Preoperative Serum Carcinoembryonic Antigen as a Marker for Predicting the Outcome of Three Cancers

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Jingzhu Nan[1], Juan Li[1], Xiujuan Li[2], Guanghong Guo[1], Xinyu Wen[1] and Yaping Tian[1]

[1]Department of Clinical Biochemistry, State Key Laboratory of Kidney Disease, Chinese PLA General Hospital, Beijing, China. [2]Department of Clinical Laboratory, Beijing Tongzhou Xinhua Hospital, Beijing, China.

ABSTRACT

BACKGROUND: Serum levels of carcinoembryonic antigen (CEA) are associated with a variety of tumors.

OBJECTIVE: This study evaluated the prognostic value of pretreatment serum CEA levels in predicting the outcomes of multiple tumors subjected to treatment.

METHODS: Prior to therapy, serum samples from 71 prostate, 46 breast, 77 gastric, and 31 pancreatic cancer patients were collected to examine serum CEA levels. The cutoff value for CEA was set as determined by the maximum Youden index. The data were analyzed by the Kaplan-Meier curves generated by the log-rank test and Cox multivariate analysis.

RESULTS: The overall survival rate for all the patients was 71.11%. The 3-year survival rate of patients with prostate, breast, gastric, and pancreatic cancers was 81.69%, 95.65%, 54.55%, and 51.61%, respectively. The 3-year survival rate showed significant statistical differences between patients with serum CEA levels <2.885 µg/L and those with serum CEA levels ⩾2.885 µg/L ($P < .001$). The statistical differences of the 3-year survival rate also existed in the men ($P = .010$) or women group ($P < .001$), as well as in the 3 different types of cancer, which include breast cancer ($P = .025$), gastric cancer ($P = .001$), and pancreatic cancer ($P = .047$).

CONCLUSIONS: Serum CEA levels can provide additional prognostic information and may be useful in treatment implementation for patients with breast, gastric, or pancreatic cancer.

KEYWORDS: Cancer, carcinoembryonic antigen, prognosis

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CORRESPONDING AUTHOR: Yaping Tian, Department of Clinical Biochemistry, State Key Laboratory of Kidney Disease, Chinese PLA General Hospital, Beijing 100853, China. Email: tianyp61@gmail.com

Carcinoembryonic antigen (CEA) is a high-molecular-weight glycoprotein (180-200 kDa) consisting of a 60% carbohydrate composition.[1,2] It is a member of the immunoglobulin supergene family and is considered to be involved in cell recognition or adhesion mechanisms.[3] When first described in 1965, CEA was demonstrated to be an antigen present in both fetal colon and colon adenocarcinomas.[4] A large number of studies have revealed CEA as a tumor marker to determine colorectal cancer diagnosis and prognosis.[5] Further studies conducted by Slentz et al[6] reported that an elevated preoperative CEA level represented a poor prognostic factor for patients with colorectal carcinoma. More specifically, these studies determined that CEA levels that failed to decrease to normal postoperative levels following curative resections for colorectal carcinoma resulted in poor prognosis.[6] A multicenter retrospective study performed in 63 hospitals determined that the preoperative level of serum CEA was a prognostic indicator of survival for patients with colorectal cancer and was independent of the disease stage at the time of diagnosis.[5]

Normal serum concentrations of CEA are considered to be lower than 5 ng/mL. Interestingly, it is not uncommon to find that CEA levels can be elevated in patients with nonmalignant liver disease because the liver is the main site for CEA metabolism. Moreover, smoking has been found to affect the serum concentration of CEA.[7,8] With exception to smoking and hepatic disorders, the specificity of CEA could be greatly improved as a cancer screening tool.

Carcinoembryonic antigen is one of the most widely used biomarkers to determine cancer activity. However, CEA is a nonspecific tumor marker and increases in CEA levels have been detected in several cancers, such as gastrointestinal tract, breast,[9] and male genitourinary cancer.[10] Presently, various studies have examined the clinical value of CEA in diagnosing cancer in patients with gastric,[11] pancreatic,[12,13] or breast cancer,[9] with exception to colorectal cancer. The tumor markers CA 724, CA 242, CA 199, and CEA were evaluated in patients with gastric cancer in a study, and it was found that the combination of these 4 tumor markers could potentially be used as the diagnostic index for gastric cancer.[14] And the study showed that the survival time of patients with CEA higher than 5 mg/L was significantly shorter than those of patients with serum CEA below 5 mg/L in N0 stage.[14] Another study by

Tas and colleagues[15] found that increased serum levels of CEA in 40% of pancreatic cancers and increased levels of all of the tumor markers used in the study, including CEA, resulted in adverse effects regarding the survival of patients. Lee et al[16] measured preoperative CA 15-3 and CEA levels in 1681 patients with breast cancer and found that the 2 antigens were independent prognostic factors. Each of these studies indicates the prognostic significance of CEA in patients with cancers other than colorectal cancer, including gastric, pancreatic, and breast cancers. However, it is imperative to note that these findings were completed in different environments and may have been affected by factors that include the location of the country, hospital, or laboratories. In addition to these aforementioned studies, elevated CEA levels are also found in prostate cancer, and few studies have investigated the prognostic value of preoperative levels of CEA for patients with prostate cancer. Further evaluation is needed to determine the prognostic value of CEA in patients with cancer with exception to patients with colorectal cancer. In this study, we aimed to explore the prognostic value of CEA in gastric, pancreatic, breast, and prostate cancers, simultaneously.

The study herein enrolled 225 patients who were pathologically confirmed to have gastric, pancreatic, breast, and prostate cancers. These patients were followed up with a 3-year survival status. We evaluated the prognostic value of preoperative CEA levels in patients at different ages. The optimal cutoff values for preoperative serum CEA levels in predicting the outcomes of patients with cancer were reset based on our findings.

Materials and Methods

Patients

In total, 235 patients (including 71 prostate, 46 breast, 77 gastric, and 31 pancreatic cancer patients) admitted to the Department of Surgical Operation at the Chinese PLA General Hospital in Beijing between November 2009 and December 2010 were enrolled in this retrospective study. All patients were diagnosed according to the pathologic results. Each subject provided informed consent to participate in the study. This study was carried out in accordance with the Code of Ethics of the World Medical Association and the approved guidelines set forth by the Hospital Ethics Committee.

Serum samples were collected from peripheral blood by centrifugation at 3500×*g* for 7 minutes at room temperature, and then the samples were frozen at −80°C until further use. Carcinoembryonic antigen levels were measured using the electrochemical luminescence methodology (Cobas 8000 E 602; Roche, Basel, Switzerland). The CEA levels included in this analysis were for the preoperative measurements taken prior to resection or before any neoadjuvant therapy (such as preoperative chemoembolization).

Statistical analysis

Data were expressed as mean ± standard deviation or median after testing for normality using the Kolmogorov-Smirnov test and 2-sample *t*-test. The overall survival time was calculated from the date the patient was admitted to the Chinese PLA Hospital until the death of the patient or December 31, 2013, whichever date occurred first. The overall survival time was described in months and analyzed by the Kaplan-Meier curves generated with the log-rank test. Receiver operating characteristic (ROC) curves were performed to select the CEA slope thresholds to define the outcome of patients 3 years after receiving therapy. The correlation between the 3-year outcomes of patients and the CEA slopes was evaluated by the Kaplan-Meier method. All statistical analyses were performed using SPSS Software (version 19.0; IBM, Armonk, NY, USA). $P \leqslant .05$ was considered statistically significant.

Results

The general clinical characteristics of patients are presented in Table 1. There were 71 prostate cancer, 46 breast cancer, 77 gastric cancer, and 31 pancreatic cancer patients, for a total of 225 patients with cancer enrolled in this study. The median age of all enrolled patients was 60 years, with a range of 12 to 85 years. The median follow-up time was 27 months, with a range of 5 to 30 months. The Kaplan-Meier analysis of the overall survival rate was 71.11% (Figure 1). Among the enrolled patients were 144 men and 81 women, with a 3-year survival rate of 63.89% and 83.95% ($P = .002$), respectively (Figure 2A). The 3-year survival rate of prostate, breast, gastric, and pancreatic cancers was 81.69%, 95.65%, 54.55%, and 51.61%, respectively (Table 1).

After ROC analysis, the cutoff value for CEA was set to 2.885 μg/L when the maximum Youden index reached its largest value. The maximum Youden index indicates the total ability of diagnosis to identify real patients and nonpatients. So we used the cutoff value of CEA to statistical analysis.

Based on this cutoff value for CEA, all of the patients were divided into 2 groups: (1) CEA <2.885 μg/L and (2) CEA ⩾2.885 μg/L. Among these patients, 150 patients had serum CEA ⩾2.885 μg/L and 72 had CEA ⩾2.885 μg/L (Table 2 and Figure 2B). The 3-year survival rate for serum CEA <2.885 μg/L was 81.33%, whereas for patients with serum CEA ⩾2.885 μg/L it was 51.39% ($P < .001$).

In men, the 3-year survival rate for patients with serum CEA <2.885 μg/L was 73.17% and for patients with serum CEA ⩾2.885 μg/L was 52.54% ($P = .010$). In women, the 3-year survival rate for patients with serum CEA <2.885 μg/L was 91.18% and for patients with serum CEA ⩾2.885 μg/L was 46.15% ($P < .001$, Table 3 and Figure 2C and D).

In the final aspect of our study, we assembled the 4 different types of cancers under investigation into 2 subgroups, according to the results of the serum CEA levels. In the prostate cancer group, the 3-year survival rate for patients with serum CEA

Table 1. General clinical characteristics of patients (N = 225).

CHARACTERISTIC	CASE	MORTALITY CASES	MEAN SURVIVAL TIME (MONTHS)		THREE-YEAR SURVIVAL (%)	95% CI		χ^2	*P* VALUE
			ESTIMATE	SE		LOWER	UPPER		
Age (median), years	60 (range: 12-85)								
Men	144	52	28.16	1.03	63.89	26.14	30.18	9.871	.002
Women	81	13	32.59	0.96	83.95	30.71	34.47		
Total	225	65	29.76	0.76	71.11	28.27	31.24		
Prostate cancer									
Men	71	13	33.37	0.88	81.69	31.65	35.09		
Breast cancer									
Women	46	2	35.37	0.58	95.65	34.23	36.51		
Gastric cancer									
Men	57	29	24.40	1.83	49.12	20.82	27.99	2.358	.125
Women	20	6	29.05	2.54	70.00	24.07	34.03		
Total	77	35	25.61	1.52	54.55	22.62	28.60		
Pancreatic cancer									
Men	16	10	18.44	3.60	37.50	11.39	25.49	3.413	.065
Women	15	5	28.80	2.93	66.67	23.07	34.53		
Total	31	15	23.45	2.51	51.61	18.53	28.38		

Abbreviation: CI, confidence interval; SE: standard error.

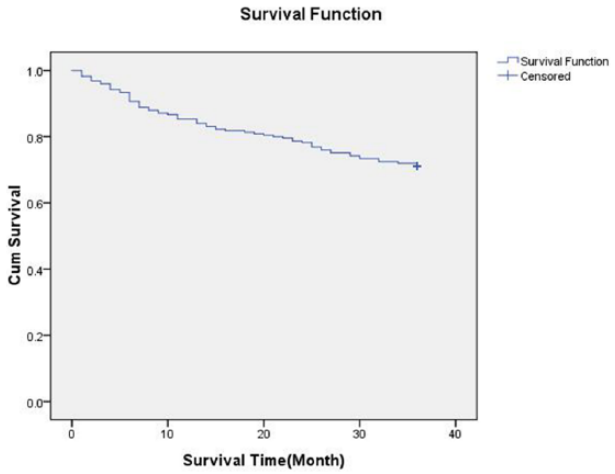

Figure 1. Three-year survival curves for 225 patients with the indicated cancer type (N = 225).

<2.885 μg/L was 84.09% and for patients with serum CEA ⩾2.885 μg/L was 77.78% (*P* = .493). In the breast cancer group, the 3-year survival rate for patients with serum CEA <2.885 μg/L was 97.62% and for patients with serum CEA ⩾2.885 μg/L was 75.00% (*P* = .025). In the gastric cancer group, the 3-year survival rate for patients with serum CEA <2.885 μg/L was 70.45% and for patients with serum CEA ⩾2.885 μg/L was 33.33% (*P* = .001). In patients with pancreatic cancer, the 3-year survival rate for patients with serum CEA <2.885 μg/L was 65.00% and for patients with serum CEA ⩾2.885 μg/L was 25.00% (*P* = .047) (Table 4 and Figure 3A to D). These results were statistically different for serum CEA <2.885 μg/L and serum CEA ⩾2.885 μg/L in patients with gastric, pancreatic, and breast cancers.

Discussion

Serum biomarkers have exhibited great significance in the diagnosis and management of cancer, to include screening, diagnosis, prognosis, monitoring, treatment, as well as identifying relapse.[17] Because of the ease of measuring serum biomarkers, relatively low costs, and sensitivity to detect early metastasis, CEA was one of the most widely used biomarkers for patients with colorectal cancer. Normally, serum CEA concentrations are below 5 ng/mL. In contrast to healthy conditions, elevated serum CEA levels have been found in other types of cancers aside from colorectal cancer, to include gastric,[18] pancreatic,[19] breast,[9,16,20] and genitourinary cancers.[10] According to the 2014 Facts and Figures Annual Report generated by the American Cancer Society, breast cancer is the most frequent form of cancer in women. There was an estimated 232 670 new cases of invasive breast cancer in the United Sates during the

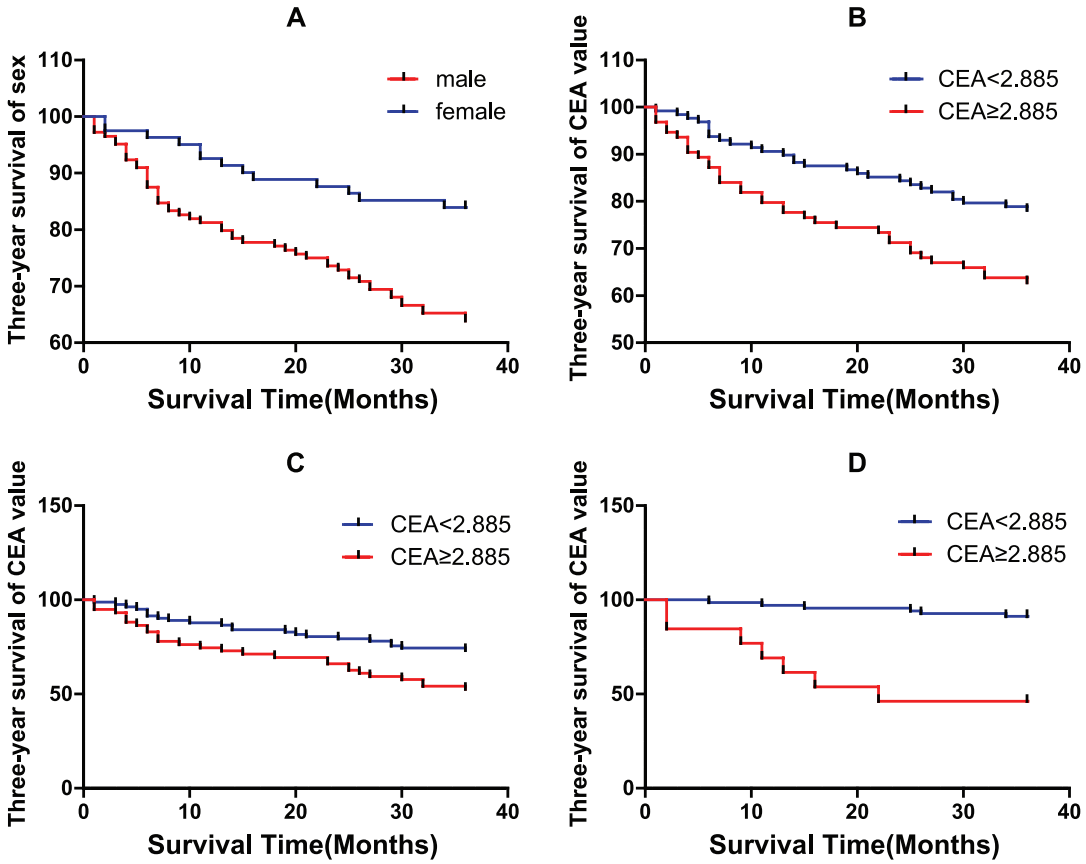

Figure 2. Three-year Kaplan-Meier survival curves for 225 patients with cancer classified by sex and carcinoembryonic antigen (CEA) value. (A) Men versus women ($P = .002$), (B) CEA <2.885 versus ⩾2.885 for all of the 255 patients ($P < .001$), (C) CEA <2.885 versus ⩾2.885 in men patients ($P = .010$), and (D) CEA <2.885 versus ⩾2.885 in women patients ($P < .001$).

Table 2. Three-year survival rate using serum CEA concentration from 255 patients with cancer.

CHARACTERISTIC	CASE	MORTALITY CASES	MEAN SURVIVAL TIME (MONTHS)		THREE-YEAR SURVIVAL (%)	95% CI		χ^2	*P* VALUE
			ESTIMATE	SE		LOWER	UPPER		
CEA (μg/L)									
<2.885	150	28	32.27	0.75	81.33	30.81	33.73	24.121	0.000
⩾2.885	72	35	25.11	1.60	51.39	21.98	28.24		
Total	222	63	29.95	0.75	71.62	28.48	31.42		

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; SE: standard error.

year 2014. Also noted in 2014 are the new cases of prostate cancer, which ranked the highest in men living in the United States. Another deleterious cancer type is pancreatic cancer, which is a leading cause of cancer-related mortality. Treatment for pancreatic cancer has limited efficacy, and the 5-year survival rate remains at about 6% for patients. For many patients with cancer, the serum measurements acquired at the time of initial diagnosis reported elevated CEA levels. In composite, it remains unclear whether pretreatment to lower serum CEA levels affects the 3-year survival of patients and whether serum CEA levels of 5 ng/mL was an optimal cutoff value for predicting the outcome of the patients. To combat these issues and further elucidate the use of biomarkers, the identification of biomarkers, specifically CEA, that detect cancer activity and are associated with the outcome of the patients with the aforementioned cancer types is highly warranted.

In this study, we evaluated 255 patients to include 72 prostate cancer, 46 breast cancer, 77 gastric cancer, and 31 pancreatic cancer patients. We determined the pretreatment levels of serum CEA among each of the 255 patients and conducted a 3-year follow-up during the years that range from 2010 to 2013. The results showed that the 3-year overall survival rate

Table 3. Three-year survival rate of patients with cancer as men and women.

CHARACTERISTIC		CASE	MORTALITY CASES	MEAN SURVIVAL TIME (MONTHS)		THREE-YEAR SURVIVAL (%)	95% CI		χ^2	*P* VALUE
				ESTIMATE	SE		LOWER	UPPER		
Men	CEA (μg/L)									
	<2.885	82	22	30.39	1.21	73.17	28.03	32.76	6.631	.010
	⩾2.885	59	28	25.71	1.76	52.54	22.27	29.15		
	Total	141	50	28.43	1.02	64.54	26.43	30.44		
Women	CEA (μg/L)									
	<2.885	68	6	34.54	0.67	91.18	33.24	35.85	21.934	.000
	⩾2.885	13	7	22.39	3.75	46.15	15.03	29.74		
	Total	81	13	32.59	0.96	83.95	30.71	34.47		

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; SE: standard error.

Table 4. Three-year survival rate of patients with gastric, breast, pancreatic, and prostate cancers.

CHARACTERISTIC		CASE	MORTALITY CASES	MEAN SURVIVAL TIME (MONTHS)		THREE-YEAR SURVIVAL (%)	95% CI		χ^2	*P* VALUE
				ESTIMATE	SE		LOWER	UPPER		
Prostate cancer	CEA (μg/L)									
	<2.885	44	7	33.80	1.11	84.09	31.63	35.67	0.469	.493
	⩾2.885	27	6	32.67	1.45	77.78	29.83	35.50		
Breast cancer	CEA (μg/L)									
	<2.885	42	1	35.92	0.05	97.62	35.86	36.05	5.058	.025
	⩾2.885	4	1	29.25	5.85	75.00	17.79	40.71		
Gastric cancer	CEA (μg/L)									
	<2.885	44	13	29.64	1.62	70.45	26.46	32.81	11.786	.001
	⩾2.885	33	22	20.24	2.53	33.33	15.29	25.19		
Pancreatic cancer	CEA (μg/L)									
	<2.885	20	7	27.00	2.91	65.00	21.30	32.70	3.950	.047
	⩾2.885	8	6	17.63	4.52	25.00	8.77	26.48		

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; SE: standard error.

for all of the patients was 71.11%. The 3-year survival rate was significantly higher in women than in men ($P < .05$), which may have been a result of patients with breast cancer being diagnosed, usually, at an early stage, and the survival rate for patients with breast cancer was highest among the 4 cancers.

We performed ROC analysis using cancer-specific death as an end point to determine the cutoff value of serum CEA as previously recommended.[21] Receiver operating characteristic analysis may be useful when comparing the prognostic accuracy of the nonlinear models and the conventional risk-stratification schemes.[22] Our results indicate that when the Youden index reached the highest value, the survival rate was significantly different between patients with serum CEA ⩾2.885 ng/mL and <2.885 ng/mL (Table 2). We further analyzed the influence of gender on survival rate, and these results indicated that in the gender subgroup, patients with serum CEA

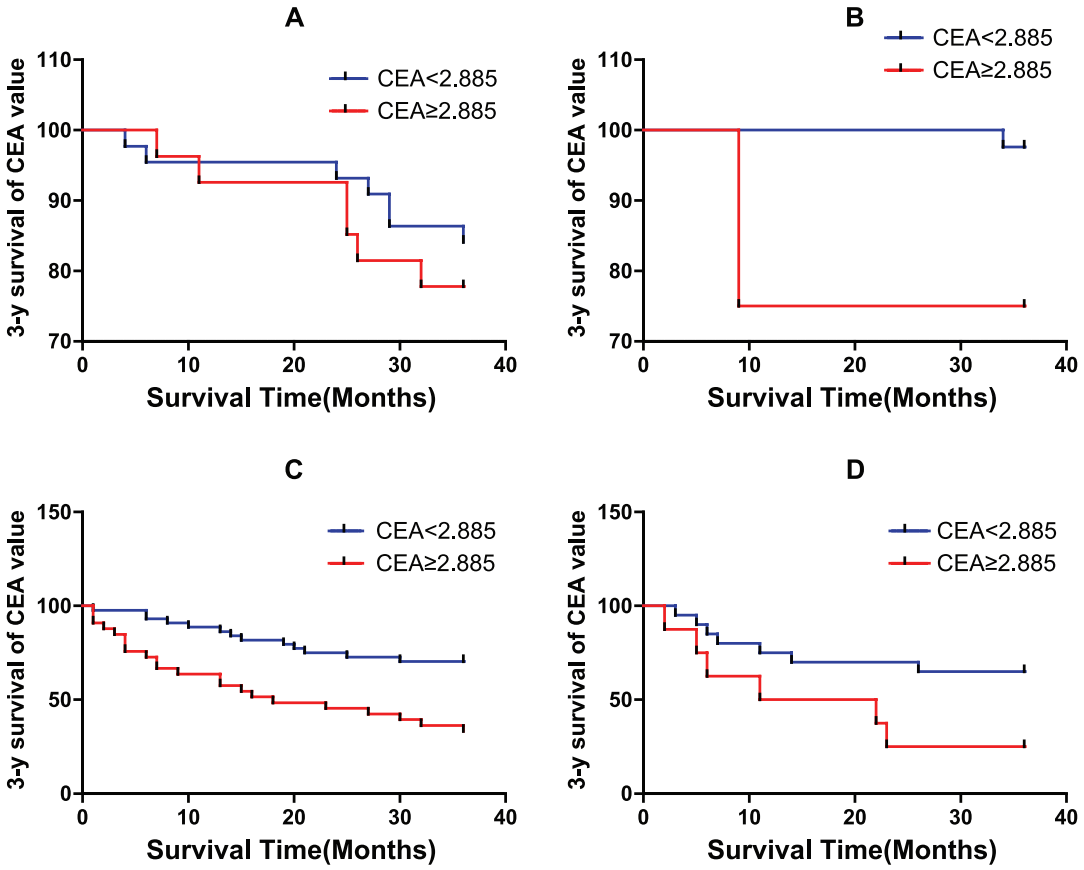

Figure 3. Three-year Kaplan-Meier survival curves for patients with different types of cancers. (A) CEA <2.885 versus ⩾2.885 in patients with prostate cancer ($P = .493$), (B) CEA <2.885 versus ⩾2.885 in patients with breast cancer ($P = .025$), (C) CEA <2.885 versus ⩾2.885 in patients with gastric cancer ($P = .001$), and (D) CEA <2.885 versus ⩾2.885 in patients with pancreatic cancer ($P = .047$). CEA indicates carcinoembryonic antigen.

⩾2.885 ng/mL and CEA <2.885 ng/mL ($P < .01$) had different survival rates. To analyze the 3-year survival rate in different types of tumors, we grouped the patients together according to the disease type. The results showed that patients with serum CEA ⩾2.885 ng/mL and CEA <2.885 ng/mL ($P < .01$) had different survival rates in patients with breast, gastric, and pancreatic cancers; however, the survival rates were no different in patients with prostate cancer. Shimada et al[23] conducted a systematic review of more than 4900 publications using PubMed as a search engine and database to evaluate the clinical significance of serum tumor markers in patients with gastric cancer. These findings showed that CEA was associated with the TNM factor and stage and that elevated CEA levels were associated with liver and peritoneal metastases.[23] This report also suggested that monitoring pretreatment tumor markers (CEA, CA 199, and CA 724) could be useful for recurrence detection or response evaluation. In this report, the investigators used serum CEA ⩾5 ng/mL as the cutoff value.[23] Another study conducted by Park et al reported that serum levels of CA 15-3 and CEA were associated with host tumor burden and were independent prognostic factors in disease-free survival as well as in distant relapse-free survival for patients with breast cancer. The investigators defined the cutoff value with a different method using the 95th percentile of healthy individuals (3.88 ng/mL for CEA).[24] Kim et al[25] found that preoperative serum CA 19-9 and CEA levels can be used for assessing tumor resectability (R0 resection) in patients with pancreatic adenocarcinoma. In their study, the cutoff concentration to predict resectability using CEA levels was 2.47 ng/mL. The aforementioned reports defined the cutoff value for CEA using a different method compared with our studies herein. In our study, the appropriate cutoff value was established to serum CEA levels of 2.885 ng/mL. Although the cutoff point for serum CEA levels was different in comparison with other reports, we did find that elevated serum pretreatment levels of CEA have an effect on the 3-year survival outcome of patients with gastric, breast, and pancreatic cancers. Preoperative levels of serum CEA may also be applied to assess the associated risks of patients. On the contrary, our studies did not show evidence that CEA has prognostic value for patients with prostate cancer, although previous studies have reported elevated serum CEA levels in patients with prostate cancer. In this study, our results suggest that clinicians should more closely monitor patients with levels of serum CEA ⩽5 μg/L.

There were 2 noteworthy advantages in this study. First, we investigated the prognostic value of serum preoperative CEA levels in 4 types of cancer simultaneously that could reduce the influence of technical factors. Second, we performed ROC

analysis to determine the optimal cutoff value of CEA in lieu of the recommendations provided by the manufacturer. Of note is a major limitation to our study, which is the relatively small number of study subjects.

In conclusion, the study herein evaluated the prognostic value of serum CEA in 4 types of cancer. It revealed that preoperative serum CEA levels may be an index for the 3-year survival status for gastric, breast, and pancreatic cancers. In addition, CEA levels can provide prognostic information and may be useful toward treatment implementation. Furthermore, our studies suggest that physicians should implement a regimen that monitors more closely patients whose preoperative serum CEA levels are ⩾2.885 μg/L to ensure the most effective treatment options.

Author Contributions

Conceived and designed the experiments: Yaping Tian and Xinyu Wen. Patient follow-up: Jingzhu Nan. Data entry: Xiujuan Li. Performed statistical analyses: Jingzhu Nan and Juan Li. Wrote the paper: Jingzhu Nan. Article modification: Guanghong Guo.

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