

## ORIGINAL ARTICLE

# Serum CEA and CA19-9 Levels are Associated with the Presence and Severity of Colorectal Neoplasia

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### SUMMARY

**Background:** High concentrations of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were found in the serum of patients with colon cancer. We performed the present work to investigate the association between elevated levels of serum biomarkers (CEA and CA19-9) and shortened survival in patients with colon cancer.

**Methods:** We examined patients who underwent colonoscopies between 2001 and 2014 and measured and analyzed the serum CEA and CA19-9 levels of 362 participants.

**Results:** Elevated CEA concentrations were found to be associated with advanced invasion, lymph node metastasis, and short survival. Elevated CA19-9 concentrations also were associated with lymph node metastasis and short survival.

**Conclusions:** Elevated serum CEA or CA19-9 levels were found to be associated with shortened survival. (Clin. Lab. 2018;64:xx-xx. DOI: 10.7754/Clin.Lab.2017.170914)

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#### KEY WORDS

colon cancer, carcinoembryonic antigen, CA19-9, survival

#### INTRODUCTION

Colorectal cancer (CC) is the fourth most common cause of cancer-related death worldwide, accounting for more than 1.2 million new cases every year [1]. The incidence of CC is rapidly increasing in Asia, especially in China in recent years [2-4]. There is a growing body of evidence supporting the use of novel biomarkers for early detection of colon cancer [5]. Several serum biomarkers have been found to be useful in the management of patients with cancer. (6) Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) have been extensively evaluated for their efficacy in the diagnosis and management of colon cancer [6].

CEA is used in clinical practice as a tumor-associated antigen for CC, which is why serum CEA is markedly upregulated in most CC patients [6,7]. CEA affects tumorigenesis by enhancing tumor cell survival and in-

ducing tumor angiogenesis [8]. Serum CEA is a good prognostic biomarker for monitoring the recurrence of CC after curative resection, and it can be administered preoperatively for assistance in staging, surgical planning, and predicting prognosis [9].

CA19-9 is an antigen defined by monoclonal antibody binding to CA19-9, the tumor surface marker [10]. Serum CA19-9 levels are elevated in individuals with gastrointestinal cancers, such as gastric cancer, and it also has been used as a tumor marker of CC in clinical practice, usually accompanied by CEA [11]. Several previous studies have shown that significantly higher concentrations of CEA or CA19-9 are found in CC tissue [12-14]. A few studies also have investigated the associations between circulating serum CEA or CA19-9 concentrations and colon cancer [15,16]. These studies, however, included small sample sizes of fewer than 200 subjects and have shown contradictory results [15-17]. The purpose of the current study was to determine whether elevated serum CEA and CA19-9 levels are associated with the presence of colon cancer and whether the levels of these antigens differ with patient survival.

## MATERIALS AND METHODS

The patients in the current study (n = 362) underwent surgical resection at the Department of General Surgery of Taizhou People's Hospital between January 2001 and June 2010 and were pathologically confirmed as having colon cancer. Their clinicopathological data were retrospectively analyzed. This study was approved by the research ethics committee of Taizhou People's Hospital.

### Serum CEA and CA19-9 detection

We centrifuged 2 mL serum from the patients with colon cancer for 10 minutes and then separated and stored the supernatant at -80°C. After the collection of samples, we rewarmed the samples at room temperature. We measured the concentrations of serum CEA and CA19-9 by electrochemiluminescence immunoassay. The kit was from Roche, and the reagents were used following the instructions. The principal instrument was a Roche electrochemical luminescence meter (Cobas 6000). All operations were performed in strict accordance with the instructions in the kit and instruments. Positive criteria: CEA > 5.0 ng/mL, CA19-9 > 35.0 U/mL.

### Statistical analysis

Data are expressed as frequency (%). We compared the prevalence of colorectal lesions between subjects with normal and abnormal ranges of serum CEA and CA19-9 using chi-squared analysis. We performed multivariate logistic regression analysis to determine whether abnormal levels of serum CEA and CA19-9 were independently associated with a higher risk of overall CC. We estimated the adjusted odds ratio (AOR) with 95% confidence intervals (CIs) for the association of abnormal

levels of serum CEA and CA19-9 with the presence of overall CC after adjusting for potential confounding variables such as age, gender, invasion (T), and lymph node metastasis (LNM).

p-values < 0.05 were considered indicative of statistical significance. SPSS Version 21 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

## RESULTS

### Patient demographics

We reviewed records of 362 patients who had been diagnosed with CC, of whom 316 had advanced disease (T3+4). Their median follow-up period was 60 months. In this study, 57.2% of the patients were men (207/362), 39.22% (142/362) had elevated preoperative serum CEA levels, 15.47% (56/362) had elevated preoperative serum CA19-9 levels, and 43.37% (157/362) had elevated preoperative serum CEA + CA19-9 levels (Table 1 - 3).

### Factors that correlated with CEA and CA19-9 level

Invasion/T stages (T1+2 vs. T3+4, p = 0.017) and LNM (p = 0.006) were associated with CEA ( $X^2$  analysis, Table 1). LNM (p = 0.008) was associated with CA19-9 (Table 1 - 3).

### Factors correlated with overall survival

In univariate analysis, CEA (p = 0.000, OR = 2.668, 95% confidence interval [CI]: 1.877 - 3.862), CA19-9 (p = 0.000, OR = 2.532, CI: 1.871 - 3.782), LNM (p = 0.000, OR = 2.026, CI: 1.610 - 2.551), and invasion (p = 0.011, OR = 1.493, CI: 1.097 - 2.033) were associated with OS (Table 4).

Also, as shown in Table 3, CEA (p = 0.000, OR = 2.208, CI: 1.515 - 3.217), CA19-9 (p = 0.037, OR = 1.583, CI: 1.029 - 2.437), and LNM (p = 0.000, OR = 1.875, CI: 1.462 - 2.404) continued to be associated with OS by multivariate analyses (Table 5). CC patients who had high CEA levels, high CA19-9 levels, or deep invasion had a greater risk of death than those who had low CEA levels, low CA19-9, and early invasion.

Kaplan-Meier curves and log rank tests further showed patients with high CEA to have shorter mean OS (low CEA: 104.995 months, high CEA: 82.463 months, p < 0.05; Figure 1A) compared with patients with CA19-9 (low: 114.196 months; high: 57.438 months; Figure 1B), CEA + CA19-9 (high: 73.19 months; low: 115.26 months; Figure 1C).

## DISCUSSION

Colon cancer is a common type of malignant tumor. Its incidence in southern China, especially in the southeast coastal areas, is significantly higher than in northern China. Because of changes in patient habits, the environment, and patient diet, the current incidence of colon

**Table 1. Relationship between CEA expressions in CC patients and their clinical pathological features.**

Clinical parameter		CEA		P
		0	1	
Tumor size	≥ 5	120	78	0.943
	< 5	100	64	
Lymph node metastasis	N0	137	63	0.006
	N1	65	61	
	N2	17	18	
	N3	1	0	
Invasion	T1	2	3	0.017
	T2	34	7	
	T3	135	97	
	T4	49	35	
Gender	Female	91	64	0.486
	Male	129	78	
Age	< 60	104	53	0.062
	≥ 60	116	89	

**Table 2. Relationship between CA19-9 expressions in CC patients and their clinical pathological features.**

Clinical parameter		CA19-9		P
		0	1	
Tumor size	≥ 5	170	28	0.443
	< 5	136	28	
Lymph node metastasis	N0	178	22	0.008
	N1	101	25	
	N2	27	8	
	N3	0	1	
Invasion	T1	4	1	0.095
	T2	40	1	
	T3	194	38	
	T4	68	16	
Gender	Female	127	28	0.237
	Male	179	28	
Age	< 60	133	24	0.933
	≥ 60	173	32	

cancer in China has increased significantly. The onset of colon cancer is often difficult to see. The patient may develop bloody stools or may gradually develop diarrhea and constipation, as the cancer reaches the late stage; hence, there is a need for early diagnosis and treatment [16].

Methods of diagnosing colon cancer mainly include fecal occult blood testing, imaging, and endoscopy. With

the development of the field of molecular biology, our available knowledge regarding tumor markers has developed rapidly. These developments made the present serological examination of patients with colon cancer possible. Some common serum markers for the detection of CC are CEA and CA19-9. CEA is an acidic glycoprotein that is isolated from colonic adenocarcinoma and embryonic colonic mucosa. It is relatively com-

Table 3. Relationship between CEA + CA19-9 expressions in CC patients and their clinical pathological features.

Clinical parameter		CEA + CA19-9		P
		0	1	
Tumor size	≥ 5	116	82	0.409
	< 5	89	75	
Lymph node metastasis	N0	130	70	0.003
	N1	60	66	
	N2	15	20	
	N3	0	1	
Invasion	T1	2	3	0.011
	T2	33	8	
	T3	126	106	
	T4	44	40	
Gender	Female	84	71	0.418
	Male	121	86	
Age	< 60	99	58	0.031
	≥ 60	106	99	

Table 4. Cox univariate regression models for prediction of overall survival.

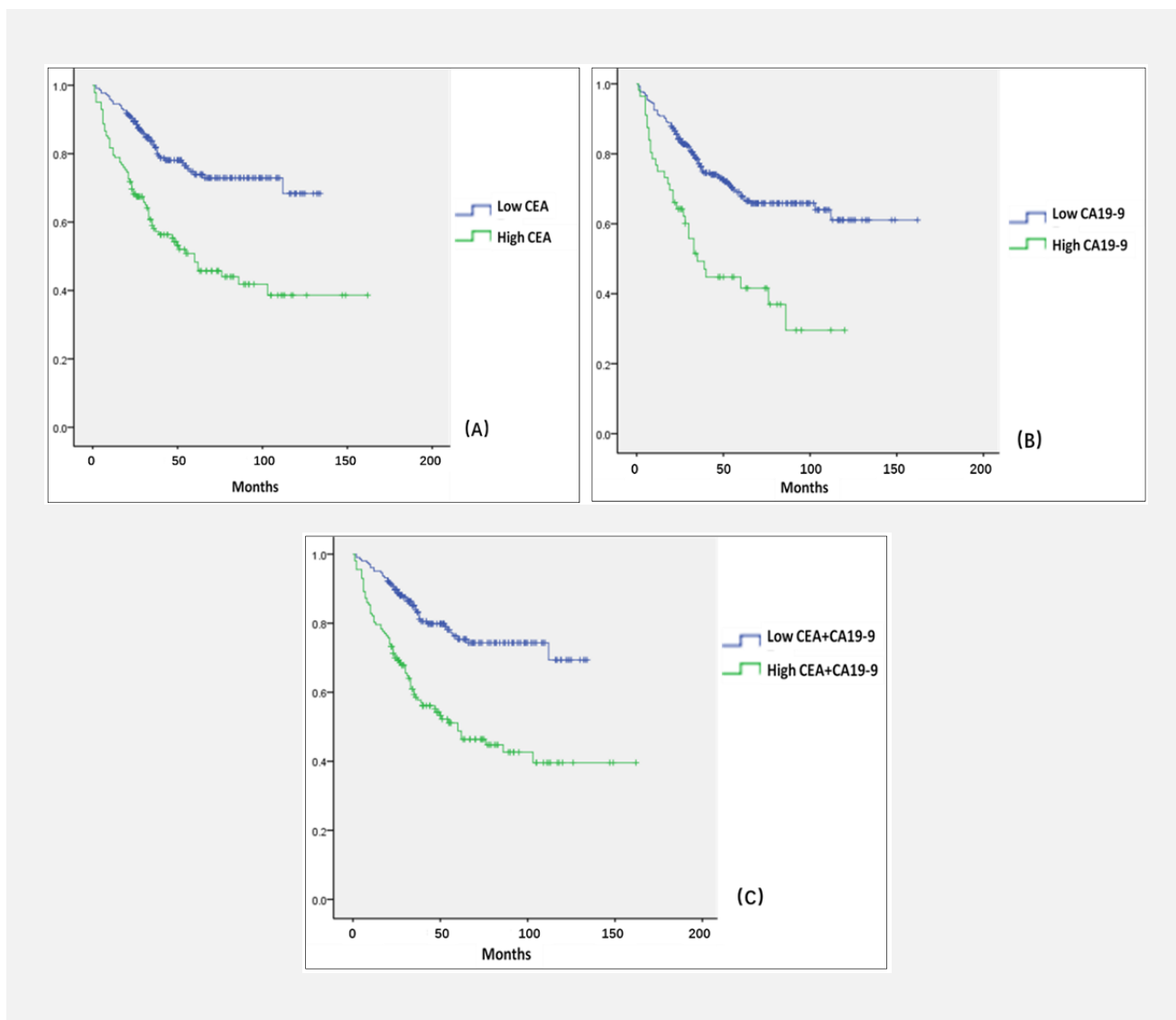
	B	SE	Wald	df	Sig	Exp (B)	95.0% CI Exp (B)	
							Down	Up
CEA	0.989	0.185	28.619	1	0.000	2.688	1.871	3.862
CA19-9	0.925	0.207	20.055	1	0.000	2.523	1.683	3.782
LNМ	0.706	0.117	36.149	1	0.000	2.026	1.610	2.551
Invasion	0.401	0.157	6.481	1	0.011	1.493	1.097	2.033
Tumor size	-0.147	0.184	0.638	1	0.425	0.863	0.602	1.238
Gender	0.136	0.187	0.530	1	0.466	1.146	0.795	1.651
Age	0.152	0.185	0.672	1	0.412	1.164	0.810	1.674

Abbreviations: B - Regression coefficient estimates, SE - standard error of estimates, Wald - Wald test - statistical probability value, df - degrees of freedom, Sig - significance level p, Exp (B) - effect estimates, 95.0% CI Exp (B) - 95% confidence interval effect estimates.

Table 5. Cox multivariate regression models for prediction of overall survival.

	B	SE	Wald	df	Sig	Exp (B)	95.0% CI Exp (B)	
							Down	Up
CEA	0.792	0.192	16.990	1	0.000	2.208	1.515	3.217
CA19-9	0.460	0.220	4.364	1	0.037	1.583	1.029	2.437
LNМ	0.628	0.127	24.505	1	0.000	1.875	1.462	2.404
Invasion	0.258	0.168	2.375	1	0.123	1.295	0.932	1.799
Tumor size	-0.109	0.188	0.341	1	0.559	0.896	0.621	1.294
Gender	0.308	0.189	2.659	1	0.103	1.361	0.940	1.971
Age	0.208	0.188	1.222	1	0.269	1.231	0.851	1.780

Abbreviations: B - Regression coefficient estimates, SE - standard error of estimates, Wald - Wald test - statistical probability value, df - degrees of freedom, Sig - significance level p, Exp (B) - effect estimates, 95.0% CI Exp (B) - 95% confidence interval effect estimates.



**Figure 1. Kaplan-Meier survival curves and log rank test results for levels of CEA, CA19-9, and CEA+CA19-9.**

**A - Mean overall survival (OS) (months) for colon cancer (CC) patients with high CEA was significantly shorter than that of CC patients with low CEA ( $p < 0.05$ ), B - Mean OS (months) for CC patients with high CA19-9 was significantly shorter than for CC patients with low CA19-9 ( $p < 0.05$ ). C - Mean OS (months) for CC patients with high CEA + CA19-9 was significantly shorter than for CC patients with low CEA + CA19-9 ( $p < 0.05$ ).**

mon in clinical applications. CA19-9 is an oligosaccharide-related antigen isolated from colon cancer cell lines. It shows elevated expression in a variety of cancers, such as colorectal, pancreatic, and hepatobiliary [17].

Surgery is the first-choice treatment for colon cancer, for which the cure rate can exceed 80%. The prognosis of colon cancer is worse upon deep tumor invasion and lymph node metastasis. At present, many clinical indicators of patient survival are not pronounced enough to be useful during prognosis. There may be cross-duplication between some indicators, which not only wastes medical resources but also may affect the prognosis

[18]. The survival rate of CEA-positive patients was significantly lower than that of CEA-negative patients, as indicated using the Kaplan-Meier method. The survival rate of CA19-9-positive patients was significantly lower than that of CA19-9-negative patients ( $p < 0.05$ ), which indicated that the survival rate of the colon cancer patients was within a reasonable range. By detecting serum CEA and CA19-9 levels, prognosis can be judged in advance of surgery.

The results of single-factor Cox proportional hazards model showed that CEA-positive and CA19-9-positive scores were significantly closely correlated with colon cancer patient survival ( $p < 0.05$ ). A multivariate Cox

proportional hazards model showed CEA-positive scores, CA19-9-positive scores, and lymph node metastases were the main independent risk factors ( $p < 0.05$ ).

### CONCLUSION

Elevated serum CEA was significantly correlated with lymph node metastasis and invasion. We found elevated serum CA19-9 levels to be significantly correlated with lymph node metastasis. Co-presentation of elevated serum CEA or CA19-9 levels were significantly closely correlated with age, lymph node metastasis, and invasion. Our data from multivariate Cox regression analyses showed high CEA, CA19-9, and lymph node metastasis to be independent predictors of shorter survival in patients with CC.

### Declaration of Interest:

The authors declare that they have no conflicts of interest.

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