Original Article

Red Cell Distribution Width as a Predictor of Malignancy in Patients Who Underwent Upper Gastrointestinal System Endoscopy

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Abstract

Introduction: Red cell distribution width (RDW) has predictive properties in different benign and malignant diseases. **Aim:** Our aim was to evaluate the predictive value of RDW for malignant gastric lesions by upper gastrointestinal screening. **Materials and Methods:** Data of 91 male patients (Group A) who underwent upper gastrointestinal endoscopy and subsequent surgery for gastric malignancy and age-matched 91 healthy male patients (Group B) with benign disorders were reviewed in this retrospective cohort study. The pathology reports, laboratory parameters, and demographics of the patients were recorded for comparison. Receiver operating characteristic curves were plotted for RDW, and a threshold for prediction of malignancy was calculated. **Results:** The average age of the patients with gastric cancer was 62 (interquartile range [IQR]: 53–70) years. The difference in RDW levels between Group A and Group B was found to be significant: 14.40% (IQR: 13.40–16.40) versus 13.10% (IQR: 12.55–13.50) for the malignant and benign groups, respectively, $P = 0.000$. The area under the curve was 0.81 (95% confidence interval [CI]: 0.76–0.86), $P = 0.000$. For the threshold of 13.45%, the positive predictive value (PPV) for malignancy was found to be 69.15 (95% CI: 61.77–75.67) and negative predictive value (NPV) was 70.45 (95% CI: 62.60–77.26). **Conclusion:** RDW was found to have a PPV for malignancy in nearly two-thirds of the patients and had a similar NPV.

Keywords: *Endoscopy, gastric malignancy, red cell distribution width, stomach cancer*

Introduction

Gastric cancer is one of the most common cancers.[1] The lifetime probabilities of getting diagnosed with and dying from gastric cancer are 1.5% and 1.0%, respectively.[2] Gastric cancer is one of the most frequent causes of cancer-related deaths globally, with an overall survival rate of 15%–20%, and although the incidence is declining, the prognosis remains dismal.[3] In addition, up to 50% of patients have nonspecific symptoms or dyspepsia.[4] A systematic review revealed that nearly 20% of the global population have dyspeptic symptoms.[5] Dyspepsia refers to a set of upper gastrointestinal symptoms such as epigastric fullness, nausea, vomiting, or heartburn, with epigastric pain as the primary complaint.[6] However, on upper gastrointestinal endoscopic evaluation, gastric cancer is found in only 1%–2% of patients with dyspepsia.[7]

Early pathognomonic symptoms are rare, and weight loss and persistent abdominal pain are the most common symptoms at initial diagnosis, followed by nausea, anorexia, or dysphagia in approximately one-third patients and melena in one-fifth.[8]

Red cell distribution width (RDW) has been used to discriminate different types of anemia.[9] It is a measure of the heterogeneity of the volume of peripheral red blood cells and is automatically reported by laboratory blood analyzers in a complete blood cell count panel.[10]

RDW has been found to be related to an elevated risk of cardiovascular disease and all-cause mortality.[11,12] The underlying mechanisms remain unknown, but elevated serum levels of RDW may occur due to inflammation or poor nutritional status.[13] Inflammation and malnutrition are known risk factors of cancer, and chronic inflammation may lead to cancer in several organs.[14,15]

We aimed to investigate the predictive value of RDW for gastric malignancy as an easy to measure blood test parameter when performing screening endoscopy for dyspeptic symptoms. Our hypothesis was that RDW levels are elevated in patients

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with a gastric malignancy compared to patients of the same age and sex without malignancy. Elevated RDW may be an additional warning sign which may point to a systemic malignancy when performing an upper gastrointestinal endoscopic screening.

Materials and Methods

This was a retrospective cohort study which was performed in the surgical endoscopy subdivision of the general surgery department between January 2015 and July 2018. The study was carried out on patients who were diagnosed with gastric cancer by upper gastrointestinal system endoscopic evaluation. The study was performed in accordance with the ethical standards of the local ethics committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 after getting approval from the ethics committee (number January 17, 2019/8).

The patients enrolled in this study comprised patients with gastric cancer and an age- and sex-matched control group of patients who were selected randomly from a group of otherwise healthy patients who had undergone operations for benign diseases. They were given a number by the computer, and the numbers were selected by a random number generator. The normal range of RDW was 11%–14.6%. Fasting blood samples of the patients were obtained in the morning within 1 month of hospitalization.

The exclusion criteria were as follows: the presence of hematological disorders, female sex (to maintain homogeneity and rule out any probable difference in RDW due to sex, males were chosen because three-fourths of the patients were male), active inflammation, iron supplementation therapy, recent venous thrombosis (past 6 months), and recent blood transfusion (past 3 months).

Statistical analysis

Statistical analysis was performed using Jamovi (Version 1.2, the jamovi project (2020), (www.jamovi.org). Categorical variables were expressed as frequencies and percentages. All continuous and categorical variables were assessed for normal distribution. Continuous variables were compared using Mann–Whitney U-test for nonnormally distributed parameters. Categorical variables were analyzed using Pearson's Chi-square test. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

The variables RDW and hemoglobin were compared between the two groups. We investigated whether there was any significant difference in RDW values between the patients with malignant gastric disease and those with benign disorders. The main outcome was the prediction of malignancy in the study group by utilizing RDW.

Results

There were 131 patients diagnosed with a pathologically confirmed malignant disease (Group A). Thirty-seven (28%) patients were female, and in three cases, no complete blood count tests were available within the study period. Overall, 91 patients in the gastric malignancy group were compared with 91 age- and sex-matched otherwise healthy patients who had undergone interventions for benign diseases (Group B). Both the groups were tested for normality, and the data were found to be nonnormally distributed. The difference in RDW levels between Group A and Group B was found to be significant, 14.40 (interquartile range [IQR]: 13.40–16.40) and 13.10 (IQR: 12.55–13.50) in the malignant and benign groups, respectively, $P = 0.000$. There was also a significant difference in the hemoglobin levels between the malignant and benign disease groups on performing nonparametric analysis, 12.30 (IQR: 11.00–14.20) versus 14.80 (IQR: 14.13–15.78), respectively ($P = 0.000$) [Table 1].

Receiver operator characteristic (ROC) curves were plotted for RDW to identify a cutoff value for prediction of malignant behavior. The area under the curve (AUC) was 0.81 (95% confidence interval [CI]: 0.76–0.86), $P = 0.000$ [Figure 1]. We calculated the positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio for RDW at a cutoff value of 13.45, which was found to predict malignancy in approximately two-third of the patients [Table 2].

However, to rule out the effect of anemia as a cofounder, we also checked the levels of hemoglobin and mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration to be within the normal levels to rule out the possible effect of anemia on RDW. There were 58 male patients (out of 91) with hemoglobin levels above the normal level 12 g/dL according to our laboratory. Two patients were further excluded because of MCV levels beyond normal limits. The remaining nonanemic 56 patients and the matched control group were evaluated to decide a cutoff for malignancy. When a threshold of 14% was taken for RDW to predict malignancy, the PPV was near 78% with a NPV of 55% [Table 3].

Discussion

RDW is a measure of the variability in the circulating erythrocyte size and is based on the width of the erythrocyte volume distribution curve; the larger values reflect greater variability.[16] RDW has been investigated in various disease

Table 1: The characteristics of the study groups

	n	Hemoglobin levels (g/dL)	RDW (%)
Benign disorders (IQR)	91	14.80 (14.13 15.78)	13.10 (12.55 13.50)
Gastric malignancy group (IQR)	91	12.30 (11.00 14.20)	14.40 (13.40 16.40)

The median age of both the groups was 62 (IQR 53-70) years. IQR: Interquartile range, RDW: Red cell distribution width

Table 2: Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value of red cell distribution width for gastric malignancy at optimal cutoff level

RDW	95% CI		+LR	−LR	95% CI	
	Sensitivity	Specificity			PPV	NPV
>13.45	71.43 (61.00-80.41)	68.48 (57.96-77.77)	2.427	0.42	69.15 (61.75-75.68)	70.79 (62.99-77.53)

RDW: Red cell distribution width, CI: Confidence interval, +LR: Positive likelihood ratio, −LR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value

Table 3: Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio, positive predictive value, negative predictive value of red cell distribution width at optimal cutoff level for nonanemic patients

RDW	95% CI		+LR	-LR	95% CI	
	Sensitivity	Specificity			PPV	NPV
>14%	25.00 (14.39-38.37)	92.86 (82.71-98.02)	3.50	0.81	77.78 (55.11-90.89)	55.32 (51.15-59.42)

RDW: Red cell distribution width, CI: Confidence interval, +LR: Positive likelihood ratio, −LR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value

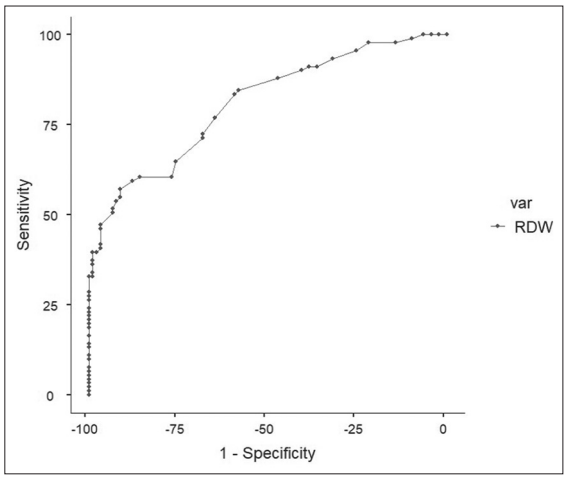

Figure 1: The area under the curve was 0.81 (95% confidence interval: 0.76–0.86), *P* = 0.000

settings both as a diagnostic approach and as a prognostic tool. A meta-analysis found that there was a graded increase in the risk of death with higher RDW values (P = 0.001), and for every 1% increment in RDW, total mortality risk increased by 14%.[17] The possible usefulness of RDW as a potential tumor-related parameter maybe because of an indirect mechanism. From epidemiological studies, it has been concluded that chronic inflammation makes individuals susceptible to various types of cancers and underlying infections; thus, inflammatory responses are estimated to be linked to 15%–20% of all cancer deaths globally.[18] Some studies have reported the correlation of RDW with inflammation, and it has been proposed as an index of activity in autoimmune diseases; additionally, in a study, RDW was found to be related to age, body mass index and inflammatory parameters (plasma viscosity, erythrocyte sedimentation rate, fibrinogen, leukocyte, and neutrophil count).[19,20]

In another study, an elevated RDW level was shown to be associated with poor prognosis in patients with hepatocellular cancer as a part of a prognostic system in conjunction with platelet/lymphocyte ratio, especially in patients with early-stage disease who underwent potentially curative resection, with a possible underlying mechanism related to poor nutritional status and inflammation.[21] Similarly, in a study on hematological parameters in patients with urothelial carcinoma of the bladder, RDW was found to be significantly higher in the malignant group than in healthy individuals (14 [IQR: 11–18] vs. 13 [IQR: 11–16], P = 0.05).[22]

Wang *et al*.[23] retrospectively analyzed the clinical and laboratory data of renal cell carcinoma (RCC) cases and controls and demonstrated that RDW values were significantly higher in patients with RCC than in controls. Furthermore, they also found a positive association between RCC stage and grade and the RDW level. The area under the curve (AUC) of RDW was 0.624 (95% CI: 0.578–0.670) for predicting RCC. They calculated an optimal cutoff value of RDW for predicting RCC as 12.85% (sensitivity: 65.09% and specificity: 51.50%).

Chen *et al*.[24] reported a retrospective analysis of 277 esophageal squamous cell carcinoma patients who underwent radical esophagectomy with a median follow-up of 42.5 months. The patients were divided into Group A (RDW ≥14.5%) and Group B (RDW <14.5%). Patients with RDW <14.5% were reported to have a significantly better 5-year cancer-specific survival than those with RDW ≥14.5%. Subsequently, an elevated RDW was found to be an independent prognostic factor for cancer-specific survival.

Spell *et al*.[25] studied 127 patients who had right-sided colon cancer. Among them, 107 (84%) patients had an elevated RDW, and it was revealed that the elevated RDW had high sensitivity (0.84) and specificity (0.88) for identifying right-sided colon cancer. Therefore, they inferred that RDW may be useful as a cost-effective screening tool for colon cancer.

Ay *et al*.[26] analyzed 115 patients with colon polyps and 30 with colon cancer and found that RDW values were

significantly higher in patients with colon cancer compared to those with colonic polyps. They proposed that RDW may be used as an early-warning biomarker for solid colon tumors.

Brusco *et al*.[27] studied celiac disease patients and discovered that increased RDW was the most frequent hematological abnormality in these patients (58%), followed by anemia (31%), and iron deficiency (29%). Moreover, after 1 year of gluten-free diet, the RDW levels of the patients reduced to the normal range in the above study.

Similarly, Pietrzyk *et al*.[28] evaluated RDW in gastric cancer patients and healthy individuals in a retrospective study and concluded that gastric cancer patients had significantly higher mean RDW values (14.9 ± 3.9) than healthy individuals (12.2 ± 0.7). Therefore, they suggested that an elevated RDW level in a patient with upper gastrointestinal symptoms may be utilized as an indication for upper gastrointestinal endoscopy to screen for probable gastric cancer.

Interestingly, RDW has been demonstrated to be mostly normal in patients with irritable bowel syndrome. Balaban *et al*.[29] evaluated patients with inflammatory bowel diseases versus patients with irritable bowel syndrome and investigated the RDW differences between them. The results revealed that two-thirds of the celiac disease patients had elevated RDW levels, compared to 9% of the irritable bowel syndrome patients. These findings are promising since they suggest that in a patient with upper gastrointestinal symptoms, RDW levels may help to decide whether to screen patients. However, since such studies are scarce and the number of study patients was insufficient, additional studies are required, especially prospective ones.

Our study has the limitation that it was a retrospective cohort study with a moderate sample size which did not allow detailed subgroup analysis. However, both the groups were age and sex matched to improve the statistical quality.

Conclusion

RDW levels may be helpful to distinguish malignant gastric diseases from benign ones. The cutoff value of 13.45 deduced from the ROC curve analysis was found to have a PPV for malignancy in nearly two-third of the patients.

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Conflicts of interest

There are no conflicts of interest.

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