

Original Article

Serum CEA level lost its prognostic value in gastric cancer patients with AB blood type

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Abstract: Background: Little is known about the relationship between ABO blood groups and serum CEA level in gastric cancer patients. The aim of this study was to investigate the prognostic value of serum CEA level in gastric cancer patients with different ABO blood types. Materials and Methods: From September 2008 to April 2015, a total of 3234 gastric cancer patients who underwent radical gastrectomy were retrospectively analyzed in our institution. The clinicopathological characteristics and survivals were recorded. The prognostic value of serum CEA level within different ABO blood groups were analyzed. Results: The ratio of male to female patients was 3.5:1. The median age was 57.4 years (range 20-87). In all, 980 cases (30.3%) were blood type A, 935 cases (28.9%) were blood type B, 331 cases (10.2%) were blood type AB and 988 cases (30.6%) were blood type O. The positive rate of preoperative serum CEA was 19.0%. The overall survival of patients with negative and positive CEA level were 60.2% vs 34.4% for A blood type ($P<0.001$), 63.6% vs 44.5% for B blood type ($P<0.001$), 64.7% vs 36.2% for O blood type ($P<0.001$), 59.9% vs 46.1% for AB blood type ($P=0.210$). Serum CEA level was an independent prognostic factor for patients with A, B, O blood type (all $P<0.05$). However, serum CEA level was not a prognostic factor for patients with AB blood type ($P=0.898$). The level of CEA were significantly associated with gender, tumor size, tumor location, differentiation degree, tumor depth and lymph node metastasis in patients with AB blood type (all $P<0.05$). Conclusions: Serum CEA was an independent prognostic factor in gastric cancer patients with non-AB blood type, but lost its prognostic value in patients with AB blood type.

Keywords: Gastric cancer, ABO blood groups, CEA, prognosis

Introduction

Gastric Cancer is one of the malignancies threatening human health, the incidence and mortality of gastric cancer in China is highest around the world [1]. Radical resection is the optimal option for medical fit patients with resectable gastric cancer. Tumor markers are always being used to assess the outcomes of gastric cancer patients after radical surgery, among which serum CEA is one of the most common markers used to predict the prognosis and monitor the disease progression of gastric cancer patients.

The ABO blood group system, which was first discovered by Karl Landsteiner in 1900, is the most common means to classify the type of blood groups and is most widely used in clinical

practice among numerous blood group systems [2]. The prognostic impact of the ABO blood groups on survival was investigated in a series of tumors, including renal cell carcinoma [3], esophageal cell carcinoma [4], pancreatic cancer [5] and bladder cancer [6]. However, the results of these studies are inconsistent. Our previous study [7] revealed that ABO blood groups were not associated with the outcomes of gastric cancer patients. However, blood type AB was a favorable prognostic factor among patients who smoked and patients with stage III tumors.

As mentioned above, both blood groups and serum CEA could predict the prognosis of gastric cancer, but the connection between them remains unknown. Thus, the aim of this study was to investigate the prognostic value of

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Table 1. Clinicopathological characteristics of gastric cancer patients

Characteristics	No. of patients	Percent (%)
Age (year)		
≤60	1906	58.9
>60	1328	41.1
Gender		
Male	2514	77.7
Female	720	22.3
Tumor size		
≤4 cm	1657	51.2
>4 cm	1577	48.8
Tumor location		
Upper	1023	31.6
Middle	540	16.7
Lower	1435	44.4
Cross-district	236	7.3
Differentiation status		
Well	359	11.1
Moderately	814	25.2
Poorly	1882	58.2
Signet ring cell or mucinous	179	5.5
Borrmann type		
I	255	9.7
II	796	30.2
III	1269	48.1
IV	317	12.0
T stage		
T1	617	19.1
T2	495	15.3
T3	1165	36.0
T4	957	29.6
N stage		
N0	1162	35.9
N1	617	19.1
N2	561	17.3
N3	894	27.6
Serum CEA		
Negative	2619	81.0
Positive	615	19.0
ABO blood groups		
A	980	30.3
B	935	28.9
AB	331	10.2
O	988	30.6

serum CEA level in gastric cancer patients with different ABO blood types.

Materials and methods

This study was performed in Xijing Hospital of Digestive diseases, Fourth Military Medical University. From September 2008 to April 2015, a total of 3297 gastric cancer patients who underwent radical gastrectomy in our center were retrospectively analyzed. All patients included in this study met the following criteria: 1. without distant metastasis, 2. with radical gastrectomy, 3. with preoperative serum CEA measured, 4. without other malignancy, 5. without neoadjuvant chemotherapy. This study was approved by the Ethics Committee of Xijing Hospital, and written informed consent was obtained from all patients before surgery.

Serum CEA level was determined within 7 days before surgery. The recommended cut-off value of serum CEA level was 5.0 ng/ml, testing level beyond the cut-off value was considered as positive.

All patients were treated with proximal, distal or total gastrectomy with D2 lymphadenectomy. The surgical procedure was based on the recommendations of the Japanese Gastric Cancer Treatment Guidelines. Preoperative data including gender, age, ABO blood types, tumor location and serum CEA were recorded. The tumor size, differentiation status, tumor depth and lymph node metastasis were collected according to the pathological examination. Patients were followed every 3 months by enhanced chest and abdominal CT and gastroscopy. The last follow-up time was September 2015.

SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) was employed for data analysis. Overall survival was calculated from the date of surgery to the date of death or the last follow-up. The Kaplan-Meier method was used to estimate survival, and the log-rank test was used to assess the survival differences between different levels of serum CEA. Discrete variables were analyzed by Chi-squared test or Fisher's exact test. Significant risk factors identified by univariate analysis were further assessed by multivariate analysis using the logistic regression analysis. A *P* value of 0.05 was used as the threshold for statistical significance.

Results

The clinicopathological characteristics were summarized in **Table 1**. The ratio of males to

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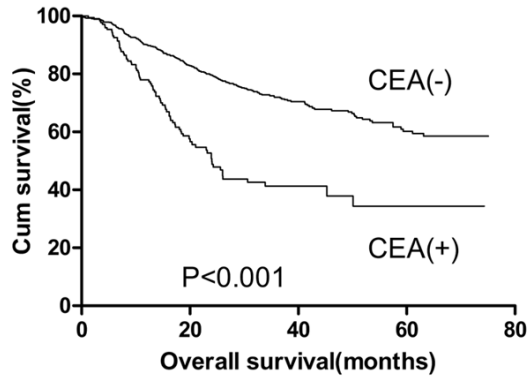


Figure 1. Overall survival for gastric cancer patients with A blood type stratified by different level of preoperative serum CEA.

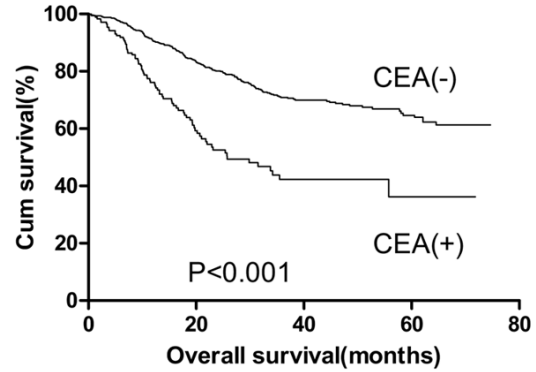


Figure 3. Overall survival for gastric cancer patients with O blood type stratified by different level of preoperative serum CEA.

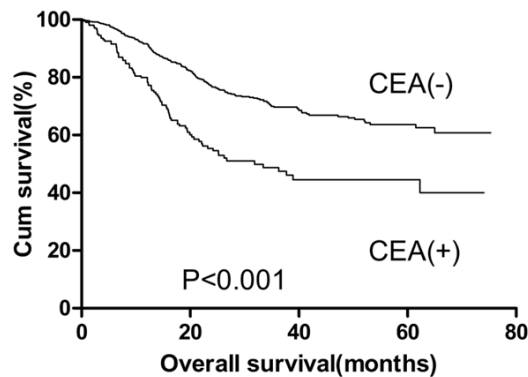


Figure 2. Overall survival for gastric cancer patients with B blood type stratified by different level of preoperative serum CEA.

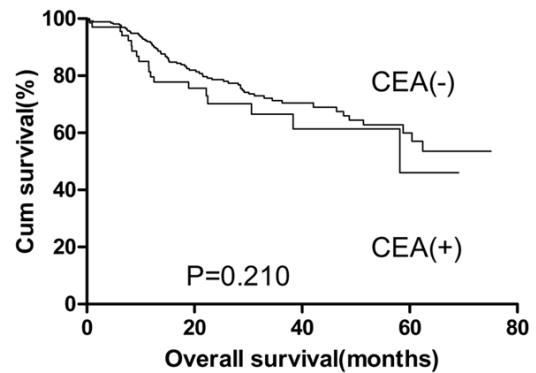


Figure 4. Overall survival for gastric cancer patients with AB blood type stratified by different level of preoperative serum CEA.

females was 3.5:1. Their median age was 57.4 years (range 20-87 years). Of these 3297 patients, 980 cases (30.3%) were blood type A, 935 cases (28.9%) were blood type B, 331 cases (10.2%) were blood type AB and 988 cases (30.6%) were blood type O. Overall, the positive rate of preoperative serum CEA were 19.0%.

The 5-year overall survival for gastric cancer patients with the four ABO blood groups according to different levels of serum CEA were analyzed. The overall survival of patients with negative and positive CEA level were 60.2% vs 34.4% for A blood type (**Figure 1**, $P<0.001$), 63.6% vs 44.5% for B blood type (**Figure 2**, $P<0.001$), 64.7% vs 36.2% for O blood type (**Figure 3**, $P<0.001$), 59.9% vs 46.1% for AB blood type (**Figure 4**, $P=0.210$).

The prognostic value of preoperative serum CEA level for gastric cancer patients in total and different ABO blood groups were analyzed using univariate and multivariate analysis and listed in **Tables 2-6**, respectively. The results showed that serum CEA level was an independent prognostic factor for patients with A, B, O blood type (all $P<0.05$). However, serum CEA level was not a prognostic factor for patients with AB blood type ($P=0.898$).

The clinicopathological characteristics of gastric cancer patients with AB blood type between serum CEA-negative and CEA-positive groups were compared and summarized in **Table 7**. No significant difference was found between the two groups with respect to age, Borrmann type (all $P>0.05$). The levels of CEA were significantly associated with gender, tumor size, tumor loca-

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Table 2. The univariate and multivariate analysis of CEA level for gastric cancer patients in total GC patients

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.301	1.146-1.476	0.000	1.284	1.110-1.485	0.001
Tumor size	3.214	2.782-3.713	0.000	1.507	1.269-1.789	0.000
Differentiation degree	1.475	1.347-1.615	0.000	1.118	1.003-1.246	0.044
Borrmann type	1.560	1.427-1.706	0.001	1.213	1.100-1.337	0.000
T stage	2.235	2.058-2.427	0.000	1.353	1.201-1.526	0.001
N stage	2.035	1.915-2.163		1.627	1.507-1.755	0.000
Serum CEA	2.414	2.104-2.769	0.000	1.678	1.433-1.965	0.000

Table 3. The univariate and multivariate analysis of CEA level for gastric cancer patients in GC patients with A blood type

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Tumor size	3.055	2.345-3.980	0.000	1.520	1.112-2.077	0.009
Differentiation degree	1.514	1.278-1.794	0.000	1.170	0.939-1.457	0.161
Borrmann type	1.394	1.186-1.637	0.001	1.186	0.988-1.424	0.067
T stage	2.190	1.882-2.548	0.000	1.359	1.088-1.698	0.007
N stage	2.965	1.758-2.197	0.000	1.541	1.341-1.772	0.000
Serum CEA	2.798	2.173-3.602	0.000	2.178	1.617-2.934	0.000

Table 4. The univariate and multivariate analysis of CEA level for gastric cancer patients in GC patients with B blood type

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Tumor size	3.276	2.522-4.256	0.000	1.348	0.971-1.872	0.075
Differentiation degree	1.447	1.233-1.699	0.000	0.989	0.823-1.189	0.134
Borrmann type	1.782	1.512-2.099	0.000	1.333	1.114-1.594	0.002
T stage	2.262	1.949-2.626	0.000	1.399	1.121-1.747	0.003
N stage	2.314	2.060-2.600	0.000	1.905	1.635-2.220	0.000
Serum CEA	2.335	1.839-2.964	0.000	1.547	1.176-2.035	0.002

Table 5. The univariate and multivariate analysis of CEA level for gastric cancer patients in GC patients with O blood type

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.540	1.221-1.942	0.000	1.496	1.146-1.954	0.003
Tumor size	3.345	2.563-4.365	0.000	1.332	0.980-1.811	0.067
Tumor location	0.828	0.736-0.932	0.002	0.831	0.728-0.948	0.006
Differentiation degree	1.471	1.243-1.741	0.000	1.267	1.038-1.548	0.020
Borrmann type	1.720	1.457-2.031	0.001	1.272	1.056-1.531	0.011
T stage	2.437	2.083-2.850	0.000	1.454	1.164-1.186	0.001
N stage	1.939	1.743-2.158	0.000	1.521	1.333-1.736	0.000
Serum CEA	2.544	1.969-3.287	0.000	1.586	1.182-2.126	0.002

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Table 6. The univariate and multivariate analysis of CEA level for gastric cancer patients in GC patients with AB blood type

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Tumor size	3.049	1.947-4.775	0.000	2.338	1.359-4.023	0.002
Differentiation degree	1.521	1.134-2.040	0.000	1.175	0.842-1.640	0.342
T stage	1.851	1.462-2.344	0.000	1.162	0.851-1.586	0.345
N stage	1.753	1.447-2.125	0.000	1.444	1.147-1.819	0.002
Serum CEA	1.393	0.849-2.285	0.210	1.016	0.574-1.799	0.898

Table 7. The clinicopathological characteristics of gastric cancer patients with AB blood type grouped by different levels of serum CEA

Parameters	CEA(-)	CEA(+)	P value
Age			0.54
≤60	145 (54.9)	34 (50.7)	
>60	119 (45.1)	33 (49.3)	
Gender			0.005
Male	188 (71.2)	59 (88.1)	
Female	76 (28.8)	8 (11.9)	
Tumor size			0.028
≤4 cm	146 (55.3)	27 (40.3)	
>4 cm	118 (44.7)	40 (59.7)	
Tumor location			0.012
Upper	75 (28.4)	33 (49.3)	
Middle	32 (12.1)	7 (10.4)	
Lower	138 (52.3)	23 (34.3)	
Cross-district	19 (7.2)	4 (6.0)	
Differentiation degree			0.035
Well	29 (11.0)	6 (9.0)	
Moderately	77 (29.2)	21 (31.3)	
Poorly	151 (57.2)	33 (49.3)	
Signet ring cell or mucinous	7 (2.7)	7 (10.4)	
Borrmann type			0.299
I	16 (8.0)	8 (12.9)	
II	69 (34.5)	17 (27.4)	
III	95 (47.5)	27 (43.5)	
IV	20 (10.0)	10 (16.1)	
T stage			0.008
T1	65 (24.6)	4 (6.0)	
T2	42 (15.9)	11 (16.4)	
T3	80 (30.3)	26 (38.8)	
T4	77 (29.2)	26 (38.8)	
N stage			0.003
N0	92 (34.8)	13 (19.4)	
N1	54 (20.5)	16 (23.9)	
N2	57 (21.6)	9 (13.4)	
N3	61 (23.1)	29 (43.3)	

tion, differentiation degree, tumor depth and lymph node metastasis (all $P < 0.05$).

Discussion

In last two decades, serum CEA has been widely used in monitoring disease progression and predicting the prognosis of gastric cancer patients. Gastric cancer patients with positive serum CEA level are always supposed to be with poor prognosis. Previously, we found that ABO blood groups were associated with the prognosis of gastric cancer patients ever smoked or patients with stage III tumor. However, no study has explored the connection between ABO blood groups and serum CEA level in gastric cancer patients. Thus, we evaluated the prognostic value of serum CEA level in gastric cancer patients with different ABO blood types. We found that preoperative serum CEA level was an independent prognostic factor for gastric cancer patients with non-AB blood type, but lost its predictive value in patients with AB blood type.

CEA was first identified in 1965 by Gold and Freedman in human colon cancer tissue extracts [8]. The positive rate of the preoperative serum CEA has been reported to range from 14.8% to 37% [9], which is consistent with our results. Many investigations have supported preoperative serum CEA as a predictor for the prognosis of gastric cancer [10-12], but denied by others [13, 14]. Until recently, Deng et al performed a meta-analysis includ-

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ing 14651 cases to analyze the association between pretreatment serum CEA level and risk of mortality in gastric cancer, and demonstrated that the preoperative serum CEA is likely an independent prognostic predictor for gastric cancer patients [15]. In our present study, we also found that serum CEA level was an independent risk factor for the prognosis of gastric cancer.

Although previous studies have explored correlations between ABO blood groups and cancer survival, the results varied widely. With regard to gastric cancer, Qiu et al [16] reported that there was no significant difference between ABO blood groups and survival of patients. However, in a retrospective analysis of 1412 cases of gastric cancer who had undergone curative surgery, Xu et al demonstrated that the AB blood group was a favorable prognostic factor [17]. The mechanisms by which the ABO blood groups influence the outcomes of cancer patients had been discussed previously and mostly deemed multifactorial. Some potential mechanisms, including immunosurveillance of the malignant cell lines, intracellular adhesion, and chronic inflammation, have been proposed to explain the association between ABO blood groups and the tumor initiation, progression and metastasis [18].

The ABO blood groups are determined by carbohydrate moieties (including A and B antigens) displayed on the surface of red blood cells and anti-A and anti-B antibodies in the serum. The two antigens are oligosaccharide antigens also highly expressed on the surface of many epithelial cells, including urogenital, skin cells and gastrointestinal cells. Found in a variety of malignancies, the expression of ABO blood group antigens on tumor cells is modified by hypermethylation of ABO gene promoter, which is one of the characteristics of malignant neoplasms [19]. The variations in ABO blood group antigens on tumor cells has been shown to affect cell proliferation significantly and linked both to increased oncogenic potential and to greater risk of tumor invasiveness and metastatic spread, thereby increasing cell motility through changes in the glycosylation of integrins [20]. Moreover, the loss of expression of blood group antigens is linked with more aggressive biological features, which has been observed in a variety of malignancies [18]. Furthermore, alterations in tumor expression of

the A and B glycosyltransferases could affect surrounding epithelial cell surface antigens, and thereby cellular adhesion and signaling [3]. These findings indicated that the ABO blood group antigens might play a role in mediating the microenvironment in gastric cancer patients, and thus influenced the initiation and progression of gastric cancer.

Additionally, recent studies have revealed that single-nucleotide polymorphisms at the ABO blood group gene locus are significant determinants of tumor necrosis factor-alpha (TNF- α) [21] and soluble intercellular adhesion molecule 1 (sICAM-1) [22]. TNF- α , an inflammatory cytokine secreted by the macrophage or tumor cells, is closely related to modulate cell apoptosis and inhibit tumorigenesis [23]. The soluble ICAM-1, a member of the immunoglobulin superfamily of adhesion receptors, influences cancer-related inflammation and the metastatic capability of tumor cells by cell adhesion functions [24]. These data raise the possibility that ABO blood groups may change the systemic inflammatory response and thus suggest an additional mechanism by which ABO blood type may influence cancer survival.

There were several limitations in our present study. First, in order to explore if the prognostic value of serum CEA level within different ABO blood groups in a rational way and with minimal bias, we just selected gastric cancer patients who underwent radical gastrectomy, other types were not discussed in this study. Second, it was a single center retrospective analysis, multicenter studies are needed to further verify the findings in our present study.

Conclusions

In summary, preoperative serum CEA level was an independent prognostic factor for gastric cancer patients with non-AB blood type, but lost its predictive value in patients with AB blood type.

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Disclosure of conflict of interest

None.

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