Original Article

# The Value of Red Cell Distribution Width and Its Correlation with Other Parameters in Ovarian Cancer

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## Abstract

**Background:** The red cell distribution width (RDW) is a measure of the range of variation in the red blood cell size. It reflects red blood cell volume heterogeneity and is a part of the whole blood cell count. The 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. **Aim of the Study:** This study investigated the correlation between the RDW and ovarian cancer by observing changes in the RDW in patients with different stages of ovarian cancer. **Patients and Methods:** A case–control study involving 50 females with ovarian cancer and 50 healthy females conducted at Baghdad Oncology Teaching Hospital, and Al-Imamian Al-Kadhimiyain Medical City from January 1, 2022, to December 30, 2022. Data collection included demographic data, complete blood count with the calculation of platelets to lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), transferrin saturation, and cancer antigen 125 (CA-125). Adult females with histologically proven ovarian cancer were included in this research. Patients with conditions that affect red blood cells were excluded from the study. **Results:** The mean age was 52.6 ± 10.4 years old for the cases and 50.0 ± 11.4 years for the control group. Platelets count (PLT), absolute neutrophil count (ANC), PLR, NLR, RDW, and CA-125 were significantly higher in the women with ovarian cancer in comparison to the control group ($P < 0.001$). RDW values were found to be positively correlated with white blood cell, PLT, ANC, NLR, PLR, and CA-125 values ($P < 0.001$). RDW values were also positively associated with cancer stage; thus, higher values of RDW are to be expected with a higher stage of cancer ($P < 0.001$). The optimal cutoff point for RDW was found to be 14.6% with a sensitivity of 92%, specificity of 90%, and an area under the curve of 96%. **Conclusion:** The RDW is increased with ovarian cancer, and a clear cutoff point for the prediction of ovarian cancer has been observed. Furthermore, RDW was positively correlated with cancer stage and inflammatory markers including PLT, ANC, PLR, NLR, and a tumor marker CA-125.

**Keywords:** Inflammatory factor, ovarian cancer, red cell distribution width

## Introduction

Globally, ovarian cancer ranks as the sixth most common cancer in women, with an age-standardized incidence rate of 6.6/100,000, and the seventh leading cause of cancer-related deaths, boasting an age-standardized mortality rate of 4.0/10,000. Challenges in early detection stem from late presentations and the limitations of screening methods such as cancer antigen 125 (CA-125) estimation and transvaginal sonography, both of which lack specificity. Consequently, diagnoses often occur in later stages, resulting in lower cure rates and heightened morbidity due to limited treatment efficacy. In Iraq, where the latest available data are from 2018, ovarian cancer ranks as the seventh most prevalent cancer in women, with an incidence rate of 3.81 per 100,000 population according to the Iraqi Cancer Board.[1-5]

CA-125, a high-molecular-weight mucinous glycoprotein present on the surface of ovarian cancer cells, has been pivotal in screening, detecting, and managing ovarian cancer for the past 4 decades. Serum CA-125 levels, quantified in ovarian cancer patients, show elevation in 50% of early-stage tumors

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and 92% of advanced-stage tumors, with a defined cutoff value of 35 U/mL. Accepted uses of CA-125 include determining malignancy in pelvic masses, identifying the ovarian origin of cancers with an unknown primary, monitoring ovarian cancer response to systemic chemotherapy, and screening for ovarian cancer in high-risk populations such as those with a strong family history or BRCA1/2 mutations.[6,7]

Red cell distribution width (RDW) is a parameter assessed in complete blood cell count panels, comprising RDW standard deviation (RDW-SD) and RDW coefficient of variation and reflecting red blood cell size heterogeneity. Conventionally, employed to analyze anemia types, recent studies position RDW as an inflammatory marker with potential implications for predicting overall mortality in various inflammatory diseases. Calculated by dividing mean corpuscular volume by red blood cell SD and multiplied by 100, RDW serves as a diagnostic tool for anemia's underlying causes. Conditions linked to anemia include cancer, cardiovascular disease, kidney and liver diseases, thalassemia, chronic illnesses (e.g. Crohn's disease, diabetes, and HIV), and vitamin/mineral deficiencies. Long-lasting infections or significant blood loss may also induce anemia. In cancer patients, RDW emerges as an independent prognostic factor, potentially linked to inflammatory markers and malnutrition. Elevated RDW may serve as a bridge between inflammation and tumorigenesis, correlating with poor cancer prognosis. White cell counts, particularly neutrophil, lymphocyte, and platelet counts, and their combinations (neutrophil-to-lymphocyte ratio [NLR] and platelet-to-lymphocyte ratio [PLR]), have shown prognostic value in various cancers, reflecting heightened innate immune and inflammatory responses.[8-13]

## Patients and Methods

### Study design and settings

A case–control study involving 50 females with ovarian cancer and 50 healthy subjects was conducted at Baghdad Oncology Teaching Hospital, and Al-Imamian Al-Kadhimiyain Medical City from January 1, 2022, to December 30, 2022. A convenient sampling method was used to enroll the participants in this study.

### Data collection

Demographic data for both patients and controls were collected by direct interview, and data on blood biomarkers were retrieved from hospital paper records. The complete blood count analysis was done by the device named XB-300 (an automated 3-part differential hematology analyzer); the data were complete blood count (hemoglobin [Hb], white blood cell [WBC] count, platelets count [PLT], absolute neutrophil count [ANC], and red blood cell distribution width [RDW]), with a calculation of PLR, NLR, transferrin saturation, and CA-125 which was done with ELISA assay.

### Inclusion criteria

Any female aged 18 years and older for both controls and patients with histopathologically proven ovarian cancer were included in this research.

**Table 1: Age and blood biomarkers in cases and control groups and the statistical difference between them**

| Characteristics | Cases ($n=50$)[a] | Control ($n=50$)[a] | $P$[b] |
|---|---|---|---|
| Age (years) | 52.6±10.4 | 50.0±11.4 | 0.2 |
| Hb (g/dL) | 11.8±0.8 | 12.7±0.8 | <0.001 |
| WBC count ($\times10^9$/L) | 7.6±1.6 | 7.2±0.8 | 0.14 |
| Platelets count ($\times10^9$/L) | 345.6±94.1 | 232.9±32.9 | <0.001 |
| ANC (cells/µL) | 5.368±1.301 | 4.588±652.4 | <0.001 |
| PLR | 212.9±74.6 | 110.3±16.5 | <0.001 |
| NLR | 3.2±0.8 | 2.2±0.3 | <0.001 |
| RDW (%) | 16 (14–20) | 13 (12–17) | <0.001 |
| TS (%) | 25 (21–32) | 26 (21–30) | 0.4 |
| CA-125 (U/mL) | 235.0 (89.2–462.0) | 6.0 (4.9–8.0) | <0.001 |

[a]Mean±SD, median (IQR), [b]Welch two-sample *t*-test, Wilcoxon rank-sum test. Hb: Hemoglobin, ANC: Absolute neutrophil count, PLR: Platelets to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, RDW: Red cell distribution width, TS: Transferrin saturation, WBC: White blood cell, SD: Standard deviation, IQR: Interquartile range, CA-125: Cancer antigen-125

**Table 2: Association between biomarkers and the likelihood of ovarian cancer in addition to red blood cell**

| Characteristics | OR | 95% CI | $P$* |
|---|---|---|---|
| Age (years) | 1.02 | 0.99–1.06 | 0.2 |
| Hb (g/dL) | 0.32 | 0.18–0.53 | <0.001 |
| WBC count | 1.00 | 1.00–1.00 | 0.14 |
| Platelets count | 1.03 | 1.02–1.04 | <0.001 |
| ANC | 1.00 | 1.00–1.00 | 0.5 |
| PLR | 1.07 | 1.04–1.10 | 0.02 |
| NLR | 4.5 | 2.8–6.9 | 0.003 |
| RDW | 3.32 | 3.9–7.2 | <0.001 |
| CA-125 | 1.36 | 1.15–2.21 | 0.031 |

*$P$: $P$ significant at <0.05. OR: Odds ratio, CI: Confidence interval, Hb: Hemoglobin, ANC: Absolute neutrophil count, PLR: Platelets to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, Red cell distribution width (RDW), WBC: White blood cell, CA-125: Cancer antigen-125

### Exclusion criteria

Patients with comorbidities including thrombosis, iron deficiency anemia, blood disorder, kidney disease, cerebrovascular accident, and diabetes were excluded from this study. In addition, patients with recent blood transfusion within 3 months were also excluded from the study.

### Ethical issues

Ethical and scientific approval for the research was obtained from the Scientific Committee at the Department of Internal Medicine, Iraqi Board for Medical Specialization. Verbal consent was obtained from all patients before starting data collection and after explaining the aims of the study and assuring confidentiality.

### Statistical analysis

R software packages (dplyr, gt_summery, and ggplot) were used for data processing, administration, and statistical analysis ("R version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria"). Depending on whether the distribution was normal

or skewed, continuous variables were expressed as means and SDs or medians with range. Categorical variables were expressed as frequency and percentages. The Welch's *t*-test (for normally distributed variables) and Wilcoxon rank-sum test or Kruskal–Wallis test (for nonnormally distributed variables) were performed. The difference between categorical variables was investigated using either the Chi-square test or Fisher's exact test, depending on the context. Spearman's rank correlation coefficient was used to study the correlation between study parameters. Youden method was used for calculating the optimal cutoff point for the diagnosis of ovarian cancer, and univariate logistic regression was used to calculate the odds ratio (OR) for the risk of ovarian cancer. $P$ <0.05 was considered statistically significant.

## Results

One hundred participants were included in this case–control study, it involved 50 patients and 50 controls. The mean age was 52.6 ± 10.4 years old for the patient and 50.0 ± 11.4 years for the control group. PLT, ANC, PLR, NLR, RDW, and CA-125 were significantly higher in the women with ovarian cancer in comparison to the control group ($P < 0.001$). The median (range) Hb values in cases were 11.8 (10.6–13.5) and in the control group were 12.7 (11–14), with a statistical difference between the two groups ($P < 0.001$). In regard to WBC count, the median (range) was 7.4 (3.6–12) for the cases and for the control group 7.1 (5.8–9.1), cell $\times 10^9$/L with a $P = 0.14$. PLT ranged from 157 to 600 in cases and 189.0–347.0 cell $\times 10^9$/L in the control group as shown in Table 1.

On the other hand, transferrin saturation did not show much difference between the cases and control. Regarding ovarian cancer staging [Figure 1], the most prevalent stage was stage III (44%), followed by stage IV (36%) and stage II (14%).

In regard to the assessment of the risk of ovarian cancer, a univariate logistic regression analysis was conducted, and it was found that increasing the RDW values by one, increased the likelihood of ovarian cancer by three folds (OR =3.32, $P < 0.001$) in this study. Furthermore, higher values of PLT, PLR, NLR, and CA-125 were associated with an increased risk of ovarian cancer as shown in Table 2.

To study the correlation between RDW and other study parameters, Spearman's correlation coefficient was calculated as shown in Table 3. Except for transferrin saturation, RDW values were found to be positively correlated with WBC, PLT, ANC, NLR, PLR, and CA-125 values ($P < 0.001$) and negatively correlated with Hb value (rho = −0.45, $P < 0.001$).

The association between RDW and ovarian cancer staging was shown in Figure 2, and it was found that RDW was positively associated with cancer stage; thus, higher values of RDW are to be expected with higher stage of cancer.

The optimal cutoff point for the prediction of ovarian cancer in this study was calculated using the Youden method for the different blood biomarkers. The cutoff point, sensitivity, specificity, and area under the curve (AUC) are illustrated in

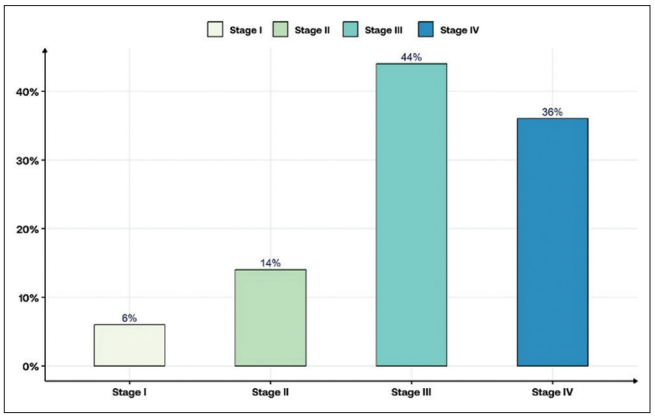


**Figure 1:** Proportion of the stages of ovarian cancer

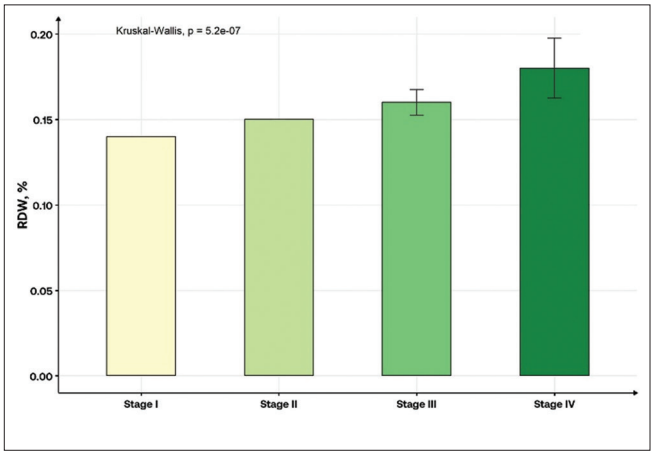


**Figure 2:** Median and interquartile range of RDW values in different cancer stages ($P < 0.001$). Red cell distribution width RDW: Red cell distribution width

Table 4. The optimal cutoff point for RDW was 14.6% with a sensitivity of 92% and specificity of 90%.

## Discussion

Ovarian cancer is one of the most common gynecological cancers that rank third after cervical and uterine cancers. It has the worst prognosis and the highest mortality rate.[14] It has been historically called "the silent killer" because the symptoms of the disease cannot be seen until advanced stages.[15] Consequently, many cases of ovarian cancer present for the first time at an advanced stage with a poor prognosis. Therefore, developing a method for an early diagnosis and treatment became an essential part of the medical research work.[15] RDW and other blood parameters have been studied and identified by Lu *et al*., Kemal *et al*., Smirne *et al*., Ay *et al*., and Wei *et al*. as potential biomarkers for the diagnosis as well as prognosis of several types of cancer, including ovarian cancer. Consequently, we have conducted the current research to evaluate the diagnostic values of blood biomarkers.[16-20]

Using the International Federation of Gynecology and Obstetrics staging for ovarian cancer, stage III was found to

**Table 3: Correlation analysis between red blood cell and other study parameters**

| Characteristics | Correlation coefficient (rho) | $P^b$ |
|---|---|---|
| Hb (g/dL) | −0.45 | <0.001 |
| WBC count | 0.2 | 0.04 |
| Platelets count | 0.5 | <0.001 |
| ANC | 0.41 | <0.001 |
| PLR | 0.6 | <0.001 |
| NLR | 0.64 | <0.001 |
| CA-125 | 0.75 | 0.005 |
| TS | −0.07 | 0.4 |

[b]Spearman's rank correlation Rho. Hb: Hemoglobin, ANC: Absolute neutrophil count, PLR: Platelets to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, RDW: Red cell distribution width, WBC: White blood cell, CA-125: Cancer antigen-125

**Table 4: Biomarkers cutoff point for the prediction of ovarian cancer**

| Characteristics | Cutoff point | Sensitivity (%) | Specificity (%) | AUC (%) |
|---|---|---|---|---|
| Hb (g/dL) | 12.32 | 62 | 72 | 75 |
| WBC count (×10⁹/L) | 8.41 | 32 | 90 | 57 |
| Platelets count (×10⁹/L) | 284.0 | 74 | 94 | 86 |
| ANC (cells/µL) | 5408.5 | 48 | 92 | 70 |
| PLR | 137.8 | 82 | 92 | 93 |
| NLR | 2.567 | 76 | 98 | 91 |
| CA-125 (U/mL) | 40.2 | 86 | 100 | 99 |
| RDW (%) | 14.6 | 92 | 90 | 96 |

Youden method. Hb: Hemoglobin, ANC: Absolute neutrophil count, PLR: Platelets to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, RDW: Red cell distribution width, WBC: White blood cell, AUC: Area under the curve, CA-125: Cancer antigen-125

be the most prevalent among our patients (44%), followed by Stage IV (36%) and Stage II (14%). Similarly, Li *et al*.[21] had 63% of their patients with Stage III disease, followed by stage IV. On the other hand, Stage I disease was found to be the most abundant among the participants in the study by Qin *et al*.,[22] whereas Stage III and IV comprised less than half of their samples. These studies have been carried out in China, and their participants had a mean age of 44–47 years, more than 5 years younger than our participants. This combined with a possibly more effective application of cancer screening programs in their country might contribute to the lower incidence of a more advanced stage of disease in those studies. In addition, disease awareness, population education, and sample selection may play a role in the abovementioned differences.[22]

This study has evaluated the value of a set of biomarkers, through a full blood count, and compared between both groups. The platelet count was found to be significantly higher in patients with ovarian cancer as opposed to the control group ($P < 0.001$). This result came in concordance with that of Ak *et al*.[15] who further stated that thrombocytosis might be associated with an advanced disease. On the other hand, Qin *et al*.[22] did not find a significant difference between the two groups. Moreover, a retrospective study evaluating the value of some blood markers in differentiating between benign and malignant ovarian tumors concluded that the platelet count was significantly lower among patients with ovarian cancer.[23] Such contradiction in the results may be explained by the variable role platelets might play in cancer pathogenesis. Mantovani *et al*. claimed that certain factors (mainly cancer-related inflammation) involved in tumorigenesis have been found to stimulate platelet production.[24] Gasparyan *et al*. suggested that a link is present between inflammation and tumor development, and thus, platelet consumption during the inflammatory process may contribute to lower platelet count among cancer patients.[25]

This study found that ANC and RDW were much higher among cancer cases than in the control group ($P < 0.001$). This supports what Qin *et al*. concluded, which may improve the differential diagnosis of ovarian cancer and benign ovarian tumors.[23]

Verabelly *et al*., however, stated that no significant association was found between RDW and ovarian cancer in their cross-sectional study which involved 90 patients with a diagnosis of ovarian epithelial tumors.[26] In Verabelly *et al*., 60% of the cases had a diagnosis of benign ovarian tumor, 7.8% with malignant tumors, and 42% with borderline tumor. Nevertheless, the fact that only 7.8% of their overall study sample was diagnosed with ovarian cancer, it could explain the difference in results between the two studies.[26] CA-125 levels were found to be significantly higher in our sample with ovarian cancer as opposed to the control group ($P < 0.001$). A number of studies had a similar result.[21,23,26] Furthermore, Ak *et al*. reached a conclusion that a marker combining CA-125 with NLR can help discriminate between benign and malignant ovarian pathologies.[15]

Similar to Qin *et al*.,[22] we found Hb to be significantly lower in cases compared to the control group. Many mechanisms for a low Hb level in cancer patients have been suggested, and one mechanism relates the inflammatory cytokines involved in cancer pathogenesis to play a role in inhibiting the stimulatory effect of erythropoietin on bone marrow erythrocyte stem cells.[27]

To identify the value of the aforementioned biomarkers and its association with ovarian cancer, a logistic regression analysis was carried out. RDW, PLR, and NLR were found to significant increase the individual's risk for having ovarian cancer by many folds (OR =3.32, OR =1.07, and OR =4.5, respectively). This makes those biomarkers highly suggestive of an ovarian cancer diagnosis when found elevated in suspected patients. Moreover, the studies suggested that elevated RDW, NLR, and PLR may have a prognostic value in survival of ovarian cancer.[15,21] Li *et al*. claimed that higher levels of the aforementioned markers were associated with poorer overall and recurrence-free survival rates.[21] Ak *et al*., on the other hand, found a significantly excess amount of ascites among those with higher NLR and PLR values at the time of diagnosis; this may be explained by the idea that higher values are associated with higher stages of cancer and thus may predispose to increasing amount of ascites.[15]

Platelets and ANC were found to carry some extra risk of ovarian cancer when elevated beyond a certain value. Ak *et al*. pointing to ANC role as a prognostic factor, claimed that a lower ANC was associated with longer overall survival and higher platinum sensitivity.[15] Soonthornthum *et al*. and Canzler *et al*. as well suggested a probable role for thrombocytosis in survival (PLT ≥400 × $10^3$/$mm^3$) when identified in ovarian cancer patients.[28,29]

The possible correlation between RDW and other blood biomarkers was evaluated. WBC, platelets, PLR, ANC, NLR, and CA-125 were positively related to RDW ($P < 0.001$). Similarly, Qin *et al*.'s case–control study in which they found that RDW was correlated with CA-125 ($R = 0.89$, $P < 0.001$), NLR ($R = 0.62$, $P < 0.001$), and PLR ($R = 0.18$, $P = 0.024$),[22] whereas Hb was found to be negatively correlated to RDW (rho = −0.45, $P < 0.001$). Again, Qin *et al*. had a similar conclusion (RDW vs. Hb, $R = -0.67$, $P < 0.001$).[22] This study's findings showed that RDW was positively associated with the cancer stage; thus, the more advanced the cancer stage is, the higher RDW value will be. Qin *et al*.[22] dataset was in line with the study results, whereas Li *et al*. and Verabelly *et al*. did not observe such a relationship.[21,26] The cutoff point for RDW was found to be 14.6% with a sensitivity and specificity of 92% and 90%, respectively, for the diagnosis of ovarian cancer. A similar cutoff point has been identified by Li *et al*.[21] (cutoff point =14.15%). In addition, Qin *et al*. confirmed that RDW has a high sensitivity of more than 76%, a specificity of 70.3%, and an AUC of 0.82 for distinguishing between ovarian cancer and benign ovarian tumors.[23]

## Conclusion

The study identified RDW, PLR, NLR, and CA-125 as biomarkers with the highest predictive value for diagnosing ovarian cancer in patients under suspicion. RDW, in particular, showed a strong correlation with cancer stage, indicating its potential as both a prognostic and predictive factors for disease severity. Moreover, RDW demonstrated positive correlations with CA-125, ANC, PLR, NLR, and platelet count, whereas Hb exhibited a negative correlation.

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### Conflicts of interest

There are no conflicts of interest.

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