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ORIGINAL ARTICLE

The Clinical Application Value of RDW, CA153, and MPV in Breast Cancer

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SUMMARY

Background: **Early detection of tumors is beneficial to the treatment of patients. Certain indicators in the blood routine, such as red blood cell distribution width (RDW), are considered to be used to assess the patient's condition and prognosis. Mean platelet volume (MPV) is also used to assess the prognosis of patients. Carbohydrate antigen 153 (CA153) is considered to be a more specific antigen marker for breast cancer. The purpose of our study was to explore the diagnostic value of RDW, MPV, and CA153 for breast cancer (BC) and breast hyperplasia (BH).**

Methods: **The study included 104 breast cancer patients, 100 breast hyperplasia patients, and 100 healthy controls. CA153 was detected by an automatic electrochemical luminescence analyzer (Cobas e601, Roche Diagnostics, Switzerland). The concentration of RDW and MPV in serum was measured by Sysmex XN-10-B3 (Sysmex, Japan).**

Results: **Compared with the breast hyperplasia group, the RDW and CA153 of the breast cancer group were increased. The healthy control group, mammary gland hyperplasia group, and breast cancer were positively correlated with RDW and CA153. Logistic regression results show that increasing age, increasing RDW, and increasing CA153 can increase the risk of breast cancer. The area under the ROC (AUC) analysis showed that the combined specificity and sensitivity of the combined application of RDW, MPV, and CA153 for the identification of breast cancer is better than that of a single marker.**

Conclusions: **The combined application of RDW, MPV, and CA153 can improve the differential diagnosis of breast cancer and breast hyperplasia.**

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KEY WORDS

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INTRODUCTION

Breast cancer (BC) is of the most common cancers that threatens women's health [1-3]. Having a family history of breast cancer increases the risk of breast cancer [4-6]. The risk factors for breast cancer also include menarche (< 12 years old) and menopausal age (> 55 years old); marriage and childbirth history; chest has been exposed to high-dose radiation; estrogen levels; weight and obesity; long-term excessive drinking; and gene mutations [4,7]. Early detection and early treatment can effectively treat cancer.

Breast hyperplasia is thought to be related to hormone imbalance [8], especially hormones such as estrogen and progesterone. With the change of the menstrual cycle, there will be changes in hyperplasia and rejuvenation. For some reason, the endocrine hormone metabolism is imbalanced, the level of estrogen is increased, and hyperplasia and incomplete recovery of breast tissue can occur.

Studies have shown that red cell distribution width (RDW) serves as a relevant inflammation index for breast cancer patients [9]. At the same time, RDW is considered to be a prognostic indicator of solid tumors [10,11]. Carbohydrate antigen 153 (CA153) is the most important specific marker for breast cancer [12]. CA153 in 30% - 50% of breast cancer patients is significantly increased, and the change in its content is closely related to the treatment effect. It is the best indicator for breast cancer patients to diagnose and monitor postoperative recurrence and observe the efficacy [12,13]. CA-153 dynamic measurement is helpful for early detection of recurrence of stage II and stage III breast cancer patients after treatment [14]. Mean platelet volume (MPV) is an indicator of platelet activation [15]. Various genetic changes, disease occurrence, risk factors, and treatment methods can affect platelet activation. In general, increased peripheral platelet destruction leads to increased MPV in patients with thrombocytopenia. MPV is reduced in patients with thrombocytopenia caused by bone marrow disease. In infected patients, MPV is normal or increased during local inflammation. Omar M et al. found that the increase or decrease of MPV is a factor that can be prognostic in patients with non-small cell carcinoma (NSCLC) [16]. A study by Li MM et al. indicates that patients with breast cancer liver metastases have significantly lower MPV [17]. MPV is also associated with the treatment and prognosis of breast cancer patients [18].

However, the clinical application of RDW, CA153, and MPV combined diagnosis in breast cancer has not been reported. Therefore, this study aims to explore the role of age, RDW, CA153, and MPV in the diagnosis of breast cancer.

MATERIALS AND METHODS

Subjects

We conducted a retrospective study of breast cancer patients diagnosed in the Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou, China from January 2018 to December 2019. The study included 104 women with breast cancer, 100 with breast hyperplasia, and 100 healthy volunteers as controls. The subjects of this study were all diagnosed as breast cancer by pathological biopsy for the first time and did not receive chemotherapy before diagnosis. The following patients were excluded: anemia and other blood diseases, cardiovascular disease, various types of diabetes, kidney disease, patients who had received iron therapy or had a history of blood transfusion within the past three months. The research has been approved by the Ethics Committee.

Methods

Samples of 4.0 mL of fasting venous blood were collected from all patients and the control group. The serum was centrifuged at 4,000 rpm for 10 minutes. CA-153 was detected by an automatic electrochemical luminescence analyzer (Cobas e 601, Roche Diagnostics, Switzerland). The concentration of RDW and MPV in serum was measured by Sysmex XN-10-B3 (Sysmex, Japan) [19]. All tests are performed by following the Code of Practice Manual.

Statistical analysis

Data analysis was performed using SPSS 25.0 software. All data were tested by the Kolmogorov-Smirnov test. Normally distributed data are expressed as $x \pm s$. Non-normal distribution data is represented as M (P25, P75). One-way analysis of variance was used to analyze the differences between the three sets of baseline data. Tukey's test is used to compare the two groups between the three groups of indicators. Spearman's correlation was used to analyze the correlation between the three groups of people with RDW and CA153. Logistic regression preliminarily established a model for the three indicators. The combined prediction probability of each combined biomarker was calculated by binary logistic regression. The area under the curve (AUC) uses MedCalc Statistics software. The ROC curve can be used to test the significance of differences between statistical regions. p-value < 0.05 (two tailed) indicates a statistical difference.

RESULTS

All patients (n = 304) were female. There were 104 cases in the breast cancer group (age range: 26 - 80 years old). There were 100 patients in the mammary gland hyperplasia group (age range: 18 - 56 years), and the study also included 100 healthy controls (age range: 23 - 65 years). In the ages of these three groups, the

Table 1. Clinical characteristics of the participants.

	Breast cancer	Breast hyperplasia group	Control group	p
Number	104	100	100	
Age (years)	50.17 ± 10.39 [a]	35.59 ± 8.84	37.00 ± 9.47 [c]	< 0.001
RDW, (fL)	47.71 ± 9.53 [a]	40.50 ± 4.07	40.22 ± 3.27 [c]	< 0.001
MPV, (fL)	10.02 ± 0.95	10.22 ± 1.04 [b]	9.44 ± 1.21 [c]	< 0.001
CA153, U/mL	19.15 ± 11.98 [a]	11.98 ± 6.00	10.14 ± 4.73 [c]	< 0.001

Note: p-values were calculated by one-way ANOVA tests.
Abbreviations: CA153 - cancer antigen 153, MPV - mean platelet volume, RDW - red cell distribution width.
[a] Shows a significant difference (p < 0.05) between Breast cancer group and Breast hyperplasia group (Tukey's test).
[b] Shows a significant difference (p < 0.05) between Breast hyperplasia group and control group (Tukey's test).
[c] Shows a significant difference (p < 0.05) between Breast cancer group and control group (Tukey's test).

Table 2. Logistic regression analysis of RDW, MPV, and CA153 after adjusting for age factors.

Variables in the Equation									
								95% C.I. for EXP (B)	
		B	S.E.	Wald	df	Sig.	Exp (B)	lower	upper
Step 1 [a]	age	0.165	0.029	32.434	1	< 0.001	1.180	1.114	1.249
	RDW	0.252	0.055	21.239	1	< 0.001	1.287	1.156	1.432
	MPV	-0.399	0.252	2.507	1	0.113	0.671	0.409	1.100
	CA153	0.098	0.028	12.134	1	< 0.001	1.103	1.044	1.166
	constant	-15.294	3.620	17.849	1	< 0.001	2.2787E-7		

[a.] Variable(s) entered on step 1: Age, RDW, MPV, CA153.

Table 3. Predictive efficiency of each marker for diagnosis of breast cancer.

Markers	AUC (95% CI)	Youden index J	Sensitivity (%)	Specificity (%)	+PV	−PV
RDW	0.827 (0.768 - 0.877)	0.558	80.8	75.0	77.1	78.9
MPV	0.565 (0.494 - 0.634)	0.150	51.0	64.0	59.6	55.7
CA153	0.715 (0.648 - 0.776)	0.372	69.2	68.0	69.2	68.0
RDW + MPV + CA153	0.866 (0.812 - 0.910)	0.610	74.0	87.0	85.6	76.3

Abbreviations: +PV - positive predictive value, AUC - area under curve, CI - confidence interval, -PV - negative predictive value.

breast cancer group was higher than the breast hyperplasia group and the control group ($p < 0.05$). For the RDW index, the breast cancer group is also higher than the mammary gland hyperplasia group and the control group ($p < 0.05$). For MPV indicators, the control group was less than the breast cancer group and breast hyperplasia group ($p < 0.05$). For the CA153 index, the breast cancer group is also higher than the breast hyperplasia group and healthy control group ($p < 0.05$). The patient's baseline characteristics are shown in Table 1. Correlation analysis results showed that in the healthy control group, mammary gland hyperplasia group, and

Table 4. Pairwise comparison of ROC curves.

	CA153 vs. combined	CA153 vs. RDW	CA153 vs. MPV	MPV vs. RDW	MPV vs. combined	RDW vs. combined
Difference between areas	0.151	0.112	0.150	0.262	0.301	0.039
Standard error	0.034	0.046	0.054	0.050	0.045	0.019
95% confidence interval	0.084 - 0.218	0.021 - 0.203	0.045 - 0.256	0.164 - 0.361	0.214 - 0.389	0.002 - 0.076
Z statistic	4.445	2.418	2.795	5.207	6.737	2.050
p	< 0.001	0.016	0.005	< 0.001	< 0.001	0.040

Note: Combined: RDW + MPV + CA153.

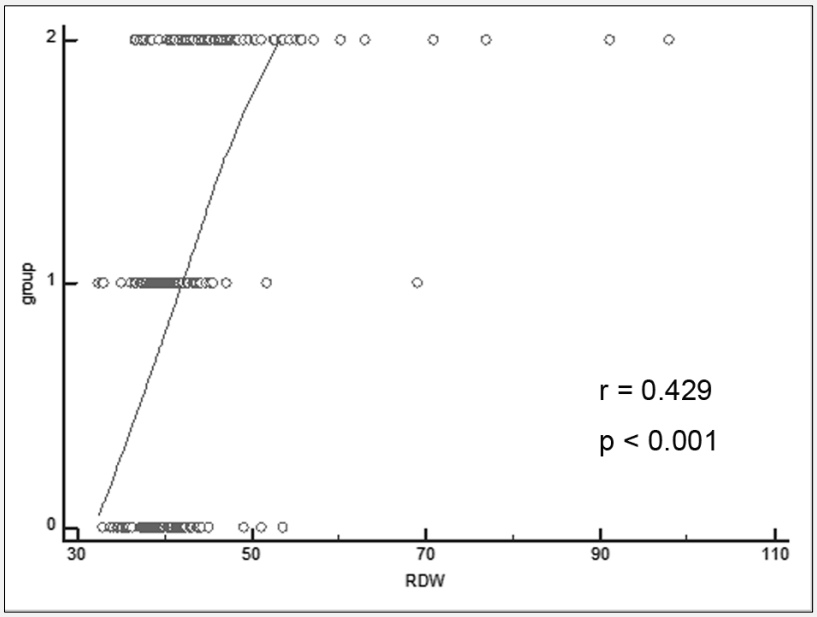

Figure 1. Correlation between the distribution width of red blood cells and three groups of cases.

breast cancer group, the levels of RDW and CA153 increased sequentially and showed a positive correlation. (Figure 1 and Figure 2).

The logistic regression analysis model established by RDW, CA153, MPV, and age factors between the breast cancer group and the healthy control group is shown in Table 2. Set the respective variables X1 = age, X2 = RDW, X3 = MPV, X4 = CA153, and obtain the regression model of probability prediction of breast cancer as LogitP = -15.294 + 0. 165 age + 0. 252 RDW + 0. 098 CA153 variable.

The results of the ROC curve are shown in Figure 3 and Table 3. RDW, MPV, and CA153 were 0.827 (0.768 - 0.877), 0.565 (0.494 - 0.634), and 0.715(0.648 - 0.776). Among these three parameters, MPV's diagnostic sensitivity is higher than that of RDW and CA153, and the diagnostic specificity of CA153 is higher than RDW and MPV. However, the test combination of the three parameters showed the maximum AUC of 0.866 (0.812 - 0.910). The combination of the three has a better comprehensive diagnostic performance. Besides, the pairwise comparison of the AUC of the ROC curve shows that the comprehensive prediction index is statistically different from the three indexes ($p < 0.001$) (Table 4).

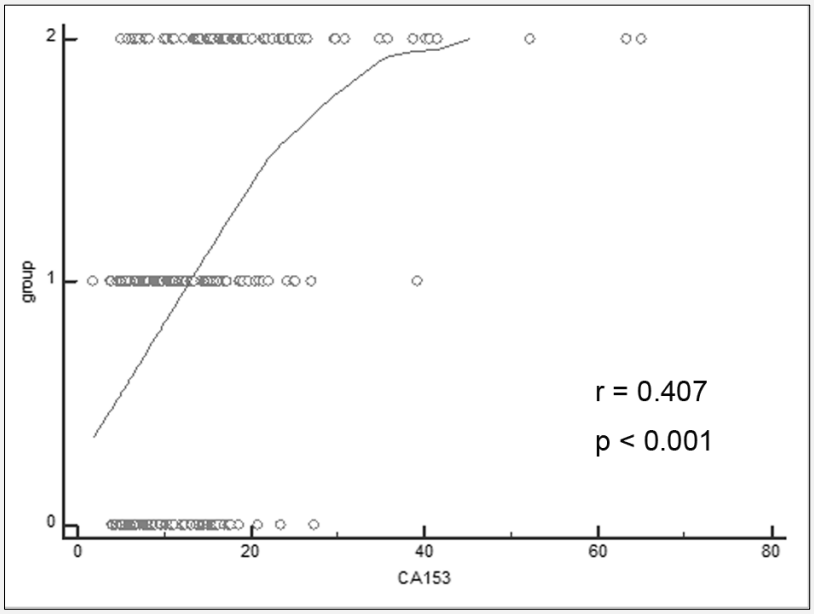

Figure 2. Correlation between CA153 and three groups of cases.

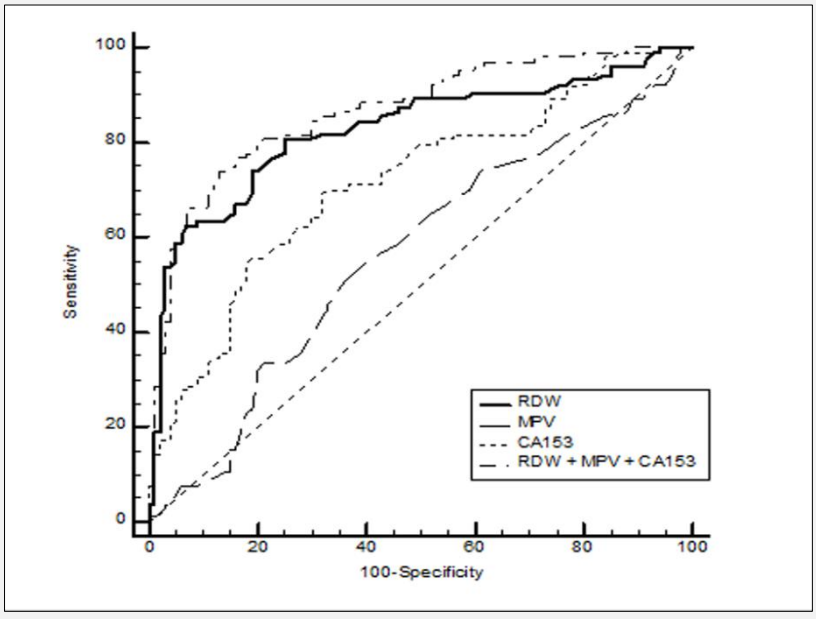

Figure 3. ROC curve of three indicators.

DISCUSSION

To our knowledge, the main basis for diagnosing breast cancer is histopathological examination. Presently, the diagnosis of breast cancer includes medical imaging, genetic testing, pathological examination, and hematological indicators. Early diagnosis and interventional therapy can effectively prevent breast cancer and significantly improve the survival rate of breast cancer patients [20]. Our results show that the levels of RDW and CA153 in breast cancer patients have increased to varying degrees relative to healthy people and patients with breast hyperplasia. Consistent with the studies of Sun H et al. and Zhao S et al. [9,21]. Logistic regression result show that age factors may also be risk factors for breast cancer. This is consistent with the research findings of Antony MP et al. [22]. Besides, the ROC curve shows that compared with a single index, the combination of RDW, MPV, and CA153 can have better diagnostic efficacy.

Red blood cell distribution width (RDW) is a parameter of routine blood detection, used to reflect the variability of red blood cell size. Recent studies have shown that an increase in RDW value is thought to be related to the degree of inflammation [20]. The research of Seretis C et al. shows that compared with patients with breast fibroadenoma, the RDW of breast cancer patients is significantly increased [11]. This result is consistent with the results of this study. Studies have shown that increased or decreased RDW can predict the prognosis of breast cancer patients [10,23].

MPV is regarded as a marker of inflammation in routine blood tests. A study by Mutlu H et al. found that MPV can predict the prognosis of neoadjuvant chemotherapy in patients with locally advanced breast cancer (LABC) [24]. Logistic regression analysis in this study further shows that MPV is not independently related to breast cancer risk. But study by Sun H et al. showed that MPV is associated with breast cancer lymph node metastasis. The source of the difference may be related to the limitation of the small amount of specimen.

CA153 is an important marker of breast cancer. The results of this study show that CA153 is higher in the cancer group than the mammary gland hyperplasia group, which is consistent with existing studies [21,25-27]. The diagnosis and treatment of breast cancer can be further identified in conjunction with histopathology. Compared with MPV and CA153, RDW has higher sensitivity. But in general, the combination of the three has higher sensitivity and specificity for the differentiation of breast cancer and breast hyperplasia. It is suggested that the application of the combination of blood routine indexes and tumor markers can improve the early diagnosis of breast cancer and the differential diagnosis of breast hyperplasia.

In conclusion, this study shows that the combined use of RDW, MPV, and CA153 can help early diagnosis of breast cancer and differential diagnosis of breast hyperplasia. This can effectively improve the diagnostic efficiency of breast cancer. Of course, this study has limitations. The amount of specimens in this study is relatively small. Therefore, a large number of multi-center specimens will be needed to strengthen these results in the future.

Declaration of Interest:
The authors declare that they have no conflicts of interest.

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