# Potential diagnostic value of the hematological parameters lymphocyte–monocyte ratio and hemoglobin–platelet ratio for detecting colon cancer

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**Abstract**

**Objective:** To evaluate the efficacy of using the lymphocyte–monocyte ratio (LMR), hemoglobin–platelet ratio (HPR), and carcinoembryonic antigen (CEA) levels alone or in combination for diagnosing colon cancer.

**Methods:** We assessed 124 consecutive patients who were pathologically diagnosed with colon cancer and 131 patients who were diagnosed with benign colon tumors in this retrospective study. We then analyzed correlations between LMR, HPR, and clinicopathological findings. The diagnostic values of LMR, HPR, and CEA alone or in combination in colon cancer patients were evaluated by receiver operating characteristic curves.

**Results:** The median LMR, HPR, and CEA values in colon cancer patients showed significant correlation with the depth of tumor invasion, lymph node metastasis, and TNM stage. Moreover, there was a significant difference in HPR between patients with tumor size $\geq 5$ cm and those with tumor size $< 5$ cm. Compared with LMR, HPR, or CEA alone, combinations of CEA with LMR, CEA with HPR, and HPR with LMR all had higher area under the curve values, among which the combination of all three (LMR, HPR, and CEA) had the highest area under the curve.

**Conclusion:** The combination of LMR, HPR, and CEA may be a valuable indicator for monitoring colon cancer.

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## Introduction

With the change of people's lifestyle and diets, the incidence rate of colon cancer has dramatically increased.[1] It was estimated that there would be more than 1.1 million new colon cancer cases and 576,000 deaths worldwide in 2020.[2] In China, colon cancer has the fifth highest incidence and mortality rates among all cancers.[3] Colon cancer is typically an asymptomatic disease before it progresses to advanced stages. The 5-year survival rate of patients with early-stage colon cancer can reach 90%, whereas the 5-year survival rate of patients with metastatic colon cancer drops to 11.7%.[4] Therefore, the early detection and treatment of colon cancer is critical. Colonoscopy is highly useful for diagnosing colon cancer, but it is invasive, inconvenient, and expensive.[5] Colonoscopy can also return false negative results. Hence, exploring effective non-invasive diagnostic biomarkers to distinguish between colon cancer and benign colon tumors is essential.

Recently, a study indicated that inflammatory cells and mediators are important to the tumor microenvironment.[6] Both local and systemic inflammatory responses can promote the occurrence of colon cancer and the development of cancer cells by stimulating the immune microenvironment.[7] The lymphocyte–monocyte ratio (LMR) has been shown to be related to systemic inflammation and to be of clinical value in various diseases.[8–11] Patients with malignant tumors often exhibit anemia, and a reduced hemoglobin–platelet ratio (HPR) is related to poor clinical outcomes in nasopharyngeal carcinoma and renal cell carcinoma.[12,13] Carcinoembryonic antigen (CEA) is a member of the immunoglobulin superfamily that acts as an intracellular adhesion molecule.[14] Currently, CEA is the most important common serum biomarker for detecting and monitoring colon cancer but its sensitivity and specificity are insufficient.[15] Therefore, this study explored the value of preoperative LMR, HPR, and CEA alone or in combination for diagnosing colon cancer and also to investigate whether these markers are associated with disease stage.

## Methods

### Study design and setting

In this retrospective study, we collected the clinical data of consecutive patients who were pathologically diagnosed with colon cancer and admitted to the Affiliated Nanjing Jiangbei Hospital of Nantong University (Nanjing, China) between January 2015 and April 2020. Because this study involved human participants, it was designed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The institutional review board of the Affiliated Nanjing Jiangbei Hospital of Nantong University approved this study (No. 20180030) and waived informed consent due to its retrospective design.

All patients' details have been de-identified. The reporting of this study conforms to STROBE guidelines.[16]

## Study population

The inclusion criteria were as follows: 1) patients with complete data; and 2) patients who had undergone surgical resection after being diagnosed with colon cancer by two pathologists. The exclusion criteria were as follows: 1) patients with infections, blood diseases, cardiovascular diseases, cerebrovascular diseases, other systemic diseases, other cancers, or a past history of tumors; 2) patients who had received anti-cancer treatment before surgery, such as chemotherapy or radiotherapy; and 3) patients who had recently received a blood transfusion. All patients were assessed based on the 8th edition of the AJCC colon cancer staging system.

## Data collection

In this study, data within one week before surgery were collected retrospectively from hospital records. Routine examinations of blood samples were performed using a Beckmann780 (Beckman Coulter, Brea, CA, USA). The laboratory data included white blood cells, hemoglobin, platelets, lymphocytes, and monocytes. Preoperative serum CEA levels were detected using a Roche e6000 analyzer (Roche Diagnostics, Basel, Switzerland). HPR and LMR were calculated as follows: HPR = hemoglobin/platelet count; LMR = lymphocyte count/monocyte count.

## Statistical analysis

Continuous variables that satisfied a normal distribution are represented by mean ± standard deviation, and these data were compared between two groups using the Student's *t*-test. Otherwise, data are represented as median (interquartile range) and were compared using nonparametric tests. Receiver operating characteristic (ROC) curve analysis was conducted to identify optimal cutoff values, specificity, sensitivity, positive predictive value, negative predictive value, area under the curve (AUC), and the diagnostic value of LMR, HPR, and CEA. $P < 0.05$ was considered to indicate statistical significance. GraphPad Prism 7 (GraphPad Software, Inc., San Diego, CA, USA) and SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) were used for data analyses.

## Results

### Clinical characteristics of the subjects

In total, 124 patients with colon cancer were assigned to the colon cancer group and 131 patients diagnosed with colon polyps or colon adenomas were assigned to the benign colon tumor group. Clinical characteristics of the colon cancer and benign colon tumor groups are shown in Table 1. Clinical characteristics of the colon cancer and healthy controls groups are shown in Supplementary Table 1. The colon cancer group included 74 men and 50 women, with an average age of 65.83 ± 12.37 years. The benign colon tumor group included 81 men and 50 women, with an average age of 63.71 ± 11.20 years. The two groups did not significantly differ in age or sex. As shown in Table 1 and Figure 1, compared with the benign colon tumor group, LMR and HPR levels were significantly lower in the colon cancer group. However, the colon cancer group had higher levels of CEA than the benign colon tumor group.

### Correlations between LMR, HPR, and CEA and clinicopathological features in colon cancer

As shown in Table 2, the median LMR, HPR, and CEA values in colon cancer

**Table 1.** Comparison of clinical characteristics between the colon cancer and benign colon tumor groups.

| | Colon cancer group (n = 124) | Benign colon tumor group (n = 131) | P-value |
|---|---|---|---|
| Age, years | 65.83 ± 12.37 | 63.71 ± 11.20 | 0.153 |
| Sex (male, %) | 74 (59.68%) | 81 (61.83%) | 0.725 |
| Hemoglobin (g/L) | 120.00 (96.25, 131.75) | 148.00 (139.00, 153.00) | <0.001 |
| WBC ($\times 10^9$/L) | 6.30 (4.8, 8.51) | 5.80 (5.00, 7.00) | 0.098 |
| Platelet ($\times 10^9$/L) | 210.50 (170.75, 263.25) | 198.00 (161.0, 226.0) | 0.005 |
| Lymphocyte ($\times 10^9$/L) | 1.31 (1.05, 1.72) | 1.57 (1.28, 2.01) | <0.001 |
| Monocyte ($\times 10^9$/L) | 0.40 0.29, 0.52) | 0.32 (0.25, 0.41) | <0.001 |
| LMR | 3.24 (2.37, 4.81) | 4.91 (4.03, 6.24) | <0.001 |
| HPR | 0.52 (0.41, 0.68) | 0.75 (0.63, 0.90) | <0.001 |
| CEA (ng/mL) | 4.17 (2.35, 11.84) | 2.14 (1.28, 3.05) | <0.001 |

WBC, white blood cell; LMR, lymphocyte-monocyte ratio; HPR, hemoglobin-platelet ratio; CEA, carcinoembryonic antigen.
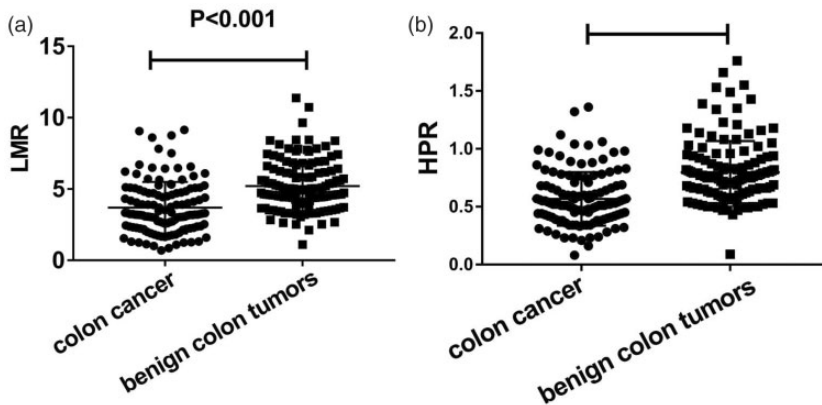


**Figure 1.** Comparison of lymphocyte-monocyte ratio (LMR) and hemoglobin-platelet ratio (HPR) between the colon cancer and benign colon tumor groups. (a) LMR in the two groups and (b) HPR in the two groups.

patients showed significant correlation with the depth of tumor invasion, lymph node metastasis, and TNM stage. However, they were not associated with distant metastasis. There was a significant difference in HPR between patients with tumor size ≥5 cm and those with tumor size <5 cm.

## Diagnostic efficacy of LMR, HPR, and CEA alone or in combination in colon cancer

As shown in Table 3 and Figure 2, ROC curve analysis revealed that the optimum cut-off values for LMR, HPR, and CEA were 3.28, 0.62, and 3.08, respectively. The AUC values of LMR, HPR, and CEA were 0.745 (95% confidence interval [CI]: 0.684–0.806), 0.765 (95% CI: 0.706–0.824), and 0.744 (95% CI: 0.684–0.804), respectively. The combination of LMR and CEA (AUC: 0.801, 95% CI: 0.750–0.861) demonstrated higher diagnostic value than using LMR or CEA alone ($P < 0.001$). Similar results were observed for the combination of HPR and CEA (AUC: 0.844, 95% CI: 0.794–0.893; $P < 0.001$).

**Table 2.** Correlation between clinicopathological features and LMR, HPR, and CEA in colon cancer.

| | N | LMR | *p* | HPR | *P* | CEA | *P*-value |
|---|---|---|---|---|---|---|---|
| Tumor invasion (T stage) | | | | | | | |
| T1 + T2 | 19 | 4.39 (3.07, 5.64) | 0.033 | 0.61 (0.47, 0.83) | 0.039 | 2.85 (1.87, 5.28) | 0.028 |
| T3 + T4 | 105 | 3.21 (2.28, 4.64) | | 0.52 (0.39, 0.66) | | 4.48 (2.44, 12.43) | |
| Lymph node metastasis | | | | | | | |
| NO | 61 | 3.88 (2.85, 5.33) | 0.019 | 0.56 (0.41, 0.79) | 0.046 | 3.10 (1.98, 9.29) | 0.011 |
| YES | 63 | 3.18 (2.18, 4.32) | | 0.51 (0.42, 0.60) | | 5.76 (2.60, 16.24) | |
| Stage | | | | | | | |
| I/II | 61 | 3.88 (2.85, 5.33) | 0.019 | 0.56 (0.41, 0.79) | 0.046 | 3.10 (1.98, 9.29) | 0.011 |
| III/IV | 63 | 3.18 (2.18, 4.32) | | 0.51 (0.42, 0.60) | | 5.76 (2.60, 16.24) | |
| Distant metastasis (M stage) | | | | | | | |
| M0 | 116 | 3.22 (2.37–4.71) | 0.290 | 0.52 (0.41–0.68) | 0.745 | 4.05 (2.35–11.44) | 0.246 |
| M1 | 8 | 4.90 (2.51–5.90) | | 0.52 (0.40–0.79) | | 11.00 (4.63–112.63) | |
| Tumor size (cm) | | | | | | | |
| <5 | 75 | 3.20 (2.48, 4.91) | 0.210 | 0.56 (0.47, 0.77) | 0.002 | 4.16 (2.35, 11.31) | 0.513 |
| ≥5 | 49 | 3.26 (2.29, 4.75) | | 0.47 (0.32, 0.61) | | 4.17 (2.33, 15.08) | |

LMR, lymphocyte-monocyte ratio; HPR, hemoglobin-platelet ratio; CEA, carcinoembryonic antigen.

**Table 3.** Diagnostic value of LMR, HPR, and CEA, alone or in combination, for distinguishing colon cancer from benign colon tumors.

| | Cut-off value | Sensitivity | Specificity | +LR | −LR | AUC |
|---|---|---|---|---|---|---|
| LMR | 3.28 | 52.40 | 92.40 | 6.89 | 0.52 | 0.745 (0.684–0.806) |
| HPR | 0.62 | 69.40 | 77.90 | 3.14 | 0.39 | 0.765 (0.706–0.824) |
| CEA | 3.08 | 62.10 | 76.30 | 2.62 | 0.50 | 0.744 (0.684–0.804) |
| LMR + CEA | 0.49 | 74.19 | 82.40 | 4.23 | 0.31 | 0.806 (0.750–0.861) |
| HPR + CEA | 0.453 | 84.15 | 77.86 | 3.68 | 0.24 | 0.844 (0.794–0.893) |
| HPR + LMR + CEA | 0.57 | 72.58 | 90.84 | 7.92 | 0.30 | 0.863 (0.816–0.909) |

LMR, lymphocyte-monocyte ratio; HPR, hemoglobin-platelet ratio; CEA, carcinoembryonic antigen; +LR, positive likelihood ratio; −LR, negative likelihood ratio.

The combination of LMR, HPR, and CEA had the overall largest AUC (0.863, 95% CI: 0.816–0.909).

## Discussion

Colon cancer is one of the most common malignant tumors worldwide and seriously endangers human health. When colon cancer is suspected, prompt diagnostic evaluation is critical. Although colonoscopy is the gold standard for colon cancer testing, it is limited as a routine screening method because of its high cost, health risks, and invasiveness.[17] Thus, there is an urgent need to find a fast, accurate, and less invasive diagnostic index for colon cancer. Chronic inflammation can promote tumor occurrence, invasion, and metastasis.[18] Recently, hematological markers of inflammation, such as LMR and HPR, have begun attracting clinical attention because they have been shown to have value for the diagnosis and prognosis of certain cancers.[19,20] However, the clinical value of combining these indicators with CEA to monitor colon cancer has not been sufficiently investigated.
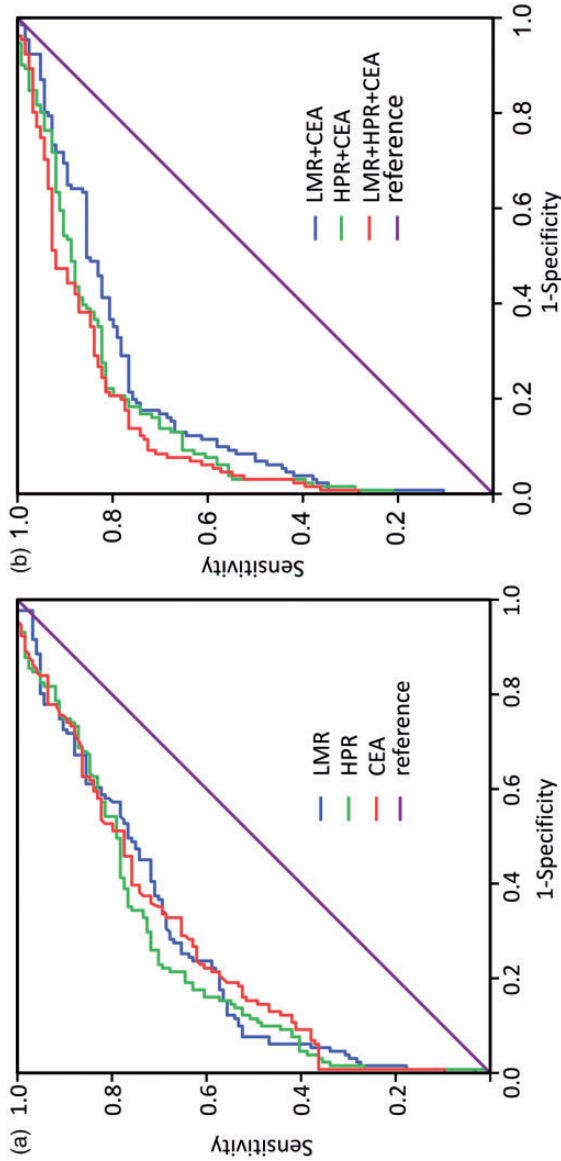
**Figure 2.** Diagnostic value of lymphocyte-monocyte ratio (LMR), hemoglobin-platelet ratio (HPR), and carcinoembryonic antigen (CEA) levels, alone or in combination, for distinguishing colon cancer from benign colon tumors.

In this study, we evaluated the diagnostic performance of the hematological parameters LMR and HPR and the tumor marker CEA, alone and in combination, for diagnosing colon cancer. To our knowledge, there has been little research on the value of combining these three indicators for diagnosing colon cancer. Our results showed that LMR was significantly lower in the colon cancer group than in the benign colon tumor group, which was consistent with previous findings.[21,22] For example, Li et al.[22] reported that LMR values were significantly lower in colon cancer patients than in benign colon tumor patients, indicating that LMR may be a good predictor of colon cancer. They also reported that high pre-operative LMR was associated with better clinicopathological features, including decreased depth of invasion, less lymph node metastasis, earlier tumor stage, and smaller tumor size, in agreement with our conclusions. Another study showed that LMR can be used as a prognostic marker in colorectal cancer, with low LMR being correlated with decreased overall survival.[23]

To our knowledge, there have been few studies on the clinical value of HPR in diseases. Mo et al.[20] explored the clinical value of HPR in 235 patients with rectal cancer, 113 patients with benign rectal diseases, and 229 healthy controls and found that rectal cancer patients had significantly lower HPRs than did patients with benign rectal diseases or healthy controls. Our findings are in accordance with those of Mo et al.[20] A previous study used HPR to predict overall survival in locally advanced nasopharyngeal cancer, concluding that low HPR was associated with poor 3-year overall survival.[12] Similarly, we found that low pre-operative HPR was linked to worse clinicopathological features, including increased depth of invasion, more lymph node metastasis, more advanced tumor stage, and larger tumor size.

CEA is a commonly used auxiliary diagnostic index for gastrointestinal tumors that has been widely used in the differential diagnosis of various malignant tumors.[24] Our research showed that CEA levels were significantly higher in the colon cancer group than in the benign colon tumor group (4.17 [2.35–11.84] vs. 2.14 [1.28–3.05]). Moreover, CEA levels were significantly higher in patients with advanced colon cancer than in those with early-stage disease ($P = 0.011$). However, a single inflammatory index is easily affected by many factors when detecting colon cancer. The combination of inflammatory biomarkers and tumor markers may improve the reliability of colon cancer diagnoses.[22] We found that the combined use of LMR, HPR, and CEA produced a greater AUC value and higher sensitivity and specificity compared with using LMR, HPR, or CEA alone. As far as we know, our study is the first to explore the diagnostic efficacy of the combination of LMR, HPR, and CEA in colon cancer.

Our results may be explained by the following mechanism. Lymphocytes play a crucial role in inhibiting the proliferation and metastatic spread of tumor cells by recognizing tumor antigens and directly inducing tumor cell lysis or by releasing specific chemotactic and pro-inflammatory cytokines.[25] A decrease in lymphocytes could lead to reduced immune surveillance and a weakening of lymphocyte-mediated immune responses to tumor progression. Monocytes are innate immune cells of the mononuclear phagocyte system that are important regulators of cancer development.[26] Additionally, growth factors and chemokines produced by tumor cells can cause monocytes in tumor tissues to differentiate into tumor-associated macrophages.[27] Macrophages can initiate tumorigenesis and promote tumor progression by producing high levels of reactive oxygen species, fibroblast growth factor, and

other factors.[28,29] Studies have shown that cancer patients may present with anemia and thrombocytosis. Growing tumors may cause bone marrow suppression and disorders of iron metabolism due to the secretion of inflammatory cytokines, leading to tumor-induced anemia.[20,30] Low hemoglobin levels cause tumor hypoxia and enhance tumor growth; additionally, anemia can promote angiogenesis and DNA mutations in tumor cells.[31] Platelets promote cancer progression, metastasis, and angiogenesis by producing growth and angiogenic factors. Cancer cells can release platelet agonists to induce platelet activation.[32,33] According to the above mechanisms, the combination of LMR or HPR with CEA may be a potential biomarker for monitoring colon cancer.

This study has some limitations. First, a relatively small number of samples were included and all subjects were Asians from a single hospital; thus, multicenter, large-scale studies are warranted. Second, this study was a retrospective case-control study. The results may be affected by specific confounders, so prospective cohort studies are still needed. Third, we did not investigate the pathogenesis of decreased LMR and HPR. Therefore, molecular biology studies are necessary to explore the mechanism of decreased LMR and HPR in colon cancer patients.

In conclusion, LMR, HPR, and CEA may be valuable for the differential diagnosis of colon cancer and benign colon tumors and they provide the most reliable results when used in combination as opposed to being used alone.

## Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

## Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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## Supplemental material

Supplemental material for this article is available online.

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