Pre-treatment Controlling Nutritional Status (CONUT) Score and Carcinoembryonic Antigen Level Provide Tumour Progression and Prognostic Information in Gastric Cancer – A Retrospective Study

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Abstract

Background

This study explores the role of combining the controlling nutritional status (CONUT) score and the carcinoembryonic antigen (CEA) level on predicting tumour stage and prognosis in gastric cancer (GC) patients.

Methods

A total of 682 GC patients were included in this retrospective study. CONUT scores and CEA levels were combined to establish a new scoring system: CONUT-CEA score. Cut-off values for distinguishing patients between stage IV and non-stage IV were established by receiver operating characteristic curves. Cut-off values for predicting prognosis were determined by maximum χ^2 method.

Results

The CONUT and CEA cut-off values for discriminating stage IV patients from non-stage IV patients were 2.0 and 5.58 ng/ml, respectively. Logistic regression model demonstrated that high CONUT-CEA score was related to advanced tumour stage. Among non-stage IV patients, CONUT and CEA cut-off values of 2.0 and 9.50 ng/ml predicted overall survival (OS), respectively. The Cox proportional risk model revealed that high CONUT-CEA score was notable related to decreased OS (2 vs 0: hazard ratios (HR) =2.358, 95% confidence intervals (CI)=1.412–3.940, $P=0.001$) and decreased disease-free survival (2 vs 0: HR=1.980, 95% CI=1.072–3.656, $P=0.003$).

Conclusions

The CONUT-CEA score may be a good biomarker for predicting tumour stage and prognosis in GC patients.

1. Background

Despite great progress in diagnosis and treatment, gastric cancer (GC) remains the fourth most common malignant tumour and the third leading cause of cancer death globally [1]. There are no symptoms or only nonspecific symptoms present at the time of early-stage diseases; consequently, GC is generally diagnosed in advanced stages [2]. Furthermore, patients with the same tumour stage may have different outcomes because of their heterogeneity [3]. Accordingly, accurately evaluating the tumour progression and prognosis of GC patients is helpful for developing individualised treatment programmes to improve prognosis. Tumour progress depends not only on tumour characteristics but also on the nutritional status, systemic inflammation status and immune-compromised status of the patients [4].

Controlling nutritional status (CONUT), a newly developed scoring instrument, consists of three blood indexes: serum albumin (ALB) concentration, total number of peripheral blood lymphocytes and total cholesterol concentration. CONUT was initially reported as a screening instrument to evaluate the nutritional status of patients [5–8]. The prognostic values of CONUT for a variety of human tumours have been reported in recent years. It can be used to predict the prognosis of breast, bladder and lung cancer and the prognosis of GC patients [7, 9–11]. The effect of the CONUT score on the prognosis of GC patients was first reported in 2018 [12]. Since then, other studies on the effect of CONUT on the prognosis of GC have been published, but the results were inconsistent. Some studies reported that the overall survival (OS) of GC patients with high CONUT scores was significantly lower than those with low CONUT scores [12–15], but the CONUT score cut-off values differed among studies. Liu X et al. [16] and Suzuki S et al. [15] found that the CONUT score can independently predict cancer-specific survival (CSS). However, Kuroda D et al. [12] reported that the CONUT score had no significant effect on CSS. Moreover, these studies only analysed patients with Tumour-Node-Metastasis (TNM) stages I–III and did not include stage IV patients. The treatment and prognosis of stage IV and non-stage IV patients are different. Therefore, evaluating the preoperative clinical stage is key to choosing the appropriate treatment. Inflammation, nutrition and other indicators may be altered in stage IV patients. Hence, the CONUT score may be able to predict preoperative stage IV GC.

Carcinoembryonic antigen (CEA), a structural antigen expressed on the surface of tumour cells, is one of the most commonly used biomarkers of GC [17]. CEA levels are often used in the early detection of cancer, and some studies have shown that CEA levels are related to preoperative predictions and can reflect tumour characteristics [18]. CEA levels have been used as a prognostic indicator in GC [19–21]. However, due to its low sensitivity and high false-positive rate, the role of CEA as an independent prognostic marker has always

been controversial [22, 23]. Although CEA levels have limited value as an independent prognostic factor, some research has shown that the combinations of CEA levels and other indicators can increase their prognostic sensitivity [24, 25].

In this retrospective study, CONUT scores and CEA levels were combined to establish a new scoring system: CONUT-CEA score. This study analysed the role of combinations of pre-treatment CONUT score and CEA levels on tumour stage, and accessed the predictive value of the combined detection of the CONUT score and CEA levels on the prognosis of GC patients.

2. Methods

2.1. Patient population

This analysis included patients with GC who were diagnosed and treated at the First Affiliated Hospital of Fujian Medical University in Fujian, China between 2008 and 2011. This study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University and obtained the informed consent of all participants.

The exclusion criteria were as follows: (1) patients who had gastroduodenal diseases, haematologic diseases, autoimmune diseases, systemic inflammatory diseases, infections, thyroid disease, coronary artery disease, renal function failure, severe liver disease or other malignancies; (2) patients who had incomplete clinical and pathologic data; (3) patients who had previous surgery or radiotherapy and chemotherapy and (4) patients who had used corticosteroids, acetylsalicylic acid or statins within the previous three months.

Based on these criteria, we enrolled 682 patients, including 504 men and 178 women, the median age was 61.0 years (interquartile range (IQR) = 54.0–69.0 years, range: 18–87 years). Of the patients, 148 cases (21.7%) were stage I, 183 cases (26.8%) were stage II, 227 cases (33.3%) were stage III and 124 cases (18.2%) were stage IV. Stage I, II and III were defined as non-stage IV. Tumours were classified according to the seventh edition of the AJCC/TNM tumour staging system [24]. In the non-stage IV patients, 282 (50.5%) had proximal GC and 276 (49.5%) had distal GC; all the non-stage IV patients were subjected to radical operation. Seventy-four patients with stage IV GC were subjected to surgery, and the remaining 50 patients did not receive surgery and were diagnosed as stage IV by imaging examinations.

Stage IV GC was diagnosed as follows: (1) metastasis of the liver, lung, bone, pancreas and other organs; (2) peritoneal dissemination; and (3) metastasis of distant lymph nodes.

2.2. Clinical assessment and laboratory data

Medical records and laboratory results were retrospectively reviewed. Age, sex, smoking status, alcohol intake, clinical characteristics, lymphocytes, ALB and total cholesterol level were collected from the patients’ medical records. All peripheral venous blood samples were collected in the morning after fasting for one night (at least 8 hours). The CONUT scores were calculated from the ALB concentration, total blood cholesterol level and total peripheral lymphocyte count (Table 1).

Table 1
Nutritional status assessment according to CONUT scoring system

Parameters	Undernutrition degree			
	Normal	Light	Moderate	Severe
Serum albumin (g/dl)	≥ 3.50	3.00–3.49	2.50–2.99	< 2.50
Score	0	2	4	6
Total lymphocyte count (/mm ³)	≥ 1600	1200–1599	800–1199	< 800
Score	0	1	2	3
Total cholesterol (mg/dl)	≥ 180	140–179	100–139	< 100
Score	0	1	2	3
CONUT score = Serum albumin score + Total lymphocyte count score + Total cholesterol score				

CONUT-CEA score was established by combining CONUT scores and CEA levels, including CONUT-CEA score-1 and CONUT-CEA score-2. Cut-off values of CONUT scores and CEA levels for distinguishing between stage IV and non-stage IV patients were established, and the

CONUT-CEA score-1 was calculated based on the above cut-off values. Cut-off values of CONUT scores and CEA levels for predicting OS in non-stage IV patients were established, and the CONUT-CEA score-2 was calculated based on the above cut-off values.

2.3. Follow-up

For the non-stage IV patients, follow-up was conducted every three months during the first two years after resection, every six months during the next three years and every year thereafter. Postoperative follow-up included physical examination, laboratory examination, gastroscopy and chest/abdominopelvic computed tomography. The last follow-up was performed on September 1, 2019. The definition of OS was from the date of radical operation to death or the last follow-up. The definition of disease free survival (DFS) was from the date of radical operation to the date of local tumour recurrence and/or metastasis or the date of the last follow-up. The main endpoint was OS, and the secondary endpoint was DFS.

2.4. Statistical analyses

Cut-off values for distinguishing patients between stage IV and non-stage IV were established by receiver operating characteristic(ROC) curves. A binary logistical regression model was used to established parameters related to stage IV GC. Cut-off values of CONUT and CEA to predict prognosis were determined by maximum χ^2 method, this analysis uses the R maxstat software package (R Foundation for Statistical Computing, Vienna, Austria). The Kaplan–Meier method was used to determine the influence of each variable on OS and DFS, and log-rank tests were used to compare the survival curves. A Cox proportional risk model was used for the univariate and multivariate analyses to determine the influence of clinical parameters on the prognosis of OS and DFS. Significant variables in the univariate analysis ($P < 0.05$) were entered into the multivariate regression models, and the data were represented as hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were performed using SPSS software 19.0 (SPSS Inc., Chicago, IL, USA) and R version 3.5.2 software (Institute for Statistics and Mathematics, Vienna, Austria). A P -value < 0.05 was considered significant.

3. Results

3.1. Patient characteristics

Among the 682 patients, the CONUT score ranged from 0 to 11. The median CONUT value was 1 (IQR = 0–3). The CEA level ranged from 0.200 to 1000.0 ng/ml, the median CEA level was 2.41 ng/ml (IQR = 1.44–5.21 ng/ml). Of the non-stage IV patients, 282 (50.5%) had proximal GC and 276 (49.5%) had distal GC. After radical surgery in the non-stage IV cases, the median follow-up duration was 101 (range: 1–130) months; for patients who were alive at the end of this study, the median follow-up duration was 109 (range: 71–130) months. The baseline clinical characteristics of the patients are shown in Table 2.

Table 2
Demographic and clinical characteristics of the study population

Characteristics	Value	Percentage	Median(IQR)
Number of patients	682		
Age(years)			61(54, 69)
≥ 75	76	11.1%	
< 75	606	88.9%	
Sex(male)			
male	504	73.9%	
female	178	26.1%	
Smoking			
Yes	168	24.6%	
No	514	75.4%	
Alcohol intake			
Yes	64	9.38%	
No	618	90.6%	
BMI(kg/m ²)			21.9(19.8, 23.9)
≥ 25	97	14.2%	
< 25	585	85.8%	
ALB (g/dl)			3.78(3.50,4.08)
Lymphocyte (mm ³)			1710(1340,2050)
Cholesterol (mg/dl)			170.9(147.3,201.1)
CONUT			1(0,3)
CEA			2.41(1.44,5.21)
Clinical TNM stage			
I	148	21.7%	
II	183	26.8%	
III	227	33.3%	
IV	124	18.2%	
Tumor location (TNM stage I-III)	558		
Proximal	282	50.5%	
Distal	276	49.5%	
T stage(TNM stage I-III)			
T1	108	19.4%	
T2	72	12.9%	
T3	142	25.5%	

IQR: interquartile range; BMI: body mass index; CONUT: Controlling nutritional status; CEA: Carcinoembryonic antigen; ALB: Albumin; TNM: Tumour-Node-Metastasis.

Characteristics	Value	Percentage	Median(IQR)
T4	236	42.3%	
N stage(TNM stage I-III)			
N0	229	41.0%	
N1	98	17.6%	
N2	88	15.8%	
N3	143	25.6%	
Histological type (TNM stage I-III)			
Differentiated	209	37.5%	
Undifferentiated	349	62.5%	
Postoperative Complications (TNM stage I-III)			
No	463	83.0%	
Yes	95	17.0%	
Neurovascular invasion (TNM stage I-III)			
No	292	52.3%	
Yes	266	47.7%	
Adjuvant chemotherapy (TNM stage I-III)			
Absent	233	41.8%	
Present	325	58.2%	
IQR: interquartile range; BMI: body mass index; CONUT: Controlling nutritional status; CEA: Carcinoembryonic antigen; ALB: Albumin; TNM: Tumour-Node-Metastasis.			

The baseline clinical characteristics of the non-stage IV and stage IV cases are shown in Table 3. No significant differences were noted in sex, age, BMI, smoking status and alcohol intake ($P > 0.05$).

Table 3
Comparison of the clinical indexes between stage IV and non-stage IV groups.

	Total N = 682(%)	Stage IV group N = 124(%)	Non-stage IV group N = 558(%)	χ^2/F	p
Sex				0.973	0.324
female	178(26.1)	28(22.6)	150(26.9)		
male	504(73.9)	96(77.4)	408(73.1)		
Age				1.008	0.315
< 75	606(88.9)	107(86.3)	499(89.4)		
≥ 75	76(11.1)	17(13.7)	59(10.6)		
Smoking				0.634	0.426
No	514(75.4)	90(72.6)	424(76.0)		
Yes	168(24.6)	34(27.4)	134(24.0)		
Alcohol				0.430	0.512
No	613(89.9)	105(88.2)	508(90.2)		
Yes	69(10.1)	14(11.8)	55(9.8)		
BMI (kg/m ²)				0.033	0.856
<25	585(85.8)	107(86.3)	478(85.7)		
≥ 25	97(14.2)	17(13.7)	80(14.3)		
CONUT		2.56 ± 2.29	1.86 ± 1.92	6.584	0.002
CEA		45.70 ± 140.4	9.073 ± 52.63	63.245	0.005
BMI: body mass index; CONUT: Controlling nutritional status; CEA: Carcinoembryonic antigen.					

3.2. Relationship between pre-treatment tumour stage and CONUT/CEA

The median (IQR) CONUT score of the stage IV patients was 2 (1–4), and that of the non-stage IV patients was 1 (0–3). The CONUT score of stage IV patients was significantly higher than that of non-stage IV patients ($P = 0.002$) (Table 3). The median (IQR) CEA of the stage IV patients was 4.30 (1.77–11.93) ng/ml, and that of the non-stage IV patients was 2.28 (1.41–4.43) ng/ml. The CEA of the stage IV patients was significantly higher than that of the non-stage IV patients ($P = 0.005$) (Table 3).

According to the ROC curves, the area under the curve (AUC) was 0.592 (95% CI: 0.535–0.649) for discriminating stage IV patients from non-stage IV patients based on the CONUT score, and the AUC was 0.651 (95% CI: 0.580–0.695) for discriminating stage IV patients from non-stage IV patients based on the CEA level (Fig. 1a and b). According to the ROC analysis, the cut-off value of CONUT was 2.0, the sensitivity and specificity were 0.436 and 0.708, respectively. The cut-off value of CEA was 5.58 ng/ml, the sensitivity and specificity were 0.460 and 0.815, respectively.

According to the CONUT and CEA cut-off values, cases were split into the following groups: high (≥ 2 ; $n = 217$) and low CONUT status (< 2 ; $n = 465$) or high (≥ 5.58 ng/mL; $n = 160$) and low CEA status (< 5.58 ng/mL; $n = 522$).

3.3 Relationship between tumour stage and CONUT-CEA score

The CONUT-CEA score-1 ranged from 0 to 2 as follows: score of 0, neither high CONUT (≥ 2) nor high CEA (≥ 5.58 ng/mL); score of 1, either high CONUT or high CEA; score of 2, both high CONUT and high CEA. A CONUT-CEA score-1 of 0, 1 and 2 was noted in 367 (53.8%), 253 (37.1%) and 62 (9.09%) cases. The CONUT-CEA score-1 of the stage IV group was significantly higher than that of the non-stage IV group ($P = 0.000$) (Table 4). The univariate and multivariate logistic regression model displayed that high CONUT-CEA score-1 was correlated with stage IV ($P < 0.001$) (Table 5).

Table 4
Relationship between tumor stage and the CONUT-CEA score

	CONUT-CEA score-1(%)			p
	0 (n = 367)	1 (n = 253)	2 (n = 62)	0.000
Stage IV group (n = 124)	40(32.3)	57(46.0)	27(21.8)	
Non-stage IV group (n = 558)	327(58.6)	196(35.1)	35(6.27)	

Table 5
Risk factors related to diagnose as stage IV: univariate and multivariate logistic regression analysis

	Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P
Sex(female vs male)	0.793	0.500-1.258	0.325	0.809	0.486-1.346	0.414
Age(≥ 75 vs < 75)	1.344	0.753-2.396	0.317	1.004	0.539-1.870	0.991
Smoking(yes vs no)	1.195	0.770-1.856	0.426	1.063	0.632-1.790	0.817
Alcohol(yes vs no)	1.293	0.690-2.422	0.422	1.324	0.652-2.688	0.437
BMI(≥ 25 vs < 25)	0.949	0.540-1.668	0.856	1.368	0.753-2.486	0.303
CONUT-CEA score-1						
1 vs 0	2.377	1.529-3.696	0.000	2.451	1.559-3.855	0.000
2 vs 0	6.306	3.462-11.489	0.000	6.810	3.649-12.710	0.000

3.4. The optimal cut-off values for forecasting the prognosis of non-stage IV cases

The optimal CONUT and CEA cut-off values were 2.0 and 9.50 ng/ml, respectively, for predicting OS of non-stage IV cases (Fig. 2). The CONUT-CEA score-2 ranged from 0 to 2 as follows: score of 2, high CONUT (≥ 2) and high CEA (≥ 9.50 ng/ml); score of 1, either high CONUT or high CEA; score of 0, neither high CONUT nor high CEA. A CONUT-CEA score-2 of 0, 1 and 2 was noted in 357 (64.0%), 175 (31.4%) and 26 (4.66%) patients, respectively. CONUT, CEA and CONUT-CEA score-2 were significantly associated with the prognosis of OS and DFS based on the Kaplan–Meier method and log-rank tests ($P < 0.05$, Fig. 3).

3.5. Univariate and multivariate analyses of OS

As shown in Table 6, $\text{CONUT} \geq 2$, $\text{CEA} \geq 9.5$ ng/ml, high CONUT-CEA score-2, age ≥ 75 years, T stage, N stage, TNM stage, histological type and neurovascular invasion were established as significant prognostic factors of OS in the univariate analysis (all $P < 0.05$).

Table 6
Univariate and multivariate analyses for OS and DFS among patients with gastric cancer

	Overall Survival						Disease-free Survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
CONUT (≥ 2 vs. <2)	2.185	1.674–2.853	0.000	-	-	-	1.756	1.280–2.408	0.000	-	-	-
CEA (≥ 9.5 vs. <9.5)	1.819	1.273–2.599	0.001	-	-	-	1.681	1.105–2.557	0.015	-	-	-
CONUT-CEA score-2 (1 vs. 0)	2.083	1.582–2.744	0.000	1.647	1.241–2.188	0.001	1.757	1.272–2.427	0.001	1.452	1.046–2.016	0.026
CONUT-CEA score-2 (2 vs. 0)	3.339	2.028–5.499	0.000	2.358	1.412–3.940	0.001	2.475	1.352–4.531	0.003	1.980	1.072–3.656	0.029
Age (≥ 75 vs. <75)	2.423	1.713–3.426	0.000	2.400	1.672–3.444	0.000	1.511	0.964–2.369	0.072	-	-	-
Sex (female vs. male)	1.323	0.997–1.756	0.052	-	-	-	1.375	0.990–1.909	0.057	-	-	-
Smoking	0.783	0.566–1.083	0.139	-	-	-	0.727	0.491–1.075	0.110	-	-	-
Alcohol	0.964	0.602–1.542	0.878	-	-	-	0.888	0.504–1.566	0.683	-	-	-
BMI (≥ 25 vs. <25)	0.730	0.485–1.098	0.131	-	-	-	0.811	0.508–1.295	0.381	-	-	-
Tumor location (distal vs. proximal)	0.778	0.597–1.014	0.063	-	-	-	0.846	0.621–1.153	0.289	-	-	-
T stage (T2 VS. T1)	2.450	1.18–5.086	0.016	-	-	-	2.132	0.898–5.060	0.086	-	-	-
T stage (T3 VS. T1)	5.262	2.844–9.736	0.000	-	-	-	4.615	2.262–9.418	0.000	-	-	-
T stage (T4 VS. T1)	6.660	3.682–12.045	0.000	-	-	-	5.926	2.990–11.747	0.000	-	-	-
N stage (N1 VS. N0)	2.810	1.822–4.335	0.000	-	-	-	2.878	1.660–4.988	0.000	-	-	-
N stage (N2 VS. N0)	4.028	2.646–6.133	0.000	-	-	-	5.724	3.465–9.457	0.000	-	-	-
N stage (N3 VS. N0)	5.850	4.031–8.490	0.000	-	-	-	6.221	3.907–9.907	0.000	-	-	-
TNM stage (II vs. I)	3.889	2.254–6.710	0.000	2.721	1.543–4.799	0.001	3.813	1.916–7.588	0.000	2.820	1.378–5.772	0.005
TNM stage (III vs. I)	8.697	5.179–14.606	0.000	5.848	3.352–10.205	0.000	9.566	5.003–18.290	0.000	6.634	3.300–13.335	0.000
Histological type (undifferentiated vs. differentiated)	1.523	1.145–2.026	0.004	1.104	0.813–1.498	0.526	1.637	1.164–2.304	0.005	1.063	0.742–1.524	0.737
Complications (yes vs. no)	0.677	0.217–2.115	0.502	-	-	-	1.099	0.735–1.642	0.646	-	-	-

BMI: body mass index; CONUT: Controlling nutritional status; CEA: Carcinoembryonic antigen; ALB: Albumin; TNM: Tumour-Node-Metastasis; OS, Overall survival; DFS, Disease-free survival.

	Overall Survival					Disease-free Survival						
Neurovascular invasion (yes vs. no)	2.619	1.988–3.451	0.000	1.563	1.158–2.110	0.004	2.735	1.969–3.799	0.000	1.475	1.033–2.104	0.032
Adjuvant chemotherapy (present vs. absent)	1.279	0.974–1.680	0.076	-	-	-	1.118	0.816–1.532	0.487	-	-	-
BMI: body mass index; CONUT: Controlling nutritional status; CEA: Carcinoembryonic antigen; ALB: Albumin; TNM: Tumour-Node-Metastasis; OS, Overall survival; DFS, Disease-free survival.												

In the Cox multivariate analysis, high CONUT-CEA score-2 (1 vs 0: HR = 1.647, 95%CI = 1.241–2.188, P = 0.001; 2 vs 0: HR = 2.358, 95%CI = 1.412–3.940, P = 0.001), age $\geq$ 75 years (HR = 2.400, 95%CI = 1.672–3.444, P = 0.000), elevated TNM stage (II vs I: HR = 2.721, 95%CI = 1.543–4.799, P = 0.001; III vs I: HR = 5.848, 95%CI = 3.352–10.205, P = 0.000), and neurovascular invasion (HR = 1.563, 95%CI = 1.158–2.110, P = 0.004) were notable related to decreased OS (Table 6).

3.6. Univariate and multivariate analyses of DFS

According to the univariate analysis (Table 6), CONUT $\geq$ 2, CEA $\geq$ 9.5 ng/ml, high CONUT-CEA score-2, age $\geq$ 75 years, T stage, N stage, TNM stage, histological type and neurovascular invasion were established as significant prognostic factors of DFS (all P < 0.05).

According to the Cox multivariate analysis, high CONUT-CEA score-2 (1 vs 0: HR = 1.452, 95%CI = 1.046–2.016, P = 0.001; 2 vs 0: HR = 1.980, 95%CI = 1.072–3.656, P = 0.003), elevated TNM stage (II vs I: HR = 2.820, 95%CI = 1.378–5.772, P = 0.000; III vs I: HR = 6.634, 95%CI = 3.300–13.335, P = 0.000), and neurovascular invasion (HR = 1.475, 95%CI = 1.033–2.104, P = 0.000) were notable related to decreased DFS (Table 6).

4. Discussion

In the present study, CONUT scores and CEA levels were combined to establish the CONUT-CEA score, which is a new scoring system used for predicting the preoperative stage and postoperative prognosis of GC patients. The present study demonstrated that the CONUT-CEA score plays an important role in discriminating patients with stage IV GC from those with non-stage IV GC, and high CONUT-CEA score was notable related to poor OS and DFS in non-stage IV GC patients. To our knowledge, this study is the first to determine the role of the CONUT-CEA score in the staging and prognostic evaluation of GC.

A CONUT cut-off value of 2 was used to preoperatively determine whether the patient was stage IV or non-stage IV. The present study also showed high CONUT levels ($\geq$ 2) was associated with worse OS and DFS. The CONUT cut-off value in the present study was the same as that reported by Ryo S et al. [14]. The CONUT score is calculated according to the ALB concentration, total blood cholesterol level and total peripheral lymphocyte count. In addition to reflecting nutritional status, ALB can reflect systemic inflammation [26]. Pro-inflammatory cytokines decrease ALB by regulating the synthesis of albumin in the liver [27, 28]. The total number of lymphocytes reflects the host's immune response to the tumour [29]. Low peripheral blood lymphocyte counts lead to insufficient immune responses of the host to cancer cells, leading to cancer progression [30–32]. The total cholesterol concentration is related to tumour progression and the prognosis of various cancers [33, 34]. Tumour growth requires cholesterol consumption, leading to cholesterol lowering [35]. The CONUT score can reflect nutritional status, the systemic inflammation status and immune response. Nutritional damage and immunosuppression in cancer patients promote the chronic inflammatory response of cancer cells [36–38]. Additionally, systemic inflammation and malnutrition are the main reasons for the reduction of interleukin-2 and interleukin-3 levels, leading to the impairment of tumour immune function and the increase of tumour cell proliferation [36, 38]. The increased production of vascular endothelial cell growth factors is related to chronic inflammation, malnutrition and immunosuppression in GC patients [39].

CEA is a glycosylated protein with a glycosylated form of salivary fucosylation [40]. As a selectin ligand, CEA promotes the metastasis of cancer cells [41, 42]. CEA levels are closely associated with tumour burden, so the elevation of CEA levels may be correlated with the pathological stage and prognosis of cancer. Some researches have found that CEA levels are related to pathological stage and can predict prognosis and recurrence in GC, and some studies also reported that high CEA levels above the upper limit of normal indicate a poor outcome in GC; however, the cut-off values of CEA remain unclear. Eui Soo Han et al. [43] found that the CEA levels of GC patients with extensive peritoneal seeding were significantly higher than those of other stages, but the ROC curve did not determine the cut-off

values of CEA. Xiaowen Liu et al. [44] found that the increase of serum CEA levels was related to the GC pathological stage and lymph infiltration, but they did not show the cut-off value of CEA. A study conducted by Park et al. [45] found a high recurrence rate in CEA-positive GC patients. Takahashi et al. [46] founded that patients with high CEA levels, particularly a CEA ratio more than twice the normal upper limit, experience more frequent cancer recurrence. Jong-Chan Lee et al. [47] also found that patients with CEA levels more than twice the normal limit had a poor prognosis. Jun Xiao et al. [48] reported that a cut-off value of 30.02 ng/ml could be applied to distinguish between patients with a poor prognosis and good prognosis.

In the present study, according to the ROC analysis results, CEA cut-off value of 5.58 ng/ml can be used to judge whether patients were in stage IV preoperatively. When assessing prognosis, the present study unveiled that CEA levels ≥ 9.50 ng/ml was related to worse OS and DFS in non-stage IV patients after radical operation. Moreover, the CEA levels were nearly twice as high as normal limits, which was close to the results reported by Kim et al. [49] and Jong-Chan Lee [47] et al.

Tumour progression is known to be associated with tumour characteristics, host nutritional status, systemic inflammation status and immunocompromised status. Therefore, identifying parameters that can reflect both tumour characteristics and host state can provide a better prognostic value. Meanwhile, CEA levels were found to be related to invasion of tumour cells [39–41], and the CONUT score can reflect the nutritional, inflammation and immune response state. The multivariate logistic analysis of the present study showed that high CONUT-CEA score was related to advanced tumour stage. So we believe that the CONUT score combined with the CEA level can improve the preoperative diagnosis of GC stage. Moreover, the current study demonstrated that the CONUT-CEA score was a more effective candidate prognostic biomarker in patients undergoing surgical resection of GC than the CONUT score or CEA level alone displayed in Table 6.

There were some limitations in this study. First of all, this was a retrospective study at one centre, so the possibility of selection bias cannot be completely controlled. Second, we cannot assess the influence of the postoperative CONUT score and CEA level on the prognosis of GC. Third, different nutritional supports after surgery were inevitable, which may confuse our results.

5. Conclusions

In summary, the CONUT score and CEA level are useful for the differential diagnosis of stage IV and non-stage IV GC, and the combination of these measurements is more helpful than each factor alone. Additionally, the CONUT score and CEA level are helpful for forecasting OS and DFS in GC patients after radical gastrectomy. Assessing preoperative CONUT-CEA score may help develop effective strategies for GC treatment. CONUT and CEA, as inexpensive and convenient markers, can play an important role in treatment decision-making and follow-up in GC.

Abbreviations

CONUT

Controlling nutritional status; CEA: Carcinoembryonic antigen; ALB: Albumin; AUC: Area under the curve; ROC: Receiver operating characteristic; CI: Confidence intervals; CSS: Cancer-specific survival; OS: Overall survival; DFS: Disease-free survival; GC: Gastric cancer; HR: Hazard ratios; TNM: Tumour-Node-Metastasis

Declarations

Acknowledgements

None.

Authors' contributions

LYY and PWW drafted the overall design of the study. XQC and PWW wrote the manuscript. XQC and XMS obtained and analysed the data. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the first or correspondence authors on reasonable request.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (approval no: MRCTA, ECFAH of FMU [2019] 200). Written informed consent for data collection and analysis was obtained from the respective patients.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Receiver operating characteristic curves of CONUT score (A) and CEA (B) to discriminate stage IV group and non-stage IV group. CONUT, controlling nutritional status; CEA, carcinoembryonic antigen.

Figure 1

Receiver operating characteristic curves of CONUT score (A) and CEA (B) to discriminate stage IV group and non-stage IV group. CONUT, controlling nutritional status; CEA, carcinoembryonic antigen.

Figure 2

Cut-off value for CONUT(A) and CEA(B). The maximum difference in overall survival was achieved when the CONUT score was 2.0 and CEA level was 9.50 ng/ml. CONUT, controlling nutritional status; CEA, carcinoembryonic antigen.

Figure 2

Cut-off value for CONUT(A) and CEA(B). The maximum difference in overall survival was achieved when the CONUT score was 2.0 and CEA level was 9.50 ng/ml. CONUT, controlling nutritional status; CEA, carcinoembryonic antigen.

Figure 3

Kaplan-Meier analysis of the effects of each variable on OS and DFS. CONUT, controlling nutritional status; CEA, carcinoembryonic antigen; OS, Overall survival; DFS, Disease-free survival.

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Kaplan-Meier analysis of the effects of each variable on OS and DFS. CONUT, controlling nutritional status; CEA, carcinoembryonic antigen; OS, Overall survival; DFS, Disease-free survival.