

Clinical Utility of Red Blood Cell Distribution Width for the Diagnosis and Prognosis of Cervical Cancer

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Background: The width of red blood cell distribution (RDW) is correlated with some diseases, but its clinical value and prognostic role in cervical cancer is unclear.

Methods: We used receiver operating characteristic curves to evaluate the diagnostic ability of RDW and other clinical parameters in cervical cancer based on a case-control design. Using retrospective data, we explored the correlation of RDW with overall (OS) and progression-free (PFS) survival using Kaplan-Meier analysis and univariate and multivariate Cox regression with the hazard ratio (HR) and 95% confidence interval (CI). A restricted cubic plot was used to evaluate the nonlinear association between RDW and prognosis risk.

Results: RDW was significantly higher in cases than in controls (14.6 ± 1.7 vs 12.5 ± 1.8 , $P < 0.001$). It showed high diagnostic accuracy for cervical cancer, with a sensitivity of 79.3%, specificity of 65.6%, and area under the curve of 0.802 (95% CI, 0.775–0.827) with a cutoff value of 13.88. There was a significant positive correlation between RDW and C-reactive protein ($r = 0.434$, $P = 0.023$). Multivariate Cox regression indicated that it was independently associated with a poorer PFS (HR, 2.05; 95% CI, 1.25–3.18, $P < 0.001$) and OS (HR, 2.73; 95% CI, 1.61–4.64, $P < 0.001$). RDW > 14.66 showed a nonlinear increased risk for a poor PFS and OS.

Conclusion: RDW is an easy, quick, and inexpensive tool for the early detection and risk management of cervical cancer. A greater RDW is associated with a poor prognosis in cervical cancer.

Keywords: cervical carcinoma, red blood cell distribution width, diagnostic, prognosis

Introduction

Cervical cancer is a common malignancy in women worldwide, especially in low- and middle-income countries.¹ In 2012, cervical cancer was the 11th most common female malignancy and the ninth most common cause of cancer mortality in high-income countries, while in low- and middle-income countries it was the second most common type of cancer and third most common cause of cancer death.² Given the prevalence of cervical cancer, early detection and diagnosis are important and patients with precancerous lesions in the early screening stage are not diagnosed accurately and treated.³ Current molecular markers for diagnosing cervical cancer are imperfect and better molecular markers are needed to identify the lesion level for early evaluation of the prognosis and intervention.⁴

The inflammatory response plays an important role in tumor occurrence and development.⁵ Some inflammatory indicators are used as independent prognostic factors for patients with colorectal and lung cancer.^{6,7} One inflammatory marker is the width of red blood cell distribution (RDW),^{8,9} which can be used to assess the inflammatory response in diseases such as atherosclerosis and prostate cancer.^{10–12} However, its specific role in the diagnosis and management of tumors remains unclear, especially given the cross-effects of tumor radiotherapy and immunotherapy. Therefore, this

study analyzed the changes in RDW in normal women and patients with cervical cancer, and explored its significance in the prognosis and efficacy of cervical cancer patients receiving radical radiotherapy.

Methods

Study Population

We respectively collected clinical data for 460 patients with unresectable cervical cancer on concurrent chemoradiotherapy. The included patients had cervical cancer confirmed by a cervical biopsy and pathological examination and complete baseline data at diagnosis, including chest and abdominal computed tomography (CT), pelvic magnetic resonance imaging, and gynecological and lymph node ultrasound for disease staging and routine blood results. Patients were excluded if they had a clinical infection, blood disease, hemoglobin below 80 g/L, history of blood transfusion, severe autoimmune disease, and other malignancies in the past 3 months.

The healthy control population was an unmatched population without cervical cancer seen at the health examination center during the same period. Potential controls with a history of blood transfusion, various infections, malignancy, and other systemic inflammatory diseases were excluded. This study was approved by the Xiangya Hospital Central South University and was conducted in accordance with the Declaration of Helsinki. Study subjects provided informed consent before participating.

Data Collection

Routine blood parameters were assessed before treatment using 5 mL of venous blood collected on an empty stomach in the morning in tubes containing ethylenediamine tetraacetic acid-K2. RDW, the white blood cell count (WBC), platelet count, lymphocyte count, red blood cell count (RBC), and hemoglobin were determined from whole blood using bioelectrical impedance analysis with an automatic blood cell analyzer (SN-900; Sysmex, Japan). High-density lipoprotein (HDL-C), total cholesterol, albumin, prealbumin, blood glucose, and C-reactive protein (CRP) were determined using a Siemens ADVIA 2400 automatic biochemical analyzer. The tumor markers neuron-specific enolase, squamous cell carcinoma antigen, and carcinoembryonic antigen (CEA) were detected with an automatic serum electrochemiluminescence analyzer (E601, Roche). For cervical cancer patients, we also collected their age, histology (squamous or non-squamous), differentiation (poor, middle, or high), FIGO stage (I to III),¹³ and lymph node metastasis (Yes or No).

Follow-Up Data

To assess the association between RDW and the prognosis of cervical cancer patients, we confirmed follow-up outcomes from medical records and by contacting the patients. The follow-up period was from June 2011 to December 2019. The primary outcomes were progression-free (PFS) and overall (OS) survival. OS was defined as the time from treatment to death and PFS was defined to as the time from treatment to local recurrence, distant metastasis, or death.^{14,15}

Statistical Analysis

Normally distributed continuous variables are expressed as the mean \pm standard deviation; the means were compared between the case group and controls using independent *t*-tests. Non-normally distributed continuous variables are expressed as the median and quartile and were compared using the Mann–Whitney *U*-test. Categorical variables are expressed as a number and percentage and the chi-square test was used to compare proportions in the two groups. Receiver operating characteristic curves (ROC) were plotted to evaluate the clinical value of RDW and other parameters for distinguishing cervical cancer and the area under the curve (AUC) was calculated; AUC>0.5 with *P*<0.05 indicated significant diagnostic ability. The Spearman and Pearson correlation coefficients were calculated to evaluate the associations between RDW and clinical parameters.

To explore the role of RDW in the prognosis of cervical cancer, we divided the cervical cancer patients into two groups according to the mean RDW (RDW>14.66 and RDW \leq 14.66) and compared clinical parameters between the groups. Kaplan–Meier analysis was used to compare the PFS and OS curves of the groups. Uni- and multivariate Cox regressions were performed to explore the correlations of RDW with PFS and OS in cervical cancer patients and the

hazard ratio (HRs) and 95% confidence intervals (CIs) were calculated. All analyses were done using SPSS 23.0. Finally, we plotted the restricted cubic spline to assess the linear or nonlinear associations between RDW and PFS and OS. This plot was fitted using Stata 14.0. $P < 0.05$ was considered significant.

Results

Diagnostic Accuracy of RDW for Cervical Cancer

We first compared the general characteristics of the case ($n=460$) and control ($n=480$) groups. Table 1 shows the general characteristics of both groups. The mean RDW was significantly higher in cases (14.6 ± 1.7 vs 12.5 ± 1.8 , $P < 0.001$). There were no significant differences in mean age ($P=0.529$), HDL-C ($P=0.263$), TC ($P=0.264$), glucose ($P=0.564$), platelets ($P=0.487$), WBC ($P=0.615$), or lymphocytes ($P=0.237$) between the groups. The case group tended to have lower albumin, prealbumin, hemoglobin, neuron specific enolase, and squamous cell carcinoma antigen levels, and RBC (all $P < 0.001$) than controls. The CRP and CEA levels were higher in the case group (both $P < 0.001$).

Next, we evaluated the diagnostic accuracy of RDW and other clinical parameters for cervical cancer. RDW had high diagnostic accuracy for cervical cancer. The sensitivity was 79.3%, specificity was 65.6%, and AUC was 0.802 (95% CI, 0.775–0.827, Figure 1) with a cutoff value of 13.88. The albumin (AUC 0.788; 95% CI, 0.761–0.814), squamous cell carcinoma antigen (AUC 0.785; 95% CI, 0.625–0.851), hemoglobin (AUC 0.771; 95% CI, 0.742–0.797), prealbumin (AUC 0.671; 95% CI, 0.640–0.701), neuron specific enolase (AUC 0.661; 95% CI, 0.630–0.691), CRP (AUC 0.621; 95% CI, 0.589–0.652), and CEA (AUC 0.635; 95% CI, 0.604–0.666) showed moderate diagnostic accuracy for cervical cancer. Table 2 shows the results for other nonsignificant parameters.

Correlation Between RDW and Clinical Parameters

Table 3 shows the correlation coefficients for RDW with other parameters. There were significant positive correlations between RDW and CRP ($r=0.434$, $P=0.023$) and WBC ($r=0.310$, $P=0.047$), while RDW was not correlated with other parameters (all $P > 0.05$).

Association Between RDW and the Prognosis of Cervical Cancer

The prognosis analysis included 440 cervical cancer patients on radical radiotherapy. These were divided into high- and low-RDW groups according to the mean value of RDW (14.66). Compared to the low-RDW group, the high-RDW group tended to have poor differentiation (46.2% vs 31.6%, $P=0.002$) and lymph node metastasis (29.7% vs 16.2%, $P=0.001$).

Table 1 Comparison of General Characteristic Between Control Group and Case Group

Parameters	Control	Case	t	P
Age, year	49.4±9.6	49.8±10.0	-0.630	0.529
HDL-C, mmol/L	1.47±0.49	1.44±0.52	1.120	0.263
TC, mmol/L	4.8±0.8	4.7±0.8	1.117	0.264
Albumin, g/L	48.2±5.1	42.1±5.1	17.434	<0.001
Prealbumin, g/L	258.7±44.6	230.4±45.2	9.662	<0.001
Glucose, mmol/L	4.61.4±	4.5±1.4	0.577	0.564
C-reactive, mg/L	2.1±1.2	2.6±1.1	-6.617	<0.001
Red blood cell, $10^{12}/L$	5.4±1.2	4.1±1.2	17.268	<0.001
Platelet, $10^9/L$	215.0±13.1	215.6±13.9	-0.696	0.487
White blood cell, $10^9/L$	5.7±1.8	5.7±1.8	-0.504	0.615
Lymphocyte, $10^9/L$	1.6±0.5	1.6±0.6	1.182	0.237
Red cell distribution width, %	12.5±1.8	14.6±1.7	-18.506	<0.001
Hemoglobin, g/L	134.4±8.7	124.2±10.3	2.343	0.019
Neuron Specific Enolase, ng/mL	4.4±1.4	3.7±1.4	16.360	<0.001
Squamous cell carcinoma antigen, ng/mL	1.8±0.5	1.1±0.5	8.944	<0.001
CEA, ng/mL	2.5±0.6	2.8±0.6	-7.611	<0.001

Note: Bold text: significant P value.

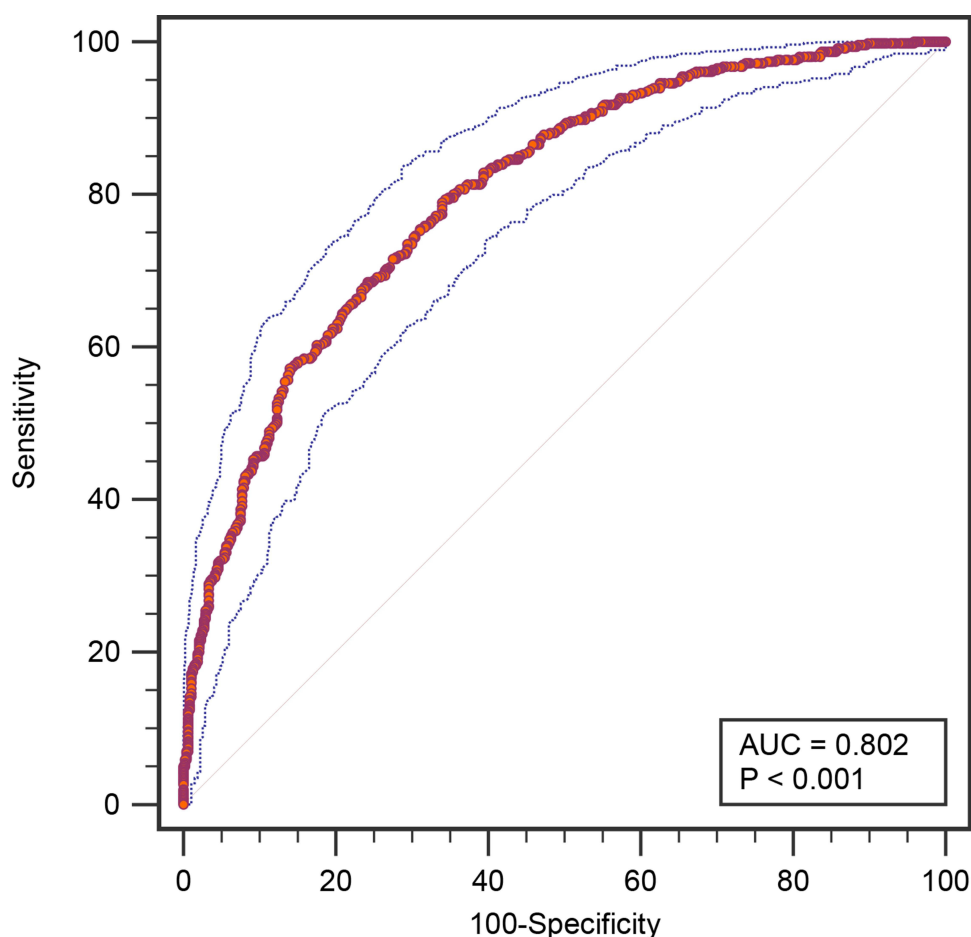


Figure 1 Receiver operating characteristic curve of RDW for diagnosing cervical cancer (Red dotted line: fitted curve; Blue dotted line: upper and lower range of 95% confidence interval of fitted curve. Red solid line: reference line).

There were no differences in mean age ($P=0.310$), histology type ratio ($P=0.372$), or FIGO stage ratio ($P=0.285$) (Table 4). The Kaplan–Meier analysis indicated that patients with $RDW > 14.66$ had a poorer PFS ($P < 0.001$, Figure 2A) and OS ($P < 0.001$, Figure 2B) than those with $RDW \leq 14.66$.

We assessed whether RDW is an independent predictor of PFS (Table 5) and OS (Table 6) in cervical cancer. For PFS, both univariate (HR, 2.16; 95% CI, 1.45–3.21, $P < 0.001$) and multivariate (HR, 2.05; 95% CI, 1.25–3.18, $P < 0.001$) Cox regression indicated that RDW was independently associated with a poorer PFS. Lymph node metastasis (HR, 1.27; 95% CI, 1.09–1.86, $P < 0.023$), FIGO stage (HR, 1.47; 95% CI, 1.19–2.89, $P = 0.005$), and WBC (HR, 2.16; 95% CI, 1.45–3.21, $P < 0.001$) were also associated with PFS. For OS, the univariate (HR, 2.99; 95% CI, 1.78–5.03, $P < 0.001$) and multivariate (HR, 2.73; 95% CI, 1.61–4.64, $P < 0.001$) Cox regression also suggested that RDW was an independent predictor of OS, as were lymph node metastasis (HR, 1.48; 95% CI, 1.01–2.69, $P = 0.008$) and CRP (HR, 1.19; 95% CI, 1.10–1.69, $P = 0.024$), while the differentiation type was negatively associated with OS (HR, 0.36; 95% CI, 0.17–0.65). The restricted cubic spline plot indicated that patients with $RDW > 14.66$ had a nonlinear increased risk for a poor PFS compared to the threshold value of 14.66 ($P < 0.001$, Figure 3A), and patients with $RDW < 14.66$ had reduced risk for a poor OS, while patients with $RDW > 14.66$ had an increased risk ($P < 0.001$, Figure 3B).

Discussion

This study found that RDW has relatively high diagnostic ability for cervical cancer, with an AUC of 0.802. There was a positive correlation between RDW and CRP. The survival data showed that a high RDW was associated with a poor

Table 2 Clinical Utility of RDW in the Diagnosis of Cervical Carcinoma

Parameters	AUC	SE	P	95% CI
Age, year	0.504	0.019	0.828	0.467–0.541
HDL-C, mmol/L	0.479	0.019	0.270	0.442–0.516
TC, mmol/L	0.475	0.019	0.185	0.438–0.512
Albumin, g/L	0.788	0.015	0.000	0.761–0.814
Prealbumin, g/L	0.671	0.017	0.000	0.640–0.701
Glucose, mmol/L	0.506	0.019	0.752	0.474–0.538
C-reactive, mg/L	0.621	0.018	0.000	0.589–0.652
Red blood cell, $10^{12}/L$	0.783	0.015	0.000	0.755–0.809
Platelet, $10^9/L$	0.512	0.019	0.535	0.479–0.544
White blood cell, $10^9/L$	0.511	0.019	0.543	0.479–0.544
Lymphocyte, $10^9/L$	0.525	0.019	0.191	0.492–0.557
Red cell distribution width, %	0.802	0.014	0.000	0.775–0.827
Hemoglobin, g/L	0.771	0.015	0.008	0.742–0.797
Neuron Specific Enolase, ng/mL	0.661	0.018	0.000	0.630–0.691
Squamous cell carcinoma antigen, ng/mL	0.785	0.013	0.000	0.625–0.851
CEA, ng/mL	0.635	0.018	0.000	0.604–0.666

Note: Bold text: significant P value.

Table 3 Correlation Analysis Among RDW and Other Parameters

Parameters	r	P
Age, year	−0.030	0.536
HDL-C, mmol/L	0.025	0.595
TC, mmol/L	0.079	0.097
Albumin, g/L	0.014	0.770
Prealbumin, g/L	0.055	0.253
Glucose, mmol/L	−0.054	0.262
C-reactive, mg/L	0.434	0.023
Red blood cell, $10^{12}/L$	0.035	0.470
Platelet, $10^9/L$	0.028	0.553
White blood cell, $10^9/L$	0.310	0.047
Lymphocyte, $10^9/L$	0.017	0.717
Hemoglobin, g/L	−0.067	0.161
Neuron Specific Enolase, ng/mL	0.002	0.973
Squamous cell carcinoma antigen, ng/mL	−0.066	0.168
CEA, ng/mL	−0.013	0.792

Note: Bold text: significant P value.

PFS and OS and was an independent predictor of both. There was a nonlinear association between RDW and increased risk for a poor prognosis. Our results provide new insight for managing cervical cancer.

There are various methods for diagnosing cervical cancer, including serum tumor markers, which are objective, handy, and noninvasive. Serum cancer antigen (CA) 125, p53, p16/Ki-67, and other tumor markers are important for early cervical cancer screening, diagnosis, and prognosis. While CA125 and p53 have high sensitivity, their low specificity and high misdiagnosis rate necessitate combining them with other examinations or more tumor markers for diagnosis.¹⁶ The sensitivity and specificity of P16/KI-67 are higher than those of HR-HPV DNA, so p16/KI-67 improves the screening of precancerous lesions.¹⁷ The sensitivity of CA19-9 alone in the diagnosis of cervical cancer was 60%, lower than that of combined detection (86.7%) with CEA, squamous cell carcinoma antigen, and CA125.¹⁸ The sensitivity and specificity of CYFRA21-1 in the diagnosis of cervical cancer were 87.14% and 88.33%, respectively,

Table 4 Association Between RDW and Clinical Characteristics in Patients with Cervical Carcinoma

Parameters	RDW>14.66	RDW≤14.66	χ^2	P
Age			1.031	0.310
<45	28(13.2%)	38(16.7%)		
≥45	184(86.8%)	190(83.3%)		
Histology			0.796	0.372
Squamous	14(6.1%)	9(4.2%)		
Non-squamous	214(93.9%)	203(95.8%)		
Differentiation			9.941	0.002
Poor	98(46.2%)	72(31.6%)		
Middle/high	114(53.8%)	156(68.4%)		
FIGO stage			2.513	0.285
I	13(5.7%)	17(8.0%)		
II	204(89.5%)	179(84.4%)		
III	11(4.8%)	16(7.5%)		
Lymph node metastasis			11.381	0.001
Yes	63(29.7%)	37(16.2%)		
No	149(70.3%)	191(83.8%)		

Note: Bold text: significant P value.

the highest diagnostic accuracy among single biomarkers.¹⁹ Our results indicate that RDW has an intermediate ability to diagnose cervical cancer. Combined application is the best way to achieve the highest sensitivity and specificity.

Some studies have assessed the diagnostic ability of RDW in other tumors. A study of 633 colorectal cancers and 1050 controls reported that using RDW to diagnose colorectal cancer had a sensitivity of 53.1% and specificity of 77.7%.²⁰ Han et al reported that the sensitivity was 50.3% and specificity was 63.7% in esophageal cancer.²¹ The diagnostic value of RDW is moderate in other cancers, while our results indicate that RDW has high diagnostic ability in cervical cancer. Continuous infection with high-risk human papillomavirus is the main cause of cervical cancer. Currently, the main clinical screening method for cervical cancer is cervical fluid-based cytology combined with HPV detection.²² However, cytological testing is subjective and the probability of a missed diagnosis is high.²³ The specificity of HPV testing is lower and there is a possibility of overtreatment.²⁴ New molecular biomarkers are not available for routine clinical practice due to high costs.²⁵ As a routine hematology parameter, RDW is an easy, quick, and low-cost biomarker for preliminary screening.

Previous studies have suggested that RDW is an independent prognostic factor in various tumors. Koma et al reported that an elevated RDW was associated with poor survival in lung cancer.²⁶ Ge et al found that an elevated preoperative RDW ($\geq 15\%$) at diagnosis may independently predict poorer OS in patients with oral squamous cell carcinoma.²⁷ Yao

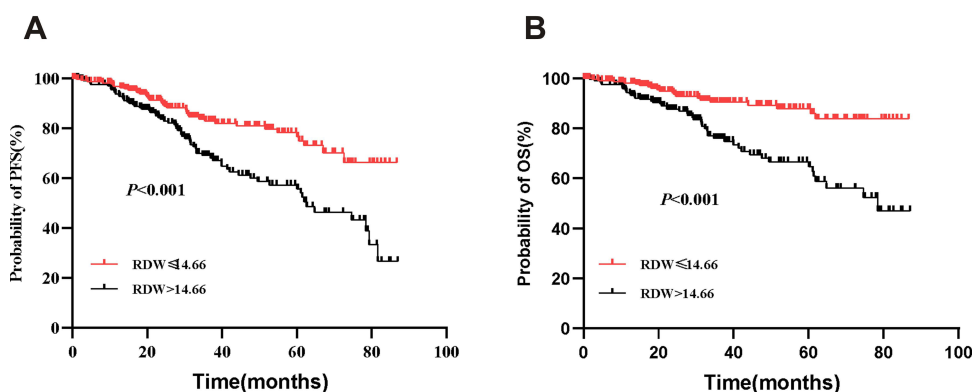
**Figure 2** Association RDW and prognosis of cervical cancer; (A) PFS, (B) OS.

Table 5 Univariate and Multivariate Cox Regression of RDW on Progression-Free Survival

Parameters	HR	95% CI		P	HR	95% CI		P
PFS								
RDW	2.16	1.45	3.21	<0.001	2.05	1.25	3.18	<0.001
Lymph_node_metastasis	1.32	1.17	2.02	0.011	1.27	1.09	1.86	0.023
Histology	2.55	0.81	8.06	0.110				
Stage	1.53	1.23	3.04	0.002	1.47	1.19	2.89	0.005
Differentiation	1.05	0.70	1.57	0.805				
Age	1.16	0.69	1.96	0.570				
HDL-C	0.91	0.49	1.66	0.747				
TC	0.99	0.40	2.47	0.988				
Albumin	0.66	0.22	1.96	0.450				
Prealbumin	0.67	0.34	1.33	0.255				
Glucose	0.64	0.39	1.03	0.065				
C-reactive	1.30	1.04	2.00	0.033	1.07	1.01	1.69	0.041
Red blood cell	0.76	0.45	1.28	0.306				
Platelet	0.14	0.02	1.19	0.072				
White blood cell	1.09	0.72	1.66	0.123				
Lymphocyte	0.83	0.46	1.51	0.550				
Hemoglobin	0.50	0.11	2.40	0.388				
Neuron Specific Enolase	1.01	0.68	1.49	0.972				
Squamous cell carcinoma antigen	1.09	0.63	1.87	0.763				
CEA	1.08	0.51	2.30	0.843				

Table 6 Univariate and Multivariate Cox Regression of RDW on Overall Survival

Parameters	HR	95% CI		P	HR	95% CI		P
RDW	2.99	1.78	5.03	<0.001	2.73	1.61	4.64	<0.001
Lymph_node_metastasis	2.01	1.24	3.26	0.005	1.48	1.01	2.69	0.008
Histology	1.60	0.50	5.10	0.425				
Stage	1.06	0.42	2.65	0.903				
Differentiation	0.37	0.15	0.80	<0.001	0.36	0.17	0.65	0.014
Age	0.93	0.46	1.88	0.841				
HDL-C	1.33	0.60	2.93	0.480				
TC	0.77	0.25	2.32	0.639				
Albumin	0.41	0.11	1.53	0.184				
Prealbumin	0.66	0.29	1.53	0.337				
Glucose	0.71	0.39	1.29	0.265				
C-reactive protein	1.22	1.12	2.07	0.003	1.19	1.10	1.69	0.024
Red blood cell	0.75	0.40	1.43	0.387				
Platelet	0.33	0.02	4.49	0.405				
White blood cell	1.21	0.71	2.07	0.479				
Lymphocyte	1.01	0.48	2.13	0.978				
Hemoglobin	0.39	0.06	2.68	0.340				
Neuron Specific Enolase	1.13	0.69	1.87	0.628				
Squamous cell carcinoma antigen	0.91	0.47	1.75	0.776				
CEA	0.97	0.39	2.44	0.950				

et al reported that high pretreatment RDW levels in breast cancer patients were associated with a poor OS and disease-free survival.²⁸ Other studies have examined lung, bladder, endometrial, ovarian, and thyroid cancers.^{29–33} These results combined with ours indicate that RDW may be a universal factor in tumors. The mechanism may be as follows. RDW is

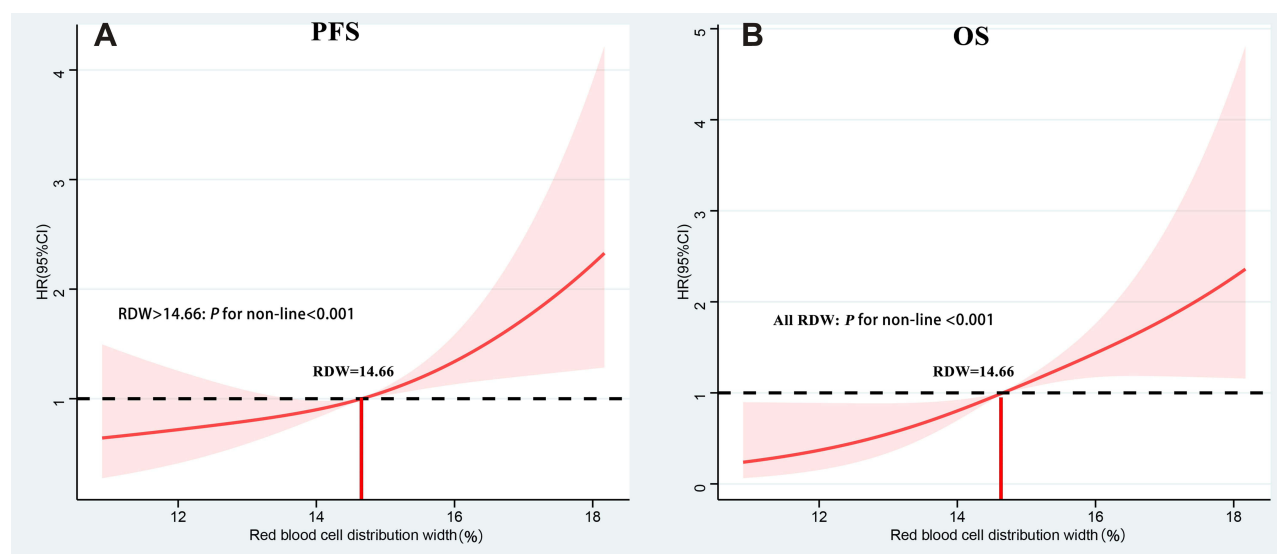


Figure 3 The restricted cubic spline plot indicated that correlation of RDW with PFS (A) and OS (B) showed non-line trend.

a measure of size heterogeneity among red blood cells and research suggests that a high RDW plays an important role in predicting mortality in patients with chronic or progressive inflammatory disease, which is directly influenced by the inflammatory response and oxidative stress.^{34,35} RDW is commonly associated with increased inflammatory response or malnutrition in cancer patients, caused by impaired iron release from reticuloendothelial macrophages, inhibited response to erythropoietin, and reduced RBC survival through the production of inflammatory markers.⁸ Our results indicate that RDW level is related to cancer differentiation and lymph node metastasis. The positive correlation between RDW and CRP suggests that the role of RDW in prognosis is related to inflammation. Another reason may be oxidative stress. Both endogenous and exogenous active oxygen sources lead to increased intracellular oxidative stress. Excessive active oxygen contamination can lead to the destruction and modification of cell macromolecules, the most important of which is genomic DNA, which can produce mutations. In addition, oxidative stress regulates the expression of downstream target genes involved in DNA repair, cell proliferation, and antioxidants.³⁶ The regulation of gene expression by oxidative stress is partly achieved by activating or inhibiting transcription factors and second messengers. Single nuclear polymorphisms in oxidative DNA repair and enzymatic antioxidants are important for determining the potential human cancer risk. In a rapid atrial pacing model, the increased RDW was related to oxidative stress and inflammation. Just like inflammation, oxidative stress may reduce RBC survival, leading to an increased RDW.³⁷ This may also be related to the chronic anemia caused by irregular vaginal bleeding in most cervical cancer patients, because RDW can reflect anemia status.^{38–40} Finally, RDW is associated with malnutrition, which is an independent risk factor for nosocomial infections and is associated with poor outcomes, such as reduced treatment effectiveness and survival.⁴¹ Our results support these explanations because significant differences in prealbumin and hemoglobin were observed.

This study has some limitations. First, a larger study is required to validate our findings. Second, the RDW cutoff for diagnosing cervical cancer is close to the normal level, so caution is necessary when applying it in other populations. Third, the mechanism exploration is speculation based on previous studies and mechanism research is needed. Finally, selection and recall bias may exist due to the inherent limitations of a retrospective study.

In conclusion, our study suggests that RDW is an easy, quick, and inexpensive tool for the early detection and risk management of cervical cancer. An elevated RDW is associated with a poor prognosis in cervical cancer. Further research is needed to validate these findings.

Data Sharing Statement

Please contact the corresponding author for original data availability.

Ethics Approval and Consent to Participate

This study was approved by Xiangya Hospital Central South University and was consistent with the Declaration of Helsinki.

Patient Consent for Publication

Study subjects provided written informed consent prior to participation.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest in this work.

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