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Diagnostic values of MMP-7, MMP-9, MMP-11, TIMP-1, TIMP-2, CEA, and CA19-9 in patients with colorectal cancer

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Abstract

Objective: Colorectal cancer (CRC) is one of the most common and lethal malignancies. The identification of precise and noninvasive biomarkers is urgently needed to aid the early diagnosis and clinical management of CRC.

Methods: A total of 112 patients with CRC and 115 healthy control subjects were included in this study. Serum levels of matrix metalloproteinase (MMP)-7, MMP-9, MMP-11, tissue inhibitor of metalloproteinase (TIMP)-1, and TIMP-2 were analyzed by enzyme-linked immunosorbent assay, and carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 levels were measured using an automatic immunoassay analyzer.

Results: MMP-7, MMP-9, MMP-11, TIMP-1, TIMP-2, CEA, and CA19-9 levels were all significantly higher in CRC patients compared with healthy controls. MMP-7, TIMP-1, and CEA levels were also closely related to clinicopathologic features in patients with CRC. The combination of serum CEA, MMP-7, and TIMP-1 significantly improved the diagnostic value compared with any single marker (area under the curve 0.858–0.890). Furthermore, a combined detection model including MMP-7, TIMP-1, and CEA improved both the specificity and sensitivity for detecting CRC.

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Conclusions: The results showed that combined detection of CEA, MMP-7, and TIMP-1 in serum could provide a specific and sensitive biomarker for the diagnosis of CRC.

Keywords
Colorectal cancer, biomarker, combined detection, diagnosis, matrix metalloproteinase-7, carcinoembryonic antigen, tissue inhibitor of metalloproteinase-1

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related deaths worldwide. The incidence of CRC has been rising continuously in recent decades in line with changes in diet and lifestyle, resulting in 1.85 million incident cases and more than 900,000 deaths per year globally.[1] CRC is typically asymptomatic in the early stages, and most patients with CRC thus have advanced-stage disease and/or extensive metastasis at the time of diagnosis.[2] Although invasive tests such as colonoscopy can help to reduce the incidence and mortality of CRC, the routine clinical use of colonoscopy remains limited because of its invasive nature.[3] There is thus an urgent need to identify precise and non-invasive biomarkers to aid the early diagnosis and clinical management of CRC.

Matrix metalloproteinases (MMPs) comprise a family of zinc-containing endopeptidases with critical implications in physiological and pathological processes.[4] Remodeling and degradation of the extracellular matrix by MMPs are important mechanisms involved in tumor angiogenesis, invasion, and metastasis. Several subtypes of MMPs, including MMP-2, MMP-9, and MMP-11, have been identified as potential biomarkers of malignancy.[5] In addition, the stability of the extracellular matrix is mediated by the balance of proteolytic activity, regulated by MMPs and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs).[6] TIMP-1 and TIMP-2 have been shown to influence various pathologic states, including regulating tumor initiation, invasion, and metastatic growth.[7] Ongoing clinical studies have confirmed the clinical relevance of increased tissue levels, and in some cases serum levels, of some MMPs and TIMPs in diseases such as gastric cancer, breast cancer, malignant gliomas, and prostate cancer.[8,9] However, the clinical value of circulating MMPs and TIMPs in the diagnosis and treatment of patients with CRC is currently ambiguous.

In the present study, we investigated serum levels of MMP-7, MMP-9, MMP-11, TIMP-1, and TIMP-2, as well as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 in patients with CRC and in healthy controls, and assessed their usefulness as diagnostic markers.

Patients and methods

Study subjects

We enrolled consecutive patients with CRC admitted to Meizhou People's Hospital, China, from December 2019 to October 2020. The inclusion criteria were: (a) newly diagnosed CRC confirmed by

endoscopy and pathology; (b) age over 18 years; (c) no history of neoadjuvant therapy or surgical intervention; (d) no hematological or solid malignancies; and (e) adequate bone marrow, renal, and liver functions. The exclusion criteria were: (a) history of autoimmune disease or immunodeficiency; (b) history of immunosuppressive therapy or anti-inflammatory medicine; (c) history of infectious diseases; (d) pregnant or lactating women; and (e) incomplete relevant demographic and clinicopathologic data. Patients in our hospital undergoing colonoscopy and physical examinations during the same period, with no obviously abnormal biochemical indexes, were screened as healthy controls. Information on basic characteristics was collected for all the patients. The present study was approved by the ethics committee at Meizhou People's Hospital (No. MPH-HEC 2019-C-105) and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants for use of their biological material.

Blood sample collection and processing

Fasting venous blood samples were collected from each participant in the morning, before surgery and any other treatment. Samples were centrifuged at 3000 $\times g$ for 15 minutes to separate the serum, and the supernatant was frozen at -80°C until further analysis. All specimens had no evidence of jaundice, hemolysis, and lipids.

Enzyme-linked immunosorbent assay (ELISA)

Serum biomarker levels were measured using commercially available ELISA kits for MMP-7, MMP-9, TIMP-1, TIMP-2 (all R&D System, Minneapolis, MN, USA), and MMP-11 (Abnova, Taipei, Taiwan), and serum CEA and CA19-9 levels were measured using an ARCHITECT i2000sr automatic immunoassay analyzer with supporting reagents (Abbott Diagnostics, Chicago, IL, USA). All testing procedures were performed in accordance with the manufacturers' instructions. The intensity of color developed in each well was measured using a microplate reader (Molecular Devices, Sunnyvale, CA, USA) at an absorbance of 450 nm (correction wavelength 540 nm). All determinations were performed in duplicate. Serum C-reactive protein (CRP) levels were measured using an automatic biochemical analyzer (AU5800, Beckman Coulter, Brea, CA, USA).

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 23.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables were presented as mean $\pm$ standard deviation, and non-normally distributed data were expressed as median and interquartile range (25th–75th percentile). Categorical variables were expressed as numbers and percentage. The normality of the distributions were assessed using the Kaplan–Meier method. Continuous variables were compared between two groups using the Mann–Whitney U test or Kruskall–Wallis H test, as needed. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were determined to assess the diagnostic power of the serum biomarkers for CRC. A P value <0.05 was considered statistically significant.

Results

Clinical characteristics of patients and controls

A total of 112 patients with CRC (age range: 31–74 years) and 115 age- and sex-matched controls (age range: 41–79 years) were enrolled in this study from December

2017 to August 2019. The baseline and clinical characteristics of the patients and controls are summarized in Table 1.

Correlation of serum biomarker levels with clinical characteristics in CRC patients

The relationships between serum biomarker levels and various clinicopathologic parameters in patients with CRC are summarized in Table 2. MMP-7 levels were significantly higher in patients with colon cancer (P=0.035), lymph node metastasis (P=0.041), and poor differentiation grade (P=0.039). TIMP-1 levels were significantly elevated in patients with higher clinical stage (P<0.001), lymph node metastasis (P<0.001), and distant metastasis

Table 1. Characteristics of 112 colorectal cancer patients and 115 controls.

Patient characteristic	CRC patients, n (%)	Controls, n (%)	*P*
Age			
Mean ± SD, years	60.51 ± 9.27	59.66 ±8.48	0.473
Sex			
Male	79 (70.54)	68 (59.13)	0.095
Female	33 (29.46)	47 (40.87)	
Primary tumor location			
Colon	61 (54.46)	-	
Rectum	51 (45.54)	-	
Side			
Right	25 (22.32)	-	
Left	81 (72.32)	-	
Transverse	6 (5.36)	-	
Clinical stage			
I	5 (4.46)	-	
II	34 (30.36)	-	
III	37 (33.04)	-	
IV	36 (32.14)	-	
Clinical-T stage			
T1	1 (0.89)	-	
T2	9 (8.04)	-	
T3	62 (55.36)	-	
T4	40 (35.71)	-	
Lymph node metastasis			
No	41 (36.61)	-	
Yes	71 (63.39)	-	
Distant metastasis			
No	76 (67.86)	-	
Yes	36 (32.14)	-	
Differentiation			
Well	2 (1.79)	-	
Moderate	98 (87.50)	-	
Poor	12 (10.71)	-	
Polyp			
Positive	22 (19.64)	-	
Negative	90 (80.36)	-	

CRC, colorectal cancer; SD, standard deviation.

Table 2. Correlation of serum biomarkers levels with clinical characteristics in patients with colorectal cancer.

Variable	n	MMP-7 (ng/mL)	MMP-9 (ng/mL)	MMP-11 (ng/mL)	TIMP-1 (ng/mL)	TIMP-2 (ng/mL)	CEA (ng/mL)	CA19-9 (U/mL)	CRP (mg/L)
Age (years)									
≥60	66	14.67 (11.03, 18.63)	282.40 (218.02, 339.72)	34.31 (24.93, 47.22)	230.11 (158.78, 285.53)	71.67 (52.98, 90.70)	6.82 (2.79, 32.52)	6.97 (2.05, 32.33)	47.84 (21.71, 72.30)
<60	46	12.86 (10.73, 17.62)	287.19 (232.76, 362.65)	35.97 (23.33, 43.14)	259.43 (161.45, 320.73)	52.66 (40.20, 78.65)	4.65 (2.61, 15.35)	16.74 (3.71, 49.78)	36.07 (11.22, 52.82)
P		0.254	0.362	0.841	0.350	**0.004**	0.296	0.091	0.147
Sex									
Male	79	14.28 (11.00, 18.33)	284.98 (220.55, 350.15)	36.11 (23.27, 43.96)	242.11 (178.33, 304.51)	64.95 (44.17, 87.40)	5.51 (2.54, 28.86)	7.57 (3.27, 31.34)	45.15 (14.94, 71.33)
Female	33	13.82 (10.34, 18.04)	288.81 (224.44, 359.74)	33.77 (28.16, 46.18)	224.43 (141.88, 325.76)	61.83 (43.34, 85.67)	9.21 (3.04, 44.05)	25.09 (3.24, 54.06)	41.54 (23.46, 68.13)
P		0.574	0.941	0.473	0.621	0.499	0.266	0.307	0.835
Primary tumor location									
Colon	61	14.74 (11.30, 19.29)	293.83 (221.58, 363.62)	37.28 (26.78, 46.79)	244.44 (158.57, 305.25)	63.41 (44.14, 86.54)	7.29 (2.50, 36.40)	16.74 (3.46, 47.33)	46.39 (17.13, 69.96)
Rectum	51	12.66 (10.15, 16.76)	272.78 (217.22, 341.03)	32.77 (23.27, 41.01)	236.45 (167.67, 319.41)	64.95 (44.88, 89.75)	5.21 (2.82, 17.13)	6.62 (3.02, 29.41)	42.67 (22.59, 66.49)
P		**0.035**	0.214	0.244	0.979	0.670	0.536	0.216	0.575
Side									
Right	25	17.54 (12.87, 19.39)	282.86 (204.02, 364.25)	37.94 (26.67, 46.34)	244.44 (172.73, 305.25)	63.54 (46.27, 88.20)	6.88 (2.58, 57.24)	32.33 (6.17, 86.39)	46.39 (19.54, 96.47)
Left	81	13.42 (10.70, 16.95)	285.56 (228.70, 353.36)	33.60 (23.65, 44.15)	236.45 (157.49, 310.68)	63.41 (44.14, 83.06)	5.02 (2.58, 13.73)	6.97 (2.81, 25.42)	41.54 (19.66, 66.48)
Transverse	6	11.81 (9.69, 40.29)	296.04 (108.95, 361.78)	40.88 (26.35, 52.63)	291.08 (141.58, 331.05)	87.04 (56.93, 113.20)	34.97 (28.46, 92.92)	44.31 (2.86, 180.30)	49.18 (4.49, 58.42)
P		0.069	0.908	0.495	0.866	0.313	**0.017**	0.206	0.544
Clinical stage									
I+II	39	12.61 (10.52, 16.14)	312.98 (245.47, 361.75)	36.34 (25.02, 47.19)	142.78 (111.91, 236.45)	54.90 (38.72, 84.32)	2.84 (1.98, 7.82)	6.05 (2.88, 17.82)	45.65 (21.45, 66.94)
III+IV	73	15.10 (11.13, 18.81)	272.78 (206.31, 340.16)	33.77 (24.61, 43.41)	268.62 (221.14, 333.97)	68.82 (51.40, 90.14)	8.99 (3.82, 57.24)	13.16 (3.41, 58.72)	37.33 (14.41, 69.90)
P		0.062	0.303	0.658	**<0.001**	**0.020**	**<0.001**	**0.029**	0.625
Clinical-T stage									
T1+T2	10	11.05 (10.18, 14.00)	288.12 (211.23, 371.95)	28.04 (22.26, 46.28)	208.54 (88.85, 331.01)	46.81 (37.37, 85.54)	4.78 (2.32, 7.24)	17.49 (6.28, 33.24)	57.80 (39.40, 72.91)
T3+T4	102	14.67 (11.09, 18.56)	285.27 (221.93, 348.49)	35.09 (24.93, 45.65)	242.96 (168.04, 306.63)	64.00 (46.23, 86.84)	6.07 (2.71, 32.52)	7.43 (3.24, 45.88)	40.70 (17.89, 66.54)
P		0.065	0.830	0.554	0.444	0.217	0.293	0.749	0.124
Lymph node metastasis									
No	41	12.46 (10.59, 16.01)	306.17 (230.42, 361.22)	36.34 (25.79, 47.05)	144.78 (113.74, 247.81)	54.90 (37.18, 82.76)	2.84 (2.01, 8.52)	6.11 (2.98, 18.13)	45.65 (23.12, 68.78)
Yes	71	15.31 (11.10, 19.02)	277.26 (210.43, 341.03)	33.77 (24.56, 43.96)	268.06 (220.91, 331.67)	71.10 (51.40, 90.53)	8.99 (3.83, 58.45)	11.52 (3.38, 58.42)	37.33 (13.33, 69.96)
P		**0.041**	0.096	0.635	**<0.001**	**0.010**	**<0.001**	0.064	0.588
Distant metastasis									
No	76	13.45 (10.55, 17.35)	288.73 (221.23, 349.60)	33.36 (23.76, 47.12)	217.65 (136.07, 278.30)	60.55 (42.57, 86.60)	4.47 (2.45, 9.38)	7.39 (3.14, 26.04)	46.04 (22.59, 70.74)
Yes	36	16.24 (11.66, 19.58)	281.34 (211.91, 374.54)	39.27 (25.96, 43.69)	298.33 (222.13, 338.34)	71.20 (56.18, 91.03)	32.11 (5.21, 199.68)	25.74 (3.33, 82.02)	28.14 (5.12, 66.42)
P		0.055	0.718	0.387	**<0.001**	0.095	**<0.001**	0.054	0.216
Differentiation degree									
Well+moderate	100	13.62 (10.96, 17.50)	286.81 (220.6, 356.63)	34.88 (25.20, 46.08)	239.83 (158.35, 307.92)	63.48 (44.35, 87.21)	5.41 (2.48, 26.06)	7.71 (3.34, 34.32)	45.69 (17.07, 69.90)
Poor	12	19.69 (11.88, 23.46)	267.71 (178.36, 356.95)	33.84 (18.54, 40.25)	244.22 (193.11, 376.49)	68.91 (47.00, 85.44)	59.69 (7.16, 191.06)	18.53 (2.33, 52.95)	36.06 (30.36, 56.11)
P		**0.039**	0.829	0.504	0.625	0.679	**0.005**	0.581	0.902
Polyp									
Positive	22	15.21 (11.19, 18.90)	290.48 (244.17, 367.57)	32.59 (24.47, 42.76)	253.56 (143.83, 285.53)	69.96 (40.26, 91.89)	5.17 (2.62, 14.73)	27.58 (4.04, 68.38)	34.00 (8.06, 59.32)
Negative	90	13.80 (10.79, 17.90)	282.39 (217.01, 345.79)	35.07 (24.64, 47.01)	234.45 (165.50, 324.83)	63.41 (45.46, 85.34)	6.58 (2.77, 33.35)	7.57 (3.06, 35.48)	45.55 (20.96, 71.12)
P		0.442	0.425	0.692	0.786	0.588	0.341	0.113	0.239

Data expressed as median and interquartile range (25th–75th percentile).

MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

($P < 0.001$). TIMP-2 levels were significantly higher in older patients ($P=0.004$), and in patients with higher clinical stage ($P<0.001$) and lymph node metastasis ($P<0.001$). CEA levels were significantly correlated with primary tumor side, TNM stage, lymph node metastasis, distant metastasis, and differentiation grade (all $P<0.05$). Higher levels of CA19-9 were significantly associated with clinical stage ($P=0.029$). However, serum MMP-9, MMP-11, and CRP levels were not correlated with clinical characteristics in patients with CRC.

Comparison of serum biomarkers between CRC patients and healthy controls

The relationship between expression levels of serum biomarkers in the CRC patients and healthy controls is shown in Figure 1. Expression levels of serum MMP-7, MMP-9, MMP-11, TIMP-1, TIMP-2, CEA, and CA19-9 were all significantly higher in CRC patients compared with the healthy controls (all $P<0.01$).

Clinical value of serum biomarker detection for diagnosis of CRC

ROC curves were analyzed to determine the diagnostic values of the serum biomarkers and their combinations for CRC (Figure 2 and Table 3). CEA was able to diagnosis CRC with a relatively high AUC of 0.814 (95% confidence interval [CI]: 0.756–0.873). The AUC values for MMP-7 and TIMP-1 were 0.708 (95% CI: 0.640–0.775) and 0.749 (95% CI: 0.685–0.812), respectively, which allowed reliable differentiation between CRC patients and healthy controls. The AUC values for MMP-9, MMP-11, TIMP-2, and CA19-9 showed lower diagnostic values for CRC (range: 0.628–0.669. The combination of serum CEA, MMP-7, and TIMP-1 significantly improved the diagnostic value (AUC 0.858–0.890) compared with any single biomarker.

The sensitivity and specificity of the investigated serum biomarkers are summarized in Table 3. MMP-7 showed the highest sensitivity among the tested biomarkers (87.4%), and was higher than MMP-9 (82.0%). The highest sensitivity in the combined detection model was found for the combination of CEA and TIMP-1 (80.2%). The specificity of the tested biomarkers was highest for CA19-9 (92.2%), which was higher than for CEA (89.6%). The combination of CEA, MMP-7, and TIMP-1 also demonstrated high specificity (91.3%).

Discussion

CRC is one of the most common and lethal malignancies, affecting millions of people globally each year.[1] The subclinical signs of early CRC are indiscernible, and endoscopic surveillance is currently the recommended gold standard method for diagnosing CRC.[3] However, the invasive nature, expense, and complications of colonoscopy make its use unrealistic for CRC screening in apparently healthy people. The screening and early detection of CRC thus remain a clinical challenge, highlighting the need to identify novel biomarkers to aid the diagnosis of CRC. The present results showed that serum levels of MMP-7, MMP-9, MMP-11, TIMP-1, TIMP-2, CEA, and CA19-9 were all up-regulated in CRC patients compared with healthy controls, and MMP-7, TIMP-1, and CEA were closely related to the clinicopathologic features in CRC patients. These serum biomarkers accordingly showed relatively good diagnostic values, according to ROC curve analyses, and could thus represent useful diagnostic markers for CRC.

MMPs comprise a family of enzymes with proteolytic activity against a broad range of extracellular proteins, with

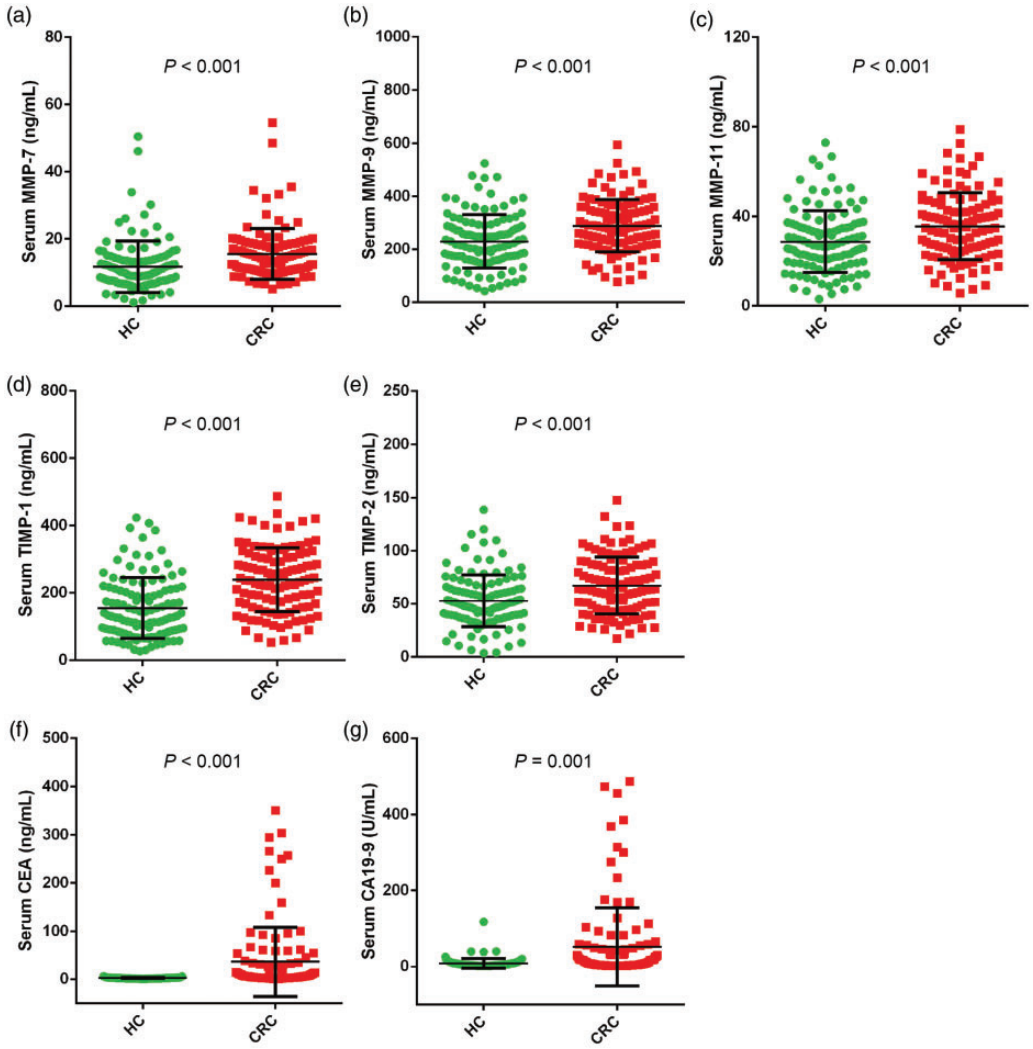

Figure 1. Levels of serum biomarkers in patients with colorectal cancer (CRC) and healthy controls (HC) MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

important roles in the regulation of tumor invasion and metastatic growth.[10] Roeb et al.[11] and Pesta et al.[12] confirmed that MMP-7 expression levels were higher in CRC tissues compared with normal tissues, and Wu et al.[13] demonstrated that expression levels of MMP-7 were related to tumor metastasis and prognosis in patients with CRC. Vočka et al.[14] and Barabás et al.[15] also reported that serum levels of MMP-7 could distinguish between CRC patients and healthy controls, consistent with the current finding. Moreover, the present study also revealed that increased serum MMP-7 levels correlated with primary tumor side, lymph node metastasis, and differentiation grade. These results support a crucial role for MMP-7 in the development

Table 3. Clinical value of serum biomarkers for diagnosis of colorectal cancer.

Markers	AUC	Standard error	95% CI	*P*	Sensitivity (%)	Specificity (%)	Cut-off
MMP-7	0.708	0.035	0.640–0.775	<0.001	87.4	51.3	9.88
MMP-9	0.669	0.036	0.599–0.739	<0.001	82.0	46.1	210.11
MMP-11	0.639	0.037	0.567–0.712	<0.001	51.4	73.0	34.83
TIMP-1	0.749	0.032	0.685–0.812	<0.001	59.5	79.1	219.33
TIMP-2	0.648	0.037	0.577–0.720	<0.001	53.2	72.2	62.40
CEA	0.814	0.030	0.756–0.873	<0.001	65.8	89.6	3.78
CA19-9	0.628	0.038	0.552–0.703	0.001	42.3	92.2	16.64
CEA+MMP-7	0.858	0.025	0.809–0.907	<0.001	75.7	84.3	-
CEA+TIMP-1	0.879	0.022	0.835–0.923	<0.001	80.2	80.0	-
CEA+MMP-7+TIMP-1	0.890	0.021	0.849–0.930	<0.001	70.3	91.3	-

AUC, area under curve; CI, confidence interval; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

of CRC. Overexpression of MMP-9 and MMP-11 has also been reported in both tissues and serum of patients with CRC, and may be associated with clinicopathological features and prognosis in these patients.[16–19] Similarly, the current study indicated that serum MMP-9 and MMP-11 levels were significantly increased in CRC patients; however, in contrast to previous studies, elevated serum MMP-9 and MMP-11 levels were not significantly associated with clinicopathological parameters. This apparent inconsistency may be attributed to inhomogenous patient populations and differences between colon and rectal cancers among studies.

The balance between MMP and TIMP expression is intrinsic to the processes of cancer invasion and progression.[20] Increased levels of TIMP-1 and TIMP-2 have previously been observed in a variety of cancers, including tumors of the digestive system, and their overexpression was associated with clinicopathological features and a poor prognosis.[21–23] In the present study, serum TIMP-1 and TIMP-2 levels were also significantly elevated in CRC patients compared with healthy controls, in accordance with earlier reports from Nielsen et al.[24] and Roayaei et al.[25] Regarding the relationship with clinicopathological parameters, we demonstrated that high serum TIMP-1 expression was closely correlated with TNM stage, lymph node metastasis, and distant metastasis in patients with CRC, while elevated serum TIMP2 was associated with age, TNM stage, and lymph node metastasis. These findings were basically consistent with previous studies, and reinforce the idea that TIMP-1 and TIMP-2 might participate concurrently in multiple regulatory functions during CRC progression, and may thus have potential as diagnostic biomarkers for CRC.

Highly sensitive, specific, and convenient markers are required for CRC diagnosis and monitoring. CEA and CA19-9 are classical biomarkers used across a broad spectrum of cancers, and are commonly used for postoperative surveillance and for monitoring outcome efficacy in patients with CRC.[26] In the current study, the AUC for serum CEA was 0.814, which was similar to that reported previously.[27,28] Only MMP-7 and TIMP-1 levels showed better diagnostic values, and thus deserve close attention, whereas MMP-9, MMP-11, TIMP-2, and CA19-9 appeared less promising. Both the

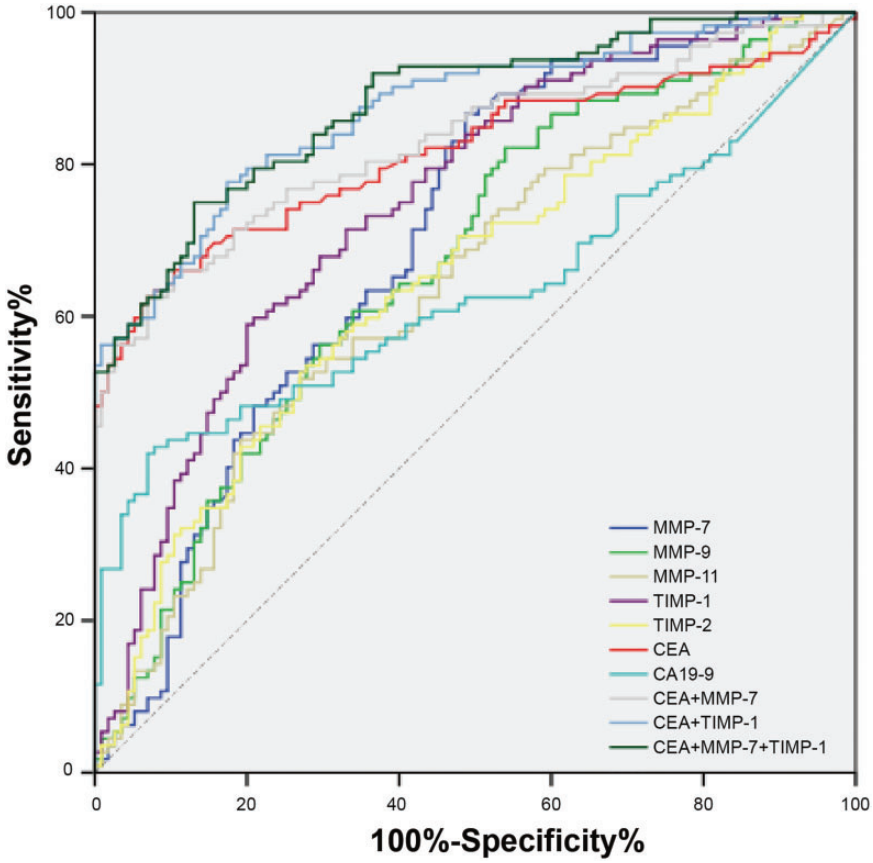

Figure 2. Receiver operating characteristic curves for serum biomarkers for diagnosing colorectal cancer MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

specificity and sensitivity were improved using a combined detection model including MMP-7, TIMP-1, and CEA, with acceptable results. We therefore recommend combined detection of these three markers to improve the diagnostic accuracy for CRC.

This study had several potential limitations. First, the sample size was relatively small, and further studies with larger sample sizes are needed. Furthermore, all the patients enrolled in this study were from a single institution, and the conclusions therefore need to be validated in other populations.

In conclusion, the present study demonstrated significant differences in seven potential biomarkers between patients with CRC and healthy controls. Serum levels of several biomarkers were also closely correlated with clinicopathologic features in CRC patients. Notably, a combined biomarker model including MMP-7, TIMP-1, and CEA could provide a specific and sensitive diagnosis of CRC. Future larger studies are needed to evaluate the clinical feasibility of using MMP-7 and TIMP-1 as biomarkers for CRC, and to clarify their roles in the pathogenesis of CRC.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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