The combined detection of hematological indicators is used for the differential diagnosis of colorectal cancer and benign-colorectal lesions

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Abstract.
OBJECTIVE: This article aims to investigate the clinical value of hemoglobin/red cell distribution width ratio (Hb/RDW), C-reactive protein/albumin ratio (CAR) and plateletcrit (PCT) combined with carcinoembryonic antigen (CEA) in colorectal cancer (CRC) auxiliary diagnosis.

METHODS: We retrospectively analyzed in 718 subjects (212 with CRC, 209 with benign colorectal lesions (BCL), 111 with other cancers, and 186 healthy controls).

RESULTS: The CAR, PCT, and CEA in the CRC group were higher than those in the BCL, other cancers, and the healthy control group. However, Hb/RDW in the CRC group was lower than the other three groups. Moreover, there were significant differences in Hb/RDW and CEA among different T-N-M stages (all \( P < 0.05 \)). Multivariate logistic regression showed that low level of Hb/RDW and high level of CAR, CEA, PCT were risk factors for CRC, and are correlated with CRC stage. Additionally, the area under the receiver operating characteristic curve (AUC) of Hb/RDW + CEA (AUC: 0.735), CAR + CEA (AUC: 0.748), PCT + CEA (AUC: 0.807) was larger than that of Hb/RDW (AUC: 0.503), CAR (AUC: 0.614), or PCT (AUC: 0.713) alone (all \( P < 0.001 \)) in distinguishing CRC from BCL.

CONCLUSIONS: Hb/RDW, CAR, PCT, and CEA are independent risk factors for CRC. Hb/RDW, CAR, and PCT combined with CEA have significant value for auxiliary differential diagnosis of CRC and BCL.

Keywords: Hemoglobin/red cell distribution width ratio, C-reactive protein/albumin ratio, plateletcrit, carcinoembryonic antigen, colorectal cancer

1. Introduction

Colorectal cancer (CRC) is a common malignancy of the digestive system [1]. Inflammation is involved in the development and progression of cancer [2], with at least 15% of tumors being caused by inflammations [3]. As a commonly used indicator of inflammation, C-reactive protein (CRP) is widely used in the diagnosis of inflammation-related diseases and prognostic evaluation of tumors. Meanwhile, serum albumin (Alb) is commonly used to evaluate the patient’s nutritional status and the prognosis of malignant tumors in inflammation-related diseases. C-reactive protein/albumin ratio (CAR), a ratio of CRP to Alb, offers a more accurate and comprehensive assessment for postoperative recovery in patients with malignant...
5. Hemoglobin (Hb) is a known prognostic marker for CRC, the effect of anemia on prognosis has been shown in CRC and other cancers [7]. Currently, red cell distribution width ratio (RDW), a parameter to evaluate the heterogeneity of red blood cell size, has been also used to diagnose cancer such as CRC [8]. A recent study [9] found that the Hb/RDW, a ratio of Hb to RDW, was a more powerful indicator of prognosis above Hb or RDW alone in esophageal cancer. Tham et al. [10] has evaluated prognostic utility of Hb/RDW in head and neck tumors. Therefore, this study aimed to explore the clinical value of Hb/RDW, CAR, PCT, and CEA in the diagnosis of CRC, and this is the first study to explore the diagnostic value of Hb/RDW in CRC.

2. Patients and methods

2.1. Patients

This retrospective study analyzed four patient groups from the First Affiliated Hospital of Guangxi Medical University in China: (1) those who were first diagnosed with CRC from April 2015 to December 2020; (2) those who were diagnosed with benign colorectal lesions (BCL) such as colorectal polyps and colorectal adenoma in the same period; and (3) those diagnosed as malignant tumors other than colorectal cancer, such as nasopharyngeal carcinoma, thyroid carcinoma, etc. (4) healthy controls. All patients with cancer were diagnosed after finding cancer cells or tissues by pathological biopsy. Patients with CRC had no treatment before. Fasting venous blood samples from each patient were collected in the morning and placed in an EDTA-K2 anticoagulation tube (2 mL) or a non-anticoagulated tube (5 mL). The levels of whole blood cell parameters, including hemoglobin (Hb), red cell distribution width (RDW), platelet count (PLT), and PCT, were determined using a Beckman Coulter LH780 (Beckman Coulter Inc., Brea, CA, USA). Serum levels of CRP and Alb were measured using a Hitachi 7600 automatic biochemical analyzer (Hitachi High-Technologies Corp., Tokyo, Japan). Serum CEA levels were determined using a Roche E600 (Roche Diagnostics, Basel, Switzerland).

2.2. Detection of related inflammatory indicators

Blood samples were collected before patients underwent colorectal cancer resection, and they had not been treated before. Fasting venous blood samples from each patient were collected in the morning and placed in an EDTA-K2 anticoagulation tube (2 mL) or a non-anticoagulated tube (5 mL). The levels of whole blood cell parameters, including hemoglobin (Hb), red cell distribution width (RDW), PLT, and PCT, were determined using a Beckman Coulter LH780 (Beckman Coulter Inc., Brea, CA, USA). Serum levels of CRP and Alb were measured using a Hitachi 7600 automatic biochemical analyzer (Hitachi High-Technologies Corp., Tokyo, Japan). Serum CEA levels were determined using a Roche E600 (Roche Diagnostics, Basel, Switzerland).

2.3. Statistical analysis

All data were analyzed using SPSS 19.0 (IBM Corp., Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation or median (quartile), and continuous data were expressed in frequency or rate. Data were compared using the Mann-Whitney U test between two groups and using the Kruskal-Wallis rank sum test among the three groups. The chi-square test was used to compare the frequencies. Spearman's rank correlation was used to analyze the correlation between each indicator and staging of CRC patients. A P value of < 0.05 was considered significant. Multivariate logistic regression was used to evaluate the risk factors. Icon drawing was performed using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA). MedCalc version 18.0 (MedCalc Software, Mariakerke, Belgium) was used to calculate sensitivity, specificity, and the AUC.

3. Results

The CRC group comprised 212 patients (134 men (63.21%) and 78 women (36.79%)) with a mean age of 58.89 ± 11.90 years. Meanwhile, the BCL group comprised 209 patients (137 men (65.55%) and 72 women (34.45%)) with a mean age of 56.54 ± 13.55 years; the other cancers group comprised 111 patients (69 men (62.16%) with a mean age of 55.88 ± 8.14. Finally,
Table 1

Comparison of laboratory indicators among the four groups

<table>
<thead>
<tr>
<th>Indicator</th>
<th>CRC group</th>
<th>BCL group</th>
<th>Other cancers</th>
<th>Healthy controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>212</td>
<td>209</td>
<td>111</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>134 (63.21%)</td>
<td>137 (65.55%)</td>
<td>69 (62.16%)</td>
<td>121 (65.05%)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>58.89 ± 11.90</td>
<td>56.54 ± 13.55</td>
<td>55.88 ± 8.14</td>
<td>55.92 ± 14.70</td>
<td>0.068</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>119 (105–133)</td>
<td>127 (119–140)</td>
<td>125 (116–136)</td>
<td>134 (126–141)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PLT (10^9/L)</td>
<td>289 (226–347)</td>
<td>199 (183–278)</td>
<td>263 (225–312)</td>
<td>216 (184–243)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>4.62 (1.70–11.98)</td>
<td>2.96 (1.54–6.62)</td>
<td>1.65 (0.95–2.99)</td>
<td>1.40 (0.90–2.60)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alb (g/L)</td>
<td>38.0 (35.5–40.4)</td>
<td>41.9 (39.2–43.9)</td>
<td>40.2 (37.1–43.4)</td>
<td>42.4 (41.3–43.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RDW</td>
<td>0.14 (0.13–0.16)</td>
<td>0.13 (0.12–0.14)</td>
<td>0.14 (0.13–0.15)</td>
<td>0.13 (0.12–0.13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CAR</td>
<td>0.12 (0.04–0.32)</td>
<td>0.07 (0.04–0.16)</td>
<td>0.04 (0.02–0.07)</td>
<td>0.03 (0.02–0.06)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCT</td>
<td>0.26 (0.20–0.32)</td>
<td>0.20 (0.16–0.24)</td>
<td>0.23 (0.19–0.27)</td>
<td>0.22 (0.19–0.25)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hb/RDW</td>
<td>872 (686–1015)</td>
<td>1008 (870–1148)</td>
<td>931 (805–1015)</td>
<td>1068 (969–1140)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CEA (ng/ml)</td>
<td>25.91 ± 108.21</td>
<td>2.77 ± 3.43</td>
<td>4.05 ± 7.18</td>
<td>1.86 ± 0.85</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Notes: Data are expressed as mean ± standard deviation or median (quartile). P value is analyzed by one-way ANOVA tests or Kruskal-Wallis H test or Wilcoxon rank sum test. *indicates differences between CRC group and BCL group; P < 0.05; †indicates differences between CRC group and Other cancers; P < 0.05; ‡indicates differences between CRC group and healthy control group; P < 0.05. Abbreviations: Alb, albumin; BCL, benign colorectal lesions; CAR, C-reactive protein/albumin ratio; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRP, C-reactive protein; Hb, Hemoglobin; Hb/RDW, hemoglobin/red cell distribution width ratio; PCT, plateletcrit; PLT, platelet.

3.1. The relationship between Hb/RDW, CAR, PCT, CEA and clinicopathological features in CRC

Among the four groups (P = 0.068, Table 1), Hb/RDW, CAR, PCT, and CEA were significantly...
Table 2

<table>
<thead>
<tr>
<th>T-N-M</th>
<th>n</th>
<th>Hb/RDW (760–1098)</th>
<th>CAR (0.04–0.21)</th>
<th>PCT (0.05–0.36)</th>
<th>CEA (0.04–0.21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1+T2</td>
<td>42</td>
<td>941</td>
<td>0.09 (0.04–0.21)</td>
<td>0.120</td>
<td>0.24 ± 0.08</td>
<td>0.099</td>
</tr>
<tr>
<td>T3+T4</td>
<td>170</td>
<td>854 (668–1001)</td>
<td>0.14 (0.05–0.36)</td>
<td>0.28 ± 0.10</td>
<td>0.09 ± 0.08</td>
<td>5.16 (2.26–13.99)</td>
</tr>
<tr>
<td>Node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>99</td>
<td>933 (731–1042)</td>
<td>0.09 (0.04–0.21)</td>
<td>0.23 ± 0.09</td>
<td>0.948</td>
<td>3.13 (1.84–8.20)</td>
</tr>
<tr>
<td>N1–N4</td>
<td>113</td>
<td>822 (632–981)</td>
<td>0.17 (0.07–0.43)</td>
<td>0.27 ± 0.11</td>
<td>6.23 (2.62–15.69)</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>179</td>
<td>921 (740–1021)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.23 ± 0.09</td>
<td>0.01</td>
</tr>
<tr>
<td>M1</td>
<td>33</td>
<td>700 (574–831)</td>
<td>0.37 (0.16–0.92)</td>
<td>0.31 ± 0.10</td>
<td>23.11 (5.33–96.23)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Data are expressed as mean ± standard deviation or median (quartile). P value was analyzed by rank sum test. Abbreviations: CAR, C-reactive protein/albumin ratio; CEA, carcinoembryonic antigen; Hb/RDW, hemoglobin/red cell distribution width ratio; PCT, plateletcrit; T-N-M, tumor, node and metastasis.

Fig. 2. Correlation analysis between Hb/RDW (A), CAR (B), PCT (C), CEA (D) and stages. The number 1, 2, 3, 4 in the stage represents the TNM stage of CRC: I II III IV. Abbreviations: CAR, C-reactive protein to leukocyte ratio; CEA, carcinoembryonic antigen; Hb/RDW, hemoglobin/red cell distribution width ratio; PCT, plateletcrit.

Table 3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb/RDW</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CAR</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCT</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CEA</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CAR, C-reactive protein/albumin ratio; CEA, carcinoembryonic antigen; Hb/RDW, hemoglobin/red cell distribution width ratio; PCT, plateletcrit.

different among the four groups (all P < 0.001, Table 1). Hb/RDW in the CRC group were lower than those in the BCL, other cancers and healthy control groups (P < 0.001, Fig. 1A). However, CAR (P < 0.001, Fig. 1B), PCT (P < 0.001, Fig. 1C), and CEA (P < 0.001, Fig. 1D) in the CRC group were significantly higher than the other three groups. There was a negative correlation between Hb/RDW (P < 0.001, Fig. 2A) and stage in the CRC group, a positive correlation between CAR (P < 0.001, Fig. 2B), PCT (P = 0.023, Fig. 2C), and CEA (P < 0.001, Fig. 2D) and stage in the CRC group.
Table 4

<table>
<thead>
<tr>
<th>Indicators</th>
<th>CRC vs. BCL</th>
<th>CRC vs. other cancers</th>
<th>CRC vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sen</td>
<td>Sp</td>
<td>AUC</td>
<td>Sen</td>
</tr>
<tr>
<td>Hb/RDW</td>
<td>77.83</td>
<td>23.44</td>
<td>0.503</td>
</tr>
<tr>
<td>Hb/RDW + CEA</td>
<td>46.23</td>
<td>92.82</td>
<td>0.735</td>
</tr>
<tr>
<td>CAR</td>
<td>58.49</td>
<td>79.90</td>
<td>0.748</td>
</tr>
<tr>
<td>CAR + CEA</td>
<td>58.02</td>
<td>77.51</td>
<td>0.713</td>
</tr>
<tr>
<td>PCT</td>
<td>58.02</td>
<td>77.51</td>
<td>0.713</td>
</tr>
<tr>
<td>PCT + CEA</td>
<td>51.42</td>
<td>96.17</td>
<td>0.807</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the receiver operating characteristic curve; BCL, benign colorectal lesions; CAR, C-reactive protein/albumin ratio; CEA, carcinoembryonic antigen; CRC, colorectal cancer; Hb/RDW, hemoglobin/red cell distribution width ratio; PCT, plateletcrit; Sen, Sensitivity; Sp, Specificity.

Moreover, there were significant differences in Hb/RDW, CAR among different stages, and T-N-M stages in the CRC group (all $P < 0.05$); CAR showed a difference in different lymphnode metastasis and distant metastasis (both $P < 0.001$); PCT showed a difference in different depth of invasion and distant metastasis in the CRC group (both $P < 0.05$, Table 2).

3.3. Diagnostic value of Hb/RDW, CAR, and PCT combined with CEA for distinguishing CRC from other cancers, BCL or healthy controls

The AUC of Hb/RDW + CEA (AUC: 0.693), CAR + CEA (AUC: 0.790), PCT + CEA (AUC: 0.710) was larger than that of Hb/RDW (AUC: 0.567), CAR (AUC: 0.755), or PCT (AUC: 0.623) alone (all $P < 0.001$, Table 4) in auxiliary distinguishing CRC from other cancers.

The AUC of Hb/RDW + CEA (AUC: 0.735), CAR + CEA (AUC: 0.748), PCT + CEA (AUC: 0.807) was larger than that of Hb/RDW (AUC: 0.503), CAR (AUC: 0.614), or PCT (AUC: 0.713) alone (all $P < 0.001$, Fig. 3), and the specificity of Hb/RDW (92.82), CAR (79.90) and PCT (96.17) combined with CEA was improved in auxiliary distinguishing CRC from BCL compared with each of them used alone (Table 4).

Additionally, the AUC of Hb/RDW + CEA (AUC: 0.892), CAR + CEA (AUC: 0.893), PCT + CEA (AUC: 0.857) was larger than that of Hb/RDW (AUC: 0.792), CAR (AUC: 0.816), or PCT (AUC: 0.672) alone (all $P < 0.001$, Fig. 4), and the sensitivity of Hb/RDW (74.06), CAR (69.81) and PCT (67.45) combined with CEA was improved in auxiliary distinguishing CRC from healthy controls compared with each of them used alone (Table 4).

4. Discussion

The annual incidence of CRC has continuously increased [11]. Given that patients are generally asymptomatic during the early stage of the disease, CRC diagnosis is usually delayed, and most patients are di-
A study by Connolly et al. [21] reported that thrombosis is an important cause of progression in most cancers. PCT is a PLT indicator closely associated with inflammation-related diseases and can be used to monitor changes in the disease state of ulcerative colitis [22]. Studies have shown that PCT is helpful in the assessment of cancer-related pathological conditions [23], and can also be used as a diagnostic indicator of autoimmune gastritis, functional dyspepsia [24], and benign and malignant thyroid diseases [25]. Ma et al. [26] and Ozaksit et al. [27] showed that high levels of PCT have certain significance in distinguishing ovarian cancer tumors patients from benign lesions.

In this study, the PCT was higher in the CRC group than that in the other three groups, which is consistent with the previous view that the levels of inflammatory factors are elevated in cancer onset. We also found that PCT was positively correlated with staging; PCT was significantly different in varying tumor stages, depth of invasion, distant metastasis, and these findings are similar to those reported by Mahdavi-Zafarghandi et al. [26] and Ozaksit et al. [27]. This suggests that PCT may be a potential marker of CRC progression.

Hb/RDW has been used to evaluate the prognosis of head and neck tumors and esophageal squamous cell carcinoma [9,10]. In our study, Hb/RDW in the CRC group was significantly lower than that in the other three groups. Hb/RDW was also significantly different in varying tumor stages, depth of invasion, lymph node metastasis, and distant metastasis. We also found Hb/RDW was negatively correlated with staging of CRC, decreased Hb/RDW ratio was associated with advanced CRC, which was similar to Sun et al. [9]. Obviously, a low Hb/RDW was indicative of aggressive tumor behavior and advanced tumor stage. Low levels of Hb may accelerate tumor angiogenesis by causing hypoxia, and is associated with tumor invasion, metastasis [28]. Increased RDW is reportedly associated with systemic inflammation, which might be mediated by inflammation [29,30]. All of which suggest that Hb/RDW has higher value for clinical pathological staging of CRC. Additionally, among these indicators, Hb/RDW has the highest sensitivity for distinguishing CRC from BCL (77.83%); Hb/RDW combined with CEA has the highest sensitivity for distinguishing CRC from healthy controls (74.06%).

CEA is a glycosylated protein expressed on the surface of tumor cells and is often used as a diagnostic marker for gastrointestinal tumors, such as CRC and gastric cancer [31–33]. In this study, the CEA level in the CRC group was significantly higher than that in the...
BCL and healthy control group. This finding is similar to the results reported by Rao et al. [34].

In addition, multivariate logistic regression showed that low level of Hb/RDW and high level of CAR, CEA, PCT were risk factors for CRC. To sum up, Hb/RDW, CAR, and PCT combined with CEA yielded a greater AUC than that of Hb/RDW, CAR, and PCT alone in distinguishing CRC from BCL or healthy controls, and their specificity have increased. Furthermore, Hb/RDW, CAR, PCT, CEA are all related to the pathological stage of CRC, indicating that changes in their values are closely associated to the progress of CRC. Therefore, Hb/RDW, CAR, and PCT combined with CEA have significant value for differential diagnosis of CRC and BCL, and the specificity of Hb/RDW, CAR and PCT combined with CEA were improved in the diagnosis of CRC.

This study has some limitations, including its single-center, retrospective design. However, this study is valuable in that it explored the value of Hb/RDW, CAR, and PCT combined with CEA in the auxiliary differential diagnosis of CRC. All of them are easy to detect clinically, and their combination has better auxiliary diagnostic efficacy than used alone, especially with Hb/RDW. Moreover, Hb/RDW was used for the first time to diagnostically evaluate CRC.

Acknowledgments

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Ethical approval

The study protocol (Approval Number: 2021 (KY-E-339)) was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, and all the participants were orally informed and agreed.

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This study did not receive any funding in any form.

Conflict of interest

The authors declare that they have no conflict of interest.

Competing interest

The authors have declared that no competing interest exists.

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Patient consent for publication

The manuscript did not contain the patient’s identity information, and all participants agreed to publish.

Authors’ contributions

Conception: ZX, LFQ.
Interpretation or analysis of data: ZX, WYY, QYY.
Preparation of the manuscript: WYY, QYY.
Revision for important intellectual content: ZX, WYY, QYY, LFQ.
Supervision: LFQ.

Abbreviations

Alb, albumin; AUC (95% CI), Area under the ROC curve (95% Confidence interval); BCL, benign colorectal lesions; CAR, C-reactive protein/albumin ratio; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRP, C-reactive protein; Hb, Hemoglobin; Hb/RDW, hemoglobin/red cell distribution width ratio; PCT, plateletcrit; PLT, platelet; RDW, red cell distribution width.

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