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Original Article

Prediction model of objective response after neoadjuvant chemotherapy in patients with locally advanced gastric cancer

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Abstract: Background: Neoadjuvant chemotherapy (NAC) plays an important role in the therapeutic strategy of locally advanced gastric cancer (LAGC). However, the response of LAGC after NAC varies among different patients. The objective response after NAC has proven to be an excellent indicator for benefiting from NAC, yet effective predictors of objective response are still lacking. The present study aimed to identify potential predictors of objective response in LAGC patients treated with NAC. Methods: Clinicopathological data from 267 patients with LAGC who received NAC and met the inclusion criteria between July 2009 and December 2018 were retrospectively reviewed. Patients were randomly divided into the training and test sets at a 2:1 ratio. Univariate analysis was used to investigate whether any factors were correlated with objective response in the training set. Multivariate logistic regression analysis was applied to find independent predictors. A risk score model was then constructed based on the independent predictors, and its performance in predicting objective response was validated in the test set. Results: Univariate analysis found that gender, age, short axis diameter of the largest regional lymph node (LN_{max}), serum total protein content, CEA detection value, tumor location, tumor differentiation, signet ring cell carcinoma component and Borrmann type were potential predictors for objective response. In multivariate logistic regression analysis, gender, LN_{max} and signet ring cell carcinoma component were independent predictors for objective response. Based on independent predictors, we developed a prediction model for objective response. Conclusions: We found gender, LN_{max} and signet ring cell carcinoma component were independent predictors for objective response. The prediction model is a good tool to predict the objective response for LAGC patients treated with NAC, which can be applied to guide clinical practice.

Keywords: Local advanced gastric cancer, neoadjuvant chemotherapy, objective response, prediction model, recist, survival time

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1, 2]. More than 70% of cases occur in developing countries, especially in Eastern Asia (mainly in China), which accounts for half the global incidence and the highest estimated mortality rate [2]. In China, GC is the second leading cause of cancer-related deaths [3]. Hitherto, surgery is the only treatment that can cure GC. However, the 5-year overall survival (OS) rate of GC after curative surgery remains poor, only approximately 20-30% worldwide [4-7]. Although the detection rate of early-stage cancer is improving, most patients were diagnosed as having locally advanced gastric cancer (LAGC) with poor prognosis [8]. To improve the clinical outcome of patients with LAGC, multimodality therapies are desirable.

With the development of advanced chemotherapy and treatment concepts, perioperative chemotherapy (PCT) has been identified as an effective and safe approach for LAGC [9-12].

Currently, PCT is recommended as an important component of the standard regimen for LAGC by the National Comprehensive Cancer Network (NCCN) guidelines. PCT consists of neoadjuvant and adjuvant chemotherapy. Compared to surgery alone, adjuvant chemotherapy (AC) has been proven to improve the disease-free survival (DFS) and overall survival (OS) of GC patients [13, 14]. In addition, neoadjuvant chemotherapy (NAC) can also bring many potential benefits for GC patients, such as promoting tumor downstaging, thus increasing the chance of curative resection, eliminating potential micrometastasis, preventing or reducing tumor recurrence and metastasis, and improving tumor-associated symptoms [9, 15, 16]. Several randomized controlled trials (RCTs) have shown that NAC can improve survival in patients with LAGC.

Korean scholars conducted a study on patients with LAGC and esophagogastric junction cancer [17]. The results showed that the 3-year progression-free survival (PFS) was 66.3%, and the 5-year PFS was 60.4% in the PCT group, which were significantly higher than those in the direct surgery group (60.2% and 55.6%, respectively) (P=0.023), suggesting that for patients with LAGC, the therapeutic strategy of NAC could significantly prolong the patients' PFS. In China, the RESOLVE study also explored the value of NAC in LAGC [18]. The results showed that 3-year disease-free survival (DFS) in group A (direct surgery and SOX regimen as AC) was lower than that in group C (SOX regimen as PCT and surgery) (54.78% vs. 62.02%, 95% CI: 0.62-0.99, P=0.045), suggesting that NAC with the SOX regimen could improve DFS in patients with LAGC.

However, not all patients will benefit from NAC. Approximately 15% of patients show tumor progression after treatment with NAC [9, 10, 16]. Therefore, predicting the patients' response to NAC and identifying who cannot benefit from NAC have very important clinical significance to improve the efficacy of NAC.

The standard evaluation of the chemotherapeutic response is usually based imageologically on the response evaluation criteria for solid tumors (RECIST), which depend on the size of tumors observed on CT [19]. RECIST (version 1.1) records four response categories: (1) complete response (CR: disappearance of all target lesions), (2) partial response (PR: at least a 30% decrease in the sum of the longest diameter of target lesions), (3) progressive disease (PD: at least a 20% increase in the sum of the longest diameter of target lesions, or the appearance of one or more new lesions), and (4) stable disease (SD: small changes that do not meet the above criteria) [20]. Patients with an objective response (CR and PR) had better survival than those with SD and PD. Hence, it is essential to identify efficient predictors for objective response. However, there is no available prediction model for objective response. If a prediction model for objective response in LAGC could be established, we could select suitable patients to receive NAC and personalize the treatment.

In the present study, we performed a single-center, retrospective study to investigate the potential predictors of objective response for LAGC patients receiving NAC and developed a risk score model to predict objective response as an evidence-based tool for selecting patients who would benefit from NAC.

Methods

Patient selection and pretreatment evaluation

Data from patients pathologically diagnosed with GC by gastroscopic biopsy in Shanghai Rui Jin Hospital between July 2009 and December 2018 were collected retrospectively. A total of 267 patients with locally advanced gastric cancer (LAGC) who received NAC were enrolled. The study was approved by the Human Ethics Committee of Shanghai Jiao Tong University School of Medicine Ruijin Hospital, and all patients provided informed consent. The pretreatment evaluation included medical history, physical examination, routine blood examination, liver and kidney function tests, electrolyte examination, tumor markers (CA125, CA199, CA724, CEA, and AFP), chest X-ray, electrocardiogram, and abdominal and pelvic multidetector row computed tomography (MDCT). All patients were staged according to the 7th edition classification system of the American Joint Committee on Cancer [21]. Using MDCT, only patients with invasion of the serous layer, regional lymph node metastasis and no distant metastasis ($cT_4N_+M_0$) were enrolled. Patients were excluded if they had severe cardiac, hepatic, or renal disease.

Neoadjuvant chemotherapy and evaluation

The chemotherapy drug regimens included 5-fluorouracil-based, platinum-based, and taxane-based regimens, such as EOX, SOX, DOX, DOS, XELOX, and FLOT. Most patients received three cycles of NAC. A few patients received additional cycles. Before each chemotherapy cycle, routine blood examination and liver and kidney function tests were performed. After all cycles, we carried out a comprehensive examination, including all the above pretreatment evaluations. The imaging evaluation of the response of NAC was based on the Response Evaluation Criteria In Solid Tumor (RECIST 1.1) [22], in which tumor responses were divided into four grades: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively.

Adjuvant chemotherapy and follow-up

All patients were scheduled to receive adjuvant chemotherapy (AC) regardless of postoperative pathology. Even if pCR was achieved, 3-4 cycles of AC were required. In principle, the chemotherapy regimen was the same as the NAC regimen. However, if the patient's physical condition was not good, the dosage or number of drugs was reduced as appropriate. Patients were treated with AC in the outpatient department, and a hematologic examination was conducted before each chemotherapy cycle. After the end of the chemotherapy course, comprehensive examinations including hematological indicators and abdominal pelvic MDCT were conducted. Patients were followed up with regular follow-up visits, both outpatient and telephone.

Data collection and statistical analysis

The clinical and pathological variables before NAC included sex, age, body mass index (BMI), hemoglobin, leukocyte, neutrophil, lymphocyte, thrombocyte, prealbumin, total protein, albumin, CA125, CA199, CA724, CEA, AFP, tumor location, tumor differentiation, signet ring cell carcinoma component, Borrmann type, and the short axis diameter of the regional largest lymph node (LN_{max}). The LN_{max} was measured with MDCT. We took the largest regional lymph node around the stomach as the measurement target and measured the short axis diameter of the lymph node on the largest horizontal cross section. Survival time after initial diagnosis of GC was also recorded by follow-up.

Univariate analysis was used to investigate whether any factors were correlated with objective response. A cohort of 267 patients with an imaging evaluation was randomly divided into a training set (n=178) and a test set (n=89) at a 2:1 ratio. Using the training set, factors with 2-sided $P<0.05$ in the univariate analysis were included in a multivariate stepwise logistic regression analysis to establish the prediction model for objective response. For the potential predictors, which were originally continuous variables, we performed a receiver-operating characteristic (ROC) curve analysis using the observed outcomes and identified an optimal cut-off value that maximized the area under the curve (AUC) of the ROC curve. The risk scores were defined by the independent predictors and their beta-coefficients. To generate simple integer-based point scores for each predictor, we assigned scores by the beta-coefficients in the final logistic regression analysis as an approximate integer. The total score was calculated for each patient by summing the score of each predictor. The AUC of the ROC curve that was generated using the observed outcomes and risk score was also calculated. In addition, using a particular cut-off value for the risk score to classify the patients into high-risk and low-risk groups, we calculated the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV). The prediction model was validated in the test set.

Finally, the survival analysis was performed between both groups of patients, not only the PR vs. SD+PD groups but also the high-risk vs. low-risk groups. A nonparametric Mann-Whitney rank test or t test was used for analysis of quantitative data. Chi-square test was used in comparison of categorical data. All statistical tests were two-tailed, and the differences were statistically significant at $P<0.05$. Data were analyzed using SPSS software version 19 (IBM Statistical Product and Service Solutions, Armonk, USA). The ROC curve and K-M survival curve were constructed by GraphPad Prism Version 5 (GraphPad Software, USA).

Results

Characteristics of the study population

The study population comprised 199 males and 68 females, with a male-to-female ratio of 2.9:1. The median age at diagnosis was 63 (range: 21-80) years. Among the 267 patients,

162 patients (60.7%) had an objective response. The demographic and clinicopathological characteristics of patients who received NAC with or without objective response were compared (**Table 1**). The sex, age, total protein, tumor location, tumor differentiation, signet ring cell carcinoma component, Borrmann type and value of LN_{max} were significantly different between the PR and SD+PD groups (P<0.05). The study population was then randomly divided into 178 patients in the training set and 89 in the test set at a 2:1 ratio.

Imaging evaluation and surgery

According to the RECIST criteria, there were 162 patients with PR, 99 with SD and 6 with PD. Since all patients with $cT_4N_+M_0$ stage receiving NAC had a higher tumor load, there was no complete response. Among 162 PR patients, 154 (95.1%) received radical surgery, 3 (1.9%) received palliative surgery and 5 (3.1%) refused surgery because their symptoms had improved greatly. Among 99 SD patients, 75 (75.8%) received radical surgery, 10 (10.1%) received palliative surgery, 2 (2.0%) received gastrointestinal bypass surgery, 2 (2.0%) received exploratory laparotomy only, and 10 (10.1%) refused surgery. Among the 6 PD patients, three patients received either radical surgery, palliative surgery, or gastrointestinal bypass surgery. The other three patients did not receive surgery.

Therefore, a total of 249 patients underwent surgery. Radical and palliative surgery were performed in 230 (92.4%) and 14 (5.6%) patients, respectively. Three (1.2%) patients underwent gastrointestinal bypass surgery resulting from pyloric obstruction. Because of the extensive spread of the disease, particularly in the peritoneum, two (0.8%) of these patients underwent laparoscopic exploration only. All operations were performed by the same surgical team. The specimens of 244 patients who underwent gastrectomy (both radical and palliative) were sent for pathological diagnosis. Among them, 22 patients achieved pathologic complete response (pCR).

Univariate analysis in the training set

To identify factors related to objective response, the demographic and clinicopathological characteristics of patients in the training set were compared by performing univariate analysis (**Table 2**). We found that gender (*P*=0.001), age (*P*=0.024), LN_{max} (P<0.001), total protein (*P*=0.04), CEA (*P*=0.039), tumor location (*P*=0.007), tumor differentiation (*P*=0.044), signet ring cell carcinoma component (P<0.001) and Borrmann type (P<0.001) showed significant differences between the PR and SD+PD groups. The well-differentiated and signet ring cell carcinoma component pathological pictures are shown below (**Figure 1**). For the continuity variables, we conducted ROC analysis to determine the optimal cut-off point for objective response. We found that age (60 y), LN_{max} (1.27 cm), total protein (64 g/L) and CEA (2.84 ng/mL) exhibited optimal cut-off points for objective response. The sensitivity, specificity and AUC values of age were 45.83%, 71.70% and 0.60±0.04 (95% CI: 0.52-0.68; P=0.02). For LN_{max}, the sensitivity, specificity and AUC values were 72.22%, 57.55% and 0.67±0.04 (95% CI: 0.59-0.75; P<0.001). For total protein, the three values were 62.32%, 56.19% and 0.59±0.04 (95% CI: 0.51-0.68; P=0.04). For CEA, the three values were 65.71%, 51.89% and 0.59±0.04 (95% CI: 0.51-0.68; P=0.04). Therefore, patients with objective response were more likely to be male and have age ≥60 y, LN_{max} >1.27 cm, total protein ≥64 g/L, CEA ≥2.84 ng/mL, tumor located in the cardia, well-differentiated histology, no signet ring cell carcinoma component and Bormann type I/II.

Multivariate analysis and derivation of the prediction model

To further search for independent predictors for objective response, multivariate logistic regression analysis was performed based on the nine potential predictors related to objective response identified by univariate analysis. We found that sex, LN_{max} and signet ring cell carcinoma component were independent predictors for objective response (**Table 3**).

Therefore, using the beta coefficients derived from the regression, the risk score of objective response was then calculated through a 3-factor prediction model (sex, LN_{max}, and signet ring cell carcinoma component). Since the beta-coefficients of the three factors were similar, and for the convenience of application, we assigned one point to each factor (**Table 4**). The final scores ranged from 0 to 3 points. According

Table 1. Univariate analysis: characteristics of the whole study population

Characteristics	Total (N=267)	PR (n=162)	SD+PD (n=105)	P
Gender (n [%])				0.018*
Male	199 (74.5)	129 (79.6)	70 (66.7)	
Female	68 (25.5)	33 (20.4)	35 (33.3)	
Age (y)				0.048§
Median (range)	63 (21-80)	63 (28-80)	61 (21-77)	
BMI (kg/m^2)				0.342§
Median (range)	22.6 (14-36.3)	22.7 (14-31.3)	22.4 (15.7-36.3)	
Hemoglobin (g/L)				0.675§
Median (range)	121 (44-167)	119 (50-167)	121.5 (44-158)	
Leukocyte (10^9/L)				0.341§
Median (range)	5.7 (2.4-19.7)	5.9 (2.7-16.5)	5.4 (2.4-19.7)	
Neutrophil (10^9/L)				0.376§
Median (range)	3.4 (1.3-17.2)	3.5 (1.3-11.0)	3.3 (1.4-17.2)	
Lymphocyte (10^9/L)				0.463§
Median (range)	1.5(0.7-7.5)	1.5 (0.7-2.9)	1.4 (0.7-7.5)	
Thrombocyte (10^9/L)				0.973§
Median (range)	230 (82-924)	230 (82-924)	229 (99-875)	
Prealbumin (g/L)				0.165§
Median (range)	203 (79-354)	206 (120-354)	196 (79-319)	
Total Protein (g/L)				0.006#
Mean ± SD	63.5±6.1	64.3±6.2	62.2±5.7	
Albumin (g/L)				0.124§
Median (range)	36 (19-47)	36.5 (19-46)	36 (21-47)	
CA125 (U/mL)				0.146§
Median (range)	12.5 (3.8-314.1)	13 (3.9-314.1)	11.8 (3.8-196.3)	
CA199 (U/mL)				0.338§
Median (range)	9.2 (0.8-10315.0)	9.2 (0.8-3646.1)	9.2 (0.8-10315.0)	
CA724 (U/mL)				0.065§
Median (range)	3.2 (0-287.9)	2.6 (0.1-131.9)	4.5 (0-287.9)	
CEA (ng/mL)				0.137§
Median (range)	2.5 (0.5-1475.6)	2.7 (0.6-1400.5)	2.3 (0.5-1475.6)	
AFP (ng/mL)				0.599§
Median (range)	2.7 (0.7-10783.5)	2.7 (0.9-3220.2)	2.6 (0.7-10783.5)	
Location (n [%])				0.001*
Cardia	78 (29.2)	59 (36.4)	19 (18.1)	
Body	68 (25.5)	42 (25.9)	26 (24.8)	
Antrum	78 (29.2)	44 (27.2)	34 (32.4)	
Whole stomach	43 (16.1)	17 (10.5)	26 (24.8)	
Differentiation (n [%])				0.026*
Well	142 (53.2)	95 (58.6)	47 (44.8)	
poor	125 (46.8)	67 (41.4)	58 (55.2)	
Signet ring cell (n [%])				<0.001*
Yes	49 (18.4)	14 (8.6)	35 (33.3)	
No	218 (81.6)	148 (91.4)	70 (66.7)	
Borrmann (n [%])				<0.001*
I	11 (4.1)	10 (6.2)	1 (1.0)	
II	10 (3.7)	10 (6.2)	0 (0.0)	
III	223 (83.5)	139 (85.8)	84 (80.0)	
IV	23 (8.7)	3 (1.8)	20 (19.0)	
LN_{max} (cm)				<0.001§
Median (range)	1.23 (0.28-5.1)	1.45 (0.28-5.05)	1.03 (0.43-3.89)	

LN_{max}: the diameter of the largest lymph node. *: χ^2 test (compares the counts of categorical responses between 2 or more independent groups). §: Mann-Whitney rank test (a nonparametric alternative to the 2 sample t test compares the means of 2 independent groups). #: T test (compare the means of 2 independent groups).

Table 2. Univariate analysis: characteristics in the training set

Characteristics	Total (N=178)	PR (n=106)	SD+PD (n=72)	P
Gender (n [%])				0.001*
Male	137 (77.0)	91 (85.8)	46 (63.9)	
Female	41 (23.0)	15 (14.2)	26 (36.1)	
Age (y)				0.024§
Median (range)	63 (21-80)	63 (30-80)	61 (21-75)	
<60	63 (35.4)	30 (28.3)	33 (45.8)	0.016*
≥60	115 (64.6)	76 (71.7)	39 (54.2)	
BMI (kg/m^2)				0.711§
Median (range)	22.7 (15.7-36.3)	22.7 (17.9-29.7)	22.5 (15.7-36.3)	
Hemoglobin (g/L)				0.526§
Median (range)	121.5 (44-162)	119 (50-162)	122.5 (44-158)	
Leukocyte (10^9/L)				0.664§
Median (range)	5.7 (2.4-16.9)	5.8 (2.7-16.5)	5.5 (2.4-16.9)	
Neutrophil (10^9/L)				0.598§
Median (range)	3.4 (1.3-13.5)	3.5 (1.3-11.0)	3.4 (1.4-13.5)	
Lymphocyte (10^9/L)				0.636§
Median (range)	1.5 (0.7-7.5)	1.5 (0.8-3.0)	1.4 (0.7-7.5)	
Thrombocyte(10^9/L)				0.625§
Median (range)	223 (82-531)	224.5 (82-531)	221 (116-462)	
Prealbumin (g/L)				0.285§
Median (range)	205.5 (102-354)	207 (120-354)	202 (102-319)	
Total Protein (g/L)				0.040#
Mean ± SD	63.5±6.0	64.2±6.0	62.3±5.8	
<64	89 (50.0)	46 (43.4)	43 (59.7)	0.033*
≥64	89(50.0)	60 (56.6)	29 (40.3)	
Albumin (g/L)				0.317#
Mean ± SD	35.9±4.3	36.2±4.4	35.5±4.3	
CA125 (U/mL)				0.430§
Median (range)	12.4 (3.8-185.7)	12.6 (3.9-185.7)	11.7 (3.8-171.0)	
CA199 (U/mL)				0.226§
Median (range)	8.7 (0.8-10315.0)	8.5 (0.8-3646.1)	9.1 (1.8-10315.0)	
CA724 (U/mL)				0.066§
Median (range)	3.0 (0-287.9)	2.5 (0.5-100.1)	4.3 (0-287.9)	
CEA (ng/mL)				0.039§
Median (range)	2.5 (0.6-598.9)	2.9 (0.6-598.9)	2.2 (0.7-360.3)	
<2.84	97 (54.5)	51 (48.1)	46 (63.9)	0.038*
≥2.84	81 (45.5)	55 (51.9)	26 (36.1)	
AFP (ng/mL)				0.366§
Median (range)	2.5 (0.9-10783.5)	2.5 (0.9-3220.2)	2.5 (1.0-10783.5)	
Location (n [%])				0.007*
Cardia	53 (29.8)	41 (38.7)	12 (16.7)	
Body	43 (24.2)	26 (24.5)	17 (23.6)	
Antrum	52 (29.2)	26 (24.5)	26 (36.1)	
Whole stomach	30 (16.8)	13 (12.3)	17 (23.6)	
Differentiation (n [%])				0.044*
Well	105 (59.0)	69 (65.1)	36 (50.0)	
poor	73 (41.0)	37 (34.9)	36 (50.0)	

Signet ring cell (n [%])				<0.001*
Yes	31 (17.4)	8 (7.5)	23 (31.9)	
No	147 (82.6)	98 (92.5)	49 (68.1)	
Borrmann (n [%])				<0.001*
I	8 (4.5)	7 (6.6)	1 (1.4)	
II	6 (3.4)	6 (5.7)	0 (0.0)	
III	150 (84.3)	91 (85.8)	59 (81.9)	
IV	14 (7.9)	2 (1.9)	12 (16.7)	
LN_{max} (cm)				<0.001§
Median (range)	1.2 (0.3-5.1)	1.4 (0.3-5.1)	1.0 (0.5-3.5)	
<1.27	97 (54.5)	45 (42.5)	52 (72.2)	<0.001*
≥1.27	81 (45.5)	61 (57.5)	20 (20.8)	

LN_{max}: the diameter of the largest lymph node. *: χ^2 test (compares the counts of categorical responses between 2 or more independent groups). §: Mann-Whitney rank test (a nonparametric alternative to the 2 sample t test compares the means of 2 independent groups). #: *T* test (compare the means of 2 independent groups).

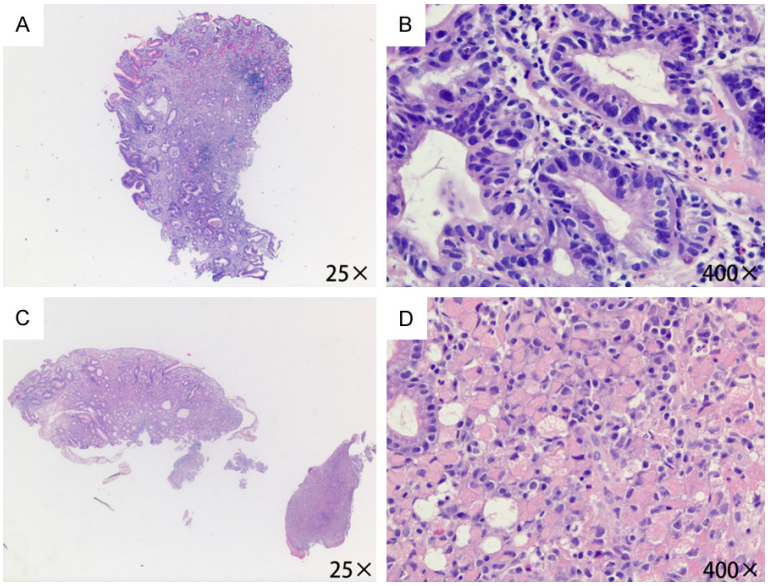

Figure 1. The typical pathological pictures of well-differentiated (A, 25×; B, 400×) and signet ring cell carcinoma component (C, 25×; D, 400×) in gastric cancer.

to the risk score system, we calculated the sum scores of the patients in the training set. The AUC of the risk score model for predicting objective response was 0.75±0.04 (95% CI: 0.67-0.82; *P*<0.001). The optimal cut-off for the risk score model was 2 points, which was based on the ROC curve analysis (**Figure 2A**). The patients were then categorized into low-risk (<2 points) and high-risk (≥2 points) objective response groups. The sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value), and accuracy in the training set were 89.62%, 47.22%, 71.43%, 75.56%, and 72.47%, respectively. For the 0- to 3-point risk score, the objective response rate for each score in training set was 0%, 27.50%, 62.16% and 83.05%, respectively.

Validation of the risk score model

To validate the risk score model for objective response, we performed the ROC in the test set (**Figure 2B**). The AUC was 0.65±0.06 (95% CI: 0.53-0.77; P=0.017). Objective responses were found in 43.48% and 69.70% of patients in the low-risk and high-risk objective response groups, respectively. The sensitivity, specificity, PPV, NPV, and accuracy in the test set were 82.14%, 39.39%, 69.69%, 56.52%, and 66.29%, respectively. For the 0- to 3-point risk score, the objective response rate for each score in test set was 20%, 50%, 63.89% and 76.67%, respectively. We considered that the higher the score, the higher the probability of objective response would be.

Survival analysis

The survival time we used was recorded from the initial diagnosis by gastroscopy. In this study, the median follow-up was 33 months.

Table 3. Multivariate analysis: variables correlated with objective response in the training set

Variables	B	P**	OR	95% CI
Gender (male/female)	1.318	0.004	3.736	1.522-9.172
Age (≥/<60)	-0.728	0.065	0.483	0.223-1.047
LN_{max} (≥/<1.27 cm)	-1.101	0.005	0.333	0.153-0.723
Total Protein (≥/<64 g/L)	-0.557	0.158	0.573	0.264-1.242
CEA (≥/<2.84 ng/mL)	-0.420	0.292	0.657	0.301-1.436
Location	0.251	0.176	1.285	0.894-1.847
Differentiation (well/poor)	0.216	0.593	1.241	0.562-2.738
Signet ring cell (Yes/No)	-1.337	0.012	0.263	0.092-0.747
Borrmann	0.965	0.068	2.626	0.929-7.418

B: beta coefficient; OR: odds ratio; 95% CI: 95% confidence interval. **: multivariable logistic regression analysis.

Table 4. Risk score system for objective response for LAGC treated with NAC

Predictors	Score	
	0	1
Gender (male/female)	female	male
LN_{max} (≥/<1.27 cm)	<1.27	≥1.27
Signet ring cell (Yes/No)	Yes	No

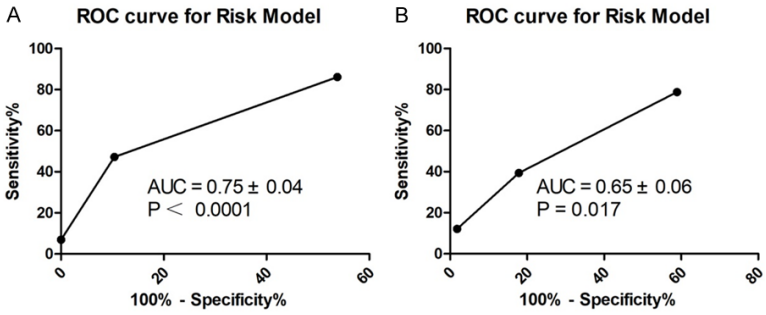

Figure 2. ROC curve of the risk score model in the training (A) and test set (B).

We plotted the Kaplan-Meier (K-M) survival curve and found that the survival of the patients was significantly different between the PR and SD+PD groups (**Figure 3A-C**). For all patients, the 3-year survival rates in the two groups were 79.15% and 51.43%. In addition, patients in the high-risk group had better survival than those in the low-risk group (**Figure 3D**). The 3-year survival rates in the different risk groups were 74.69% and 49.21%, respectively. For 230 patients who underwent radical surgery, the time to recurrence (TTR) was also followed up. There were significant difference between the high and low-groups (**Figure 3E**). Patients in low-risk group were more likely to relapse than high-risk score patients (P< 0.05). The benefit in survival was clinically meaningful.

Discussion

Currently, perioperative chemotherapy (PCT) is considered the standard therapy for LAGC. PCT for advanced T4 patients has been suggested by most guidelines, including NCCN [23], ESMO [24], Japanese [25], and CSCO guidelines [26].

However, the risk of tumor progression during NAC is still prevalent. Some patients may tolerate toxic, uneconomic, and futile chemotherapy, resulting in noncurative surgery because of tumor progression [27]. The response to NAC is under intensive focus, particularly with respect to objective response (CR+PR). Therefore, we investigated the predictors of objective response and developed a prediction model to guide individual treatment decisions. To the best of our knowledge, this is the first report of a prediction model for objective response in LAGC treated with NAC.

In this study, 162 patients (60.7%) exhibited an objective response after NAC. These patients had a better prognosis than patients with poor response (P<0.001). In the training set, we found nine factors associated with objective response. They were gender, age, LN_{max}, total protein, CEA, tumor location, tumor differentiation, signet ring cell carcinoma component and Borrmann type (**Table 2**). Among them, gender, LN_{max} and signet ring cell carcinoma component were independent predictors for objective response (**Table 3**).

This study found that male patients in the training set were more likely to obtain an objective response after receiving NAC (P=0.001). The rates of objective response in males and

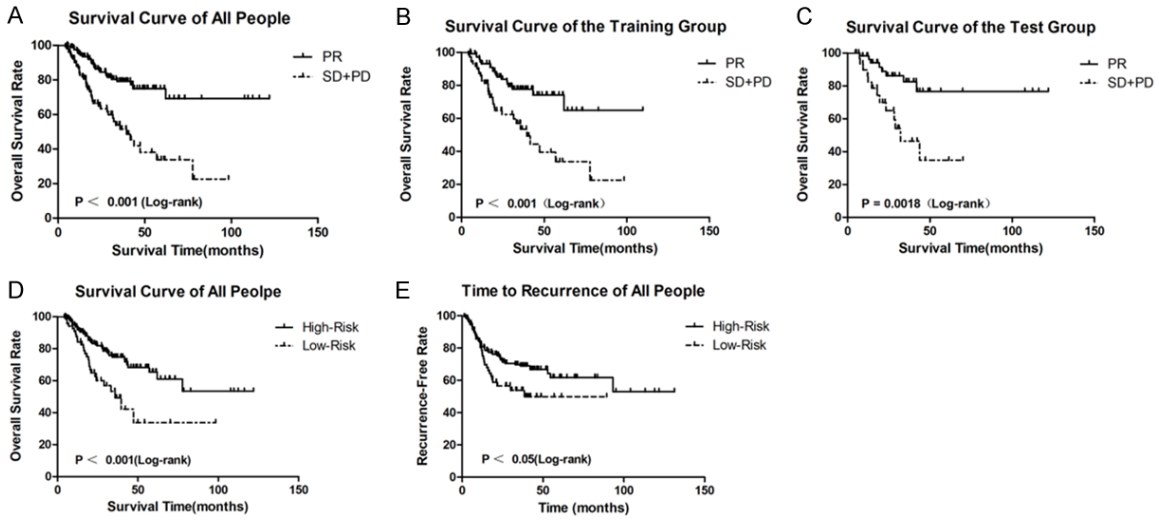

Figure 3. Survival analysis of patients in different groups. A. Survival analysis for all patients between PR and SD+PD group. B. Survival analysis for patients in training group between PR and SD+PD. C. Survival analysis for patients in test group between PR and SD+PD. D. Survival analysis for all patients between High-Risk and Low-Risk group. E. Time to recurrence for all patients between High-Risk and Low-Risk group.

females were 66.42% and 36.59%, respectively. The reason for this discrepancy may be that the female patients were in a weaker physical state than the male patients, and therefore, the dose of chemotherapy was often reduced as appropriate. In addition, we found that the proportion of Borrmann IV gastric cancer in female patients was significantly higher than that in male patients (16.18% vs. 6.03%, P=0.01). We also found that Borrmann type was significantly associated with the NAC response (P<0.001). The analysis showed that patients with Borrmann type IV had little benefit from NAC. Accordingly, some studies have found that Borrmann IV gastric cancer has more advanced and unfavorable clinicopathological factors than other Borrmann types. Borrmann IV gastric cancer has a poor prognosis, so early detection and radical resection are essential to improve the prognosis of patients with this type of cancer [28, 29]. Therefore, for female LAGC patients with Borrmann type IV, direct surgery may be better than NAC.

In addition, we found that elderly patients seemed to respond better to NAC. Perhaps, compared to those in young patients, the tumors in elderly patients showed relatively slow progression. We found that although age had no significant correlation with tumor differentiation (P=0.326), it was significantly correlated with the signet ring cell carcinoma component (P=0.034) and Borrmann type (P= 0.018). Young patients were more likely to have signet ring cell carcinoma component and Borrmann type IV, which may lead to poor response to NAC. Kim et al [30] have also reported that Borrmann type IV is more frequent in young patients than in elderly patients; in addition, elderly patients have good differentiation, but younger patients have poor differentiation and signet ring cell carcinoma. Compared with poorly differentiated GC, well-differentiated GC is regarded to yield superior survival [31]. A previous study showed well-differentiated histology as an important clinical predictor of chemotherapeutic response [32]. Similarly, in our study, we observed that well-differentiated histology and no signet ring cell carcinoma component were related to objective response in the training set (P=0.044; P<0.001).

In the current study, LN_{max} was significantly associated with objective response (P<0.001). To the best of our knowledge, this is the first report of the use of LN_{max} to predict the objective response to NAC in LAGC. Lymph nodes are an important part of the immune system. Regional lymph nodes have an antitumor effect and act as a defense barrier to prevent the spread of tumor cells. Therefore, when tumor cells invade the lymph nodes, the immune cells inside lymph nodes proliferate rapidly to resist

tumor invasion, and the volume of lymph nodes increases. If the regional lymph nodes are unable to block and clear these tumor cells, the tumor cells will spread along the outlet of lymph nodes. We speculate that patients with large regional lymph nodes have strong immunity and that NAC can help these patients kill the tumor cells in lymph nodes. However, advanced studies are essential to confirm this result.

We also found that tumor location was associated with the NAC response. Patients with cancer of the gastric cardia were more likely to receive an objective response than patients with cancer in other parts of the stomach (P=0.002). MAGIC [9] and the FNCLCC & FFCD trial [10] have demonstrated the efficacy and safety of NAC for gastric cancer. In both studies, esophageal adenocarcinoma and esophagogastric junction cancer accounted for a large proportion. We speculated that cardiac cancer was similar to esophagogastric junction cancer and had a better chemotherapeutic response.

In this study, serum total protein was found to be associated with the efficacy of chemotherapy. Patients with higher total protein had a greater chance of obtaining an objective response. This factor has been established to be a nutritional indicator, so patients with high total protein tend to have better nutritional status, which can enable patients to complete NAC and be beneficial for their NAC response. In addition, we also found that a high level of serum CEA was related to the objective chemotherapy response in the training set (P=0.039), but the same result was not obtained in the total population (P=0.137). Sun et al [33] reported that pretreatment CEA >50 ng/ml has a positive predictive value for clinical disease progression after NAC. We considered neither our study sample size nor theirs to be large enough to illustrate the relationship between serum CEA level and the NAC response. Thus, further research is needed to elucidate this hypothesis.

Furthermore, based on the three independent predictors (gender, LN_{max} and signet ring cell carcinoma component), we developed a prediction model for objective response in LAGC treated with NAC (**Table 4**), which showed fair-to-good discrimination. Each predictor was assigned one point. From 0 to 3 points, the objective response rate for each point is 20%, 50%, 63.89% and 76.67% in the test set. According to the newly developed risk score model with a cut-off score of 2 points, 68.70% of the high-risk score group (≥2 points) had an objective response in the test set. We constructed a K-M survival curve between the high- and low-risk score groups. The survival of the patients was significantly different between the high-risk score and low-risk score groups (P<0.001) (**Figure 1D**). Patients in the high-risk score group had a 25.48% improvement in 3-year survival compared to that in patients with a low-risk score. We concluded that this prediction model would help predict not only the NAC response but also the survival of LAGC patients. This prediction model is intuitive, simple and convenient for clinical application. To date, there is no applicable prediction model for objective response in clinical practice. This model can guide clinical work so that we can better select the right LAGC patients for whom NAC may or may not be recommended.

This was a retrospective study. A further prospective study is essential to confirm the prediction model. All patients treated with NAC had LAGC with a clinical stage of $cT_4N_+M_0$. Perhaps NAC can also be applied to patients with an earlier stage than $cT_4N_+M_0$, which may be more advantageous than direct surgery. Despite the limitations of this study, we developed a prediction model for objective response in LAGC that can guide the clinical use of NAC. Further investigation is warranted to examine the efficacy and accuracy of this prediction model.

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Disclosure of conflict of interest

None.

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