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Research Article

Comparison between Clinical Utility of CXCL-8 and Clinical Practice Tumor Markers for Colorectal Cancer Diagnosis

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Owing to the high incidence and mortality rates of colorectal cancer (CRC), novel biomarkers for CRC diagnosis are critically needed. Therefore, this study is aimed at exploring the clinical utility of serum C-X-C motif chemokine 8 (CXCL-8) for CRC diagnosis and progression compared to the routinely used biomarkers, carcinoembryonic antigen (CEA), and carbohydrate antigen-19-9 (CA19-9). This study included 227 patients with CRC, 110 patients with colorectal adenoma (CA), and 123 healthy participants, who were recruited from the Fujian Medical University Union Hospital from July 1, 2019 to October 31, 2020. Serum concentrations of CXCL-8, CEA, and CA19-9 were detected using enzyme-linked immunosorbent assay and chemiluminescent microparticle immunoassay. Clinicopathological features of patients with CRC were collected and analyzed. The diagnostic efficacy of CXCL-8, CEA, and CA19-9 for CRC was evaluated using receiver operating characteristic (ROC) curves. We found that the serum concentrations of CXCL-8, CEA, and CA19-9 were significantly higher in patients with CRC than those in patients with CA and healthy controls. The diagnostic sensitivity of CXCL-8 alone was higher than those of CEA and CA19-9 both and when combined; thus, CXCL-8 may be better at discriminating patients with CRC from healthy controls and patients with CA. Moreover, combining CXCL-8 with CEA or CA19-9 improved their respective diagnostic performances in distinguishing patients with CRC from CA patients and healthy participants. Notably, we also found that serum concentrations of CXCL-8 were positively correlated with metastases and tumor size. Therefore, our study suggests that serum CXCL-8 may serve as an improved biomarker for CRC diagnosis compared to the traditional tumor markers CEA and CA19-9. Moreover, our findings indicate the potential efficacy of serum CXCL-8 levels as a CRC prognostic biomarker.

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies of the colon or rectum and has caused mass mortality in recent years [1, 2]. Approximately 881,000 people died from CRC in 2018, corresponding to more than 2400 cancer deaths on average per day worldwide [3]. Owing to economic growth, increasing urbanization, and lifestyle westernization, a substantial incidence and mortality rate has been observed in China, which imposes a heavy social and economic burden on individuals, families, and countries [4]. Colorectal adenomas (CA) are benign tumors of the colon or rectum and precursors of most CRCs, which take 5–10 years to develop into adenocarcinomas [5]. Moreover, it is difficult for clinicians to distinguish patients with CRC from patients with CA. Therefore, the early detection and diagnosis of CRC can reduce patient mortality and financial burden. Currently, several clinically useful methods, such as colonoscopy, rectoscopy, fecal occult blood test, and computed tomography, are used in the diagnosis of CRC; however, they have several limitations, such as invasiveness, high cost, low sensitivity, and low specificity [6, 7].

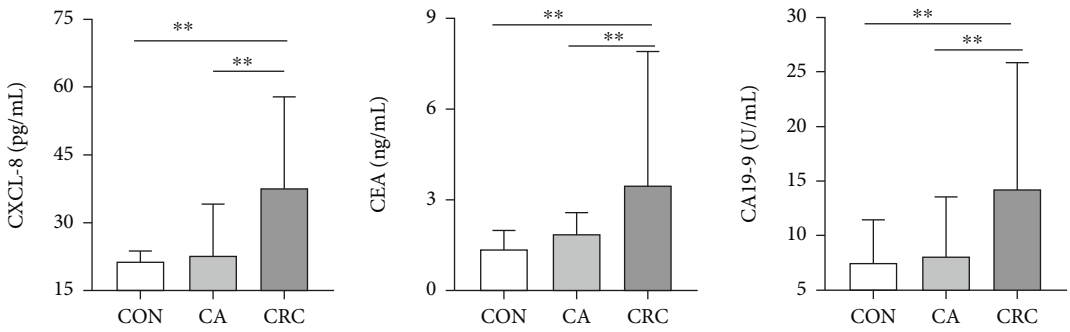

Figure 1: Serum concentrations of CXCL-8, CEA, and CA19-9 in patients with CRC, patients with CA, and healthy controls (CON). Data are presented as the median with the interquartile range. $^{**}p < 0.01$.

Alternatively, serum biomarker measurements can be used, as this method is less invasive and cheaper than others. However, the clinical practice tumor markers currently used have a poor diagnostic performance, especially for the early diagnosis of CRC [8]. Thus, it is essential to develop a minimally invasive, affordable, and, most importantly, more sensitive and specific approach for the early detection of CRC.

Many pathogenic factors are involved in CRC, and chronic inflammation is of utmost importance [9]. There is an increasing recognition that the inflammatory mediators and cellular effectors are important components of tumor microenvironment (TME). Regardless of its origin, inflammation in TME has a number of tumor-promoting effects [10]. Moreover, this cancer-related inflammation appears to be critical for better understanding the pathophysiology of cancer and the possibilities of its therapy and management [11]. Chemokines are a family of low-molecular cytokines which facilitate communication between tumor and nontumor cells within the TME. Many studies have shown that chemokines may facilitate neoplasm progression, which has made them the focus of investigations. Based on the positions of key cysteine residues, chemokines are grouped into four classes (CC, CX3C, CXC, and XC) [12]. C-X-C motif chemokine 8 (CXCL-8; also known as IL-8) is a small soluble peptide in the C-X-C chemokine family [13]. Early studies reported that CXCL-8 has many functions that promote cell proliferation, differentiation, migration, and survival [14]. Several studies have reported that serum CXCL-8 may represent a biomarker for esophageal [15, 16] and pancreatic cancers [17]. This suggests that serum CXCL-8 may be a candidate biomarker for certain tumors. Several studies have revealed the upregulation of CXCL-8 in CRC cells and CRC tissue and a correlation of CXCL-8 expression with a worse prognosis for patients with CRC [18, 19]. However, to the best of our knowledge, blood serum CXCL-8 has rarely been reported as a clinical biomarker for CRC diagnosis.

Therefore, our study aimed to detect the serum level of CXCL-8 in patients with CRC and compare this chemokine to current tumor markers to establish whether it may be considered an improved tumor marker for CRC diagnosis. Furthermore, we assessed whether CXCL-8 may be a potential candidate prognostic biomarker by evaluating the association between CXCL-8 and clinicopathological parameters in patients with CRC. Our findings suggest that CXCL-8 may be a potential biomarker for CRC diagnosis and progression.

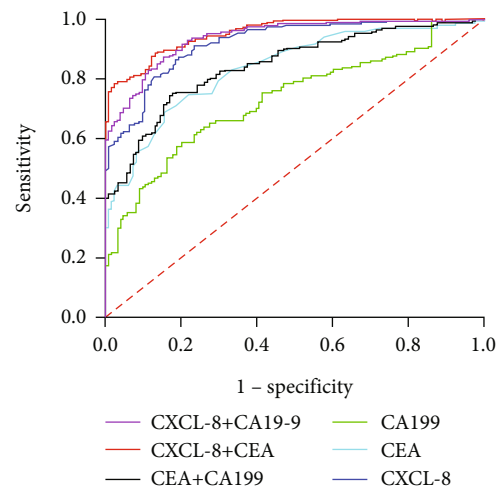

Figure 2: ROC curves of CXCL-8, CEA, and CA19-9 alone and combined for discriminating patients with colorectal cancer from healthy participants.

2. Materials and Methods

2.1. Study Participants. Serum samples were collected from 227 patients (143 men and 84 women, median age (interquartile range): 61 (53–71) years) with newly diagnosed CRC. The controls included 110 patients with colorectal adenoma (CA; 67 men and 45 women, 56 (51–64) years), and 123 healthy participants (51 men and 72 women, 54 (41–65) years). All subjects were recruited from the Fujian Medical University Union Hospital (Fuzhou, China) between July 1, 2019 and October 31, 2020. The clinicopathological data of patients with CRC were recorded, including sex, age, tumor location, tumor size, tumor differentiation, TNM staging according to the American Joint Committee on Cancer classification guidelines [20], and nerve and vascular invasion. The main exclusion criteria were presence of infection, a history of cancer hyperpyrexia, pregnancy,

Table 1: Statistical values of CXCL-8, CEA, and CA19-9 alone and combined for the differential diagnosis between patients with colorectal cancer and healthy participants.

Variable	AUC	Accuracy (%)	Cut-off value	Sensitivity (%)	Specificity (%)	95% Confidence interval	
						Lower limit	Upper limit
CXCL-8	0.920	84.57	24.92	86.34	81.30	89.24	94.80
CEA	0.837	57.43	5	34.80	99.19	75.59	87.88
CA19-9	0.730	45.43	37	15.86	100	67.81	78.26
CXCL-8 + CEA	0.954	85.14		78.41	97.56	93.51	97.22
CXCL-8 + CA19-9	0.940	84.86		82.82	88.62	91.62	96.26
CEA + CA19-9	0.844	77.43		74.45	82.93	80.34	88.41

haematological disease, intestinal obstruction or intestinal perforation at initial diagnosis, and incomplete information. This study was approved by the Institutional Medical Research Ethics Committee (2021KJCX013) of the Fujian Medical University Union Hospital (China). Informed consent for clinicopathological information and sample collection was provided by all participants.

2.2. Analysis of Serum CXCL-8, CEA, and CA19-9 Concentrations. Venous blood (5 mL) was obtained from all the participants. Venous blood samples from patients with CRC and CA were collected prior to any medical intervention. Serum was obtained by centrifugation at 3,000 rpm for 10 min and then stored at -80°C for subsequent measurements. The serum CXCL-8 concentration was measured using an enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. A standard curve was constructed for each plate to calculate the absolute concentration. The serum concentrations of CA19-9 and CEA were measured using chemiluminescent microparticle immunoassay using a Cobas 6000 analyzer (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. The cut-off value for normal CA19-9 was less than 37 U/mL and that for normal CEA was less than 5 ng/mL.

2.3. Statistical Analyses. Statistical analyses were performed using GraphPad Prism for window (version 5.0; GraphPad Software Inc., San Diego, CA, USA) or SPSS software for window (version 21.0; IBM, Armonk, NY, USA). The concentrations of the three markers did not conform to a normal distribution according to the normality test; therefore, nonparametric statistical analyses were applied [21]. The Mann–Whitney U test was performed to compare two groups, whereas the Kruskal-Wallis test was used for three or more group comparisons [21]. The diagnostic characteristics of CXCL-8, CEA, and CA19-9 were assessed using receiver operating characteristic (ROC) curves. The Youden index was used to determine the optimal cut-off value to differentiate between healthy controls, patients with CA, and patients with CRC. Combination analysis was performed using binary logistic regression. The relationship between the variables and the occurrence of CRC was evaluated using logistic regression; the odds ratio (OR) was adjusted for covariates [22]. The correlation between the serum concentrations of CXCL-8, CEA, and CA19-9 and the clinicopathological characteristics were determined using Spearman's rank method. The estimated coefficients were calculated by maximum likelihood method. The entry method was used for variable selection. The calibration was assessed via the Hosmer-Lemeshow goodness-of-fit test [22]. Differences were considered statistically significant at $p < 0.05$.

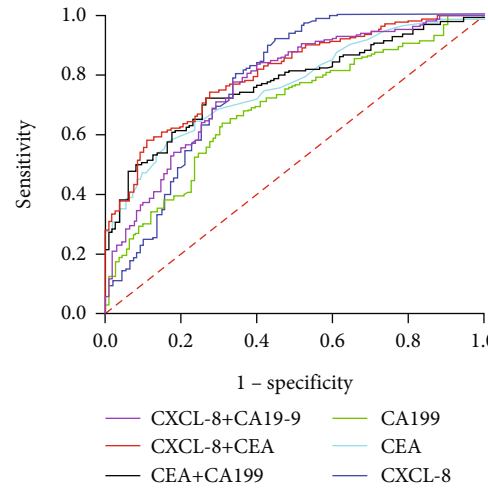

Figure 3: ROC curves of CXCL-8, CEA, and CA19-9 alone and combined for discriminating patients with colorectal cancer and patients with colorectal adenoma.

3. Results

3.1. Serum Concentrations of CXCL-8, CEA, and CA19-9 in Patients with CRC. Figure 1 shows the serum concentrations of CXCL-8, CEA, and CA19-9 in the clinical samples. The serum levels of all the markers were significantly higher ($p < 0.001$) in patients with CRC than in patients with CA and healthy participants.

3.2. Evaluation of Serum CXCL-8 as a Potential Biochemical Marker for CRC Diagnosis. We evaluated the clinical utility of CXCL-8 as a biochemical marker for CRC diagnosis compared to CEA and CA19-9, which are the most common serum biochemical markers in CRC diagnostics.

First, we evaluated the usefulness of CXCL-8 as a biomarker for the differential diagnosis between patients with

Table 2: Statistical values of CXCL-8, CEA, and CA19-9 alone and together for the differential diagnosis between patients with colorectal cancer and patients with colorectal adenoma.

Variable	AUC	Accuracy (%)	Cut-off value	Sensitivity (%)	Specificity (%)	95% Confidence interval	
						Lower limit	Upper limit
CXCL-8	0.774	77.15	24.92	86.34	58.18	71.51	83.35
CEA	0.760	54.89	5	34.80	96.36	70.82	81.04
CA19-9	0.686	42.43	37	15.86	97.27	62.67	74.49
CXCL-8 + CEA	0.804	73.59		74.01	72.73	75.71	85.10
CXCL-8 + CA19-9	0.768	73.88		77.53	66.36	71.36	82.19
CEA + CA19-9	0.767	72.41		71.81	73.64	71.67	81.70

Table 3: Performance of CXCL-8, CEA, and CA19-9 for predicting the colorectal cancer occurrence risk.

Variables	No. subjects	Cut-off value	Multivariate analysis		
			OR	95% CI	p value
CEA (ng/mL)	298	<5	1 (R)	—	
	79	≥5	13.83	3.11 – 61.50	0.001
CA19-9 (U/mL)	340	<37	1 (R)	—	
	37	≥37	7.96	0.97 – 65.13	0.053
CXCL-8 (pg/mL)	135	<24.92	1 (R)	—	
	242	≥24.92	7.76	4.06 – 14.86	<0.001

CRC and healthy participants. The areas under the ROC curve (AUCs) for CXCL-8, CEA, and CA19-9 as parameters in CRC diagnostics were 0.920, 0.837, and 0.730, respectively (Figure 2 and Table 1). At a cut-off value of 24.92 for CXCL-8, we observed that the diagnostic sensitivity of CXCL-8 was higher (86.34%) than that of CEA (34.80%) and CA19-9 (15.86%) (Table 1). Our results also showed that CXCL-8 alone had better sensitivity and accuracy for discriminating patients with CRC from healthy controls than that of CEA and CA19-9 together (Table 1). Notably, the diagnostic utility of CEA and CA19-9 was improved when combined with CXCL-8 (Table 1). As shown in Figure 2 and Table 1, the AUCs for CXCL-8 + CEA and CXCL-8 + CA19-9 were 0.954 and 0.939, respectively, which were significantly higher than that for CEA + CA19-9 (AUC: 0.844). Moreover, the sensitivity and specificity of CXCL-8 + CEA and CXCL-8 + CA19-9 were considerably higher than those of CEA + CA19-9.

Next, we used ROC analysis to evaluate the efficacy of CXCL-8 in the differential diagnosis between patients with CRC and those with CA. As shown in Figure 3 and Table 2, the AUCs for CXCL-8, CEA, and CA19-9 were 0.774, 0.760, and 0.686, respectively, suggesting that CXCL-8 has no better diagnostic performance in distinguishing between CRC and CA. However, the diagnostic utility of CEA and CA19-9 was improved when combined with CXCL-8 (Figure 3 and Table 2). Notably, our results also showed that CXCL-8 alone had better sensitivity and accuracy for discriminating CRC from CA than that of CEA and CA19-9 alone or together (Table 2).

Taken together, these results indicate that serum concentrations of CXCL-8 may represent an improved novel biochemical marker for CRC diagnostics compared to clinical practice tumor markers.

3.3. Performance of CXCL-8, CEA, and CA19-9 for Predicting CRC Occurrence Risk via Cut-off Values. The correlation between several risk factors and CRC risk was initially evaluated using univariate analysis to identify the risk factors that qualified for the multivariate model (data not shown). All three markers were found to be associated with an increased risk of CRC occurrence and were entered into the multivariate analysis. Finally, only the serum concentrations of CXCL-8 and CEA ($p = 0.000$, OR = 7.76 $p = 0.001$, and OR = 13.83, respectively) were significant risk factors for CRC occurrence (Table 3).

3.4. Association between Serum Concentrations of CXCL-8, CEA, and CA19-9 and Clinicopathological Characteristics in Patients with CRC. After determining the performance of serum CXCL-8 concentrations in assessing CRC, we further analyzed the association between the markers and the clinicopathological characteristics of the patients. The assessment of the relationship between the marker serum concentrations and the clinicopathological parameters revealed that serum concentrations of CXCL-8 increased with TNM stage, T stage, N stage, and nerve invasion, although these differences were not statistically significant (Table 4). However, these differences were statistically significant for the serum CEA levels (Table 4). For the M stage, serum levels of all the markers were found to be significantly higher in the patients with distant metastases (M1) than in patients without distant metastases (M0, $p < 0.05$) (Table 4). Additionally, patients with CRC with a tumor

Table 4: Relationship between the serum CXCL-8, CEA, and CA19-9 levels and the clinicopathological features of patients with colorectal cancer.

Clinicopathological characteristics	No. subjects	CXCL-8 (pg/mL)	CEA (ng/mL)	CA19-9 (U/mL)
Location				
Colon	122	37.58 (27.36–55.68)	3.90 (2.20–8.63)	14.28 (7.98–27.09)
Rectum	105	37.75 (29.12–62.14)	3.00 (1.80–6.80)	14.17 (8.48–23.74)
p value		0.458	0.111	0.580
TNM stage				
I	42	37.66 (28.56–56.82)	2.60 (1.48–4.75)	13.78 (7.62–23.59)
II	83	36.27 (27.38–62.06)	3.20 (2.00–8.60)	13.36 (7.50–25.86)
III	85	36.83 (28.12–56.98)	3.70 (2.10–7.75)	14.36 (9.40–24.45)
IV	17	53.38 (35.24–71.14)	8.40 (4.75–38.50)	22.71 (12.11–109.40)
p value		0.423	**<0.001**	0.073
T stage				
T1	11	38.98 (33.83–67.80)	1.50 (1.20–2.90)	11.21 (1.33–19.96)
T2	34	35.96 (28.93–55.05)	2.92 (1.80–5.78)	14.30 (8.77–23.59)
T3	154	36.33 (27.38–55.38)	3.60 (2.08–8.40)	13.86 (7.98–25.87)
T4	28	41.61 (31.35–69.72)	6.65 (2.35–20.68)	20.12 (11.60–48.44)
p value		0.416	**0.001**	0.077
N stage				
N0	123	36.27 (27.42–54.69)	2.90 (1.80–5.70)	13.65 (7.75–24.39)
N1	60	47.16 (31.39–78.31)	3.90 (2.45–9.05)	13.94 (9.27–24.70)
N2	44	35.95 (28.16–51.60)	4.90 (2.00–11.65)	17.12 (11.05–27.54)
p value		0.062	**0.016**	0.260
M stage				
M0	206	36.33 (27.72–55.38)	3.20 (1.90–6.20)	13.91 (8.14–23.46)
M1	21	53.38 (37.52–65.47)	8.40 (4.20–28.52)	23.52 (12.72–77.58)
p value		**0.039**	**<0.001**	**0.007**
Histological grade				
High	6	39.52 (32.71–66.49)	3.25 (2.20-4.30)	15.83 (8.62-22.43)
Moderate	206	37.66 (27.92–57.85)	3.40 (1.90-7.60)	13.91 (8.00-25.04)
Low	15	40.94 (35.28–55.24)	4.70 (1.95-14.65)	22.71 (14.34-36.18)
p value		0.718	0.621	0.095
Vascular invasion				
Present	41	38.15 (26.34–56.93)	4.20 (2.20–8.70)	16.60 (9.16–3.19)
Absent	175	38.16 (28.69–64.66)	3.35 (1.90–7.20)	13.84 (7.87–23.49)
Unknown	11	35.97 (32.71–37.63)	4.15 (2.60–6.10)	19.11 (13.96–25.04)
p value		0.638	0.523	0.082
Nerve invasion				
Present	66	39.42 (28.85–76.51)	4.20 (2.60–14.40)	15.00 (9.16–35.27)
Absent	155	36.98 (27.63–53.46)	3.00 (1.80–5.95)	13.86 (7.83–22.76)
Unknown	5	56.11 (37.52–81.40)	3.00 (2.90–5.30)	19.96 (8.40–22.71)
p value		0.184	**0.007**	0.165
Tumor size (cm)				
<5	129	36.11 (27.72–53.54)	2.90 (1.80–5.70)	14.50 (8.14–23.46)
≥5	98	42.80 (29.02–76.20)	4.15 (2.40–9.40)	13.84 (8.80–32.91)
p value		**0.034**	**0.009**	0.294

Data are presented as the median with the interquartile range and are statistically significant at $p < 0.05$ (bold).

Table 5: Spearman's rank correlations between the serum concentrations of CXCL-8, CEA, and CA19-9 and the clinicopathological characteristics among patients with colorectal cancer.

		TNM stage	T stage	N stage	M stage	Tumor size	Histological grade	Vascular invasion	Nerve invasion	CEA	CA19-9	CXCL-8
TNM stage	r	1.000	**0.678****	**0.875****	**0.456****	0.085	**0.146***	**-0.151***	**-0.274****	**0.265****	**0.136***	0.075
	p		**<0.001**	**<0.001**	**<0.001**	0.102	**0.014**	**0.012**	**<0.001**	**<0.001**	**0.021**	0.131
T stage	r	**0.678****	1.000	**0.446****	**0.324****	**0.158****	**0.207****	**-0.114***	**-0.319****	**0.244****	**0.139***	0.048
	p	**<0.001**		**<0.001**	**<0.001**	**0.009**	**0.001**	**0.044**	**<0.001**	**<0.001**	**0.018**	0.237
N stage	r	**0.875****	**0.446****	1.000	**0.400****	-0.044	**0.143***	**-0.128***	**-0.179****	**0.186****	0.104	0.037
	p	**<0.001**	**<0.001**		**<0.001**	0.257	**0.016**	**0.027**	**0.003**	**0.002**	0.060	0.290
M stage	r	**0.456****	**0.324****	**0.400****	1.000	0.029	0.109	-0.084	-0.097	**0.277****	0.181	**0.117***
	p	**<0.001**	**<0.001**	**<0.001**		0.334	0.050	0.103	0.072	**<0.001**	0.003	**0.039**
Tumor size	r	0.085	**0.158****	-0.044	0.029	1.000	0.093	-0.012	**-0.188****	**0.173****	0.070	**0.122***
	p	0.102	**0.009**	0.257	0.334		0.080	0.431	**0.002**	**0.005**	0.148	**0.034**
Histological Grade	r	**0.146***	**0.207****	0.143	0.109	0.093	1.000	0.099	-0.055	0.064	**0.125***	0.001
	p	**0.014**	**0.001**	0.016	0.050	0.080		0.069	0.204	0.168	**0.030**	0.493
Vascular invasion	r	**-0.151***	**-0.114***	**-0.128***	-0.084	-0.012	0.099	1.000	**0.231****	-0.046	-0.055	0.028
	p	**0.012**	**0.044**	**0.027**	0.103	0.431	0.069		**<0.001**	0.247	0.203	0.335
Nerve invasion	r	**-0.274****	**-0.319****	**-0.179****	-0.097	**-0.188****	-0.055	**0.231****	1.000	**-0.202****	**-0.118***	-0.067
	p	**<0.001**	**<0.001**	**0.003**	0.072	**0.002**	0.204	**<0.001**		**0.001**	**0.039**	0.159
CEA	r	**0.265****	**0.244****	**0.186****	**0.277****	**0.173****	0.064	-0.046	**-0.202****	1.000	**0.423****	0.015
	p	**<0.001**	**<0.001**	**0.002**	**<0.001**	**0.005**	0.168	0.247	**0.001**		**<0.001**	0.409
CA19-9	r	**0.136***	**0.139***	0.104	**0.181***	0.070	**0.125***	-0.055	**-0.118***	**0.423****	1.000	-0.001
	p	**0.021**	**0.018**	0.060	**0.003**	0.148	**0.030**	0.203	**0.039**	**<0.001**		0.491
CXCL-8	r	0.075	0.048	0.037	**0.117***	**0.122***	0.001	0.028	-0.067	0.015	-0.001	1.000
	p	0.131	0.237	0.290	**0.039**	**0.034**	0.493	0.335	0.159	0.409	0.491	

$^{*}p < 0.05$, $^{**}p < 0.01$ (bold).

size ≥5 cm showed significantly higher CXCL-8 and CEA concentrations than those with a tumor size <5 cm ($p < 0.05$) (Table 4). However, no significant associations were observed between any of the marker levels and location, histological grade, or vascular invasion.

Correlations between the marker serum concentrations and clinicopathological characteristics of malignancy were assessed using the Spearman's rank correlation test (Table 5). Serum CXCL-8 levels were significantly correlated with the M stage ($p = 0.039$) and tumor size ($p = 0.034$) in patients with CRC (Table 5). Taken together, these findings indicate that serum CXCL-8 concentration is associated with an advanced clinicopathologic status in patients with CRC (Table 6). Table 6 shows all the acronym and full name in the article.

4. Discussion

In this study, we found that serum concentrations of CXCL-8 were significantly higher in patients with CRC than in patients with CA and healthy controls. Serum CXCL-8 alone had a better diagnostic sensitivity and accuracy in distinguishing CRC patients from CA patients and healthy participants than CEA and CA19-9 alone or in combination. Moreover, the addition of CXCL-8 improved the diagnostic sensitivity of CEA and CA19-9 in distinguishing patients with CRC from CA patients and healthy controls. Furthermore, serum CXCL-8 levels were significantly associated with M stage and tumor size.

CXCL-8 is a small soluble C-X-C chemokine that functions in chronic inflammation and cancer development [13, 14]. Many investigations have indicated that CXCL-8 plays an important role in tumor angiogenesis and invasion and is linked with distant metastases in CRC [23–25]. However, these studies have mainly assessed the expression levels of chemokines in CRC cell lines and tissues. To the best of our knowledge, serum CXCL-8 has rarely been reported as a biochemical marker for the diagnosis and prognosis of CRC.

CRC remains a severe global problem as it is a life-threatening malignancy with high morbidity and mortality. Therefore, recent studies have focused on improving early

Table 6: All acronym and full name in the article.

Acronym	Full name	Acronym	Full name
CRC	Colorectal cancer	OR	Odds ratio
CXCL-8	C-X-C motif chemokine 8	ROC	Receiver operating characteristic
CEA	Carcinoembryonic antigen	TME	Tumor microenvironment
CA19-9	Carbohydrate antigen-19-9	CON	Healthy controls
CA	Colorectal adenoma	AUC	Area under the curve

diagnostic methods for CRC. Endoscopy is currently the gold standard for the diagnosis of CRC; however, it had the lowest patient compliance rate owing to bowel preparation requirements and discomfort during the test. Furthermore, patients with serious cardiopulmonary insufficiency, intestinal perforation, or enterostenosis cannot undergo invasive tests [26, 27]. In general, serum biochemical marker measurements impose minimal inconvenience compared to endoscopy and provide lower financial expenses for patients. However, the diagnostic performance of the current clinical practice tumor markers, CEA and CA19-9, has been demonstrated to be poor, especially for stratifying the early stages of CRC [28, 29], which was further confirmed in our study. Our data showed that CXCL-8 had better diagnostic sensitivity and accuracy than CEA and CA19-9 alone or together for CRC detection. Notably, our findings also indicated that the combined use of CXCL-8 with CEA or CA19-9 improved their individual performances for CRC diagnosis. Moreover, the AUC for CXCL-8 (0.920) was significantly higher than that in a previous report (0.778) [30], in which there were 59 patients with CRC and 46 healthy participants. Moreover, CA is precursors of most CRC, and it is difficult to make a differential diagnosis between patients with CRC and patients with CA [28]. Notably, we found for the first time that CXCL-8 had a better diagnostic sensitivity and accuracy CEA and CA19-9 alone or together in differentiating CRC from CA. Additionally, our results indicate that the combined use of CXCL-8 with CEA or CA19-9 improved their diagnostic value. Notably, like CEA, serum CXCL-8 levels were a significant risk factor for CRC occurrence. Therefore, we can speculate that serum CXCL-8 might be a better candidate as a tumor biochemical marker for the diagnosis of CRC than the routine clinical practice markers CEA and CA19-9.

Analysis of the relationship between serum CXCL-8 concentrations and clinicopathological features indicated that serum levels of CXCL-8 were significantly associated with distant metastasis and tumor size, which was further verified by Spearman's correlation test. Rubie et al. [31] also evaluated the association between serum CXCL-8 levels and the clinicopathological characteristics of CRC, and they found that CXCL-8 was highly overexpressed in CRC tissues, which correlated with the depth of tumor invasion and tumor size [32, 33]. These findings also indicate that serum CXCL-8 may be an additional prognostic biomarker for CRC.

However, this study had its limitations. First, this study had a single-center retrospective design that might have caused deviation toward subject selection and analysis. Moreover, we failed to obtain overall survival information for CRC; therefore, the correlation between serum CXCL-8 and overall survival for CRC was not assessed. Therefore, prospective multicenter studies with large sample sizes are required to assess the clinical utility of serum CXCL-8 levels for CRC diagnosis and its correlation with overall survival.

5. Conclusions

In summary, our results suggest that serum CXCL-8 may be a better biochemical tumor marker for CRC diagnosis than routine clinical blood-based markers or may be a suitable adjunct. Notably, we found a significant association between serum CXCL-8 levels and the clinicopathological features of patients with CRC, suggesting its use as a prognostic marker.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Zhengyuan Huang and Zhaozhong Li contributed equally to this work. Yingping Cao and Pingxia Lu are the corresponding authors that contributed equally to this work.

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