



## Original Research

## Preoperative red blood cell distribution width as an independent prognostic factor in metastatic renal cell carcinoma

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## ABSTRACT

**Objective:** This study aimed to explore the prognostic value of preoperative red blood cell distribution width (RDW) in patients with metastatic renal cell carcinoma (mRCC).

**Methods:** Clinicopathological data of 230 patients with mRCC treated at the First Affiliated Hospital of Chongqing Medical University and the Chinese PLA General Hospital from January 2008 to December 2018 were retrospectively analyzed. Patients were stratified according to the optimal cut-off value of RDW calculated using X-tile software. The prognostic value of RDW was analyzed using the Kaplan-Meier curve with log-rank test and univariate and multivariate Cox proportional hazards models.

**Results:** A total of 230 patients were included. The optimal cut-off value of RDW obtained using X-tile software was 13.1%. The median Progression-free survival (PFS) and Overall survival (OS) of all populations were 12.06 months (IQR: 4.73–36.9) and 32.20 months (IQR: 13.73–69.46), respectively. Kaplan-Meier curves showed that patients with high RDW had worse PFS and OS than those with low RDW (median PFS of 9.7 months vs. 17.9 months,  $P = 0.002$ , and median OS of 27.8 months vs. 45.1 months,  $P = 0.012$ , respectively). Multivariate analysis showed that RDW was an independent risk factor for PFS (HR: 1.505; 95% CI: 1.111–2.037;  $P = 0.008$ ) and OS (HR: 1.626; 95% CI: 1.164–2.272;  $P = 0.004$ ) in mRCC after cytoreductive nephrectomy.

**Conclusion:** Preoperative RDW was independently associated with PFS and OS in patients with mRCC and may be a potential predictor of survival outcomes in mRCC.

## Introduction

Renal cell carcinoma (RCC), derived from renal tubular epithelial cells, is one of the most common malignant tumors of the urinary system worldwide. According to statistics, there were approximately 431,288 new cases and 179,368 deaths due to RCC worldwide in 2020 [1]. Partial nephrectomy or radical nephrectomy are the primary treatment modality for localized RCC [2]. Approximately 15% of patients have metastatic renal cell carcinoma (mRCC) at initial diagnosis [3], and 20% of patients with localized RCC will experience recurrence and metastasis after surgical treatment [4]. The prognosis of patients with mRCC is poor, with a median survival of approximately 12.5–18.8 months [5,6]. With the advent of immunotherapy in recent years, more options have become available for the treatment of mRCC [7]. Immune checkpoint inhibitors (ICI) in combination with tyrosine kinase inhibitors (TKI) have achieved significant clinical benefit in many phase III clinical

studies compared to TKI monotherapy [8]. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic models are common models for predicting the survival of mRCC patients worldwide [9]. However, patients with different clinicopathological characteristics and treatment methods have variable prognosis. Currently, there is no established model to determine the prognosis of patients with mRCC who underwent cytoreductive nephrectomy. Therefore, it is necessary to identify cheap and easily available predictive markers to predict the prognosis of patients with mRCC who underwent cytoreductive nephrectomy.

Red blood cell distribution width (RDW) is a simple and inexpensive parameter that reflects the size of red blood cells, and is often used to identify anemia in clinical practice [10]. In many types of cancer, inflammatory conditions may exist before tumorigenesis, since malignant changes can induce an inflammatory microenvironment [11].

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Inflammation *in vivo* can lead to erythrocyte maturation disorders by interfering with the erythrocyte membrane and inducing abnormal RDW [10]. In recent years, it has been reported that RDW level was related to the prognosis of colon, gastric, bladder, and liver cancers [12–15]. However, the prognostic value of preoperative RDW for mRCC remains unclear. Therefore, we hypothesized that preoperative RDW can predict the prognosis of patients with mRCC.

## Methods

### Patients and study design

This retrospective study included 230 patients with metastatic renal cancer who underwent cytoreductive nephrectomy at the First Affiliated Hospital of Chongqing Medical University and the Chinese PLA General Hospital between January 2008 and December 2018. The inclusion criteria were as follows: (1) pathologically confirmed patients with mRCC who underwent cytoreductive nephrectomy; (2) routine blood examination within one week before surgery; (3) complete clinical data before surgery. The exclusion criteria were as follows: (1) co-infection, immune, or hematological diseases; (2) presence of other malignant tumors; and (3) incomplete clinical and pathological data. This study was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University and Chinese PLA General Hospital. All patients signed informed consent forms. All the procedures were conducted in accordance with the Declaration of Helsinki.

### Data collection

The clinical data of each patient, including age, sex, body mass index (BMI), primary tumor characteristics (tumor site, histological subtype, tumor size, T stage, N stage, number of metastases, sarcomatoid differentiation, tumor necrosis, and Fuhrman grade), and targeted therapy (tyrosine kinase inhibition), were carefully collected. Tumor TNM staging was performed according to the American Joint Committee on Cancer (AJCC) TNM classification system (version, 2017). Each patient's preoperative whole blood was drawn one week before surgery. Laboratory hematological parameters were collected, including hemoglobin, hematocrit, red blood cell count, and distribution width. Progression-free survival (PFS) was defined as the time from surgery to disease progression, death from any cause, or the end of follow-up. Overall survival (OS) was defined as the time from surgery to death from any cause or the end of follow-up.

### Statistical analysis

Data analyses were performed using the SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism software (version 8.0; GraphPad Software Inc., San Diego, CA, USA). X-tile software (version 3.6.1, Yale University, New Haven, CT, USA) was used to determine the optimal cut-off value for RDW [16]. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as medians and interquartile ranges. Categorical and continuous variables were analyzed using the chi-square test and Mann-Whitney U test, respectively. OS and PFS were analyzed using the Kaplan–Meier method with the log-rank test. Univariate and multivariate hazard ratios with 95% CIs were determined using the Cox proportional hazards method. A two-sided *P*-value < 0.05 was considered statistically significant for all analyses, and all confidence intervals were stated at the 95% confidence level.

## Results

### Patient and clinical–pathological features

In total, 230 patients were included in this retrospective study. The

optimal cutoff value for RDW was 13.1% as determined by the X-tile software (Fig. 1). Based on the cutoff value of RDW, the patients were divided into low RDW group ( $\leq 13.1\%$ ) and high RDW group ( $> 13.1\%$ ), which included 93 and 137 patients, respectively. The baseline clinical and pathological characteristics of the two groups of patients are shown in Table 1. Group difference analysis showed that the presence of more than two metastatic lesions was more likely in the high RDW group when compared with the low RDW group (59.9 vs. 43.0%,  $P = 0.012$ ), and hemoglobin (13.5 vs. 12.3,  $P < 0.001$ ) and hematocrit (40.7 vs. 37.9,  $P < 0.001$ ) were significantly higher in the low RDW group than in the high RDW group. There were no significant differences between the high and low RDW groups in terms of age ( $P = 0.169$ ), gender ( $P = 0.356$ ), BMI ( $P = 0.502$ ), tumor site ( $P = 0.185$ ), histological subtype ( $P = 0.893$ ), tumor size ( $P = 0.469$ ), T stage ( $P = 0.114$ ), N stage ( $P = 0.704$ ), sarcomatoid differentiation ( $P = 0.700$ ), tumor necrosis ( $P = 0.064$ ), Fuhrman grade ( $P = 0.202$ ), targeted therapy ( $P = 0.287$ ) and red blood cell count ( $P = 0.057$ ). At the end of follow-up, a total of 187 (81.3%) patients had progression of their disease, while 160 (69.6%) patients died from any cause. The median follow-up time was 31.6 (interquartile range [IQR]: 15.7–61.1) and 22.9 (IQR: 12.3–49.9) months in the low and high RDW groups, respectively.

### The relationship between RDW level and mRCC prognosis

Based on the cut-off value of RDW, we divided all patients into high RDW ( $> 13.1\%$ ) and low RDW ( $\leq 13.1\%$ ). Kaplan–Meier survival analysis was performed using the log-rank test, with OS and PFS as end-points. The median PFS and OS of all populations in this study were 12.06 months (IQR: 4.73–36.9) and 32.20 months (IQR: 13.73–69.46), respectively. Kaplan–Meier curves showed that patients with high RDW had significantly worse PFS and OS than those with low RDW (median PFS of 9.7 months vs. 17.9 months,  $P = 0.002$  (Fig. 2A) and median OS of 27.8 months vs. 45.1 months,  $P = 0.012$  (Fig. 2B), respectively).

### The results of Cox regression analysis

We used Cox proportional hazards models separately for PFS and OS to determine whether preoperative RDW could be an independent prognostic factor for mRCC. The results of univariate Cox regression analysis showed statistical differences between PFS and T-stage (HR: 1.525; 95% CI: 1.139–2.042;  $P = 0.005$ ), number of metastases (HR: 1.472; 95% CI: 1.102–1.966;  $P = 0.009$ ), Fuhrman grade (HR: 1.485; 95% CI: 1.110–1.998;  $P = 0.008$ ) and RDW (HR: 1.582; 95% CI: 1.173–2.14;  $P = 0.003$ ). We found significant inverse correlations between RDW and hemoglobin, hematocrit and red blood cell count using Spearman correlation test (Table 2). Therefore, these parameters were not included in the final multivariate analysis of PFS and OS. In multivariate Cox regression analysis, Fuhrman grade (HR, 1.356; 95% CI: 1.003–1.832;  $P = 0.048$ ) and RDW (HR: 1.505; 95% CI: 1.111–2.037;  $P = 0.008$ ) were independent risk factors for PFS in patients with mRCC who underwent cytoreductive nephrectomy (Table 3).

The second model of univariate Cox regression analysis revealed

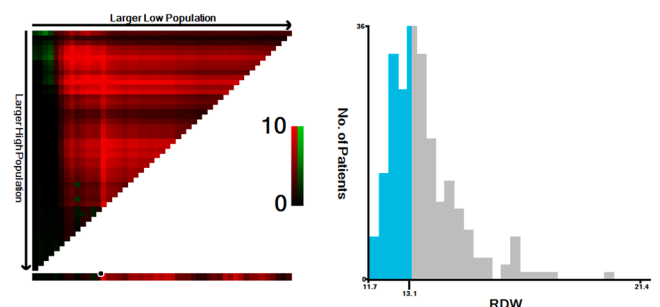
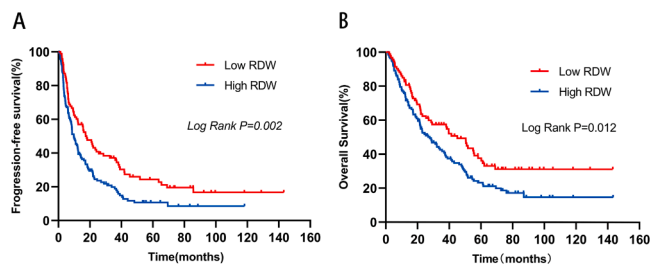


Fig. 1. Determination of cut-off values for RDW by X-tile software.

**Table 1**  
The clinical and pathological baseline characteristics of two groups.

Characteristics		Low RDW( $\leq 13.1, n = 93$ )		High RDW( $> 13.1, n = 137$ )		P value
		n	%	n	%	
Gender	Male	76	81.7%	105	76.6%	0.356
	Female	17	18.3%	32	23.4%	
Age, years	$\leq 55$	50	53.8%	61	44.5%	0.169
	$> 55$	43	46.2%	76	55.5%	
BMI, kg/m <sup>2</sup>	$\leq 24$	44	47.3%	71	51.8%	0.502
	$> 24$	49	52.7%	66	48.2%	
Tumor site	Left	44	47.3%	77	56.2%	0.185
	Right	49	52.7%	60	43.8%	
Histological subtype	Clear cell	84	90.3%	123	89.8%	0.893
	Non-clear cell	9	9.7%	14	10.2%	
Tumor size, cm	$\leq 7$	50	53.8%	67	48.9%	0.469
	$> 7$	43	46.2%	70	51.1%	
T-stage	T1+T2	60	65.2%	75	54.7%	0.114
	T3+T4	33	34.8%	62	45.3%	
N-stage	N0	62	66.7%	88	64.2%	0.704
	N1	31	33.3%	49	35.8%	
Number of metastases	$< 2$	53	57.0%	55	40.1%	0.012
	$\geq 2$	40	43.0%	82	59.9%	
Sarcomatoid differentiation	Absent	82	88.2%	123	89.8%	0.700
	Present	11	11.8%	14	10.2%	
Tumor necrosis	Absent	59	63.4%	70	51.1%	0.064
	Present	34	36.6%	67	48.9%	
Fuhrman grade	G1+G2	48	51.6%	59	43.1%	0.202
	G3+G4	45	48.4%	78	56.9%	
Targeted therapy	Absent	46	49.5%	58	42.3%	0.287
	Present	47	50.5%	79	57.7%	
Hemoglobin, g/dL		13.5	12.0–14.4	12.3	10.0–14.0	$< 0.001$
Hematocrit, %		40.7	38.4–42.0	37.9	35.8–39.9	$< 0.001$
Red blood cell count, $10^6/\text{mm}^3$		4.7	4.2–5.1	4.5	3.9–5.0	0.057
Follow-up, median (IQR)		31.6	15.7–61.1	22.9	12.3–49.9	0.055

Abbreviations: RDW, red blood cell distribution width; BMI, body mass index; IQR, interquartile range.



**Fig. 2.** Kaplan-Meier survival analysis for PFS and OS according to RDW level. (A) Kaplan-Meier curve for PFS. (B) Kaplan-Meier curve for OS.

**Table 2**  
The correlations between RDW and other peripheral blood parameters.

Variable	r	P value
Hemoglobin	-0.374	$< 0.001$
Hematocrit	-0.418	$< 0.001$
Red blood cell count	-0.228	$< 0.001$

statistical differences between OS and tumor size (HR: 1.530; 95% CI: 1.119–2.093;  $P = 0.008$ ), T-stage (HR: 1.371; 95% CI: 1.004–1.871;  $P = 0.047$ ), number of metastases (HR: 1.608; 95% CI: 1.172–2.207;  $P = 0.003$ ), Fuhrman grade (HR: 1.901; 95% CI: 1.383–2.613;  $P < 0.001$ ), targeted therapy (HR: 0.577; 95% CI: 0.423–0.788;  $P = 0.001$ ) and RDW (HR: 1.510; 95% CI: 1.091–2.092;  $P = 0.013$ ). The multivariate analysis using these variables showed that Fuhrman grade (HR: 1.679; 95% CI: 1.220–2.361;  $P = 0.002$ ), targeted therapy (HR: 0.548; 95% CI: 0.399–0.753;  $P < 0.001$ ), and RDW (HR: 1.626; 95% CI: 1.164–2.272;  $P = 0.004$ ) were independent risk factors for OS in patients with mRCC who underwent cytoreductive nephrectomy (Table 4).

## Discussion

In the past decade, advances in targeted therapy have dramatically changed the prognosis of patients with mRCC. In fact, many biological drugs such as sorafenib, sunitinib, axitinib, and everolimus are now available for use in the clinic [5,6]. However, intermediate-risk patients may still have a survival benefit from cytoreductive nephrectomy [17]. The IMDC and MSKCC prognostic models have been well established in predicting the prognosis of mRCC but have not been fully validated in this setting. Therefore, evaluation of prognostic factors of patients after cytoreductive nephrectomy need to be further studied. Inflammatory mediators are important components of the tumor microenvironment [18]. The systemic inflammatory response is closely related to the proliferation, progression, and metastasis of tumor cells [11]. Recently, various peripheral blood inflammatory markers have been used to predict the prognosis of patients with mRCC and have been shown to be independent factors affecting the prognosis of patients. In a retrospective study of 141 patients with mRCC, Huszno et al. also found that higher neutrophil-to-lymphocyte ratio (NLR) was associated with worse OS (HR: 2.1, 95% CI 1.23–3.59), but was not shown to be an independent prognostic factor for PFS. The authors also showed that platelet-to-lymphocyte ratio (PLR) was associated with worse OS (HR: 2.2, 95% CI 1.25–3.88) and PFS (HR: 2.25, 95% CI 1.48–3.43) [19]. Similarly, Nader Marta et al. retrospectively analyzed the data of 276 patients diagnosed with mRCC treated with pazopanib and sunitinib. The results of this study confirmed that high NLR ( $> 3.5$ ) and PLR ( $> 200$ ) were associated with inferior OS (median 9.6 months vs. 17.8 months,  $P < 0.001$ ; median 10.3 months vs. 17 months,  $P = 0.002$ , respectively) in patients [20].

RDW is a parameter of routine preoperative blood examination, which has the advantages of low detection cost and easy clinical access. Inflammation in the body can cause erythrocyte maturation disorders by interfering with the erythrocyte membrane, inducing abnormal RDW [10]. In addition, oxidative stress, which is usually increased in patients

**Table 3**  
Univariate and multivariate Cox regression analyses of clinical-pathological parameters for progression-free survival.

Parameter	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age			0.811			
≤55	1(Reference)					
>55	0.966	0.725–1.287				
Gender			0.152			
Male	1(Reference)					
Female	1.284	0.913–1.806				
BMI			0.561			
≤24	1(Reference)					
>24	0.918	0.688–1.225				
Tumor site			0.652			
Left	1(Reference)					
Right	1.068	0.801–1.424				
Histology subtype			0.109			
Clear cell	1(Reference)					
Non-clear cell	1.467	0.918–2.344				
Tumor size			0.050			
≤7	1(Reference)					
>7	1.334	1.000–1.779				
T-stage			0.005			0.140
≤T2	1(Reference)			1(Reference)		
>T2	1.525	1.139–2.042		1.273	0.924–1.753	
N-stage			0.073			
N0	1(Reference)					
N1	1.317	0.975–1.779				
Number of metastases			0.009			0.101
<2	1(Reference)			1(Reference)		
≥2	1.472	1.102–1.966		1.204	0.875–1.658	
Fuhrman Grade			0.008			0.048
G1+G2	1(Reference)			1(Reference)		
G3+G4	1.485	1.110–1.998		1.356	1.003–1.832	
Sarcomatoid differentiation			0.994			
Absent	1(Reference)					
Present	1.002	0.630–1.594				
Tumor necrosis			0.131			
Absent	1(Reference)					
Present	1.25	0.936–1.668				
Targeted therapy			0.102			
Absent	1(Reference)					
Present	0.787	0.590–1.049				
RDW			0.003			0.008
≤13.1	1(Reference)			1(Reference)		
>13.1	1.582	1.173–2.14		1.505	1.111–2.037	

Abbreviations: RDW, red blood cell distribution width; BMI, body mass index.

with tumors, can reduce red blood cell survival and increase RDW [21]. Recently, the prognostic significance of RDW in urological malignancies has attracted increased attention. In a retrospective study, Patel et al. evaluated 58 patients with metastatic penile cancer treated with chemotherapy, and found that the high RDW group (> 13.9%) had a worse OS than the low RDW group (< 13.9%) (median 15.0 months vs. 37.0 months,  $P = 0.025$ ) [22]. Yilmaz et al. revealed that high hemoglobin to RDW ratio (HRR) was significantly associated with better OS (HR: 0.201, 95% CI: 0.085–0.476,  $P < 0.001$ ) and better PFS (HR: 0.401, 95% CI: 0.206–0.780,  $P = 0.007$ ) in muscle-invasive bladder cancer [15].

In the present study, we retrospectively analyzed the clinicopathological data of 230 patients with mRCC and found that RDW was an independent risk factor for mRCC. The optimal cut-off value of RDW was 13.1%, and the results of survival analysis showed that patients with higher RDW levels had shorter OS and PFS than the patients with lower RDW levels. Aktepe et al. also demonstrated the predictive power of RDW in metastatic renal cancer receiving targeted therapy [23]. However, only 104 patients were included in their study, whereas our study included 230 patients. In addition, the cut-off value of RDW in their study was 15.4%, while our cut-off was 13.1% as determined by the X-tile software. These findings may be related to the measurement instrument and the sample size. In this study, we also found that the Fuhrman grade was independently associated with OS and PFS in mRCC,

which has been validated in previous studies [24].

However, this study has certain limitations. First, this was a retrospective study that included only Chinese patients and a small sample size, and thus was inevitably subject to selection bias. Therefore, our findings need to be verified by a prospective multicenter, large-sample study data. Second, we used the X-tile software method to determine the optimal cut-off value of RDW because there is currently no uniform method to define the cut-off RDW value. Finally, peripheral blood biomarkers are only complementary to traditional prognostic factors to predict the prognosis of mRCC patients and still cannot replace it.

## Conclusion

To the best of our knowledge, this is the first study to explore the role of preoperative RDW in predicting tumor prognosis in patients with mRCC who underwent cytoreductive nephrectomy. The present study demonstrated that higher RDW (> 13.1%) was significantly correlated with poorer OS and PFS in patients with mRCC. RDW, a common, inexpensive, and readily available preoperative blood parameter, can be used as a predictor of tumor prognosis in patients with mRCC in clinical practice.

**Table 4**  
Univariate and multivariate Cox regression analyses of clinical-pathological parameters for Overall survival.

Parameter	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age			0.829			
≤55	1(Reference)					
>55	1.035	0.759–1.411				
Gender			0.180			
Male	1(Reference)					
Female	1.283	0.891–1.848				
BMI			0.245			
≤24	1(Reference)					
>24	0.832	0.609–1.135				
Tumor site			0.689			
Left	1(Reference)					
Right	1.065	0.781–1.453				
Histology subtype			0.062			
Clear cell	1(Reference)					
Non-clear cell	1.603	0.977–2.629				
Tumor size			0.008			0.210
≤7	1(Reference)			1(Reference)		
>7	1.530	1.119–2.093		1.234	0.888–1.715	
T-stage			0.047			0.733
≤T2	1(Reference)			1(Reference)		
>T2	1.371	1.004–1.871		1.059	0.760–1.476	
N-stage			0.154			
N0	1(Reference)					
N1	1.265	0.916–1.747				
Number of metastases			0.003			0.078
<2	1(Reference)			1(Reference)		
≥2	1.608	1.172–2.207		1.348	0.967–1.881	
Fuhrman Grade			<0.001			0.002
G1+G2	1(Reference)			1(Reference)		
G3+G4	1.901	1.383–2.613		1.697	1.220–2.361	
Sarcomatoid differentiation			0.143			
Absent	1(Reference)					
Present	1.432	0.885–2.316				
Tumor necrosis			0.068			
Absent	1(Reference)					
Present	1.337	0.979–1.826				
Targeted therapy			0.001			<0.001
Absent	1(Reference)			1(Reference)		
Present	0.577	0.423–0.788		0.548	0.399–0.753	
RDW			0.013			0.004
≤13.1	1(Reference)			1(Reference)		
>13.1	1.510	1.091–2.092		1.626	1.164–2.272	

Abbreviations: RDW= red blood cell distribution width; BMI = body mass index.

#### Data availability

The data used to support the findings of this study are included within the article.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### CRediT authorship contribution statement

**Zongjie Wei:** Data curation, Formal analysis, Writing – original draft. **Fan Zhang:** Data curation, Formal analysis, Writing – original draft. **Xin Ma:** Data curation. **Weiyang He:** Writing – review & editing. **Xin Gou:** Conceptualization, Visualization. **Xu Zhang:** Conceptualization, Visualization. **Yongpeng Xie:** Conceptualization, Visualization, Writing – review & editing.

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