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A Nomogram for Prediction of Survival in Patients After Gastrectomy Within Enhanced Recovery After Surgery (ERAS): A Single-Center Retrospective Study

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Background: Enhanced Recovery After Surgery (ERAS) programs can optimize clinical outcomes and have been widely used across multiple specialties, but a personalized prediction model involving ERAS for the prognosis of gastric cancer is lacking.

Material/Methods: We retrospectively collected clinical data on 725 gastric cancer patients within ERAS who underwent curative gastric resection in the Affiliated Hospital of Qingdao University from 2007 to 2014. Kaplan-Meier method, log-rank test, and Cox proportional risk model were used to determine the independent prognostic factors of patients. The accuracy of model was evaluated by C-index, calibration curve, and Decision Curve Analysis (DCA), and the receiver operator characteristic (ROC) curve was used to compare the nomogram model with the predictive value of TNM staging system.

Results: The 5-year overall survival (OS) of 725 patients within ERAS was 72.5%. Age at diagnosis, T stage, N stage, and postoperative complications were determined to be independent factors affecting the prognosis of patients within ERAS, and nomogram model was constructed. The C-index of the training group was 0.809 and that of the verification group was 0.804; the calibration curves and DCA of the 2 groups showed good accuracy. Through verification, we found that, compared with the TNM staging assessment method, the nomogram model was more accurate in predicting the prognosis of gastric cancer.

Conclusions: This study identified factors affecting the prognosis of patients with gastric cancer, and we constructed the first prognostic nomogram model in ERAS mode to facilitate postoperative personalized prognostic evaluation.

MeSH Keywords: Nomograms • Stomach Neoplasms • Survival Rate

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Background

Gastric cancer (GC) is one of the most common malignant tumors in humans, and it remains the third leading cause of cancer-related death worldwide [1,2]. With the continuous improvement of medical technology, the morbidity and mortality rates of gastric cancer have decreased in the past 50 years [3,4]. However, the recurrence and metastasis rates of gastric cancer are still high, and the long-term overall survival rates have not significantly improved [5]. Predictions are common in all areas of gastric cancer treatment, from screening to hospice. Indeed, oncology is usually primarily a predictive problem. Accurate prediction of the prognosis of different individuals has a significant impact on the selection of suitable treatment strategies for gastric cancer patients. Unfortunately, the clinical TNM stage alone cannot accurately predict the overall prognosis of patients after surgery [6]. Therefore, it is of vital importance to establish a reliable model to predict the survival rate of high-risk patients and formulate individualized treatment strategies.

The concept of Enhanced Recovery After Surgery (ERAS) was first put forward by Dr. Henrik Kehlet and refers to a series of optimized perioperative management programs to minimize the stress state of surgical patients, to reduce the occurrence of complications, and improve the clinical outcome of patients [7,8]. Subsequently, ERAS has gained increasing attention in different branches of surgery and has been widely studied in colorectal, gastric, pancreatic, liver, and bariatric surgery. In addition, the implementation of ERAS can reduce the hospitalization cost of gastric cancer patients, and help to improve the survival rate of cancer patients [9]. However, a prognostic model has not previously been established to accurately predict the survival of patients with gastric cancer under the ERAS mode.

In recent years, a variety of statistical prediction models have been developed for most cancers [10,11]. A nomogram is such a forecasting tool that creates a simple graphical representation of a statistical predictive model that generates a numerical probability of a clinical event [12,13]. The establishment of numerous nomogram prognostic models based on different races and different treatment schemes has led to some progress in prediction of individual response and individualized therapy regimens. More prognostic nomogram models are needed from different countries and regions to reduce the mortality of patients with gastric cancer. Subsequent studies found that use of nomograms has more advantages than the traditional TNM staging system for many cancers [14,15]. Therefore, it was proposed as an alternative or even a new standard for predicting overall survival (OS).

In this study, we analyzed the independent risk factors affecting prognosis based on the postoperative population of gastric cancer patients within ERAS. The prognostic nomogram model using ERAS was established for the first time and was found to have utility in personalized precision prediction.

Material and Methods

Patients

From January 2007 to November 2014, 3102 consecutive patients with gastric cancer who underwent gastrectomy at the Department of General Surgery, Affiliated Hospital of Qingdao University were retrospectively analyzed. Among them, 894 patients received ERAS during the perioperative period. According to the standard of nano-excretion, 725 patients were included in this study. Then, based on a training set ratio verification set of approximatively 7: 3, 529 patients were included in the training set and 196 patients were included in the verification set. The inclusion criteria were: 1) gastric cancer was proven via gastroscopic biopsy, and 2) radical surgery could be performed by preoperative evaluation. Exclusion criteria were: 1) incomplete clinical data(n=17), 2) preoperative examination and intraoperative detection of distant metastasis or invasion of surrounding tissues and organs (n=6), 3) neo-adjuvant therapy before surgery (n=25), 4) gastric stump carcinoma (n=4); 5) pathologically confirmed non-adenocarcinoma (n=8); 6) combined organ resection (n=19), 7) palliative surgery (n=86), and 8) unable to evaluate the operation because of severe cardiopulmonary or other system diseases (n=4). All procedures were approved by the Ethics Committee of Affiliated Hospital of Qingdao University. All patients provided informed consent.

Study design

The clinicopathological data of gastric cancer patients were collected, such as sex, BMI, age at diagnosis, ASA classification [16,17], comorbidity, tumor size, location, differentiation, Borrmann type, GI reconstruction, intraoperative blood transfusion, surgical approach, gastrectomy type, T stage, N stage, and AJCC pTNM stage [18], perioperative malnutrition, complications, and postoperative chemotherapy. The primary endpoint was overall survival (OS), which was defined as the time from diagnosis until death or last follow-up. It is recommended that all patients with gastric cancer should be followed up regularly according to clinical guidelines after completing primary surgical treatment. Kaplan-Meier method was used for single-factor survival analysis of training set data. The log-rank test was used to compare differences in survival rate. X-tile plots were used to accurately and automatically select the optimum cut-off based on the highest χ^2 value (i.e., minimum *P*-value) [19]. Age at diagnosis and tumor size were precisely divided based on the optimal cut-off value generated by X-tile software version 3.6.1 (Yale University School of Medicine, USA).

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Table 1. Postoperative complications.

Type of complications	Training cohort (n=529)		Validation cohort (n=196)	
	Mean±SD/No (%)		Mean±SD/No (%)	
Total no. of complications	87	(16.4)	29	(14.8)
Local complications				
Wound	20	(3.8)	7	(3.6)
Fluid collection/abscess	7	(1.3)	2	(1.0)
Intra-abdominal bleeding	6	(1.1)	1	(0.5)
Intraluminal bleeding	7	(1.3)	0	(0.0)
Intestinal obstruction	5	(0.9)	3	(1.5)
Anastomosis stricture	7	(1.3)	3	(1.5)
Anastomotic leakage	5	(0.9)	2	(1.0)
Pancreatitis/Pancreatic leakage	10	(1.9)	4	(2.0)
Systemic complications				
Pulmonary	8	(1.5)	2	(1.0)
Urinary	2	(0.4)	1	(0.5)
Hepatic	3	(0.6)	0	(0.0)
Cardiac	0	(0.0)	0	(0.0)
Others	7	(1.3)	4	(2.0)
Clavien-Dindo classification				
II	67	(12.7)	24	(12.2)
IIIa	9	(1.7)	3	(1.5)
IIIb	7	(1.3)	1	(0.5)
IV	2	(0.4)	1	(0.5)
V	2	(0.4)	0	(0.0)

Classification of postoperative complications

Complications were defined as any deviation from the normal postoperative course [20]. According to the Clavien-Dindo classification, postoperative complications were recorded within 30 days after surgery (Table 1) [21]. The information on complications was abstracted from the Electronic Medical Record System (EMRS). In addition, the postoperative complications were divided into 2 groups: local complications and systemic complications [22]. Briefly, local complications included wound complication, fluid collection/abscess, intra-abdominal bleeding, intraluminal bleeding, intestinal obstruction, anastomosis stricture, leakage, and pancreatitis/pancreatic fistula. Systemic complications included pulmonary, urinary, hepatic, cardiac, and others (Table 1). In case a patient had multiple concurrent complications, only the original or the most severe one was considered.

Nomogram construction

The Kaplan-Meier method and log-rank test were used for univariate survival analysis, while the χ^2 test was used for the comparison of categorical variables. Meaningful predictive factors were screened out ($P<0.05$) and Cox's proportional hazards regression model was used for multivariate analysis. Nomograms were constructed using independent prognostic factors in the training set data [23]. The construction of nomograms for 1-, 3-, and 5-year OS prediction was performed using the RMS software package in R software version 3.1.3 (*https://www.r-project.org/*).

Validation of nomograms and statistical analysis

We used the concordance index (C-index) to measure differences between performance and predicted results of the nomograms [24]. The value of C-index ranged from 0.5 to 1, in which 0.5 considered no discrimination at all and 1.0 represented perfect discrimination [25]. Calibration curves were used to compare the predicted results of the nomogram with the actual results, while the 45-degree line was used as the optimal model [26]. The DCA algorithm can be used as a comprehensive method for evaluating prediction models [27]. Using the receiver operator characteristic (ROC) curve, the prognostic value of

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Table 2. Patient and tumor characteristics in the training and validation cohorts.

Characteristic	Training cohort (n=529)		Validation cohort (n=196)	
	Mean±SD/No (%)		Mean±SD/No (%)	
Sex				
Male	375	(70.9)	144	(73.5)
Female	154	(29.1)	52	(26.5)
Age (years)				
≤62	249	(47.1)	97	(49.5)
>62	280	(52.9)	99	(50.5)
BMI				
≤25	352	(66.5)	124	(63.3)
>25	177	(33.5)	72	(36.7)
ASA classification				
I	23	(4.3)	8	(4.1)
II	363	(68.6)	134	(68.4)
III	143	(27.0)	54	(27.6)
Comorbidity				
Diabetes mellitus	56	(10.6)	20	(10.2)
Heart disease	123	(23.2)	42	(21.4)
COPD	17	(3.2)	7	(3.6)
Hepatitis	4	(0.8)	2	(1.0)
No comorbidity	329	(62.2)	125	(63.8)
Tumor size				
≤3	219	(41.4)	89	(45.4)
3–5	147	(27.8)	65	(33.2)
>5	163	(30.8)	42	(21.4)
Tumor location				
Cardia/fundus	53	(10.0)	19	(9.7)
Body	90	(17.0)	40	(20.4)
Antrum/pylorus	386	(73.0)	137	(69.9)
Tumor differentiation				
Well	28	(5.3)	10	(5.1)
Moderate	81	(15.3)	31	(15.8)
Poor	420	(79.4)	155	(79.1)
Borrmann type				
I	59	(11.2)	24	(12.2)
II	139	(26.3)	51	(26.0)
III	309	(58.4)	116	(59.2)
IV	22	(4.2)	5	(2.6)
GI reconstruction				
Billroth-I	338	(63.9)	125	(63.8)
Billroth-II	128	(24.2)	40	(20.4)
Roux-en-Y	63	(11.9)	31	(15.8)

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Table 2 continued. Patient and tumor characteristics in the training and validation cohorts.

Characteristic	Training cohort (n=529)		Validation cohort (n=196)	
	Mean±SD/No (%)		Mean±SD/No (%)	
Intraoperative blood transfusion				
Yes	38	(7.2)	13	(6.6)
No	491	(92.8)	183	(93.4)
Surgical approach				
Laparoscopic	67	(12.7)	32	(16.3)
Open	462	(87.3)	164	(83.7)
Gastrectomy type				
Total gastrectomy	50	(9.5)	17	(8.7)
Subtotal gastrectomy	479	(90.5)	179	(91.3)
Extent of LN dissection				
D2	378	(71.5)	141	(71.9)
D2+	151	(28.5)	55	(28.1)
Depth of invasion				
T1	120	(22.7)	46	(23.5)
T2	78	(14.7)	21	(10.7)
T3	182	(34.4)	83	(42.3)
T4a	137	(25.9)	40	(20.4)
T4b	12	(2.3)	6	(3.1)
Number of positive LN				
N0	236	(44.6)	84	(42.9)
N1	94	(17.8)	19	(9.7)
N2	100	(18.9)	27	(13.8)
N3a	78	(14.7)	50	(25.5)
N3b	21	(4.0)	16	(8.2)
Total LN (Mean±SD)	30.3±11.3		31.0±12.5	
AJCC pTNM stage*				
I	161	(30.4)	47	(24.0)
II	128	(24.2)	64	(32.7)
III	240	(45.4)	85	(43.4)
Perioperative malnutrition				
Yes	362	(68.4)	127	(64.8)
No	167	(31.6)	69	(35.2)
Complications				
Yes	87	(16.4)	29	(14.8)
No	442	(83.6)	167	(85.2)
Postoperative chemotherapy				
Yes	246	(46.5)	95	(48.5)
No	283	(53.5)	101	(51.5)

* The 8th AJCC classification criteria.

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Table 3. Univariate and multivariate Cox proportional hazard analyses of OS with GC patients.

Variable	Univariate analysis			Multivariate analysis		
	HR (95%CI)		P-value	HR (95%CI)		P-value
Sex (Male vs. Female)	0.822	(0.554–1.221)	0.333			
Age	2.044	(1.411–2.961)	<0.001*	1.802	(1.199–2.710)	0.005*
BMI	0.681	(0.456–1.016)	0.060			
ASA classification			0.562			
I	Reference					
II	1.149	(0.466–2.831)	0.763			
III	1.389	(0.547–3.527)	0.489			
Comorbidity	1.100	(0.773–1.566)	0.597			
Tumor size			<0.001*			0.958
≤3	Reference			Reference		
3–5	2.462	(1.494–4.055)	<0.001*	0.956	(0.557–1.642)	0.871
>5	4.233	(2.684–6.675)	<0.001*	0.924	(0.539–1.582)	0.772
Tumor location			<0.001*			0.130
Cardia/fundus	Reference			Reference		
Body	0.499	(0.283–0.878)	0.016*	0.552	(0.301–1.011)	0.054
Antrum/pylorus	0.376	(0.238–0.594)	<0.001*	0.652	(0.396–1.075)	0.094
Tumor differentiation			0.033*			0.981
Well	Reference					
Moderate	5.205	(0.684–39.585)	0.111	1.148	(0.135–9.773)	0.900
Poor	8.237	(1.150–58.988)	0.036*	1.091	(0.133–8.961)	0.936
Borrmann type			<0.001*			0.150
I	Reference			Reference		
II	1.209	(0.483–3.030)	0.685	0.464	(0.174–1.233)	0.124
III	3.030	(1.335–6.968)	0.008*	0.780	(0.319–1.905)	0.585
IV	7.509	(2.814–20.036)	<0.001*	0.985	(0.326–2.981)	0.979
Intraoperative blood transfusion	1.840	(1.056–3.205)	0.031*	1.598	(0.882–2.895)	0.122
Surgical approach (laparoscopic *vs.* open)	1.633	(0.826–3.229)	0.159			
Gastrectomy type (subtotal *vs.* total gastrectomy)	2.291	(1.447–3.626)	<0.001*	1.000	(0.600–1.664)	0.999
Extent of LN dissection (D2 *vs.* D2+)	0.963	(0.660–1.404)	0.844			
Depth of invasion			<0.001*			0.001*
T1	Reference			Reference		
T2	2.747	(0.804–9.386)	0.107	3.150	(0.791–12.543)	0.104
T3	8.373	(3.001–23.364)	<0.001*	10.323	(1.624–65.630)	0.013*
T4a	19.150	(6.981–52.535)	<0.001*	20.236	(2.909–140.750)	0.002*
T4b	39.875	(12.264–129.649)	<0.001*	35.632	(4.744–267.653)	0.001*

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Table 3 continued. Univariate and multivariate Cox proportional hazard analyses of OS with GC patients.

Variable	Univariate analysis			Multivariate analysis		
	HR (95%CI)		P-value	HR (95%CI)		P-value
Depth of invasion			<0.001*			<0.001*
N0	Reference			Reference		
N1	2.634	(1.382–5.020)	0.003*	2.305	(1.117–4.758)	0.024*
N2	6.274	(3.622–10.866)	<0.001*	4.359	(2.057–9.235)	<0.001*
N3a	9.898	(5.726–17.110)	<0.001*	5.330	(2.497–11.378)	<0.001*
N3b	13.232	(6.375–27.268)	<0.001*	7.314	(2.822–18.957)	<0.001*
Total LN (continuous)	1.014	(0.999–1.029)	0.066			
AJCC pTNM stage			<0.001*			0.236
I	Reference			Reference		
II	2.271	(0.952–5.413)	0.064	0.269	(0.057–1.275)	0.098
III	12.036	(5.864–24.707)	<0.001*	0.296	(0.046–1.902)	0.200
Perioperative malnutrition	1.503	(1.015–2.226)	0.042*	1.001	(0.638–1.571)	0.996
Complications	1.922	(1.288–2.868)	0.001*	1.648	(1.072–2.532)	0.023*
Postoperative chemotherapy	2.197	(1.537–3.141)	<0.001*	1.037	(0.691–1.556)	0.859

HR – hazard ratio; CI – confidence interval.

the predictive model and the 8th edition of the AJCC TNM staging was compared using MedCalc medical statistical software. All statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Armonk, NY, USA), and $P<0.05$ was considered to indicate a statistically significant difference. In addition, the hazard ratio (HR) and its 95% confidence interval (CI) were also calculated.

Results

Patient clinicopathological characteristics

The clinicopathological factors of 725 gastric cancer patients within ERAS between January 2007 and December 2014 are shown in Table 2. In the training data sets, the follow-up times ranged from 3 to 7 years, with the median follow-up time was 43.1 months. Among a total of 529 patients, 375 (70.9%) patients were male and 154 (29.1%) were female. The patients' median age was 63 years, ranging from 30 years to 90 years. The OS of the patients was 75.6%, of which the 1-, 3-, and 5-year survival times were 91.7%, 79.6%, and 76.7%, respectively. In the validation cohort, the OS of the patients was 76.0%, and the 1-, 3-, and 5-year survival times were 92.3%, 79.5%, and 77.9%, respectively.

Sifted independent risk factors and development of the nomogram model

Before constructing the nomogram model, clinicopathological features were evaluated using univariate and multivariate analysis (Table 3). Age at diagnosis, tumor size, location, differentiation, Borrmann type, intraoperative blood transfusion, gastrectomy type, T stage, N stage, AJCC pTNM stage, perioperative malnutrition, complications, and postoperative chemotherapy were correlated with OS based on the univariate Kaplan-Meier method and log-rank test ($P<0.05$). Subsequently, a Cox proportional hazards regression model was used to analyze meaningfully related factors. According to multivariate analysis, age at diagnosis, T stage, N stage, and complications were identified as independent predictors of OS (Table 3). Based on the aforementioned results, we combined these 4 predictors (Figure 1). By projecting the points corresponding to each variable to the "Points" axis, summing the total scores gives the corresponding prediction results [26].

Performance assessment and validation of the nomogram

In this study, discrimination and calibration were used to verify the established nomogram model with 1000 bootstrap resamples [28,29]. In the validation set, the independent risk factors in the nomogram were examined using the clinical data

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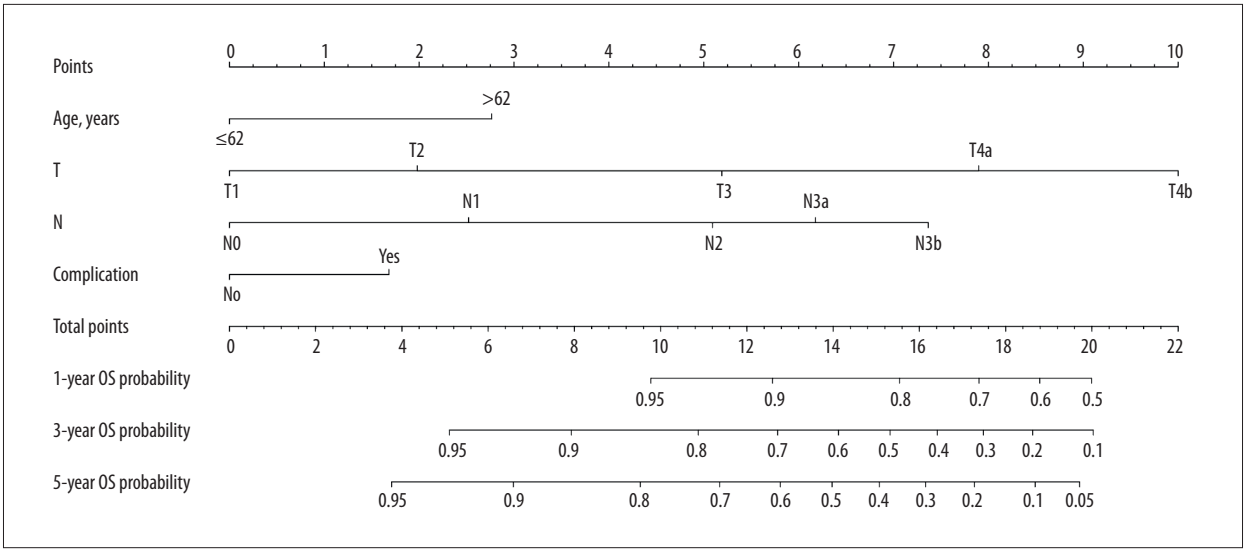

Figure 1. Prognostic nomogram of 1-year, 3-year and 5-year overall survival of resected GC patients within ERAS. Covariates were assessed for the patient and given a point in the nomogram. A higher total number of points indicated a higher likelihood of poor clinical outcomes and shorter expected survival. T – 8th edition of AJCC (American Joint Committee on Cancer) T staging; N – 8th edition of AJCC N staging.

of 196 patients with gastric cancer. The discrimination was appraised by C-index. The C-index correctly predicted the probability of positive events in a survival prediction model through a group of randomly selected patients [24]. In the primary set, the C-index for the OS nomogram was 0.809 (95% CI: 0.778–0.840), while the validation cohort for the OS nomogram was 0.804 (95% CI: 0.749–0.859). Another verification was calibrated to compare the predicted survival rate and the actual survival rate. The calibration curve shows the effect of the correction and compares the actual survival rate and the survival rate predicted by the model in the form of an image. Figure 2 showed that the calibration maps for the probability of 1-, 3-, and 5-year OS had good agreement between the prediction by nomogram and actual observation in the development and validation cohort. DCA was used to analyze the clinical value with clinical consequences of a decision considered [30]. The DCA for the nomogram is presented in Figure 3, which demonstrated that the developed nomogram showed better ability to predict survival than the all patients dead scheme and the no patients dead scheme [27,30]. Furthermore, the DCA suggested that the nomogram prediction model had a considerable net clinical benefit. In summary, the nomogram model had good prediction ability and clinical application value for patients within ERAS.

Comparison of predictive value between the nomogram model and TNM staging

In clinical studies, ROC analysis is useful for assessing different screening or diagnostic tests [31]. The nomogram prediction model was compared with the ROC curve of the 8th edition AJCC TNM staging (Figure 4). In the primary cohort, the AUC of the nomogram prediction model in the first, third, and fifth year was 0.830, 0.839, and 0.849, respectively, which was significantly higher than that of AJCC TNM in the 8th Edition (0.754, 0.763 and 0.757). At the same time, in the verification set, the AUC of nomogram prediction model in the 1-, 3-, and 5-year OS was 0.840, 0.835, and 0.848, respectively. However, the AUC of TNM in the first, third, and fifth year was only 0.742, 0.748, and 0.756, respectively, indicating that the nomogram is more beneficial than the 8th AJCC staging system in predicting OS.

Discussion

Gastric cancer is a common malignant tumor of the digestive tract, and radical resection is the most effective treatment for patients [1]. Accurate prognostic evaluation is important in correctly treating the disease. The AJCC TNM staging and histological classifications are the most commonly used prognostic evaluation systems at present. However, patients with the same stage often have a significantly different prognosis, indicating that the current staging system cannot provide accurate prognostic information [32,33]. Therefore, it is urgent to establish a convenient scientific prognosis prediction system to supplement the current staging system, in order to improve the accuracy of prognosis prediction and treatment selection.

Since its establishment in 2010, the ERAS Society has issued a series of guidelines, including clinical guidelines for gastrectomy in 2014. All the ERAS Society guidelines are freely available at *www.erassociety.org*. The application of ERAS concepts

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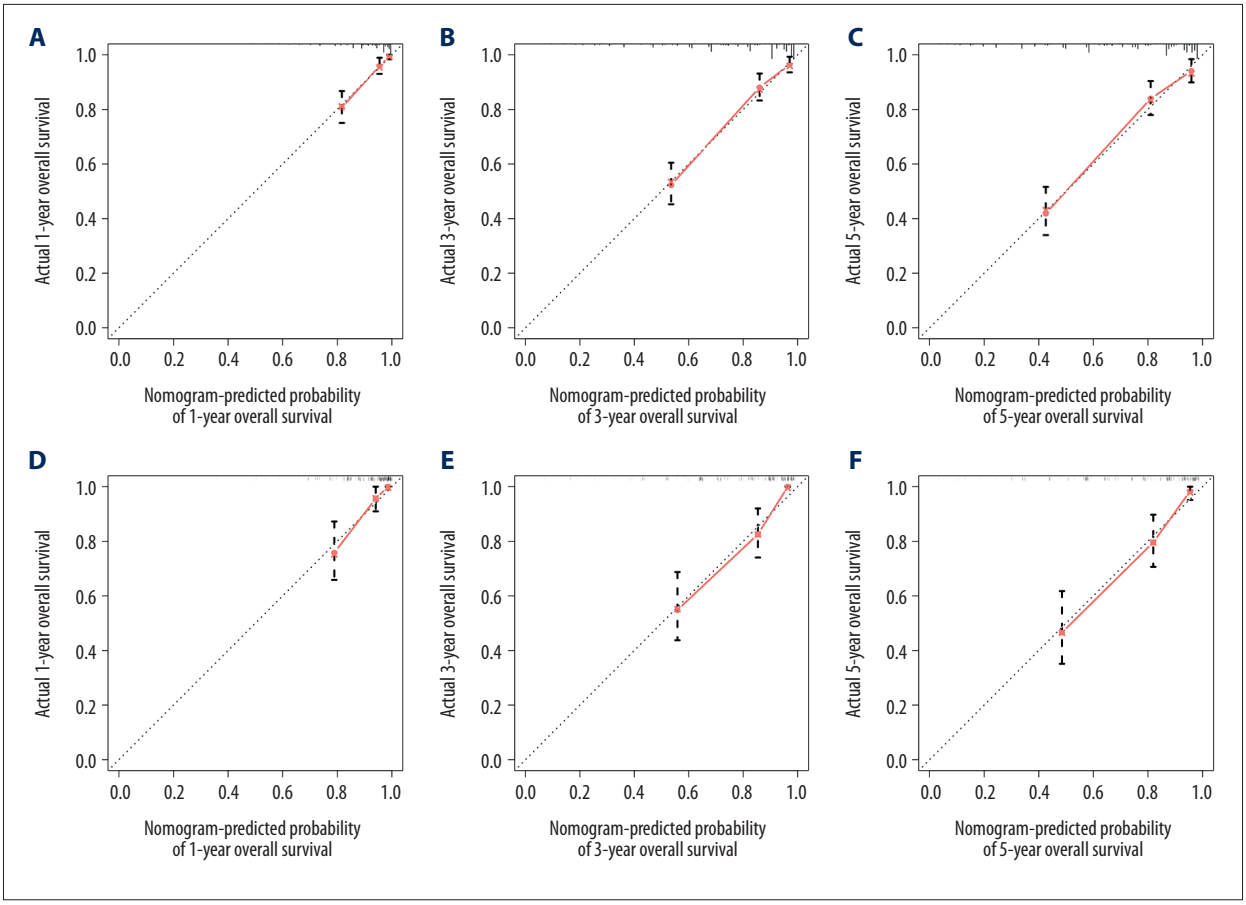

Figure 2. The plots of bootstrap calibration of 1-year, 3-year, and 5-year overall survival. Calibration curves of the OS nomogram in training set at 1 year (**A**), 3 years (**B**), and 5 years (**C**). Calibration curves of the OS nomogram in the validation set at 1 year (**D**), 3 years (**E**), and 5 years (**F**). Dotted lines represent the ideal predictive model, and the solid red line represents the observed model.

in different branches of surgery has unique advantages and characteristics, and many retrospectives and prospective studies on the application of ERAS in radical surgery have been carried out [34,35]. In addition, use of ERAS reduces hospitalization costs, improves the clinical outcome of patients, and even helps improve the survival rate of cancer patients [7,8]. These advantages make ERAS one of the best surgical innovations to be developed in recent decades, far ahead of many technological innovations. Briefly, the classical ERAS can be divided into 3 time periods: preoperative, intraoperative, and postoperative, including many intervention measures and factors verified by evidence-based medicine. Although ERAS has achieved excellent results in improving the clinical outcome of patients, the program still lacks a suitable model to predict treatment efficacy.

At present, research on ERAS has mostly focused on short-term outcomes of patients, and there are few reports on long-term prognosis. In 2010, the first prospective RCT study on use of ERAS in gastric cancer was published by our team [9]. Fortunately, the paper has been widely cited in some important studies [17, 36]. We found that this protocol can improve the prognosis of patients with gastric cancer. Gustafsson and Curtis performed a retrospective study of the effect of ERAS on the prognosis of colorectal cancer patients, suggesting that ERAS can prolong survival and improve the prognosis of patients [37,38]. Tan [39] used "marginal gains" to explain the principle of ERAS program to improve patient prognosis: The ERAS pathway usually consists of more than 20 programs, and every detail improved during the perioperative period may lead to corresponding benefits for patients. The gradual accumulation of these benefits will have a significant impact on the outcome. Nevertheless, more research is needed to verify the long-term oncologic outcomes, safety, and efficacy of ERAS. The present study retrospectively collected clinical data and follow-up information of 529 patients undergoing standard gastric curative resection under ERAS conditions. The 5-years overall survival rate of patients undergoing ERAS protocols was 72.5%. This result was significantly higher compared to prognosis of gastric cancer after traditional perioperative treatment during

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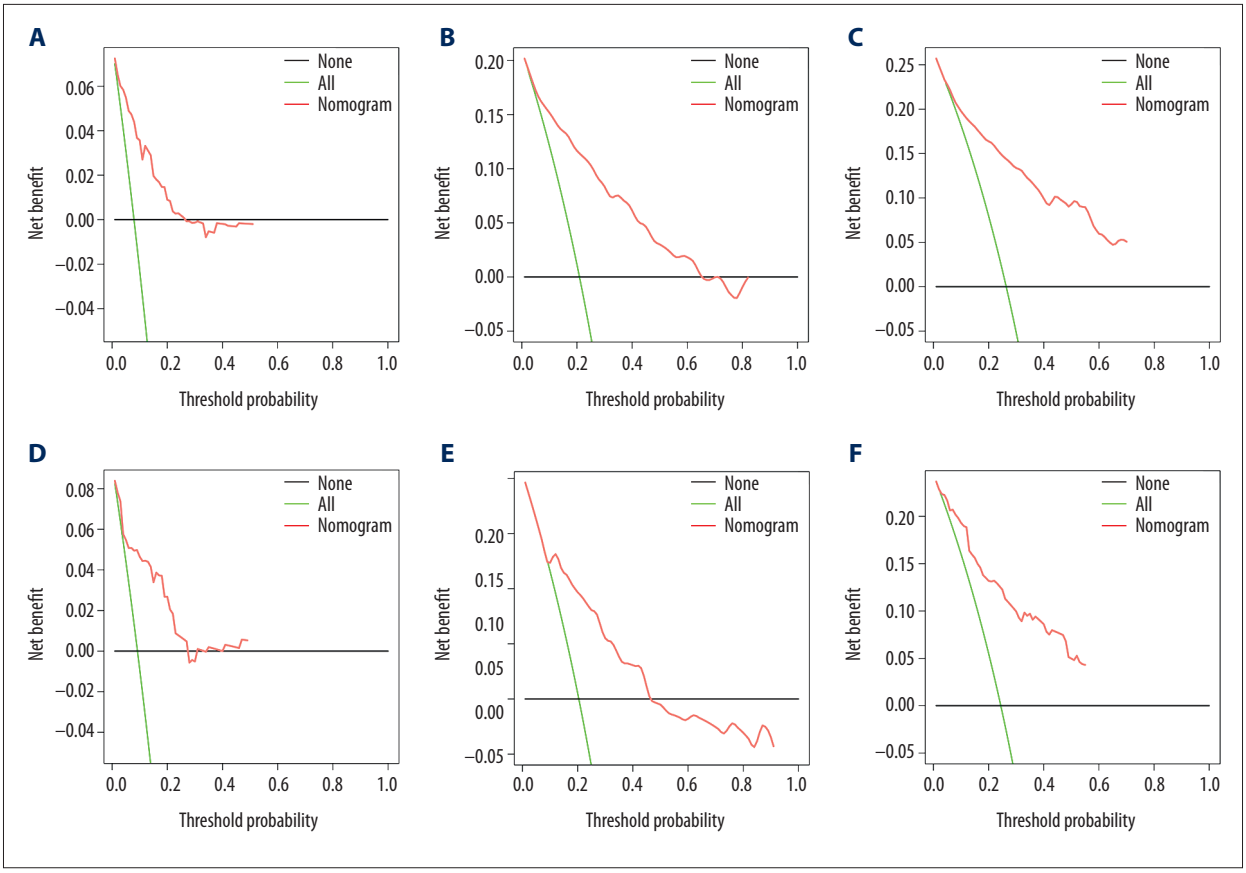

Figure 3. DCA for the nomograms (**A–C**). DCA for the OS nomogram in the training set (**D–F**). DCA for the OS nomogram in the validation set. The net benefit was plotted versus the threshold probability. The red line depicts the nomogram. The green and black lines represent the net benefit of the strategy of treating all patients and no patients, respectively.

the same period. Through univariate and Cox multivariate survival analysis, postoperative complications, T stage, N stage, and age at diagnosis were found to be independent risk factors affecting the prognosis of patients. The nomogram prediction model was successfully constructed based on independent risk factors determined by survival analysis. Its C-index is higher than 0.8 in both the training and verification sets, which shows a good prediction accuracy.

Postoperative complications are an essential quality parameter for measuring the results of ERAS regulatory pathways [7,36], and the occurrence of postoperative complications is regarded as an essential factor leading to poor prognosis [40]. Use of ERAS can reduce the incidence of postoperative complications of colorectal cancer [41]. Studies have shown that grade 3 (Clavien-Dindo grade) complications of gastric cancer patients in the ERAS approach are significantly lower than those in patients receiving traditional perioperative management. This study again proves that the prognosis of gastric cancer patients can be improved by effectively preventing postoperative complications in ERAS mode. Previous studies have found that as the age of diagnosis increases, the OS of patients with gastric cancer decreases [42]. The results of the present study confirm this conclusion. However, the individual's physical condition or socioeconomic condition may affect the age at diagnosis, which will lead to selection bias. In addition, the staging of gastric cancer patients included in this study was the 8th edition of AJCC TNM staging. Both univariate and Cox multivariate analysis showed that the depth of tumor invasion and regional lymph node stage were independent factors affecting prognosis. However, although the AJCC TNM staging system has a good ability to predict the prognosis of postoperative gastric cancer patients, it does not include some necessary prognostic factors, such as age, tumor differentiation, and the choice of surgical options. Without considering the above factors, treating all patients in the same TNM stage as having the same type of cancer cannot adequately include the heterogeneity of prognoses.

The nomogram model makes up for the deficiency of AJCC TNM staging. The prognosis model constructed in this study includes socio-demographic characteristics and postoperative factors, in addition to the T stage and N stage. Unlike the AJCC TNM staging system, the nomogram builds a graphical

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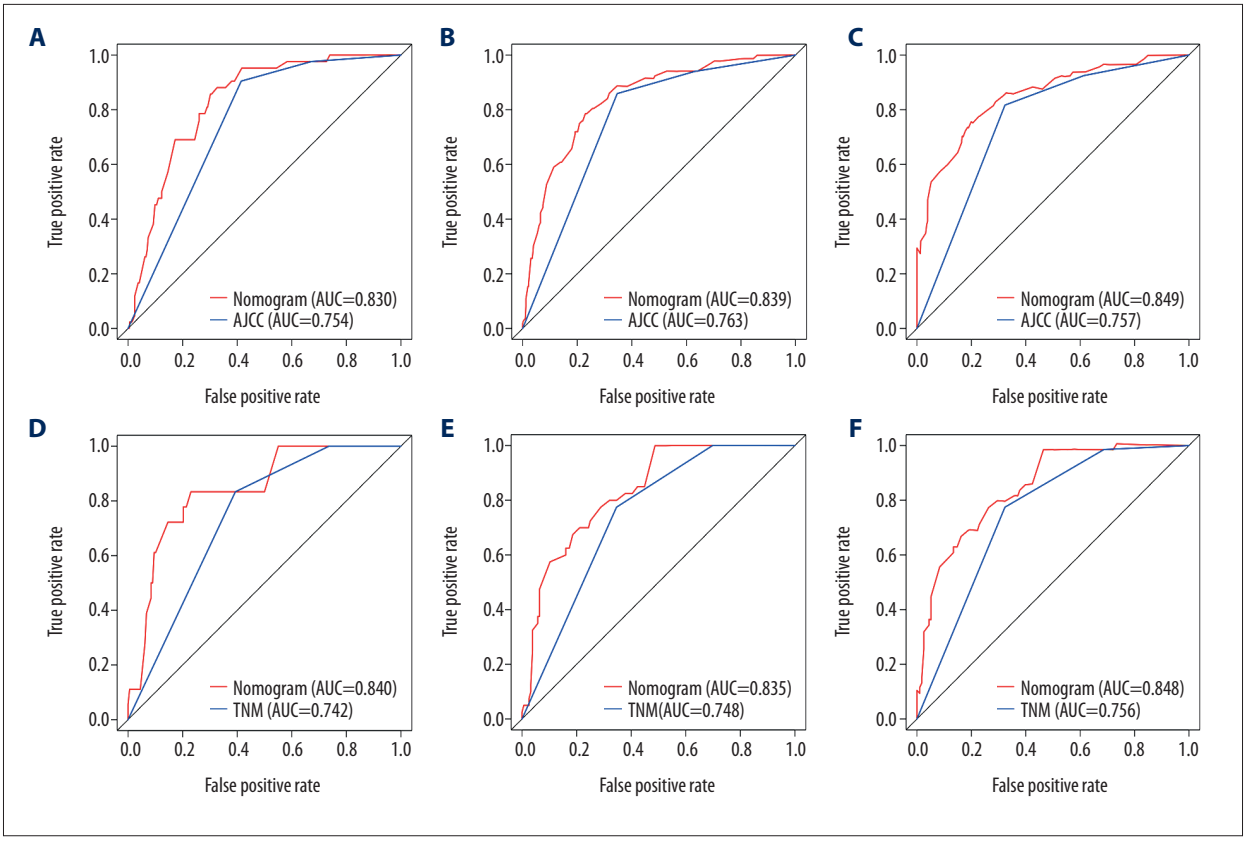

Figure 4. Comparison of ROC curves between the nomogram prediction model and 8th edition AJCC TNM staging for prediction of OS at 1 year (**A**), 3 years (**B**), and 5 years (**C**) in the training set and at 1 year (**D**), 3 years (**E**), and 5 years (**F**) in the validation set. The red lines represent the nomogram prediction of OS. The blue lines depict the TNM staging prediction of OS.

statistical prognosis model based on biological and clinical factors, and can predict the probability of a specific individual clinical events (such as death or tumor recurrence) [23,26]. Moreover, temporal verification was used in this study. It was a prospective assessment of a model, independent of the primary data and training process [43]. Therefore, it could be regarded as external verification in time. Calibration mapping showed that the nomogram-predicted 1-, 3-, and 5-year overall survival rates are in good agreement with actual values. DCA is a simple mathematical model for assessing the feasibility and benefits of forecasting tools [27]. It introduces a loss of function to examine the pros and cons of statistical inference results. DCA shows that the nomogram prognosis model has an excellent clinical benefit, which was confirmed by AUC, showing that use of nomogram models under ERAS protocols is superior to the traditional AJCC TNM system in predicting the overall survival of patients after GC.

The present study comprehensively analyzed the prognostic factors of postoperative patients within ERAS and established an accurate and convenient nomogram prognostic model, which carried internal verification in our center to evaluate the performance of the model accurately. However, there were still some shortcomings in this study. Firstly, this study was a retrospective study and the existence of some unknown factors lead to bias was inevitable. Moreover, tumor markers, gene mutations, and other biological information were not included in the final model. Therefore, the predicted value of the nomogram model does not represent the absolute accurate probability of postoperative prognosis. Furthermore, the follow-up time was short in the verification cohort. In addition, to evaluate the performance of the model more accurately, external verification based on other centers is also needed.

In future studies, we will use data from other ERAS centers to further verify the model developed in this study, and we will also explore the inclusion of other prognostic variables into the model to improve its accuracy. We will also try to use other regression methods to improve the precision of prediction.

Conclusions

The application of ERAS can optimize clinical outcomes and has been widely used across multiple specialties. Moreover, in recent years, more and more attention has been focused

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on predictive tumor models. This study identified factors affecting the prognosis of patients within ERAS. Our nomogram model is the first to be published involving ERAS for the prognosis of gastric cancer. Individualized survival predictions are more easily accommodate the individual patient's needs than generic classification with a large number of heterogeneities. This presents a critical step toward improving gastric cancer treatment with ERAS.

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Conflict of interest

None.

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