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Diagnostic value of carcinoembryonic antigen combined with cytokines in serum of patients with colorectal cancer

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Abstract

In clinical practice, colorectal cancer (CRC) is difficult to distinguish from ulcerative colitis and colon polyps. Practical markers are useful for diagnosing and treating patients with CRC. Carcinoembryonic antigen (CEA) is a biomarker for diagnosing patients with CRC. However, the diagnostic sensitivity and specificity of CEA are not high. Interleukin (IL)-10, IL-17A, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and transforming growth factor beta (TGF-β) are assumed to be closely related to the occurrence and development of human cancer. Some have been used as diagnostic markers in CRC. It remains unclear whether cytokines in combination with CEA could be used as biomarkers for the diagnosis of CRC. Serum levels of IL-10, IL-17, TNF-α, IFN-γ, and TGF-β in patients with CRC, ulcerative colitis, colonic polyps, stomach cancer, and healthy controls were measured by enzyme-linked immunosorbent assay. The serum level of CEA was detected using electrochemiluminescence. The value of the cytokines combined with CEA as a biomarker panel for the diagnosis of CRC was assessed. CEA, IL-10, IL-17A, TNF-α, and TGF-β levels were significantly increased in CRC. CEA displayed a higher specificity than the other cytokines. IL-17A, TNF-α, and TGF-β displayed higher sensitivities than CEA, IL-10, and IFN-γ in the diagnosis of CRC. The combination of serum CEA, IL-17A, and TNF-α achieved higher diagnostic efficacy for CRC (area under the curve = 0.935). The combination of CEA, IL-17, and TNF-α has better diagnostic efficacy than CEA alone in CRC. A panel containing IL-17A, TNF-α, and CEA could be a promising molecular biomarker panel to diagnostically differentiate CRC from ulcerative colitis, colon polyps, and stomach cancer.

Abbreviations: AUC = an area under the ROC curve, CEA = carcinoembryonic antigen, CRC = colorectal cancer, IFN-γ = interferon-gamma, IL = interleukin, ROC = receiver operating characteristic, STAT3 = signal transducer and activator of transcription 3, TGF-β = transforming growth factor beta, TNF-α = tumor necrosis factor-alpha, UC = ulcerative colitis.

Keywords: biomarker, CEA, colorectal cancer, cytokine, diagnosis

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies in China.[1] Patients with early stage CRC have a good prognosis. However, the diagnosis is difficult.[2] Carcinoembryonic antigen (CEA) is a diagnostic biomarker for CRC and for more than 10 solid tumors. Practical diagnostic markers are important for diagnosing and treating patients with CRC.[3,4]

Inflammation is crucial in tumorigenesis, tumor progression, and metastasis.[5,6] CRC often features dense infiltration of cytokine-producing immune and inflammatory cells.[5] Inflammatory bowel disease and ulcerative colitis (UC) are important diseases that involve inflammation.[6,7] Certain cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-17A, are key factors in determining the contribution of the inflammatory process in CRC.[5,8,9] Cytokines are involved in the occurrence and development of tumors.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The protocol of the present study conformed to the ethical standards of the Declaration of Helsinki. All procedures were approved by the Ethics Committee of An'Kang Central Hospital Faculty of Medicine (An'Kang, China, approval no.2020-137). Informed consent was obtained from each patient, according to the committee's regulations.

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The tumor microenvironment contains high levels of proinflammatory cytokines including TNF-α, IL-17A, and interferon-gamma (IFN-γ), and anti-inflammatory cytokines such as IL-10, transforming growth factor beta (TGF-β), and IL-18.[6,10] IL-17A and TNF-α are produced in excess in early colonic lesions in a mouse model of sporadic CRC.[11] IFN-γ promotes tumor growth and metastasis of CRC.[12] The level of IL-10 in the serum of CRC patients is associated with cancer recurrence rate. IL-10 is highly expressed in the serum of CRC patients; the lower the expression levels of IL-10, the lower is the cancer recurrence rate.[13] TGF-β promotes the differentiation of Th17 cells and tumorigenesis in mice and blockade of TGF-β signaling can activate tumor immunity in the tumor microenvironment.[9,14] Research on the relationship between cytokines and CRC has mainly focused on the mechanism and immunotherapy. It remains unclear whether cytokines or cytokines in combination with other markers could be used as biomarkers for the diagnosis of CRC.

We hypothesized that the combination of cytokines and traditional tumor markers would improve the early diagnostic sensitivity and specificity of CRC. To assess this, we measured the serum levels of CEA, TNF-α, IL-17A, IFN-γ, TGF-β, and IL-10 in patients with CRC. We additionally evaluated their value for the auxiliary diagnostic evaluation of CRC to provide more accurate potential molecular biomarkers for the diagnosis of patients with CRC.

2. Materials and Methods

2.1. Sample collection

Samples were collected from 182 patients aged 33 to 74 years diagnosed at the An'kang Central Hospital from January 2020 to May 2021. They included 53 CRC, 38 UC, 27 colon polyps, and 64 stomach cancer patients. The control group comprised 50 healthy subjects 35 to 64 years of age. All the subjects were primary patients who had not received any treatment. The patients examined were in clinical stages I, II, or III, according to the TNM classification. Clinical diagnoses were confirmed by histopathological examination of tissue samples. Serum was collected stored at –80°C until analysis. This study was approved by the Ethics Committee of An'kang Central Hospital (An'Kang, China, approval no.2020-137). All patients provided signed informed consent.

2.2. Measurement of serum cytokine levels

Serum levels of CEA, TNF-α, IL-17A, IFN-γ, TGF-β, and IL-10 in patients were measured using enzyme-linked immunosorbent assays according to the manufacturer's instructions (DAKEWE, Inc. Shenzhen, China). Serum CEA levels were determined according to the standard operation specifications of the electrochemiluminescence immunoassay. Data below the minimum threshold of the standard curve were excluded.

2.3. Statistical analyses

One-way ANOVA followed by Tukey's multiple comparison test was applied to assess the significance of differences between multiple treatment groups using GraphPad Prism (Graph Pad Software, San Diego, CA). The prediction probability of each index was obtained by logistic fitting regression, and the receiver operating characteristic (ROC) curve was analyzed to determine the value of the panel of biomarkers in the diagnosis of CRC. An area under the ROC curve (AUC) < 0.5 indicated poor diagnostic accuracy, while the closer the AUC was to 1, the higher was the diagnostic accuracy. The differences were judged to be statistically significant at $P < .05$.

3. Results

3.1. Serum CEA levels

Analyses of the baseline data in Table 1 revealed no significant differences in age or sex among the 5 groups of patients. Among the 5 groups, serum CEA levels in subjects with CRC and stomach cancer were significantly higher than those in healthy volunteers and patients with UC or colon polyps ($P < .01$; Fig. 1). However, there was no significant difference between the patients with CRC and those with stomach cancer (Fig. 1). The results revealed that serum CEA was expressed at higher levels in both CRC and stomach cancer, and so might not be suitable as a specific biomarker for CRC.

3.2. Serum IL-17a, TNF-α, and IFN-γ levels

Among the 5 groups, serum levels of IL-17A and TNF-α in patients with CRC were significantly higher than those in patients with UC, colon polyps, and healthy volunteers ($P < .01$; Fig. 2A and 2B). The levels of TNF-α in the CRC group were significantly higher than those in all control groups ($P < .01$; Fig. 2B). IFN-γ levels did not differ significantly between patients with CRC and healthy controls. However, IFN-γ levels were higher in patients with UC than in those with CRC ($P < .05$; Fig. 2C). These results suggest that proinflammatory cytokines, such as IL-17A and TNF-α, may be potential biomarkers for CRC.

3.3. Serum IL-10 and TGF-β levels

The serum levels of IL-10 were higher ($P < .05$) in patients with CRC than in those with UC, colon polyps, and healthy volunteers ($P < .01$; Fig. 3A). No significant differences were evident between patients with CRC and stomach cancer (Fig. 3A). Serum TGF-β levels were significantly higher in patients with CRC than in healthy volunteers (Fig. 3B, $P < .05$). The data revealed that anti-inflammatory cytokines such as IL-10 and TGF-β are less specific diagnostic markers for CRC. The IL-17A and TNF-α proinflammatory cytokines could be potential biomarkers for CRC.

Table 1

Demographic data of recruited patients.

Characteristic	Colorectal cancer	Stomach cancer	Ulcerative colitis	Colon polyps	Healthy subjects	*P* value
Numbers	53	64	38	27	50	
Age (years)	41–73	38–72	33–68	38–73	35–64	.072
Gender						.058
Male	33	35	20	12	28	
Female	20	29	18	15	22	
Clinical stage						
Stage I/II	23	28				
Stage III/IV	30	36				

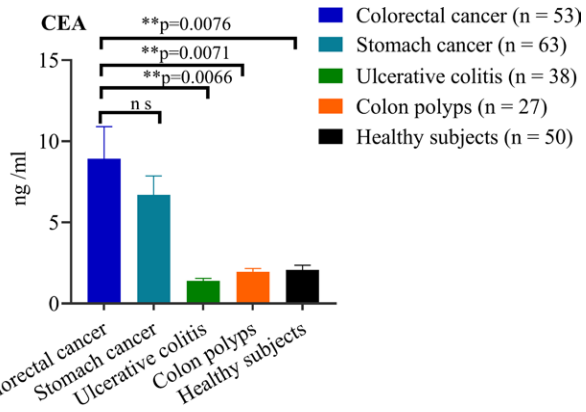

Figure 1. Serum CEA levels in healthy subjects (n = 50) and patients with colorectal cancer (n = 53), stomach cancer (n = 63), ulcerative colitis (n = 38), or colon polyps (n = 27). *, $P < .05$; **, $P < .01$. CEA = carcinoembryonic antigen.

3.4. CRC diagnostic efficacy of CEA, IL-17a, TNF-α, IFN-γ, IL-10, and TGF-β expression

The diagnostic performance of IL-17A, TNF-α, IFN-γ, IL-10, and TGF-β as biomarkers of CRC was examined by comparing CRC patients with stomach cancer, UC, group, and colon polyps patients as well as healthy volunteers as the control group. Logistic regression analysis was performed. ROC curves were drawn on the biomarkers individually and in combination. As shown in Table 2 and Fig. 4A–C, the AUC values of IL-17A and TNF-α (0.88) were higher than those of CEA (0.71), IFN-γ (0.65), IL-10 (0.80), and TGF-β (0.61). However, CEA showed the highest specificity (78.8%) compared to the other 5 biomarkers. CEA combined with 1 cytokine did not lead to an increased AUC value compared to CEA alone (Table 2). Conversely, the specificity of CEA combined with 1 cytokine was lower than that of CEA alone. We further addressed whether CEA combined with 2 cytokines could increase the sensitivity and specificity of CRC diagnosis. CEA combined with IL-17A and TNF-α produced an increased AUC value compared to CEA combined with IL-10 and TGF-β. Combining CEA, IL-17A, and TNF-α resulted in the highest AUC value (0.935) among all the individual biomarkers and combinations. The sensitivity and specificity reached 96.2% and 80.4%, respectively. The combination of CEA, IL-17A, and TNF-α also displayed the highest value with a 95% confidence interval (0.895–0.963). The combination also yielded the highest Youden index (0.76). Although combining CEA, IL-10, and TGF had the highest diagnostic specificity (91.6%), its sensitivity only reached 58.5%. These results suggest that the combination of CEA, IL-17A, and TNF-α has a preferable diagnostic effect as a diagnostic marker of CRC.

4. Discussion

CEA serves as a tumor marker and has been widely used in the early diagnosis of CRC. However, CEA is expressed in many types of tumors and lacks specificity.[3,4] In the present study, the specificity of CEA was 78.8% for the diagnosis of CRC. The CEA level is also high found in the serum of patients with stomach cancer. Cytokines are small proteins produced by many cell types. They are important in tumorigenesis, tumor invasion, immune responses, and inflammation.[15,16] Cytokines can be used as potential biomarkers for the early diagnosis of CRC.[17] High

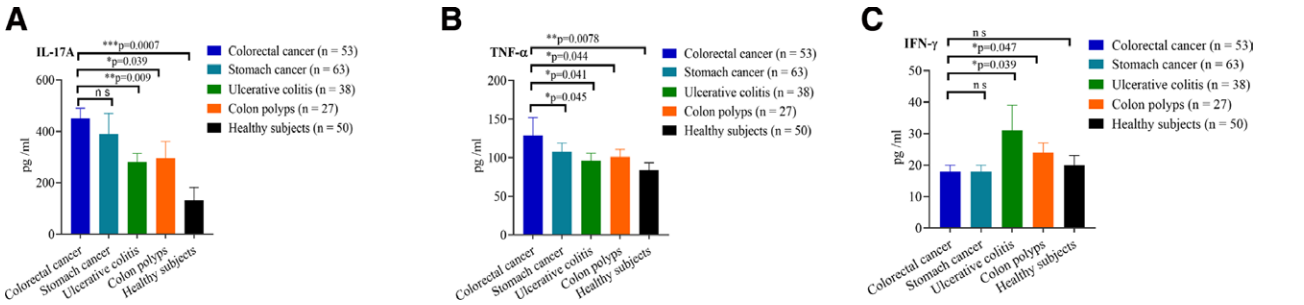

Figure 2. Distribution of serum IL-17A, TNF-α, and IFN-γ levels among healthy subjects (n = 50) and patients with colorectal cancer (n = 53), stomach cancer (n = 63), ulcerative colitis (n = 38), or colon polyps (n = 27): (A) IL-17A; (B) TNF-α, (C) IFN-γ. *$P < .05$; **$P < .01$; ***$P < .0001$. IFN-γ = interferon-gamma, IL = interleukin, TGF-β = transforming growth factor beta, TNF-α = tumor necrosis factor-alpha.

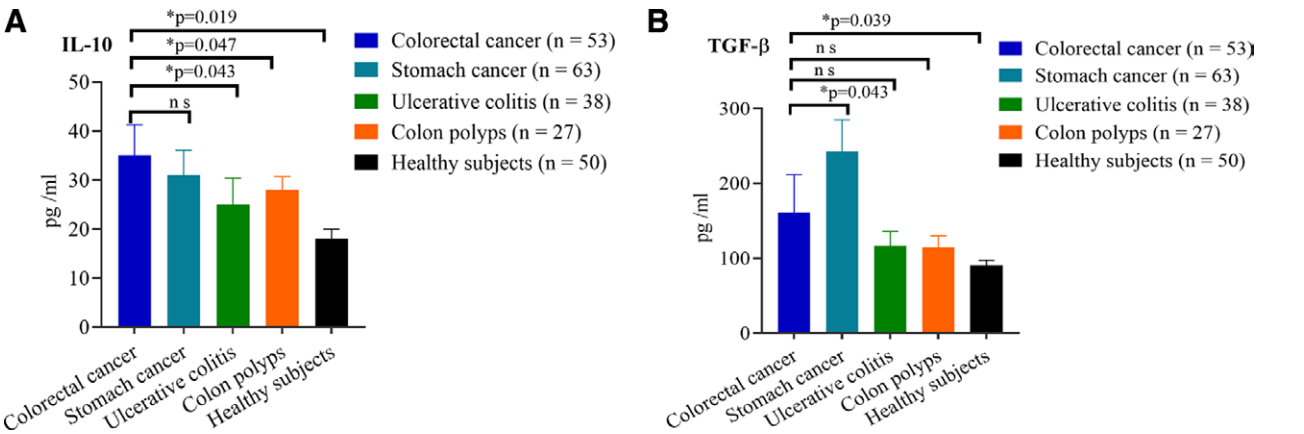

Figure 3. Distribution of serum IL-10 and TGF-β among healthy subjects (n = 50) and patients with colorectal cancer (n = 53), stomach cancer (n = 63), ulcerative colitis (n = 38), or colon polyps (n = 27): (A) IL-10 (B) TGF-β. *$P < .05$. IL = interleukin, TGF-β = transforming growth factor beta.

Table 2

Diagnosis performance of serum CEA, IL-17A, TNF-α, IFN-γ, IL-10, and TGF-β for colorectal cancer.

Index	AUC	*P* value	Sensitivity (%)	Specificity (%)	95%CI	Youden index
CEA	0.713	<.0001	59.5	78.8	0.65–0.77	0.3726
IL-17A	0.88	<.0001	97.1	62.3	0.88–0.92	0.7542
TNF-α	0.88	<.0001	96.2	54.7	0.83–0.91	0.6040
IFN-γ	0.65	<.0001	60.9	60.4	0.58–0.71	0.3512
IL-10	0.80	<.0001	83.0	55.3	0.74–0.84	0.4418
TGF-β	0.61	<.0001	98.1	40.8	0.54–0.67	0.3890
CEA + IL-17A	0.89	<.0001	98.1	55.3	0.84–0.93	0.7430
CEA + IL-10	0.81	<.0001	90.6	50.8	0.74–0.87	0.4516
CEA + IFN-γ	0.71	<.0001	95.2	38.5	0.64–0.78	0.3855
CEA + TGF-β	0.70	<.0001	86.8	44.7	0.62–0.79	0.383
CEA + TNF-α	0.88	<.0001	98.1	54.7	0.84–0.93	0.6305
CEA + IL-10 + TGF-β	0.813	<.0001	58.5	91.6	0.75–0.86	0.5011
CEA + IL-17A + TNF-α	0.935	<.0001	96.2	80.4	0.89–0.96	0.7667

CEA = carcinoembryonic antigen, IFN-γ = interferon-gamma, IL = interleukin, TGF-β = transforming growth factor beta, TNF-α = tumor necrosis factor-alpha.

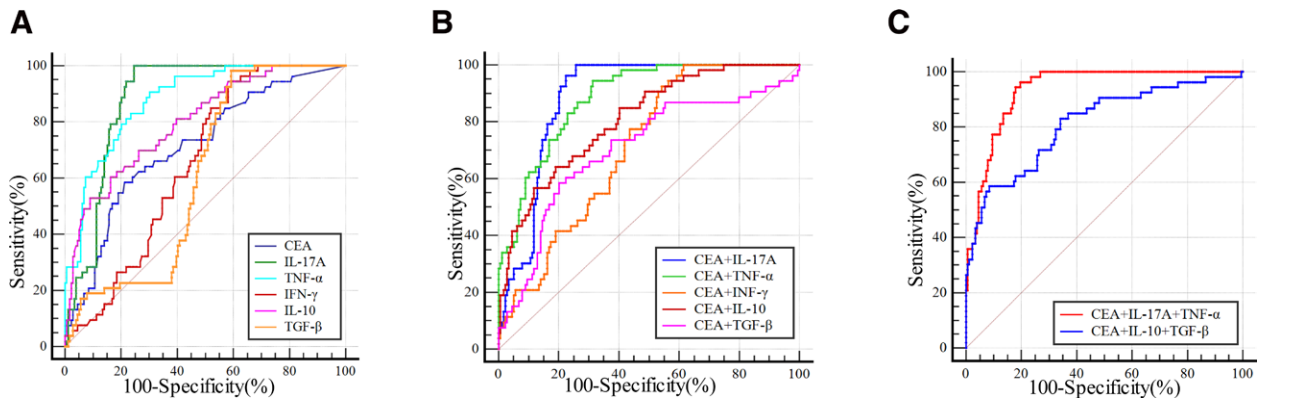

Figure 4. ROC curves of CEA, IL-17A, TNF-α, IFN-γ, IL-10, TGF-β, and the their combinations for colorectal cancer (CRC). (A) ROC curves of CEA or single cytokine for the diagnosis of CRC. (B) ROC curves of CEA combined with single cytokine for the diagnosis of CRC. (C) ROC curves of CEA combined with 2 cytokines for the diagnosis of CRC. CEA = carcinoembryonic antigen, IFN-γ = interferon-gamma, IL = interleukin, ROC = receiver operating characteristic, TGF-β = transforming growth factor beta, TNF-α = tumor necrosis factor-alpha.

levels of IL-4, IL-8, and TGF-β have been observed in the serum of CRC patients. However, the specificity of cytokines in the diagnosis of CRC has not been addressed.[17] Our results suggest that the specificity of a single cytokine (IL-17A, TNF-α, IFN-γ, IL-10, or TGF-β) for the diagnosis of CRC is low. Therefore, a single cytokine is not a suitable diagnostic marker of CRC. Instead, cytokines combined with CEA may be useful for CRC diagnosis. Interestingly, the specificity of CEA combined with a single cytokine was lower than that of CEA alone. However, the results with CEA combined with 2 cytokines (IL-17A and TNF-α) indicate the potential value in the diagnosis of CRC.

The relationship between inflammation and tumorigenesis has been conclusively established over the last 20 years.[18–20] Evidence supports the involvement of inflammation in the initiation and development of CRC.[5,6] CRC often features the dense infiltration of cytokine-producing immune cells.[6,18] Cytokines play a decisive role in the initiation of inflammation.[10,15] Proinflammatory cytokines that include TNF-α, IL-17A, and IFN-γ are upregulated in CRC and promote development of this cancer.[5,8,9,21] The accumulation of IL-17A, TNF-α, and IFN-γ sustains CRC cell growth through the activation of signal transducer and activator of transcription 3 (STAT3) and nuclear factor-kappa B.[5,6] These data suggest that the IL-17A, TNF-α, and IFN-γ proinflammatory cytokines are associated with the development and progression of CRC and may be potentially valuable as biomarkers for the diagnosis of CRC. We found elevated serum TNF-α and IL-17A levels in CRC patients compared to those in healthy controls. However, high levels of TNF-α and IL-17A have also been observed in stomach cancer, UC, and colon polyps. We found that serum TNF-α and IL-17A levels were not only increased in CRC patients, but also elevated in stage III breast cancer patients.[22,23] These data suggest that TNF-α and IL-17A cannot be used as specific biomarkers for the diagnosis of CRC patients. Logistic regression analysis further supported our opinion that the specificity of TNF-α and IL-17A in the diagnosis of CRC is lower than that of CEA. Surprisingly, our results revealed that serum IFN-γ levels did not significantly increase in CRC patients compared to healthy controls. However, elevated serum IFN-γ levels have been observed in UC. UC is an important risk factor for colon cancer development.[18] Chronic inflammation causes oxidative damage to DNA, leading to p53 mutations in colon cancer cells.[5,18] We speculate that elevated IFN-γ may promote the transformation of colitis to colon cancer because IFN-γ has an antitumor role by regulating major histocompatibility complex molecule expression and also promotes the migration of malignant cells toward blood vessels by stimulating chemokine expression in chronic inflammation.[5,21] However, these results were not consistent with the descriptions of increased serum IFN-γ levels in patients with CRC.[5,6,8] One possibility is that the role of IFN-γ may depend on the different stages of tumor development. Another reason is that few cases were collected in the current study.

The anti-inflammatory cytokines TGF-β and IL-10 participate in both the initiation and progression of cancer.[10] IL-10 inhibits

proinflammatory cytokine expression and dampens antigen presentation, cell maturation, and differentiation, allowing tumor cells to evade immune surveillance mechanisms.[24] IL-10 may cause long-term STAT3 phosphorylation and thus has a pro-tumorigenic effect by activating STAT3.[16] Elevated IL-10 levels are associated with a poor prognosis in diffuse B cell lymphoma.[25] In the present study, serum IL-10 levels in patients with CRC were significantly higher than those in healthy subjects and those with UC or colon polyps. Thus, it is possible that increased IL-10 levels may promote the development of CRC. However, high levels of IL-10 have also been observed in stomach cancer. IL-10 is not a suitable biomarker for the diagnosis of colon cancer, although serum IL-10 is elevated in patients with CRC. Similarly, logistic regression analysis confirmed that IL-10 has low specificity for CRC diagnosis. The role of TGF-β in CRC is paradoxical.[10] In the early stages, TGF-β exerts antitumorigenic effects by inhibiting proliferation and stimulating apoptosis. In cancer induction, TGF-β suppresses the antitumor activity of immune cells to facilitate metastasis.[5] High TGF-β1 expression has been observed in CRC tissue.[26] In the current study, the data showed that serum TGF-β levels in patients with CRC and stomach cancer were significantly higher compared to healthy subjects. However, TGF-β levels in patients with CRC were lower than those in patients with stomach cancer. This suggests that TGF-β may also promote tumor development, but it is not specific for CRC.

Pro- and anti-inflammatory cytokines play different roles depending on the tumor microenvironment.[5,15,19] A single cytokine is not suitable for the diagnosis of CRC, although the sensitivity of cytokines in cancer is high. Therefore, we combined CEA and cytokines to improve the specificity and sensitivity of CRC diagnosis for CRC. The combination of inflammatory cytokines and CEA was helpful in distinguishing CRC from stomach cancer, UC, and colon polyps, and has good clinical application value. However, further prospective studies are needed to determine the trusted cutoff values of circulating cytokines and CEA in many more patients to establish a direct relationship with CRC.

5. Conclusion

Our results suggest that serum CEA, IL-10, IL-17A, TNF-α, and TGF-β levels are significantly increased in CRC. However, a single factor is not suitable as a biomarker for the diagnosis of colon cancer. The combination of IL-17A, TNF-α, and CEA has better diagnostic efficacy for CRC than CEA alone or CEA combined with IL-10 and TGF-β.

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Author contributions

Y.M., Y.Z., and Y.B. performed the immunoassays. L.H. and D.L. collected the patient and control samples. D.W. and Y.W. performed the data analysis. Y.M. drafted the manuscript. Y.M. and Q.W. designed the study and revised the manuscript. All authors read and approved the final manuscript.
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Methodology: Dandan Li, Dan Wang, Mengying Wang.
Software: Ya Zhang, Longmei He.
Writing – original draft: Yunfeng Ma.
Writing – review & editing: Xiaoqin Wang.

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