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The Clinical Significance and Diagnostic Value of Coagulation Function, Fecal Occult Blood in Combination with Tumor Markers in Colorectal Cancer

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Abstract

Background: A single tumor marker has limitations in the diagnosis of colorectal cancer. This study investigates the diagnostic value of the combined detection of coagulation function, fecal occult blood, and tumor markers in colorectal cancer.

Methods: The total number of 262 patients with colorectal cancer confirmed in our hospital from January 2021 to September 2023 were selected as the observation group, and 266 patients with colorectal polyps diagnosed in the same period were selected as the control group. By comparing the differences in coagulation function, fecal occult blood, and tumor markers between the two groups, the indicators related to colorectal cancer were screened out, and the diagnostic value of single indicator detection and combined detection was discussed.

Results: The differences in expression in prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), and Fecal occult blood (FOB) were statistically significant between the observation group and the control group ($P<0.05$). The maximum area under the receiver operating characteristic curve (ROC) curve for the combined detection of PT, FIB, FOB, CEA, and CA19-9 was 0.903. The combined detection of PT, FIB, CEA, CA19-9, and FOB was superior to the separate detection ($P<0.05$).

Conclusion: This retrospective analysis reveals that combined testing is crucial in diagnosing colorectal cancer, as it can enhance the accuracy and specificity of colorectal tumor diagnosis compared to testing alone.

Keywords: Coagulation function; FOB; CEA; CA199; Colorectal cancer.

Introduction

Colorectal cancer, as a common clinical malignant tumor, has no obvious symptoms in its clinical manifestation in the early stage [1, 2]. But if it worsens, we can notice changes in bowel habits, the characteristics of feces, stomach pain, or other discomfort [3]. These clinical symptoms are frequently disregarded. The World Health Organization states that when treatment choices are limited, it is frequently detected at an advanced stage [4]. The diagnosis of colorectal cancer involves laboratory tests, endoscopy, imaging, and pathological examination [5-8]. Patients' acceptance of endoscopy differs [9]. For certain individuals, individual financial conditions may restrict radiological testing and delay the prompt diagnosis of their illness. Therefore, high patient acceptance and appropriate colorectal cancer screening tests

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are particularly important. To a certain extent, the process of tumor occurrence and development can be reflected by tumor markers [10-12]. The commonly used indicators for colorectal cancer include carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199) [13]. It has been found that tumor growth can activate the coagulation process and produce pro-coagulant substances[14-16]. These substances induce an inflammatory response and further stimulate the production of pro-coagulant substances by tumor cells. Tumor thrombi's development is intimately associated with this process. The fecal occult blood (FOB) test is commonly used as a screening tool for early detection of gastrointestinal tumors [17, 18]. It is a convenient, non-invasive, and cost-effective method. This paper presents a retrospective analysis of patient data from our hospital between January 2021 and September 2023. This study looks into the diagnostic utility and applicability of combined tests and single indicator testing for tumor markers, coagulation function, and FOB in colorectal cancer.

Materials and Methods

General information

The observation group consisted of 262 patients confirmed with colorectal cancer in our hospital between January 2021 and September 2023, comprising 149 males and 113 females aged 18-93 years. The control group comprised 266 patients diagnosed with colorectal polyps at the same time, including 160 males and 106 females aged 13-84 years. The observation group was divided into a metastatic group and a non-metastatic group based on the presence or absence of tumor metastasis. Out of 262 patients with colorectal cancer, 120 had metastasis. There was no significant difference between male and female patients ($\chi2=0.585$, $P=0.444$). The median age was 61 (53,68) in the observation group and 56 (48,65) in the control group. This study was approved by the Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: 1 The observation group was diagnosed with colorectal cancer through pathology, while the control group was diagnosed with polyp disease of conscience through pathology. 2 The results of the observation group refer to the time of patient admission, before the first surgery or chemotherapy.3 The patient-related information is complete. Exclusion criteria: 1 Colorectal cancer combined with other malignant tumors. 2 The patient has a coagulation disorder. 3 The laboratory data for the patient were incomplete.

Methods

Upon patient admission, fecal and fasting venous blood samples were collected. FOB was detected using an automatic stool analyzer (KUF10). The coagulation function was measured by the Wolfen automatic coagulation analyzer. The coagulation functions comprise fibrinogen (FIB), prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT). Tumor markers CEA and CA199 were detected using the Abbott Alinity I system.

Statistical Analysis

SPSS 25.0 was used for statistical analysis. The count data were analyzed using the $\chi2$ test and expressed as n. Continuous variables that conform to a normal distribution should be described as $\bar{x} \pm s$. The t-test was conducted to compare the differences between the two groups. CEA and CA199 data were non-normally distributed and described by median and quartiles M (Q1, Q3). The non-parametric Mann-Whitney U test was used to compare the two groups. The significance level was $\alpha=0.05$.

Results

Comparison of coagulation function between observation and control groups

Blood coagulation abnormalities have a significant role in the emergence and growth of malignant tumors [19]. Tests for bleeding and clotting can offer helpful hints to elucidate the biological activity of malignancies. They are also necessary for rapid intervention, monitoring the risk of thrombosis and bleeding, and evaluating the prognosis of cancer patients. They can also be a helpful tool in predicting the risk of problems and tracking the effectiveness of treatment. We focus on some common associated coagulation factors in our study. Table 1 show that the observation group had higher levels of PT and FIB compared to the control group, while APTT and TT were lower in the observation group. Significant differences in PT, TT, and FIB were observed between the two groups ($P<0.001$). These results indicate that the coagulation state of the two groups differed under different pathological conditions.

Table 1: Comparison of coagulation function between the two groups ($\bar{x} \pm s$)

Group	n	PT(s)	APTT(s)	TT(s)	FIB(g/L)
Observation Group	262	11.673±0.843	30.766±3.017	14.188±1.138	3.520±0.915
Control Group	266	11.394±0.870	31.145±3.157	14.645±1.063	2.904±0.516
t		3.736	-1.412	-4.772	9.513
P		<0.001	0.158	<0.001	<0.001

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Comparison of FOB results between the two groups

Finland pioneered the FIT (fecal immunochemical tests) concept in the early 1980s, and since then, the test has been used all around the world for FOB detection. Colorectal cancer screening based on faecal immunochemical tests is critical for disease morbidity and mortality. Our finding shows that the observation group had a 93% positive rate for occult blood. A statistically significant difference in FOB was found when comparing the results of the two patient groups (P<0.001) (Table 2).

Comparison of CEA and CA199 between the two groups of patients

The expression levels of CEA and CA199 serve as indicators for guiding treatment in cases of metastatic colorectal cancer. As such, we analysed and compared the expression of CEA and CA199 between the observation group and the control group. The CEA and CA199 of both groups did not follow a normal distribution; therefore the non-parametric Mann-Whitney U test was used. According to Table 3, the difference between CEA and CA199 was statistically significant (P<0.001).

Correlation between coagulation function, FOB, CEA, CA199 in colorectal cancer

To further explore the correlation between coagulation index, faecal occult blood, CEA, CA199, and colorectal cancer, we made the following analysis. Table 4 shows that PT, TT, FIB, FOB, CA199, and CEA were all found to be correlated with the outcome of colorectal cancer through logistic univariate regression analysis. These six factors were also included in logistic multifactorial regression analysis, which suggested that PT, FIB, FOB, CA199, and CEA were correlated with the occurrence of colorectal cancer.

Comparison of coagulation function of patients with and without metastasis of colorectal cancer in the observation group

Colorectal cancer has a high incidence and mortality. Approximately 20% of new colorectal cancer diagnoses involve metastatic disease at presentation, and an additional 25% of patients initially diagnosed with localized disease will later develop metastases [5]. As a result, we conducted a more in-depth investigation into the relationship between commonly used clinical targets and tumor metastasis. As

Table 2: Comparison of FOB results between the two groups (n)

Group	Positive	Negatives
Observation Group (n=262)	244	18
Control Group (n=265)	108	158
χ2	163.888	
P	<0.001	

Table 3: Comparison of CEA and CA199 levels between the two groups [M (Q1, Q3)]

Group	n	CEA (ng/ml)	CA199(U/ml)
Observation Group (n=262)	262	4.365(2.290-10.910)	10.065(3.610-30.970)
Control Group (n=265)	265	2.010(1.730-2.980)	4.690(2.490-10.640)
P		<0.001	<0.001

Table 4: Correlation between indicators and the risk of developing colorectal cancer

Detection indicators	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P	OR (95%CI)	P
PT	1.467(1.193-1.803)	<0.001	1.407(1.036-1.909)	0.029
APTT	0.961(0.908-1.016)	0.16		
TT	0.682(0.579-0.804)	<0.001	1.097(0.834-1.444)	0.508
FIB	4.075(2.906-5.715)	<0.001	3.157(1.909-5.220)	<0.001
CA199	1.033(1.019-1.048)	<0.001	1.016(1.001-1.032)	0.037
CEA	1.371(1.248-1.507)	<0.001	1.252(1.130-1.387)	<0.001
FOB	19.831(11.584-33.950)	<0.001	18.552(9.348-36.821)	<0.001

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shown in Table 5, PT, APTT, and FIB were higher in the metastatic group than in the non-metastatic group, and the differences between the results were not statistically significant. As shown in Table 6, the median CEA, CA199 results of patients in the metastatic group were higher than those in the non-metastatic group, and the difference was statistically significant (P<0.05).

Diagnostic efficacy of PT, FIB, FOB, CEA, CA199 alone and combined to diagnose colorectal cancer

It has been found that the combined detection of coagulation function and tumor markers in colorectal cancer patients can improve the diagnostic efficiency of benign and malignant colorectal diseases [20]. We not only combined coagulation function and tumor markers, but also FOB to draw the ROC curve and judge the diagnostic efficacy. The ROC curve analysis of single PT, FIB, CA199, and CEA and the combination in the observation group and the control group are presented in Figure 1. The AUC of the ROC analyses for the four single tested markers in colorectal cancer were: PT: 0.598; FIB: 0.734; CA199: 0.645; CEA: 0.757. The AUC of the ROC analyses of combined diagnosis in colorectal cancer were PT+FIB+CEA+CA199: 0.831; PT+FIB+CEA+FOB: 0.880; PT+FIB+CA199+FOB: 0.895; FIB+CEA+CA199+FOB: 0.899; PT+CEA+CA199+FOB: 0.884; PT+FIB+CEA+CA199+FOB: 0.903. In our study, we can display that combined application can greatly improve the efficiency of diagnosis. Details are shown in Table 7.

Table 5: Coagulation function comparison with and without tumor metastasis in the observation group ($\bar{x} \pm s$)

Group	n	PT(s)	APTT(s)	TT(s)	FIB(g/L)
metastasis group	120	11.754±0.842	30.846±3.040	14.096±1.107	3.620±0.982
non-metastasis group	142	11.604±0.840	30.698±3.006	14.265±1.161	3.435±0.848
t		1.473	0.395	-1.198	1.624
P		0.152	0.693	0.232	0.101

Table 6: Comparison of patients with and without metastatic CEA and CA199 in the observation group [M (Q1, Q3)]

Group	n	CEA (ng/ml)	CA199(U/ml)
metastasis group	120	5.290(2.796-18.200)	13.770(4.138-77.992)
non-metastasis	142	3.215(1.958-8.756)	7.415(3.490-19.37)
P		<0.001	0.018

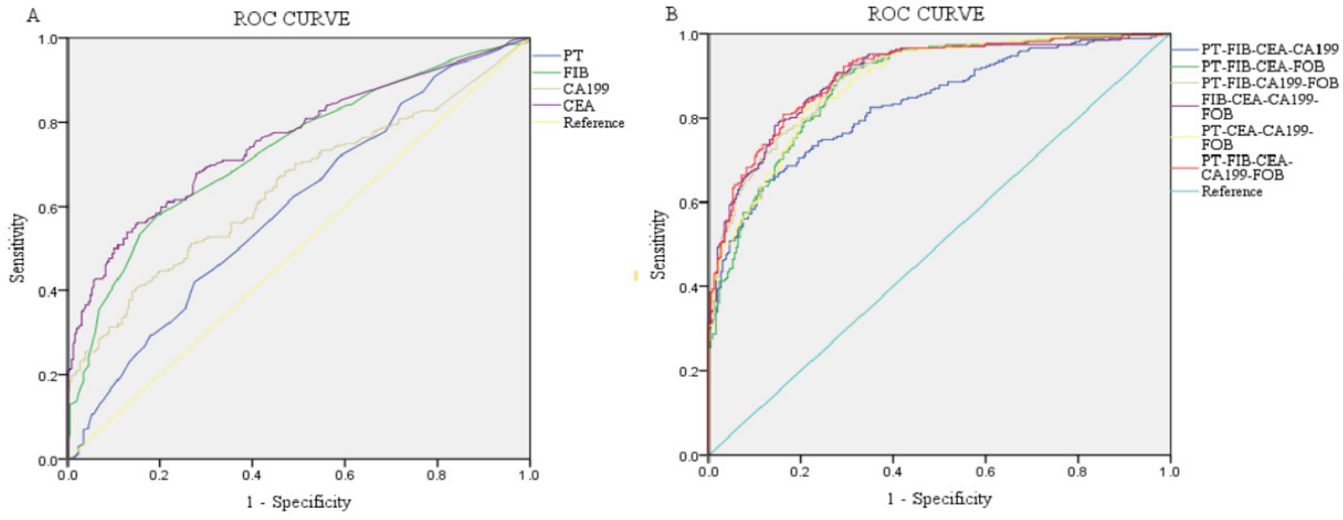

Figure 1: ROC curves for colorectal cancer diagnosis by single (A) and combined tests (B)

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Table 7: Diagnostic efficacy of single and combined tests for the diagnosis of colorectal cancer

Detection Mode	AUC	95%CI	Sensitivity (%)	Specificity (%)	P
PT	0.598	0.550~0.646	0.42	0.726	<0.001
FIB	0.734	0.691~0.776	0.58	0.805	<0.001
CA199	0.645	0.598~0.692	0.397	0.861	<0.001
CEA	0.757	0.716~0.798	0.561	0.85	<0.001
PT‡FIB-CEA-CA199	0.831	0..797~0.866	0.649	0.88	<0.001
PT‡FIB-CEA-FOB	0.88	0..851~0.908	0.901	0.711	<0.001
PT‡FIB-CA199-FOB	0.895	0..869~0.921	0.893	0.718	<0.001
FIB-CEA-CA199-FOB	0.899	0..873~0.926	0.782	0.857	<0.001
PT-CEA-CA199-FOB	0.884	0..856~0.911	0.824	0.786	<0.001
PT‡FIB-CEA-CA199-FOB	0.903	0..878~0.928	0.809	0.838	<0.001

Discussion

Colorectal cancer seriously affects and threatens the health of our residents [21]. The morbidity and death rates from colorectal cancer have remained high in China in recent times [22]. Colorectal cancer screening can reduce the incidence and mortality of colorectal cancer [23]. Malignant tumors have no obvious clinical features in the early stages, but when they develop into later stages, the condition is difficult to control, so early detection, early diagnosis, and early treatment are significant. At the moment, the most widely used tumor markers for colorectal cancer screening are CEA and CA199 [24, 25]. Studies have reported that changes in CEA are particularly associated with the progression of colorectal cancer and are also used to monitor disease progression [26-28]. CA199 is found not only in the colon but also in other normal tissues. It is relatively non-specific and can be elevated in some benign conditions [29]. As the illness worsens, CA199 levels rise, and as it gets better, they fall. When tumor cells appear in the body, they can secrete tissue factors and other substances, activate the coagulation system, cause changes in coagulation function, and become involved in the growth and development of tumors. However, it is not a specific diagnostic tool and can be caused by various diseases. This test is solely used to detect bleeding in the gastrointestinal tract and can offer an initial indication of gastrointestinal pathology. The study results indicate a statistically significant difference between the coagulation indices PT, TT, and FIB of the patients in the observation group and the control group. Logistic multifactorial regression analysis suggests that PT, FIB, FOB, CA199, and CEA are associated with the development of colorectal cancer. Liver cells synthesize and secrete fibrinogen, an acute-phase protein that increases in response to tissue injury, inflammation, or infection. Fibrinogen plays a crucial role in coagulation, and its elevated levels indicate a hypercoagulable state [30, 31]. FIB promotes the metastasis of cancer cells by adhering to platelets or endothelium [32, 33]. The coagulation function did not differ significantly between metastatic and non-metastatic patients in the observation group. This result is at odds with published research and other studies [34]. The variation may be attributed to differences in the disease progression during the patient's initial test. The observation group in this study had a 93% FOB positive rate, which is important for the diagnosis of colorectal cancer and in line with the findings of a few studies [35, 36]. CEA is expressed at low levels in the healthy population and increases with tumor progression and metastasis [26]. CA199 is not normally expressed or is poorly expressed in the general population, it may be elevated in benign gastrointestinal diseases and will decline when the benign disease regresses [37]. Only when malignant tumors occur, CA199 will continue to rise [38-40]. The differences in this study were statistically significant, both in the observation group and the control group, and whether colorectal cancer metastasized in the observation group. These results indicate a significant increase in CEA and CA199 with the progression of the disease. In this study, ROC curves were used to analyze the results of PT, FIB, CEA, CA199, and FOB. In the single-item test, the area under the CEA curve was the largest at 0.757, with a sensitivity of 0.561 and a specificity of 0.850. When testing four items in combination of the FIB, CEA, CA199, and FOB, the largest area under the curve was 0.899, and the sensitivity and specificity separately were 0.824 and 0.857. Detecting all five items of PT, FIB, CEA, CA199, and FOB simultaneously produced a 0.903 area under the curve, 0.903sensitivity, and 0.838specificity. The information above makes it clear that, in comparison to single-item detection, multiple-item detection results in varied degrees of improvement. When five items are tested simultaneously, the biggest area under the curve is seen. In conclusion, PT, FIB, and FOB in conjunction with the tumor markers CEA and CA199 can enhance the diagnostic efficacy of colorectal cancer. This combination has a large reference value and distinctly increases the diagnosis's sensitivity and specificity.

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Ethics Statement

This study was approved by the central ethics committee of The Sixth Affiliated Hospital, Sun Yat-sen University, Ethics No.2024ZSLYEC-325. Written informed consent has been obtained from the individual(s) or their legal guardian/ next of kin or from the patients/participants in this study.

Authors' Contributions

Study administration, validation, and design: Yuanmei Zhang, Yongsheng Huang, Shuwei Ren.

Methodology: Shengming Lai.

Acquisition and interpretation of data: Shengming Lai, Zhongchao Huang, Haiyan Huang.

Writing-original manuscript: Shuwei Ren.

Study supervision: Shuwei Ren.

All authors read and approved the final manuscript.

Competing interest

The authors declare that they have no competing interests.

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