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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

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Case Control Study

Diagnostic accuracy of the multi-target stool DNA test in detecting colorectal cancer: A hospital-based study

Han-Lu Gao, Le-Bin Lv, Wang-Fang Zhao, Qi-Wen Lu, Jin-Qing Fan

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Abstract

BACKGROUND

The multi-target stool DNA test (MT-sDNA) has potential utility in the detection of colorectal cancer (CRC), but validation of its clinical accuracy has been limited in China.

AIM

To evaluate the diagnostic performance of MT-sDNA and investigate the combined diagnostic value of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 199 (CA199) with MT-sDNA in CRC and adenomas.

METHODS

We evaluated the performance of the MT-sDNA kit based on a hospital clinical trial. In this case-control study, 135 participants from the Affiliated Hospital of Medical School of Ningbo University, including 51 CRC patients, 23 patients with adenomas, and 61 healthy controls were enrolled. We used a risk scoring system to determine the positivity of tests with histological diagnosis or colonoscopy as the reference standard.

RESULTS

The main indices of sensitivity, specificity and accuracy were evaluated. The sensitivity and specificity for CRC detection were 90.2% and 83.3%, respectively, with an accuracy of 89.8%. For adenoma, the sensitivity and specificity were 56.5% and 68.9%, respectively, with an accuracy of 73.1%. The sensitivity and

specificity of MT-sDNA combined with CEA in the diagnosis of adenoma were 78.3% and 60.7%, respectively.

CONCLUSION

The MT-sDNA test showed better performance in the detection of CRC, which was superior to AFP, CEA, and CA199 separately, but not for predicting adenomas. The combination of MT-sDNA with CEA further improved the sensitivity for adenoma diagnosis.

Key Words: Colorectal cancer; MT-sDNA; Cancer diagnosis; Adenoma; Sensitivity; Specificity

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Core Tip: The sensitivity and specificity for colorectal cancer (CRC) detection were 90.2% and 83.3%, respectively, with an accuracy of 89.8%. For adenoma, the sensitivity and specificity were 56.5% and 68.9%, respectively, with an accuracy of 73.1%. The multi-target stool DNA (MT-sDNA) test showed better performance for the detection of CRC, which was superior to alpha-fetoprotein, carcinoembryonic antigen (CEA), and carbohydrate antigen 199 separately, but not for predicting adenomas. The sensitivity and specificity of MT-sDNA combined with CEA in the diagnosis of adenoma were 78.3% and 60.7%, respectively, which suggested that combined detection has certain advantages in adenoma diagnosis. This study can help clinicians select a standardized and optimal management strategy for the treatment of these patients.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in terms of incidence rate and the fifth-leading cause of cancer-related deaths in China[1]. In the USA, age-standardized mortality and incidence rates of CRC have recently significantly decreased[2]. Several screening tests, including colonoscopy and the fecal occult blood test (FOBT), are currently used in CRC detection[3]. In addition, tumor markers such as alpha-fetoprotein (AFP), carbohydrate antigen 199 (CA199) and carcinoembryonic antigen (CEA) are common indices used in the diagnosis of CRC[4]. Colonoscopy is unlikely to potentially increase screening rates due to its invasive nature and inconvenience for patients[5]. The FOBT, CA199 and CEA, the most widely used noninvasive tools in CRC screening, lack diagnostic accuracy[6]. In light of this situation, new methods for CRC screening and diagnosis are required[7]. The multi-target stool DNA (MT-sDNA) test was added as a recommended CRC screening option in the 2016 US Preventive Services Task Force and 2018 American Cancer Society guidelines[8,9].

Recently, the MT-sDNA test has arrived in the commercial market and has been optimized in terms of improved sensitivity, sample storage and platform analysis[10]. Cologuard®, the only MT-sDNA kit available in the United States, was approved by the US Food and Drug Administration to evaluate 11 biomarkers, such as *KRAS* gene mutation, methylation markers and hemoglobin[9]. The commercial kit ColoClear® from New Horizon Health (NHH) Technology combines with N-myc downstream-regulated gene 4 (NDRG4) and Bone Morphogenetic Protein 3 (BMP3) methylation, and *KRAS* mutation has been proved to have good sensitivity and specificity in Hubei, China[11]. However, another Chinese study showed that the MT-sDNA kit may not be suitable for predicting CRC due to decreased specificity[12]. More evidence is needed for the extensive use of the MT-sDNA test in China. Moreover, combination analyses of tumor markers with the MT-sDNA test are still sparse. The goal of this research was to evaluate the accuracy of the MT-sDNA method in the diagnosis of CRC and to compare the diagnostic performance of different tumor markers combined with MT-sDNA, using histological and colonoscopy confirmation as reference methods.

MATERIALS AND METHODS

Study design

The study was performed in the Affiliated Hospital of Medical School of Ningbo University and

approved by the institutional ethics review committee. The approved identifier number is KY20201111. All subjects signed an informed consent and were told the MT-sDNA results. The primary measures of this research, including sensitivity, specificity, and accuracy, were investigated to evaluate the consistency of the commercial kit ColoClear® (NHH Technology) compared with the reference standards of histopathologic or colonoscopy examination.

Participant enrollment

A total of 135 participants were recruited from January 2020 to March 2021 in the Affiliated Hospital of Medical School of Ningbo University. Participants who visited inpatient or endoscopy centers were eligible for recruitment. The inclusion criteria were: age > 35 years, and a diagnosis of CRC or adenoma. The exclusion criteria were: A previous diagnosis of CRC, inflammatory bowel disease, familial adenomatous polyposis syndrome, other cancers and cognitive impairment. All participants provided informed consent and the study was approved by the Human Research and Ethics Committee of the Affiliated Hospital of Medical School of Ningbo University.

Laboratory examinations

Fecal samples (4-5 g) were collected prior to bowel preparation for colonoscopy examination in patients with colorectal polyps and before surgical removal of intestinal tumor tissue from CRC patients. All experimental procedures related to the MT-sDNA tests [KRAS mutation, NDRG4, BMP3 methylation and Fecal Immunochemical Test (FIT)] were carried out in the laboratory of NHH Technology (Hangzhou, China). The details regarding probes and primers, as well as the risk prediction algorithm were the same as those in a previously published article[13]. In this risk prediction model, a risk score is provided as a single output. If the risk score value was ≥ 165 , the test was considered "positive". If the risk score was < 165, the test was regarded as "negative"[11]. Three serum biomarkers, CA199, CEA, and AFP levels were determined by the Department of Testing, Affiliated Hospital of Ningbo University School of Medicine.

Clinical procedures

Histological diagnosis and colonoscopy were the reference criteria for determining the accuracy of the kit for validating screening performance. All pathological diagnoses were in accordance with the diagnostic criteria of the 2010 World Health Organization Classification of Gastrointestinal Neoplasms.

Statistical analysis

The sensitivity and specificity were analyzed by receiver operating characteristic (ROC) curves with the area under the ROC curve (AUC) and 95%CI calculated for the MT-sDNA test. Statistical analysis was performed using SPSS software (version 23.0, IBM Corp., USA). The t-test and chi-square test were adopted to compare the differences among different groups. $P < 0.05$ was considered statistically significant.

RESULTS

Basic demographic characteristics

One patient who did not meet the inclusion criteria was excluded, and 135 subjects were finally included (Figure 1). The basic demographic characteristics of the 135 enrolled patients are summarized in Table 1. The group of patients with CRC, adenoma and normal controls comprised 51, 23 and 61 participants, with an average age and standard deviation of 66.14 ± 9.47 , 60.13 ± 12.40 and 54.18 ± 10.30 , and a female-to-male ratio of 2.4, 1.88 and 1.03, respectively. The rectum was the most common tumor site (52.94%) in CRC patients. Ulcerative type, medium differentiation and Dukes stage A accounted for 78.43%, 72.55% and 78.43% of CRC, respectively. 95.74% of CRC patients had adenocarcinoma.

Comparison of tumor marker expression among the study subjects

As shown in Table 2, the levels of tumor biomarkers AFP, CEA, CA199 and the risk score were elevated in CRC patients compared with healthy controls ($P < 0.05$). Regarding the tumor biomarkers, the value of CEA was higher in adenoma patients compared with healthy controls, and the risk score was obviously increased in adenoma patients compared with healthy controls, but no significant differences between adenoma patients and healthy controls were observed in terms of AFP and CA199 ($P > 0.05$).

Diagnostic value of MT-sDNA and tumor markers in CRC and adenoma

We tested the diagnostic value of MT-sDNA and tumor markers in healthy controls. We found that in CRC, the AUC value, the sensitivity and specificity of MT-sDNA was similar to the combined detection results of MT-sDNA and CEA, and the AUC value was 89.8% (Table 3 and Figure 2A), indicating that there was no significant difference in diagnostic value between the MT-sDNA test and combined test in CRC.

Table 1 Basic demographic characteristics of cases and controls, *n* (%)

Variable	Case group		Control group
	Colorectal cancer	Adenomas	Healthy subjects
Gender			
Female	36 (70.60)	15 (65.20)	31 (51.81)
Male	15 (29.49)	8 (34.80)	30 (49.18)
Age			
mean $\pm$ SD	66.14 $\pm$ 9.47	60.13 $\pm$ 12.40	54.18 $\pm$ 10.30
< 60 yr	16 (31.40)	10 (43.50)	42 (68.90)
$\geq$ 60 yr	35 (68.60)	13 (56.50)	19 (31.10)
Education level			
Junior high school and below	42 (82.40)	14 (60.90)	16 (26.20)
Senior high school and above	9 (17.60)	9 (39.10)	45 (73.80)
BMI			
< 23.00	31 (60.80)	12 (52.20)	21 (34.42)
$\geq$ 23.00	20 (39.20)	11 (47.80)	40 (65.57)
Tumor location			
Colon	24 (47.06)	-	-
Rectum	27 (52.94)	-	-
Pathogenic type			
Protruding type	7 (13.73)	-	-
Infiltrating type	4 (7.84)	-	-
Ulcerative type	40 (78.43)	-	-
Differentiation			
High	4 (7.84)	-	-
Medium	37 (72.55)	-	-
Low	10 (19.61)	-	-
Histological type			
Adenocarcinoma	49 (95.74)	-	-
Other types	2 (4.26)	-	-
Dukes stage			
A	40 (78.43)	-	-
B	10 (19.61)	-	-
C	1 (1.06)	-	-
D	0 (0.0)	-	-

BMI: Body mass index.

As shown in Table 4 and Figure 2B, the sensitivity and specificity of MT-sDNA combined with CEA in the diagnosis of adenoma were 78.3% and 60.7%, and the diagnostic accuracy was 80.4%, which was higher than the MT-sDNA and CEA test alone, with an accuracy of 73.1% and 76.1%, respectively (Table 4 and Figure 2B).

Table 2 Evaluation of the expression of different tumor markers between cases and controls, *n* (%)

Variable	Case group		Control group	P value	
	Colorectal cancer	Adenomas	Healthy subjects	CRC patients vs healthy controls	Adenoma patients vs healthy controls
AFP					
mean ± SD	5.87 ± 17.59	3.03 ± 1.57	3.32 ± 1.36	0.03	0.43
≤ 7 µg/L	47 (92.20)	22 (95.70)	61 (100.00)		
> 7.1 µg/L	4 (7.80)	1 (4.30)	0 (0.00)		
CEA					
mean ± SD	37.12 ± 149.74	5.21 ± 3.58	2.20 ± 1.58	0.00	0.00
≤ 5 µg/L	34 (66.70)	11 (47.80)	56 (91.80)		
> 5.1 µg/L	17 (33.30)	12 (52.20)	5 (8.20)		
CA199					
mean ± SD	63.05 ± 276.78	13.39 ± 10.19	9.77±8.89	0.01	0.15
≤ 25 µ/mL	41 (80.40)	18 (78.30)	59 (96.70)		
> 25.1 µ/mL	10 (19.60)	5 (21.70)	2 (3.30)		
Complex value					
mean ± SD	806.54 ± 289.28	351.61 ± 369.85	105.11 ± 90.95	0.00	0.00
< 165	5 (9.80)	13 (56.52)	59 (96.72)		
≥ 165	46 (90.20)	10 (43.48)	2 (3.28)		

AFP: Alpha-feto protein; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199.

Table 3 Diagnostic value of tumor markers and multi-target stool DNA test in colorectal cancer

Detection method	AUC (%)	Sensitivity (%)	Specificity (%)	P value
AFP	41.3	35.3	48.8	0.264
CEA	73.2	60.8	63.1	0.001
CA199	62.5	49.0	69.0	0.069
DNA	93.3	90.2	83.3	0.000
DNA+CEA	94.7	90.2	75.0	0.000

AFP: Alpha-feto protein; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199.

DISCUSSION

Screening for CRC is crucial as it can improve patient outcome when diagnosed at an early stage[14]. The MT-sDNA test was developed for colorectal screening in recent years[15]. In the present study, we recruited 135 participants who all underwent histological or colonoscopy examination, the MT-sDNA test and tumor biomarker detection. We found that the risk score of MT-sDNA was significantly increased in CRC and adenoma patients compared with healthy controls which potentially makes it a promising non-invasive tumor biomarker for CRC detection[16].

We also found that the diagnostic accuracy, sensitivity and specificity of the risk score were 89.8%, 90.2% and 83.3% for CRC, respectively. The diagnostic sensitivity of MT-sDNA was lower in the present study compared with 92.3% in the United States study[17], possibly due to the younger age of the participants[18].

Similar to other studies, our study demonstrated that the sensitivity of MT-sDNA in the diagnosis of adenoma was low[19], indicating that MT-sDNA is not suitable for the diagnosis of adenoma, although previous studies have shown that the sensitivity of the MT-sDNA test was relatively high for advanced

Table 4 Diagnostic value of tumor markers and multi-target stool DNA test in adenoma

Detection method	AUC (%)	Sensitivity (%)	Specificity (%)	P value
AFP	42.1	34.8	54.1	0.263
CEA	76.1	69.6	62.3	0.000
CA199	59.2	56.5	65.6	0.196
DNA	73.1	56.5	68.9	0.001
DNA+CEA	80.4	78.3	60.7	0.000

AFP: Alpha-feto protein; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199.

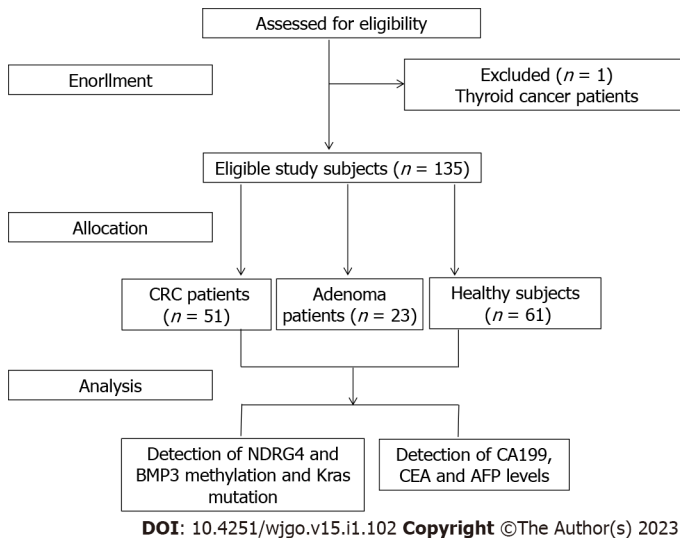


Figure 1 Flow diagram of participant selection. CRC: Colorectal cancer; AFP: Alpha-feto Protein; CEA: Carcinoembryonic Antigen; CA199: Carbohydrate Antigen 199.

adenomas[20-22]. Previous studies mostly focused on comparing the accuracy of MT-sDNA and FIT detection, whereas no studies have focused on the combination of tumor markers and the MT-sDNA test in the diagnosis of adenoma. We confirmed the diagnostic accuracy of the risk score and tumor biomarkers for adenoma. We noted that, in the detection of adenoma, the accuracy and sensitivity of CEA combined with MT-sDNA increased which suggested that this combination has certain advantages in the diagnosis of adenoma. In addition, compared with MT-sDNA alone, the diagnostic accuracy of CEA combined with MT-sDNA tended to be superior for CRC detection, but there was no increase in sensitivity. This indicated that the combination had little effect on the diagnosis of CRC.

This study has several limitations. One limitation is the small sample size; thus, we did not subdivide adenomas and the accuracy of the results requires further verification. In addition, the relationship between overall survival and the risk score could not be determined due to the limited follow-up time. Therefore, analyses with longer follow-up duration should be conducted.

CONCLUSION

In summary, the present research found that the risk score of fecal MT-sDNA was increased in CRC and adenoma patients. MT-sDNA has high diagnostic value in the diagnosis of CRC. The combination of MT-sDNA and CEA could improve sensitivity, although the specificity decreased in adenoma detection. Fecal MT-sDNA together with CEA is helpful in diagnosing patients at high-risk of adenoma. This can help clinicians to select a standardized and optimal management strategy for the treatment of these patients.

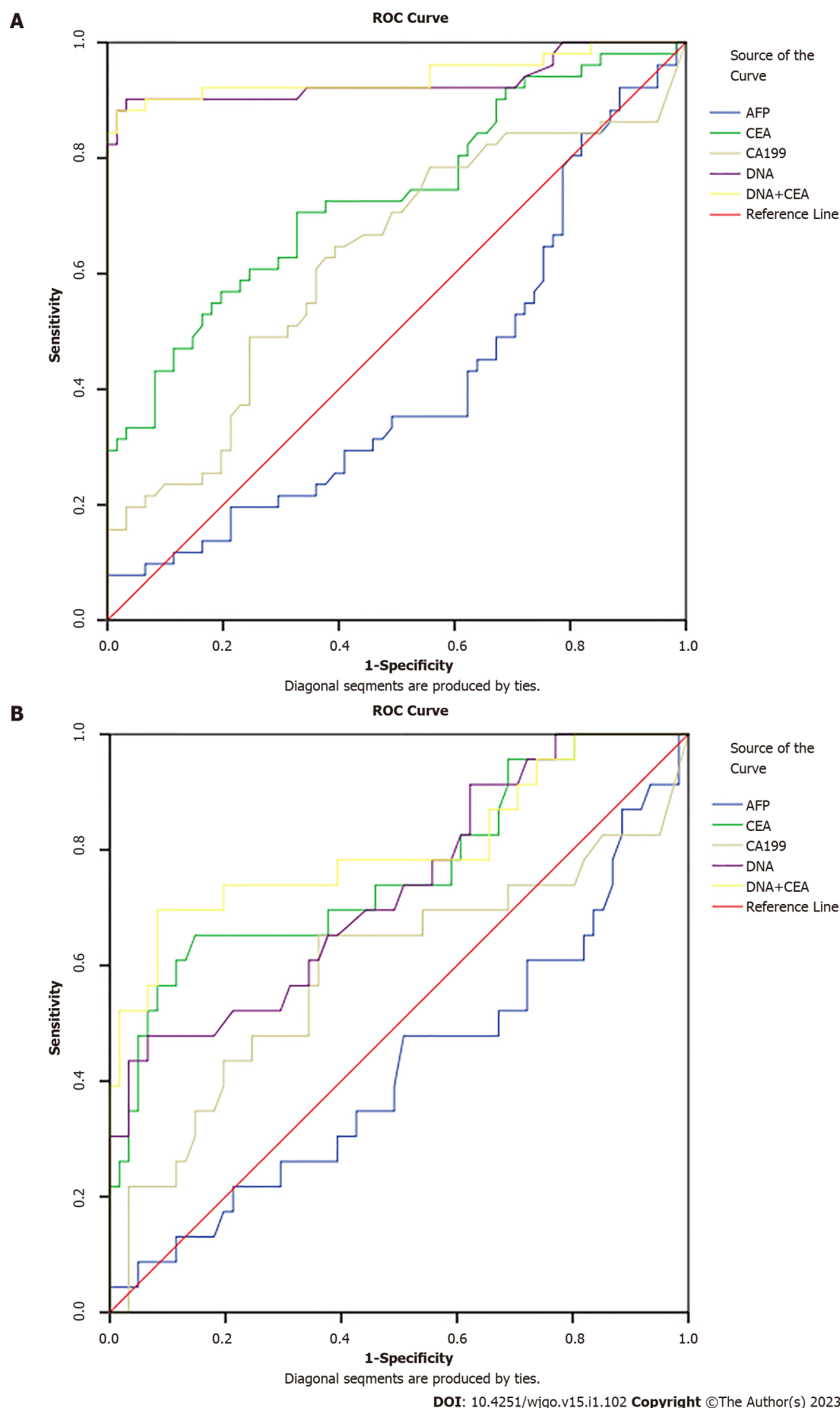


Figure 2 The receiver operating characteristic curves of tumor markers were analyzed to assess colorectal cancer and colorectal

adenomas. A: Colorectal cancer; B: Colorectal adenomas. ROC: Receiver operating characteristic; AFP: Alpha-feto protein; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199.

ARTICLE HIGHLIGHTS

Research background

The multi-target stool DNA test (MT-sDNA) has potential utility in the detection of colorectal cancer (CRC), but validation of its clinical accuracy has been limited in China.

Research motivation

More evidence is needed for the extensive use of the MT-sDNA test in China. Moreover, combination analyses of tumor markers with the MT-sDNA test are still sparse.

Research objectives

The goal of this research was to evaluate the accuracy of the MT-sDNA method in the diagnosis of CRC and to compare the diagnostic performance of different tumor markers combined with MT-sDNA.

Research methods

In this study, routine clinical test results [alpha-fetoprotein, carcinoembryonic antigen (CEA), and carbohydrate antigen 199] and MT-sDNA test were used as evaluation indexes for the combined diagnosis of colorectal cancer and adenoma, so as to improve the diagnostic performance of this research.

Research results

The sensitivity and specificity for CRC detection were 90.2% and 83.3%, respectively, with an accuracy of 89.8%. For adenoma, the sensitivity and specificity were 56.5% and 68.9%, respectively, with an accuracy of 73.1%.

Research conclusions

The MT-sDNA test showed better performance for the detection of CRC, which was superior to alpha-fetoprotein, CEA, and carbohydrate antigen 199 separately, but not for predicting adenomas. The sensitivity and specificity of MT-sDNA combined with CEA in the diagnosis of adenoma were 78.3% and 60.7%, respectively, which suggested that combined detection has certain advantages in adenoma diagnosis.

Research perspectives

This study can help clinicians select a standardized and optimal management strategy for the treatment of these patients.

FOOTNOTES

Author contributions: Gao HL performed data analysis and wrote the manuscript; Zhao WF and Lu QW participated in the collection of human material; Lv LB performed data collection and collation; Fan JQ designed the study and corrected the manuscript.

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