Predictive Values of the Selected Inflammatory Index in the Progression of Colon Cancer Patients

Li Huang
Guangxi Medical University First Affiliated Hospital
Zuojian Hu
Guangxi Medical University First Affiliated Hospital
Ruixian Luo
People's Hospital of Guangxi Zhuang Autonomous Region
Hailan Li
People's Hospital of Guangxi Zhuang Autonomous Region
Ziji Yang
People's Hospital of Guangxi Zhuang Autonomous Region
Zhuning Mo (mozhn@139.com)
People's Hospital of Guangxi Zhuang Autonomous Region https://orcid.org/0000-0001-9627-5241

Primary research

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Abstract

Background: Ample evidence has revealed that the lymphocyte-to-monocyte ratio (LMR), albumin-to-globulin ratio (AGR) and mean platelet volume (MPV) are cancer-related inflammatory markers. The present study aimed to assess a better diagnostic marker for the progression of colon cancer.

Methods: This retrospective study enrolled 251 patients with colon cancer, 171 patients with benign colon diseases, and 187 healthy control subjects from January 2012 to September 2020. The receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to determine the diagnostic values of the selected inflammatory index.

Results: The levels of LMR, AGR and MPV were decreased in the colon cancer group compared with the healthy control and benign colon disease groups. The LMR, AGR and MPV were all correlated with tumor size. Moreover, LMR and AGR was associated with lymph node metastasis and clinical stage, AGR was related to distant metastasis. Both the LMR (p = 0.030) and AGR (p = 0.005) were negatively correlated with the concentration of carcinoembryonic antigen (CEA). The AUC value of MPV combined with CEA had a good diagnostic ability for distinguishing controls from colon cancer cases (AUC = 0.950) and patients with benign colon diseases (AUC = 0.886). Meanwhile, the combination of LMR or AGR with CEA could enhance the diagnostic efficacy (AUC; 0.746 for LMR + CEA, 0.737 for AGR + CEA) of detecting colon cancer from benign colon diseases.

Conclusions: CEA combined with the selected inflammatory index may be used as better blood-based biomarkers in the progression of colon cancer patients.

Background

Colon cancer comprised the highest incidence in tumors of the digestive system and represented a commonly diagnosed malignant tumor worldwide in 2020[1]; it was the fourth most frequent cause of cancer morbidity and fifth leading cause of cancer mortality in China in 2015[2]. Due to the lack of obvious manifestations, most colon cancer patients have silent symptoms for years. More than 50% of colon cancer patients are clinically diagnosed at the advanced cancer stage[3]. Therefore, effective screening protocols are essential for colon cancer detection. As well known, fecal occult blood test (FOBT) is a cheap and convenient screening method for colon cancer[4]. Nevertheless, the result is frequently affected by many dietary factors, multiple drugs, and upper or lower gastrointestinal bleeding site, which may lead to false positives and subsequent unnecessary tests and panic[5]. Other methods that colonoscopy and biopsy have been used as ideal methods for the diagnosis of early colon cancer[6], but these inspections greatly increase the physical and financial burden on patients harboring colonic diseases, resulting in poor compliance. Hence, low-cost, non-invasive and easily obtainable markers have important significance for the diagnosis and prevention of colon cancer.

Several serum tumor markers have been commonly used in colon diseases, such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 242 (CA242) [7, 8]. CEA is considered the primary marker, with almost all researches and clinical practices for the detection and monitoring of colon cancer used this indicator[9]. However, several studies discovered that CEA possessed low sensitivity and could not appropriately present the complete potency for clinical diagnosis and treatment in colorectal cancer[10]. Thus, more reliable and powerful biomarkers of identifying the colon cancer are expected to obtain.

In recent years, many inflammatory parameters from peripheral blood and serum have been evaluated in the diagnosis and prognosis of multiple malignancies, including colorectal cancer[11, 12], such as circulating neutrophils[13], lymphocytes[14], monocytes[15], platelets[16], mean platelet volume (MPV)[17] and albumin[18]. Due to the release of chemokines and cytokines, MPV is, as an early indicator of platelet activation, an inflammatory marker. Several reports discovered that it was closely related to the occurrence, features, and outcomes of many neoplasms[19–21]. As crucial components of host immunity, lymphocytes can infiltrate into the tumor microenvironment, and they play a vital role in cell-mediated immunity, preventing the proliferation and metastatic activity of colorectal cancer[22]. Systemic inflammation can induce changes in the hematological system, leading to a significant decrease of lymphocytes[23, 24]. Lymphocytopenia is considered an insufficient immune response against tumor, resulting in hyperproliferation and tumorigenesis. Conversely, the excess circulating monocytes gather and settle in solid tumor tissues after being mediated by chemokines of inflammatory cytokines; they are then differentiated into tumor-associated macrophages with specific phenotypic characteristics[25]. Increasing evidence has demonstrated that the accumulation of tumor-associated macrophages in the tumor sites contributes to the angiogenesis, tumorigenesis, and pathogenesis of colon cancer[26]. As a result, the relatively lower number of lymphocytes is an indicator marker of weak immune response, and the elevated monocyte count is a microenvironment monitor of high tumor burden. Therefore, lymphocyte to monocyte ratio (LMR), as a reflection of systemic inflammation and immunological statuses, may have a crucial role in the progression of colon cancer. The albumin-to-globulin ratio (AGR) which combines serum albumin and globulin, is a routinely available and cost-effective marker and associated with the process of inflammatory and nourishment state. Accumulated evidence displayed that AGR was an independent and useful predictor in the prognosis of colon cancer by regulating cells and/or releasing several mediators[27]; moreover, elevated AGR was a favorable factor for better clinical outcomes[12]. Hence, we hypothesized that AGR may have a significant diagnostic value in colon cancer.

Up to now, to our knowledge, studies have rarely investigated the diagnostic role of these three inflammatory parameters (LMR, AGR and MPV) in the progression of colon cancer, especially for persons with benign colon diseases. Therefore, this study investigated the value of LMR, AGR and MPV combined or not with CEA in the progression of colon cancer.

Material And Method

Patients

For the present study, 251 colon cancer patients, 171 patients with benign colon diseases, and 187 healthy controls were recruited at the First Affiliated Hospital of Guangxi Medical University. In colon cancer participants with new diagnoses, the disease was confirmed by histology and treated with surgical resection. Clinical staging of colon cancer was conducted accorded to the seventh edition of the American Joint Committee on Cancer/TNM tumor staging criteria. Patients with other cancers, cardiovascular disease, diabetes mellitus, hematological disease, autoimmune disease, recent blood transfusion, or treatment with other therapies, such as radiotherapy and chemotherapy, were excluded. Colon polyps, colon adenomas, and colonitis were included as benign colon disease patients who were diagnosed by colonoscopy and histopathology. Healthy controls comprised healthy subjects undergoing physical examination during the same period. This research was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.

Data Collection

All data were collected from the hospital's electronic medical records, including gender, age, white blood cells (WBC), platelets, hemoglobin, lymphocyte, monocyte, albumin, globulin, MPV, CA19-9, CA242 and CEA. Whole blood-cell parameters were detected with a Beckmann 780 device (Beckman Coulter, Brea, CA). The levels of albumin and total protein were analyzed by a Hitachi 7600 automatic biochemical analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan). The concentration of serum CEA was tested by using a Roche E6000 analyzer (Roche Diagnostics, Basel, Switzerland). Architect i2000 and its reagents (Abbott GmBH Diagnostika, Wiesbaden-Delkenheim, Germany) were used to evaluated the serum CA19-9 values. The level of serum CA242 was determined using Enzyme Linked Immunosorbent Assay (CanAg Company, Sweden). The ratios of interest were calculated as follows: LMR = lymphocyte count / monocyte count and AGR = albumin / (total protein – albumin).

Statistical analysis

The Kolmogorov–Smirnov test was used to detect the distribution of the continuous variables. All the data failed to satisfy the normal distribution; median and interquartile ranges were applied for non-normal data. Differences between groups in laboratory parameters and clinical characteristics were calculated using the Mann–Whitney nonparametric U test. The Spearman correlation coefficient was conducted to detect correlations between inflammatory index (LMR, AGR and MPV) and CEA in the colon cancer group. The receiver operating characteristic (ROC) curve and area under the curve (AUC) were calculated by MedCalc statistical software (version 18.1.1). Data processing and analysis were determined by SPSS 16.0 statistical software package, using a significance level of 0.05.

Results

Patient characteristics

Basic information and laboratory parameters are summarized in Table 1. The median age of the colon cancer patients, benign colon diseases cases, and control individuals were 56 (46–64), 48 (41–56), and 53 (49–60) years, respectively. No intergroup difference was observed in gender among the three groups. The measured results for WBCs, platelets, monocytes, and CEA were higher in the colon cancer patients compared with those in the healthy and benign colon disease subjects. Conversely, the levels of median hemoglobin, lymphocytes, albumin, MPV, LMR, and AGR were significantly lower in the colon cancer group than they were in the control and benign colon disease groups, and there were statistical differences in LMR (Fig. 1A), AGR (Fig. 1B) and MPV (Fig. 1C) among the three groups. Except for the healthy controls and colon cancer cases, the values of CA19-9 were evident discrepancies between other groups. The concentrations of CA242 were not available in the benign colon disease group, and there was difference between the healthy control group and colon cancer group.

Table 1
Basic information and laboratory parameters among colon cancer, benign colon diseases and healthy control groups

Characteristics	Healthy controls (N=187)	Benign colon diseases (N=171)	Colon cancer (N=251)	P^a	P^b	P^c
Gender (Male/Female)	99/88	90/81	140/111	0.556	0.525	0.953
Age (years)	53.0(49.0-60.0)	48.0(41.0-56.0)	56.0(46.0-64.0)	0.092	<0.001	<0.001
WBC ($\times10^9$/L)	6.10(5.17-6.71)	6.30(5.20-7.46)	6.41(5.33-7.70)	0.001	0.453	0.028
Hemoglobin (g/L)	143.00(135.10-150.60)	131.00(120.00-142.70)	117.00(99.00-130.80)	<0.001	<0.001	<0.001
Platelet ($\times10^9$/L)	202.20(179.50-227.80)	230.20(193.60-276.50)	275.00(228.50-345.00)	<0.001	<0.001	<0.001
MPV (fL)	9.32(9.14-9.82)	8.30(7.80-8.93)	8.11(7.42-8.70)	<0.001	0.013	0.003
Lymphocyte ($\times10^9$/L)	2.03(1.74-2.41)	2.10(1.64-2.63)	1.83(1.55-2.22)	<0.001	<0.001	0.381
Monocyte ($\times10^9$/L)	0.41(0.33-0.50)	0.48(0.37-0.58)	0.50(0.41-0.62)	<0.001	0.012	<0.001
Albumin (g/L)	46.70(45.0-48.20)	42.60(39.40-45.20)	38.50(36.10-41.10)	<0.001	<0.001	<0.001
Globulin (g/L)	27.10(25.30-29.20)	26.00(23.20-28.70)	26.10(23.70-28.80)	0.001	0.381	0.000
CEA (ng/ml)	0.71(0.39-1.30)	1.74(1.08-2.61)	2.71(1.56-7.28)	<0.001	<0.001	<0.001
CA242	4.09(0.00-7.45)	-	5.15(0.01-18.90)	<0.001	-	-
CA19-9	12.31(7.47-21.84)	8.90(4.44-15.95)	10.46(5.41-24.13)	0.239	0.013	<0.001
LMR	5.13(4.24-5.87)	4.67(3.67-5.60)	3.63(2.86-4.51)	<0.001	<0.001	0.002
AGR	1.72(1.57-1.86)	1.63(1.43-1.91)	1.49(1.31-1.65)	<0.001	<0.001	0.028

WBC, white blood cells; MPV, mean platelet volume; CEA, carcinoembryonic antigen; CA242, carbohydrate antigen 242; CA19-9, carbohydrate antigen 19-9; LMR, lymphocyte-to-monocyte ratio; AGR, albumin-to-globulin ratio.

[a]: colon cancer vs healthy controls

[b]: colon cancer vs benign colon diseases;

[c]: benign colon diseases vs healthy controls

Correlations between LMR, AGR, MPV and the clinicopathological characteristics in patients with colon cancer

There was a negative correlation presented between CEA and the LMR (r = −0.137, p = 0.030) (Fig. 2A) and AGR (r = −0.178, p = 0.005) (Fig. 2B) in the colon cancer group, respectively. Nevertheless, no correlation was observed between AGR and MPV (r = 0.012, p = 0.846) (Fig. 2C). According to the seventh edition of the American Joint Committee on Cancer/TNM tumor stage, the clinicopathological characteristics of the 251 patients carrying colon cancer are shown in Table 2. The levels of LMR, AGR and MPV in the colon cancer group were all closely related to the tumor size, but not associated with serosa invasion. Moreover, the AGR and LMR were correlated with lymph node metastasis and clinical stage. The colon cancer patients with M0 had significantly higher levels of AGR compared to the cases with M1 (p = 0.013).

Table 2
Correlation between LMR, AGR, and MPV and clinicopathological features in colon cancer

	N	LMR	*P*	AGR	*P*	MPV	*P*
Tumor invasion (T stage)							
T1 + T2	86	3.63(2.83-4.87)	0.513	1.46(1.33-1.62)	0.602	8.10(7.53-8.73)	0.973
T3 + T4	165	3.63(2.89-4.36)		1.50(1.31-1.66)		8.14(7.40-8.69)	
Lymph node metastasis (N stage)							
N0	177	3.75(2.85-4.87)	**0.033**	1.52(1.33-1.68)	**0.025**	8.10(7.34-8.69)	0.300
N1-N3	74	3.44(2.90-4.12)		1.43(1.31-1.58)		8.17(7.60-8.71)	
Distant metastasis (M stage)							
M0	242	3.63(2.94-4.52)	0.366	1.50(1.32-1.65)	**0.013**	8.11(7.44-8.70)	0.900
M1	9	3.09(2.48-4.28)		1.19(1.04-1.44)		8.16(6.90-8.97)	
Tumor size (cm)							
<5	159	3.85(3.00-4.65)	**0.004**	1.52(1.34-1.67)	**0.002**	8.20(7.60-8.80)	**0.026**
≥5	92	3.26(2.70-4.17)		1.43(1.15-1.60)		7.90(7.14-8.60)	
Clinical stage							
I + II	179	3.77(2.95-4.86)	**0.013**	1.52(1.33-1.69)	**0.002**	8.10(7.40-8.70)	0.833
III + IV	72	3.43(2.80-4.03)		1.44(1.23-1.57)		8.17(7.49-8.69)	

LMR, lymphocyte-to-monocyte ratio; AGR, albumin-to-globulin ratio; MPV, mean platelet volume.

Logistic regression used to distinguish colon cancer from controls

The correlation between several potential risk factors and colorectal cancer was analyzed by binary logistic regression (Table 3), including gender, age, MPV, CA242, CA19-9, CEA, LMR, and AGR. Thus, the results were gender (odd ratio [OR] = 0.892, 95% confidence interval [CI] = 0.610–1.304, p = 0.556), age (OR = 1.013, 95% CI = 0.994–1.031, p = 0.174), MPV (OR = 0.089, 95% CI = 0.055–0.143, p < 0.001), CA242 (OR = 1.061, 95% CI = 1.033–1.089, p < 0.001), CA19-9 (OR = 1.012, 95% CI = 1.002–1.022, p = 0.019), CEA (OR = 2.855, 95% CI = 2.223–3.666, p < 0.001), LMR (OR = 0.547, 95% CI = 0.466–0.644, p < 0.001), and AGR (OR = 0.036, 95% CI = 0.015–

0.088, $p < 0.001$). The above important indexes ($p < 0.05$) were selected as potential independent predictors for further multivariate analysis. After multivariate analysis, MPV($\beta = -2.352$, $p < 0.001$), LMR($\beta = -0.306$, $p = 0.001$), AGR ($\beta = -4.091$, $p < 0.001$) and CEA ($\beta = 0.967$, $p < 0.001$) were also recognized as crucial markers in the occurrence of colon cancer. The optimal model (logit $P = 0.967 \times$ CEA $- 0.306 \times$LMR $- 4.091 \times$ AGR $- 2.352 \times$ MPV + 27.383) was set up for differencing colon cancer cases from controls. The AUC, sensitivity, and specificity were reach up to 0.964, 90.84%, and 92.51%, respectively.

Table 3
Screening for significant predictors that distinguished colon cancer from healthy controls by using univariate and multivariate analyses

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*	OR	95%CI	*P*
Gender	0.892	0.610-1.304	0.556			
Age(years)	1.013	0.994-1.031	0.174			
MPV	0.089	0.055-0.143	<0.001	0.095	0.050-0.180	<0.001
CA242	1.061	1.033-1.089	<0.001	1.013	0.969-1.058	0.567
CA19-9	1.012	1.002-1.022	0.019	0.997	0.988-1.006	0.465
CEA	2.855	2.223-3.666	<0.001	2.630	1.928-3.588	<0.001
LMR	0.547	0.466-0.644	<0.001	0.736	0.612-0.886	0.001
AGR	0.036	0.015-0.088	<0.001	0.017	0.003-0.080	<0.001

MPV, mean platelet volume; CA242, carbohydrate antigen 242; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; LMR, lymphocyte-to-monocyte ratio; AGR, albumin-to-globulin ratio. CI, confidence interval; OR, odd ratio.

Diagnostic efficacy of LMR, AGR, CEA and MPV alone or in combination to differentiate colon cancer from other subjects

The results of the ROC curve analysis are presented in Table 4 and Fig. 3. The AUC value of the combination of MPV and CEA was 0.950 (95% CI = 0.925–0.968, positive likelihood ratio [PLR] = 9.48, negative likelihood ratio [NLR] = 0.097), positive predictive value [PPV] = 92.7%, negative predictive value [NPV] = 88.5%), which possessed a good diagnostic ability for distinguishing colon cancer cases from healthy controls. Meanwhile, the sensitivity and specificity of the combination of MPV and CEA was separately increased to 91.24% and 90.37%. Compared to the benign colon disease subjects, the AUC value of combination for LMR and CEA was 0.746 in subjects with colon cancer, which had greater ability than other indicators alone or in combination. However, the sensitivity of combination for LMR and CEA (75.30%) was lower than LMR (77.29%) and AGR (83.27%) alone. To predict colon cancer, the optimal cut-offs of LMR, AGR, MPV and CEA in the benign colon disease subjects were 4.58, 1.71, 7.80 and 3.44, respectively. For the diagnosis of benign colon disease individuals, the combined use of MPV and CEA resulted in a better AUC (0.886) and sensitivity (84.80%) than other indicators individually or in combination in the controls. But the specificity of the combination of MPV and CEA (84.49%) was inferior to MPV (96.79%) or AGR (89.84%).

Table 4
Diagnostic efficacy of LMR, AGR and CEA used alone or in combination to differentiate colon cancer from benign colon diseases

	Cutoff	Sensitivity (%)	Specificity (%)	PLR	NLR	PPV (%)	NPV (%)	AUC (95% CI)	*P*
LMR[a]	3.78	55.38	88.77	4.93	0.50	86.9	59.7	0.778(0.736-0.816)	<0.001
AGR[a]	1.59	66.53	71.12	2.30	0.47	75.6	61.3	0.756(0.713-0.796)	<0.001
MPV[a]	8.93	83.27	96.79	25.95	0.17	97.2	81.2	0.894(0.862-0.922)	<0.001
CEA[a]	1.35	80.08	78.07	3.65	0.26	83.1	74.5	0.870(0.835-0.900)	<0.001
LMR[a]+AGR[a]	0.64	65.74	88.24	5.59	0.39	88.2	65.7	0.819(0.780-0.854)	<0.001
LMR[a]+MPV[a]	0.60	82.47	94.65	15.42	0.19	95.4	80.1	0.916(0.886-0.940)	<0.001
AGR[a]+MPV[a]	0.65	78.49	96.26	20.97	0.22	96.6	76.9	0.923(0.894-0.946)	<0.001
LMR[a]+CEA[a]	0.47	86.45	81.82	4.75	0.17	86.5	81.8	0.895(0.863-0.922)	<0.001
AGR[a]+CEA[a]	0.46	84.86	80.75	4.41	0.19	85.5	79.9	0.889(0.856-0.917)	<0.001
MPV[a]+CEA[a]	0.45	91.24	90.37	9.48	0.097	92.7	88.5	0.950(0.925-0.968)	<0.001
LMR[b]	4.58	77.29	53.22	1.65	0.43	70.8	61.5	0.688(0.642-0.732)	<0.001
AGR[b]	1.71	83.27	42.11	1.44	0.40	67.9	63.2	0.655(0.607-0.700)	<0.001
MPV[b]	7.80	38.25	74.85	1.52	0.82	69.1	45.2	0.571(0.523-0.619)	0.011
CEA[b]	3.44	43.43	87.72	3.54	0.64	83.8	88.8	0.686(0.639-0.730)	<0.001
LMR[b]+AGR[b]	0.66	53.39	78.95	2.54	0.59	78.8	53.6	0.717(0.671-0.759)	<0.001
LMR[b]+MPV[b]	0.65	51.39	80.70	2.66	0.60	79.6	53.1	0.698(0.652-0.742)	<0.001
AGR[b]+MPV[b]	0.61	62.15	69.01	2.01	0.55	74.6	55.4	0.680(0.633-0.724)	<0.001

CEA, carcinoembryonic antigen; LMR, lymphocyte-to-monocyte ratio; AGR, albumin-to-globulin ratio; MPV, mean platelet volume; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; AUC, area under curve.

	Cutoff	Sensitivity (%)	Specificity (%)	PLR	NLR	PPV (%)	NPV (%)	AUC (95% CI)	*P*
LMR[b]+CEA[b]	0.54	75.30	63.74	2.08	0.39	75.3	63.7	0.746(0.702-0.787)	<0.001
AGR[b]+CEA[b]	0.58	58.57	76.02	2.44	0.55	78.2	55.6	0.737(0.693-0.779)	<0.001
MPV[b]+CEA[b]	0.59	51.39	83.63	3.14	0.58	82.2	54.0	0.715(0.669-0.758)	<0.001
LMR[c]	5.02	63.16	53.48	1.36	0.69	55.4	61.3	0.595(0.542-0.646)	0.002
AGR[c]	1.46	30.41	89.84	2.99	0.77	73.2	58.5	0.567(0.514-0.619)	0.032
MPV[c]	8.98	77.78	96.79	24.24	0.23	95.7	82.6	0.856(0.815-0.891)	<0.001
CEA[c]	1.05	77.19	66.31	2.29	0.34	67.7	76.1	0.776(0.729-0.818)	<0.001
LMR[c]+AGR[c]	0.54	40.35	83.42	2.43	0.72	69.0	60.5	0.610(0.558-0.661)	0.000
LMR[c]+MPV[c]	0.55	74.85	95.19	15.55	0.26	93.4	80.5	0.864(0.824-0.898)	<0.001
AGR[c]+MPV[c]	0.55	71.35	96.79	22.24	0.30	95.3	78.7	0.851(0.810-0.887)	<0.001
LMR[c]+CEA[c]	0.42	73.68	74.33	2.87	0.35	72.4	75.5	0.779(0.733-0.821)	<0.001
AGR[c]+CEA[c]	0.43	70.18	72.19	2.52	0.41	69.8	72.6	0.773(0.726-0.816)	<0.001
MPV[c]+CEA[c]	0.38	84.80	84.49	5.47	0.18	83.3	85.9	0.886(0.848-0.917)	<0.001

CEA, carcinoembryonic antigen; LMR, lymphocyte-to-monocyte ratio; AGR, albumin-to-globulin ratio; MPV, mean platelet volume; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; AUC, area under curve.

Discussion

Colon cancer is closely associated with inflammation which has been unraveled as a crucial hallmark in all the steps of colon tumorigenesis, including initiation, invasion, progression, and metastasis[28]. Recent work has elucidated that cancer-associated inflammatory markers are increasingly used in the early diagnosis and prognosis of malignant tumors and closely related with the progression of diseases[29, 30]. Therefore, this study assessed the diagnostic efficacy of the common inflammatory indexes (LMR, AGR, and MPV) and detected whether they could be used as surrogate markers in the progression of colon cancer.

In this retrospective analysis, we discovered that the healthy controls had significantly higher MPV compared to the benign colon disease patients and colon cancer patients, which was consistent with the result of Lalosevic et

al.[31], but contrary to the findings of Li et al.[32] and Kilincalp et al.[33]. The differences may be due to health groups included criteria and population selection. We found that the MPV values in the first two articles (Lalosevic and Li) were 9.06 and 10.7, which were similar to the results of this study (9.32), but the wide gulf was obtained from the article of Kilincalp in the MPV values (7.82). Moreover, previous research illustrated that MPV was connected with obesity, smoking and so on[34], which may also differ among the studies population, resulting in the inconsistent outcomes. Although no association was demonstrated between clinical stage and MPV in our current finding, the results revealed that the MPV levels in patients with stage III–IV were higher than that in cases with stage with I–II, which was similar to Li's study[32]. And the present study is the first research revealing the correlation between MPV and the tumor size.

In concordance with previous results, the colon cancer patients had a lower LMR level than the benign colon disease patients and healthy controls did. For example, Evrim et al.[35] observed that the level of monocyte-to-lymphocyte ratio (MLR) was higher in the gastric cancer group than it was in the intestinal metaplasia and healthy control groups. A study by Luo et al.[36] found that MLR was significantly elevated in patients carrying urothelial carcinoma of the bladder relative to healthy controls. Moreover, our study disclosed that the level of LMR was significantly correlated with the features of colon cancer, such as lymph node metastasis, tumor size, and clinical stage. Indeed, Ozawa et al.[37] demonstrated that cancer-specific survival was significantly worse in patients with low LMR levels than in high-LMR patients, and LMR may be an independent prognostic marker for stage III and IV colon cancer patients[38]. Peng et al.[39] assessed the prognosis of patients harboring colorectal liver-only metastases and elucidated that elevated LMR predicted a favorable outcome in both 5-year recurrence-free survival and overall survival of patients with lymph node metastases and liver tumor up to a diameter of less than 5 cm. Furthermore, several meta-analyses have demonstrated that malignant patients with high preoperative LMR have better predicted clinical outcomes compared with patients with low LMR in populations comprising Asians, digestive system carcinomas, non-metastatic diseases and early disease stages[40, 41], which confirmed our findings.

Emerging evidence suggests that AGR is mainly used as a clinical indicator for several kinds of cancers. Growing tumors induce hypoalbuminemia via secreting inflammatory cytokines, which may inhibit albumin synthesis and promote albumin loss, resulting in weak systemic response. Rasouli et al.[42] reported that patients with malignant tumors had a decreased concentration of albumin, which were measured by colorimetric methods, compared with healthy controls, which was accordant with the present study results. Globulin, as a reflector for most proinflammation protein, was increased by the accumulation of acute-phase proteins and immunoglobulins[43]. The AGR, which is compatible with hypoalbuminemia and hyperglobulinemia, may be able to more accurately reflect the nutritional and inflammatory state, and thus, is associated with the progression of neoplasia. The electrophoretic data of serum proteins showed that the AGR was significantly decreased in 85 patients harboring cancer relative to controls[42]. Cheng et al.[44] confirmed that the globulin-to-albumin ratio (GAR), was significantly higher in the subjects with liver disease compared with individuals with no evidence of liver disease. Quite a few studies revealed that patients with lower pretreatment AGR were related to worse survival than higher AGR subjects in colorectal cancer[45], gastric cancer[46], pancreatic cancer[47], nasopharyngeal carcinoma[48], and esophageal cancer[49]. Moreover, a significant correlation based on the above-mentioned researches was observed between clinical characteristics and the level of AGR, such as lymph node metastasis, tumor size, distant metastasis, and tumor stage. In agreement with previous studies, this study found that the value of AGR in the colon cancer patients was lower than that in the benign colon diseases and

healthy individuals; furthermore, it showed that the AGR was associated with lymph node metastasis, distant metastasis, tumor size, and clinical stage.

CEA is a serum glycoprotein that is mainly secreted by cells of the large intestine, and it has been widely applied as a tumor marker for the malignant characteristics of colorectal cancer. Unfortunately, high levels of CEA are not present in about 15% of large intestine cancers, and elevated CEA is commonly revealed in severe malignant tumors[50]. In clinical practice, increased circulating levels of CEA are observed not only in cancer patients but also in some benign intestinal lesions. Therefore, the sensitivity and effectiveness of CEA are not sufficient for clinical diagnosis and treatment, but CEA has a high specificity in colorectal cancer[51, 52], as well as in differentiating colorectal cancer patients from those with benign colorectal diseases[53].

Consistent with previous studies, the sensitivity and diagnostic value of CEA were not noticeable in identifying colon cancer from benign colon diseases (43.43%, 0.686), while the specificity was up to 87.72%. Whereas we found that CEA combined with LMR or AGR generated a significantly better diagnostic sensitivity and AUC than CEA used alone in discriminating colon cancer patients and benign colon diseases cases. Similar to this pilot study, a previous report displayed that LMR possessed a moderate ability (AUC = 0.71) and could contribute to distinguishing patients carrying gastric cancer from those with intestinal metaplasia[35], the diagnostic efficiency was similar to that of our study in colon cancer. Meanwhile, the AUC value of MPV combined with CEA had a good diagnostic ability and sensitivity for distinguishing controls from colon cancer patients (AUC = 0.950 and 91.24%) and patients with benign colon diseases (AUC = 0.886 and 84.49%), was superior compared with individual indicators and related reporter. For example, Milica et al.[31] revealed that ROC curve analysis showed high diagnostic efficacy of NLR, PLR and MPV in CRC patients compared with individual markers (AUC = 0.904). In many malignancies, AGR exhibited good diagnostic efficacy (AUC = 0.81) in differentiating cancer patients from healthy controls[42], which squared with our results. All these findings suggest that the combination of CEA with LMR, AGR or MPV could not only be used as a colon cancer diagnostic biomarker but may also improve the diagnostic efficiency of detecting the progression of patients harboring colon cancer.

There are certain potential limitations in the current research. On the one hand, this is a retrospective analysis of a relatively small sample size from a single center, so selection bias and statistical validity should be noted, which may affect the final results about the associations between the LMR or AGR and colon cancer. We failed to stratify benign colon diseases due to the relatively small sample size. On the other, confounding factors, including dietary habits and family histories, cannot be completely ruled out, which may prevent us from drawing any firm conclusions. Therefore, a large-scale, prospective study with multiple centers is still needed to validate these results.

Conclusion

This study first described that the LMR and AGR were correlated with CEA and colon cancer, as well as lymph node metastasis, tumor size, distant metastasis and clinical stage. Moreover, the combination of the LMR, AGR or MPV with CEA can enhance sensitivity and diagnostic efficacy and may be a helpful diagnostic marker for differentiating colon cancer from benign colon diseases and healthy controls.

Abbreviations

WBC: white blood cell; MPV, mean platelet volume; CA242, carbohydrate antigen 242; CA19-9, carbohydrate antigen 19-9; ROC: receiver-operating characteristic curve; AUC: area under curve; CI: confidence interval; OR, odd ratio; FOBT: fecal occult blood test; LMR: lymphocyte-to-monocyte ratio; AGR: albumin-to-globulin ratio; CEA: carcinoembryonic antigen; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; GAR: globulin-to-albumin ratio; MLR: monocyte-to-lymphocyte ratio

Declarations

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Authors' contributions

Li Huang, Zuojian Hu and Ruixian Luo contributed equally to this work and should be considered as co-first authors. Zhuning Mo drafted the overall design of this paper as the corresponding authors. Li Huang and Zhuning Mo wrote the article. Zuojian Hu collected the laboratory data. Ruixian Luo and Hailan Li analyzed the data. All authors contributed substantially to its revision.

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Availability of data and materials

The datasets supporting the conclusions of this article is included within the

article

Ethics approval and consent to participate

This research was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, and informed consent was obtained from all the participants.

Consent for publication

This manuscript is approved by all authors for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

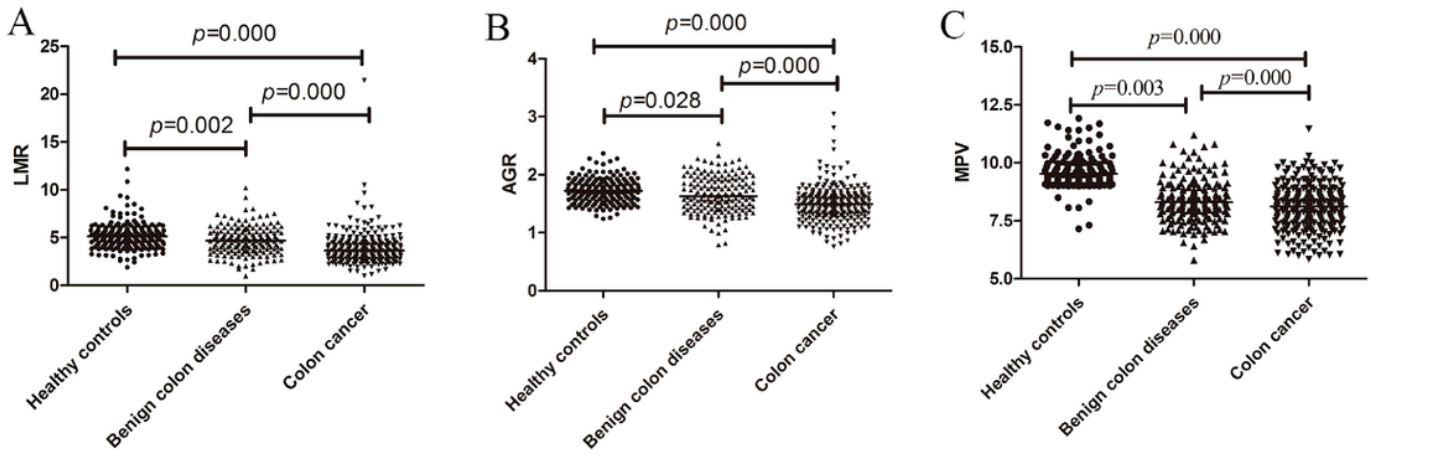

Figure 1

Comparison of LMR and AGR among three groups. A: LMR. B: AGR. C: MPV. LMR lymphocyte-to-monocyte ratio, AGR albumin-to-globulin ratio, MPV mean platelet volume.

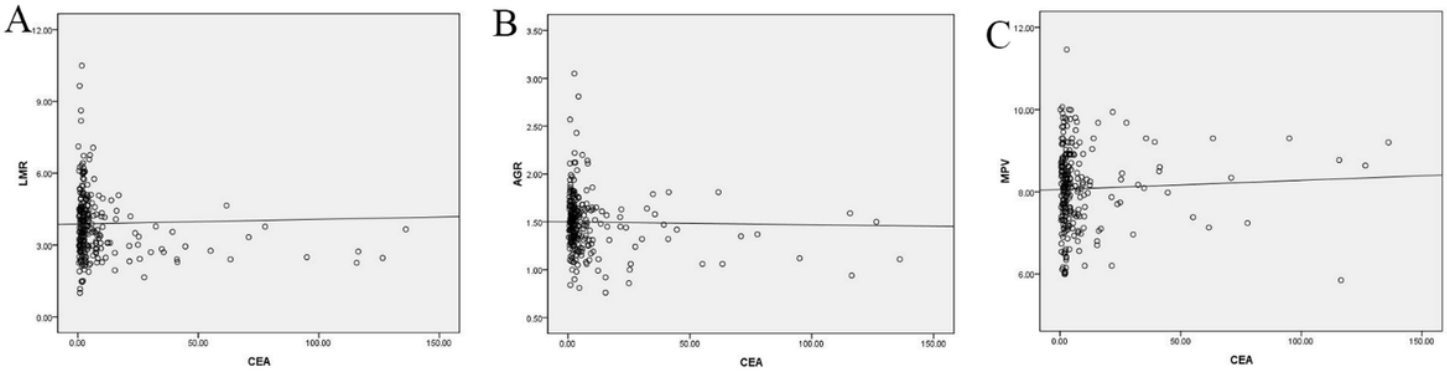

Figure 2

Correlation analysis of LMR, AGR, MPV and CEA in patients with colon cancer. A: LMR and CEA in patients with colon cancer. B: AGR and CEA in patients with colon cancer. C: MPV and CEA in patients with colon cancer. LMR lymphocyte-to-monocyte ratio, AGR albumin-to-globulin ratio, MPV mean platelet volume, CEA carcinoembryonic antigen.

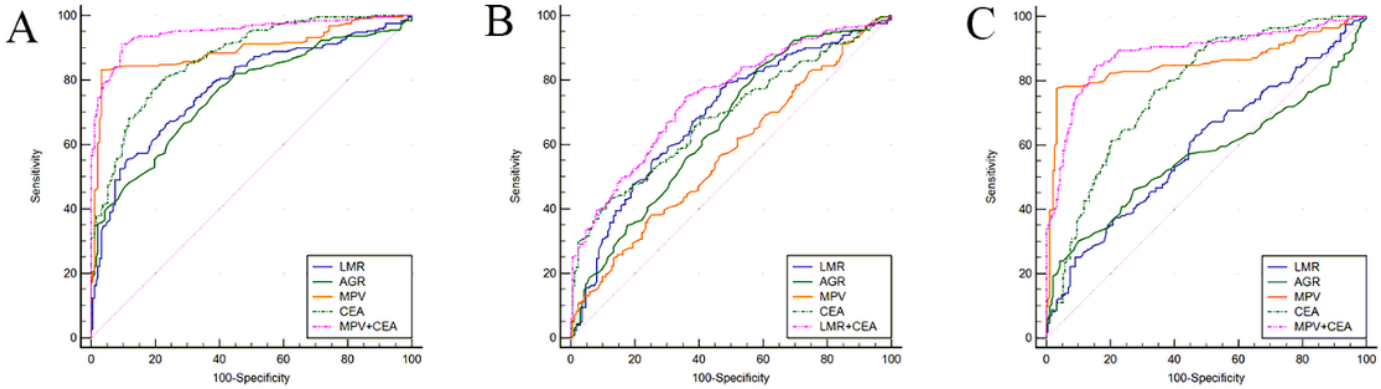

Figure 3

The diagnostic value of LMR, AGR and MPV used alone or in combination with CEA in the progression of colon cancer. A: colon cancer vs healthy controls. B: colon cancer vs benign colon diseases. C: benign colon diseases vs healthy controls. LMR lymphocyte-to-monocyte ratio, AGR albumin-to-globulin ratio, MPV mean platelet volume, CEA carcinoembryonic antigen.