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Original Article

Combined detection of preoperative serum CEA, CA19-9 and CA242 improve prognostic prediction of surgically treated colorectal cancer patients

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Abstract: We assessed the prognostic significance of preoperative serum carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and carbohydrate antigen 242 (CA242) levels in surgically treated colorectal cancer patients. The relationship of preoperative serum CEA, CA19-9 and CA242 levels with disease characteristics was investigated in 310 patients. Correlation between tumor markers was investigated using Pearson correlation test. Univariate and multivariate survival analyses were used to study the relationship between preoperative tumor markers and prognosis [disease free survival (DFS) and overall survival (OS)]. Kaplan-Meier analysis with log rank test was used to assess the impact of tumor marker levels on survival. Positive rate of preoperative serum CEA, CA19-9 and CA242 were 54.84%, 47.42% and 37.10%, respectively. High preoperative CEA level was associated with tumor size (P = 0.038), T stage (P < 0.001) and AJCC stage (P = 0.002). High preoperative CA19-9 level was associated with tumor AJCC stage (P = 0.023). Preoperative CA242 positively correlated with CEA (P < 0.001) and CA19-9 (P < 0.001). Combining the three markers was of independent prognostic value in CRC (HR = 2.532, 95% CI: 1.400-4.579, P = 0.002 for OS; and HR = 2.366, 95% CI: 1.334-4.196, P = 0.003 for DFS). Combined detection of preoperative serum CEA, CA19-9 and CA242 is of independent prognostic value for management of CRC patients treated surgically.

Keywords: Carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 242, prognosis, colorectal cancer

Introduction

Colorectal cancer (CRC) represents the third most common and the third most lethal cancer in the world [1]. In 2012, more than 1,360,600 individuals were diagnosed with colorectal cancer and almost 693,900 died from this malignancy worldwide [2]. Despite advances in surgical and adjuvant therapy, the long-term survival of this disease was not satisfactory because of tumor recurrence and metastasis [3]. Classification of high- and low-risk patients with colorectal cancer requires a different strategy. Early intervention is more conducive to successful treatment. Preoperative assessment and classification of patient outcomes is of great clinical significance.

Serological tumor markers play an important role in the diagnosis, monitoring, prognosis and even treatment of many cancers [4, 5]. Serum tumor markers are non-invasive, low-cost, popular and convenient tools for widespread clinical application. In colorectal cancer, serum tumor assays are valuable adjuncts to clinical examination in preoperative assessment and postoperative monitoring of patients [6].

Carcinoembryonic antigen (CEA), first introduced as a tumor-associated serum biomarker by Gold and Freedman in 1965, was the most widely used tumor marker [7]. CEA occurs in malignant tissue especially gastrointestinal carcinomas, benign disease and also in normal healthy individuals. Due to low sensitivity and specificity, CEA is of no value in colorectal can-

cer screening [8]. Although CEA is related to poor outcome of CRC patients [9], its role as an independent prognostic factor for CRC is controversial. Some studies showed that preoperative CEA is an independent predictor of survival, whereas others reported adverse conclusions [10-12]. Carbohydrate antigen 19-9 (CA19-9) was an isolated Lewis antigen of the MUC1 protein, extracted from colon cancer cell line SW1116 in 1979 [13]. CA19-9 was used in the diagnosis and prognosis of pancreatic cancer, colorectal cancer, gastric cancer and other gastrointestinal tumors [14-16]. Compared with CEA, CA19-9 is a less sensitive marker in colorectal cancer and is often used in combination with CEA to manage CRC patients. Carbohydrate antigen 242 (CA242), first defined in 1983, was obtained by immunizing mice with a human colorectal carcinoma cell line COLO 205 and fusion with the Sp 2/0 mouse myeloma cell line [17]. A meta-analysis revealed that serum CA242 played an important role in the diagnosis of pancreatic cancer [18]. Recent studies showed that CA242 was a prognostic factor in colorectal cancer [19]. The purpose of the present investigation was to assess the significance of preoperative serum tumor markers CEA, CA19-9 and CA242 in predicting outcome [disease-free survival (DFS) and overall survival (OS)] of surgically treated CRC patients. The results showed that the combined preoperative CEA, CA19-9 and CA242 was an independent prognostic factor and improved the prognostic value in patients with colorectal cancer after surgery.

Materials and methods

Patients and inclusion criteria

This retrospective study enrolled 310 patients admitted to Department of General Surgery, First People's Hospital, Shanghai Jiao Tong University from January 2003 to December 2010 and was approved by the Institutional Review Boards of Shanghai Jiao Tong University Affiliated Shanghai First People's Hospital Medical Center. All patients received tumor resection in this hospital under the same surgical team and provided informed consents in advance. The inclusion criteria were: (i) Patients received curative tumor resection, (ii) Tumor histopathology indicated colorectal adenocarcinoma, (iii) Patients had not received any chemotherapy or radiotherapy before surgery, (iv) Preoperative serum was available and CEA, CA19-9 and CA242 levels were detected, (v) Patients were available for follow-up. The clinicopathological features and staging were determined according to the American Joint Committee on Cancer TNM (AJCC) classification guidelines [20].

Serum CEA, CA19-9, and CA242 level evaluation

A total of 5 ml fasting peripheral venous blood was obtained from each patient the day before surgery. Using C12 protein biochip system (Shanghai Health-Digit Co, Ltd, China), the serum levels of CEA, CA19-9 and CA242 were detected [21-23]. According to the manufacturer's instructions, the cutoff values for CEA, CA19-9 and CA242 were 5 ng/ml, 35 U/ml and 20 U/ml, respectively, and a value lower than the cutoff was considered negative.

Follow-up

All patients were followed up at 3-month intervals for the first 2 years, and then at 6-month intervals thereafter. Follow-up evaluation included patient's history, physical examination, laboratory test, ultrasonic inspection, X-rays and computed tomography (CT) as needed. The last follow-up was performed in January 2014 via telephone, with a median follow-up time of 71 months (range, 37-129 months). Overall survival (OS) was determined from the time of surgery to death from CRC or to the last follow-up time. Disease-free survival (DFS) was defined as the time from surgery until tumor recurrence (local or metastatic) or death due to CRC.

Statistical analysis

The IBM SPSS version 20.0 software for Windows (IBM, Armonk, NY, USA) was used for data analysis. The precise level of tumor markers were expressed as median, mean and range value. Relationship between serum tumor markers and CRC clinicopathological variables was determined using Pearson's Chi-square test or Fisher exact test. Pearson correlation analysis was used in correlation analysis of CEA, CA19-9 and CA242. Survival curves were plotted using Kaplan-Meier method and analyzed by log rank test. The Cox proportional hazards model was performed for univariate and

Table 1. Characteristic of 310 colorectal cancer patients

Variable	n	CEA- (n = 140)	CEA+ (n = 170)	*P*-value	CA19-9- (n = 163)	CA19-9+ (n = 147)	*P*-value	CA242- (n = 195)	CA242+ (n = 115)	*P*-value
Age (year)										
< 65	138	71	67	0.051	81	57	0.067	94	44	0.098
≥ 65	172	69	103		82	90		101	71	
Sex										
Male	152	61	91	0.088	83	69	0.497	99	53	0.481
Female	158	79	79		80	78		96	62	
Location										
Colon	176	76	100	0.490	89	87	0.424	109	67	0.723
Rectum	134	64	70		74	60		86	48	
Size (cm)										
< 5	174	88	86	0.038*	88	86	0.492	105	69	0.343
≥ 5	136	52	84		75	61		90	46	
T stage										
T1	20	12	8	< 0.001*	14	6	0.164	15	5	0.384
T2	58	39	19		35	23		39	19	
T3	166	68	98		83	83		104	62	
T4	66	21	45		31	35		37	29	
N stage										
N0	191	88	103	0.906	108	83	0.111	125	66	0.400
N1	86	38	48		37	49		49	37	
N2	33	14	19		18	15		21	12	
AJCC stage										
I	64	41	23	0.002*	43	21	0.023*	46	18	0.214
II	127	47	80		65	62		79	48	
III	119	52	67		55	64		70	49	
Differentiation										
Well	51	26	25	0.648	26	25	0.182	33	18	0.628
Moderate	190	83	107		107	83		122	68	
Poor	69	31	38		30	39		40	29	

*$P < 0.05$.

multivariate analyses of OS and DFS. The confidence intervals (CIs) were set at 95% and a *P*-value of < 0.05 (two-sided) was considered statistically significant.

Results

Patient demographics

From January 2003 to December 2010, 2825 CRC patients received surgical resection in our medical center. Based on our strict inclusion criteria, 310 patients were enrolled in our retrospective study finally. Of these, 152 patients were men (49.0%) and 158 patients were women (51.0%). The median age was 65.90 years (range: 24-89 years). Distribution of the patients based on the American Joint Committee on Cancer TNM classification (AJCC) by stage of the primary CRC was as follows: 64 (20.6%) with stage I disease, 127 (41.0%) with stage II disease and 119 (38.4%) with stage III disease (**Table 1**).

Correlation between tumor markers and clinicopathological variables

The median preoperative CEA, CA19-9 and CA242 levels were 5.08 ng/ml (mean, 17.56; range, 0.20-1171.11), 11.08 U/ml (mean, 32.46; range, 0.60-555.22) and 12.36 U/ml (mean, 21.53; range, 0.10-200.00), respective-

Table 2. Correlation between tumor markers CEA, CA19-9 and CA242

	CEA	CA19-9	CA242
CEA			
Pearson correlation	1	0.072	0.368**
significance (two-tailed)		0.208	0.000
N	310	310	310
CA19-9			
Pearson correlation	0.072	1	0.612**
significance (two-tailed)	0.208		0.000
N	310	310	310
CA242			
Pearson correlation	0.368**	0.612**	1
significance (two-tailed)	0.000	0.000	
N	310	310	310

**Significant at level of P = 0.01 (two-tailed).

ly. Of the 310 patients, 170 (54.84%) showed positive preoperative serum CEA levels (≥ 5 ng/ml), 147 (47.42%) contained positive preoperative serum CA19-9 levels (≥ 35 U/ml) and 115 (37.10%) manifested high positive preoperative serum CA242 levels (≥ 20 U/ml) (**Table 1**). The positive rate for CEA, CA19-9 and CA242 was 54.84%, 47.42% and 37.10%, respectively. Positive serum CEA levels significantly correlated with tumor size (P = 0.038), T stage (P < 0.001) and AJCC stage (P = 0.002). Positive preoperative serum CA19-9 levels were significantly correlated with AJCC stage (P = 0.023).

Correlation between tumor markers

Pearson Correlation revealed that CEA was positively correlated with CA242 (P < 0.001, r = 0.368), but not with CA19-9 (P = 0.208, r = 0.072) while CA19-9 positively correlated with CA242 (P < 0.001, r = 0.612). Additional statistics is presented in **Table 2**.

Combined detection of CEA, CA19-9 and CA242

The combined effect was assessed by considering the combined value as negative when all the three markers were negative, otherwise rated as positive. The combination of the three biomarkers increased positive rate from 54.84% to 71.61%. Combined detection of the three markers appeared to be significantly correlated with patient age (P = 0.006), T stage (P < 0.001) and AJCC stage (P = 0.001) (**Table 3**).

Survival and tumor markers

Kaplan-Meier survival analysis was based on different preoperative serum CEA, CA19-9 and CA242 levels. Log rank test was used to evaluate their significance in OS and DFS. Compared with low serum levels, high levels of serum CEA, CA19-9 CA242 and combined markers appear to have decreased the OS (P = 0.027, 0.031, 0.002 and 0.001, respectively) (**Figure 1A-D**). Compared with low serum levels, high levels of serum CEA, CA19-9, CA242 and combined markers appear to have decreased the DFS (P=0.002, 0.002, 0.002 and 0.001, respectively) (**Figure 2A-D**).

Univariate and multivariate analysis of OS and DFS

We performed Cox proportional hazards regression analysis to determine the prognostic value of clinicopathological factors including preoperative tumor markers. We first studied preoperative tumor markers individually, and then simultaneously. Factors that showed prognostic significance (P < 0.05) in the univariate analysis were included in the multivariate analysis.

In univariate analysis, tumor size, N stage, AJCC stage, differentiation, CEA level, CA19-9 level, CA242 level and the combined markers showed significant association with OS (P = 0.007, P = 0.001, P =0.016, P = 0.001, P = 0.001, P = 0.002, P = 0.001 and P = 0.002, respectively) (**Table 4**). In multivariate analysis, only tumor size, N stage, differentiation and the three markers combined, were independent prognostic factors (HR 1.634, 95% CI 1.065-2.507, P = 0.024; HR 1.528, 95% CI 1.163-2.007, P=0.002; HR 2.129, 95% CI 1.488-3.046, P < 0.001 and HR 2.532, 95% CI 1.400-4.579, P = 0.002, respectively) (**Table 4**).

Univariate analysis of tumor size, T stage, N stage, differentiation, CEA level, CA19-9 level, CA242 level and the combined three markers showed significant association with DFS (P = 0.004, P = 0.037, P = 0.001, P = 0.002, P = 0.003, P = 0.003, P = 0.002 and P = 0.002, respectively) (**Table 4**). Multivariate analysis revealed only tumor size, N stage, differentiation and the three markers were independent prognostic factors (HR 1.696, 95% CI 1.113-2.584, P = 0.014; HR 1.514, 95% CI 1.518-1.978, P = 0.002; HR 2.302, 95% CI 1.429-

Table 3. Correlation between clinicopathologic factors and combined tumor markers

Variable	n	Combined 3 markers		*P*-value
		Negative	Positive	
Sum	310			
Age (year)				
< 65	138	50	88	0.006*
≥ 65	172	38	134	
Sex				
Male	152	37	115	0.121
Female	158	51	107	
Location				
Colon	176	47	129	0.451
Rectum	134	41	93	
Size (cm)				
< 5	174	53	121	0.360
≥ 5	136	35	101	
T stage				
T1	20	10	10	< 0.001*
T2	58	25	33	
T3	166	46	120	
T4	66	7	59	
N stage				
N0	191	91	130	0.113
N1	86	22	64	
N2	33	5	28	
AJCC stage				
I	64	30	34	0.001*
II	127	31	96	
III	129	27	92	
Differentiation				
Well	51	14	37	0.983
Moderate	190	54	136	
Poor	69	20	49	

*P < 0.05.

2.889, P < 0.001 and HR 2.366, 95% CI 1.334-4.196, P = 0.003 respectively) (**Table 4**).

Discussion

The American Joint Cancer Commission/tumor-node-metastasis (AJCC/TNM) classification is widely used as a guideline for staging and represents the best prognostic indicator of outcomes in colorectal cancer patients [20, 24]. Histopathological types are also reported to predict the outcome of CRC patients [25]. In clinical practice, accurate AJCC TNM staging and histopathological analysis depend on postoperative pathological detection and diagnosis, which is the gold standard for cancer diagnosis. However, serum tumor markers are easily detected presurgically. Serum CEA, CA19-9 and CA242 are now widely used as tumor markers for both prognostic prediction and post-treatment surveillance of patients with colorectal cancer. Recent studies have focused on the prognostic value of serum tumor markers in CRC [26, 27]. However, they usually focused on only one or two markers on special stage CRC patients or their sample sizes were small. To the best of our knowledge, limited work has been conducted to simultaneously investigate the prognostic value of multiple preoperative tumor markers in CRC patients.

Our findings indicate that CRC patients with larger tumor size (> 5 cm) tend to have high serum CEA levels. Kirat HT et al reported that a preoperative CEA level greater than 5 ng/ml correlated with bigger tumor size in colon cancer [28]. In gastric cancer, high preoperative CEA and CA19-9 levels correlated with bigger tumor size [29]. The interaction between CEA and tumor bulk may explain our observations. Tumor markers are produced by tumor cells following abnormal oncogene expression. Greater tumor size implied higher number of tumor cells suggesting a potential correlation between CEA levels and tumor mass.

The influence of tumor histological grade on plasma CEA levels has been controversial with some reports showing moderately differentiated tumors associated with higher serum CEA levels compared with poorly differentiated and well-differentiated tumors [30, 31]. Studies showed poorly differentiated tumors contained the highest serum CEA level [32]. Other studies reported well-differentiated carcinomas with the highest level of CEA [33, 34]. Our results suggested no significant differences between histologically differentiated colorectal tumors, consistent with some studies [35, 36]. Multicenter studies with larger sample sizes are needed to resolve this controversy.

Consistent with other studies [19, 37-39], our findings confirm that high levels of preoperative CEA and CA19-9 markers were associated with advanced tumors including T and AJCC stages. Tumor staging is the best prognostic indicator of outcome in colorectal cancer. However, a few patients with similar pathologic stages may dis-

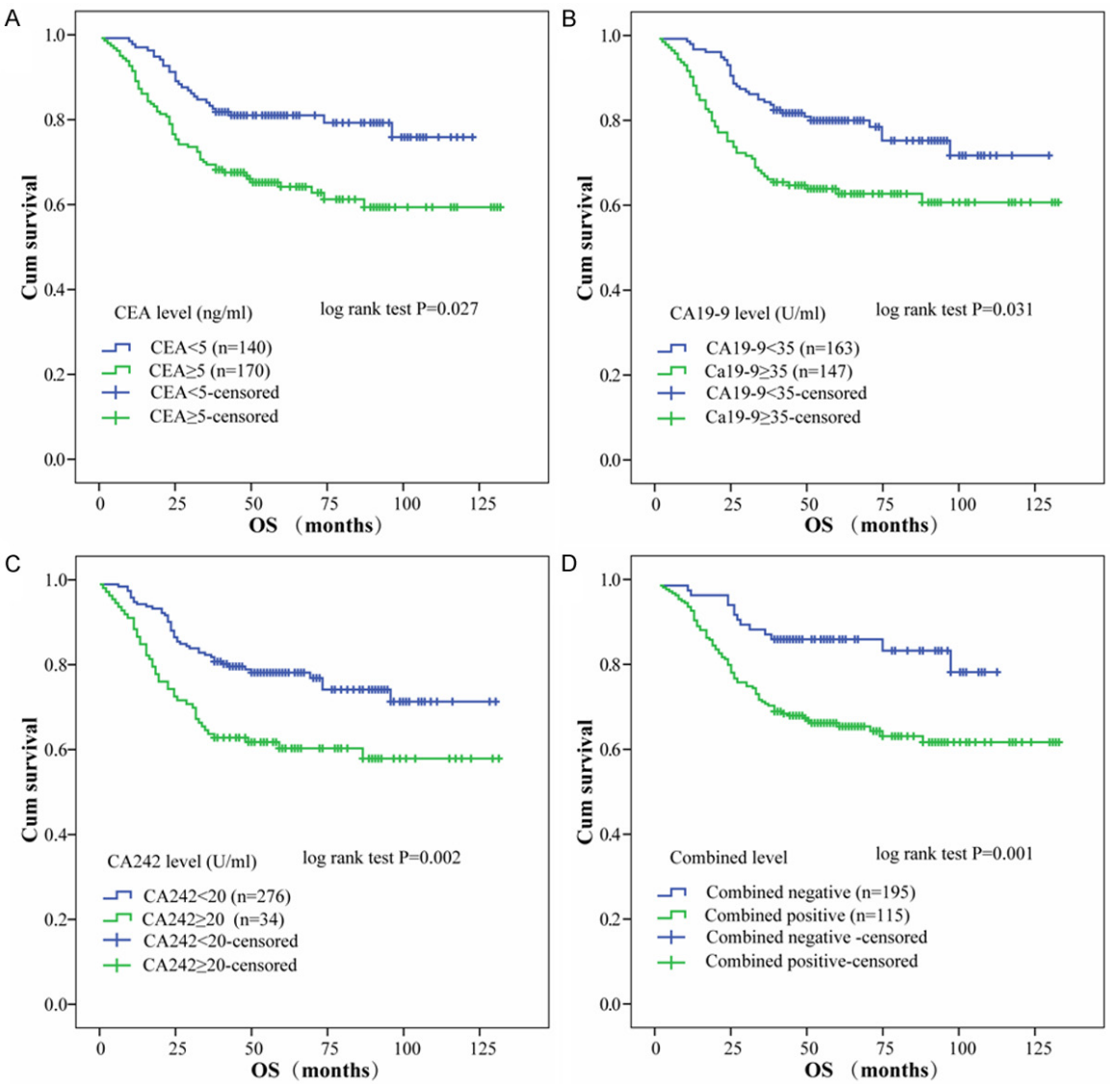

Figure 1. Kaplan-Meier survival curves depicting outcomes according to the level of preoperative CEA, CA19-9 and CA242 levels. A. Preoperative CEA levels with overall survival; B. Preoperative CA19-9 levels with overall survival; C. Preoperative CA242 levels with overall survival; D. Combined Preoperative CEA, CA19-9 and CA242 levels with overall survival.

play considerable variation in clinical outcomes. Therefore, prognostic factors that are independent of tumor stage and capable of identifying patients with different clinical outcomes for further treatment are desirable. We found that the expression of CEA, CA19-9 and CA242 was associated with advanced disease and poorer survival. The prognosis was poorer in patients with CEA more than 5 ng/ml. Similar results were obtained in CRC patients with higher CA19-9 and CA242 levels. Interestingly, although high CEA, CA19-9 and CA242 levels were associated with poorer outcome, none of them was an independent prognostic biomarker according to our study. Multivariate analysis revealed that combined detection of these three serum tumor markers was an independent prognostic indicator.

In our study, the positive rates for CEA, CA19-9 and CA242 were 54.84%, 47.42% and 37.10%, respectively. Studies have reported widely varying rates of these markers, for example, 20.67%-82.22% for CEA [14, 28, 40-42] probably due to different sample volumes, detection assays and cut-off values used. The CA242

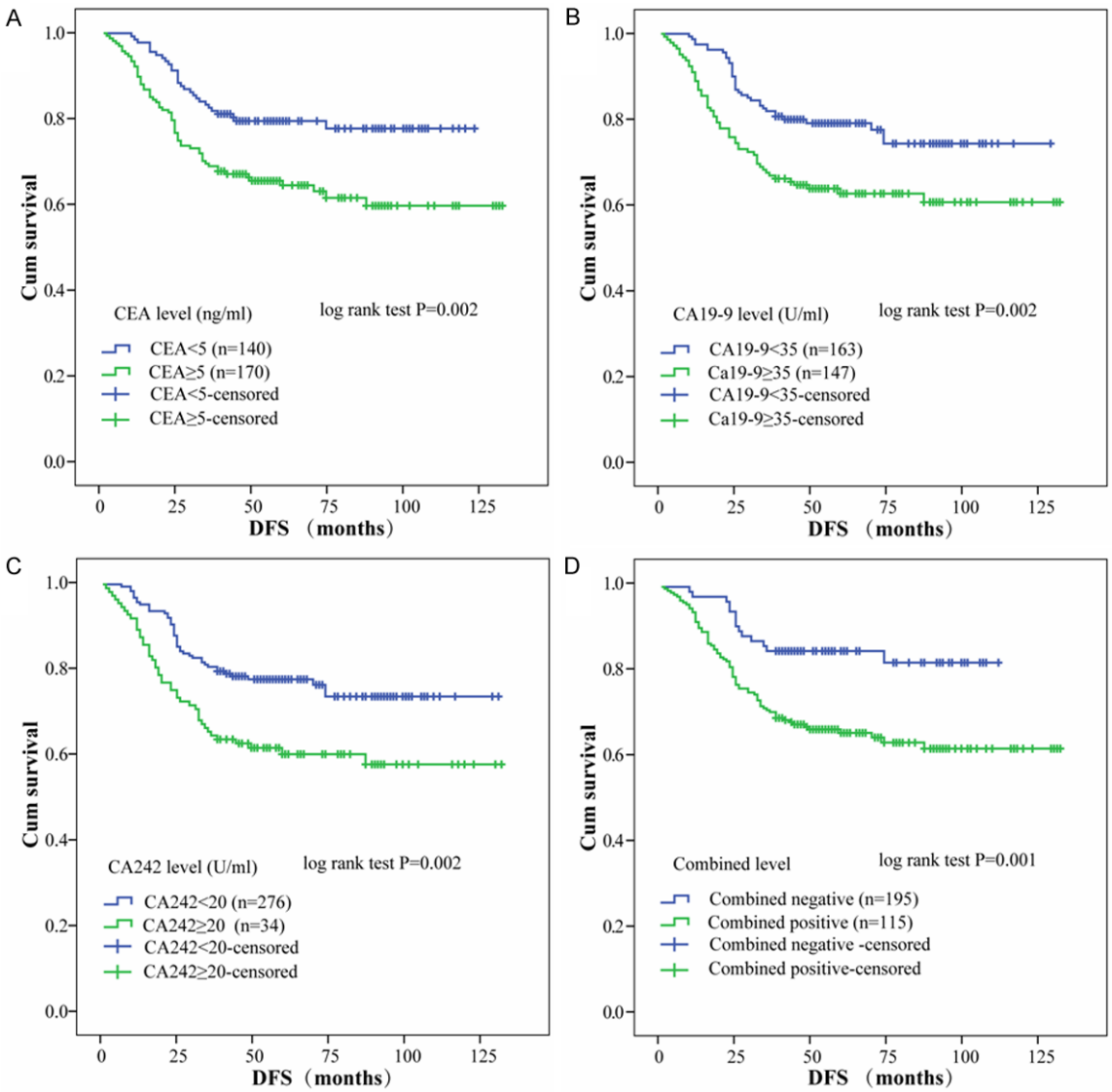

Figure 2. Kaplan-Meier survival curves depicting outcomes according to the level of preoperative CEA, CA19-9 and CA242 levels. A. Preoperative CEA levels with disease free survival; B. Preoperative CA19-9 levels with disease free survival; C. Preoperative CA242 levels with disease free survival; D. Combined Preoperative CEA, CA19-9 and CA242 levels with disease free survival.

level was highly consistent with CA19-9 in diagnosis and prognosis of CRC [39]. Our study confirms that CA242 not only correlated with CA19-9 but also CEA. Studies have indicated that the combined detection of tumor markers may improve diagnostic value and prognostic significance compared with single tumor marker. Combining the three markers yielded a positive rate of 71.61% suggesting that the combination of these markers maybe preferable to single tumor marker in improving diagnostic accuracy.

In 2007, the European Group on Tumor Markers (EGTM) published evidence-based clinical practice guidelines for the use of tumor markers in CRC [43]. CEA has been recommended for prognostic surveillance following curative resection and monitoring of therapeutic response in advanced disease. However, the EGTM guidelines found insufficient data to recommend the popular tumor markers comprising CEA, CA19-9 and CA242 for screening, diagnosis, staging, surveillance, or therapeutic monitoring of patients with CRC. Our study indicated that a com-

Table 4. Univariate and multivariate analysis of overall survival and disease free survival

Variable	OS				DFS			
	Univariate HR (95% CI)	*P*-value	Mutivariate HR (95% CI)	*P*-value	Univariate HR (95% CI)	*P*-value	Mutivariate HR (95% CI)	*P*-value
Age								
< 65	1	0.053			1	0.070		
≥ 65	1.543 (0.995-2.393)				1.486 (0.968-2.281)			
Sex								
Male	1	0.114			1	0.085		
Female	0.710 (0.465-1.085)				0.693 (0.457-1.052)			
Location								
Colon	1	0.660			1	0.762		
Rectum	0.909 (0.593-1.392)				0.937 (0.617-1.425)			
Size								
< 5 cm	1	0.007*	1.634 (1.065-2.507)	0.024*	1	0.004*	1.696 (1.113-2.584)	0.014*
≥ 5 cm	1.789 (1.169-2.738)				1.852 (1.218-2.815)			
T stage								
T1	1	0.053			1	0.037*	1.129 (0.781-1.631)	0.520
T2	1.795 (0.393-8.193)				1.801 (0.395-8.221)			
T3	3.578 (0.872-14.692)				3.855 (0.940-15.807)			
T4	3.962 (0.934-16.809)				4.009 (0.945-17.007)			
N stage								
N0	1	0.001*	1.528 (1,163-2.007)	0.002*	1	0.001*	1.514 (1.158-1.978)	0.002*
N1	1.324 (0.810-2.164)				1.413 (0.877-2.277)			
N2	2.881 (1.663-4.991)				2.805 (1.622-4.850)			
AJCC stage								
I	1	0.016*	1.027 (0.611-1.726)	0.919	1	0.009*	1.004 (0.529-1.904)	0.991
II	1.824 (0.901-3.692)				1.906 (0.944-3.849)			
III	2.627 (1.320-5.229)				2.796 (1.409-5.548)			
Differentiation								
Well	1	0.001*	2.129 (1.488-3.046)	< 0.001*	1	0.002*	2.032 (1.429-2.889)	< 0.001*
Moderate	3.948 (1.429-10.910)				3.224 (1.290-8.054)			
Poor	6.360 (2.239-18.061)				5.165 (2.003-13.317)			
CEA (Negative vs. Positive)	2.099 (1.332-3.307)	0.001*	1.460 (0.798-2.670)	0.219	1.968 (1.264-3.062)	0.003*	1.358 (0.754-2.445)	0.308
CA19-9 (Negative vs. Positive)	1.997 (1.298-3.073)	0.002*	1.139 (0.509-2.549)	0.751	1.902 (1247-2.900)	0.003*	1.088 (0.485-2.441)	0.837
CA242 (Negative vs. Positive)	1.984 (1.303-3.021)	0.001*	1.523 (0.741-3.131)	0.253	1.918 (1.269-2.900)	0.002*	1.539 (0.748-3.165)	0.242
Combined 3 markers (Negative vs. Positive)	2.599 (1.441-4.688)	0.002*	2.532 (1.400-4.579	0.002*	2.446 (1.383-4,326)	0.002*	2.366 (1.334-4.196)	0.003*

*P < 0.05.

bination of CEA, CA19-9 and CA242 improved diagnostic sensitivity of CRC from 54.84% to 71.61%. Combined analysis of preoperative CEA, CA19-9 and CA242 enables classification of patients into groups with distinct survival probabilities and the best prognostic significance in colorectal cancer after surgery. These data imply that a combined detection of tumor markers might be a more efficient strategy in clinical practice.

Our study is limited by its retrospective nature and single-center design. We also failed to stratify patients on the basis of different postoperative treatments such as chemotherapy, radiotherapy and other adjuvant therapies, which affect patient outcomes. Multi-center, high-quality, stratified and prospective studies including postoperative treatments are needed to confirm the clinical significance of combination serum tumor markers.

In summary, preoperative serum levels of CEA, CA19-9 and CA242 are associated with poor outcome in patients with colorectal cancer. However, none of them appears to be an independent prognostic factor. Tumor size, T stage, N stage, AJCC stage, differentiation and combined detection of CEA, CA19-9 and CA242 were also related to poor outcome. Tumor size, N stage, differentiation and combined detection of CEA, CA19-9 and CA242 were independent prognostic factors for CRC. A combined analysis of preoperative serum CEA, CA19-9 and CA242 provides adequate data for clinical assessment and management of CRC.

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Disclosure of conflict of interest

None.

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