



Inflammation-based markers can predict the prognosis of geriatric patients with metastatic colorectal cancer receiving first-line chemotherapy

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Background: Relationship between inflammatory factors and survival or efficacy of first-line treatment in elderly patients with metastatic colorectal cancer (MCRC) who received first-line chemotherapy has not been clarified.

Methods: A total of 186 MCRC patients aged ≥ 65 years, receiving chemotherapy between January 1, 2004 and October 1, 2015 were identified. Pretreatment levels of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), lactate dehydrogenase (LDH), C-reactive protein (CRP) and the neutrophil-to-lymphocyte ratio (NLR) were measured. Effect of these inflammatory factors on overall survival (OS) and first-line progression-free survival were analyzed.

Results: Median age was 72 years. Median PFS and OS were 6.70 months and 25.62 months. CEA ≥ 85 ng/mL ($P=0.010$), CA 19-9 ≥ 32.97 U/mL ($P=0.010$), LDH ≥ 325 U/L ($P=0.015$), CRP ≥ 11 mg/L ($P=0.004$) and NLR ≥ 2.12 ($P=0.045$) were associated with poor OS. Furthermore, LDH ($P=0.025$) was demonstrated as an independent prognostic factor of OS for all patients, so did the combination of CEA with CA 19-9 ($P=0.009$). When predicting the one, three and five-year survival, combination of CEA with CA 19-9 had higher sensitivity compared with CEA alone or CA 19-9 alone respectively. For right-sided colon cancer, CEA ($P<0.001$) and CA 19-9 ($P=0.003$) were related with OS and CEA ($P=0.002$) was the independent prognostic factor. For left-sided colorectal cancer, inflammatory factors related with OS were LDH ($P=0.039$), CRP ($P=0.004$) and NLR ($P=0.020$) and CRP ($P=0.040$) was the independent prognostic factor. Only high level CA19-9 (≥ 32.97 U/mL $P=0.024$) was related with decreased PFS in univariate analysis. However, no inflammatory factors were contained in multivariate COX regression.

Conclusions: CEA, CA 19-9, LDH, CRP and NLR were related with OS in geriatric patients with MCRC. Right-sided and left-sided groups had different independent prognostic markers, CEA and CRP respectively.

Keywords: Colorectal cancer; geriatric patient; inflammation; carcinoembryonic antigen (CEA); carbohydrate antigen 19-9 (CA 19-9); lactate dehydrogenase (LDH); C-reactive protein (CRP); neutrophil-to-lymphocyte ratio (NLR)

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Introduction

Scientists have investigated the close relationship between cancer and inflammation disease for many years. It is well-recognized that cancer associated with microorganism chronic infection, for example, hepatitis B virus (HBV) with hepatic cancer, EB-Virus with nasopharyngeal carcinoma. The individuals of inflammatory bowel disease, ulcerative colitis and Crohn's disease, have an increased risk of colorectal cancer (1). In recent years, as Mierke, C.T suggested (2), inflammatory reactions play a vital role in tumor proliferation, apoptosis and metastasis (3-6).

Many indicators in the blood increase not only as inflammation appears but also when cancer occurs (7-9), including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), lactate dehydrogenase (LDH), C-reactive protein (CRP) and the neutrophil-to-lymphocyte ratio (NLR). As a glycoprotein, CEA is only produced by gastrointestinal tissue in fetal development, and the production ceases before birth. However, it is usually augmented in the presence of gastrointestinal or other adenocarcinomas. CA 19-9 is elevated mainly in lung cancer and cancers of the digestive system, including pancreatic cancer, cholangiocarcinoma and CRC. LDH, an enzyme existing in nearly all living cells, can catalyze the conversion of lactate to pyruvic acid and back. It is well known that many tumors can express high levels of LDH (10), including colorectal cancer (11), non-small cell lung cancer (12), lymphoma, breast and gynecologic cancers (13). CRP, an inflammatory marker, is elevated in many types of cancer (14) and is discovered to be significantly elevated in lung cancer (14) and colorectal cancer (15). NLR, used as a marker of subclinical inflammation in medicine, is associated with poor prognosis in many types of cancer (16). These markers are inexpensive to test and are readily available for standard examination before treatment, so we could use them to conveniently stratify patients in the clinical practice with little expense.

Colorectal cancer is ranked as the fourth most prevalent cancer and the second leading cause of cancer deaths in the US, as indicated by the latest statistics (17). Age has been confirmed as the most important risk factor for developing colorectal cancer in epidemic studies (18). In the UK, over 66.7% of patients diagnosed with colorectal cancer were older than 65 years according to data collected between 2007 and 2009. By contrast, elderly patients are often excluded in clinical trials for their limited regenerative ability, lower resistance to disease, syndromes and

sicknesses, and more comorbidities compared with young adults (19,20).

Since no previous studies about the effect of inflammation on the efficacy of chemotherapy and the prognosis in colorectal cancer for the geriatric population were carried out, the present study was undertaken to elucidate this problem by studying elderly patients with MCRC at our institution. The palliative medical treatment for those patients included chemotherapy alone or combined with targeted therapy, the latter therapy account for less than 20%. Most of elder patients couldn't afford the expense of targeted therapy and some with poor physical status couldn't tolerate intensive therapy. Therefore, this study, formulating the effect of different inflammatory factors on survival or first-line chemotherapy efficacy in elderly patients with MCRC, focused on groups with chemotherapy alone in first-line treatment.

Methods

Patient eligibility

Patients above the age of 65 years, diagnosed with MCRC, and treated with first-line chemotherapy at our institution between January 1, 2004 and October 1, 2015 were identified. All patients included have been histologically proven CRC at primary tumor sites. And the diagnosis of metastasis diseases was based mainly on clinical and radiologic findings while histological evidence for few patients. At least two cycles of palliative chemotherapy were given to every patient, and pretreatment values of inflammatory markers, LDH, CRP, CEA, CA 19-9 and NLR, were collected to analysis. Patients who had other cancer or acute and chronic infectious disease or received hormone treatments were excluded from our study. Basic characteristic information for all the patients was collected. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2017000366.

Laboratory measurements of LDH, CRP, CEA, CA 19-9 and NLR

The inflammatory plasma factors included in our study were measured in each included patient before treatment initiation using laboratory devices in our cancer center. LDH and CRP were included in a biochemical test

performed using the Hitachi Automatic Analyzer 7600-020 (Tokyo, Japan), and CEA and CA 19-9 in serum tumor marker tests were measured using the Roche Elecsys 2010 Chemistry Analyzer (Basel, Switzerland). NLR was counted as the neutrophil-to-lymphocyte ratio, and neutrophils and lymphocytes were measured by routine blood examination (XE-5000TM Automated Hematology System). The normal range of CEA and CA 19-9, LDH and CRP in blood were 0–5 ng/mL, 0–35 U/mL, 109–245 U/L, and 0–8.2 mg/L. NLR, as a specific value, did not have standard normal range.

Patient follow-up

The primary endpoint of the current study was to define the prognostic value of LDH, CRP, CEA, CA19-9 and NLR levels with regard to OS in patients with MCRC who were treated with palliative chemotherapy. The secondary endpoint was PFS for first-line palliative chemotherapy. OS was defined as the time from the initiation of palliative first-line chemotherapy to the date of death or the last day of follow-up, September 18, 2016, and PFS was defined as the time from the start of chemotherapy to disease progression or death caused by cancer after first-line treatment.

Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Frequencies and descriptive statistics were used to compare basic patient characteristics. The univariate analyses between prognostic variables and OS or PFS were performed using Kaplan–Meier curves with long-rank test. Cox proportional hazards regression model was used to evaluate the association between selected prognostic factors and OS or PFS in multivariate models and hazard ratio (HR) and its associated 95% confidence interval (95% CI) estimation. Only variables associated with highly significant P value (<0.05) at the univariate analysis were included in the multivariate model. All markers were sought out to provide a new cut-off point in our study that could classify all patients into two groups with the most significantly different overall survival time. The cut-off values for inflammatory markers were determined according to the minimum P value method (21–25). It's a procedure that selects the cut-off point that minimizes the significance level of a log-rank test with comparison of the two groups defined by the cut-off point. This procedure adjusts the significance level for maximal

selection (24). Receiver operating characteristic (ROC) curves were constructed to evaluate the prognostic values of combination of CEA with CA 19-9. We set the combination of CEA with CA 19-9 as one value which contained three categories: CEA ≥ 85 ng/mL and CA 19-9 ≥ 32.97 U/mL; CA 19-9 ≥ 32.97 U/mL or CEA ≥ 85 ng/mL; CEA <85 ng/mL and CA 19-9 <32.97 U/mL. All analyses considered P<0.05 as statistically significant results.

Results

Patient characteristics

A total of 186 patients, 135 (72.6%) males and 51 (27.4%) females, with 1,028 cycles of first-line chemotherapy and a mean of 5.5 cycles, were followed up for 5 to 95.1 months (median 19.9 months). At the end of our study, 32 patients (17.2%) dropped the study and 134 patients (72.0%) died. 1-, 3- and 5-year survival rate were 72.8%, 22.8% and 10.2%. In order to avoid bias, the monitoring time for all survivors was more than 2 years. All patients were more than 65 years of age with a median age of 72 (range, 65–85). OS was analyzed in all patients and PFS was analyzed in 99 patients (53.2%). Median PFS for first-line chemotherapy was 6.70 months (95% CI, 5.74–7.66) and median OS was 25.62 months (95% CI, 21.07–30.18). Primary tumor sites were divided into right- (ascending and transverse colon) and left-sided (descending and sigmoid colon and rectum) colorectal cancer. We divided treatment regimens mainly into five group: FOLFOX, oxaliplatin plus 5-fluorouracil (5-FU) plus calcium folinate (CF); FOLFIRI, irinotecan plus 5-FU plus CF; CapOX, capecitabine plus oxaliplatin; CapIRI, capecitabine plus irinotecan; capecitabine. After univariate analysis, we found it was no significant difference of OS between each different treatment regimens. And there was still no significant difference of OS in mono-chemotherapy and combination chemotherapy. The basic clinical and pathologic characteristics of all cases and the association of these characteristics with OS are shown in *Table 1*.

Prognostic effect of CEA, CA 19-9, LDH, CRP and NLR on OS

The values of LDH, CRP, CEA, CA 19-9 and NLR before the first-line chemotherapy were used in the analysis. By univariate analysis, showed in *Table 2* and *Figure 1*, OS was most significantly reduced in the CEA ≥ 85 ng/mL

Table 1 Baseline characteristics in geriatric patients with advanced colorectal cancer

Characteristics	Number	Percentage (%)	P value ^a
Gender			0.151
Male	135	72.6	
Female	51	27.4	
Age (median 72 years)			0.208
>72	91	48.9	
65–72	95	51.1	
Karnofsky Performance Status			—
<80	0	0	
≥80	136	73.1	
Missing	50	26.9	
Primary tumor sites			0.479
Right-sided	50	26.9	0.224 ^b
Left-sided	66	35.5	
Rectal	65	34.9	
Missing	5	2.7	
Pathological grading			0.078
Grade I	6	3.2	0.032 ^c
Grade II	112	60.2	
Grade III	34	18.3	
Missing	34	18.3	
Clinical stage IV	186	100.0	—
Liver metastasis			0.061
Yes	128	68.8	
No	58	31.2	

Table 1 (continued)

($P=0.010$), or CA 19-9 ≥ 32.97 U/mL group ($P=0.010$), and LDH ≥ 325 U/L ($P=0.015$), the CRP ≥ 11 mg/L group ($P=0.004$) and the NLR ≥ 2.12 group ($P=0.045$). Therefore, the cut-off values for CEA, CA 19-9, LDH, CRP and NLR were 85 ng/mL, 32.97 U/mL, 325 U/L, 11 mg/L and 2.12, respectively, in the subsequent analysis. In addition to these inflammation related markers, primary pathological grading (grade I–II *vs.* grade III: $P=0.043$) and celiac metastasis ($P=0.060$) were also included in the multivariate analysis model. As shown in *Table 3*, it was found that LDH

Table 1 (continued)

Characteristics	Number	Percentage (%)	P value ^a
Celiac metastasis			0.069
Yes	42	22.6	
No	144	77.4	
Lung metastasis			0.893
Yes	64	34.4	
No	122	65.6	
First-line chemotherapy			0.420
FOLFOX	72	38.7	0.994 ^d
FOLFIRI	18	9.7	
CapOX	59	31.7	
CapIRI	9	4.8	
Capecitabine	28	15.1	

^a, P values between patients' characteristics and overall survival were calculated using the Kaplan-Meier method with log-rank test. ^b, P value was calculated when primary tumor sites was divided as right-sided and left-sided colorectal cancer. ^c, P value was calculated when first-line treatments were divided as grade I–II and grade III. ^d, P value was calculated when first-line chemotherapy was divided as mono-chemotherapy and combination chemotherapy. FOLFOX, oxaliplatin plus 5-fluorouracil (5-FU) plus calcium folinate (CF); FOLFIRI, irinotecan plus 5-FU plus CF; CapOX, capecitabine plus oxaliplatin; CapIRI, capecitabine plus irinotecan.

($P=0.025$) were independent prognostic factors for OS (*Table 3*).

When combining the most popular prognostic factors in CRC, CEA and CA 19-9, median OS was 33.68, 19.61 and 17.58 months in groups with CEA <85 ng/mL and CA 19-9 <32.97 U/mL group, CEA ≥ 85 ng/mL or CA 19-9 ≥ 32.97 U/mL group and group CEA ≥ 85 ng/mL and CA 19-9 ≥ 32.97 U/mL group, respectively (*Figure 2*). In COX regression analysis, including the same factors as above, found that the combination of CEA with CA 19-9 was also an independent factor for OS (HR =1.44; 95% CI, 1.10–1.90; $P=0.009$). When predicting the 1-, 3- and 5-year survival, combination of CEA with CA 19-9 had higher sensitivity compared with CEA and CA 19-9 respectively, demonstrated in *Figure 2*. Interestingly, we found CEA had higher specificity in predicting 1-, 3- and 5-year survival.

Table 2 Overall survival (OS) and first-line progression-free survival (PFS) in different groups

Factors	Colorectal cancer			Right-sided colorectal cancer			Left-sided colorectal cancer		
	Patients number	Median survival (95% CI), months	P value*	Patients number	Median survival (95%CI), months	P value*	Patients number	Median survival (95%CI), months	P value*
Overall survival									
CEA (ng/mL)			0.010			<0.001			0.138
<85	123	26.12 (22.22–30.02)		35	21.13 (12.95–29.30)		87	28.52 (23.53–33.50)	
≥85	33	15.87 (9.34–22.40)		8	6.21 (4.62–7.80)		25	19.06 (13.89–24.22)	
CA 19-9 (U/mL)			0.010			0.003			0.083
<32.97	67	30.55 (21.88–39.23)		23	26.05 (12.59–39.52)		43	31.47 (23.88–39.07)	
≥32.97	85	19.61 (18.13–21.10)		20	11.04 (1.81–20.27)		65	23.26 (16.86–29.66)	
LDH (U/L)			0.015			0.070			0.039
<325	134	25.50 (19.18–31.81)		38	19.65 (16.37–22.92)		95	26.91 (22.16–31.66)	
≥325	21	16.99 (6.59–27.39)		5	7.85 (5.67–10.04)		16	17.58 (10.52–24.63)	
CRP (mg/L)			0.004			0.416			0.004
<11	61	28.72 (22.81–34.62)		16	20.47 (18.53–22.41)		44	31.54 (22.83–40.25)	
≥11	66	19.45 (12.61–26.29)		20	12.45 (2.64–22.26)		46	19.61 (16.63–22.60)	
NLR			0.045			0.885			0.020
<2.12	52	33.68 (18.50–48.85)		11	18.17 (10.41–25.93)		41	39.26 (24.81–53.71)	
≥2.12	131	24.84 (20.96–28.71)		38	20.47 (12.30–28.63)		92	24.94 (22.20–27.67)	
Progression-free survival									
CEA (ng/mL)			0.116			0.228			0.321
<85	63	7.06 (5.75–8.38)		21	7.13 (3.20–11.06)		42	6.74 (5.34–8.13)	
≥85	12	6.24 (1.45–11.04)		2	2.17 (no 95% CI)		10	6.24 (1.41–11.08)	
CA 19-9 (U/mL)			0.024			0.570			0.086
<32.97	35	8.15 (6.32–9.98)		16	8.31 (3.23–13.40)		19	8.05 (5.01–11.09)	
≥32.97	39	5.88 (3.19–8.57)		7	3.84 (0.47–7.22)		32	6.24 (4.60–7.88)	
LDH (U/L)			0.360			0.191			0.816
<325	64	7.06 (6.26–7.87)		19	7.13 (3.39–10.87)		45	7.06 (6.42–7.71)	
≥325	10	4.53 (1.38–7.69)		4	2.60 (0.00–7.10)		6	4.53 (2.09–6.98)	
CRP (mg/L)			0.847			0.996			0.575
<11	30	7.06 (6.49–7.64)		8	7.13 (3.03–11.23)		22	6.70 (4.14–9.27)	
≥11	25	6.01 (5.10–6.92)		11	4.67 (1.26–8.07)		14	6.24 (4.92–7.57)	
NLR			0.153			0.052			0.665
<2.12	30	5.65 (3.01–8.30)		8	3.02 (0.00–6.39)		22	6.74 (3.49–9.98)	
≥2.12	66	6.64 (5.71–7.57)		20	6.64 (5.99–7.29)		46	6.24 (5.26–7.23)	

*, P values were calculated using the Kaplan-Meier method with log-rank test. CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, the neutrophil-to-lymphocyte ratio; 95% CI, 95% confidence interval.

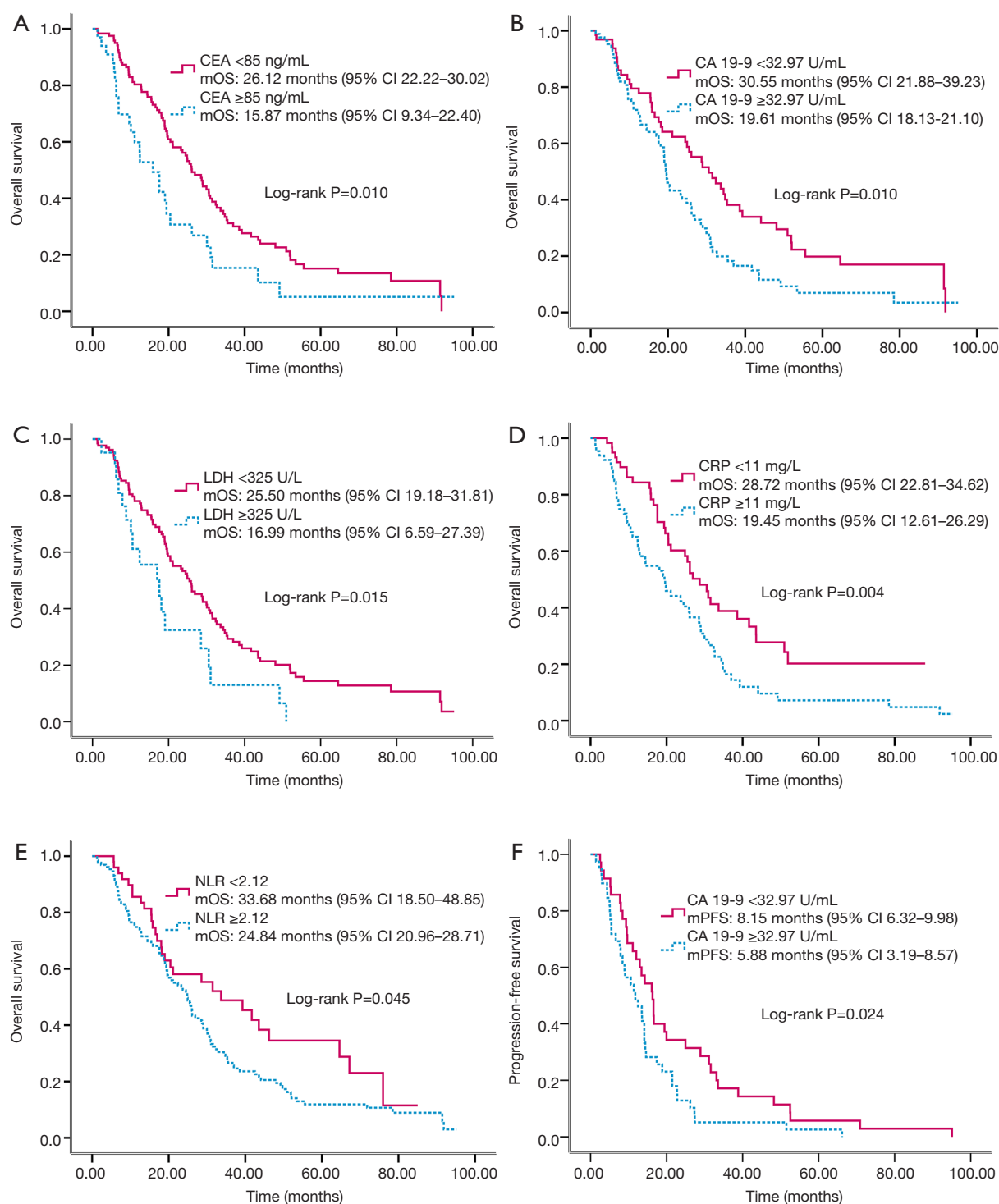


Figure 1 Kaplan-Meier curves for overall survival or progression-free survival stratified by inflammation-based markers. Kaplan-Meier curves for overall survival stratified by CEA levels (A), CA 19-9 levels (B), LDH levels (C), CRP levels (D) and NLR levels (E); Kaplan-Meier curves for progression-free survival stratified by CA 19-9 levels (F). CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, the neutrophil-to-lymphocyte ratio; mOS, median overall survival; mPFS, median progression-free survival; 95% CI, 95% confidence interval.

Table 3 Multivariate analysis of prognostic factors on overall survival (OS)

Prognostic factors	Colorectal cancer			Right-sided colorectal cancer			Left-sided colorectal cancer		
	HR	95% CI	P value*	HR	95% CI	P value*	HR	95% CI	P value*
Pathological grading	1.78	1.02–3.06	0.043	2.16	0.87–5.42	0.099	1.15	0.57–2.31	0.698
Metastasis sites	1.69	0.98–2.91	0.060	1.06	0.41–2.72	0.900	1.26	0.60–2.67	0.542
CEA	–	–	–	6.23	1.94–20.04	0.002	–	–	–
LDH	2.10	1.10–4.02	0.025	–	–	–	–	–	–
CRP	–	–	–	–	–	–	1.80	1.03–3.17	0.040

*, P values were calculated using the Cox-proportional hazard model. CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, the neutrophil-to-lymphocyte ratio; HR, hazards ratio; 95% CI, 95% confidence interval.

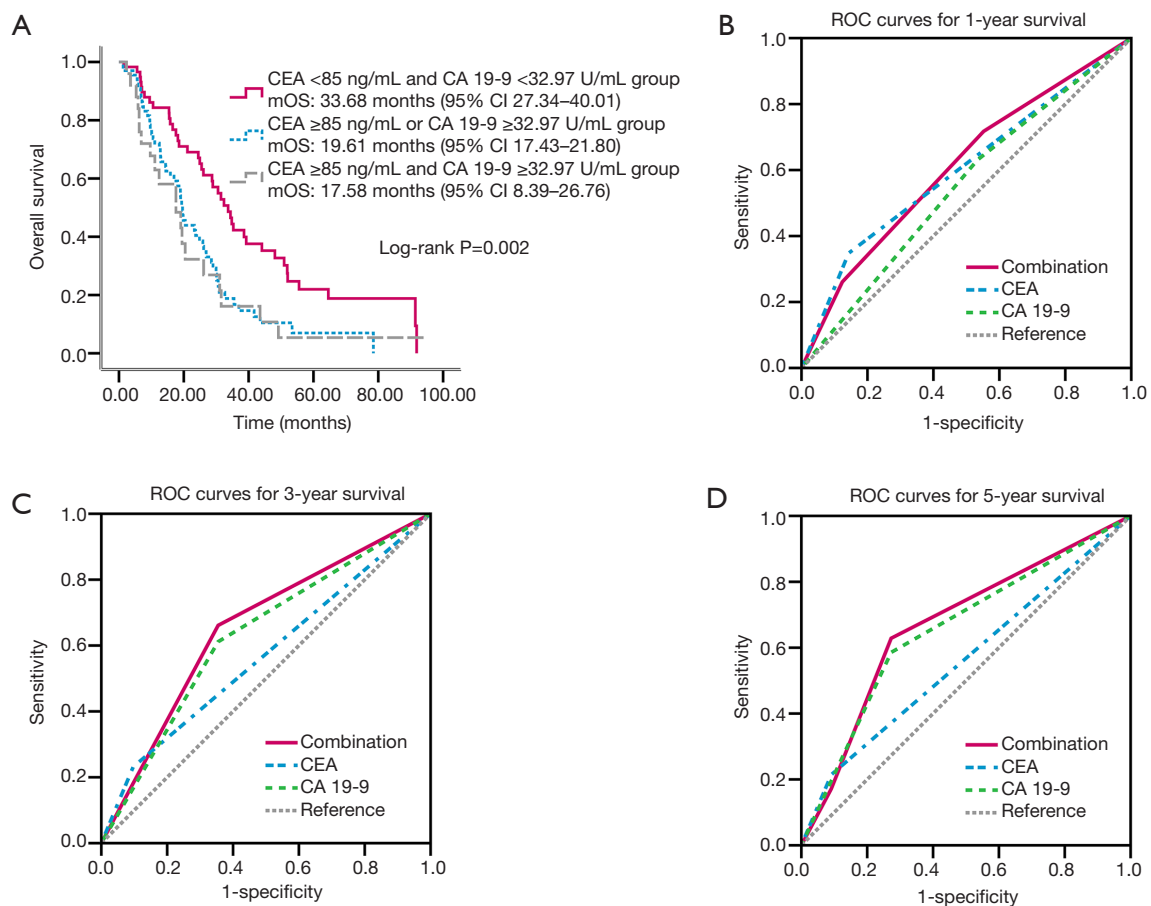


Figure 2 Combination of CEA and CA 19-9 could predict OS well and improved the sensitivity of 1-, 3- and 5-year survival prediction compared with CEA or CA 19-9 alone. Kaplan–Meier curves for overall survival stratified by combination of CEA and CA 19-9 at different levels (A); ROC curves for 1-year survival prediction (B), 3-year survival prediction (C) and 5-year survival prediction (D). CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; ROC, Receiver operating characteristic; AUC, area under curve; mOS, median overall survival; 95% CI, 95% confidence interval.

Prognostic effect of CEA, CA 19-9, LDH, CRP and NLR on OS in right- or left-sided colorectal cancer

Further analysis was done to identify the effect of these markers on OS in right- and left-sided colorectal cancer. As indicated in *Table 2*, three inflammation markers, LDH ($P=0.039$), CRP ($P=0.004$) and NLR ($P=0.020$) were prognostic factors for OS in 131 left-sided colorectal cancer patients with lower levels of markers associated with improved OS. Similar to the prior analysis, primary pathological grading ($P=0.698$) and celiac metastasis ($P=0.542$) were also included in multivariate analysis model. As shown in *Table 3*, it was found that CRP ($P=0.040$) was an independent prognostic factor for OS. For 55 patients with right-sided colon cancer, CEA ($P<0.001$) and CA 19-9 ($P=0.003$) were prognostic factors, showed in *Table 2*. As shown in *Table 3*, it was found CEA ($P=0.002$) was an independent prognostic factor for OS.

Predictive effect of CEA, CA 19-9, LDH, CRP or NLR on PFS after first-line treatment

Only CA 19-9 ($P=0.024$) appeared to be predictive of PFS in a univariate analysis (*Table 2* and *Figure 1*). However, it ($P=0.052$) was not an independent predictive factor by multivariate analysis. CEA, LDH, CRP and NLR did not have significant effects on PFS by univariate analysis (*Table 2*). The univariate analysis of the right- and left-sided colorectal cancer subgroups showed that no significant value was found as a predictive factor in both right-sided and left-sided colorectal cancer (*Table 2*).

Discussion

Inflammatory factors interacted with cancer cells on both molecular and cellular levels. On the one hand, proto-oncogenes boost expression of inflammation-associated factors and create the tumor inflammatory microenvironment; on the other hand, this specific inflammatory microenvironment promotes tumor metastasis (4). Thus, many studies have suggested that inflammatory markers could act as prognostic factors in cancer, including colorectal cancer. Elderly patients may have different anti-inflammatory intensities than the overall population as a result of their lower metabolic rate and weaker body function, and geriatric patients might suffer from more inflammation situation than a younger population because of a longer life (26-28). Therefore, we

speculate that the association between inflammation and the prognosis of CRC might be closer in geriatric patients than in the younger population.

Our findings support the hypothesis that inflammation has an important effect on the colorectal cancer mortality and the short-time efficacy of first-line therapy in elderly groups. Higher levels of inflammation markers, LDH, CRP, CEA, CA 19-9 and NLR, were closely related to a poor prognosis. In addition, LDH was independent factors in predicting OS, even when pathological grading and celiac metastasis were also taken into consideration in multivariate analysis. Furthermore, CA 19-9 was predictive of poor PFS in the univariate analysis. No inflammatory factor was associated with PFS in a multivariate analysis. As we know, PFS has a shorter window of observation and is largely affected by the different regimens administered to patients in first-line therapy. Furthermore, in this retrospective study, PFS was hard to identify as accurately as OS. To elucidate the precise relationship between inflammation and short-term treatment efficacy, we need well-devised prospective studies. Anyway, we can conclude that CEA, CA 19-9, LDH, CRP and NLR could be prognostic factors for OS.

Our subgroup analysis of the relationship between OS and primary tumor sidedness showed that CEA and CRP were independent prognostic factors for right- and left-sided colorectal cancer, respectively. Right- and left-sided colorectal cancer have different clinicopathological features and reaction to cetuximab (29), and this study furthermore found different prognostic factors for them. Compared with CEA, CRP was more representative of inflammation. Thus, we suggest that inflammation has a greater effect in left-sided colorectal cancer than right-sided colorectal cancer. As the formerly published study suggested, right-sided colon cancer has high frequency of BRAF mutation, CpG island methylation phenotype (CIMP) and microsatellite instability (MSI) (30). Conversely, left-sided tumors are characterized by chromosomal instability and a gene expression profile involving the activation of the epidermal growth factor receptor (EGFR) pathway (31). However, the study designed to compare inflammation status in right-sided colon cancer and left-sided colorectal cancer was still not available. CEA level showed significant relation with OS in right-sided colon cancer in our study, we guess it might be on account of the bigger volume of primary tumor sites as CEA also represents tumor burden. More research is needed to verify this. Besides, no significant marker was predictive of both the PFS of right-sided and left-sided colorectal cancer in our study.

NLR has recently been recognized as a prognostic indicator. Both *in vivo* and *in vitro* experiments have shown that the cytokines produced by neutrophils and other inflammatory mediators can promote the formation of a microenvironment that is conducive to the growth of tumor cells (32). Several studies have demonstrated that high NLR levels are related to poor prognosis in colorectal cancer (33-35), which is consistent with the findings that neutrophils inhibit the activity of lymphocytes and that more lymphocytes in tumors indicate a better patient prognosis (3,4,23). One meta-analysis suggested that $\text{NLR} > 1.81$ was associated with an adverse OS and PFS in colorectal carcinoma ($\text{HR} = 1.91$; 95% CI, 1.53–2.39) (16). In our retrospective study in geriatric patients with MCRC, a high NLR was associated with a poorer OS, which agreed with the published reports in general patients with colorectal cancer.

In our study, we found the super prognostic role of CEA combined with CA19-9. As we all know, tumor markers CEA and CA 19-9 are tightly related to tumor formation, metastasis and recurrence. Interestingly, it is also widely recognized that CEA and CA 19-9 could be detected increasingly as inflammation occurs. In colorectal cancer, several studies demonstrated that CEA and CA 19-9 were associated with poor PFS and OS (36-38). In gastrointestinal adenocarcinoma, CEA and/or CA 19-9 are often increased, with the former having greater specificity and sensitivity. Recent data showed that the combination of preoperative CEA and CA 19-9 levels was useful for predicting the prognosis and for monitoring recurrence and metastasis after potentially curative surgery in patients with stage II colorectal cancer (39). Furthermore, one study showed that CA 19-9 could be regarded as a marker, in addition to CEA, to monitor colorectal cancer, and patients with preoperative increased CA 19-9 levels had a poorer 5-year survival than patients with preoperative increased CEA levels (40). Our study results support that CEA and CA 19-9 could be used as prognostic factors in stage IV elderly patients. Patients with both low CEA and CA 19-9 level had best OS compared to that with anyone high level and both high level. Moreover, ROC curve showed combination of CEA and CA 19-9 improved the sensitivity of 1-year, 3-year and 5-year survival prediction. Interestingly, CEA had highest specificity but lowest sensitivity compared with CA 19-9 and combination of them. Thus, we think combination of them were more practicable in clinical.

CRP played an important role in Glasgow prognostic

score (GPS), an inflammation-based prognostic score assessed using the serum CRP and albumin levels, and has been found to be a useful prognostic factor in several types of cancer, including colorectal cancer. In our study, high CRP was significantly related to impaired OS as an independently prognostic factor in geriatric left-sided colorectal cancer patients. LDH represented an indirect marker of tumor hypoxia, neo-angiogenesis, metastasis development and poor prognosis in many cancers (41-44). In a phase III prospective, multicenter, randomized Italian Trial in Advanced Colorectal Cancer (ITACa), the authors suggested that a high LDH value was confirmed as a marker of poor prognosis (45).

Since this study was conducted in the real-world clinical practice and not in a clinical trial, this investigation showing the relationship between inflammation-based factors and OS might contain actual significant guidance for our practice. The more significant finding was that so many inflammatory factors were found to affect the prognosis of MCRC in the special group of geriatric patients. This might indicate that there is a stronger correlation between inflammation and cancer development in elderly than in young patients. However, this study was done retrospectively with some inevitable confounding factors. PFS was analyzed among half of cases in result of missing data. Moreover, the values of inflammation-based factors were measured only before palliative treatment, and potential change of these biomarkers during treatments should be considered in this study. One analysis of the FIRRE-3 trial showed CEA were decreased faster and greater in the cetuximab arm than in the bevacizumab arm (46). Another study also emphasized that the biochemical response with a chemotherapy induced decline in CEA level may be clinically more relevant than a single preoperative CEA value (47). In the future, we plan to study whether dynamic changes in these inflammatory factors have more power to predict PFS and OS of chemotherapy and targeted therapy in geriatric patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.06.27>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the institutional review board and ethics committee at the Sun Yat-sen University Cancer Center and the ethic approval number is YB2016-065. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained for this study and patient information was anonymized and de-identified prior to analysis.

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