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Elevated red blood cell distribution width contributes to poor prognosis in patients undergoing resection for nonmetastatic rectal cancer

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Abstract

Several studies have reported that elevated red blood cell distribution width (RDW) was associated with the poor prognosis of different kinds of cancers. The aim of this study was to investigate the prognostic role of RDW in patients undergoing resection for nonmetastatic rectal cancer.

We retrospectively reviewed a database of 625 consecutive patients who underwent curative resection for nonmetastatic rectal cancer at our institution from January 2009 to December 2014. The cutoff value of RDW was calculated by receiver-operating characteristic curve.

The results demonstrated that patients in high RDW-cv group had a lower overall survival (OS) ($P = .018$) and disease-free survival ($P = .004$). We also observed that patients in high RDW-sd group were associated with significantly lower OS ($P = .033$), whereas the disease-free survival (DFS) was not significantly different ($P = .179$).

In multivariate analysis, we found elevated RDW-cv was associated poor DFS (hazard ratio [HR] = 1.56, $P = .010$) and RDW-sd can predict a worse OS (HR = 1.70, $P = .009$).

We confirmed that elevated RDW can be an independently prognostic factor in patients undergoing resection for nonmetastatic rectal cancer. So more intervention or surveillance might be paid to the patients with nonmetastatic rectal cancer and elevated RDW values in the future.

Abbreviations: CEA = carcinoembryonic antigen, CI = confidence intervals, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, RDW = red blood cell distribution width, ROC = receiver-operating characteristic, TNM = tumor node metastasis.

Keywords: nonmetastatic, prognosis, rectal cancer, red blood cell distribution width, resection

1. Introduction

Rectal cancer has a high incidence and death rate in China.[1] In the past decades, the treatment for rectal cancer has made great progress with the help of multidisciplinary cooperation.[2] The acceptance of total mesorectal excision in rectal surgery has greatly reduced the local recurrence after resection. However, even undergoing radical resection, a large number patients still have poor prognosis for the local recurrence or distal metastatic postoperatively.[3–5] Up to now, we still cannot accurately predict the prognosis of different patients. In oncology surgery, 5-year survival is a crucial parameter to evaluate prognosis because overwhelming majority recurrence or metastasis will happen in 5 years after surgery.[6,7] So it is important to find some parameters to help us assess the prognosis.

Traditionally, the treatment strategy and prognosis assessment of rectal cancer mainly base on the tumor node metastasis (TNM) stage. But this is limited and not enough. Sometime even early-stage patients can have a bad prognosis. And it is still controversial about the adjuvant therapy for stage II patients.[8] With the development of Precision Medicine, we need to reference more parameters to make individualized strategy. In recent years, more and more prognostic biomarkers have been reported in different cancers, including red blood cell distribution width (RDW).[9]

RDW is a hematological parameter, which is reported in blood routine examination including RDW-cv and RDW-sd.[10] It can reflex the heterogeneity of red blood cell,[10,11] and also has some associations with systemic inflammation.[10,12,13] What is more, in recent years, many studies have reported that RDW, including RDW-cv and RDW-sd, can predict the prognosis in different

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kinds of cancers, such as lung cancer, liver cancer, and gastric cancer.[9,14–16] Nevertheless, to our best knowledge, specific data about the prognostic role of RDW in rectal cancer are still rare. If this inexpensive and convenience parameter can be used in rectal cancer for prognosis, both doctors and patients can benefit from it. So we conduct this study to assess whether RDW can predict the prognosis in nonmetastatic rectal cancer within 5 years after surgery.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the patients with rectal cancer and undergoing radical surgery in the Department of Gastrointestinal surgery, West China Hospital, Sichuan University from January 2009 to December 2014. The inclusion criteria were: rectal cancer confirmed by historical biopsy; undergoing radical resection; checked blood test in 2 weeks before surgery and RDW can be got. The exclusion criteria were: received neoadjuvant therapy; distal metastasis; presence of infection; beyond 85 years' old. Ethical approval was not necessary because this study was a retrospective study.

We collected patients' sex, age, pretreatment carcinoembryonie antigen (CEA), tumor location, tumor size, differentiation, TNM stage, vascular invasion, perineural invasion, adjuvant therapy, RDW-cv, and RDW-sd. TNM stage was assessed according to the American Joint Committee on Cancer TNM staging standard, 7th edition.

2.2. Follow-up

Follow-up was performed every 3 months intervals for the first 2 years, every 6 months intervals in the next 3 years, and every 12 months intervals after 5 years after surgery. We set up the terminal time of follow-up as 5 years after surgery. The examinations included physical examination, blood test, CEA levels, computed tomography (CT) of chest, and CT or magnetic resonance imaging (MRI) of abdominal and pelvic (every 6 months within the first 2 years and every 12 months after 2 years after surgery) and colonoscopy (every 2 years). Local recurrence was defined as the recurrent disease in the pelvis or at the incision, whereas the distant recurrence was defined as the recurrence beyond the above parts. Both of them were confirmed by biopsy, CT, or MRI. Follow-up data of all enrolled patients were available.

2.3. Statistical analysis

The primary endpoint and the secondary endpoint of this study were OS and DFS in 5 years after surgery, respectively. OS was the time of surgery to the date of death from any causes or the date of follow-up, whereas DFS was calculated from the surgery to the recurrence or end of follow-up.

The optima cutoff value of RDW was calculated by ROC curve. The χ^2 test or Fisher exact test was used to analyze the association between clinicopathologic characteristics and RDW. The OS and DFS were analyzed and compared by using the Kaplan–Meier method and the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression. Data analyses were all carried out using SPSS software (version 22.0; SPSS Inc, Chicago, IL). A P value $<.05$ was recognized as statistically significant.

3. Results

3.1. Patient characteristics

A total of 625 nonmetastatic rectal cancer patients without neoadjuvant therapy and undergoing radical resection were enrolled in this study. The last follow-up time was August 15, 2017. The median follow-up time was 60 (range 3–60) months. The cutoff values for RDW-cv and RDW-sd were 14.1% and 48.2, respectively. According to the cutoff value, patients were divided into low group and high group.

In the groups divided by RDW-cv, we found significant difference in term of age ($P<.01$), CEA ($P=.008$), tumor size ($P=.032$), TNM stage ($P=.026$), and vascular invasion ($P=.027$).Similarly, between the groups based on RDW-sd, there existed significant difference in age ($P<.001$), CEA ($P=.007$), TNM stage ($P=.003$), and vascular invasion ($P=.854$). (Table 1).

3.2. Survival outcomes

The results demonstrated that patients in high RDW-cv group had a lower overall survival (OS) ($P=.018$) and disease-free survival (DFS) ($P=.004$). (Fig. 1) We also observed that patients in high RDW-sd group were associated with significantly lower OS (P=0.033) while the DFS was not significantly different ($P=.179$) (Fig. 2).

On multivariate analysis, preoperative RDW-cv level was an independent prognostic factor of poor DFS (hazard ratio [HR]= 1.56, $P=.010$) and RDW-sd was associated with poor OS (HR= 1.70, $P=.009$) (Tables 2 and 3).

4. Discussion

RDW has obtained increasing attention in recent years, particularly in tumor field.[17–20] In our study, we evaluated the prognostic role of RDW in patients undergoing curative resection for nonmetastic rectal cancer. Based on the multivariate analysis, we found that elevated RDW-cv is associated with poor DFS (HR=1.56, $P=.010$) and elevated RDW-sd can predict poor OS (HR=1.70, $P=.009$).

RDW can indicate the variability of erythrocytes size In the past; the major role of RDW was to diagnose anemia.[10] Besides, RDW is also associated with several diseases, such as heart disease, pulmonary disease, and even tramua.[11,21] What's more, RDW is also related with some inflammatory disease including pancreatitis, hepatitis, and regarded as an indicator of the overall inflammatory, although the potential mechanism has not been demonstrated clearly.[22,23]

Several studies have demonstrated that RDW was related to poor prognosis of different cancer.[9] Most articles explained it with inflammation response in tumorgenesis. The relationship between tumor and inflammation was firstly reported in 1863 by Virchow.[24] After that, several studies have demonstrated that inflammation in microenvironment can promote the development of cancer.[25,26] Colorectal cancer is a disease, which has close association with inflammation.[25] Colorectal cancer can develop from inflammatory bowel diseases and inflammation polys.[27–29] So inflammation might play a crucial role in the development of colorectal cancer. Besides, there also are some articles indicated that inflammation can play dual role in tumorgenesis. That's to say sometimes inflammation can fight with cancer. But we think in the whole process of tumor development, the effect of promotion might be the leadership.

Table 1

Patient clinicopathological characteristics.

Characteristic	RDW-cv (n = 625)			P	RDW-sd (n = 625)			P
	Overall	Low (<14.1%)	High (≥14.1%)		Overall	Low (<48.2)	High (≥48.2)	
Sex				.194				.426
Female	241	131	110		241	179	62	
Male	384	229	155		384	274	110	
Age, y				**<.001**				**<.001**
<65	389	251	138		389	304	85	
≥65	236	109	127		236	149	87	
CEA, ng/mL				**.008**				**.007**
<5	417	254	163		417	315	102	
≥5	188	93	95		188	122	66	
Tumor location				.598				.718
Low	289	161	128		289	214	75	
Middle	253	152	101		253	180	73	
High	83	47	36		83	59	24	
Tumor size				**.032**				.249
<5	478	287	191		478	352	126	
≥5	144	72	72		144	99	45	
Differentiation				0.310				
G1 + G2	445	262	183		445	323	122	.927
G3 + G4	180	98	82		180	130	50	
TNM				**.026**				**.003**
I	180	117	63		180	140	40	
II	197	101	96		197	125	72	
III	248	142	106		248	188	60	
Vascular invasion								
No	580	327	253	**.027**	580	412	168	**.006**
Yes	45	33	12		45	41	4	
Perineural invasion								
No	601	343	258	.181	601	436	165	.854
Yes	24	17	7		24	17	7	
Adjuvant treatment								
No	218	115	103	.073	218	151	67	.188
Yes	407	245	162		407	302	105	

CEA = carcinoembryonie antigen, RDW = red blood cell distribution width, TNM = tumor node metastasis. Bold values mean $P < .05$.

In addition, many other hematological parameters have been reported in colorectal cancer for the prognosis role, including neutrophil-lymphcyte ratio,[30] lymphcyte-monocyte ratio,[31] C-reactive protein,[32] interleukin-6,[33] albumin,[34,35] platelet, and hemoglobin.[36] These parameters are also closely related with inflammatory response and anemia.

We have to mention that RDW is also a marker of anemia.[37] In fact, anemia is a common symptom in patients with colorectal cancer[38,39] and some articles demonstrated that anemia could increase postoperative morbi-mortality.[39] Besides, several studies also indicated that anemia can predict the poor prognosis of colorectal cancer.[40] And anemia can also be caused by a

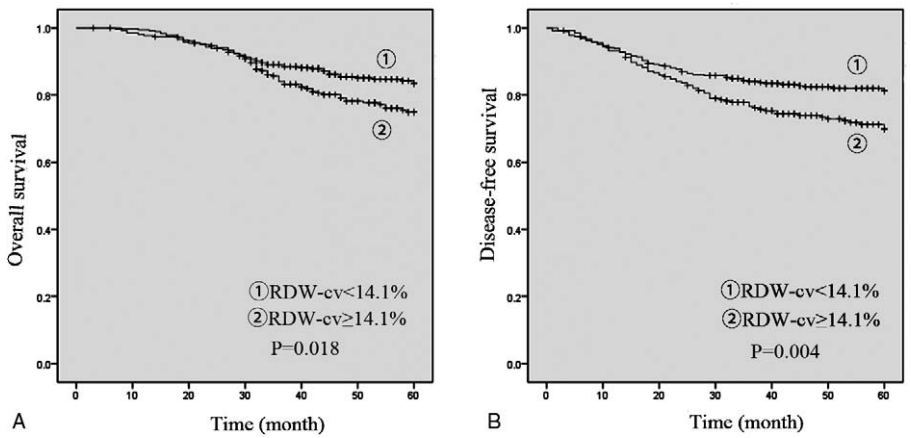

Figure 1. Preoperative RDW-cv for OS (A) and DFS (B). DFS = disease free survival, OS = overall survival, RDW = red blood cell distribution width.

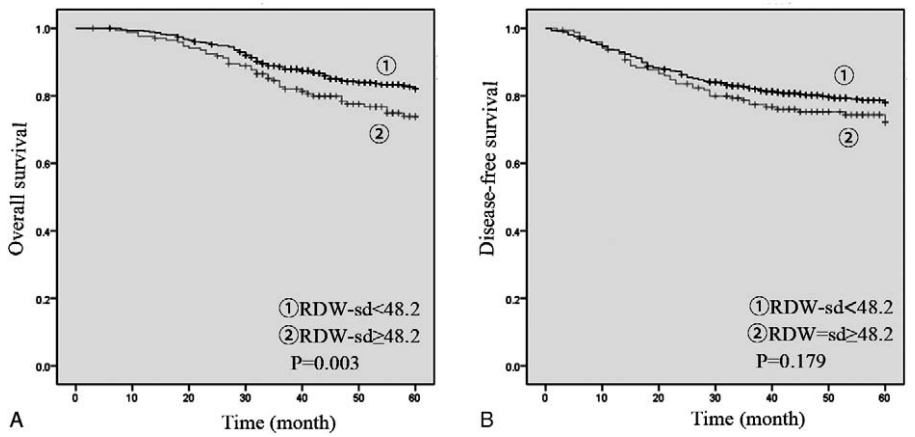

Figure 2. Preoperative RDW-sd for OS (A) and DFS (B). DFS = disease free survival, OS = overall survival, RDW = red blood cell distribution width.

systemic inflammatory response to the tumor in colorectal cancer.[41] So anemia is also related with the survival outcomes of colorectal cancer.

Above all, we have enough reason to believe that RDW is associated with the prognosis of nonmetastatic rectal cancer.

One previous study[42]reported that elevated RDW was associated with poor prognosis in patients with colorectal cancer, especially II stage disease. However, it just included 90 patients and did not present the data of rectal cancer or colon cancer independently. Besides, one previous meta-analysis[9] demonstrated that RDW might be a potential prognostic marker in patients with cancer. Nonetheless, that article included different types of tumors and number of studies dealing with each type of cancers was ≤5. In addition, there was no colorectal cancer in that article and the cutoff value of RDW was not unified. Our study suggested that RDW was associated with both OS and DFS in rectal cancer patients. Although we did not invest the specific molecular mechnishm, we thought inflammation factors could have an influence on rectal cancer survival. This is the first large-scale cohort study demonstrating that there exists association between RDW and either OS or DFS in rectal cancer. Unfortunately, this study was a retrospective study. Still, a prospective cohort study is needed to evaluate the association between RDW and OS and DFS in rectal cancer patients.

In conclusion, this study represents the first analysis of the value of preoperative RDW level in patients with nonmetastatic

Table 2

Multivariate analyses of RDW for OS in patients with nonmetastatic rectal cancer.

	RDW-cv		RDW-sd	
Characteristic	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Tumor location, cm				
Low	1 (Reference)		1 (Reference)	
Middle	0.687 (0.461–1.023)	.064	0.681 (0.458–1.013)	.058
High	0.397 (0.180–0.872)	**.021**	0.372 (0.169–0.818)	**.014**
Tumor size, cm				
<5	1 (Reference)		1 (Reference)	
≥5	1.086 (0.728–1.622)	.685	1.092 (0.732–1.629)	.666
Differentiation				
G1 + G2	1 (Reference)		1 (Reference)	
G3 + G4	1.798 (1.222–2.647)	**.003**	1.826 (1.241–2.687)	**.002**
TNM				
I	1 (Reference)		1 (Reference)	
II	2.867 (1.288–6.379)	**.010**	2.778 (1.247–6.189)	**.012**
III	6.252 (2.946–13.268)	**<.001**	6.341 (2.990–13.445)	**<.001**
Vascular invasion				
No	1 (Reference)		1 (Reference)	
Yes	1.235 (0.714–2.135)	.451	1.316 (0.757–0.288)	.331
Perineural invasion				
No	1 (Reference)		1 (Reference)	
Yes	2.127 (1.134–3.989)	**.019**	2.143 (1.145–4.008)	**.017**
RDW				
Low group	1 (Reference)		1 (Reference)	
High group	1.427 (0.983–2.072)	.062	1.701 (1.142–2.532)	**.009**

CI = confidence interval, HR = hazard ratio, RDW = red blood cell distribution width, TNM = tumor node metastasis. Bold values mean $P < .05$.

Table 3

Multivariate analyses of RDW for DFS in patients with nonmetastatic rectal cancer.

	RDW-cv		RDW-sd	
Characteristic	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Tumor location, cm				
Low	1 (Reference)		1 (Reference)	
Middle	0.748 (0.522–1.071)	.113	0.734 (0.513–1.051)	.091
High	0.408 (0.202–0.822)	**.012**	0.387 (0.192–0.781)	**.008**
Tumor size, cm				
<5	1 (Reference)		1 (Reference)	
≥5	1.285 (0.895–1.844)	.175	1.302 (0.908–1.868)	.152
Differentiation				
G1 + G2	1 (Reference)		1 (Reference)	
G3 + G4	1.757 (1.236–2.498)	**.002**	1.770 (1.244–2.519)	**.002**
TNM				
I	1 (Reference)		1 (Reference)	
II	2.515 (1.297–4.874)	**.006**	2.547 (1.313–4.940)	**.006**
III	4.435 (2.363–8.322)	**<.001**	4.575 (2.439–8.579)	**<.001**
Vascular invasion				
No	1 (Reference)		1 (Reference)	
Yes	1.688 (1.044–2.731)	**.033**	1.656 (1.018–2.695)	**.042**
Perineural invasion				
No	1 (Reference)		1 (Reference)	
Yes	2.627 (1.468–4.704)	**.001**	2.533 (1.412–4.542)	**.002**
RDW				
Low group	1 (Reference)		1 (Reference)	
High group	1.546 (1.113–2.196)	**.010**	1.381 (0.955–1.998)	.086

CI = confidence interval, HR = hazard ratio, RDW = red blood cell distribution width, TNM = tumor node metastasis. Bold values mean $P < .05$.

rectal cancer to the best of our knowledge. The analysis of our data demonstrates that preoperative RDW levels correlate with leading prognostic factors in patients undergoing surgery for rectal cancer. The predicting role of RDW is confirmed in multivariate analysis. So it seems reasonable to suggest that evaluation of the preoperative RDW level is helpful for predicting the prognosis of patients with nonmetastatic rectal cancer.

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