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Novel nomogram and risk stratification for peritoneal recurrence after curative resection in gastric cancer

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Peritoneal recurrence (PR) in gastric cancer after curative resection has poor prognosis. Therefore, we aimed to construct a nomogram to predict PR, and establish PR score for risk stratification to guide adjuvant chemotherapy. A total of 315 patients with gastric cancer after radical surgery were included, and randomly stratified into training group (n = 221) and validation group (n = 94). Univariate and multivariate analyses were used to determine predictive factors of PR. The nomogram was constructed to predict the risk of PR. We utilized the time-dependent area under the receiver operating characteristic (ROC) curves (AUCs), calibration curves, and decision curve analysis (DCA) to evaluate the performance of the nomogram. Multivariate analysis showed that tumor site, N stage, preoperative CEA, and postoperative CA199 were independent predictors of PR. A nomogram was constructed to predict PR based on these factors. The AUC value was 0.755 in the training group and 0.715 in the validation group. The calibration curves showed good agreement between prediction and observation in the training and validation groups. The decision curve analysis displayed a good net benefit of the nomogram. The novel PR score was developed and patients were stratified into the low-, medium-, and high-risk groups. For the high-risk group, postoperative adjuvant chemotherapy significantly improved patients' overall survival (OS) and disease-free survival (DFS). The establishment of nomogram facilitates the prediction of PR after radical gastrectomy, and a novel PR score may help guide adjuvant chemotherapy for gastric cancer.

Keywords Gastric cancer, Peritoneal recurrence, Nomogram, Risk stratification, Adjuvant chemotherapy

Gastric cancer (GC) is the fifth most prevalent cancer and the fourth leading cause of cancer-related deaths worldwide^{1,2}. Although surgical intervention has improved overall survival (OS) and progression-free survival (PFS) for GC patients, post-operative recurrence and metastasis remain a formidable challenge in current management^{3,4}. Peritoneal recurrence (PR) is one of the major causes of distant metastasis and death in patients with progressive GC. The median survival time for patients with peritoneal dissemination is only 3–6 months, and the 5-year survival rate is less than 3%⁵. Therefore, it is necessary to effectively assess the risk of postoperative PR in gastric cancer.

Traditional imaging modalities, such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography-computed tomography (PET-CT), still face significant challenges in the early diagnosis of peritoneal metastases, especially in cases of suspected dissemination to the peritoneum. Once patients present with peritoneal thickening, enhancement of supraperitoneal nodules, and “large omental cakes”, they are no longer in the early stages of peritoneal dissemination^{6–8}. Laparoscopic exploration is the “gold standard” for detecting occult peritoneal metastases, but it requires additional invasive operations and there is a greater risk of surgical complications, which makes it unacceptable for most patients^{9,10}. Clinicopathologic features as well as hematologic tumor markers are clinically accessible and noninvasive. A retrospective study demonstrated that combining clinical risk factors and radiomic features helped to predict peritoneal metastasis (PM)¹¹. Another study from Zhao et al. similarly found that serum glycation biomarkers and clinicopathologic

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features could predict PM of gastric cancer¹². Therefore, we hypothesize that clinical features are excellent non-invasive biomarkers for predicting PR after radical gastric cancer surgery.

However, there are still limited effective predictive models for predicting PR in GC after radical gastrectomy currently. Therefore, the aim of our study was to establish a noninvasive, low-cost nomogram that may be useful to predict the candidate who might develop PR. In addition, the PR score was constructed based on the nomogram to help guide adjuvant chemotherapy.

Materials and methods

Patient selection

The study retrospectively analysed the clinical data of patients who had been pathologically diagnosed with gastric cancer and undergone radical gastrectomy from January 2014 to June 2018 in our hospital. Patients with distant metastases, presence of other tumors, other treatments (radiotherapy, chemotherapy, or immunotherapy) before surgery, and missing clinical data were excluded. Ultimately, a total of 315 patients were enrolled in this study. TNM stage was classified according to the 8th edition of the American Joint Committee on Cancer Staging System.

Clinical characteristics

The clinicopathological characteristics included age, gender, tumor site, lauren type, T stage, N stage, pathological stage, vascular or lymphatic invasion, perineural invasion, peritoneal recurrence, adjuvant chemotherapy, preoperative carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199), postoperative CEA and CA199, and follow-up data. Adjuvant chemotherapy regimens included XELOX, SOX and FOLFOX. Hematologic tumor markers including CEA and CA199 were collected before or one week after surgery. Peritoneal recurrence was confirmed by CT, PET-CT or laparoscopy during follow-up after radical gastrectomy. Survival data included overall survival (OS) and disease-free survival (DFS). OS was the time from radical gastrectomy to death due to any cause or to the last follow-up. DFS was the time from radical gastrectomy to the first time of tumor recurrence or metastasis, or to the death due to any reason, or to the last follow-up.

Construction and validation of the nomogram

Firstly, all patients were randomly divided into training group ($n = 221$) and validation group ($n = 94$) at a ratio of 7:3. Univariate and multivariable logistic regression was used to select independent predictors of PR in the training cohort. Next, we incorporated these independent predictors into the nomogram model to predict PR. At last, we evaluated the performance of the nomogram model using the time-dependent area under the receiver operating characteristic (ROC) curves (AUCs), calibration curves, and decision curve analysis (DCA) in the training group and validation group.

PR score and risk stratification

We calculated PR score for each patient based on multivariable logistic regression analysis with linear combinations of the included variables weighted by their respective coefficients. Then, we used X-tile software to select the best cutoff value for the PR score and categorize patients into low, medium, and high risk groups.

Statistical analysis

Statistical analyses were performed using SPSS software version 25.0 and R version 4.2.1. Categorical variables were analyzed by the chi-square test or the Fisher's exact test. Univariate logistic regression analyses were conducted for each variable, and variables with $P < 0.1$ were enrolled in multivariate logistic regression analyses to identify independent predictive factors for PR. Kaplan–Meier curves and log-rank test were used to analyze OS and DFS. All statistical tests were two-sided, and P -value less than 0.05 was considered statistically significant.

Ethical approval and consent to participate

The current study was approved by the ethics committee of Fujian Medical University Union Hospital, Fuzhou, China, and conducted in accordance with the principles of the Declaration of Helsinki and its amendment. All patients provided written informed consent prior to treatment, and all the information was anonymized prior to analysis.

Results

Patients' characteristics

A total of 315 GC patients were included in this study. All patients were randomized into the training cohort ($n = 221$) and the validation cohort ($n = 94$) at a 7:3 ratio. The characteristics of the patients are shown in Table 1, and there were no significant differences in baseline clinical characteristics between two cohorts.

Factors associated with PM

In the training cohort, univariate and multivariate logistic regression analyses were utilized to analyze independent predictors of PR (Table 2). Factors with $P < 0.1$ on univariate analysis, including tumor site, lauren type, T stage, N stage, pathological stage, vascular or lymphatic invasion, perineural invasion, preoperative CEA, postoperative CEA, and postoperative CA199, were incorporated into the multivariate analysis, and the results showed that tumor site (antrum) (OR 0.443, 95% CI 0.201–0.977, $p = 0.044$), N3 stage (OR 7.851, 95% CI 1.114–55.325, $p = 0.039$), preoperative elevated CEA (OR 2.446, 95% CI 1.150–5.201, $p = 0.020$), and postoperative elevated CA199 (OR 2.703, 95% CI 1.134–6.447, $p = 0.025$) were significantly associated with PR.

Characteristics	Training cohort (n=221)	Validation cohort (n=94)	P value
Age, n (%)			
≤ 60	85 (38.5%)	45 (47.9%)	0.121
> 60	136 (61.5%)	49 (52.1%)	
Gender, n (%)			
Male	166 (75.1%)	72 (76.6%)	0.779
Female	55 (24.9%)	22 (23.4%)	
Tumor site, n (%)			
Body	65 (29.4%)	29 (30.9%)	0.935
Cardia	63 (28.5%)	29 (30.9%)	
Antrum	71 (32.1%)	27 (28.7%)	
Whole	22 (10%)	9 (9.6%)	
Lauren type, n (%)			
Intestinal	59 (26.7%)	30 (31.9%)	0.664
Diffuse	94 (42.5%)	39 (41.5%)	
Mixed	54 (24.4%)	18 (19.1%)	
Uncertain	14 (6.3%)	7 (7.4%)	
T stage, n (%)			
T1–3	38 (17.2%)	14 (14.9%)	0.615
T4	183 (82.8%)	80 (85.1%)	
N stage, n (%)			
N0	46 (20.8%)	14 (14.9%)	0.320
N1–2	78 (35.3%)	31 (33%)	
N3	97 (43.9%)	49 (52.1%)	
Pathological stage, n (%)			
I	26 (11.8%)	8 (8.5%)	0.613
II	38 (17.2%)	19 (20.2%)	
III	157 (71%)	67 (71.3%)	
Vascular/lymphatic invasion, n (%)			
No	161 (72.9%)	67 (71.3%)	0.775
Yes	60 (27.1%)	27 (28.7%)	
Perineural invasion, n (%)			
No	185 (83.7%)	79 (84%)	0.942
Yes	36 (16.3%)	15 (16%)	
Peritoneal recurrence, n (%)			
No	113 (51.1%)	51 (54.3%)	0.612
Yes	108 (48.9%)	43 (45.7%)	
Adjuvant chemotherapy, n (%)			
No	75 (33.9%)	26 (27.7%)	0.275
Yes	146 (66.1%)	68 (72.3%)	
Preoperative CEA, n (%)			
Normal	135 (61.1%)	56 (59.6%)	0.802
Elevated	86 (38.9%)	38 (40.4%)	
Preoperative CA199, n (%)			
Normal	144 (65.2%)	64 (68.1%)	0.616
Elevated	77 (34.8%)	30 (31.9%)	
Postoperative CEA, n (%)			
Normal	157 (71%)	70 (74.5%)	0.535
Elevated	64 (29%)	24 (25.5%)	
Postoperative CA199, n (%)			
Normal	180 (81.4%)	79 (84%)	0.582
Elevated	41 (18.6%)	15 (16%)	

Table 1. Baseline clinical characteristics of the training and validation cohorts.

Characteristics	Univariate analysis		Multivariate analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age				
≤ 60	Reference			
> 60	0.828 (0.481—1.425)	0.496		
Gender				
Male	Reference			
Female	0.833 (0.452—1.536)	0.559		
Tumor site				
Body	Reference		Reference	
Cardia	0.885 (0.442—1.771)	0.730	0.653 (0.291—1.463)	0.300
Antrum	0.466 (0.234—0.928)	0.030	0.443 (0.201—0.977)	0.044
Whole	2.286 (0.794—6.580)	0.125	0.809 (0.241—2.714)	0.731
Lauren type				
Intestinal	Reference		Reference	
Diffuse	1.911 (0.983—3.717)	0.056	0.864 (0.380—1.966)	0.728
Mixed	1.951 (0.920—4.136)	0.081	1.084 (0.442—2.659)	0.860
Uncertain	1.682 (0.520—5.435)	0.385	0.596 (0.140—2.543)	0.485
T stage				
T1–3	Reference		Reference	
T4	6.716 (2.678—16.843)	< 0.001	4.330 (0.734—25.542)	0.106
N stage				
N0	Reference		Reference	
N1–2	3.524 (1.501—8.275)	0.004	3.776 (0.662—21.529)	0.135
N3	7.618 (3.291—17.635)	< 0.001	7.851 (1.114—55.325)	0.039
Pathological stage				
I	Reference		Reference	
II	3.538 (0.887—14.121)	0.074	0.508 (0.045—5.675)	0.582
III	11.141 (3.209—38.672)	< 0.001	0.406 (0.015—10.949)	0.592
Vascular/lymphatic invasion				
No	Reference		Reference	
Yes	2.039 (1.112—3.739)	0.021	0.899 (0.412—1.958)	0.788
Perineural invasion				
No	Reference		Reference	
Yes	2.081 (0.994—4.358)	0.052	1.329 (0.551—3.206)	0.526
Adjuvant chemotherapy				
Yes	Reference			
No	0.949 (0.543—1.656)	0.853		
Preoperative CEA				
Normal	Reference		Reference	
Elevated	2.336 (1.343—4.065)	0.003	2.446 (1.150—5.201)	0.020
Preoperative CA199				
Normal	Reference			
Elevated	1.418 (0.814—2.472)	0.218		
Postoperative CEA				
Normal	Reference		Reference	
Elevated	1.990 (1.100—3.599)	0.023	1.057 (0.458—2.440)	0.896
Postoperative CA199				
Normal	Reference		Reference	
Elevated	2.692 (1.310—5.534)	0.007	2.703 (1.134—6.447)	0.025

Table 2. Univariate and multivariate analysis of factors associated with peritoneal recurrence in the training cohort.

Construction and validation of PR nomogram

Based on the results of the multivariate logistic regression analysis, four variables were used as significant effects

PR for the establishment of the nomogram model (Fig. 1A), including tumor site, N stage, preoperative CEA, and postoperative CA199. In the training cohort, the AUC value was 0.755 (95% CI 0.692–0.818) (Fig. 1B), and DCA showed a greater net benefit of the nomogram (Fig. 1C). In addition, the calibration curve also demonstrated good agreement between prediction and observation (Fig. 1D). Meanwhile, in the validation cohort, the AUC value was 0.715 (95% CI 0.612–0.818) (Fig. 1E). Moreover, the decision curve analysis also showed a good net benefit of the nomogram in the validation group (Fig. 1F), and the calibration curve of the validation group was also close to the ideal diagonal line (Fig. 1G).

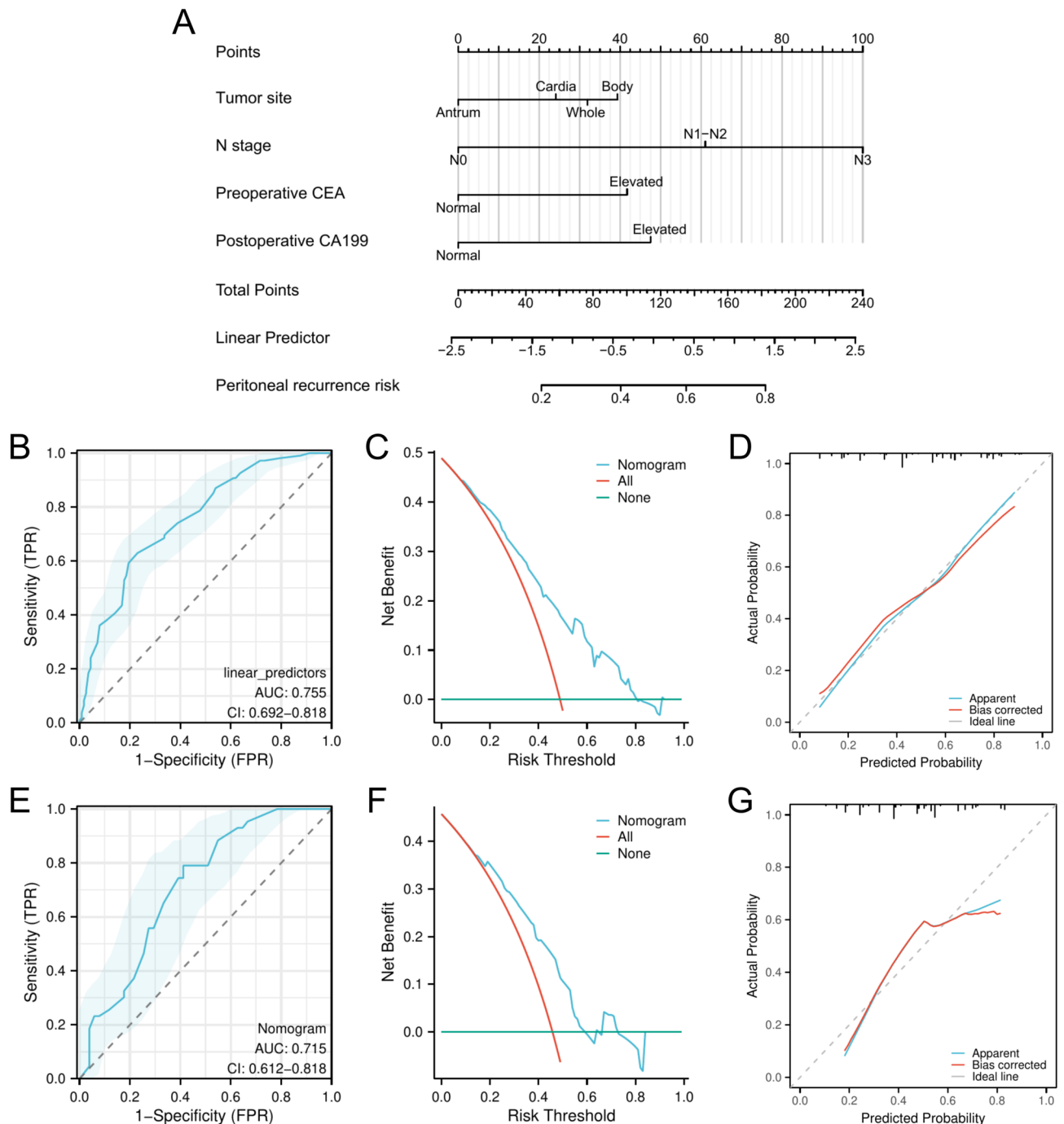


Figure 1. The construction and evaluation of nomogram. The nomogram for predicting the risk of PR (A). The area under of receiver operating characteristic curve (B), decision curve (C) calibration curve (D) for predicting the risk of PR in the training cohort. The area under of receiver operating characteristic curve (E), decision curve (F) calibration curve (G) for predicting the risk of PR in the validation cohort.

PR score based on nomogram

The PR score was developed according to the multivariate logistic regression model. The PR score was calculated as follows: PR score = 1.483 + (− 0.317, if tumor site is cardia; 0, if tumor site is body; − 0.821, if tumor site is antrum; − 0.154, if tumor site is diffuse) + (− 2.086, if N stage is N0; − 0.812, if N stage is N1–2; 0, if N stage is N3) + (0.870, if preoperative CEA is elevated; 0, if preoperative CEA is normal) + (0, if postoperative CA199 is elevated; − 0.991, if postoperative CA199 is normal). Next, the X-tile software was used to select the optimal cut-off value for the predictive score. Patients were then stratified into the low risk (predictive score < 0.23), medium risk (predictive score 0.23–1.21), and high risk groups (predictive score > 1.21). The results of the Kaplan–Meier survival analysis showed a significant decrease in OS and DFS for patients in the medium- and high-risk group compared with the low-risk group ($P < 0.05$) (Fig. 2).

PR score for adjuvant chemotherapy

Based on the PR score, patients were categorized into low, medium, and high risk groups. For the low- and medium-risk groups, postoperative adjuvant chemotherapy did not improve patients' OS but did improve DFS, whereas for the high-risk group, postoperative adjuvant chemotherapy significantly improved patients' OS and DFS (Fig. 3).

Discussion

Radical surgery is an effective treatment for early and progressive gastric cancer in the clinic, but a large proportion of patients still experience postoperative recurrence or metastasis^{13,14}. Peritoneal metastasis is the most common type of recurrence in gastric cancer and has been considered an independent predictor of poor prognosis in previous studies^{15,16}. Postoperative monitoring and timely active treatment is of great clinical significance to improve the quality of patients' survival and prolong the survival time. However, due to the limitations of each examination method, the diagnosis of most gastric cancer patients with peritoneal metastasis is difficult^{17–19}. Therefore, our study firstly developed a noninvasive, low-cost nomogram model to predict the risk of peritoneal recurrence in postoperative gastric cancer patients. Secondly, we also constructed PR score for postoperative risk stratification of gastric cancer. For patients at high risk of PR, adjuvant chemotherapy significantly improved OS and DFS. This finding is meaningful for guiding postoperative adjuvant therapy.

There are many factors affecting peritoneal recurrence after gastric cancer surgery. It has been shown that postoperative peritoneal recurrence of gastric cancer is associated with patients' clinicopathological factors. Yoo et al. reported that young age, infiltrating or diffuse type, undifferentiated tumor, plasma membrane infiltration and lymph node metastasis were independent risk factors for peritoneal recurrence²⁰. Another study from Lee et al. showed that tumor infiltration greater than T3, extensive lymph node metastasis (N3), Bormann type IV, infiltrative type (Ming's classification), and presence of venous infiltration were also independent risk factors for peritoneal recurrence²¹. In this study, we found that tumor site, lymph node metastasis, preoperative CEA and postoperative CA199 were independent predictors of peritoneal recurrence after radical gastric cancer surgery.

Lymph node metastasis is an important postoperative recurrence risk factor for gastric cancer. Patients with the presence of lymph node metastasis have a significantly higher risk of postoperative peritoneal recurrence²². Roviello et al. evaluated 441 cases of gastric cancer, of which 215 developed postoperative recurrence and peritoneal recurrence was observed in 77 patients. Multivariate analysis confirmed that lymph node metastasis was one of the risk factors for peritoneal recurrence²³. Similarly, our study showed that the risk of postoperative peritoneal recurrence in patients with N3 stage was more than seven times higher than in lymph node-negative gastric cancer patients.

In addition, serum tumor markers have been widely used in the diagnosis and dynamic monitoring of cancer, and their elevation is closely associated with recurrence, metastasis, and poor prognosis of gastric cancer²⁴. Among serum tumor markers, CEA and CA199 are the most common tumor markers used in early diagnosis

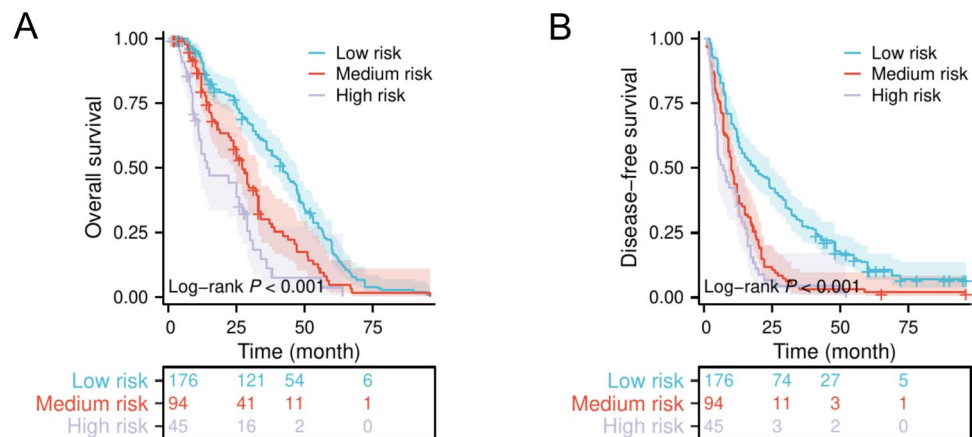


Figure 2. Kaplan–Meier survival analysis for OS (A) and DFS (B) in different risk groups according to the PR score.

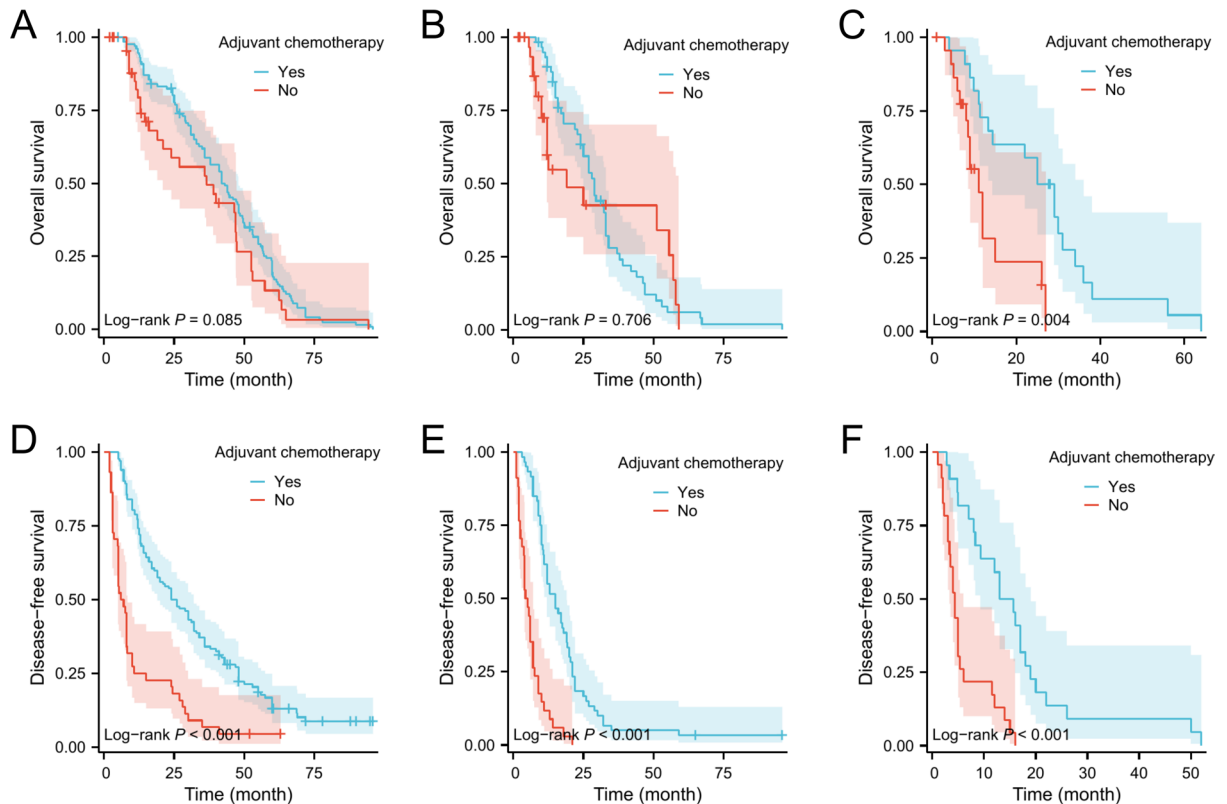


Figure 3. Kaplan–Meier survival curves for OS in gastric cancer patients stratified by chemotherapy in the low-risk group (A), medium-risk group (B), and high-risk group (C). Kaplan–Meier survival curves for DFS in gastric cancer patients stratified by chemotherapy in low-risk group (D), medium-risk group (E), and high-risk group (F).

and surveillance of gastric cancer in clinical practice. Studies have shown that serum CEA and CA199 levels provide additional prognostic information and are independently associated with poor prognosis in gastric cancer patients²⁵. These tumor markers also have been demonstrated to be strongly associated with peritoneal recurrence after gastric cancer surgery^{26,27}. In our study, we focused on the predictive value of preoperative and postoperative tumor marker changes on postoperative peritoneal recurrence in gastric cancer. We found that elevated preoperative CEA and elevated postoperative CA199 levels were independent risk factors for postoperative peritoneal recurrence. Besides, we also found that the primary tumor site was also an important factor influencing postoperative peritoneal recurrence. Compared with other sites of gastric cancer, the probability of postoperative peritoneal recurrence was significantly lower for tumors located in the gastric antrum.

The nomogram is widely used in the field of cancer and is important for guiding the decision-making of clinicians and patients. Therefore, we established a simple prediction model based on tumor site, lymph node metastasis, preoperative CEA, and postoperative CA199, which well predicted the risk of peritoneal metastasis after radical surgery for gastric cancer. Although some previous studies have established some prediction models for peritoneal metastasis after gastric cancer surgery^{16,28}, the prediction model we constructed is based on clinical information that is easily accessible in the clinic, which is very convenient for clinicians. Moreover, our study also constructed a new scoring system based on the risk of peritoneal metastasis for risk stratification of gastric cancer after surgery. We found that postoperative adjuvant chemotherapy significantly improved OS and DFS in high-risk patients. Therefore, for high-risk patients, we suggest that postoperative adjuvant chemotherapy is necessary.

The Nomogram prediction model of peritoneal metastasis of gastric cancer constructed in this study may become a simple and convenient clinical application tool, in which many parameters are easy to obtain, which may help to quickly screen high-risk patients with peritoneal metastasis of gastric cancer after surgery, and then adopt individualized treatment and follow-up system. However, there are some limitations in this study. As our study is a single-center retrospective study, there is inevitably a selection bias, which may have some impact on the stability and predictive efficacy of the nomogram, and external datasets will be needed for validation.

Conclusions

A novel nomogram was constructed to predict PR based on tumor site, N stage, preoperative CEA, and postoperative CA199. The nomogram-based PR score was developed to stratify patients into different risk groups. Postoperative adjuvant chemotherapy significantly improves prognosis in patients with high risk of PR.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

YJZ, HC and XYL conceived and designed the analysis; YHW and TJ collected the data; YHW, XLW and JWZ contributed data or analysis tools; YJZ, HC, and YHW performed the analysis and prepared Figs. 1–3. YJZ, HC and YHW wrote the paper; All authors read and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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