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ORIGINAL ARTICLE

Prognostic value of serum carcinoembryonic antigen combined with nutritional status control score in patients with colorectal cancer*

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Abstract

Objective To investigate the prognostic value of serum carcinoembryonic antigen (CEA) and controlling nutritional status (CONUT) score in patients with colorectal cancer.

Methods We retrospectively studied 261 patients with colorectal cancer in our hospital. The patients were divided into two groups by CONUT = 3 and CEA = 5 ng/mL, and the effects of CONUT score and CEA level on the prognosis and clinicopathological parameters were statistically analyzed.

Results (1) Different CONUT scores were significantly correlated with age, tumor diameter, differentiation type, and T stage ($P < 0.05$). The older the patient was, the larger the tumor diameter, undifferentiated tumor, and T stage were, the higher the CONUT score was. (2) Seventy-five patients died during the follow-up period, and 45 patients died of progression or recurrence of colorectal cancer. The 5-year overall survival (OS) rate of the low CONUT score group was significantly higher than that of the high CONUT score group, and the 5-year OS rate of the low CEA group was significantly higher than that of the high CEA group; the difference was statistically significant ($P < 0.01$). (3) According to the serum CEA level and CONUT score, the 5-year survival rates of $CEA^{low}/CONUT^{low}$, $CEA^{low}/CONUT^{high}$, $CEA^{high}/CONUT^{low}$, and $CEA^{high}/CONUT^{high}$ were 84.7%, 69%, 55.3%, and 36.1% respectively, with statistical significance ($P <0.01$). (4) The Cox multivariate analysis showed that age, CONUT score, CEA combined with CONUT score, lymph node metastasis, and distant metastasis were independent risk factors for the prognosis of colorectal cancer patients.

Conclusion: The combination of CEA detection and CONUT score can more accurately judge the prognosis of colorectal cancer patients.

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Key words: colorectal cancer; carcinoembryonic antigen; nutritional status control score

Cancer resection combined with regional lymph node dissection is the main treatment for colorectal cancer, but several patients relapse after complete tumor resection (R0 resection) [1]. The latest progress in chemotherapy has improved the prognosis of unresectable patients, and early detection of recurrence can effectively improve the survival rate of patients [2]. Serum tumor markers (TMS) are easy to measure and have potential practical value for diagnosis, predicting survival, and monitoring postoperative recurrence [3]. Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 are the most commonly used tumor markers for diagnosing, monitoring, and predicting the prognosis of patients with colorectal cancer [4]. Recent studies have shown that the prognosis of various types of cancer is also affected by the patient's inflammatory state, immune function, and nutrition, among which the correlation between nutritional status and cancer prognosis is particularly significant [5]. Controlling nutritional status (CONUT) score, including serum albumin, total cholesterol, and peripheral lymphocyte count, is considered a new tool for assessing nutritional status [6]. The purpose of this study was to explore whether the combined application of TMS and CONUT score can more accurately reflect the prognosis of patients with CRC.

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Materials and method

Research objective

This was a retrospective study, wherein a total of 261 patients with stage I-IV colorectal cancer who underwent colorectal resection between January 2007 and December 2015 were selected as the research subjects. The inclusion criteria were as follows: (1) This should be the first diagnosis and surgical treatment. (2) All cases were confirmed through surgery and pathology. (3) Clinical and follow-up data were complete. Clinicopathological results were evaluated according to the Japanese classification criteria for colorectal cancer, 8th edition. Patients were regularly examined for early recurrence through diagnostic imaging, including chest radiography, colonoscopy, ultrasound, and computed tomography. The first hematological examination after admission was taken as the baseline data, including serum albumin, total cholesterol, and peripheral blood lymphocyte count in the patient's records.

CONUT score

The CONUT score was calculated according to the patient's serum albumin, total cholesterol, and peripheral blood lymphocyte count. The specific criteria are presented in Table 1. These factors were scored according to the critical value, and the sum of these factors was regarded as the CONUT score. According to the CONUT score, the patients were divided into four groups: normal (score 0–1), mild malnutrition (score 2–4), moderate malnutrition (score 5–8), and severe malnutrition (score 9–12).

Statistical analysis

SPSS 20.0 and GraphPad Prism software (version 5.0) were used for data processing. The counting data were expressed as the number of cases, and the measurement data were expressed as the mean ± standard deviation. One-way ANOVA or chi-squared tests were used for comparison between groups. Kaplan-Meier analysis was used for survival evaluation, and the log-rank test was used for inter-group comparisons. The receiver operating characteristic (ROC) curve was used to determine the area under the curve (AUC) and the best cutoff value of the CONUT score. The Cox proportional hazards model was used to analyze prognostic factors that may affect overall survival (OS).

Table 1 CONUT scoring criteria

Index	Nutritional status			
	Normal (0–1)	Mild (2–4)	Moderate (5–8)	Severe (9–12)
Albumin (g/dL)	3.5–4.5 (0)	3.0–3.5 (2)	2.5–2.9 (4)	< 2.5 (6)
Total cholesterol (mg/dL)	> 180 (0)	140–180 (1)	100–139 (2)	< 100 (3)
Leukomonocyte (/mL)	> 1600 (0)	1200–1599 (1)	800–1199 (2)	< 800 (3)

Results

Relationship between CONUT score and clinicopathological features of patients

There were 140 patients, 79 patients, 38 patients, and 4 patients with normal, mild, moderate, and severe CONUT scores, respectively. According to the ROC analysis, the best cutoff value for OS was 3 points (AUC = 0.627, $P < 0.01$). According to these results, the patients were divided into two groups: high CONUT score group (CONUT score ≥ 3, $n = 79$) and low CONUT score group (CONUT score < 3, $n = 182$). The chi-squared test showed that the different CONUT scores were significantly correlated with patient age, tumor diameter, differentiation type, and T stage ($P < 0.05$). The older the patient was, the larger the tumor diameter, undifferentiated tumor, and T stage were, the higher the CONUT score was (Table 2).

Table 2 Relationship between CONUT scores and clinicopathological features

Index	High CONUT score ($n = 79$)	Low CONUT score ($n = 182$)	χ^2	P
Age (years)			5.381	0.020
< 70	38	60		
≥ 70	41	122		
Gender			0.144	0.704
Male	48	106		
Female	31	76		
Tumor diameter (cm)			0.033	0.856
< 4	53	120		
≥ 4	26	62		
Tumor location			3.162	0.075
Colon	50	135		
Rectum	29	47		
Differentiation type			11.580	0.001
Differentiated	64	172		
Undifferentiated	15	10		
T stage			9.189	0.002
T1/2	16	72		
T3/4	63	110		
Lymphatic metastasis			0.395	0.530
No	51	110		
Yes	28	72		
Vascular metastasis			1.049	0.306
No	58	122		
Yes	21	60		

Comparison of survival rates of patients in different CONUT score groups

Seventy-five patients died during the follow-up period, 45 died of colorectal cancer progression or recurrence, and 30 died of other causes, including other cancers (n = 12), pneumonia (n = 6), stroke (n = 5), myocardial infarction (n = 4), and other unknown causes (n = 3). There were no surgery-related deaths. The 5-year OS rate (75.8%, 138/182) in the low CONUT score group was significantly higher than that in the high CONUT score group (54.4%, 43/79) (P < 0.01; Fig. 1).

Comparison of survival rate of patients with different serum CEA levels

Serum CEA levels ranged from 0.1 to 1166 ng/mL, with an average of 16.2 ng/ml. According to the serum CEA concentration, the patients were divided into high CEA (≥ 5 ng/mL, n = 89) and low CEA groups (< 5 ng/mL, n = 172). The 5-year OS rate of patients with low CEA levels (82.6%, 142/172) was significantly higher than that of patients with high CEA levels (43.8%, 39/89) (P < 0.01; Fig. 2).

Serum CEA combined with CONUT score to evaluate the prognosis of patients

Based on the serum CEA level and the CONUT score, the patients were divided into four groups: CEA^{low}/con ut^{low} (n = 128), CEA^{low}/$CONUT^{high}$ (n = 44), CEA^{high}/$CONUT^{low}$ (n = 53), and CEA^{high}/$CONUT^{high}$ (n = 36). According to the ROC curve, the AUC values of CEA level, CONUT score, and combined detection in predicting the prognosis of patients with colorectal cancer were 0.66 (P < 0.01), 0.627 (P < 0.01) and 0.71 (P < 0.0001), respectively, suggesting that combined detection is more valuable in predicting OS in patients with colorectal cancer, as shown in Table 3. The 5-year OS rates of the cealow/contlow, cealow/conthigh, ceahigh/contlow, and ceahigh/thigh were 84.7%, 69%, 55.3%, and 36.1%, respectively. The difference was statistically significant (P < 0.01), as shown in Fig. 3.

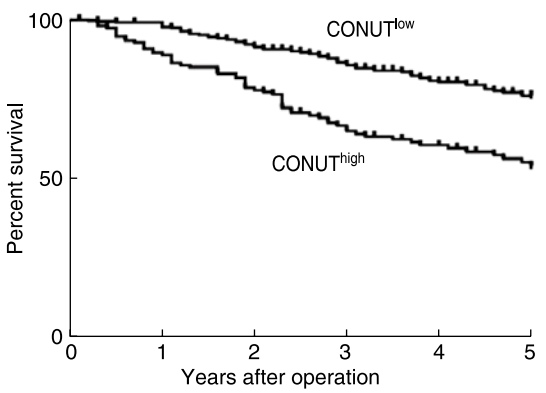

Fig. 1 Comparison of survival of patients in different CONUT scoring groups

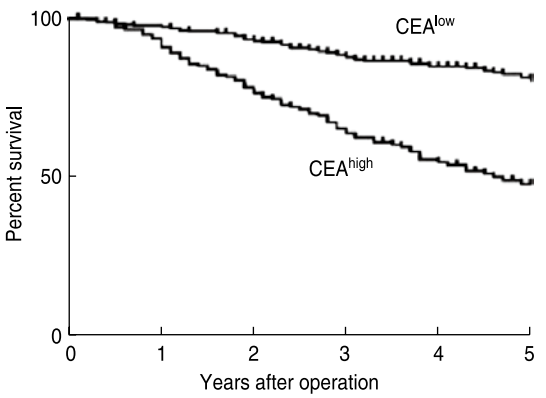

Fig. 2 Comparison of survival of patients with different serum CEA levels

Multivariate analysis of patients' survival rate

The Cox multivariate analysis showed that age, CONUT score, t-CONUT score, lymph node metastasis, and distant metastasis were independent risk factors affecting the prognosis of patients with colorectal cancer. Data was shown in Table 4.

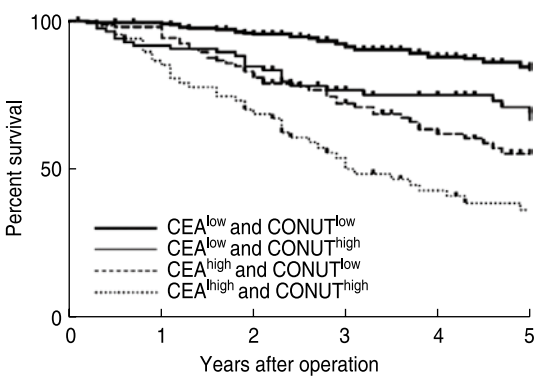

Fig. 3 Comparison of survival of patients with different serum CEA and CONUT scores

Table 3 Patient outcomes judged by three methods

Index	Sensitivity (%)	Specificity (%)	False positive (%)	False negative (%)	Positive predictive (%)	Negative predictive (%)
CEA	86.33	62.60	38.50	14.67	97.00	15.50
CONUT	92.00	76.00	26.00	8.00	98.50	33.33
Joint detection	97.50	63.50	38.50	2.50	97.88	42.64

Table 4 Multivariate analysis affecting patient survival

Index	β	SE	Wald	df	*P*	95%CI
Age	0.363	0.541	0.985	1	0.341	0.652–2.632
Gender	0.287	0.369	0.254	1	0.896	0.142–1.874
CEA	0.869	0.326	7.133	1	0.059	1.261–4.502
CONUT	0.678	0.335	4.078	1	0.041	1.021–3.980
T-Conut	0.189	0.268	8.464	1	0.009	0.495–1.398
lymphatic metastasis	0.523	0.296	2.181	1	0.038	0.951–2.993
Transfer far away	0.452	0.166	2.632	1	0.030	0.864–3.336
Degrees of differentiation	0.240	0.263	0.830	1	0.369	0.472–1.318
Tumor diameter	0.359	0.523	0.512	1	0.636	0.538–3.815

Discussion

The results of this study show that the CONUT score has a certain reference value in predicting the prognosis of patients with colorectal cancer, which is similar to that of previous reports, and proves the significance of CONUT score in postoperative patients with several cancers [7]. Previous studies have also shown that the CONUT score is an effective prognostic indicator for patients with metastatic colorectal cancer receiving first-line chemotherapy [8]. Conut scores included serum albumin, total cholesterol, and peripheral blood lymphocytes. Albumin, the most abundant plasma protein, is produced in the liver and accounts for a large proportion of all plasma proteins. It is a standard factor for evaluating the nutritional status of patients. It has been reported that [9] serum albumin is closely related to the prognosis of various cancers, including colon cancer. Peripheral blood lymphocytes are also considered to reflect the nutritional status and immune function of patients [10]. Lymphocytes include CD4 + and CD8 + T cells, natural killer cells, γ-δ T cells, and B cells, whose functions are closely related to tumor immunity. Therefore, the decrease in the number of these cells may be related to the impairment of tumor immune function, resulting in tumor progression. Some studies have shown that the number of tumor-infiltrating lymphocytes is related to the prognosis of cancer [11]. In addition, the decrease in the number of immune cells in the peripheral blood and cancer tissues is related to the poor prognosis of various cancers. Therefore, peripheral blood lymphocytes may be a good index to reflect the state of cellular immunity, including acquired immunity and humoral immunity.

The prognostic nutritional index (PNI), which includes serum albumin level and peripheral blood lymphocytes, is one of the most commonly used indicators to evaluate nutritional status [12]. Recently, PNI was found to be closely related to the prognosis of various types of cancer, indicating that nutritional status and immune status are prognostic indicators of cancer patients. In addition to serum albumin and peripheral blood lymphocytes, the OUT score also includes the measurement of serum cholesterol. It has been reported that [13] serum cholesterol is related to tumor progression and patient survival in various cancers, including colorectal cancer. This study also proved that serum CEA levels are closely related to the prognosis of patients with colorectal cancer. However, it should be noted that the CONUT score is effective in predicting the prognosis of patients with colorectal cancer, regardless of the serum CEA level. Serum CEA mainly reflects the tumor status, while the CONUT score primarily reflects the overall status of patients, including their nutritional status and immune status. According to the ROC analysis of this study, the combination of these two factors (t-cont) may provide more accurate prognostic information for patients with colorectal cancer than any factor alone. Considering the indications for adjuvant chemotherapy, the combined detection of the two may be helpful in clinical practice.

Migita *et al.* [14] used PNI to assess the preoperative immunonutritional status of patients and found that a low PNI score was associated with a higher risk of non-cancer death. A similar study showed that [15], compared with patients with high PNI scores, elderly patients with gastric cancer with a low PNI score had an increased risk of respiratory failure due to pneumonia. Overall, these findings suggest that poor nutritional status increases the risk of dying from non-cancer-related diseases after surgery. This suggests that it is beneficial to use patient-related factors to predict the prognosis of cancer patients.

In conclusion, this study found that t-CONUT is an effective index for evaluating the prognosis of patients with colorectal cancer. In view of the rapid, simple, and noninvasive determination of serum markers, t-CONUT may be a useful biomarker in a routine clinical setting. However, this study also has some limitations: (1) This study is a retrospective study; therefore, it is easy to produce a certain offset. (2) In this study, patients were divided into high and low groups with a cutoff value of 3. However, the cutoff values reported in different

reports are different, and the best cutoff value has not been recognized. (3) This was a single-center study. The number of patients included in the study was effective. A larger-scale, prospective, randomized, and controlled trial is needed to confirm this result.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

Yichao Zhang and Biao Wang contributed conception and design of the study. Yichao Zhang and Yongchuan Zhang drafted the manuscript. Gang Xiong and Xiao Pang examined research indicators and assisted in data collection. All authors read, discussed and approved the final manuscript.

Data availability statement

The data that support the findings of this study were available from the corresponding author upon reasonable request.

Ethical approval

Not applicable.

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