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ORIGINAL ARTICLE

Increased Red Blood Cell Volume Distribution Width: Important Clinical Implications in Predicting Gastric Diseases

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SUMMARY

Background: **The red blood cell distribution width (RDW) is a blood analyzer marker showing the peripheral blood erythrocyte volume heterogeneity parameters. It is a normal diagnosis index of many diseases. This study was performed to evaluate the relationship between the RDW and gastric diseases.**
Methods: **A total of 189 patients with GC, 68 patients with gastric ulcers, 92 patients with chronic gastritis, and 157 healthy controls were enrolled in this study. Each patient's RDW and other biomarkers were recorded. All of the statistical analyses and comparisons between each group were determined using SPSS16.0 software. The statistical significance level was set to a p-value < 0.05.**
Results: **The RDW was significantly higher in those patients with gastric diseases when compared to the control group ($p < 0.05$). In addition, the RDW was independently correlated with the presence of GC and gastric ulcers. Significantly positive correlations between the RDW, platelets, and platelet distribution width (PDW) were observed in those patients with GC and gastric ulcers, although there were negative correlations with the red blood cells (RBCs), hemoglobin, and mean corpuscular volume (MCV) ($p < 0.05$). In the chronic gastritis group, elevated RDW values were closely associated with the hemoglobin, platelet, and MCV values ($p < 0.05$). The specificities of the gastric diseases groups were greater than 90%.**
Conclusions: **In cases of gastric diseases, the RDW values were increased and were associated with several laboratory parameters. These finding may have important clinical implications in predicting gastric diseases.**
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KEY WORDS

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INTRODUCTION

Gastric diseases are some of the most common chronic illnesses in human beings and generally include chronic gastritis, gastric ulcers, and gastric cancer (GC). It has been estimated that more than half of the world's population has stomach trouble to varying degrees [1]. GC is the most serious gastric disease in human beings. Being the fourth most common malignancy; GC is the second leading cause of cancer deaths worldwide [2]. The top five leading causes of cancer deaths among men and women in China are cancers of the lung, bronchus, stomach, liver, and esophagus [3]. Chronic gastritis appears either as atrophic or non-atrophic, which represent different stages of the same life-long disease; in addition, chronic gastritis as the pathogenesis of gastric ulcer and GC is obvious[1].

Gastric diseases cause serious damage to one's health and affects one's quality of life. Today, *helicobacter pylori (H. pylori)* infection [4], non-steroid anti-inflammatory drug (NSAID) use [5], perceived stress [6], and smoking are considered the main causes of gastric disease. However, the mechanisms of gastric diseases remain completely unknown. Therefore, effective diagnostic methods need to be determined to prevent gastric diseases from occurring. At present, the diagnosis of gastric diseases depends on a histological examination, medical imaging, and laboratory testing. In daily clinical practice, laboratory medicine plays an especially important role in diagnosing gastric diseases. Previous articles have revealed that noninvasive serologic tests are preferred over invasive tube tests [7]. The noninvasive tests consist of the serum pepsinogen (PG) test, hydrogen breath test, and calcium carbonate breath assay [8, 9]. Recently, Roman et al. showed that amidated gastrin-17 and *H. pylori* IgG were stomach-specific biomarkers in patients with gastric diseases [10]. Moreover, some other biomarkers associated with gastric ulcers and gastritis have been observed, such as IL-21 and TGF-β [11].

The red blood cell distribution width (RDW) is a parameter for judging the heterogeneity of the red blood cell volume. In routine clinical laboratory tests, the mean red blood cell volume (MCV) is mainly used for determining the causes of anemia [12]. Previous research has shown that the RDW is associated with the prognosis in several diseases, including esophageal cancer [13], cardiovascular diseases [14], multiple sclerosis [15], and rheumatoid arthritis [16]. An increase in the RDW values has been associated with in-hospital mortality [17] and an increased mortality risk in certain community groups [18].

One recent study has shown that RDW is associated with the diagnosis and management of upper gastrointestinal haemorrhage [19]. In addition, Yazici et al. [20] have suggested that the RDW could determine the prognosis of gastric cancer. Pietrzyk et al. [21] found that the increases in RDW values could be used for screening in gastric cancer patients. However, there are very few articles studying the relationship between the RDW and other gastric diseases; therefore, the purpose of this study was to assess the association between the RDW and gastric diseases.

MATERIALS AND METHODS

Study design and population

This retrospective study population included 506 cases collected from the First Affiliated Hospital of Guangxi Medical University. The control group included 157 people with healthy check-ups (61 males, 96 females; average age 42.39 ± 12.74 years). From January 2013 through August 2016, 189 patents with GC were enrolled in the study (122 males, 67 females; average age 54.36 ± 12.95 years). There were 68 patients in the gastric ulcer group (54 males, 14 females; average age 57.85 ± 10.03 years) and 92 in the chronic gastritis group (49 males, 43 females; average age 55.59 ± 18.93 years). All of the cases were diagnosed gastroscopically and pathologically, and the following were ruled out: associations with other malignant tumors, heart disease, kidney transplantation, pneumonia, hematopoietic system disease, mental illness, other serious primary disease, acute infection, pregnancy and breast-feeding.

Laboratory measurements

The RDW value, white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (HB), platelet count, mean corpuscular volume (MCV), and mean platelet volume (MPV) were tested via an automated hematology analyzer (Beckman Coulter LH 750; Beckman Coulter, Inc., USA). The reference range of the RDW in the hospital laboratory was 10% to14%. In addition, the urea, creatinine (Cr), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured using the Hitachi 7600 automatic biochemical analyzer (Hitachi, Japan). The alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), CA125, and CA199 were recorded using the Roche Cobas E-601 electrochemical luminescence immunity analyzer (Roche, Switzerland).

This study complied with the principles of the Declaration of Helsinki, and all of the data was obtained with the consent of the hospitals and patients.

Statistical analysis

In this study, all of the statistical analysis data was evaluated using SPSS 16.0 software. The continuous variables were shown as the mean ± standard deviation, and the absolute variables were expressed as percentages. The comparisons between the different groups were evaluated with Student's *t*-test, one-way ANOVA, and Mann-Whitney *U* test. The chi-squared test was used for analyzing the categorical data. A bivariate correlation analysis was conducted to determine the correlation between two variables. Moreover, a receiver operating characteristics (ROC) curve analysis was constructed

Table 1. The clinical characteristics of all patients.

Parameters	GC	p	Gastric ulcer	p	Chronic gastritis	p	Healthy control
Gender (M/F)	122/67	-	54/14	-	49/43	-	62/95
Age (years)	54.36 ± 12.95	< 0.001	57.85 ± 10.03	< 0.001	55.59 ± 18.93	< 0.001	42.39 ± 12.74
WBC (* 10^9/L)	6.91 ± 2.38	0.589	6.98 ± 2.98	0.633	6.30 ± 1.85	0.016	6.80 ± 1.33
NEU (%)	4.40 ± 2.24	< 0.001	4.23 ± 2.74	0.121	3.66 ± 1.88	0.883	3.70 ± 1.02
RBC (* 10^{12}/L)	4.08 ± 0.78	< 0.001	3.84 ± 0.94	< 0.001	4.44 ± 0.56	< 0.001	4.75 ± 0.45
Hb (g/L)	110.30 ± 24.73	< 0.001	104.84 ± 27.77	< 0.001	125.17 ± 17.40	< 0.001	142.24 ± 28.06
MCV (fL)	84.16 ± 9.47	0.785	84.26 ± 10.70	< 0.001	87.93 ± 9.34	0.101	89.63 ± 4.05
MPV (fL)	8.17 ± 0.87	< 0.001	8.41 ± 1.23	< 0.001	8.35 ± 1.10	< 0.001	9.16 ± 0.84
Plt (* 10^9/L)	278.14 ± 105.02	< 0.001	263.45 ± 97.49	0.001	228.38 ± 87.33	0.462	221.06 ± 48.95
RDW (%)	0.16 ± 0.33	< 0.001	0.16 ± 0.04	< 0.001	0.14 ± 0.02	0.037	0.14 ± 0.01
UREA (mmol/L)	4.58 ± 1.49	0.035	5.16 ± 1.97	0.275	4.79 ± 1.60	0.633	4.88 ± 1.15
Cr (μmol/L)	75.63 ± 18.84	0.344	81.50 ± 17.67	0.002	74.89 ± 27.42	0.772	74.01 ± 12.97
AST (U/L)	23.78 ± 24.23	0.28	22.10 ± 7.51	0.756	22.41 ± 16.04	0.66	21.7 ± 9.47
ALT (U/L)	19.88 ± 16.13	0.089	21.29 ± 12.33	0.483	21.82 ± 28.98	0.797	22.48 ± 11.36
AFP (ng/mL)	36.37 ± 251.06	0.076	7.83 ± 30.46	0.273	2.52 ± 1.32	< 0.001	3.74 ± 2.44
CEA (ng/mL)	272.01 ± 2941.87	0.208	16.74 ± 107.22	0.243	2.14 ± 1.10	< 0.001	1.43 ± 1.38
CA125 (U/mL)	54.72 ± 177.79	< 0.001	18.34 ± 29.02	< 0.001	9.64 ± 6.52	< 0.001	5.52 ± 3.38
CA199 (U/mL)	80.98 ± 338.41	0.005	34.72 ± 82.37	0.024	18.65 ± 55.76	0.234	11.64 ± 7.83

Data are expressed as mean ± standard deviation, GC - gastric cancer, WBC - white blood cell, NEU% - neutrophilic granulocyte percentage, RBC - red blood cell, HB - hemoglobin, MCV - mean corpuscular volume, MPV - mean platelet volume, PLT - platelet, RDW - red blood cell distribution width, Cr - creatinine, AST - aspartate aminotransferase, ALT - alanine aminotransferase, AFP - alpha-fetoprotein, CEA – carcinoembryonic antigen, CA125 - cancer antigen 125, CA19-9 - carbohydrate antigen 19-9.

from sensitivity and specificity of the RDW. The statistical significance was set as $p < 0.05$.

RESULTS

Characteristics of the patients and healthy controls

A total of 506 cases accorded with the inclusion criteria, including 189 diagnosed GC cases, 68 diagnosed gastric ulcer cases, 92 chronic gastritis cases, and 157 controls. The clinical and laboratory characteristics of the patient groups and healthy group are shown in Table 1. There was a statistically significant difference in age observed between the stomach illness groups and the healthy controls ($p < 0.001$), and the RDW levels of the disease groups were significantly higher than those of the control group ($p < 0.05$). In addition, the patients with GC, gastric ulcers, and chronic gastritis showed lower RBC, HB, and MPV levels but higher CA19-9 levels.

Comparisons of the mean RDW values

When compared with the control group and the other stomach illness groups, the RDW values of the GC group were obviously higher than those of the control group ($p < 0.001$) and chronic gastritis group ($p < 0.001$), but when compared with the gastric ulcer group, there was no statistically significant difference ($p = 0.998$) (Table 2, Figure 1). The group with gastric ulcers had higher RDW values than those with chronic gastritis ($p = 0.002$) and the healthy controls ($p < 0.001$). Moreover, there was no statistical difference in the RDW level between the chronic gastritis group and the control group.

RDW and other parameters for the risk of stomach disease

RDW, CEA, CA125, CA19-9, and platelet count levels were entered into the ROC curve (Table 3, Figure 2). In GC, the areas under the curve of the RDW, CEA, CA125, and platelets were greater than 50% ($p < 0.05$), but the area under the curve of the CA19-9 was less than 50%. In the gastric ulcer cases, the area under the curve of each of the five indexes was more than 50%, while the p-value of the CA19-9 was greater than 0.05. In chronic superficial gastritis, in addition to the platelets, the areas of the other indicators were greater than 50% (CEA and CA125, $p < 0.05$).

The diagnostic accuracy of RDW for the predication of

Table 2. The comparison of mean value of RDW in different groups.

Different groups A	Different groups B	The p-value of RDW
GC	Gastric ulcer	0.998
	Chronic gastritis	< 0.001
	Health control	< 0.001
Gastric ulcer	Chronic gastritis	0.002
	Health control	< 0.001
Chronic gastritis	Health control	0.204

GC - gastric cancer, RDW - red blood cell volume distribution width.

Table 3. The area under the ROC curve of PLT, CEA, CA125, and CA199 in disease groups.

Variables	GC			Gastric ulcer			Chronic gastritis		
	Area %	p-values	95% CI	Area %	p-values	95% CI	Area %	p-values	95% CI
PLT	70.2	< 0.001	0.646 - 0.757	63.8	0.01	0.548 - 0.728	48.9	0.766	0.409 - 0.568
CEA	72.9	< 0.001	0.677 - 0.782	70.3	< 0.001	0.629 - 0.776	73.5	< 0.001	0.671 - 0.800
CA199	45.3	0.132	0.392 - 0.514	51.2	0.78	0.419 - 0.604	51.2	0.755	0.435 - 0.589
CA125	88.4	< 0.001	0.848 - 0.919	84.1	< 0.001	0.781 - 0.900	76.1	< 0.001	0.700 - 0.821

ROC - receiver operating characteristic, PLT - platelet, CEA - carcinoembryonic antigen, CA19-9 - carbohydrate antigen, 19-9 CA125 – cancer antigen, 125 CI - confidence interval.

Table 4. Diagnostic accuracy of RDW for the predication of gastric diseases.

Disease groups	Area %	p	Cutoff	Youden index %	Sensitivity %	Specificity %	95% CI
GC	71.5	< 0.001	0.145	48.6	49.2	99.4	0.660 - 0.769
Gastric ulcer	78.0	< 0.001	0.145	49.4	50.0	99.4	0.706 - 0.853
Chronic gastritis	53.0	0.437	0.145	28.7	29.3	99.4	0.446 - 0.613

GC - gastric cancer, CI - confidence interval.

stomach illness is shown in Table 4. The area under the ROC curve for RDW in the patients with GC was 71.5% (95% CI 0.660 - 0.769, $p < 0.001$), while the sensitivity and specificity were 49.2% and 99.4%, respectively. The sensitivity and specificity of RDW in the patients with gastric ulcers were 50% and 99.4%, respectively, while the area under the ROC curve was 78.0% (95% CI 0.706 - 0.853, $p < 0.001$). In the chronic gastritis patients, the sensitivity and specificity were 29.3% and 99.4%, while the area under the ROC curve was 53.0% (95% CI 0.446 - 0.613, $p = 0.437$).

Correlation of the RDW

To explore the relationships between the RDW and the other parameters in the GC, gastric ulcer, and chronic gastritis patients, a bivariate correlation evaluation was performed (Table 5). In the GC group, the RDW level was significantly negatively correlated with RBC ($r = -0.343$, $p < 0.001$), HB ($r = -0.622$, $p < 0.001$), and MCV ($r = -0.147$, $p = 0.043$), but significantly positively correlated with the age ($r = 0.184$, $p = 0.011$) and platelets ($r = 0.235$, $p = 0.001$). In the gastric ulcer patients, RDW showed significantly negative correlations with the ALT ($r = -0.240$, $p = 0.049$), RBC ($r = -0.315$,

Table 5. Correlation of various parameters with RDW in disease groups.

Parameter	GC		Gastric ulcer		Chronic gastritis	
	r	p	r	p	r	p
Age	0.184	0.011	-0.002	0.988	0.026	0.803
Urea	0.026	0.719	0.074	0.549	-0.3	0.004
CR	0.059	0.416	-0.032	0.797	-0.128	0.223
AST	0.021	0.778	-0.076	0.537	0.322	0.002
ALT	0.047	0.522	-0.24	0.049	0.106	0.315
WBC	0.048	0.509	0.034	0.78	-0.006	0.958
RBC	-0.343	< 0.001	-0.315	0.009	-0.141	0.181
HB	-0.622	< 0.001	-0.634	< 0.001	-0.628	< 0.001
PLT	0.235	0.001	0.253	0.038	0.43	< 0.001
NEU %	0.13	0.075	0.144	0.243	0.008	0.942
MCV	-0.147	0.043	-0.651	< 0.001	-0.546	< 0.001
MPV	-0.031	0.67	0.052	0.674	-0.058	0.583
AFP	-0.032	0.664	0.172	0.161	-0.049	0.643
CEA	-0.022	0.767	-0.083	0.502	0.005	0.965
CA125	0.096	0.189	0.095	0.441	-0.028	0.789
CA199	-0.031	0.671	0.175	0.155	-0.016	0.882

GC - gastric cancer, Cr - creatinine, AST - aspartate aminotransferase, ALT - alanine aminotransferase, WBC - white blood cell, NEU%: neutrophilic granulocyte percentage, RBC - red blood cell, HB - hemoglobin, MCV - mean corpuscular volume, MPV - mean platelet volume, PLT - platelet, AFP - alpha-fetoprotein, CEA - carcinoembryonic antigen, CA125 - cancer antigen, 125 CA19-9 - carbohydrate antigen 19-9.

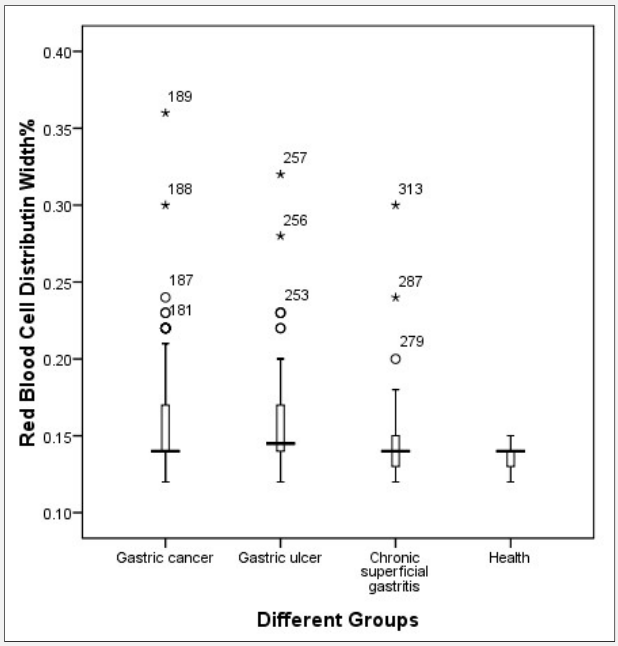

Figure 1. The RDW values in different gastric disease groups and healthy group.

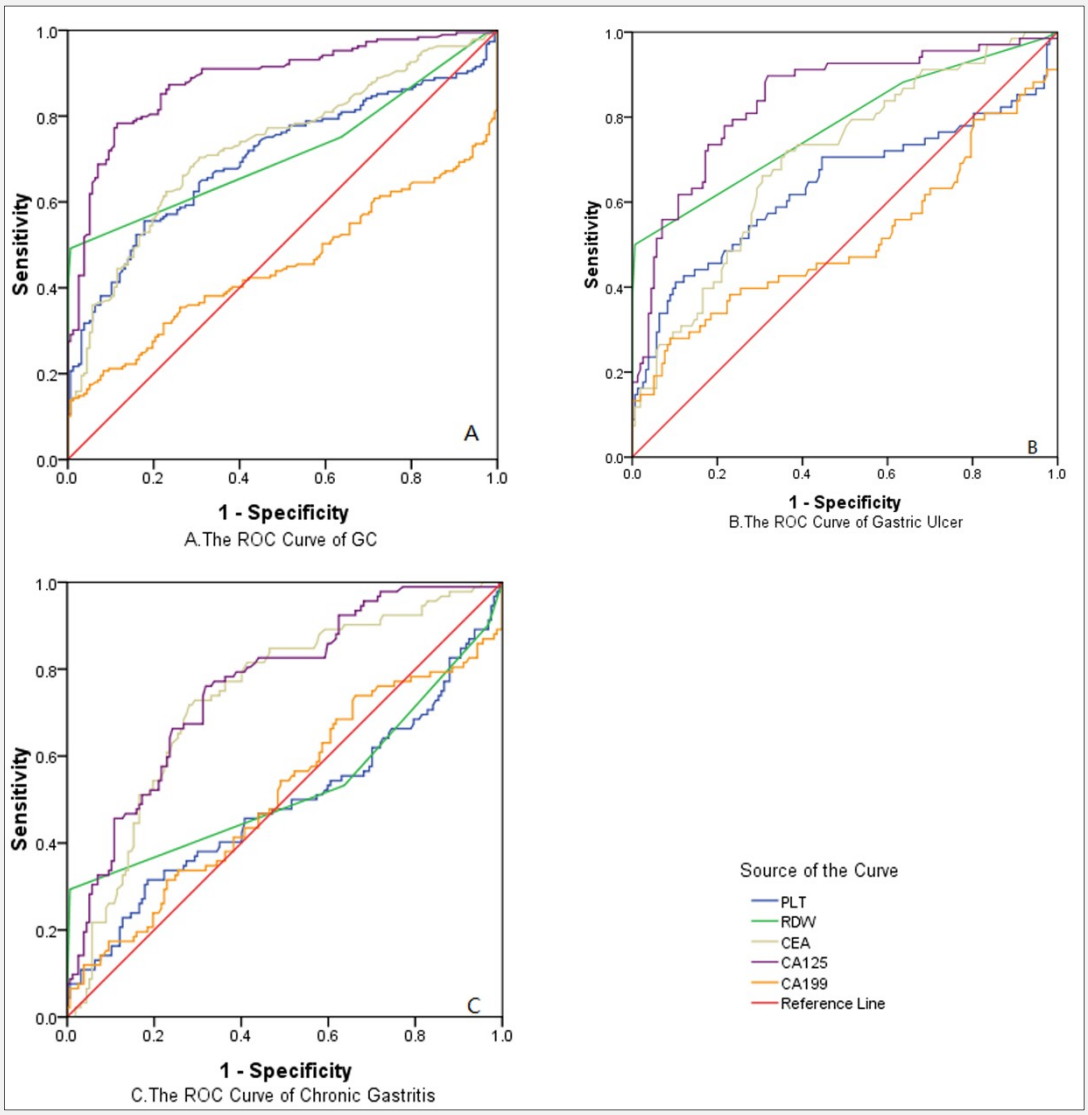

Figure 2. The ROC of GC, gastric ulcer and chronic gastritis.

A. The ROC curve for PLT, RDW, CEA, CA125, and CA199 for GC patients. B. The ROC curve for PLT, RDW, CEA, CA125, and CA199 for gastric ulcer patients. C. The ROC curve for PLT, RDW, CEA, CA125, and CA199 for chronic gastritis patients. ROC - receiver operating characteristic, PLT - platelet, CEA - carcinoembryonic antigen, CA125 - cancer antigen, 125 CA19-9 - carbohydrate antigen 19-9.

$p = 0.009$), HB ($r = -0.634$, $p < 0.001$), and MCV ($r = -0.651$, $p < 0.001$), but a significantly positive correlation with the PLT ($r = 0.235$, $p = 0.038$). In the chronic gastritis patients, the RDW showed a significantly inverse correlation with the urea ($r = -0.300$, $p = 0.004$), HB ($r = -0.628$, $p < 0.001$), MCV ($r = -0.546$, $p < 0.001$), but a significantly positive correlation with the AST ($r = 0.322$, $p = 0.002$) and PLT ($r = 0.430$, $p < 0.001$).

DISCUSSION

RDW reflects the heterogeneity of the peripheral blood erythrocyte volume and is based on the width of the RBC volume distribution curve [22]. Increased red cell destruction and ineffective red cell production can be characterized by an increased RDW [23]. RDW is a new chronic inflammatory indicator, unrelated to age, gender, or hemoglobin level, but it is connected to skin eruptions, multiple sclerosis, and ankylosing spondylitis

[15,24-27]. In addition, high RDW levels may represent nutrition deficiency [28]. Moreover, red cell destruction, ineffective hematopoiesis, chronic inflammation, and nutrition deficiency may also exist in other diseases of the digestion tract. Several recent studies have suggested that the RDW values are elevated in esophageal cancer [13] and colorectal cancer [29]. Therefore, in the current study, we extended the previous studies and researched the relationship between the RDW and gastric diseases.

The RDW values in GC, gastric ulcers, and chronic gastritis were higher than those in the control group, according to the results of this study, and we found that in GC and gastric ulcer patients the rising trend was more obvious. In addition, we demonstrated that in the three case groups the increased RDW levels were significantly negatively correlated with the HB and MCV. These results are consistent with the above report. At the same time, the ROC curve analysis showed that the cutoff point (14.5%) of the RDW could predict the presence of stomach illness. Similarly, a recent study demonstrated that the distribution of the RDW values could evaluate the severity of chronic heart failure [30]; therefore, it could also evaluate the severity of stomach diseases. The exact mechanism of correlation between a higher RDW value and gastric diseases is not yet clear. One of the most likely mechanisms is a systematic inflammatory reaction. It has been determined that an inflammatory reaction can increase the blood circulation of the inflammation factors, and although GC, gastric ulcers, and chronic gastritis belong to the inflammatory disease category, a Helicobacter pylori infection is the main reason for inflammation. In fact, one recent study found that the inflammatory cytokines TNF-α, IL-6, IL-1β, and IL-32 play important roles in gastric inflammation and cancer [31]. According to Voudoukies et al. [32], RDW levels are closely related to the other inflammatory factors in patients with inflammatory bowels.

Another possible mechanism is a nutritional imbalance. Akkermans et al. [33] showed that an elevated RDW could be helpful for identifying an iron deficiency as the cause of anemia in children. Stomach illness can result in anemia due to acute or chronic blood loss and a failure to absorbs nutrients, such as vitamin B12, iron, calcium, magnesium, and zinc [1]. Based on the above discussion, inflammation and nutrient deficiencies may be involved in higher RDW values in those patients with gastric diseases. Precancerous GC lesions include gastric ulcers and chronic gastritis; therefore, the RDW value is closely related with gastritis and GC, and RDW could be a new index of gastric diseases.

The present study does have several limitations; for example, the sample sizes were small, so the results may not reflect the characteristics of the entire population. Secondly, the increased RDW values may not have been accurate, and may have been affected by other factors. Finally, we did not dynamically evaluate the RDW values in those patients with stomach disease. Further studies should be conducted to examine the clinical role of the RDW, with increased sample sizes and dynamic testing for the RDW values.

Declaration of Interest:

The authors declare that they have no conflict of interest.

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