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The value of red cell distribution width in patients with ovarian cancer

Yuanyuan Qin, MD[a], Peng Wang, MD[a], Zhibi Huang, MD[b], Gaoming Huang, MD[b], Jingguang Tang, MD[a], Yi Guo, MD[a], Ping Huang, MD[a], Zhanfeng Lai, MD[a], Faquan Lin, MD[a,*]

Abstract

Background: The red cell distribution width (RDW) has attracted attention in the diagnosis of malignant tumors. In this study, we analyzed the correlation between the RDW and ovarian cancer by observing changes in the RDW in patients with ovarian cancer.

Methods: Patients diagnosed with ovarian cancer at the First Affiliated Hospital of Guangxi Medical University, China, from 2012 to 2016, were retrospectively analyzed. Patients diagnosed with ovarian benign tumors in our hospital during the same period comprised the control group. Differences in relevant indicators were compared between the ovarian cancer and control groups using the Mann–Whitney *U* test. Differences in the RDW at different stages of ovarian cancer were compared using one-way analysis of variance. Correlations between the RDW and experimental parameters in patients with ovarian cancer were analyzed by Spearman correlation.

Results: The RDW, absolute neutrophil count (N), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and cancer antigen 125 (CA-125) concentration were significantly higher in the ovarian cancer than control group. The hemoglobin concentration (Hb) and absolute lymphocyte count (L) were significantly lower in the ovarian cancer than control group. The RDW was significantly different among 4 different stages of ovarian cancer. Correlation analysis demonstrated that the RDW was negatively correlated with the hemoglobin concentration (Hb). The RDW was positively correlated with the cancer stage, NLR, PLR, and CA-125 concentration. The area under the receiver-operating characteristic curve of the RDW was 0.876 (95% confidence interval 0.829–0.923).

Conclusion: The RDW is associated with ovarian cancer and is a potential marker of its progression.

Abbreviations: CA-125 = cancer antigen 125, Hb = hemoglobin, L = absolute lymphocyte count, N = absolute neutrophil count, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, RDW = red cell distribution width.

Keywords: inflammatory factor, ovarian cancer, red cell distribution width

1. Introduction

Ovarian cancer has the highest mortality rate among malignant tumors of the female reproductive system.[1] The incidence of ovarian malignancies has been increasing in recent years. In 2012, 22,280 new cases of ovarian cancer were diagnosed in the United States, and 15,500 of these patients died of their ovarian cancer.[2] Global statistics in 2015 showed that about 240,000 new cases were diagnosed and 150,000 deaths occurred each year, with a mortality rate as high as 63%.[3] The ovaries are located in the pelvic cavity, and the onset of ovarian cancer is therefore occult. More than 70% of patients with ovarian cancer lack obvious clinical manifestations and therefore do not undergo effective diagnostic techniques in the early stage; thus, ovarian cancer is usually diagnosed at an advanced stage.[4] This is a leading cause of the high mortality rate associated with this cancer. Identification of low-cost biological indicators that can help to improve the early diagnosis of ovarian cancer and evaluate its prognosis thus has high clinical value.

The red cell distribution width (RDW) is a measure of the range of variation in the red blood cell size. The RDW reflects red blood cell volume heterogeneity and is a part of the whole blood cell count. The RDW is widely used in the clinical differential diagnosis of anemia-related disease.[5] Nevertheless, increasingly more evidence is showing that a high RDW is strongly associated with a risk of liver disease, cardiovascular disease, and metabolic syndrome.[6–8] Use of the RDW in the diagnosis of malignant tumors has recently attracted much attention. Related research has mainly focused on endometrial cancer, lung cancer, and liver cancer.[9–11] To the best of our knowledge, however, the relationship between the RDW and ovarian cancer has not yet been described. In the present study, we analyzed the correlation between the RDW and ovarian cancer by observing changes in the RDW in patients with ovarian cancer.

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Y.Q. and P.W. contributed equally to this work and are co-first authors.

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[a] The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, China, [b] Public Health of Guangxi Medical University.

[*] Correspondence: Faquan Lin, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, China (e-mail: fqlin1998@163.com).

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2. Patients and methods

2.1. Patients

A retrospective analysis of patients who were at the first diagnosis of ovarian cancer at the First Affiliated Hospital of Guangxi Medical University, China, from 2012 to 2016 was performed. Patients who met any of the following criteria were excluded: diabetes mellitus, cardiovascular disease, kidney disease, blood disease, acute inflammation, anemia, recent iron therapy, venous thrombosis for period of >6 months, and recent blood transfusion (within the past 3 months). Finally, 145 patients with ovarian cancer were included. In accordance with the standards established by the International Federation of Gynecology and Obstetrics in 2000, the patients were classified into groups of different cancer stages.[12] 46 patients (31.7%) had stage I cancer, 34 (23.4%) had stage II, 42 (29.0%) had stage III, and 23 (15.9%) had stage IV. 54 patients diagnosed with benign ovarian tumors in our hospital during the same time period comprised the control group. These benign tumors included mature ovarian teratomas, simple ovarian cysts, and ovarian endometriosis. This study was approved by the ethics committee of the First Affiliated Hospital of Guangxi Medical University, China.

2.2. Methods

Venous blood samples (2 mL) were obtained from each patient who were at the first diagnosis of ovarian cancer and who did not receive any treatment in the morning, and placed in EDTA-K2 anticoagulation tubes and drying tubes. Whole blood cell parameters were determined with a Beckman Coulter LH 780 hematology analyzer (Beckman Coulter, Brea, CA). The RDW, hemoglobin (Hb) concentration, total number of platelets, absolute neutrophil count (N), and absolute lymphocyte count (L) were directly obtained by the hematology analyzer. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated as follows: absolute neutrophil count/absolute lymphocyte count and total number of platelets/absolute lymphocyte count, respectively. The RDW ranged from 11.0% to 14.0% in our hospital. The serum cancer antigen 125 (CA-125) concentration was detected with a Roche E6000 analyzer (Roche Diagnostics, Basel, Switzerland).

2.3. Statistical analysis

All data were analyzed using SPSS 19.0 software (IBM Corp., Armonk, NY). The Kolmogorov–Smirnov test was used as a normality test. No measurement data met the criteria for a normal distribution ($P < .01$). Non-normally distributed measurement data are expressed as the median and quartile, and count data are expressed as frequency or rate. Differences in relevant indicators were compared between the ovarian cancer group and control group using the Mann–Whitney U test. Differences in the RDW at different stages of ovarian cancer were compared using one-way analysis of variance. The diagnostic value of the RDW was estimated by a receiver-operating characteristic (ROC) curve. The area under the ROC curve (AUC) and 95% confidence interval (95% CI) were also determined. Correlations between the RDW and experimental parameters in patients with ovarian cancer were analyzed by Spearman correlation. A P value $<.05$ was considered statistically significant.

3. Results

In all, 145 patients with ovarian cancer (mean age 47.00 years; range 37.00–51.50 years) were included in this study. According to the grading standards, 46 patients (31.7%) had stage I cancer, 34 (23.4%) had stage II, 42 (29.0%) had stage III, and 23 (15.9%) had stage IV. The mean age of the 54 patients with benign ovarian tumors in the control group was 46.50 years (range 32.75–51.25 years).

The RDW, NLR, PLR, CA-125 concentration, and absolute neutrophil count were significantly higher in the ovarian cancer than control group ($P < .05$). The Hb concentration and absolute lymphocyte count were significantly lower in the ovarian cancer than control group ($P < .05$). The age and total number of platelets were not significantly different between the ovarian cancer and control groups ($P > .05$) (Table 1). The RDW was significantly different among the 4 subgroups of ovarian cancer stages as follows: stage IV > stage III, stage III > stage II, and stage II > stage I ($P < .05$) (Fig. 1). The ROC curve showed that the AUC of the RDW was 0.876 (95% CI 0.829–0.923, $P < .001$).

Correlation analysis demonstrated that the RDW was negatively correlated with the Hb concentration and positively correlated with the cancer stage, NLR, PLR, and CA-125 concentration ($P < .05$) (Fig. 2). However, the RDW was not correlated with the absolute neutrophil count or absolute lymphocyte count (both $P > .05$).

4. Discussion

The RDW reflects the heterogeneity of the red blood cell size, and an increase in the RDW suggests that the red blood cell size is not

Table 1

Comparison of relevant parameters in the ovarian cancer and control groups.

	Ovarian cancer group (n = 145)		Control group (n = 54)		
Parameters	**Median**	**Quartile**	**Median**	**Quartile**	***P***
Age, y	47.00	37.00–51.50	46.50	32.75–51.25	.606
RDW, %	15.00	14.00–17.00	13.00	12.75–13.00	.000
Hb, g/L	101.20	92.95–113.15	122.95	115.60–126.93	.000
N, $\times 10^9$/L	5.78	3.90–8.27	4.81	3.41–5.98	.012
L, $\times 10^9$/L	1.30	0.96–1.62	2.09	1.61–2.79	.000
PLT, $\times 10^9$/L	254.00	194.00–338.00	230.00	190.75–305.50	.111
NLR	5.64	3.17–7.85	2.01	1.47–2.78	.000
PLR	205.95	138.43–322.23	118.30	73.17–160.73	.000
CA-125, U/mL	165.40	53.45–673.25	6.60	4.60–9.65	.000

Measurement data are expressed as median and quartile.

CA-125 = cancer antigen 125, Hb = hemoglobin, L = absolute lymphocyte count, N = absolute neutrophil count, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PLT = platelets, RDW = red cell distribution width.

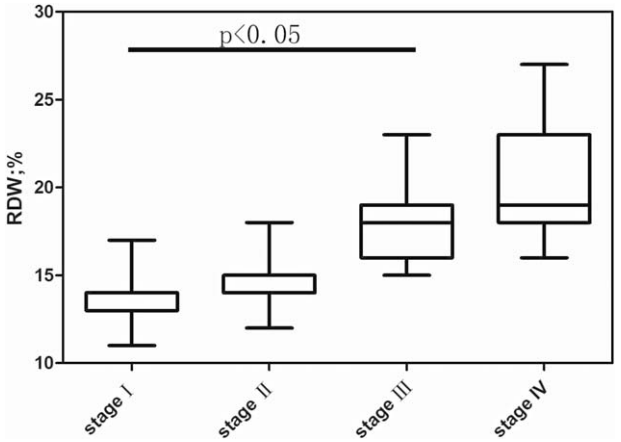

Figure 1. Comparison of RDW in different stages of ovarian cancer. RDW = red cell distribution width, Stage = cancer stage.

uniform. An increased RDW in peripheral blood smears may be associated with iron deficiency, vitamin B12, or folic acid deficiency, and Hb deficiency; hemolysis or blood transfusion can also cause an elevated RDW.[13] Some inflammatory factors, such as granulocyte colony-stimulating factor and erythropoietin, can also cause the RDW to rise by stimulating an increase in the volume of some red blood cells.[14]

In the present study, a high RDW was positively correlated with the stage of ovarian cancer; the higher the stage, the higher the RDW. Previous studies showed that the RDW increased in patients with malignant tumors,[9–11,15–18] which is consistent with the findings of the present study. Ay et al[15] compared the RDW in patients with benign and malignant tumors of the colon, including 115 patients with colon polyps and 30 with colon cancer. The RDW was significantly higher in patients with colon cancer than in those with colon polyps. Baicus et al[16] found that the RDW was remarkably increased in 61 patients with malignant tumors among 253 patients with weight loss. Seretis et al[17] confirmed that the RDW was noticeably higher in 35 patients with breast cancer than in 14 patients with breast fibromas. A previous study showed that the RDW was obviously associated with the number of metastatic lymph nodes, tumor diameter, and overexpression of human epidermalgrowth factor receptor-2. Recent studies have also confirmed that the RDW plays an important role in lung cancer. Koma et al[10] verified that a high RDW was strongly associated with the cancer stage and prognosis in 332 patients with lung cancer. In the Cox proportional-hazards model of that study, an elevated RDW was an independent risk factor for lung cancer mortality. Kemal et al[9] found that the RDW was higher in 109 patients with endometrial cancer than in 222 with benign uterine lesions, and that the RDW was associated with the cancer stage in patients with endometrial cancer. Wei et al[18] confirmed that the RDW was dramatically higher in 110 patients with primary hepatocellular carcinoma than in 68 healthy persons.

The mechanism of an elevated RDW in the blood of patients with ovarian cancer is still under investigation. Possible mechanisms may involve the effects of inflammatory factors and/or malnutrition. First, with respect to inflammatory factors, cancer is widely believed to be the result of chronic inflammation.[19] Approximately 29% of cancer deaths were associated with chronic infection in 1 study.[20] The RDW is also thought to be associated with chronic inflammation.[21] Lippi et al[22] confirmed that the RDW was positively correlated with the erythrocyte sedimentation rate and high-sensitivity C-reactive protein concentration, indicating that the RDW reflects the inflammatory state of the body. Mantovani et al[19] believed that the inflammatory response mediated by cytokines and inflam-

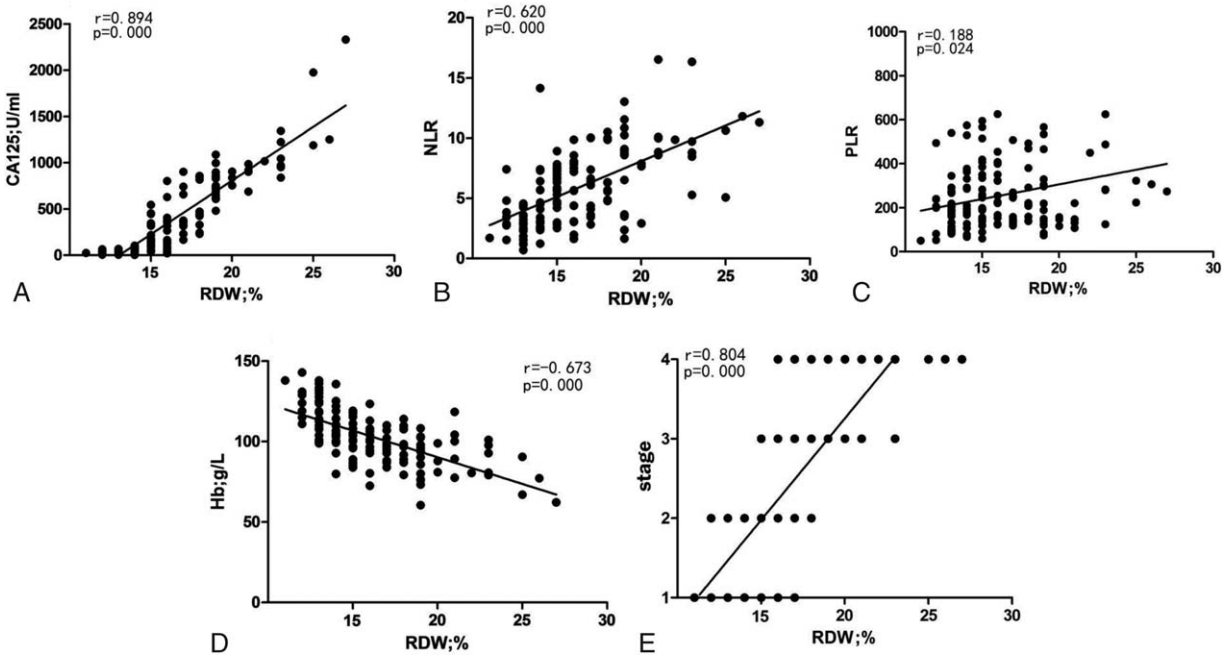

Figure 2. Correlation analysis of RDW with (A) CA-125, (B) NLR, (C) PLR, (D) Hb, and (E) cancer stage. CA-125 = cancer antigen 125, Hb = hemoglobin, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, RDW = red cell distribution width, Stage = cancer stage.

matory mediators within the tumor may lead to the development, infiltration, and metastasis of cancer. Inflammatory factors can affect iron metabolism, inhibit erythropoietin expression, and inhibit erythrocyte maturation.[23,24] Forhecz et al[13] further investigated the mechanism of the RDW increase induced by inflammatory reactions and found that inflammatory factors affected iron metabolism, shortened the life of red blood cells, and resulted in the release of large numbers of immature red blood cells from the bone marrow into the peripheral blood circulation in advance; alternatively, inflammatory factors increased the rate of ineffective hematopoiesis in the bone marrow, increased the red blood cell volume heterogeneity in peripheral blood, induced an increase in the RDW, suppressed the stimulating effect of erythropoietin on bone marrow erythroid stem cells, and prevented the antiapoptotic effect and inhibitory effect of erythropoietin on red blood cell maturation.[13] Many cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-17, are unbalanced in patients with ovarian cancer, which is a chronic inflammatory disease. Neote et al[25] detected many types of inflammatory factor receptors on the surface of red blood cells and presumed that red blood cells were involved in the inflammatory process. Hunziker et al[26] further verified that the inflammatory response and oxidative stress affected erythropoiesis and altered blood cell membrane deformability and the erythrocyte half-life cycle, thereby resulting in an increased RDW. In the present study, the absolute neutrophil count, NLR, PLR, and RDW increased, and the RDW was correlated with the NLR and PLR. These findings are consistent with previous studies showing that a variety of inflammatory factors increase and that RDW serves as an inflammatory factor during the onset of cancer. Second, with respect to malnutrition, patients with malignant tumors often have malnutrition, gastrointestinal dysfunction, and impaired immune function. These conditions result in deficiencies of iron, folic acid, and vitamin B12; different degrees of anemia; and an increased RDW.

Cancer antigen 125 (CA-125) is a clinically sensitive ovarian tumor marker. It has important diagnostic value in ovarian cancer and can be used to monitor treatment efficacy. Moreover, the CA-125 concentration has been shown to identify the chemotherapy cycle, can be used to judge disease progression, and is an important prognostic indicator.[27,28] In the present study, the CA-125 concentration remarkably increased in the ovarian cancer group, and the RDW was positively correlated with the CA-125 concentration. Moreover, the ROC curve showed that the AUC of the RDW was 0.876. Therefore, we conclude that the RDW is a potential marker for the progression of ovarian cancer. This study has shown that the RDW reflects the progression of ovarian cancer to a certain degree. The RDW reflects the stage of ovarian cancer (stage I, 13.78 ± 1.19%; stage II, 14.79 ± 1.38%; stage III, 16.50 ± 2.13%; stage IV, 18.21 ± 1.92%) and may have value in early diagnosis and assessment of disease progression of ovarian cancer in clinical practice. However, the actual clinical value of the RDW is not absolute. The sample size of the present study was small, and the specific interval in which the RDW can accurately reflect the stage of ovarian cancer will require a study with a larger sample.

This study has some limitations. This was a retrospective study of patients with ovarian cancer, and the small sample size prevents us from drawing conclusions about the correlation between the RDW and ovarian cancer. We did not collect relevant laboratory data regarding inflammatory factors (such as the erythrocyte sedimentation rate and concentrations of C-reactive protein, ILs, and TNF), erythropoietin, folic acid and vitamin B12 concentrations, and serum ferritin concentration. These indicators may greatly help to further clarify the mechanism of RDW elevation in patients with ovarian cancer. Thus, a large-scale prospective study is needed for further confirmation. Nevertheless, this is the first study on the correlation between the RDW and ovarian cancer. The data reflect the value of the RDW in patients with ovarian cancer and provide a reference for the diagnosis of ovarian cancer progression.

5. Conclusions

In summary, the RDW was correlated with the stage of ovarian cancer, suggesting that the RDW is a potential marker for disease progression in patients with ovarian cancer. RDW detection technology is more mature than in the past, and the various types of machines and their detection methods are basically uniform. The RDW is a laboratory indicator that is commonly used in the clinical setting, simple to measure, easily promoted, convenient, and inexpensive. Further investigation regarding its use is needed to help in the diagnosis and treatment of ovarian cancer.

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