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ORIGINAL ARTICLE

Retrospective Study

Prognostic value and predictive model of tumor markers in stage I to III gastric cancer patients

Ai-Hua Sun, Xin-Yu Zhang, Yang-Yang Huang, Lei Chen, Qing Wang, Xiao-Cong Jiang

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Abstract

BACKGROUND

Preoperative serum tumor markers have been widely used in the diagnosis and treatment of gastric cancer patients. However, few studies have evaluated the prognosis of gastric cancer patients by establishing statistical models with multiple serum tumor indicators.

AIM

To explore the prognostic value and predictive model of tumor markers in stage I and III gastric cancer patients.

METHODS

From October 2018 to April 2020, a total of 1236 patients with stage I to III gastric cancer after surgery were included in our study. The relationship between serum tumor markers and clinical and pathological data were analyzed. We established a statistical model to predict the prognosis of gastric cancer based on the results of COX regression analysis. Overall survival (OS) was also compared across different stages of gastric cancer.

RESULTS

The deadline for follow-up was May 31, 2023. A total of 1236 patients were included in our study. Univariate analysis found that age, clinical stage, T and N stage, tumor location, differentiation, Borrmann type, size, and four serum tumor

markers were prognostic factors of OS ($P < 0.05$). It was shown that clinical stage, tumor size, alpha foetoprotein, carcinoembryonic antigen, CA125 and CA19-9 ($P < 0.05$) were independent prognostic factors for OS. According to the scoring results obtained from the statistical model, we found that patients with high scores had poorer survival time ($P < 0.05$). Furthermore, in stage I patients, the 3-year OS for scores 0-3 ranged from 96.85%, 95%, 85%, and 80%. In stage II patients, the 3-year OS for scores 0-4 were 88.6%, 76.5%, 90.5%, 65.5% and 60%. For stage III patients, 3-year OS for scores 0-6 were 70.9%, 68.3%, 64.1%, 50.9%, 38.4%, 18.5% and 5.2%. We also analyzed the mean survival of patients with different scores. For stage I patients, the mean OS was 55.980 months. In stage II, the mean OS was 51.550 months. The mean OS for stage III was 39.422 months.

CONCLUSION
Our statistical model can effectively predict the prognosis of gastric cancer patients.

Key Words: Gastric cancer; Tumor marker; Prognosis; Overall survival; Model

Core Tip: Gastric cancer is one of the most common malignant tumors in the world, few studies have established models to evaluate the prognosis of gastric cancer patients by preoperative serum tumor markers. The relevance between serum tumor markers and clinical and pathological data was analyzed in this study. We established a statistical model to predict the prognosis of gastric cancer, The perspective model can be helpful for the diagnosis and treatment of gastric cancer.

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INTRODUCTION

Gastric cancer is one of the most common malignant tumors in the world. Although its mortality has decreased in recent years, gastric cancer remains the third most common cause of cancer-related death[1]. In China, the incidence of gastric cancer is much higher. A total of 456124 people developed gastric cancer in 2018, and gastric cancer is the second leading cause of death among Chinese cancer patients (17.5%)[2]. Therefore, the early diagnosis of gastric cancer is particularly important. According to the Chinese Society of Clinical Oncology (CSCO) guidelines, preoperative diagnosis of gastric cancer mainly depends on endoscopy, imaging and pathological examination[3]. However, preoperative serum tumor markers are still classic components with reference values.

Alpha foetoprotein (AFP), one of the earliest discovered tumor markers, plays an important role in the diagnosis and treatment of hepatocellular carcinoma[4]. It has also been shown to be associated with female reproductive system tumors such as endodermal sinus tumor[5]. Carcinoembryonic antigen (CEA) is most commonly used in the diagnosis and follow-up of colorectal and intestinal cancer, and its diagnostic value in gastric cancer has also been confirmed[6]. The level of CA-125 influences the prognosis of multiple tumors, such as non-Hodgkin's lymphoma, endometrial cancer [7,8]. In addition, it is a useful prognostic biomarker for recurrence in gastric cancer patients[9]. In previous studies, the diagnostic value of CA19-9 in colorectal cancer has been fully proven[10].

In general, serum tumor markers are strongly associated with the stage and metastasis of gastric cancer[11]. The importance of the four tumor markers we studied for the early diagnosis of gastric cancer has long been demonstrated [12]. However, few studies have established models to evaluate the prognosis of gastric cancer patients using preoperative serum tumor markers. Therefore, in this present study, we aimed to explore the diagnostic and prognostic value of four preoperative serum tumor markers in different clinical stages of gastric cancer patients by using a scoring system.

MATERIALS AND METHODS

Our study was conducted at Huizhou Municipal Central Hospital. From October 2018 to April 2020, a total of 1236 patients with stage I to III gastric cancer who had undergone surgery were included in our study. Patients with emergency operations, incompatible pathological types, unclear causes of death or death within 30 days, incomplete data, or those who were lost to follow-up were excluded (Figure 1). All procedures performed in research involving human participants were in accordance with the Declaration of Helsinki.

All patients' venous blood samples were taken into serum separator tubes within one week before surgery. Hematological parameters were determined immediately after blood sample collection using an electrochemical luminescence immunoassay analyzer (e602, Roche, Switzerland) in the clinical laboratory. The clinicopathological data of the patients,

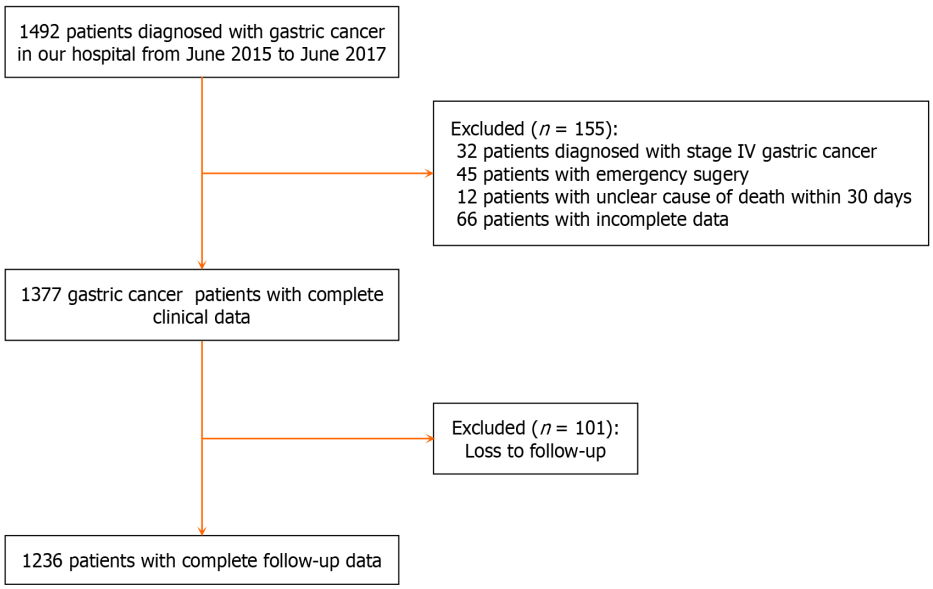

Figure 1 Flow chart of patients included in the study.

including gender, age, serum AFP, CEA, CA125, and CA19-9 levels, and pathological results were obtained from database in our hospital. The pathological stage was evaluated according to the 8th AJCC criterion for gastric cancer. None of the patients had received any chemoradiotherapy or surgery before testing for serum tumor markers. The upper normal limits of CA199, CEA, AFP and CA125 were 27 U/mL, 5 ng/mL, 5 ng/mL and 15 U/m, respectively. Furthermore, to analyze the influence of preoperative tumor markers on the prognosis of gastric cancer in different clinical stages, the weight of each marker was evaluated in our study. According to the positive numbers of tumor markers, the patients were scored from 0 to 6. The deadline for follow-up was May 31, 2020. Overall survival (OS) was recorded by telephone.

This study analyzed the influencing factors on the survival of patients with gastric cancer, then scored patients with gastric cancer according to the results of the survival analysis, and compared the prognosis of patients with different stages of gastric cancer according to their total score. The χ^2 test, Cox regression analysis and Kaplan-Meier method were used to analyze the data. All data analyses were performed using IBM SPSS 23.0 software. $P < 0.05$ have significant differences.

RESULTS

A total of 1236 patients were recruited for our study, including 937 males (75.8%) and 299 females (24.2%). The median age of these patients was 65 years, ranging from 23 to 87. The number of patients with clinicopathological stage I was 288 (23.3%), and the number of patients with stage II and III gastric cancer was 272 (22.0%) and 676 (54.7%), respectively. By the end of our follow-up period, 842 patients were alive, and 394 patients died (Table 1).

The relevance between four different tumor markers and clinical data was explored. It was shown that an elevation of AFP revealed a significant correlation with clinical stage, N stage, and survival status (Table 2). However, there was no significant difference in age, gender, differentiation, pathology type, tumor location, Borrmann type and size ($P > 0.05$; Table 2). The values of CEA were also analyzed, which showed that CEA was associated with age, clinical stage, N stage, T stage, tumor location, differentiation, Borrmann type, size, and survival status (Table 2). However, CEA was not related with gender and pathology type ($P > 0.05$; Table 2). Different from AFP and CEA, the level of CA125 was associated with T stage, N stage and clinical stage, differentiation, Borrmann type, size, and survival status (Table 2). A similar trend was observed in the increase of CA19-9, the preoperative serum CA19-9 expression was significantly different in clinical stage, T and N stage, tumor location, differentiation, pathology type, Borrmann type, size, and survival status (Table 2). However, CA199 was not related with gender and age ($P > 0.05$; Table 2).

To further analyze the factors affecting the prognosis of gastric cancer patients, we used univariate and multivariate Cox regression analysis. The univariate analysis indicated that age, clinical stage, T and N stage, tumor location, differentiation, Borrmann type, size, and four serum tumor markers were prognostic factors for OS (Table 3). However, pathology type and gender had no significance for OS ($P > 0.05$; Table 3). Furthermore, we included meaningful factors from the univariate analysis in the multivariate analysis. In multivariate analysis, the clinical stage was derived from both T and N stages, so we only included the clinical stage in multivariate analysis. The results showed that clinical stage, tumor size, AFP, CEA, CA125 and CA19-9 ($P < 0.05$; Table 3) were independent prognostic factors for OS.

Then, we analyzed the differences among these increased tumor markers based on OS. There were statistically significant differences in OS among four different tumor markers ($P < 0.05$; Figure 2A). Therefore, we conducted a

Table 1 Patient demographics and clinicopathologic features, *n* (%)

Variables	Patients (*n* = 1236)
Gender	
Male	937 (75.8)
Female	299 (24.2)
Age	
< 65	685 (55.4)
≥ 65	551 (44.6)
Drinking	
Yes	269 (21.8)
No	967 (78.2)
Smoking	
Yes	266 (21.5)
No	970 (78.5)
Operation methods	
Open surgery	1103 (89.2)
Laparoscopic surgery	133 (10.8)
Hospitalization time	
< 15 days	539 (43.6)
≥ 15 days	697 (56.4)
Clinical stage	
I	288 (23.3)
II	272 (22.0)
III	676 (54.7)
T stage	
T1	224 (18.1)
T2	127 (10.3)
T3	174 (14.1)
T4	711 (57.5)
N stage	
N0	504 (40.8)
N1	203 (16.4)
N2	227 (18.4)
N3	302 (24.4)
Tumor location	
Cardia	633 (51.2)
Gastric body	239 (19.3)
Antrum of stomach	364 (29.5)
Pathological type	
Adenocarcinoma	1168 (94.5)
Mucinous adenocarcinoma	42 (3.4)
Squamous cell carcinoma	15 (1.2)
Signet ring cell carcinoma	11 (0.9)

Degree of differentiation	
Well	19 (1.5)
High	42 (3.4)
Medium	300 (24.3)
Moderate to low	330 (26.7)
Poor	545 (44.1)
Borrmann type	
I	155 (12.5)
II	287 (23.2)
III	737 (59.6)
IV	57 (4.7)
Size	
< 5cm	690 (55.8)
≥ 5cm	546 (44.2)
Survival status	
Alive	842 (68.1)
Dead	394 (31.9)

multivariate Cox regression analysis for the four tumor markers separately, and established a statistical model based on the results. The score of each variable in the model was calculated by dividing the minimum β-coefficient from the multivariate Cox regression analysis and rounding to the nearest 0.5. The total score was calculated by summing the scores of each variable. A score-based model was developed (Table 4).

The results showed that different scores were closely related to T and N stage, clinical stage, Borrmann type, differentiation, tumor location, size and OS (Table 5). Then we selected significant variables for further analyses (Table 6).

To evaluate the impact of different scores on the prognosis of different stages of gastric cancer, Kaplan-Meier survival curves showed that the OS of patients with different scores was significantly different (Figure 2B; $P < 0.05$). Furthermore, we divided the patients into a low-score group (score ≤ 2) and a high-score group (score > 2) according to the result. We found that patients with high score had poor survival time (Figure 2C; $P < 0.05$). Next, subgroup analysis showed that the survival outcomes of patients with gastric cancer at different stages were also consistent with this finding. Patients were excluded from this analysis due to the small number of people with a stage I score of 4 ($n = 3$) and stage II scores of 5 ($n = 6$) and 6 ($n = 1$). In stage I, the 3-year OS for scores 0-3 ranged from 96.85%, 95%, 85%, and 80% (Figure 3). In stage II, this trend was slightly different. The 3-year OS for scores 0-4 were 88.6%, 76.5%, 90.5%, 65.5% and 60% (Figure 3). As for stage III, the 3-year OS for scores 0-6 were 70.9%, 68.3%, 64.1%, 50.9%, 38.4%, 18.5% and 5.2% (Figure 3). At the same time, we also analyzed the mean survival of patients with different scores. For stage I patients, the mean OS was 55.980 months. In stage II, the mean OS was 51.550 months. The mean OS of stage III was 39.422 months (Table 7).

DISCUSSION

Preoperative serum tumor markers have significant value in the diagnosis and prognosis of gastric cancer. However, in recent years, with the development of detection technology, many new methods, such as molecular detection and gene detection, have been used in gastric cancer. Fu *et al*[13] found that exosomal TRIM3 may serve as a new biomarker for gastric cancer diagnosis and might provide a new avenue for gastric cancer therapy[13]. Ma *et al*[14] reported that LncRNA PANDAR was an independent unfavorable prognostic factor in gastric cancer. Serum granulysin levels also have significant value as a novel prognostic marker of gastric cancer[15]. Due to the emergence of these detection methods, the value of serum tumor markers in the diagnosis and treatment of gastric cancer is often overlooked. According to the CSCO guideline, tumor markers still play an important role in the prognosis and therapeutic effect of gastric cancer[3]. Some researchers have found that the combined detection of multiple tumor markers can improve the early detection of digestive tract tumors[16,17].

In this study, we enrolled a total of 1236 gastric cancer patients as subjects. First, we used the χ^2 test to analyze the relationship between four tumor markers and clinicopathological parameters. Many previous studies focused on the early diagnosis of gastric cancer using tumor marker. Mo *et al*[18] found that CEA, CA199, and CA724 were significant for the diagnosis of gastric cancer, and combing these three tumor markers could improve diagnostic sensitivity and accuracy [18]. Another study the enrolled 154 patients with gastric cancer found that by readjusting the cut-off values from 5.0 ng/mL to 5.2 ng/mL for CEA and from 37.00 U/mL to 30.0 U/mL for CA19-9, the sensitivity for CA199 increased from 34.2% to 40.2%, but there was no increase for CEA[19].

Table 2 The association of demographics and clinicopathologic characteristics with four serum tumor markers

Variables	AFP		*P* value	CEA		*P* value	CA125		*P* value	CA19-9		*P* value
	Positive (*n* = 1043)	Negative (*n* = 193)		Positive (*n* = 904)	Negative (*n* = 332)		Positive (*n* = 858)	Negative (*n* = 378)		Positive (*n* = 969)	Negative (*n* = 267)	
Gender			0.200			0.072			0.072			0.809
Male	798	139		673	264		663	274		736	201	
Female	245	54		231	68		195	104		233	66	
Age			0.753			0.002			0.214			0.144
< 65	576	109		526	159		486	199		548	137	
≥ 65	467	84		378	173		372	179		421	130	
Clinical stage			0.034			0.000			0.000			0.000
I	257	31		263	25		242	46		278	10	
II	227	45		208	64		196	76		240	32	
III	559	117		433	243		420	256		451	225	
T stage			0.855			0.000			0.000			0.000
T1	193	31		208	16		181	43		214	10	
T2	108	19		104	23		110	17		121	6	
T3	146	28		116	58		109	65		128	46	
T4	596	115		476	235		458	253		506	205	
N stage			0.005			0.000			0.000			0.000
N0	446	58		430	74		392	112		462	42	
N1	171	32		150	53		145	58		166	37	
N2	185	42		151	76		149	78		152	75	
N3	241	61		173	129		172	130		189	113	
Tumor location			0.082			0.000			0.221			0.041
Cardia	537	96		433	200		444	189		485	148	
Gastric body	191	48		182	57		155	84		182	57	
Antrum of stomach	315	49		289	75		259	105		302	62	

Pathological type			1.000			0.324			0.417		0.045
Adenocarcinoma	985	183		858	310		814	354		919	249
Other	58	10		46	22		44	24		50	18
Degree of differentiation			0.606			0.049			0.014		0.002
Well, high, medium	308	53		278	83		269	92		303	58
Moderate to low, poor	735	140		626	249		589	286		666	209
Borrmann type			0.220			0.000			0.029		0.000
I and II	381	61		353	89		324	118		391	51
III and IV	662	132		551	243		534	260		578	216
Size			0.305			0.000			0.000		0.000
< 5	589	101		555	135		528	162		590	100
≥ 5	454	92		349	197		330	216		379	167
Survival status			0.000			0.000			0.000		0.000
Alive	736	106		686	156		646	196		728	114
Dead	307	87		218	176		212	182		241	153

AFP: Alpha foetoprotein; CEA: Carcinoembryonic antigen.

Ning *et al*[16] also suggested that the combination detection of TK1, CEA, CA19-9 and CA72-4 might be useful for the diagnosis of gastric cancer and colorectal cancer[16]. In our study, we found that age, clinical stage, T and N stage, tumor location, differentiation, Borrmann type, size, and 4 serum tumor markers could affect the prognosis of gastric cancer patients. However, only clinical stage and tumor markers were independent influencing factors for the prognosis of gastric cancer. In a meta-Analysis including 14651 gastric cancer patients, it was suggested that CEA may be an independent prognostic factor in gastric cancer[20]. Moreover, Jo *et al*[21] found that regarding metastatic gastric cancer, patients with higher value of CA 19-9 had shorter OS[21]. Tian *et al*[22] concluded that elevated CEA, CA19-9, CA242 and CA50 levels were associated with poorer prognosis[22], only CA 242 was a statistically independent risk factor[23]. Our conclusion was the same as this about the significant value of CEA and CA199, besides one study showed that gastric cancer is associated with CA125 and CA242[24], But only CA125 was related to the distant metastasis of gastric cancer. This indicated the significant value of CA125, in the future we will explore clinical value of CA125 for stage IV gastric cancer. However, the previous studies only examined the impact of a tumor marker on the prognosis of gastric cancer. To analyze the effect of combining four tumor markers on the prognosis of gastric cancer, we established a score-based model according to the result of Cox regression analysis to assign our patients a different score. Subsequently, differences in clinicopathological parameters among gastric cancer patients with different scores were analyzed. Similarly, Guo *et al*[23] also developed a risk assessment model based on regression coefficients derived from Cox regression analysis. It was

Table 3 Univariate and multivariate cox regression analysis for overall survival

Variables	OS	
	HR (95%CI)	*P* value
Univariate analysis		
Gender (male *vs* female)	0.922 (0.729-1.165)	0.496
Age (< 65 *vs* ≥ 65)	1.315 (1.080-1.604)	0.007
Clinical stage		
I	1 (Reference)	
II	2.876 (1.735-4.768)	0.000
III	8.712 (5.601-13.552)	0.000
T stage		
T1	1 (Reference)	
T2	1.693 (0.889-3.227)	0.019
T3	4.438 (2.634-7.478)	0.000
T4	6.330 (3.981-10.065)	0.000
N stage		
N0	1 (Reference)	
N1	2.330 (1.667-3.257)	0.000
N2	3.239 (2.383-4.401)	0.000
N3	5.201 (3.957-6.836)	0.000
Location		
Cardia	1 (Reference)	
Gastric body	1.306 (1.025-1.664)	0.031
Antrum of stomach	1.698 (1.276-2.261)	0.000
Pathological type (adenocarcinoma *vs* other)	1.209 (0.807-1.813)	0.358
Differentiation (well, high and medium *vs* moderate to low and poor)	1.776 (1.392-2.265)	0.000
Borrmann type (III *vs* other)	0.579 (0.462-0.724)	0.000
Size (< 5 *vs* ≥ 5)	0.403 (0.329-0.494)	0.000
AFP (positive *vs* negative)	1.929 (1.520-2.448)	0.000
CEA (positive *vs* negative)	3.155 (2.584-3.851)	0.000
CA125 (positive *vs* negative)	2.521 (2.067-3.074)	0.000
CA19-9 (positive *vs* negative)	3.489 (2.847-4.276)	0.000
Multivariate analysis		
Age (< 65 *vs* ≥ 65)	1.225 (0.999-1.501)	0.052
Clinical stage		
I	1 (Reference)	
II	2.102 (1.248-3.540)	0.005
III	4.860 (2.988-7.907)	0.000
Location		
Cardia	1 (Reference)	
Gastric body	1.531 (1.187-1.976)	0.051
Antrum of stomach	1.092 (0.847-1.406)	0.498
Differentiation (well, high and medium *vs* moderate to low and poor)	1.212 (0.940-1.564)	0.139

Borrmann type (III *vs* other)	0.873 (0.688-1.108)	0.265
Size (< 5 *vs* ≥ 5)	1.269 (1.020-1.578)	0.032
AFP (positive *vs* negative)	1.728 (1.359-2.198)	0.000
CEA (positive *vs* negative)	2.037 (1.646-2.522)	0.000
CA125 (positive *vs* negative)	1.739 (1.416-2.135)	0.000
CA19-9 (positive *vs* negative)	1.910 (1.535-2.377)	0.000

OS: Overall survival; HR: Hazard ratio.

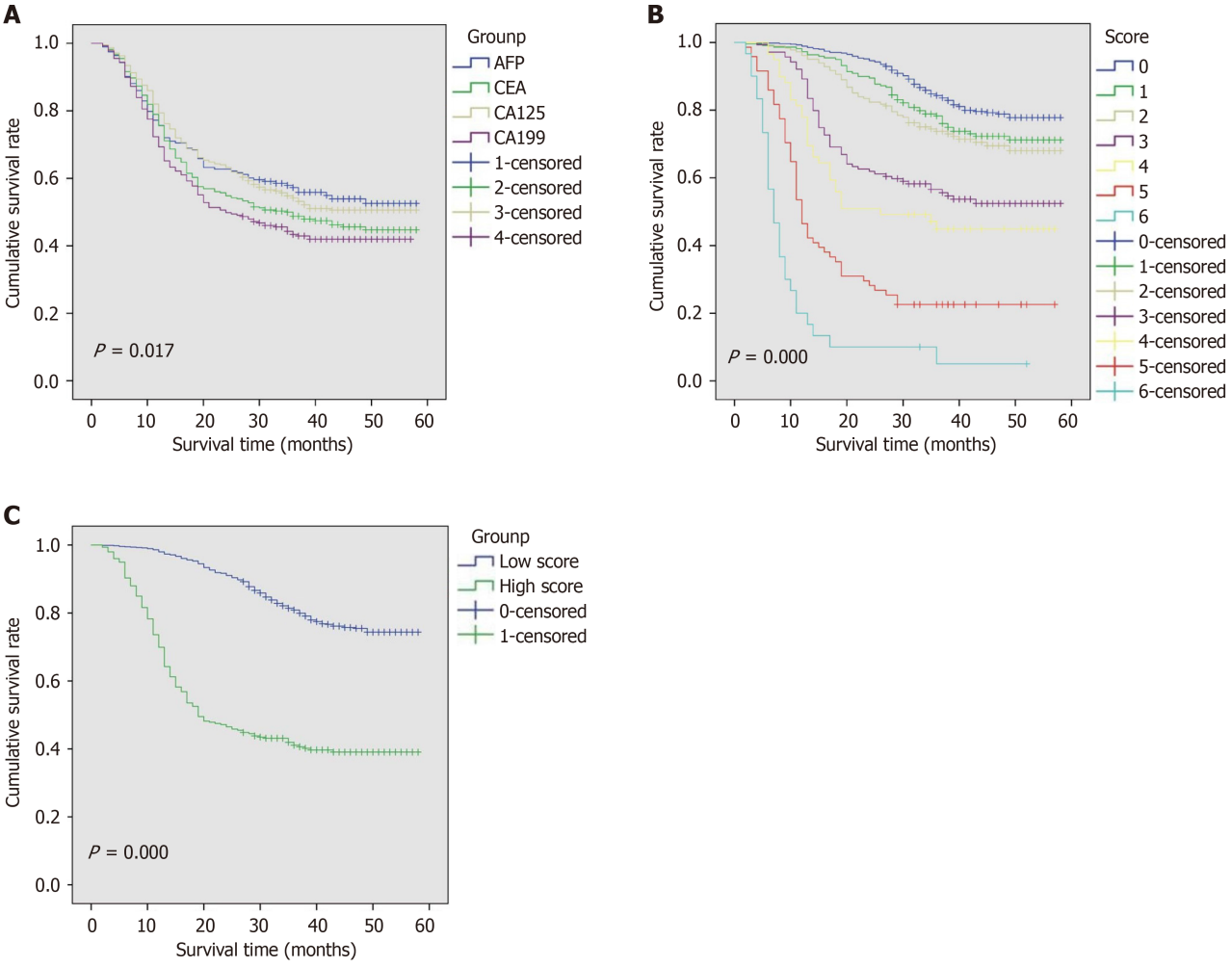

Figure 2 Overall survival. A: Overall survival (OS) according to different tumor markers in all patients; B: OS according to different scores in all patients; C: OS between high score patients and low score patients. AFP: Alpha foetoprotein; CEA: Carcinoembryonic antigen.

reported that the median survival time differed significantly among the different expression of the three tumor markers. CA72-4, a tumor marker, was not included in our study. At that time, some studies have shown that CA72-4 plays a significant role in the diagnosis and prognosis of gastric cancer. We can pay attention to this indicator in our future studies. More importantly, we also compared patients with different scores between different clinical stages. Among patients with stage II gastric cancer, those with a score of 2 had a longer mean survival and a smaller 3-year survival than those with a score of 1. Previous studies have also analyzed the prognostic evaluation of tumor markers in different stages of gastric cancer. Feng *et al*[25] found that the positive rates of CEA, CA19-9, AFP and CA125 were relatively low for early gastric cancer[25]. In addition, a Japanese study compared the evaluation of serum CEA and CA 19-9 Levels before and after surgery in stage II/III gastric cancer[26]. However, in this study, the prognostic value of the combination of these two tumor markers for gastric cancer was not studied in detail. Lin *et al*[27] specifically studied the effect of CEA and CA19-9 on the prognosis of stage III gastric cancer[27]. However, none of the studies were the same as ours. A statistical scoring model is established to predict the prognosis of gastric cancer patients according to the 4 tumor markers. In our study, we further analyzed the role of the statistical model in the prognostic of patients with different

Table 4 Multivariate cox regression analysis and assigned scores about four tumor markers

Variables	OS				
	HR (95%CI)	*P* value	β	Reference value	Score
AFP (positive *vs* negative)	1.722 (1.355-2.190)	0.000	0.543	0.543	1
CEA (positive *vs* negative)	2.311 (1.877-2.847)	0.000	0.838	0.543	2
CA125 (positive *vs* negative)	1.957 (1.595-2.401)	0.000	0.671	0.543	1
CA19-9 (positive *vs* negative)	2.504 (2.021-3.103)	0.000	0.920	0.543	2

AFP: Alpha foetoprotein; CEA: Carcinoembryonic antigen; OS: Overall survival; HR: Hazard ratio.

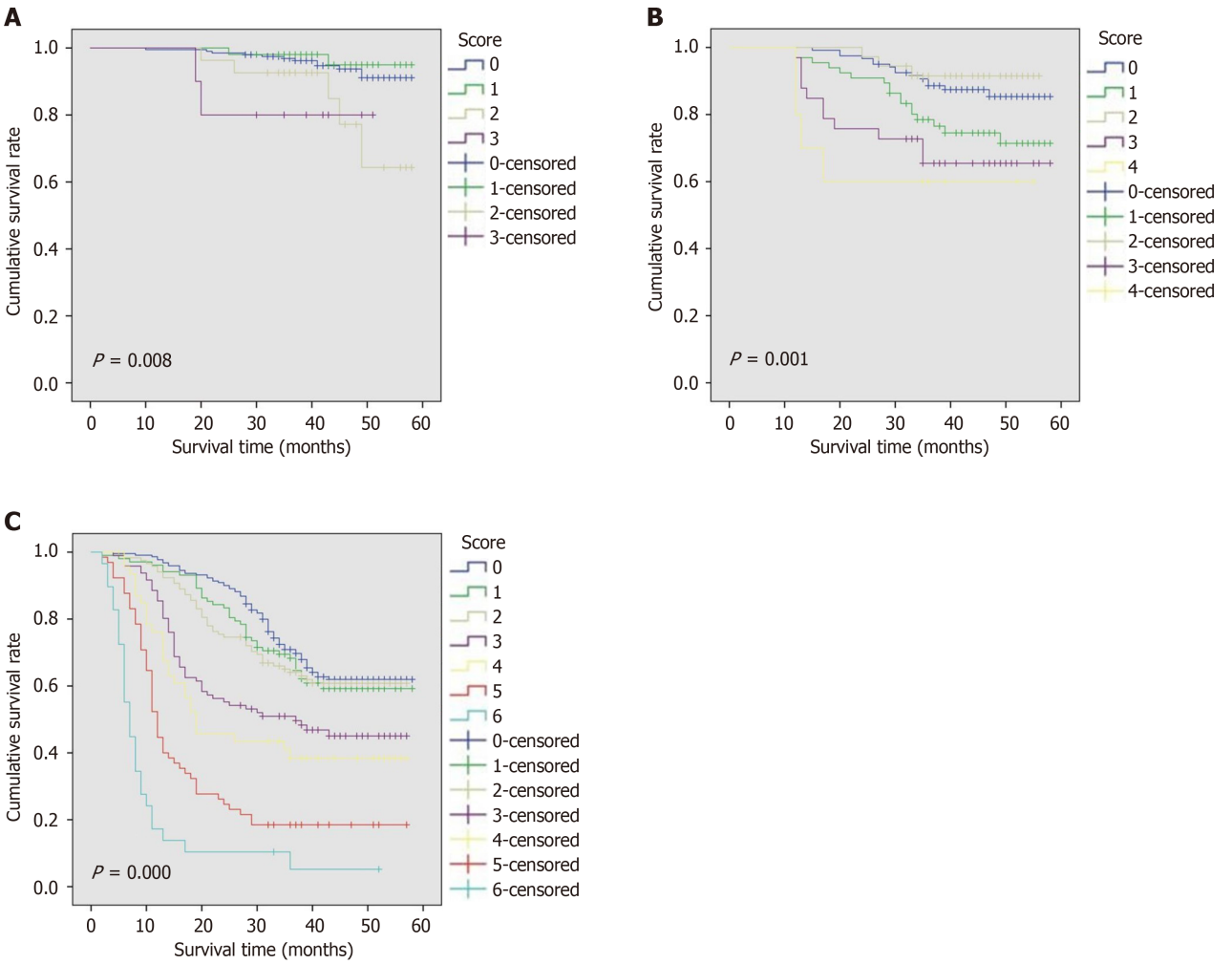

Figure 3 Overall survival according to different scores in different stages patients. A: Overall survival of patients with stage I; B: Overall survival of patients with stage II; C: Overall survival of patients with stage III.

stages of gastric cancer. Surprisingly, we found that our prognostic statistical model did not play a larger role in stage I and II than in stage III. Only in stage III gastric cancer did we find that the prognosis of gastric cancer patients became worse and worse as the score increased. But in stage I and II gastric cancer patients, we found that the mean survival time of stage I gastric cancer patients with a score of 0 and a score of 1 was 56.200 months ± 0.516 months and 56.893 months ± 0.777 months, respectively and stage II gastric cancer patients with a score of 1 and 2 were 49.802 months ± 1.778 months and 53.627 months ± 1.320 months, respectively. However, patients with the highest score had the shortest mean survival time regardless of clinical stage. This also suggested that the statistical model might be helpful in evaluating the prognosis of patients with stage I and II disease. There were also other studies on the use of scoring systems in patients with gastric cancer. Wang *et al*[28] established a scoring system to evaluate the role of second-line chemotherapy in the prognosis of patients with advanced gastric cancer based on performance status: Eastern Cooperative Oncology Group, Hb, time-to-program and other indicators[28]. In this study, the patients were divided into high-risk group and low-risk

Table 5 The association of demographics and clinicopathologic characteristics with different scores

Variables	0 (*n* = 537)	1 (*n* = 219)	2 (*n* = 181)	3 (*n* = 139)	4 (*n* = 59)	5 (*n* = 71)	6 (*n* = 30)	*P* value
Gender								0.506
Male	413	158	136	104	50	55	21	
Female	124	61	45	35	9	16	9	
Age								0.179
< 65	316	124	98	68	31	36	12	
≥ 65	221	95	83	71	28	35	18	
Clinical stage								0.000
I	197	51	27	10	3	0	0	
II	120	66	36	33	10	6	1	
III	220	102	118	96	46	65	29	
T stage								0.000
T1	147	48	15	10	3	0	1	
T2	75	22	20	9	0	1	0	
T3	56	37	27	25	13	13	3	
T4	259	112	119	95	43	57	26	
N stage								0.000
N0	292	96	64	36	11	4	1	
N1	94	40	18	27	8	15	1	
N2	73	37	44	32	14	17	10	
N3	78	46	55	44	26	35	18	
Tumor location								0.010
Cardia	268	95	97	77	37	41	18	
Gastric body	93	58	28	26	11	14	9	
Antrum of stomach	176	66	56	36	11	16	3	
Pathological type								0.236
Adenocarcinoma	514	202	172	133	54	64	29	
Other	23	17	9	6	5	7	1	
Degree of differentiation								0.013
Well, high, medium	174	64	53	41	16	8	5	
Moderate to low, poor	363	155	128	98	43	63	25	
Borrmann type								0.000
I and II	241	80	42	48	10	15	6	
III and IV	296	139	139	91	49	56	24	
Size								0.000
< 5	364	121	91	66	17	22	9	
≥ 5	173	98	90	73	42	49	21	
Survival status								
Alive	433	161	128	75	27	16	2	
Dead	104	58	53	64	32	55	28	

Table 6 Further comparison of variables with different score

Variables	*P* value							
	Clinical stage	T stage	N stage	Location	Differentiation	Borrmann type	Size	Survival status
0 *vs* 1	0.001	0.027	0.036	0.016	0.437	0.035	0.001	0.032
0 *vs* 2	0.000	0.000	0.000	0.678	0.461	0.000	0.000	0.007
0 *vs* 3	0.000	0.000	0.000	0.296	0.541	0.034	0.000	0.000
0 *vs* 4	0.000	0.000	0.000	0.077	0.464	0.000	0.000	0.000
0 *vs* 5	0.000	0.000	0.000	0.218	0.000	0.000	0.000	0.000
0 *vs* 6	0.000	0.000	0.000	0.020	0.104	0.007	0.000	0.000
1 *vs* 2	0.001	0.001	0.005	0.021	0.990	0.005	0.365	0.575
1 *vs* 3	0.000	0.001	0.005	0.071	0.956	0.725	0.160	0.000
1 *vs* 4	0.000	0.001	0.000	0.030	0.872	0.005	0.000	0.000
1 *vs* 5	0.000	0.000	0.000	0.106	0.002	0.020	0.000	0.000
1 *vs* 6	0.000	0.002	0.000	0.061	0.193	0.100	0.011	0.000
2 *vs* 3	0.092	0.481	0.061	0.541	0.967	0.033	0.653	0.002
2 *vs* 4	0.095	0.032	0.072	0.187	0.869	0.366	0.004	0.001
2 *vs* 5	0.000	0.004	0.000	0.373	0.003	0.867	0.007	0.000
2 *vs* 6	0.002	0.101	0.001	0.026	0.188	0.817	0.048	0.000
3 *vs* 4	0.445	0.206	0.316	0.521	0.864	0.016	0.018	0.351
3 *vs* 5	0.001	0.036	0.003	0.867	0.003	0.056	0.027	0.000
3 *vs* 6	0.007	0.202	0.001	0.116	0.180	0.136	0.105	0.000
4 *vs* 5	0.045	0.180	0.114	0.824	0.024	0.657	0.849	0.008
4 *vs* 6	0.069	0.329	0.065	0.348	0.306	0.774	0.907	0.000
5 *vs* 6	0.671	0.282	0.133	0.252	0.520	0.899	0.922	0.086

Table 7 Means and 95%CI for overall survival in patients with different stages and different score of gastric cancer

Stage	Score	Mean overall survival time (months)		
		Estimate	SE	95%CI
I	0 (n = 197)	56.200	0.516	55.188-57.212
	1 (n = 51)	56.893	0.777	55.371-58.416
	2 (n = 27)	52.090	2.283	47.615-56.564
	3 (n = 10)	44.700	3.985	36.889-52.511
	Overall (n = 285)	55.980	0.456	55.086-56.874
II	0 (n = 120)	54.133	0.946	52.279-55.987
	1 (n = 66)	49.802	1.778	46.316-53.288
	2 (n = 36)	53.627	1.320	51.039-56.214
	3 (n = 33)	44.903	3.293	38.449-51.357
	4 (n = 10)	38.400	6.442	25.773-51.027
	Overall (n = 265)	51.550	0.845	49.893-53.207
III	0 (n = 220)	46.927	1.052	44.864-48.989
	1 (n = 102)	44.814	1.727	41.429-48.199
	2 (n = 118)	43.357	1.661	40.102-46.613

3 (n = 96)	35.471	2.129	31.298-39.645
4 (n = 48)	31.096	3.157	24.909-37.283
5 (n = 71)	20.462	2.271	16.010-24.913
6 (n = 30)	10.966	2.240	6.576-15.355
Overall (n = 676)	39.422	0.792	37.870-40.974

group after scoring, and the survival rate of the two groups was significantly different. Our scoring system only includes serum tumor markers. We will try to incorporate more clinical indicators into the scoring system to better help us judge the prognosis of gastric cancer patients in future studies.

Not only in the diagnosis, treatment and prognosis of gastric cancer, serum tumor markers also play an important role in tumor chemotherapy. In Sun *et al*'s study, the decreases in tumor marker after chemotherapy (CEA ≥ 35%, CA19-9 ≥ 30%, or CA72-4 ≥ 40%) could predict a higher clinical benefit in patients with metastatic gastric cancer[29]. Another study analyzed the use of tumor markers in neoadjuvant chemotherapy, which showed that high levels of CEA (> 50 ng/mL) may predict clinical disease progression after neoadjuvant chemotherapy, and a decrease (> 70%) in CA72-4 may predict pathological response to neoadjuvant chemotherapy[30]. For our study, should we use different chemotherapy regimens for patients with different stages of gastric cancer?

There are still several shortcomings in our study. First, our study did not include sufficient patients with scores of 3 and 4, especially those with stage I and II gastric cancer. Second, the follow-up period was relatively short. This study analyzed only 3-year OS in patients with gastric cancer and did not include disease free survival in the follow-up program. This may have an impact on the results of our study. In addition, we did not study the impact of the combination of different tumor markers on the diagnosis and prognosis of gastric cancer patients. In subsequent studies, we can divide the four tumor markers into different groups to study their value in the diagnosis and treatment of gastric cancer.

CONCLUSION

In conclusion, preoperative serum tumor markers (AFP, CEA, CA125, CA19-9) are associated with the prognosis of different clinical stage gastric cancer, and the number of increased serum tumor markers have significant value for OS of gastric cancer patients.

FOOTNOTES

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