Prognostic effect of CEA, AFP, CA19-9 and CA242 for recurrence/metastasis of gastric cancer following radical gastrectomy

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Abstract. The present study aimed to determine the potential of carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen (CA)19-9 and CA242 in predicting recurrence/metastasis of gastric cancer in patients following radical gastrectomy. The clinical data of 368 patients with stage I-III gastric cancer who underwent radical gastrectomy were analyzed, and CEA, AFP, CA19-9 and CA242 levels were detected prior to surgery and 6-12 months following surgery. Univariate and multivariate analyses were used to evaluate the potential risk factors for post-operative recurrence/metastasis of gastric cancer, and the predictive value of CEA, AFP, CA19-9 and CA242 levels was evaluated using receiver operating characteristic (ROC) curve and area under the curve (AUC). Cumulative survival rates were calculated using Kaplan-Meier analysis, and statistical significance was evaluated using a log-rank test. Results of the univariate analysis demonstrated that open surgery, age ≥70, total gastrectomy, disease stage III, and pre-operative CA19-9 and CA242 positivity were risk factors for recurrence/metastasis. ROC curve analysis revealed that the AUC values of postoperative CA19-9 were higher than other values. According to the Kaplan-Meier survival analysis, patients with negative CEA, AFP, CA19-9 and CA242 levels prior to surgery exhibited a higher five-year survival rate than those who exhibited positive levels of these tumor markers. In addition, patients with positive CEA, AFP, CA19-9 and CA242 levels prior to surgery exhibited a significantly worse prognosis. Collectively, the results of the present study indicated that CEA, AFP, CA19-9 and CA242 exhibited potential as predictive biomarkers for recurrence/metastasis following radical gastrectomy in patients with gastric cancer. Notably, CA19-9 and CA242 may exhibit the highest potential in predicting recurrence/metastasis.

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Key words: gastric cancer, gastrectomy, tumor marker, recurrence/metastasis

Introduction

Gastric cancer is one of the most common malignant tumors worldwide, and mortality and morbidity rates are continuing to increase. Notably, the incidence of gastric cancer ranks fifth among malignant tumors, and the mortality rate is third highest, following lung and liver cancer (1-7). Radical surgery combined with adjuvant chemoradiotherapy, targeted therapy and immunotherapy has demonstrated potential in the treatment of gastric cancer; however, the five-year survival rate of patients remains low. The five-year survival rate of patients with advanced gastric cancer is <20% (8).

Gastric cancer exhibits high levels of heterogeneity, and is associated with a poor prognosis and low rates of survival. At present, targeted therapies for advanced gastric cancer include anti-human epidermal growth factor receptor 2 and vascular endothelial growth factor receptor 2, and research is focused on the use of CLDN18.2 as a potential treatment option. Notably, first-line treatment includes immunotherapy, and peri-operative clinical trials are ongoing. However, immunotherapy exhibits numerous limitations, including inconsistent treatment responses, drug resistance and treatment-associated adverse events (9-11). Thus, further investigations are required to optimize current immunotherapeutic regimens and improve the effectiveness and safety of immunotherapy in the treatment of gastric cancer.

Tumor recurrence and metastasis are the main causes of death following radical gastrectomy. Novel, non-invasive, inexpensive treatment options using serum tumor markers are required for early detection and intervention, following the recurrence or metastasis of gastric cancer (12-15).

Carcinoembryonic antigen (CEA) is a glycoprotein located in the gastrointestinal mucosal epithelia, while carbohydrate antigen (CA) is expressed at the carbohydrate sites of high-molecular weight mucins. Notably, both CEA and CA

bind to the integrin family, mediating calcium-independent intercellular adhesion. The mechanisms underlying CEA and CA are comparable to the mechanisms underlying tumor invasion and metastasis (16,17). Alpha-fetoprotein (AFP) is a glycoprotein belonging to the albumin family. AFP is closely associated with the occurrence and development of liver cancer and a variety of tumors, such as gastric, pancreatic, lung and colorectal cancer. AFP is used as a positive detection index for a variety of tumors (18), and results of a previous study revealed that AFP is significantly elevated in patients with AFP-positive gastric cancer (19). Notably, both CA19-9 and CA242 are key markers of gastric cancer (20), and these proteins, along with CEA and AFP, are routinely measured following radical gastrectomy.

Numerous previous studies assessed pre-operative serum tumor marker levels as risk factors for recurrence or metastasis (21,22); however, these studies did not focus on post-operative serum tumor marker levels. Notably, few studies investigated the association between post-operative positive tumor markers and recurrence or metastasis (23,24). Thus, early detection and timely intervention may improve the survival rate of patients with recurrence or metastasis of gastric cancer, following radical resection.

The present study aimed to determine the predictive value of CEA, AFP, CA19-9 and CA242 for recurrence/metastasis of gastric cancer following radical resection, to aid in early intervention and the treatment of patients. Receiver operating characteristic (ROC) curve, area under the curve (AUC) and univariate and multivariate analyses were used for the present study.

Materials and methods

Patients. The present study was approved (approval no. 20240651) by the Ethical Institutional Review Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine (Zhejiang, China). Patient informed consent was waived by the ethics committee as the present study is retrospective. Patients with stage I-III gastric cancer admitted to The Second Affiliated Hospital of Zhejiang University School of Medicine from January 2016 to September 2018 were enrolled in the present study. Patients were included in the present study according to the following criteria: i) Gastric cancer confirmed via gastroscopic pathology or surgical pathology; ii) a history of radical surgical resection, open or laparoscopic distal gastrectomy (DG), proximal gastrectomy (PG) or total gastrectomy (TG); iii) serum CEA, AFP, CA19-9 and CA242 levels detected prior to surgery; and iv) complete medical records. Patients were excluded from the present study according to the following criteria: i) The presence of gastric stump cancer; ii) the presence of severe infection; iii) the presence of other malignant tumors; iv) pregnancy or breastfeeding; v) no history of radical resection; vi) a history of neoadjuvant therapy; and vii) incomplete follow-up data.

According to the inclusion and exclusion criteria, a total of 368 patients with gastric cancer were enrolled in the present study, including 236 men and 132 women (age, 25-87 years). According to the TNM staging criteria of the Union of International Cancer Control and the American Joint Committee on Cancer, there were 152 patients with stage I disease, 115 patients with stage II disease and 101 patients with stage III disease. Patients included in the present study were evaluated for CEA, AFP, CA19-9 and CA242 levels at least once within 1 month prior to gastrectomy, and levels were evaluated 6 to 12 months following surgery. CEA, AFP, CA19-9 and CA242 levels of >5 ng/ml, >20 ng/ml, >37 U/ml and 20 U/ml, respectively, were considered positive prior to surgery (24-27). Post-operative serum CEA, AFP, CA19-9 and CA242 levels that exceeded the healthy range were considered positive. Recurrence and metastasis were evaluated using computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), positron Emission Tomography-CT (PET-CT) and puncture biopsy pathology.

Clinical features, such as age, pathological stage and post-operative adjuvant therapy were evaluated in 368 patients with gastric cancer. Following radical gastrectomy, all patients were followed up via outpatient or telephone follow-up for a period of 5 years, and follow-up ended in November 2023. Regular abdominal B-ultrasonography, CT, MRI, tumor marker, routine blood and PET-CT examinations were performed, and death or the end of follow-up were considered the end point of the investigation. The recurrence and metastasis of all patients with gastric cancer were analyzed, and patients were divided into recurrence/metastasis and non-recurrence/metastasis groups. Clinical characteristics, such as sex, age, depth of invasion, and CEA, AFP, CA19-9 and CA242 levels were compared between the two groups.

Statistical analysis. All data were statistically analyzed using GraphPad Prism (version, 9.1.1; GraphPad Software, Inc.). Data are presented as the number of cases and rate (%). Measurement data with normal distribution and homogeneity of variance are presented as the mean ± standard deviation ($\bar{x} \pm s$). Univariate and multivariate analyses were performed using GraphPad Prism, and Fisher's exact test and multiple logistic regression were used, respectively. A receiver operating characteristic (ROC) curve was used to calculate the area under the curve (AUC). Levels of sensitivity and specificity were used to evaluate the predictive value of CEA, AFP, CA19-9 and CA242 in the post-operative recurrence or metastasis of gastric cancer. ROC curves were calculated using the R package (version 1.18.5). Kaplan-Meier survival (followed by a log-rank test) was analyzed using the R package survival (version 3.5; https://github.com/therneau/survival). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics of patients with gastric cancer. The median age of 368 patients with gastric cancer was 60 years. Among them, 236 patients were male (64%) and 132 patients were female (36%). According to the tumor differentiation grade, 19 cases were high, 16 cases were high-moderate, 70 cases were moderate, 89 cases were moderate-low and 174 cases were low grade. Open surgery was performed in 64% of patients, and 26% of patients underwent TG. Notably, lymph node dissection was D2 in 99% of the patients. In total, 152 patients exhibited stage I disease (41%), 115 patients exhibited stage II disease (31%) and 101 patients exhibited stage III disease (28%). In addition, 63% of patients underwent

post-operative adjuvant therapy. In total, 34 (9%) patients were positive for CEA, 4 (1%) patients were positive for AFP, 39 (11%) patients were positive for CA19-9 and 23 (6%) patients were positive for CA242. At the end of follow-up, 68/368 patients exhibited recurrence/metastasis, and 300/368 patients did not experience recurrence/metastasis, with a recurrence/metastasis rate of 18% (Table I).

Univariate and multivariate analysis of post-operative recurrence/metastasis in patients with gastric cancer. All patients with gastric cancer were divided into recurrence/metastasis (n=68) and non-recurrence/metastasis groups (n=300). Results of the univariate analysis revealed no significant difference in age, sex, lymph node dissection, pre-operative CEA levels and pre-operative AFP levels between patients with recurrence/metastasis and those with non-recurrence/metastasis. Notably, age ≥70, open surgery, TG, disease stage III, pre-operative CA19-9 positivity and pre-operative CA242 positivity were risk factors for recurrence/metastasis (Table II). Results of the multivariate logistic regression analysis revealed that approach of operation was a risk factor for recurrence/metastasis. In addition, disease stage II and III were risk factors for recurrence/metastasis, compared with disease stage I (Table III).

Predictive value of post-operative CEA, AFP, CA19-9 and CA242 levels for the recurrence/metastasis of gastric cancer. Results of the ROC curve analysis revealed that the AUC values of pre-operative CEA, AFP, CA19-9 and CA242 levels in the prediction of recurrence/metastasis were 0.517, 0.513, 0.513 and 0.499, respectively (Fig. 1 and Table IV). The AUC values of post-operative CEA, AFP, CA19-9 and CA242 levels in the prediction of recurrence/metastasis were 0.608, 0.493, 0.630 and 0.568, respectively (Fig. 2 and Table IV). Notably, the AUC values of post-operative CA19-9 levels were higher than CEA, AFP and CA242.

Comparison of cumulative survival rate between patients with positive or negative CEA, AFP, CA19-9 and CA242 levels. Cumulative survival was compared between patients with positive pre-operative serum CEA, AFP, CA19-9 and CA242 levels and patients with negative pre-operative serum CEA, AFP, CA19-9 and CA242 levels. Results of the Kaplan-Meier survival analysis revealed that patients with negative pre-operative CEA, AFP, CA19-9 and CA242 levels exhibited a higher five-year survival rate than patients with positive pre-operative CEA, AFP, CA19-9 and CA242 levels. In addition, patients with positive pre-operative serum CEA, AFP, CA19-9 and CA242 levels exhibited a significantly worse prognosis than those with negative CEA, AFP, CA19-9 and CA242 levels. Notably, the differences between positive and negative pre-operative CA19-9 and CA242 levels were statistically significant (Fig. 3). The results of the present study also revealed that patients with positive post-operative serum CEA, AFP, CA19-9 and CA242 levels exhibited a poorer five-year survival rate than patients with negative post-operative serum CEA, AFP, CA19-9 and CA242 levels. Notably, these patients also exhibited a significantly worse prognosis. However, there was no statistically significant difference between positive and negative post-operative AFP, CA19-9 or CA242 levels.

Table I. Clinicopathological characteristics of 368 patients.

Characteristics	Value (%)
Median age (Range)	60 (25-87)
Sex	
Male	236 (64)
Female	132 (36)
Tumor grade	
High	19 (5)
High-moderate	16 (4)
Moderate	70 (19)
Moderate-low	89 (24)
Low	174 (48)
Approach of operation	
Open	234 (64)
Laparoscopic	134 (36)
Type of gastrectomy	
Distal gastrectomy, proximal gastrectomy	273 (74)
Total gastrectomy	95 (26)
Lymph node dissection	
D1, D1+	2 (1)
D2	366 (99)
Disease stage[a]	
I	152 (41)
II	115 (31)
III	101 (28)
Adjuvant chemotherapy	
Yes	231 (63)
No	137 (27)
Preoperative carcinoembryonic antigen	
Positive	34 (9)
Negative	334 (91)
Preoperative alpha-fetoprotein	
Positive	4 (1)
Negative	364 (99)
Preoperative carbohydrate antigen 19-9	
Positive	39 (11)
Negative	329 (89)
Preoperative carbohydrate antigen 242	
Positive	23 (6)
Negative	345 (94)
Recurrence/Metastasis	
Yes	68 (18)
No	300 (82)

[a]classification according to TNM staging of gastric cancer by the Union for International Cancer Control and the American Joint Committee on Cancer.

The results of the present study revealed that the difference between positive and negative post-operative CEA levels were statistically significant (Fig. 4).

Table II. Results of univariate analysis.

Characteristics	Value (%)		P-value
	Patients with recurrence/ metastasis(n=68)	Patients without recurrence/ metastasis (n=300)	
Age, years			0.0138
≥70	20 (30)	47 (16)	
<70	48 (70)	253 (84)	
Sex			0.1613
Male	49 (72)	187 (62)	
Female	19 (28)	113 (38)	
Operative approach			<0.0001
Open	61 (90)	127 (42)	
Laparoscopic	7 (10)	173 (58)	
Type of gastrectomy			0.0309
Distal gastrectomy, proximal gastrectomy	43 (63)	230 (77)	
Total gastrectomy	25 (37)	70 (23)	
LN dissection			0.4996
D1, D1$^+$	0 (0)	2 (1)	
D2	68 (100)	298 (99)	
Disease stage			<0.0001
I	4 (6)	148 (50)	
II	23 (34)	92 (30)	
III	41 (60)	60 (20)	
Preoperative carcinoembryonic antigen			0.2440
Positive	9 (13)	25 (8)	
Negative	59 (87)	275 (92)	
Preoperative alpha-fetoprotein			0.1570
Positive	2 (3)	2 (1)	
Negative	66 (97)	298 (99)	
Preoperative CA19-9			0.0482
Positive	12 (18)	27 (9)	
Negative	56 (82)	273 (91)	
Preoperative CA242			0.0215
Positive	9 (13)	14 (5)	
Negative	59 (87)	286 (95)	

CA, carbohydrate antigen.

Discussion

Serum tumor markers are substances that are synthesized by cells, and these are increased when the body responds to tumor cells. Levels of serum tumor markers are low in healthy tissues; however, these are significantly increased in the serum of patients with tumors.

The results of the present study revealed that serum CEA, AFP, CA19-9 and CA242 levels in patients with recurrence/metastasis were significantly higher than those in patients with non-recurrence/metastasis, suggesting that serum CEA, AFP, CA19-9 and CA242 may be associated with post-operative recurrence/metastasis in patients with gastric cancer. In addition, results of the univariate analysis demonstrated that open surgery, age ≥70, total gastrectomy, disease stage III, pre-operative CA19-9 positivity and pre-operative CA242 positivity were risk factors for recurrence/metastasis. However, these factors were not statistically significant between patients who were positive and negative for pre-operative CEA and AFP. Notably, there were no statistically significant differences in sex and lymph node dissection between patients with recurrence/metastasis and those with non-recurrence/metastasis. Of the 368 patients who underwent radical gastrectomy, only two patients underwent D1 or D1$^+$ lymph node dissection, and the remaining patients underwent D2 lymph node dissection.

Table III. Results of multivariate analysis.

Characteristics	Odds ratio	95% confidence interval	P-value
Age, ≥70	1.727	0.7984-3.699	0.1603
Sex	0.7742	0.3862-1.516	0.4612
Approach of operation	0.3657	0.1389-0.8556	0.0280
Disease stage II	8.132	2.166-40.51	0.0044
Disease stage III	22.84	6.167-114.9	<0.0001
Adjuvant chemotherapy	0.8417	0.3300-2.157	0.7170
Preoperative carcinoembryonic antigen	1.010	0.9728-1.048	0.5842
Preoperative alpha-fetoprotein	0.9997	0.9729-1.001	0.9035
Preoperative CA19-9	1.001	0.9970-1.005	0.5659
Preoperative CA242	1.000	0.9780-1.023	0.9819

CA, carbohydrate antigen.

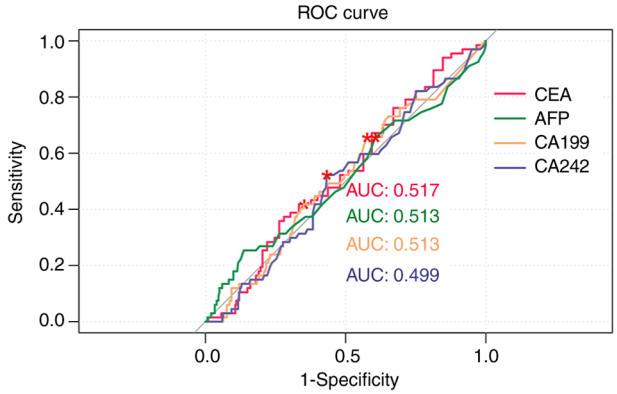

Figure 1. Receiver operating characteristic curve analyses revealed the AUC values of pre-operative CEA, AFP, CA19-9 and CA242 levels in predicting post-operative recurrence/metastasis of gastric cancer. AUC, area under the curve; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA, carbohydrate antigen.

Table IV. Evaluation value of CEA, AFP, CA19-9 and CA242 in postoperative recurrence/metastasis of gastric cancer.

	Area under the curve	Specificity	Sensitivity
Preoperative CEA	0.517	0.647	0.418
Preoperative AFP	0.513	0.393	0.657
Preoperative CA19-9	0.513	0.423	0.657
Preoperative CA242	0.499	0.567	0.522
Postoperative CEA	0.608	0.627	0.559
Postoperative AFP	0.493	0.543	0.500
Postoperative CA19-9	0.630	0.673	0.574
Postoperative CA242	0.568	0.590	0.544

CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA, carbohydrate antigen.

The results of the multivariate logistic analysis revealed that approach of operation was a risk factor for recurrence/metastasis. Compared with disease stage I, disease stages II and III were also risk factors for recurrence/metastasis of gastric cancer. Notably, these results were consistent with those of previous studies and results obtained in clinical practice (14,28,29).

ROC curve analysis was also used to further determine the predictive value of CEA, AFP, CA19-9 and CA242 levels in post-operative recurrence/metastasis of gastric cancer. The results of the present study revealed that the AUC values of pre-operative CEA, AFP, CA19-9 and CA242 levels were 0.517, 0.513, 0.513 and 0.499, respectively. These results suggested that pre-operative CEA levels exhibited a high predictive value for post-operative recurrence/metastasis in patients with gastric cancer. The AUC values of post-operative CEA, AFP, CA19-9 and CA242 levels were 0.608, 0.493, 0.630 and 0.568, respectively. These results suggested that CA19-9 may exhibit the highest potential in predicting post-operative recurrence/metastasis of gastric cancer. Notably, these results were comparable with those of previous studies (30,31).

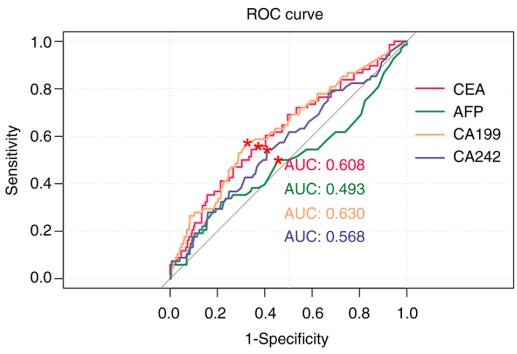

Figure 2. Receiver operating characteristic curve analysis revealed the AUC values of post-operative CEA, AFP, CA19-9 and CA242 levels in predicting post-operative recurrence/metastasis of gastric cancer. AUC, area under the curve; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA, carbohydrate antigen.

Cumulative survival was also compared between patients with negative pre-operative and post-operative serum CEA, AFP, CA19-9 and CA242 levels, and those with positive levels

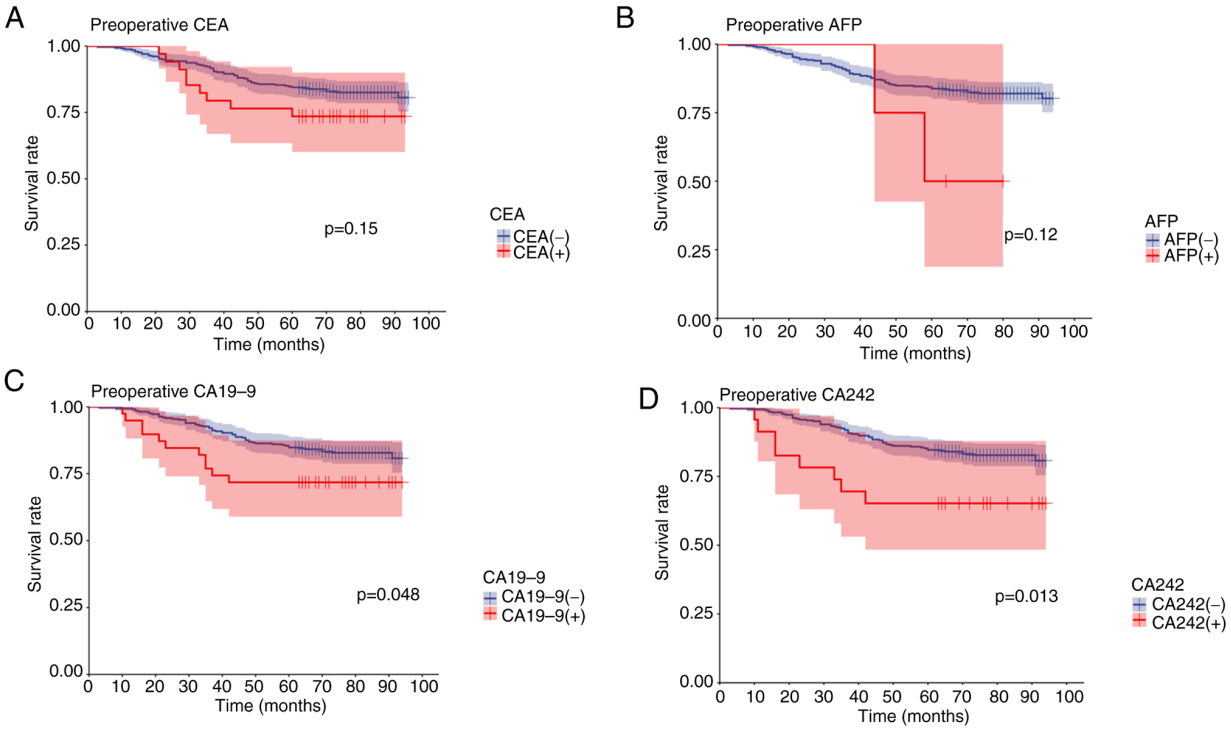

Figure 3. Association between prognosis and (A) positive or negative pre-operative serum CEA levels, (B) positive or negative pre-operative serum AFP levels, (C) positive or negative pre-operative serum CA19-9 levels and (D) positive or negative pre-operative serum CA242 levels in patients with gastric cancer. CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA, carbohydrate antigen.

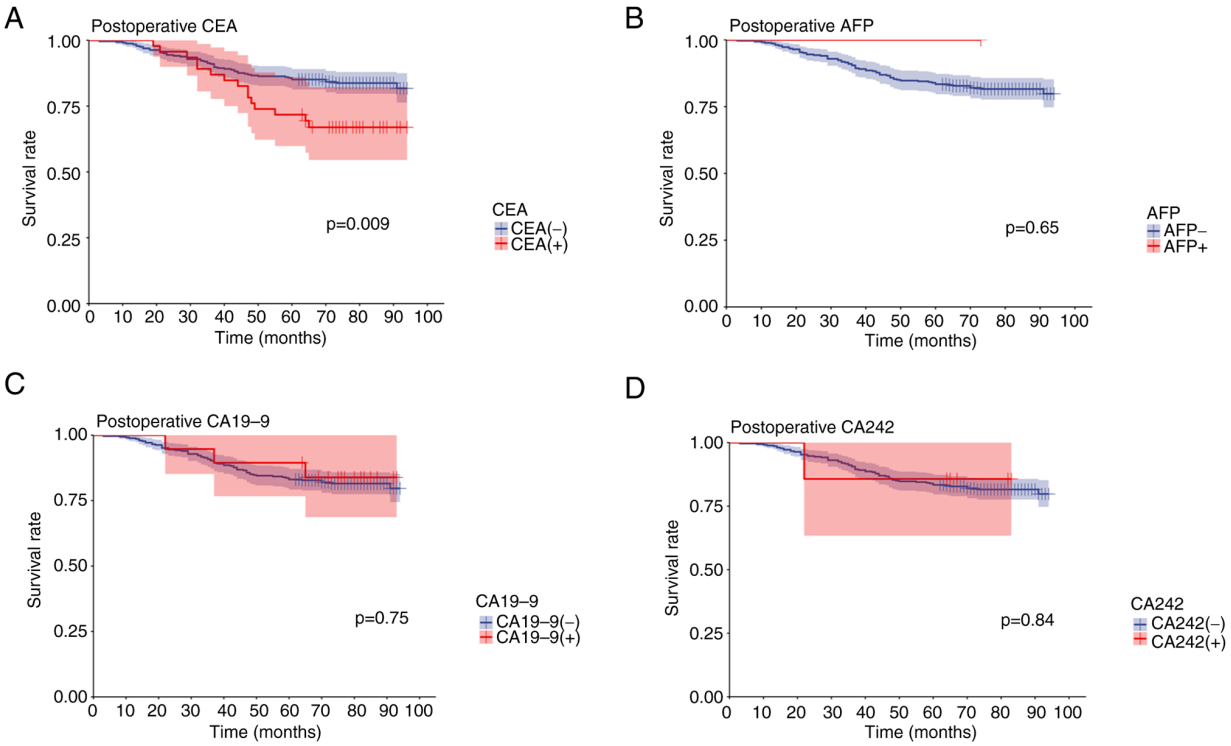

Figure 4. Association between five-year survival and (A) positive or negative post-operative serum CEA levels, (B) positive or negative post-operative serum AFP levels, (C) positive or negative post-operative serum CA19-9 levels and (D) positive or negative post-operative serum CA242 levels in patients with gastric cancer. CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA, carbohydrate antigen.

of these markers. The results of the present study indicated that patients with positive pre- or post-operative CEA, AFP, CA19-9 and CA242 levels exhibited a poorer five-year survival rate than patients with negative levels of these markers. Moreover, prognosis was significantly worse in patients with positive pre- and post-operative serum CEA, AFP, CA19-9 and

CA242 levels, compared with patients with negative levels of these markers. Previous studies revealed that elevated serum CEA and CA19-9 levels are associated with the prognosis of patients with gastric cancer (14,24,32). In the present study, elevated serum CA242 levels were also associated with the prognosis of patients with gastric cancer.

The present study provides a novel theoretical basis for the use CEA, AFP, CA19-9 and CA242 as tumor markers for the prediction of tumor recurrence and metastasis following radical gastrectomy. Thus, these serum tumor markers may exhibit potential in predicting tumor recurrence and metastasis following surgery, when combined with ctDNA. Further investigations should focus on the optimization of evaluating CEA, AFP, CA19-9 and CA242 in combination, to determine the optimal combination of tumor markers for the prediction of recurrence/metastasis of gastric cancer following radical surgery.

Collectively, the results of the present study indicated that CEA, AFP, CA19-9 and CA242 exhibited potential in the prediction of recurrence/metastasis following radical gastrectomy in patients with gastric cancer. Notably, CA19-9 and CA242 may exhibit the highest potential in predicting recurrence/metastasis. In addition, patients enrolled in the present study had undergone radical gastrectomy, and the majority of patients with elevated AFP levels presented with advanced stages of disease. Thus, patients with elevated AFP levels may have presented with liver metastases that could not be surgically resected, and were therefore not included in the present study. Thus, the present study included fewer patients with positive AFP levels, which may have led to bias.

The AUC value in the ROC curve in the present study is close to 0.5, which means that the model is weak in distinguishing between positive and negative samples. Although the results were statistically significant, the actual predictive power of the model was weak and may not have sufficient clinical significance. The importance of the results should not be overstated in the absence of sufficient differentiation. Future studies need to optimize the model and improve its prediction accuracy.

The present study used a retrospective design, which does introduce data selection bias and other potential confounding factors. Retrospective design limits the ability of causal inference and may affect the reliability of the results. Future studies need to consider multivariate analyses that include more potential confounding factors. Another limitation is our relatively small sample size, which may affect the statistical power of the study and the external validity of the results. Potential errors that can result from a small sample size. In future studies, the authors consider conducting a prospective cohort study with a larger sample size to validate our findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FL, KeC, GC and JC contributed to study conception and design. FL, SX, KaiC and MK prepared materials, and performed data collection and analysis. FL wrote the manuscript. All authors commented on the manuscript. GC and JC confirm the authenticity of all the raw data, supervised the research and revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. 20240651) by the Institutional Review Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) and was conducted in strict accordance with the principles of the Declaration of Helsinki. Patient informed consent was waived by the ethics committee as the present study is retrospective.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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