can serve as effective auxiliary indicators for mRCC screening. In the study of Wang et al. [21], the AUC of NLR screening for mRCC was 0.71, which is similar to our research data. Subsequently, we grouped patients into high and low expression groups according to the NLR and PLR levels based on ROC analysis results. The optimal cut-offs of NLR and PLR were 2.755 and 166.500, respectively, similar to the results of Ishihara et al. [22]. In addition, a close connection was identified between high NLR levels (>2.755) and higher clinical staging and Fuhrman grading and a higher risk of bone and lung metastases, while high levels of PLR (>166.500) were only closely related to higher clinical staging and Fuhrman grading. In the study of Tang et al. [23], higher NLR and PLR levels are closely linked to more advanced tumor stages and higher Furman grades in non-metastatic RCC patients, similar to our findings. Besides, Zhang et al. [24] reported that high-level NLR was closely associated with higher tumor pathological T staging, advanced age, low BMI, and radical surgery in RCC patients, while high-level PLR was strongly related to higher tumor pathological T staging, higher Fuhrman grading, low BMI, male, radical surgery, and tumor necrosis, consistent with our observations. Subsequent assessment yi-

Table 2. ROC analysis of the efficiency of NLR and PLR screening for mRCC

Indicators	AUC	95% CI	S.E	Cut-off	Sensitivity (%)	Specificity (%)
NLR	0.710	0.644-0.776	0.034	2.755	60.00	72.00
PLR	0.716	0.652-0.780	0.033	166.500	63.57	73.00

Note: ROC, receiver operating characteristic; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; mRCC, metastatic renal cell carcinoma; AUC, Area Under the ROC Curve; 95% CI, 95% Confidence Interval; S.E, Standard Error.

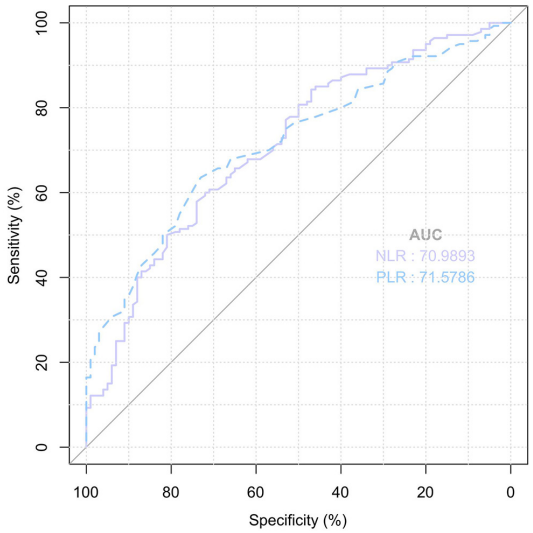

Figure 2. Diagnostic performance of NLR and PLR for mRCC screening by ROC curve analysis. Note: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; mRCC, metastatic renal cell carcinoma; ROC, receiver operating characteristic.

elded AUCs of 0.679 and 0.634 for NLR and PLR, respectively, in clinical staging, and 0.656 and 0.612 in Fuhrman grading. This suggests that although both ratios have some discriminatory capacity for these classifications in mRCC, their overall diagnostic efficacy remains limited. Previous studies have also conducted in-depth explorations on the application potential of NLR + PLR. For example, Matsuki et al. [25] pointed out the utility of pre-treatment NLR, PLR, the lymphocyte-to-monocyte ratio (LMR), and the C-reactive protein-albumin-lymphocyte (CALLY) index as effective predictive indicators for immune-related adverse events in patients with recurrent or metastatic head/neck squamous cell carcinoma. According to the report by Pacholczak-Madej et al. [26], NLR, PLR, and eosinophil counts can predict the treatment response of advanced RCC patients treated with nivolumab and ipilimumab. Moreover, NLR, lactate dehydrogenase (LDH), and the modified Glasgow Prognostic Score (mGPS) have been shown to be independent prognostic indicators for RCC survival [27].

According to statistics on patient outcomes, 114 of the 140 mRCC patients had a good prognosis after a one-year follow-up, with a good prognosis rate of 81.43%. In the study of Fujiwara et al. [28], the one-year OS of 213 mRCC patients was 88.7%. Kroeze et al. [29] reported a one-year OS of 71% in mRCC patients receiving targeted therapy or immunotherapy in combination with concurrent stereotactic radiotherapy. All the above studies showed results similar to our findings. Furthermore, an NLR ≥2.76 and a PLR ≥166.50, alongside clinical stage III-IV and Fuhrman grade 3-4, independently predicted unfavorable prognoses in mRCC patients. Thus, elevated NLR and PLR levels can help identify patients at increased risk of poor postoperative outcomes. In the research of Yanagisawa et al. [30], pretreatment NLR and PLR elevations were strongly associated with lower OS in mRCC patients, which could guide the clinical treatment of immune checkpoint inhibitors for mRCC patients, similar to our research results. As reported by Chen et al. [11], low-level NLR and PLR were strongly associated with longer OS and disease-free survival in colorectal cancer patients, which supports the accuracy of our research results. Changes in NLR levels have also been indicated to help monitor the efficacy of anti-programmed death receptor 1 (PD-1) therapy in mRCC patients and predict OS and PFS [31]. Though this study has established a correlation between NLR and PLR with the pathological characteristics and prognosis of mRCC, the specific molecular mechanisms underlying their roles in mRCC progression remain to be characterized. A high NLR is indicative of elevated neutrophil levels and reduced lymphocyte levels. Of these, low-density neutrophils promote tumor angiogenesis by upregulating vascular endothelial growth factor (VEGF), while high-density neutrophils are involved in early inflammation activation. In the tumor microenvironment, a reduction in lymphocytes leads to the suppression of the body's anti-tumor capacity, thereby facilitating tumor cell immune escape [32]. In renal cancer with

Table 3. Correlation of NLR with pathological features of mRCC patients

Factors	n	High NLR expression (n=84)	Low NLR expression (n=56)	χ^2	P
Age (years old)				0.943	0.332
<60	63	35 (41.67)	28 (50.00)		
≥60	77	49 (58.33)	28 (50.00)		
Sex				0.029	0.865
Male	111	67 (79.76)	44 (78.57)		
Female	29	17 (20.24)	12 (21.43)		
Pathological type				1.699	0.192
Clear cell renal cell carcinoma	117	73 (86.90)	44 (78.57)		
Others	23	11 (13.10)	12 (21.43)		
Clinical staging				11.632	<0.001
I-II	113	60 (71.43)	53 (94.64)		
III-IV	27	24 (28.57)	3 (5.36)		
Fuhrman grading				12.963	<0.001
Grade 1-2	90	44 (52.38)	46 (82.14)		
Grade 3-4	50	40 (47.62)	10 (17.86)		
Metastatic site				9.163	0.010
Bone	55	37 (44.05)	18 (32.14)		
Lungs	47	32 (38.10)	15 (26.79)		
Others	38	15 (17.86)	23 (41.07)		
Surgical method				0.402	0.526
Partial nephrectomy	17	9 (10.71)	8 (14.29)		
Radical nephrectomy	123	75 (89.29)	48 (85.71)		

Note: NLR, neutrophil-lymphocyte ratio; mRCC, metastatic renal cell carcinoma.

Table 4. Correlation of PLR with pathological features of mRCC patients

Factors	n	High PLR expression (n=89)	Low PLR expression (n=51)	χ^2	P
Age (years old)				1.085	0.298
<60	63	43 (48.31)	20 (39.22)		
≥60	77	46 (51.69)	31 (60.78)		
Sex				0.060	0.807
Male	111	70 (78.65)	41 (80.39)		
Female	29	19 (21.35)	10 (19.61)		
Pathological type				0.032	0.858
Clear cell renal cell carcinoma	117	74 (83.15)	43 (84.31)		
Others	23	15 (16.85)	8 (15.69)		
Clinical staging				6.748	0.009
I-II	113	66 (74.16)	47 (92.16)		
III-IV	27	23 (25.84)	4 (7.84)		
Fuhrman grading				6.992	0.008
Grade 1-2	90	50 (56.18)	40 (78.43)		
Grade 3-4	50	39 (43.82)	11 (21.57)		
Metastatic site				0.710	0.701
Bone	55	35 (39.33)	20 (39.22)		
Lungs	47	28 (31.46)	19 (37.25)		
Others	38	26 (29.21)	12 (23.53)		

Surgical method				0.411	0.521
Partial nephrectomy	17	12 (13.48)	5 (9.80)		
Radical nephrectomy	123	77 (86.52)	46 (90.20)		

Note: PLR, platelet-lymphocyte ratio; mRCC, metastatic renal cell carcinoma.

Table 5. Evaluation of NLR and PLR in predicting clinical staging of mRCC patients

Indicators	AUC	95% CI	S.E	Cut-off	Sensitivity (%)	Specificity (%)
NLR	0.679	0.578-0.780	0.052	>0.5	88.89	46.90
PLR	0.634	0.526-0.742	0.055	>0.5	85.19	41.59

Note: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; mRCC, metastatic renal cell carcinoma; AUC, Area Under the ROC Curve; 95% CI, 95% Confidence Interval; S.E, Standard Error.

Table 6. Assessment of NLR and PLR for predicting Fuhrman grading in mRCC patients

Indicators	AUC	95% CI	S.E	Cut-off	Sensitivity (%)	Specificity (%)
NLR	0.656	0.563-0.748	0.047	>0.5	80.00	51.11
PLR	0.612	0.517-0.708	0.049	>0.5	78.00	44.44

Note: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; mRCC, metastatic renal cell carcinoma; AUC, Area Under the ROC Curve; 95% CI, 95% Confidence Interval; S.E, Standard Error.

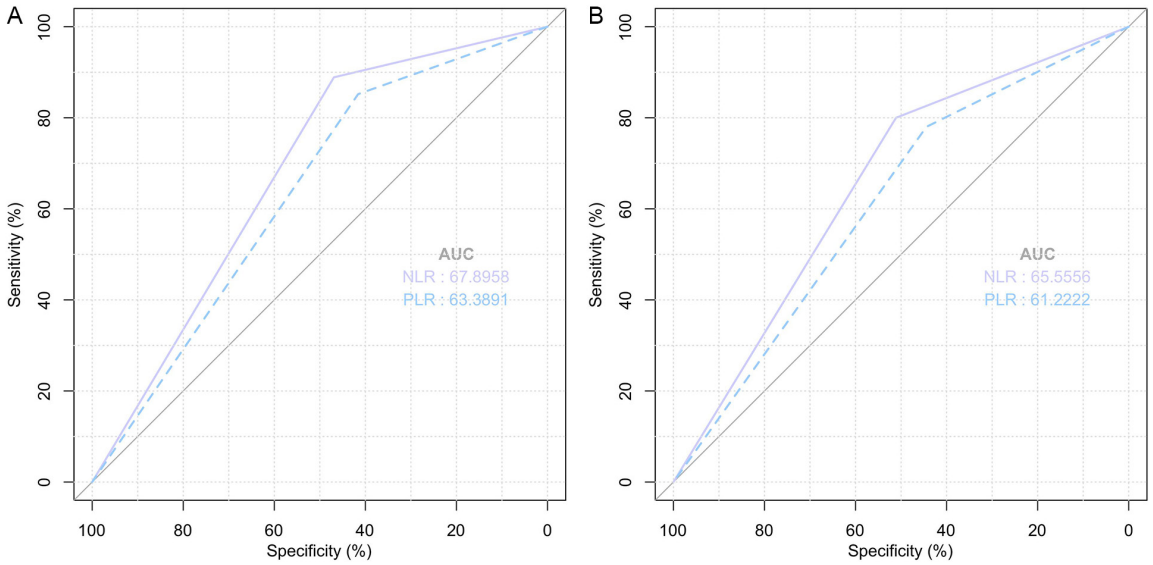

Figure 3. Diagnostic performance of NLR and PLR in predicting clinical stage and Fuhrman grade in mRCC patients. A. ROC curves for clinical stage stratification using NLR and PLR. B. ROC curves for Fuhrman grade classification using NLR and PLR. Note: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; mRCC, metastatic renal cell carcinoma; ROC, receiver operating characteristic.

tumor thrombus, a high NLR indicates that neutrophils drive tumor metastasis by forming neutrophil extracellular traps (NETosis), accompanied by an immune disorder characterized by a decline in systemic T-cell diversity, jointly promoting renal cancer progression [33]. PLR elevation, on the other hand, can reflect an increased platelet level and a reduced lymphocyte level. Platelets can promote the self-infiltration of tumor cells, hematogenous metastasis, and immune evasion, with their aggregation closely related to tumor progression [34, 35]. In the report by Zhou et al. [36], the circular RNAs expressed by lymphocytes can, by mediating

Table 7. Factors associated with postoperative outcomes in mRCC (univariate screening)

Factors	n	Favorable prognosis (n=114)	Unfavorable prognosis (n=26)	Fisher's/χ^2	P
Age (years old)				0.017	0.896
<60	63	51 (44.74)	12 (46.15)		
≥60	77	63 (55.26)	14 (53.85)		
Sex				1.966	0.161
Male	111	93 (81.58)	18 (69.23)		
Female	29	21 (18.42)	8 (30.77)		
Pathological type				1.028	0.311
Clear cell renal cell carcinoma	117	97 (85.09)	20 (76.92)		
Others	23	17 (14.91)	6 (23.08)		
Clinical staging				7.543	0.006
I-II	113	97 (85.09)	16 (61.54)		
III-IV	27	17 (14.91)	10 (38.46)		
Fuhrman grading				6.718	0.010
Grade 1-2	90	79 (69.30)	11 (42.31)		
Grade 3-4	50	35 (30.70)	15 (57.69)		
Metastatic site				4.538	0.103
Bone	55	40 (35.09)	15 (57.69)		
Lungs	47	41 (35.96)	6 (23.08)		
Others	38	33 (28.95)	5 (19.23)		
Surgical method				3.578	0.059
Partial nephrectomy	17	11 (9.65)	6 (23.08)		
Radical nephrectomy	123	103 (90.35)	20 (76.92)		
NLR				10.777	0.001
<2.76	56	53 (46.49)	3 (11.54)		
≥2.76	84	61 (53.51)	23 (88.46)		
PLR					0.022
<166.50	50	46 (40.35)	4 (15.38)		
≥166.50	90	68 (59.65)	22 (84.62)		

Note: mRCC, metastatic renal cell carcinoma; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.

Table 8. Independent predictors of postoperative outcomes in mRCC (multivariate analysis)

Factors	B	SE	Wald	P	OR	95% CI
Clinical staging	1.407	0.443	10.065	0.002	4.082	1.712-9.734
Fuhrman grading	1.049	0.426	6.068	0.014	2.854	1.239-6.573
NLR	1.230	0.626	3.866	0.049	3.422	1.004-11.661
PLR	1.155	0.557	4.292	0.038	3.174	1.064-9.465

Note: mRCC, metastatic renal cell carcinoma; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; B, Regression Coefficient; SE, Standard Error; Wald, Wald Statistic; OR, Odds Ratio; 95% CI, 95% Confidence Interval.

the Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation-driven circular RNA ATXN7 (circATXN7)-nuclear factor κB (NF-κB) signaling axis, enhance the activation of cytotoxic T lymphocytes (CTLs) and activation-induced cell death (AICD) sensitivity, thereby promoting tumor immune escape.

Based on the results of this study, we suggest integrating preoperative NLR and PLR testing into the clinical decision-making pathway for mRCC. Given that NLR and PLR increases are independently associated with more advanced clinical stage/grade and poorer prognosis, patients presenting with elevated NLR should

be managed with more aggressive strategies when selecting surgical plans (e.g., more extensive resection and lymphadenectomy) and postoperative management (e.g., intensified follow-up, early initiation of adjuvant therapy). Future research should focus on constructing clinical prediction models that integrate NLR and PLR, and prospectively validate their value in guiding postoperative treatment and dynamic monitoring, thereby promoting the transformation of NLR and PLR from prognostic markers to a clinical decision-making tool. In addition, the limitations of this study should be acknowledged. First, data on serum inflammatory markers (e.g., interleukin [IL]-6, tumor necrosis factor [TNF]-α) and immune cell subsets (the ratio of CD4-positive T lymphocytes to CD8-positive T lymphocytes [$CD4^+/CD8^+$ T-cell ratio]), the content of regulatory T cells, etc.) were not analyzed. Supplementary analysis of these data would help establish a predictive model of "inflammatory markers (NLR/PLR) → molecular targets → clinical outcomes (pathological grading/prognosis)". Second, no combined predictive model based on NLR, PLR and key clinical indicators (e.g., clinical stage, Fuhrman grading, metastasis site) was established, nor was the model's predictive performance verified (through AUC, calibration curve, and decision curve analysis [DCA]), to clarify the advantages of this model over individual indicators. Future supplementary analyses can provide powerful auxiliary tools for clinical decision-making and risk stratification in mRCC. Future improvements to this study will be based on these points.

In summary, NLR and PLR are expressed at abnormally high levels in mRCC patients, serving as auxiliary predictive indicators for the pathological progression of mRCC. For example, high NLR and PLR indicate higher clinical staging, higher Fuhrman grading, and poorer patient outcomes. High NLR can also to some extent indicate the location of metastasis in mRCC patients. Additionally, a heightened risk of unfavorable surgical outcomes is present in mRCC patients who exhibit advanced clinical staging (III-IV), high Fuhrman grading (3-4), an increased NLR (2.76 or above), and a high PLR (166.50 or above). Our findings can provide clinical guidance for the prediction of tumor metastasis, disease deterioration, and prognosis in mRCC patients.

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Disclosure of conflict of interest

None.

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