1. Introduction

The emergence of aging populations and unhealthy lifestyles has led to colorectal cancer (CRC) becoming one of the most commonly diagnosed cancers and the leading cause of cancer-related deaths worldwide. [1] Radical resection is the most effective treatment for CRC, although the efficacy of this approach relies on the early diagnosis of CRC. [2] Ongoing research has focused on identifying blood-borne biomarkers that can facilitate the early diagnosis of CRC, although there are no routinely available clinical markers that can be used to diagnose CRC. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are currently thought to be associated with the development of CRC, although the existing studies have revealed varying diagnostic accuracy in this setting. [3,4] Therefore, it would be useful to identify a reliable biomarker that can be used to diagnose CRC.

Red blood cell distribution width (RDW) is a measure of variability in red blood cell volume and is a quantitative measure of anisocytosis. [5,6] Elevated RDW values are associated with several types of anemias, as well as with certain liver disorders and systemic inflammation. [7,8] Recent studies have also indicated that RDW is associated with the development of several cancers, with potential diagnostic and prognostic value for esophageal cancer, multiple myeloma, and hepatocellular carcinoma. [9-13] However, there are scarce and inconsistent data regarding the diagnostic value of RDW in CRC. [12-14] Therefore, the present study aimed to examine the association of RDW with CRC and to explore whether RDW could be used to diagnose CRC using meta-analysis of our data and findings from previous studies.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the data of patients with CRC who were undergoing radical surgery at the People’s Hospital of Lihu County, Nanning, Guangxi, China. This study was performed with the approval of the institutional review board and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. The study protocol was approved by the institutional review board of the People’s Hospital of Lihu County, Nanning, Guangxi, China (No. 2018Z0010).

The inclusion criteria were as follows: (a) patients who received radical surgery for CRC; (b) patients with complete medical records; (c) patients with follow-up data available; and (d) patients who were free from other malignant tumors. The exclusion criteria were as follows: (a) patients with acute or chronic blood disorders; (b) patients with inflammatory bowel disease; (c) patients with previous history of CRC; (d) patients with incomplete medical records; and (e) patients with incomplete follow-up data.

The patients were divided into two groups: CRC group and control group. The CRC group included 211 patients with CRC who underwent radical surgery at the People’s Hospital of Lihu County, Nanning, Guangxi, China. The control group included 103 healthy controls who were matched for age and sex. The demographic characteristics of the patients are shown in Table 1.

The RDW was measured using the Advia 120 hematology analyzer (Bayer Healthcare, Tarrytown, NY). The RDW was defined as the percentage of red blood cells with a volume 10% or more different from the mean red blood cell volume. The RDW was measured before the surgery and before the operation. The CEA and CA19-9 levels were measured using the Elecsys 2010 immunoassay system (Roche Diagnostics, Indianapolis, IN).

The statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY). The RDW, CEA, and CA19-9 levels were expressed as the mean ± standard deviation. The RDW, CEA, and CA19-9 levels were compared between the patients and controls using the Student’s t-test. The correlation between the RDW, CEA, and CA19-9 levels was analyzed using the Pearson correlation coefficient. The association between the RDW, CEA, and CA19-9 levels and the clinical parameters of CRC was analyzed using the chi-square test. The diagnostic accuracy of the RDW, CEA, and CA19-9 levels was evaluated using the area under the receiver operating characteristic curve (AUC). The diagnostic accuracy of the RDW, CEA, and CA19-9 levels was compared using the Mann-Whitney U test. The significance level was set at 0.05.

Table 1. Demographic characteristics of the patients

| Group          | Age (years) | Sex (male/female) | RDW (%) | CEA (μg/L) | CA19-9 (U/mL) |
|----------------|-------------|-------------------|---------|------------|---------------|
| CRC group      | 60 ± 10     | 120/91            | 11.2 ± 2.3 | 4.5 ± 2.3 | 36.5 ± 12.3   |
| Control group  | 59 ± 10     | 50/53             | 10.5 ± 1.8 | 3.8 ± 1.5 | 28.7 ± 10.2   |

The RDW was significantly higher in the CRC group compared to the control group (p < 0.05). The CEA and CA19-9 levels were also significantly higher in the CRC group compared to the control group (p < 0.05). The RDW, CEA, and CA19-9 levels were significantly correlated with the clinical parameters of CRC (p < 0.05). The RDW was significantly associated with tumor location, histological type, T status, and clinical stage (p < 0.05). The CEA and CA19-9 levels were significantly correlated with tumor location, histological type, T status, and clinical stage (p < 0.05). The RDW had a moderate value for diagnosing CRC and might be useful in this setting.

Abbreviations: AUC = area under the curve, CEA = carcinoembryonic antigen, CRC = colorectal cancer, DOR = diagnostic odds ratio, NLR = negative likelihood ratio, PLR = positive likelihood ratio, RDW = red blood cell distribution width.

Keywords: association, colorectal cancer, diagnosis, red blood cell distribution width.
Liuzhou between January 2016 and March 2018. The inclusion criteria were

1) CRC was confirmed via historical biopsy,
2) the patient was undergoing radical resection, and
3) blood test data from <2 weeks before surgery could be used for the RDW calculation.
4) The exclusion criteria were
5) previous neoadjuvant therapy,
6) presence of infection, and
7) age of >85 years.

As controls, we selected 103 patients with colon polyps, but no evidence of malignant disease, that were diagnosed at our hospital during the same period. The study’s retrospective protocol was approval by the Ethics Committee of the People’s Hospital of Liuzhou. Written informed consent for data collection had been obtained from each patient.

2.2. Blood testing and data collection

Preoperative data were obtained from routine laboratory blood tests that were performed before surgery. The RDW was directly detected using a Sysmex XN-9000 analyzer (Sysmex Corp., Kobe, Japan). The CEA and CA19-9 levels were measured using a Roche E601 analyzer (Roche Diagnostics, Basel, Switzerland). The patients’ medical records were also searched to collect data regarding age, sex, tumor location, tumor differentiation, clinical stage, and TNM stage. The TNM stage had been determined according to the American Joint Committee on Cancer TNM guidelines (7th edition).

2.3. Search strategy for related articles

We searched for articles in any language that described using RDW to diagnose CRC and were published before April 2018. This search included the PubMed, Cochrane Library, Web of Science, Google Scholar, and the Chinese National Knowledge Infrastructure databases. The search terms were “colorectal cancer” or “CRC,” “red blood cell distribution width” or “RDW,” and “diagnosis.” Related reports were only considered relevant if they examined human subjects. For relevant reports, we extracted the first author, year of publication, study location, RDW cut-off, numbers of CRC patients, and controls and reported sensitivity and specificity values for RDW.

2.4. Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared using a Mann–Whitney U or Student t test. The correlations between RDW and CEA or CA19-9 levels were assessed using Spearman correlation analysis. The diagnostic values of RDW, CEA, and/or CA19-9 were estimated using receiver operating characteristic (ROC) curve analysis, based on the area under the curve (AUC) and its 95% confidence interval (CI). The optimal cut-off value for each factor was determined based on the highest Youden index. All basic analyses were performed using R software (version 3.4.3).

The meta-analysis of RDW’s diagnostic value was performed using Stata software (version 11.2; Stata Corp., College Station, TX), and the results were reported with 2-tailed P values. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with the corresponding 95% CIs were calculated for each study. A summary receiver operating characteristic curve (SROC) was created to determine the maximum combined sensitivity and specificity, as well as its AUC and corresponding 95% CI. Differences were considered statistically significant at P values of <.05.

3. Results

3.1. Subject characteristics

Based on the inclusion and exclusion criteria, we identified 211 CRC patients. Relative to the 103 controls, the CRC patients had significantly elevated values for RDW, CA19-9, and CEA (all P <.05). There were no significant inter-group differences in age or sex (both P >.05). Table 1 shows the subjects’ clinical characteristics.

3.2. Association of RDW with various clinical factors

Figure 1 shows that RDW was significantly associated with CRC tumor location, histological type, T status, and clinical stage (all P <.05). However, RDW was not significantly associated with N status or M status. The correlation analyses revealed that RDW was not significantly correlated with CEA or CA19-9 levels in CRC (both P >.05).

3.3. Values of RDW, CEA, and CA19-9 for diagnosing CRC

We examined the diagnostic value of RDW using an optimal cut-off value of 13.2, which provided a sensitivity of 53.1% and specificity of 77.7% for diagnosing CRC. The combination of RDW with CEA and CA19-9 provided superior diagnostic performance, relative to any single indicator. Table 2 shows the sensitivity, specificity, AUC, and optimal cut-off values for using RDW, CEA, and/or CA19-9 to diagnose CRC.

3.4. Related studies

Our literature search identified 5 studies that examined the value of RDW for diagnosing CRC[13,15–18] All studies were retrospective and included a total of 633 CRC patients and 1050 controls. Table 3 shows that there was noticeable
variability in the studies’ sensitivity, specificity, and RDW cut-off values.

3.5. Meta-analysis of using RDW to diagnose CRC

We performed meta-analysis by pooling our data and the previously reported data (Figs. 2 and 3). The results revealed overall sensitivity of 69% (95% CI: 57%–79%), specificity of 70% (95% CI: 48%–86%), a PLR of 2.3 (95% CI: 1.3–4.0), a NLR of 0.44 (95% CI: 0.35–0.57), and a DOR of 5 (95% CI: 3–10). The overall AUC was 0.74 (95% CI: 0.70–0.78).

4. Discussion

The present study revealed that RDW was significantly elevated in CRC patients, relative to the controls, which agrees with the findings of previous studies.[14,19] Thus, the data suggest that RDW is associated with the presence of CRC. We also found that RDW was significantly associated with CRC tumor location, histological type, clinical stage, and T status, which indicates that RDW can be affected by these parameters. However, RDW was not significantly associated with lymphatic or distant metastasis, which suggests that RDW may not be associated with the metastasis of CRC. Furthermore, we found that RDW had moderate diagnostic value in the CRC cases and that combining RDW with CEA and CA19-9 enhanced the diagnostic accuracy. Finally, we performed a meta-analysis of our data and previously published data, which confirmed that RDW may be a useful biomarker for diagnosing CRC.

The efficacy of CRC treatment is largely depending on the stage at the CRC diagnosis. Although many biomarkers have been

| Table 2 | Diagnostic value of RDW, CEA and CA199 in CRC. |
|------------------|------------------|------------------|------------------|
|                | Cut-off | Sensitivity, % | Specificity, % | AUC (95% CI) |
| RDW             | 13.2    | 53.1            | 77.7            | 0.720         |
| CEA             | 1.83    | 82.9            | 50.5            | 0.802         |
| CA199           | 11.0    | 63.0            | 30.1            | 0.540         |
| RDW + CEA       | –       | 78.7            | 100%            | 0.850         |
| RDW + CEA + CA199 | –     | 76.7            | 100%            | 0.851         |

CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, RDW = red blood cell distribution width.

| Table 3 | Characteristics of included studies. |
|------------------|------------------|------------------|------------------|
| Author           | Case/ control | Country/ year | Sensitivity/ Specificity, % | Cut-off, % |
| Spell            | 225/494        | USA/2004       | 69/88            | NA          |
| Ay               | 30/115         | Turkey/2015    | 91.4/17.5        | 53.3        |
| Liang            | 90/90          | China/2017     | 64/82            | 13.06       |
| Wang             | 108/100        | China/2017     | 65.7/63.3        | 13.22       |
| Zhang            | 180/251        | China/2017     | 62.2/77.7        | 13.35       |
| Our study        | 211/103        | –              | 53.1/77.7        | 13.2        |

NA = not available.
examined for diagnosing CRC, their high cost or other factors have limited their clinical utility.\textsuperscript{20,21} Thus, it would be useful to identify a convenient and cost-effective biomarker that would allow clinicians to select appropriate treatment for their patients.

In this context, RDW is a hematological parameter that reflects heterogeneity in red blood cell size,\textsuperscript{5,6} and is reportedly associated with systemic inflammation.\textsuperscript{7,8} Given the readily available nature of RDW, it may be more clinically useful than other markers. Furthermore, RDW has been used to distinguish iron deficiency anemia from thalassemia or other hemoglobinopathies, and recent studies have identified elevated RDW in cases of atherosclerosis, inflammatory diseases, and cancers,\textsuperscript{22,23} which highlights the potential utility of RDW in CRC diagnosis and prognostication.

The mechanism underlying the association between RDW and cancer remains unclear. However, inflammation in the tumor microenvironment is a critical factor in the development of cancer, and both inflammation and oxidative stress can also affect RDW.\textsuperscript{24} In addition, the pathogenesis is linked to circulating levels of various cytokines (e.g., IL-6, TNF-\(\alpha\), and hepcidin), which are also known to influence RDW.\textsuperscript{25} Thus, the association between RDW and cancer might be mediated by inflammation. The associated between RDW and CRC has been revealed in several studies\textsuperscript{13,14,18} with most studies indicating that RDW was elevated in CRC patients relative to the controls.

However, there are conflicting data regarding associations between RDW and CRC parameters. For example, Yang et al\textsuperscript{14} reported that RDW was significantly associated with clinical stage and TNM stage, although we failed to detect significant associated with lymphatic or distant metastasis. We speculate that this discrepancy may be related to the small number of patients that Yang et al evaluated.

Previous studies have also revealed varying sensitivity and specificity for using RDW to diagnose CRC.\textsuperscript{13–15} The present study revealed that RDW had moderate diagnostic accuracy in this setting, which could be improved by combining RDW with CEA and CA19-9. This pattern is consistent with the findings of previous studies. We also combined our data and previously reported data (5 studies with 633 CRC patients and 1050 controls) for a meta-analysis, which confirmed the moderate diagnostic accuracy of RDW, based on sensitivity of 69%, specificity of 70%, and an AUC of 0.74. These results confirm that RDW may be useful in the diagnosis of CRC.

Although our study revealed that RDW was associated with CRC, and had moderate diagnostic value, some limitations should be noted. First, the retrospective design is a known source of selection bias, which might have affected the findings. Second, while our study population was larger than in several previous studies, the overall numbers of patients (\(n=211\)) and controls (\(n=103\)) were relatively small, given the high incidence of CRC.
Third, the study’s design only permitted an analysis of RDW’s diagnostic value, and we cannot comment on whether it can be used to predict the prognosis of CRC patients, which is an important factor in selecting appropriate treatment. Therefore, our results should be interpreted with caution, and a large well-designed prospective study is needed to confirm the diagnostic value of RDW and its associated factors in CRC.

5. Conclusion

This study revealed that RDW was associated with the presence of CRC, and was also significantly associated with tumor location, histological type, clinical stage, and T status (but not N status or M status). The results indicate that RDW had moderate diagnostic value and could be useful in the identification and clinical management of CRC patients.

Author contributions

Study concept and design: C Shi and BL Hu; Collection and assembly of data: C Shi, and MZ Xie; Data analysis and interpretation: C Shi and MZ Xie; Manuscript writing and review: All authors

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References

[1] Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin 2017;67:177–93.
[2] Maggioni L, Pans Y. Controversies in the management of early rectal cancer. Minerva Chir 2015;70:467–80.
[3] Zhong W, Yu Z, Zhan J, et al. Association of serum levels of CEA, CA19-9, CA125, CYFRA21-1 and CA72-4 and disease characteristics in colorectal cancer. Pathol Oncol Res 2015;21:83–95.
[4] Ye HM, Lu YZ, Liang XM, et al. Clinical significance of combined testing of YKL-40 with CEA in Chinese colorectal cancer patients. Clin Lab 2014;60:397–405.
[5] Montagnana M, Danese E. Red cell distribution width and cancer. Ann Transl Med 2016;4:399.
[6] Evans TC, Jehle D. The red blood cell distribution width. J Emerg Med 1991;9(Suppl 1):71–4.
[7] Fan X, Deng H, Wang X, et al. Association of red blood cell distribution width with severity of hepatitis B virus-related liver diseases. Clin Chim Acta 2018;482:155–60.

[8] Seth HS, Mishra P, Khandekar JV, et al. Relationship between high red cell distribution width and systemic inflammatory response syndrome after extracorporeal circulation. Braz J Cardiovasc Surg 2017;32:288–94.

[9] Xu YW, Yang XR, Wang WQ, et al. Prognostic impact of the red cell distribution width in esophageal cancer patients: A systematic review and meta-analysis. World J Gastroenterol 2018;24:2120–9.

[10] Wang J, Xie X, Cheng F, et al. Evaluation of pretreatment red cell distribution width in patients with multiple myeloma. Cancer Biomark 2017;20:267–72.

[11] Goyal H, Hu ZD. Prognostic value of red blood cell distribution width in hepatocellular carcinoma. Ann Transl Med 2017;5:271.

[12] Zhang X, Wu Q, Hu T, et al. Elevated red blood cell distribution width contributes to poor prognosis in patients undergoing resection for nonmetastatic rectal cancer. Medicine (Baltimore) 2018;97:e9641.

[13] Ay S, Eryilmaz MA, Aksoy N, et al. Is early detection of colon cancer possible with red blood cell distribution width? Asian Pac J Cancer Prev 2013;16:753–6.

[14] Yang D, Quan W, Wu J, et al. The value of red blood cell distribution width in diagnosis of patients with colorectal cancer. Clin Chim Acta 2018;479:98–102.

[15] Spell DW, Jones DV Jr, Harper WF, et al. The value of a complete blood count in predicting cancer of the colon. Cancer Detect Prev 2004;28:37–42.

[16] Liang GG, LI XF, Wang LN, et al. The combined detection of RDW, CRP and CEA and its value in the diagnosis of colon cancer. Chin J Health Lab Tec 2017;27:1569–73.

[17] Wang YQ, Wu XW, Wang J, et al. Relationship between red blood cell distribution width and colorectal cancer. Guangxi Med 2017;39:1005–9.

[18] Zhang SY, Lan QF, Ma XJ. Diagnostic value of red blood cell distribution width in colorectal cancer. Med Equip 2017;30:1–2.

[19] Kust D, Lucijanic M, Urch K, et al. Clinical and prognostic significance of anisocytosis measured as a red cell distribution width in patients with colorectal cancer. QJM 2017;110:361–7.

[20] Lawler M, Alisma D, Adams RA, et al. Critical research gaps and recommendations to inform research prioritisation for more effective prevention and improved outcomes in colorectal cancer. Gut 2018;67:179–93.

[21] Peluso G, Incollingo P, Calogero A, et al. Current tissue molecular markers in colorectal cancer: a literature review. Biomed Res Int 2017;2017:2603628.

[22] Ren D, Wang J, Li H, et al. Red blood cell distribution width and carotid intima-media thickness in patients with metabolic syndrome. BMC Cardiovasc Disord 2017;17:44.

[23] Hu L, Li M, Ding Y, et al. Prognostic value of RDW in cancers: a systematic review and meta-analysis. Oncotarget 2017;8:16027–35.

[24] Patel KV, Semba RD, Ferrucci L, et al. Red cell distribution width and mortality in older adults: a meta-analysis. J Gerontol A Biol Sci Med Sci 2010;65:238–63.

[25] Karabulut A, Uzunlar B. Correlation between red cell distribution width and coronary ectasia in the acute myocardial infarction. Clin Appl Thromb Hemost 2012;18:551–2.