Clin. Lab. 2024;70:XXX-XXX

ORIGINAL ARTICLE

Clinical Value of Routine Biomarkers for Colorectal Patients: a Retrospective Study

Chen Jiang [1], Jian-Hui Huang [2], Hui Cong [1, 3]

[1] *Department of Blood Transfusion, Affiliated Hospital of Nantong University, Nantong, China*
[2] *Department of Pathology, Affiliated Hospital of Nantong University, Nantong, China*
[3] *Department of Laboratory Medicine, Affiliated Hospital of Nantong University, Nantong, China*

SUMMARY

Background: **Colorectal cancer (CRC) has always been one of the most common malignant tumors in the world. Whether the factors related to the diagnosis and risk of CRC can be found from the existing peripheral blood routine indicators.**
Methods: **The relevant data of patients with colorectal diseases in our hospital of about ten years were collected, the differences among the biomarkers in serum were analyzed, the risk factors were analyzed by logistic regression, the ROC was drawn, and the diagnostic efficacy was evaluated.**
Results: **Colorectal malignancies and benign diseases in AST, GGT, LDH, D-BIL, ALB, ALP, AchE, CR, TP, PA, RDW, LMR, NMR, TC, TG, HDL-C, CA19-9, CEA, Cyfra21-1, and Fer have statistical differences ($p < 0.05$). ALB, PLR, CEA, Fer, NLR, TP, GGT, and Cyfra21-1 in different malignant tumor types have statistical differences ($p < 0.05$). When CEA increased by 1, the risk of colorectal cancer increased by 45.7%. When AchE and HDL-C increased by 1, the risk of colorectal cancer decreased by 32% and 66.8%. Compared with other blood groups, blood group AB colorectal cancer patients had a shallower tumor invasion ($p = 0.047$). HDL-C were significantly weakly-correlated with tumor size ($p < 0.05$, $|r| < 0.4$). CEA, AchE, and HDL-C were combined diagnosed; the sensitivity, PPV, and accuracy were 94.35%, 95.43%, 90.77%, respectively.**
Conclusions: **The occurrence and development of colorectal cancer is the result of multi-factors, and the combined detection of multi-indicators has positive significance for the diagnosis, pathological stage, and prevention of CRC.**
(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2024.240320)

Correspondence:
Hui Cong
Department of Blood Transfusion
Affiliated Hospital of Nantong University
Nantong, 226001
China
Email: huicjs@163.com

Manuscript accepted May 13, 2024

KEYWORDS

colorectal cancer, HDL-C, CEA, blood group, AchE

LIST OF ABBREVIATIONS

CRC - colorectal cancer
AST - aspartate aminotransferase
GGT - γ-glutamyl transferase
LDH - lactate dehydrogenase
D-BIL - direct bilirubin
ALB - albumin
ALP - alkaline phosphatase
AchE - acetylcholine hydrolase
CR - creatinine
TP - total protein
PA - prealbumin

RDW - red cell volume distribution width
P-LCR - platelet-larger cell ratio
MPV - mean platelet volume
SCC - squamous cell carcinoma
TC - total cholesterol
TG - triglyceride
HDL-C - high-density lipoprotein cholesterol
LDL-C - low-density lipoprotein cholesterol
CA19-9 - carbohydrate antigen 19-9
CEA - carcinoembryonic antigen
Cyfra21-1 - cytokeratin 19 fragment
Fer - ferritin
TBIL - total bilirubin
CG - glycocholic acid
NLR - neutrophil-to-lymphocyte ratio
LMR - lymphocyte-to-monocyte ratio
PLR - platelet-to-lymphocyte ratio
NMR - neutrophil-to-monocyte ratio
SOP - standard operating procedure
AUC - area under the curve
ROC - receiver operating characteristic
VIF - variance inflation factor
PPV - positive predictive value
NPV - negative predictive value

INTRODUCTION

Colorectal cancer (CRC) has always been one of the most common malignant tumors in the world. There are about 1.93 million new cases and 94 million deaths in 2020, and the morbidity and mortality are on the rise compared with 2018 [1]. There are still differences in the morbidity and mortality among regions in the world. CRC is showing a downward trend in many developed countries and regions, but a rapid upward trend is still maintained in many low-income and middle-income countries [2]. Siegel et al. reported that the age of onset of CRC showed a younger trend, with a steady increase of about 2.1% per year in < 55 years old people [3]. In China, the incidence of colorectal cancer in rural areas shows an increasing trend [4].

At present, the treatment for CRC is mainly surgery, supplemented by radiotherapy and chemotherapy, targeted drugs, biological immunity, etc. Although the survival time of CRC has improved with the improvement of medical level, the overall prognosis of CRC is poor, and the patients have poor quality of life during survival. At present, the diagnosis of CRC mainly relies on colonoscopy. Due to its invasiveness and troublesome bowel preparation, patients prefer noninvasive examination methods. CRC generally develops from adenomas, and even experienced clinicians would miss the diagnosis during clinical colonoscopy [5]. Patients often come to see a doctor when they develop typical clinical symptoms. The earlier the diagnosis is made, the better the chance of treatment for the patient. According to the American Cancer Registry data, about 45% of the colon and rectal cancers between 2007 and 2013 were detected at an advanced stage and had a significantly poorer prognosis. The 5-year relative survival rates of stage 1 and stage 2 were 88% and 80%, respectively. It decreased to about 66% in stage 3 and 13% in stage 4 [6]. Therefore, it is necessary to find a less invasive method for the early diagnosis of CRC. At present, clinical medicine has entered the era of big data. Whether the factors related to the diagnosis and risk of CRC can be found from the existing peripheral blood routine indicators, so as to provide a theoretical basis for the diagnosis, treatment and prevention of CRC, is the purpose of this study.

MATERIALS AND METHODS

General information

A total of 139,855 patients with colorectal disease, who were treated in the Affiliated Hospital of Nantong University from January 2013 to December 2021, were retrospectively screened. Samples with incomplete data were excluded, and a total of 819 patients were included in the study. Among them, the colon benign diseases consisted of 236 cases, 160 males and 76 females (mean age 58.17 ± 13.16) and the colon cancer cases consisted of 583 cases, 393 males and 190 females (mean age 66.78 ± 10.64). Inclusion criteria: first-time admission and histologically confirmed patients who had not received chemoradiotherapy. Exclusion criteria: chronic inflammation, pregnancy, other systemic malignancies, hematological diseases, history of using anticoagulant drugs, and other chronic diseases (Figure 1).

Methods

The subjects' venous blood was collected in test tubes containing separating gel and EDTA-K_2, according to the testing purpose and requirements. The test tubes containing separating gel were centrifuged at 2,068 g for 10 minutes within 2 hours after blood coagulation, and the serum was separated for the detection of various biochemical indicators. Two test tubes containing EDTA-K_2 were used to detect blood group and blood routine respectively; all tests were completed within 2 hours. All tests were carried out under normal conditions of instruments and reagents, in-house quality control, and in strict accordance with the reagent and instrument standard operating procedure (SOP). Aspartate aminotransferase (AST, MDH method), γ-glutamyl transferase (GGT, rate method), lactate dehydrogenase (LDH, lactate substrate method), total bilirubin (TBIL, heavy nitrogen salt method), direct bilirubin (D-BIL, diazonium salt method), glycocholic acid (CG, latex-enhanced immune turbidimetric method), cholinesterase (AchE, butyryl thiocholine substrate method), alkaline phosphatase (ALP, NPP substrate-AMP buffer method), total protein (TP, biuret method), albumin (ALB, bromocresol green method), serum creatinine (Cr, sarcosine oxidase method), total cholesterol (TC, cholesterol oxidase method), triglyceride (TG, GPO-POD method),

LDL-C (direct method), HDL-C (direct method) were measured. American Beckman-Coulter AU5800 automatic biochemical assembly line was used for detection. The reagents were original Beckman-Coulter kits and calibrators, and the quality control products were two-level serum chemical quality control products from Bio-Rad. The DxI-800 (Beckman Coulter, American) automatic microparticle chemiluminescence immunoassay system was used to detect CEA, CA19-9, Cyfra21-1, Fer, and SCC. Automatic blood cell counter Sysmex-2100 (Sysmex Japan) was used for complete blood count. Neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-monocyte ratio (NMR) were calculated and derived from the relevant parameters of the complete blood count. ABO blood group and Rh(D) typing were detected by microcolumn agglutination card provided by Sudasaier Immunobiologic.

The surgical patient's tissue was resected and sent to the pathology department of our hospital for diagnosis. Information, such as patient basic information, clinical laboratory data (initial/preoperative), and clinicopathological parameters were obtained from the hospitals` computer system.

The differences in age, gender, blood group distribution, and clinical experimental indicators were compared between the different groups, binary logistic regression analysis was performed, and the AUC was calculated by ROC to assess whether the blood group was related to tumor size, pathological type and lymph node metastasis, number of lymph node metastases, degree of tumor invasion, and invasion site. This study was approved by the Ethics Committee of the Affiliated Hospital of Nantong University (2022-K057-01).

Statistical analysis

In this study, SPSS20.0 was used for statistical analysis of the data. The measurement data showed a skewed distribution, which was represented by M (25, 75). The Mann-Whitney rank sum test was used for comparison and the Kruskal-Wallis test was performed for multiple comparisons. Categorical data were expressed as n (%) and compared by using chi-squared statistics or corrected chi-squared test (Bonferroni method).

Baseline variables with univariate $p < 0.2$ were included in the hazard regression model, and the included variables were carefully selected to ensure that the final model was simple and effective taking into account the sample size of positive outcome events. A linear regression model was constructed from the dependent and independent variables of the logistic regression, a multicollinearity analysis was performed by tolerance and variance inflation factor (VIF) (tolerance > 0.1 means no significant collinearity), and binary logistic regression was used. The analysis identified independent risk factors for positive events, and finally the variables were determined by using forward stepwise regression. The ROC was drawn, the cutoff value was calculated by using the Youden index, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated to evaluate each parameter. $p < 0.05$ was considered to be statistically significant.

RESULTS

Comparison of various indicators between benign and malignant colorectal diseases

According to their age (in steps of 10 years), the patients were divided into 7 subgroups: ≤ 30, 31 - 40, 41 - 50, 51 - 60, 61 - 70, 71 - 80, and 81 - 90. We found that 60 was the cutoff point; there was statistical difference in the proportion of benign lesions and malignant tumors ($p < 0.001$), the proportion of benign diseases was higher than that of malignant tumors in the age of < 60 years, and the proportion of malignant tumors was higher than that of benign diseases in the age of > 60 years. In addition, colorectal malignancies and benign lesions in AST, GGT, LDH, D-BIL, ALB, ALP, AchE, CR, TP, PA, RDW, LMR, NMR, TC, TG, HDL-C, CA19-9, CEA, Cyfra21-1, and Fer were statistically different ($p < 0.05$); gender, blood type, T-BIL, CG, NLR, PLR, P-LCR, PDW, MPV, LDL-C, and SCC were not statistically different, as shown in Table 1.

Comparison of indicators of colorectal malignant tumors in different tissue types

According to the WHO tumor histological classification standard, 583 cases of colorectal malignant tumors were divided into adenocarcinoma, mucinous adenocarcinoma, neuroendocrine tumor, etc., and invalid samples were removed: 1 case of squamous cell carcinoma, 3 cases of gastrointestinal stromal tumor, 1 case of neurofibromatosis, 2 cases of spindle cell tumor, 28 cases of unclassified, 34 cases of focal carcinoma, and 1 case of high-grade myoepithelial carcinoma. The remaining 513 cases of CRC were compared between groups by different tissue types. The results showed that GGT, TP, ALB, NLR, PLR, CEA, Cyfra21-1, and Fer had statistical differences among them ($p < 0.05$), as shown in Table 2.

Multiple comparisons showed that the PLR, NLR, and CEA of patients with poorly differentiated adenocarcinoma were significantly higher than those of other tumor types; the difference in PLR between patients with poorly differentiated adenocarcinoma and those with well-differentiated and moderately differentiated adenocarcinoma was statistically significant ($p = 0.025$, $p = 0.015$), the difference in NLR between patients with poorly differentiated adenocarcinoma and moderately differentiated adenocarcinoma patients was statistically significant ($p = 0.003$). CEA ($p = 0.007$) and Cyfra21-1 ($p = 0.020$) with poorly differentiated adenocarcinoma were significantly higher than those of well-differentiated adenocarcinoma patients.

The levels of ALB, Fer, and TP in patients with neuroendocrine tumors were significantly higher than those in

Table 1. Comparison of various indexes between colorectal malignant tumor and benign diseases.

Variables	Colon benign diseases (n = 236), M (P_{25}, P_{75})	Colorectal malignant tumor (n = 583), M (P_{25}, P_{75})	χ^2/Z value	p-value
Gender, n (%)			0.01	0.915
Female	76 (32.2%)	190 (32.6%)		
Male	160 (67.8%)	393 (67.4%)		
Blood group, n (%)			2.26	0.520
A	66 (31.4%)	166 (29.6%)		
B	57 (27.1%)	171 (30.5%)		
O	65 (31.0%)	181 (32.3%)		
AB	22 (10.5%)	43 (7.7%)		
Age (Years)			88.366	0.000
≤ 30	9 (3.8%)	0 (0.0%)		
31 - 40	15 (6.4%)	7 (1.2%)		
41 - 50	34 (14.4%)	37 (6.3%)		
51 - 60	67 (28.4%)	106 (18.2%)		
61 - 70	71 (30.1%)	218 (37.4%)		
71 - 80	36 (15.3%)	160 (27.4%)		
81 - 90	4 (1.7%)	55 (9.4%)		
Routine biomarkers				
NLR	2.03 (1.46, 2.83)	2.04 (1.56, 2.91)	-1.24	0.213
PLR	118.06 (100.19, 171.07)	133.96 (96.83, 176.34)	-1.42	0.156
LMR	4.00 (3.04, 6.03)	3.74 (2.77, 4.71)	-5.31	0.000
NMR	8.53 (6.60, 10.83)	7.76 (6.14, 9.76)	-4.61	0.000
P-LCR	33.90 (29.80, 39.55)	31.8 (25.50, 38.70)	-0.01	0.990
MPV	11.00 (10.55, 11.75)	10.80 (10.10, 11.70)	-0.00	0.999
PDW	13.30 (12.20, 15.10)	12.90 (11.30, 14.90)	-1.46	0.143
RDW	12.60 (12.15, 13.15)	12.90 (12.40, 13.80)	-3.12	0.001
TC	4.80 (4.2, 5.4)	4.5 (3.9, 5.1)	-3.51	0.000
TG	1.25 (0.92, 1.82)	1.24 (0.93, 1.66)	-2.67	0.008
T-BIL	13.70 (10.75, 17.70)	13.80 (10.30, 17.80)	-1.71	0.087
D-BIL	2.80 (2.25, 3.70)	2.6 0 (1.90, 3.50)	-2.82	0.005
AST	22 (20, 27)	20 (17, 25)	-5.16	0.000
GGT	23.0 (15.5, 36.0)	21.0 (15.0, 32.0)	-2.08	0.038
LDH	183.0 (162.5, 210.0)	189.0 (163.0, 215.0)	-2.59	0.010
AchE	7.68 (6.70, 9.14)	6.68 (5.61, 7.78)	-7.86	0.000
CG	1.5 (1.3, 1.94)	1.7 (1.4, 2.1)	-1.79	0.073
CR	66.0 (56.0, 73.5)	68.0 (59.0, 79.0)	-2.96	0.003
ALP	76.0 (62.5, 92.5)	79.0 (67.0, 95.0)	-2.67	0.008
TP	67.8 (63.2, 71.8)	65.2 (61.4, 69.2)	-6.76	0.000
ALB	41.0 (37.6, 43.8)	38.3 (35.5, 40.7)	-10.50	0.000
PA	249 (221, 278)	215 (177, 257)	-7.11	0.000
HDL-C	1.21 (1.03, 1.415)	1.1 (0.92, 1.26)	-5.56	0.000
LDL-C	3.02 (2.45, 3.445)	2.94 (2.47, 3.45)	-.22	0.822
CEA	1.9 (1.3, 2.8)	3.7 (2.1, 7.7)	-10.44	0.000
CA19-9	4.2 (2.05, 8.9)	6.2 (2.7, 14.7)	-3.61	0.000
Cyfra21-1	1.37 (0.98, 2.14)	1.79 (1.32, 2.48)	-6.79	0.000
Fer	145.10 (93.95, 211.65)	94.20 (39.90, 178.40)	-5.55	0.000
SCC	0.73 (0.53, 0.97)	0.70 (0.50, 0.96)	-0.24	0.981

Table 2. Comparison of indicators of colorectal cancer in different tissue types.

Variables	Poorly differentiated adenocarcinoma	Moderately differentiated adenocarcinoma	Well-differentiated adenocarcinoma	Mucinous adenocarcinoma	Neuroendocrine tumor	chi-squared test/ Kruskal-Wallis test	
	(n = 45) M (P_{25}, P_{75})	(n = 414) M (P_{25}, P_{75})	(n = 27) M (P_{25}, P_{75})	(n = 14) M (P_{25}, P_{75})	(n = 13) M (P_{25}, P_{75})	χ^2/H value	p-value
Gender, n (%)						1.457	0.834
Female	15 (33.3%)	143 (34.5%)	11 (40.7%)	4 (28.6%)	3 (23.1)		
Male	30 (66.7%)	271 (65.5%)	16 (59.3%)	10 (71.4)	10 (76.9)		
Age	67.0 (58.3, 75.8)	67.0 (61.0, 75.0)	70.0 (64.5, 75.5)	68.5 (54.0, 78.5)	56.0 (40.0, 69.0)	5.997	0.199
Blood group, n (%)						10.172	0.533
A	10 (22.7%)	125 (31.3%)	6 (22.2%)	3 (21.4)	2 (20%)		
B	12 (27.3%)	121 (30.3%)	8 (29.6%)	8 (57.1%)	3 (30%)		
O	18 (40.9)	126 (31.6%)	9 (33.3%)	3 (21.4%)	4 (40%)		
AB	4 (9.1%)	27 (6.8%)	4 (14.8%)	0 (0%)	1 (10%)		
Routine biomarkers							
NLR	2.62 (1.92, 3.39)	1.96 (1.52, 2.60)	1.75 (1.45, 2.81)	2.34 (1.72, 3.95)	1.70 (0.95, 2.83)	16.200	0.003
PLR	159.09 (127.67, 188.41)	123.46 (92.58, 174.72)	112.63 (92.18, 165.95)	136.98 (111.17, 205.18)	114.47 (80.89, 158.06)	12.914	0.012
LMR	3.35 (2.23, 4.31)	3.84 (2.84, 4.84)	4.02 (3.14, 4.91)	4.07 (2.76, 4.93)	4.24 (3.30, 6.16)	8.189	0.085
NMR	7.84 (6.12, 10.96)	7.48 (5.97, 9.35)	8.31 (5.63, 8.86)	8.73 (7.29, 11.06)	8.94 (6.72, 9.51)	4.470	0.346
P-LCR	33.05 (28.43, 39.53)	31.80 (25.50, 39.05)	28.20 (23.95, 41.25)	27.90 (20.85, 35.38)	32.70 (21.70, 34.40)	7.249	0.123
MPV	11.05 (10.50,11.875)	10.80 (10.10, 11.70)	10.40 (9.85, 11.85)	10.40 (9.65, 11.38)	10.90 (9.60, 11.10)	5.506	0.239
PDW	13.15 (12.15,15.38)	13.00 (11.30, 15.00)	12.20 (11.00, 15.95)	11.65 (9.98, 13.90)	13.30 (10.50, 14.60)	6.177	0.186
RDW	2.11 (1.55, 3.85)	1.77 (1.30, 2.39)	1.51 (1.37, 2.10)	1.98 (1.21, 2.70)	1.11 (0.81, 2.73)	2.137	0.711
TC	4.25 (3.70,4.90)	4.6 (3.95, 5.20)	4.70 (3.95, 5.10)	4.15 (3.60, 4.55)	4.50 (3.50, 6.00)	6.770	0.149
TG	1.29 (0.98, 1.80)	1.27 (0.92, 1.64)	1.17 (0.95, 1.47)	1.11 (0.92, 1.71)	1.06 (0.89, 2.16)	0.568	0.967
T-BIL	13.15 (10.03, 17.48)	13.40 (10.05, 17.80)	14.30 (11.40, 20.80)	14.50 (9.88, 18.80)	16.80 (14.30, 18.80)	0.303	0.990
D-BIL	2.65 (1.80, 4.18)	2.50 (1.90, 3.30)	2.70 (2.20, 3.90)	2.80 (1.93, 4.43)	3.90 (2.20, 5.20)	1.861	0.761
AST	20.0 (17.0, 25.0)	20.0 (17.0, 25.0)	21.0 (18.0, 26.5)	18.5 (14.8, 23.5)	18.0 (16.0, 24.0)	5.009	0.286
GGT	27.5 (14.3, 44.5)	20.0 (15.0, 30.0)	27.0 (15.5, 50.0)	25.0 (17.3, 27.8)	34.0 (18.0, 44.0)	10.994	0.027
LDH	193.5 (167.0, 220.3)	188.0 (163.0, 212.5)	198.0 (159.5, 216.0)	194.5 (153.3, 220.5)	178.0 (167.0, 184.0)	1.581	0.812
AchE	6.52 (5.19, 7.58)	6.61 (5.60, 7.72)	7.00 (6.37, 8.02)	6.83 (6.08, 7.43)	7.46 (6.96, 9.39)	4.318	0.365
CG	1.7 (1.4, 1.9)	1.7 (1.3, 2.1)	1.5 (1.4, 2.1)	1.8 (1.3, 2.3)	1.8 (1.6, 2.5)	2.351	0.672

Table 2. Comparison of indicators of colorectal cancer in different tissue types (continued).

Variables	Poorly differentiated adenocarcinoma	Moderately differentiated adenocarcinoma	Well-differentiated adenocarcinoma	Mucinous adenocarcinoma	Neuroendocrine tumor	chi-squared test/ Kruskal-Wallis test	
	(n = 45) M (P_{25}, P_{75})	(n = 414) M (P_{25}, P_{75})	(n = 27) M (P_{25}, P_{75})	(n = 14) M (P_{25}, P_{75})	(n = 13) M (P_{25}, P_{75})	χ^2/H value	p-value
CR	70.0 (57.5, 81.0)	67.0 (60.0, 78.0)	74.0 (61.0, 83.5)	67.0 (55.5, 72.5)	68.0 (57.0, 77.0)	1.282	0.864
ALP	86.5 (67.3, 107.3)	78.0 (66.0, 93.5)	84.0 (75.5, 98.0)	82.0 (68.0, 102.0)	76.0 (66.0, 90.0)	4.515	0.341
TP	63.65 (58.98, 68.05)	65.70 (61.85, 69.40)	65.10 (62.50, 68.45)	61.25 (57.15, 64.60)	69.70 (63.60, 70.50)	15.047	0.005
ALB	37.55 (34.83, 40.48)	38.40 (35.70, 40.75)	38.40 (36.85, 38.75)	37.15 (33.93, 39.55)	42.60 (41.70, 44.20)	12.318	0.015
PA	217 (162, 252)	213 (179, 256)	232 (207, 267)	194 (169, 257)	232 (214, 281)	5.018	0.285
HDL-C	1.02 (0.84, 1.20)	1.11 (0.93, 1.27)	1.01 (0.92, 1.34)	1.09 (0.91, 1.32)	1.11 (1.03, 1.20)	3.640	0.457
LDL-C	2.87 (2.28, 3.23)	2.96 (2.50, 3.49)	2.89 (2.61, 3.29)	2.58 (2.17, 2.93)	2.70 (2.08, 4.27)	6.151	0.188
CEA	7.55 (2.53, 16.98)	3.50 (2.10, 6.75)	2.30 (1.65, 5.10)	5.90 (3.68, 10.40)	2.10 (1.50, 2.90)	17.681	0.001
CA19-9	6.8 (3.7, 21.6)	6.1 (2.6, 14.3)	4.0 (1.6, 18.0)	7.5 (3.2, 27.9)	4.4 (1.0, 8.6)	3.657	0.454
Cyfra21-1	2.105 (1.553, 3.845)	1.770 (1.300, 2.390)	1.510 (1.365, 2.095)	1.975 (1.213, 2.700)	1.110 (0.810, 2.730)	9.911	0.042
Fer	116.05 (49.58, 253.15)	85.30 (31.25, 163.85)	102.00 (71.85, 250.45)	79.95 (16.73, 155.45)	228.60 (143.70, 378.60)	12.385	0.015
SCC	0.67 (0.51, 0.85)	0.70 (0.51, 0.96)	0.78 (0.46, 1.17)	0.59 (0.44, 0.75)	0.80 (0.45, 1.12)	1.340	0.855

Table 3. Results of binary logistic regression analysis of age, CEA, AchE, and HDL-C.

Variables	B	S.E	Wald value	p-value	Exp (B)	Exp (B) 95% (CI)	
						Lower	Upper
> 60 years *	1.179	0.161	53.483	0.000	3.251	2.370	4.459
CEA	0.377	0.051	54.167	0.000	1.457	1.318	1.611
AchE	-0.386	0.049	62.993	0.000	0.680	0.618	0.748
HDL-C	-1.102	0.204	29.035	0.000	0.332	0.223	0.496

Note: colorectal cancer is a positive event, benign lesions are negative events.
*** Control group: < 60 years.**

Table 4. Results of binary logistic regression analysis of PLR, NLR, and CEA.

Variables	B	S.E	Wald value	p-value	Exp (B)	Exp (B) 95% (CI)	
						Lower	Upper
NLR	0.243	0.276	0.776	0.378	1.275	0.743	2.188
PLR	0.010	0.006	2.533	0.111	1.010	0.998	1.023
CEA	0.546	0.186	8.602	0.003	1.727	1.199	2.487

Note: poorly differentiated adenocarcinoma is a positive event, benign lesions are negative events.

Table 5. Diagnostic efficiency of CEA, AchE, and HDL-C.

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy
CEA	**48.71% (284/583)**	**82.63% (195/236)**	**87.38% (284/325)**	**39.47% (195/494)**	**58.41% (479/819)**
AchE	**68.78% (401/583)**	**55.51% (131/236)**	**79.25% (401/506)**	**41.85% (131/313)**	**64.80% (532/819)**
HDL-C	**91.42% (533/583)**	**22.46% (53/236)**	**74.44% (533/716)**	**51.46% (53/103)**	**71.12% (586/819)**
Combination	**94.35% (167/177)**	**55.56% (10/18)**	**95.43% (167/175)**	**50.00% (10/20)**	**90.77% (177/195)**

other types of tumors, the differences in ALB between neuroendocrine tumors patients and mucinous adenocarcinoma, poorly differentiated adenocarcinoma and moderately differentiated adenocarcinoma were statistically significant ($p = 0.012$, $p = 0.025$, $p = 0.020$), the difference in Fer between neuroendocrine tumors patients and moderately differentiated adenocarcinoma patients was statistically significant ($p = 0.036$), the difference in TP between neuroendocrine tumors patients and mucinous adenocarcinoma, poorly differentiated adenocarcinoma patients was statistically significant ($p = 0.008$, $p = 0.048$). The difference in GGT was not statistically significant after multiple comparisons, as shown in Figure 2.

Binary logistic regression analysis

Taking colorectal malignant tumor as positive event and benign lesion as negative event, four variables, age, CEA, AchE, and HDL-C, were screened out for regression model. The results in Table 1 show that with the age of 60 as the dividing line, there are differences in the proportion of benign and malignant colorectal lesions. The age was divided into two subgroups, ≤ 60 and > 60, for regression analysis. The risk of colorectal cancer was nearly 2.251 times higher for > 60 years than for ≤ 60 years.

After adjusting for age and other factors, CEA was an independent risk factor for colorectal cancer, with other variables remaining unchanged; when CEA increased by 1, the risk of colorectal cancer increased by 45.7%. AchE and HDL-C are protective factors for colorectal cancer; when they increased by 1, the risk of colorectal cancer decreased by 32% and 66.8%, respectively, as shown in Table 3.

Colorectal poorly differentiated adenocarcinoma was matched to benign disease by the PSM propensity score, with a matching tolerance of 0.02. Multivariate analysis of PLR, NLR, and CEA showed that, with other variables unchanged, when CEA increased by 1, the risk of colorectal poorly differentiated adenocarcinoma increased by 72.7%, as shown in Table 4.

ROC and diagnostic efficacy

Taking colorectal malignant tumors as positive events and benign lesions as negative events, ROC curve was drawn, and it was found that the AUC of CEA, AchE, and HDL-C were 73.0% (95% CI: 0.695 - 0.766, $p = 0.000$), 67.2% (95% CI: 0.633 - 0.712, $p = 0.000$), 57.2% (95% CI: 0.528 - 0.617, $p = 0.001$), respectively. The sensitivity of CEA, AchE, and HDL-C were 48.71%, 68.78%, and 91.42%; the PPV of CEA, AchE, and HDL-C were 87.38%, 79.25%, and 74.44%. The combined diagnostic sensitivity, PPV, and accuracy were 94.35%, 95.43%, and 90.77%, respectively, as shown in Figure 3 and Table 5.

The relationship between colorectal malignancies of different blood groups and clinicopathological parameters

There were no significant differences between different blood groups in tumor size, lymph node metastasis, number of lymph node metastasis, invasion site, TNM stage, and clinical stage. There was a statistically significant difference in the degree of tumor infiltration among different blood groups ($p = 0.047$). Compared with other blood group CRC patients, blood group AB patients mainly invaded the mucosal layer and rarely invaded the muscularis propria, as shown in Table 6.

The relationship between risk factor and clinicopathological parameters

Age was significantly weakly correlated with the number of lymph node metastasis, whether lymph node metastasis or vascular and nerve invasion ($p < 0.05$, $|r| < 0.4$). CEA was significantly weakly correlated with tumor size, number of lymph node metastasis, invasion degree of lymph node metastasis, and vascular invasion ($p < 0.05$, $|r| < 0.4$). AchE was significantly weakly correlated with tumor size and degree of invasion and HDL-C was significantly weakly correlated with tumor size ($p < 0.05$, $|r| < 0.4$), as shown in Table 7.

Table 6. The relationship between clinicopathological parameters of colorectal cancer and different blood groups.

Variable	Blood Group				Kruskal-Wallis test	p-value
	A	B	O	AB		
Tumor size (M (P25, P75))	4 (2.5, 4)	4 (3, 5)	4 (3, 5)	4 (3, 5)	1.09	0.779
Number of lymphatic metastases (M (P25, P75))	0 (0, 1.5)	0 (0, 1)	0 (0, 1)	0 (0, 1)	3.33	0.344
Lymphatic metastasis, n (%)					4.33	0.228
No	117 (70.5%)	120 (70.2%)	137 (75.7%)	26 (60.5%)		
Yes	49 (29.5%)	51 (29.8%)	44 (24.3%)	17 (39.5%)		
Infiltration, n (%)					17.11	0.047
Mucous layer	3 [a] (2.1%)	4 [a] (2.7%)	7 [a, b] (4.5%)	5 [b] (13.5%)		
Submucous layer	15 [a] (10.4%)	14 [a] (9.3%)	17 [a] (10.9%)	3 [a] (8.1%)		
Muscularis propria layer	60 [a] (41.7%)	61 [a] (40.7%)	65 [a] (41.7%)	6 [b] (16.2%)		
Serous layer	66 [a] (45.8%)	71 [a] (47.3%)	67 [a] (42.9%)	23 [a] (62.2%)		
Lymphatic vascular invasion, n (%)					4.38	0.224
No	92 (64.3%)	98 (69.0%)	111 (73.5%)	20 (58.8%)		
Yes	51 (35.7%)	44 (31.0%)	40 (26.5%)	14 (41.2%)		
Nerve invasion (n (%))					4.26	0.235
No	107 (74.8%)	120 (84.5%)	119 (79.3%)	26 (76.5%)		
Yes	36 (25.2%)	22 (15.5%)	31 (20.7%)	8 (23.5%)		
TNM stages						
T0	0 (0.0%)	1 (1.2%)	1 (1.1%)	0 (0.0%)		0.216
T1	11 (11.6%)	5 (6.2%)	15 (16.1%)	2 (7.1%)		
T2	17 (17.9%)	20 (25.0%)	11 (11.8%)	9 (32.1%)		
T3	64 (67.4%)	53 (66.2%)	65 (69.9%)	17 (60.7%)		
T4	3 (3.2%)	1 (1.2%)	1 (1.1%)	0 (0.0%)		
N0	62 (65.3%)	50 (62.5%)	57 (61.3%)	20 (71.4%)		0.895
N1	18 (18.9%)	19 (23.8%)	24 (25.8%)	5 (17.9%)		
N2	15 (15.8%)	11 (13.8%)	12 (12.9%)	3 (10.7%)		
M0	94 (98.9%)	80 (100.0%)	93 (100.0%)	28 (100.0%)		0.516
M1	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Clinical stages						0.763
0	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		
I	25 (26.3%)	21 (26.2%)	22 (23.7%)	10 (35.7%)		
II	37 (38.9%)	28 (35.0%)	35 (37.6%)	10 (35.7%)		
III	32 (33.7%)	30 (37.5%)	36 (38.7%)	8 (28.6%)		
IV	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		

Note: the difference between the two groups marked with different letters was statistically significant ($p < 0.05$). There was no statistically significant difference between groups marked with the same letter, to indicate comparison.

DISCUSSION

The occurrence and development of colorectal cancer is related to genetic lifestyle, diet, gut microflora microenvironment, inflammation, immunity, and other factors [7-9]; the benefits of early diagnosis and early treatment for CRC patients are self-evident. Given that there are currently no good, non-invasive biomarkers for the diagnosis of CRC, research on novel biomarkers, such as microRNAs and fecal bacterial markers, etc., has

Table 7. The relationship between risk factor and clinicopathological parameters.

Variables	Age		CEA		AchE		HDL-C	
	r	p-value	r	p-value	r	p-value	r	p-value
Tumor size	0.071	0.125	0.216	0.000	-0.192	0.000	-0.176	0.000
Number of lymphatic metastases	-0.153	0.001	0.156	0.001	0.007	0.879	0.078	0.083
Lymphatic metastasis	-0.090	0.029	0.160	0.000	-0.003	0.933	0.059	0.157
Infiltration degree	0.062	0.165	0.296	0.000	-0.196	0.000	-0.075	0.091
Lymphatic vascular invasion	-0.099	0.029	0.094	0.039	-0.016	0.727	0.054	0.234
Nerve invasion	-0.098	0.031	0.075	0.098	0.040	0.380	0.037	0.413

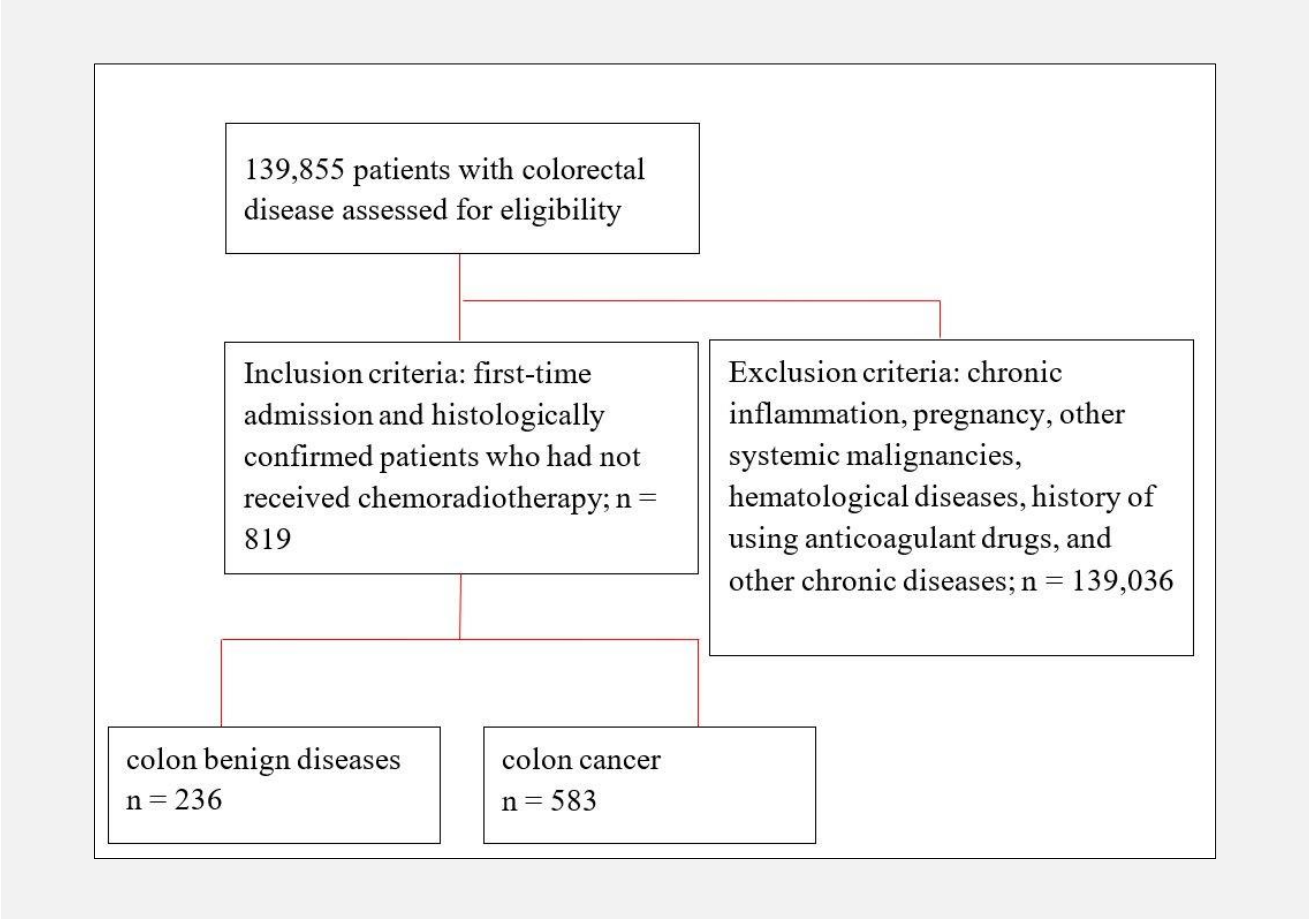

Figure 1. Determination of patient groups.

received great attention from researchers [10,11]. Although they have shown certain application value, most of them are still in the basic research stage. Some scholars have tried to use the derived data of conventional indicators for the diagnosis of CRC, such as tumor indicators, blood routine indicators, blood groups, etc. [12-14]. Most studies have had a small number of cases and the results varied from time to time. This article systematically analyzed the relationship between most routine indicators in clinical laboratories and CRC, which has not been reported in the previous literature.

Among the 583 CRC cases included in this study, patients > 60 years accounted for 74.2%. Logistic regression analysis showed that the risk of colorectal cancer in people > 60 years was nearly 2.251 times higher than

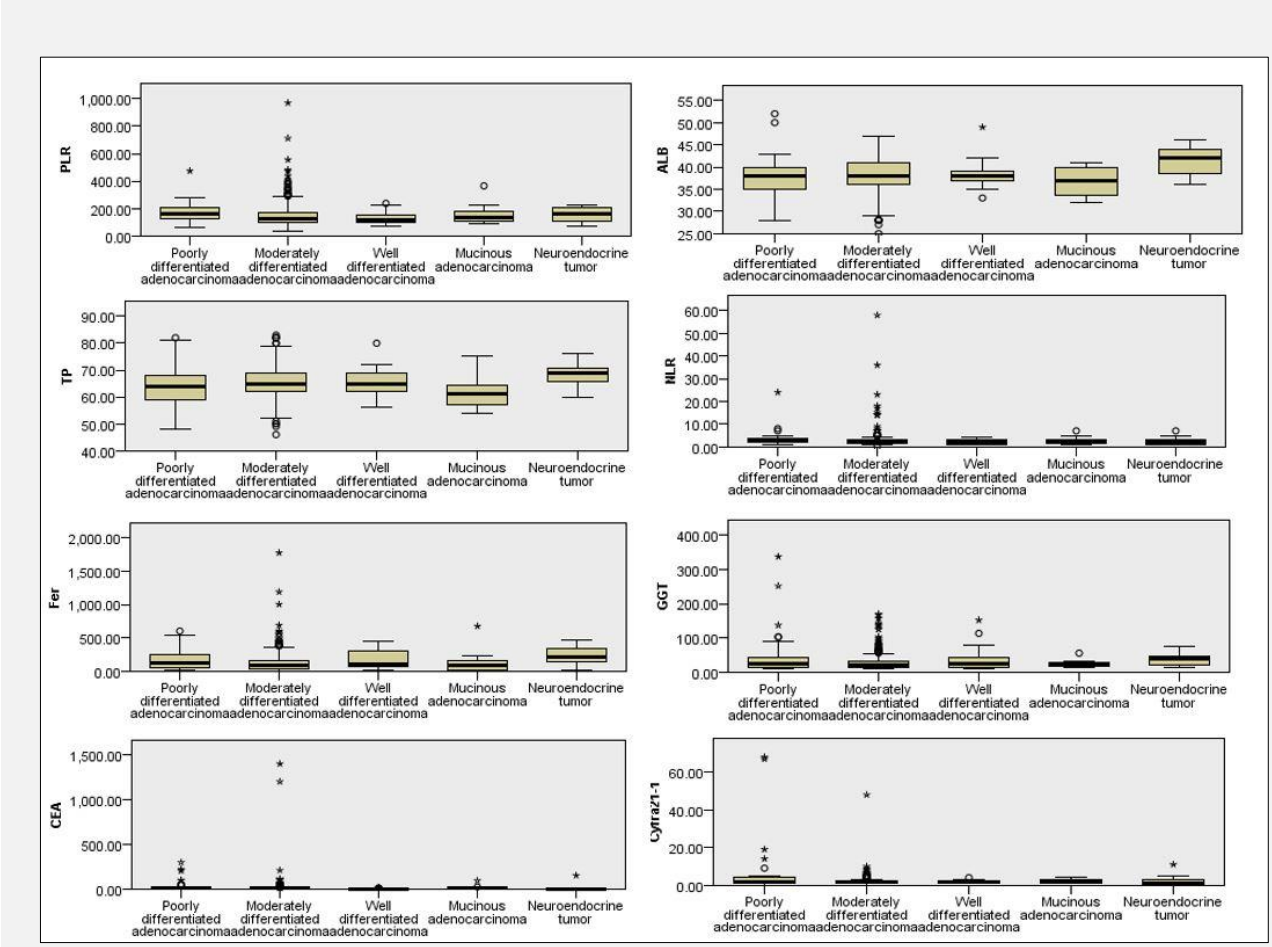

Figure 2. Multiple comparisons of colorectal malignancies with different tissue types.

that in people < 60 years, which is different from the reported increased incidence of CRC in people < 50 years [4]. This may be due to different regions, lifestyles, dietary habit, etc., which also change with age. It suggests that a healthy lifestyle is very beneficial for reducing the incidence of CRC. In addition, when conventional biomarkers were used to compare benign and malignant colorectal diseases, we found that there were no statistics in gender, blood group, T-BIL, CG, NLR, PLR, P-LCR, PDW, MPV, LDL-C, and SCC. However, there are literature reports that NLR, PLR, etc. can be used for lung cancer, gastric cancer, nasopharyngeal cancer, ovarian cancer, and other cancers [15-18]. This study found that NLR and PLR showed no difference in distinguishing benign and malignant colorectal diseases, but it showed differences between different tissue types of CRC. NLR and PLR in patients with poorly differentiated adenocarcinoma were significantly higher than other types of tumors, there was a statistically significant difference in PLR between patients with poorly differentiated adenocarcinoma and those with well-differentiated adenocarcinoma and moderately differentiated adenocarcinoma, and there was a statistically significant difference in NLR between patients with poorly differentiated adenocarcinoma and those with moderately differentiated adenocarcinoma. In addition, TP and ALB are differentially expressed in colorectal benign and malignant tumors, and the level of ALB in patients with neuroendocrine tumors is higher than in mucinous adenocarcinoma, poorly differentiated adenocarcinoma and moderately differentiated adenocarcinoma. TP in patients with neuroendocrine tumors is higher than in mucinous adenocarcinoma and poorly differentiated adenocarcinoma patients. It has been reported that ALB can be used for prognostic assessment of CRC [19], and it has also been mentioned that ALB can be used to differentiate distal and proximal CRC [20]; there has been no literature report that ALB is differentially expressed in colorectal benign and malignant tumors. As a traditional biomarker of liver function, GGT has a certain value in the diagnosis and treatment of liver cirrhosis and liver cancer. In 2012, Fentiman proposed that GGT may be a

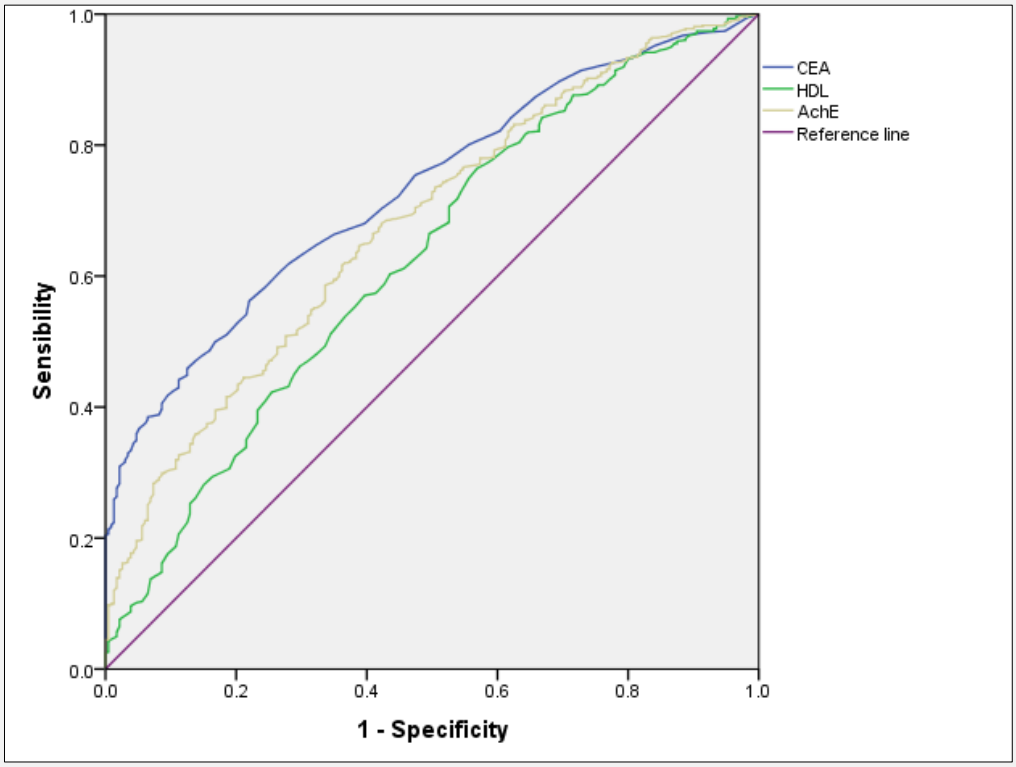

Figure 3. Taking colorectal malignant tumors as positive events and benign lesions as negative events, the ROC of three risk markers were drawn.

representative of oxidative stress, and oxidative stress is involved in the carcinogenesis process [21]. Hong suggested that GGT may be associated with colorectal precancerous lesions [22]. In this study, we found that GGT showed differences in benign and malignant CRCs and in different tissue types, which indicated that GGT was closely related to the occurrence and development of CRC. Recently, scholars have paid attention to the relationship between Fer and tumors. In liver cancer patients, excessive iron promotes carcinogenesis through the production of reactive oxygen species, damages DNA, and eventually forms alcoholic liver cancer [23], while in pancreatic cancer patients, increased Fer implies a poor prognosis, which may be related to the involvement of Fer in immunoregulation, tumor angiogenesis, and proliferation [24]. Most patients with CRC will experience intestinal bleeding, resulting in decreased iron stores in the body. In this study, we found that the plasma ferritin concentration of CRC patients was much lower than that of colorectal benign diseases, and the level of Fer in different tissue types of CRC was also different, indicating that the serum Fer concentration of CRC patients mainly depends on the status of intestinal blood loss.

The relationship between lipid metabolism and cancer has been reported in the literature, but the results are not completely consistent. Loosen found that TC and HDL-C were negatively correlated with the incidence of gastrointestinal tumors [25]. Fang found that serum TG was associated with increased risk of colorectal cancer [26]. Our study observed that TG and TC were statistically different between benign and malignant colorectal diseases, but they were not different enough to be risk factors for CRC. HDL-C was involved in antioxidant, anti-inflammatory, antithrombotic, immune regulation, and other roles [27-30], showing consistent changes in most patients, but the relationship between HDL-C and cancer is still inconclusive. Zhang found that HDL-C was inversely associated with rectal cancer, consistent with our findings that HDL-C is a protective factor for CRC [31]. However, it has been reported in the literature that HDL-C can increase the proliferation, invasion, and colony formation of cancer cells [32]. Revilla et al., through glioma, breast cancer, prostate cancer, and ovarian cancer cell experiments, confirmed this result [33]. In addition, Notarnicola found that TC and LDL-C in patients with distant metastatic CRC were significantly higher than in patients without metastases [34].

However, no significant differences between these markers with distant metastases were observed in our study, but unexpectedly, we found that HDL-C is significantly weakly associated with tumor size. This shows that lipids in blood are deeply involved in the occurrence and development of tumors through different pathways.

The ABO blood group system is mainly defined by different antigens on the surface of red blood cells and has genetic stability. Researchers have found the same antigens on epithelial cells and endothelial cells, and in-depth studies on tumors have found that the occurrence and development of many tumors are related to these antigens. The relationship between ABO blood group and tumor has become a research hotspot in recent years; most of the current research focuses on the distribution and prognosis of blood group and pancreatic cancer, gastric cancer, and liver cancer [35-37]. Our results are the first to find that CRC patients with AB blood group are more likely to involve the mucosa and less likely to involve the muscularis propria, which may add an objective indicator for assessing the degree of tumor invasion.

CEA is a traditional tumor marker, its diagnostic value in gastrointestinal tumors has also been recognized. Cytokeratins are divided into 20 different types. Cyfra21-1 is widely distributed on the surface of normal tissues. In malignant epithelial cells, activated proteases accelerate the degradation of cells, resulting in the release of a large number of cytokeratin fragments into the blood. Cyfra21-1 is currently mainly used for the diagnosis of lung cancer, which has been implicated in head and neck cancer, and breast cancer has a certain positive rate [38,39]. In this study, we found that CEA, CA19-9, and Cyfra21-1 in CRC patients were significantly higher than in benign colorectal patients, especially in poorly differentiated adenocarcinoma of CRC, with the highest concentrations of CEA and Cyfra21-1.

Binary logistic regression analysis showed that CEA was an independent risk factor for colorectal cancer; with other variables remaining unchanged, when its value increased by 1, the risk of colorectal cancer increased by 45.7% and the risk of poorly differentiated adenocarcinoma of CRC increased by 72.7%. AchE and HDL-C are protective factors for colorectal cancer; with other variables remaining unchanged, when its value increased by 1, the risk of colorectal cancer decreased by 32% and 66.8%, respectively. At present, there is no specific biomarker for CRC, and the sensitivity and specificity of each indicator alone have not reached a satisfactory level. The sensitivity, PPV, and accuracy were improved when CEA, AchE, and HDL-C were detected together. Therefore, clinical evaluation of biomarkers should pay attention to the joint judgment of multiple indicators to improve the clinical value of biomarkers.

There are still some limitations to this study. For example, most of the patients included in this study were not followed up due to lack of information. Therefore, in this paper, the prognosis was not analyzed. In addition, the multicenter combination can increase the number of CRC cases, which will make our results more convincing, and thus, will be our next work direction.

In summary, when we assess routine tumor markers, we should also pay attention to non-tumor markers such as blood lipids, blood routine, blood group, etc. The combined detection of multiple indicators is of positive significance for the diagnosis, pathological stage, prevention of CRC, etc.

Declaration of Interest:

None.

References:

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-49. (PMID: 33538338)

2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66(4):683-91. (PMID: 26818619)

3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72(1):7-33. (PMID: 35020204)

4. Wang J, Liu L, Cai Y, et al. Trends in the age-related incidence of colon and rectal cancers in China, 2005-2015. Dig Liver Dis 2021;53(7):908-14. (PMID: 33551354)

5. Repici A, Spadaccini M, Antonelli G, et al. Artificial intelligence and colonoscopy experience: lessons from two randomised trials. Gut 2022;71(4):757-65. (PMID: 34187845)

6. Cronin KA, Lake AJ, Scott S, et al. Annual report to the nation on the status of cancer, part I: National cancer statistics. Cancer 2018;124(13):2785-800. (PMID: 29786848)

7. Ray SK, Mukherjee S. Nutrigenomics and Lifestyle Facet- A modulatory molecular evidence in progression of breast and colon cancer with emerging importance. Curr Mol Med. 2022; 22(4):336-48. (PMID: 33797366)

8. Bou Malhab LJ, Abdel-Rahman WM. Obesity and inflammation: colorectal cancer engines. Curr Mol Pharmacol 2022;15(4):620-46. (PMID: 34488607)

9. Maiorino L, Daßler-Plenker J, Sun L, Egeblad M. Innate immunity and cancer pathophysiology. Annu Rev Pathol 2022;17: 425-57. (PMID: 34788549)

10. Li G, Wang Q, Li Z, Shen Y. Serum miR-21 and miR-210 as promising non-invasive biomarkers for the diagnosis and prognosis of colorectal cancer. Rev Esp Enferm Dig 2020;112(11): 832-37. (PMID: 33054296)

11. Sun C-H, Li B-B, Wang B, et al. The role of *Fusobacterium nucleatum* in colorectal cancer: from carcinogenesis to clinical management. Chronic Dis Transl Med 2019;5(3):178-87. (PMID: 31891129)

12. Singh S, Kumar R, Kumar U, Kumari R. Clinical significance and role of TK1, CEA, CA 19-9 and CA 72-4 levels in diagnosis of colorectal cancers. Asian Pac J Cancer Prev 2020;21(11):3133-6. (PMID: 33247667)

13. Li H, Lin J, Xiao Y, et al. Colorectal cancer detected by machine learning models using conventional laboratory test data. Technol Cancer Res Treat 2021;20:15330338211058352. (PMID: 34806496)

14. Cao X, Wen Z-S, Sun Y-J, Li Y, Zhang L, Han Y-J. Prognostic value of ABO blood group in patients with surgically resected colon cancer. Br J Cancer 2014;111(1):174-80. (PMID: 24901236)

15. Kemal Y, Yucel I, Ekiz K, et al. Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. Asian Pac J Cancer Prev 2014;15(6):2651-4. (PMID: 24761879)

16. Fang Z, He M, Song M. Serum lipid profiles and risk of colorectal cancer: a prospective cohort study in the UK Biobank. Br J Cancer 2021;124(3):663-70. (PMID: 33139801)

17. Lin Z, Zhang X, Luo Y, Chen Y, Yuan Y. The value of hemoglobin-to-red blood cell distribution width ratio (Hb/RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) for the diagnosis of nasopharyngeal cancer. Medicine (Baltimore) 2021;100(28):e26537. (PMID: 34260530)

18. Yildirim M, Demir Cendek B, Filiz Avsar A. Differentiation between benign and malignant ovarian masses in the preoperative period using neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios. Mol Clin Oncol 2015;3(2):317-21. (PMID: 25798260)

19. Kubat M, Bozkirli BO, Yazicioglu MO, Gundogdu RH. Does albumin level change the strength of the memorial sloan kettering cancer center nomogram used to predict 5-year survival in patients with colon cancer? J Coll Physicians Surg Pak 2022;32(4): 467-72. (PMID: 35330519)

20. Knekt P, Hakulinen T, Leino A, Heliövaara M, Reunanen A, Stevens R. Serum albumin and colorectal cancer risk. Eur J Clin Nutr 2000;54(6):460-2. (PMID: 10878646)

21. Fentiman IS. Gamma-glutamyl transferase: risk and prognosis of cancer. Br J Cancer 2012;106(9):1467-8. (PMID: 22531718)

22. Hong T-C, Yang H-C, Chen C-L, et al. Relationship between serum gamma-glutamyl transferase level and colorectal adenoma. PLoS One 2020;15(10):e0240445. (PMID: 33048943)

23. Tran KT, Coleman HG, McCain RS, Cardwell CR. Serum biomarkers of iron status and risk of primary liver cancer: a systematic review and meta-analysis. Nutr Cancer 2019;71(8):1365-73. (PMID: 31044614)

24. Lin S, Fang Y, Lin Y, et al. Meta-analysis of the prognostic value of pretreatment serum ferritin in hepatobiliary and pancreas (HBP) cancers. BMJ Open 2021;11(5):e040801. (PMID: 34049899)

25. Loosen SH, Kostev K, Luedde M, Luedde T, Roderburg C. Low blood levels of high-density lipoprotein (HDL) cholesterol are positively associated with cancer. J Cancer Res Clin Oncol 2022; 148(11):3039-46. (PMID: 34897572)

26. Fang T, Wang Y, Yin X, et al. Diagnostic sensitivity of NLR and PLR in early diagnosis of gastric cancer. J Immunol Res 2020; 2020:9146042. (PMID: 32211444)

27. Cedó L, Metso J, Santos D, et al. Consumption of polyunsaturated fat improves the saturated fatty acid-mediated impairment of HDL antioxidant potential. Mol Nutr Food Res 2015;59(10): 1987-96. (PMID: 26118785)

28. Jia C, Anderson JLC, Gruppen EG, et al. High-density lipoprotein anti-inflammatory capacity and incident cardiovascular events. Circulation 2021;143(20):1935-45. (PMID: 33840204)

29. Mineo C, Deguchi H, Griffin JH, Shaul PW. Endothelial and antithrombotic actions of HDL. Circ Res 2006;98(11):1352-64. (PMID: 16763172)

30. Larbi A, Fortin C, Dupuis G, Berrougui H, Khalil A, Fulop T. Immunomodulatory role of high-density lipoproteins: impact on immunosenescence. Age (Dordr) 2014;36(5):9712. (PMID: 25216565)

31. Zhang X, Zhao X-W, Liu D-B, et al. Lipid levels in serum and cancerous tissues of colorectal cancer patients. World J Gastroenterol 2014;20(26):8646-52. (PMID: 25024621)

32. Liu Y-Y, Lin S-J, Chen Y-Y, et al. High-density lipoprotein cholesterol as a predictor of poor survival in patients with nasopharyngeal carcinoma. Oncotarget 2016;7(28):42978-87. (PMID: 27304186)

33. Revilla G, Cedó L, Tondo M, et al. LDL, HDL and endocrine-related cancer: From pathogenic mechanisms to therapies. Semin Cancer Biol 2021;73:134-57. (PMID: 33249202)

34. Notarnicola M, Altomare DF, Correale M, et al. Serum lipid profile in colorectal cancer patients with and without synchronous distant metastases. Oncology 2005;68(4-6):371-4. (PMID: 16020965)

35. Li Y, Liu L, Huang Y, Zheng H, Li L. Association of ABO polymorphisms and pancreatic Cancer/ Cardiocerebrovascular disease: a meta-analysis. BMC Med Genet 2020;21(1):41. (PMID: 32093636)

36. Lu L-L, Zhang Y-H, Yao M-H, et al. ABO blood groups and liver cancer: prospective results from an HBsAg cohort study. BMJ Open 2021;11(5):e044039. (PMID: 33980521)

37. Yu H, Xu N, Li Z-K, et al. Association of ABO blood groups and risk of gastric cancer. Scand J Surg 2020;109(4):309-13. (PMID: 31282314)

38. Rudhart SA, Gehrt F, Birk R, et al. Clinical relevance of CYFRA 21-1 as a tumour marker in patients with oropharyngeal squamous cell carcinoma. Eur Arch Otorhinolaryngol 2020;277(9): 2561-71. (PMID: 32285192)

39. Xue F, Meng Y, Jiang J. Diagnostic Value of dynamic enhanced magnetic resonance imaging combined with serum CA15-3, CYFRA21-1, and TFF1 for breast cancer. J Healthc Eng 2022; 2022:7984591. (PMID: 35392152)