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ORIGINAL RESEARCH

A Modified ypTNM Staging System–Development and External Validation of a Nomogram Predicting the Overall Survival of Gastric Cancer Patients Received Neoadjuvant Chemotherapy

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Purpose: Neoadjuvant chemotherapy is now widely used in gastric cancer patients. However, the current 8th ypTNM staging system is developed based on patients with less extensive lymph node dissection and the predictive value is relatively limited. In this study, we aim to develop and validate a nomogram that predicts overall survival in gastric cancer patients received neoadjuvant chemotherapy.

Patients and Methods: From January, 2007 to December, 2014, 471 patients receiving neoadjuvant chemotherapy at our center were enrolled in the study. Based on the Cox proportional hazard model, a nomogram was developed from them and then an external validation was conducted on a cohort of 239 patients from another cancer center.

Results: The overall survival (OS) rates of 1 year and 3 years were 90.0% and 64.1%, respectively. Body mass index category, tumor location, T stage and N stage were independent prognostic factors for the survival outcome. The C-index of the model was 0.74 in the development cohort and 0.69 in the validation cohort. Our nomogram also showed good calibration in both cohorts.

Conclusion: We developed and validated a nomogram to predict the 1- and 3-year OS of patients who received neoadjuvant chemotherapy and radical gastrectomy with D2 lymph node dissection. This nomogram predicts survival more accurately than the AJCC TNM staging system, which is the current golden standard.

Keywords: stomach neoplasms, perioperative chemotherapy, survival, nomograms

Introduction

Gastric cancer is the fifth common cancer and the third leading cause of cancer-related deaths worldwide.[1] Nowadays, surgery is the most widely used treatment for patients with localized gastric cancer.[2–4] However, after curative resection, the survival rate for locally advanced gastric cancer (AGC) remains to be unsatisfactory.[5–7] To improve patients' survival, a variety of studies have examined the treatment effect of additional chemotherapy and radiotherapy.[8–10] Among these, neoadjuvant chemotherapy (or perioperative chemotherapy) was first advocated by Wilke et al.[11] It is now widely accepted that neoadjuvant chemotherapy (NAC) can help improve patients' tolerance, increase curative resection rate, decrease tumor metastasis, and thus increase the survival rate.[12–14] As a result of its increasing popularity, there is now an increasing need for practical tools to predict individual survival after NAC.

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To our knowledge, the only predictive system for patients received neoadjuvant chemotherapy was the American Joint Committee on Cancer (AJCC) ypTNM staging system, which was established according to the local invasion depth, the number of positive lymph nodes, and distant metastasis.[2] However, this system was developed from patients with less extensive lymph node dissection (less than D2) and thus may not be well applied to patients underwent D2 lymphadenectomy. In our previous study, we conducted a validation of this system (patients at T0 stage excluded)[15] and demonstrated that although ypTNM staging system was effective for staging, its predictive value was limited with a relatively low C-index (0.657). In addition, patients with a T0 stage were not included in ypTNM staging system and thus cannot be evaluated. Furthermore, other prognostic factors related to individual survival have not been taken into consideration, such as age, body mass index (BMI), tumor size, histology, and chemotherapy regimen. Thus, new tools are needed to predict individual survival.

Previously, no survival nomograms of gastric cancer patients focused on patients received neoadjuvant chemotherapy.[16,17] In this study, through evaluating data from 471 consecutive patients undergoing neoadjuvant chemotherapy, we aimed to develop a nomogram to predicts overall survival. External validation was then conducted to test the generalizability of our model on a cohort of 239 patients from a different center.

Materials and Methods

Patients

From January 1st, 2007 to December 31st, 2014, a total of 484 gastric cancer patients at Peking University Cancer Hospital in Beijing, China were retrospectively enrolled in this study. The patients were pathologically diagnosed with gastric adenocarcinoma and received no treatment before neoadjuvant chemotherapy. All patients included in this study were proved to be locally advanced gastric cancer of clinical stage II–III by CT and diagnostic staging laparoscopy. Many of our patients were enrolled in clinical trials for neoadjuvant chemotherapy. For other patients, we would suggest both neoadjuvant chemotherapy and surgery plus adjuvant chemotherapy, a shared decision would then be made after a discussion with patients. The extent of resection for gastric cancer was total or distal gastrectomy with D2 lymphadenectomy. After surgery, all of the patients were recommended to receive adjuvant chemotherapy until perioperative chemotherapy cycles added up to eight cycles. Patients with distant metastasis were excluded from the study. Other exclusion criteria included 1) patients with gastrointestinal stromal tumors, lymphoma, neuroendocrine carcinoma, carcinoid tumor; 2) patients with remnant gastric cancer; 3) patients died within the perioperative period; 4) patients received chemotherapy for other diseases within 6 months; 5) patients whose dissected lymph node are less than 15; 6) patients received neoadjuvant radiotherapy, molecular targeted therapy, or intraperitoneal chemotherapy. Eventually, 471 out of 484 patients were selected and enrolled in our study.

Previous information on demographic, treatment, and pathology were collected, including age, sex, BMI, ASA score, ECOG score, family history, chemotherapy regimen, surgery method, surgery approach, anastomosis way, blood loss, tumor location, tumor diameter, T stage, number of dissected lymph node, number of positive lymph node, histological type, differentiated type, and cancerous embolus situation.

For validation, we enrolled 239 patients who met the same inclusion and exclusion criteria at Sun Yat-sen University Cancer Center (Guangzhou, China) in the validation cohort. In this cohort, data of risk factors in the final nomogram were collected.

Follow Up

After the surgery, patients were followed up regularly via physical examination, radiological examination, endoscopic examination, and laboratory examination. These examinations were performed every 3 to 6 months during the first 2 years, then every 6 months until the fifth year, and then once every year.

Statistic Analysis

To build the nomogram for survival prediction, the univariate Cox regression model was applied to each variate and those with a two-sided p-value <0.05 were then included in the multivariable model. A backward stepwise selection method was used for variable selection in binary Cox regression. A nomogram was then developed based on the selected variables.

The performance of the nomogram was measured by its discrimination and calibration. The discrimination of the nomogram was measured by the concordance index (CI). Calibration, which compares predicted survival with actual survival, was also used to evaluate the model. We plotted the calibration curves for the actual survival against the

nomogram predicted survival probabilities to assess the agreement, using 1000 bootstrap re-samples to decrease the overfitting bias.

We used restricted cubic splines to fit the continuous variables to allow for nonlinearity in the relationship between these variables and survival time.

We conducted all analyses using R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value <0.05 was considered statistically significant.

Ethical Standards

The Ethics Committee of Peking University Cancer Hospital approved this study. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Written informed consent was obtained from all patients prior to inclusion in the study. This study does not involve animal study.

Results

Descriptive Statistics of the Training Cohort

A total of 471 patients were included in this cohort. The baseline characteristics of the participants were provided in Table 1. Overall, 360 (76.4%) patients were males. The average age was 59 (±10.1) years old, with 153 (32.5%) over 65 years old. The average preoperative chemotherapy duration was 2.79 (±1.00) cycles, and surgery was then performed. Most patients (450, 95.5%) were in good preoperatory conditions with an ECOG score of 0 or 1. After surgery, most patients (79.9%) were proved to be at pathologic stage II/III. The median follow-up duration was 38.5 (±21.7) months, with 193 patients died during the follow-up period (41%). Overall, the 1-year and 3-year OS rates were 90.0% and 64.1%, respectively. The pathology complete remission (pCR) rate was 6.4%.

Development of the Nomogram

Clinicopathological factors were further evaluated by univariate analysis with the Cox regression model. BMI, chemotherapy cycles, tumor location, multi-organ resection, T stage, N stage, and diameter in the long axis were identified as risk factors for OS (Table 2).

All the variables above were included in the multivariant analysis, and after the stepwise regression process, T stage, N stage, BMI group, and tumor location were

Table 1 Baseline Characteristics of the Study Population (n=471)

Variable	Mean (SD)/N (%)
Male	360 (76.4)
Age≥65	153 (32.5)
BMI (%)	
Underweight	26 (5.5)
Normal range	304 (64.5)
Overweight	127 (27.0)
Obese	14 (3.0)
Family history = Yes (%)	85 (18.0)
ECOG Score (%)	
0	305 (64.8)
1	145 (30.8)
2	21 (4.5)
Chemotherapy Regimen (%)	
Platinum based	417 (88.5)
Paclitaxel based	54 (11.5)
Cycle (mean (sd))	2.79 (1.00)
ASA (%)	
1	62 (13.2)
2	328 (69.6)
3	80 (17.0)
4	1 (0.2)
Operation duration (minute,mean (sd))	210.73 (63.54)
Operation Approach (%)	
LAG	24 (5.1)
Open	446 (94.7)
TLG	1 (0.2)
Gastrectomy Type (%)	
Distal	185 (39.3)
Proximal	52 (11.0)
Thoracic abdominal joint	15 (3.2)
Total	219 (46.5)
Multi-organ excision= Yes (%)	38 (8.1)
Blood Loss (mean (sd))	171.9 (317.1)
Tumor Location (%)	
Lower	208 (44.2)
Middle	61 (13.0)
Upper	173 (36.7)
Whole	29 (6.2)
Diameter in short axis (mean (sd))	4.21 (3.21)
T (%)	
0	30 (6.4)
1	33 (7.0)
2	67 (14.2)
3	66 (14.0)
4	275 (58.4)

(*Continued*)

Table 1 (Continued).

Variable	Mean (SD)/N (%)
N (%)	
0	175 (37.2)
1	98 (20.8)
2	84 (17.8)
3	114 (24.2)
Differentiate Grade (%)	
High	36 (7.6)
Low	333 (70.7)
Middle	102 (21.7)

Abbreviations: BMI body mass index: Underweight: BMI<18.5 kg/m^2; Normal: 18.5 kg/m^2≤BMI<25kg/m^2; Overweight: 25kg/m^2 ≤BMI<30kg/m^2; Obese: BMI≥30kg/m^2. ASA, American Society of Anesthesiologists; ECOG, Eastern Clinical Oncology Group; LAG, laparoscopic-assisted gastrectomy; TLG, total laparoscopic gastrectomy; platinum-based therapy includes SOX S-1 + oxaliplatin, XELOX capecitabine + oxaliplatin, FOLFOX 5-FU + leucovorin + oxaliplatin. Paclitaxel-based therapy includes Capecitabine + Paclitaxel.

included in the final multivariable model for OS. A nomogram was then developed based on our Cox proportional hazard model (Figure 1).

Validation of the Nomogram

In the training cohort, the C-index of the OS model was 0.74 in the training cohort and 0.75 in bootstrap validations. The calibration curves for 1-year and 3-year OS were shown in Figures 2A and B. The x-axis was the nomogram predicted survival, and the y-axis was the actual survival calculated by the Kaplan–Meier method.

In the validation cohort, the C index was 0.693 (95% CI, 0.671–0.715). Good calibration was also shown for the 1-year, 3-year OS (Figure 2C and D).

Our model also showed superiority in discrimination compared with the AJCC TNM system (8th edition). In our previous study, the discrimination of the TNM staging system was evaluated and the C-index was 0.657.[15]

Discussion

To make an appropriate clinical decision, it is critical for physicians to determine the prognosis of patients who have received neoadjuvant chemotherapy. Prognostic nomograms based on clinicopathologic factors have been developed for patients who received neoadjuvant chemotherapy for breast,[18] esophageal,[19] and colorectal cancer.[20] However, no nomogram for gastric cancer was available due to limited data.

To our knowledge, although prognostic factors for gastric cancer patients received neoadjuvant chemotherapy had been widely studied before,[21,22] the ypTNM staging system was the only predictive model available. However, this system was developed from patients with less extensive lymphadenectomy (less than D2), and thus, the predictive value might be limited. In our previous study, it was shown that the discriminative ability of this system was not high enough to meet clinical demand.[15] Moreover, the new ypTNM staging system did not address pCR and ypT0N1 patients. In this study, we developed a nomogram to predict the OS for targeting patients and conducted validation to prove its efficacy.

In our final model, T stage, N stage, BMI group and tumor location were independent prognostic factors for survival. It was not surprising to find that T and N stages both independently affect the prognosis. The prognostic role of T and N had been widely discussed and consensus had been reached that a higher stage correlated with a worse prognosis.

BMI was the only demographic factor correlated with overall survival in our final model and individuals with a higher BMI had a better prognosis. Several studies are in line with our finding on this point. Kong et al and Tokunaga et al reported a higher 5-year survival after gastrectomy for overweight patients.[23,24] However, in some other cases, BMI was associated with less lymph node dissection, more surgical complications and higher perioperative morbidity.[25,26] Possible explanations for the positive influence of BMI on survival might be that a patient with a higher BMI tends to have a better nutrition status, which increases the tolerance of both neoadjuvant chemotherapy and gastrectomy and thus improve overall survival. In addition, the negative influence of the BMI partly attributed to the increased surgery difficulty and insufficient lymph node dissection. However, all patients included in our research received enough lymph node dissection (D2); thus, the negative influence of a higher BMI might partly be offset.

Tumor location was also selected in the final model. Patients with tumors at the lower third lived longer than those with an upper part disease, and those with a tumor diffused at the whole stomach suffered the worst prognosis. This phenomenon was in accordance with many previous studies. The negative influence on survival of an upper part disease was shown in both single and multivariant analyses.[27,28] In a meta-analysis conducted by Petrelli et al, it was shown that compared with distal tumors, proximal tumors suffered a 25% increased risk of mortality.[29] Tumors spreading throughout the whole stomach also showed a negative influence, which was also reported in other pieces of research.[30,31] Although

Table 2 Univariant & Multivariant Analysis for Overall Survival

Variables	Univariant Analysis			Multivariant Analysis (Backward Stepwise)		
	HR	95% CI	P	HR	95% CI	P
Gender						
Male	Reference					
Female	0.91	0.64–1.28	0.574			
BMI			0.004			0.070
<18.5	Reference			Reference		
18.5–25.0	0.55	0.34–0.90	0.017	0.67	0.40–1.11	0.116
25.0–30.0	0.39	0.23–0.69	0.001	0.55	0.31–0.97	0.040
≥30.0	0.18	0.04–0.78	0.022	0.21	0.05–0.91	0.037
Age						
<65	Reference					
≥65	1.26	0.95–1.69	0.118			
Chemotherapy regimen						
Platinum based	Reference					
Paclitaxel based	1.24	0.81–1.90	0.332			
Chemotherapy cycles	1.24	1.08–1.42	0.002			
ASA Score			0.782			
1	Reference					
2	1.03	0.68–1.57	0.882			
≥3	1.18	0.71–1.95	0.496			
ECOG Score			0.117			
0	Reference					
1	1.35	1.00–1.82	0.049			
2	1.38	0.74–2.57	0.307			
Operation duration	1.00	1.00–1.01	0.800			
Surgery approach			0.568			
LAG/TLG	Reference					
Open	1.35	0.60–3.1	0.470			
Blood loss	1.00	1.00–1.00	0.692			
Location			<0.001			0.023
Upper	Reference			Reference		
Middle	1.25	0.81–1.95	0.319	1.00	0.64–1.57	0.992
Lower	0.95	0.68–1.32	0.750	0.82	0.58–1.15	0.243
Whole	3.50	2.19–5.60	<0.001	1.73	1.05–2.83	0.031
Multi-organ resection (yes)	1.86	1.22–2.86	<0.001			
ypT stage			<0.001			0.055
0	Reference			Reference		
1	2.54	0.49–13.11	0.265	2.20	0.42–11.40	0.349
2	4.82	1.12–20.77	0.035	3.07	0.70–13.43	0.136
3	8.43	2.00–35.63	0.004	3.87	0.89–16.88	0.072
4	10.37	2.57–41.86	<0.001	4.75	1.14–19.77	0.032
ypN stage			<0.001			<0.001
0	Reference			Reference		
1	1.51	0.94–2.50	0.088	1.29	0.78–2.13	0.316
2	3.41	2.21–5.27	<0.001	2.59	1.65–4.07	<0.001
3	6.02	4.05–8.95	<0.001	4.19	2.74–6.40	<0.001

(*Continued*)

Table 2 (Continued).

Variables	Univariant Analysis			Multivariant Analysis (Backward Stepwise)		
	HR	95% CI	P	HR	95% CI	P
Diameter in long axis	1.13	1.09–1.17	<0.001			
Differentiation			0.097			
High	Reference					
Middle	0.55	0.32–0.95	0.031			
Low	0.71	0.45–1.12	0.140			

somehow controversial, this phenomenon may be attributed to two aspects, the biological nature of the tumor and different gastrectomy. For the biology nature, some pieces of research correlated an upper part disease with a higher incidence of HER2 positivity, which is an independent risk factor for overall survival.[32,33] And the increased risk of a diffused disease may be attributed to the aggressive biological features. For gastrectomy, patients with a proximal or diffused cancer always receive a total gastrectomy instead of a distal gastrectomy, which may lead to more complications and worse survival outcomes.[34]

Based on the prognostic factors above, a nomogram was then developed. With pT0 patients included and more risk factors considered, this nomogram may be applied to a broader population of patients. Besides, with a c-index of 0.74 in the training cohort and 0.69 in the validating cohort and good calibration, this nomogram predicted more accurately than the 8th AJCC stage system, whose c-index was 0.66. In addition, compared with the TNM system, our nomogram provided a visible tool easy to use. Thus, our nomogram may contribute to prognosis prediction and decision-making.

There were also several limitations to our study. First, our study did not contain patients at stage IV, so the implications in those patients were limited Second, due to the limited samples and the retrospective nature of our research, bias might exist. Lastly, the samples of ypT0 patients were limited. Thus, the predictive value of our model remained to be seen within them.

Conclusion

We developed and validated a nomogram to predict the 1 year and 3-year OS of patients undergoing neoadjuvant chemotherapy, radical gastrectomy, and D2 lymph node dissection. This nomogram uses readily available clinicopathologic

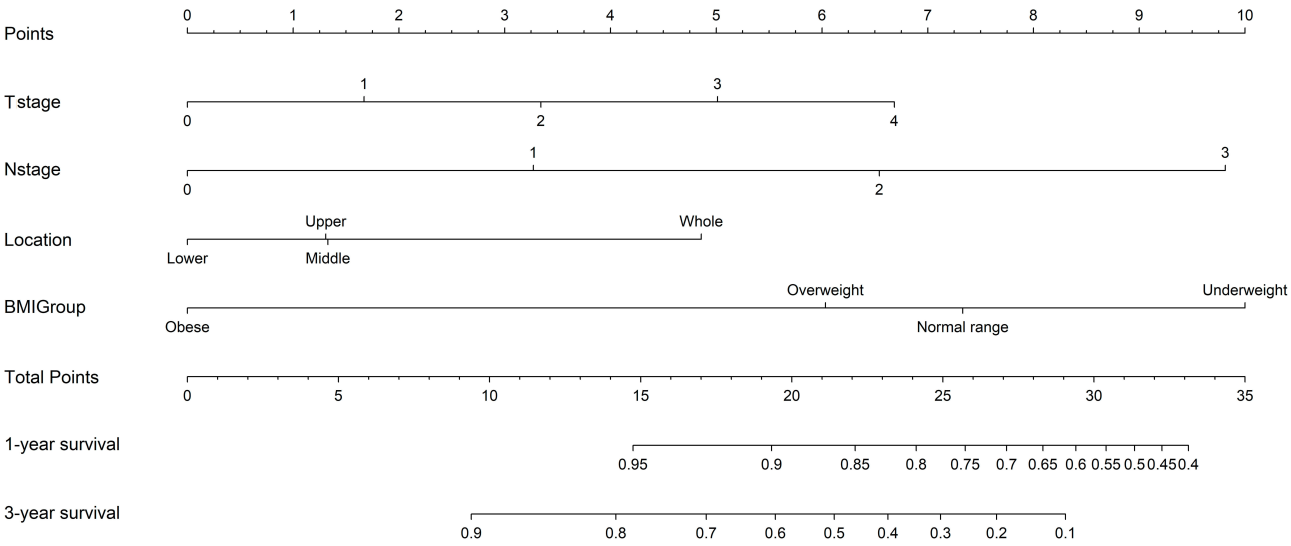

Figure 1 Nomogram was developed from 4 clinicopathological parameters (T stage, N stage, BMI group and Tumor Location) to predict 1- and 3-year survival. The first step to calculate the survival probability is to assign points for each parameter by drawing a vertical line from that variable to the points scale. The second step is to sum all the points and draw a vertical line from the total point to calculate the probability of survival.

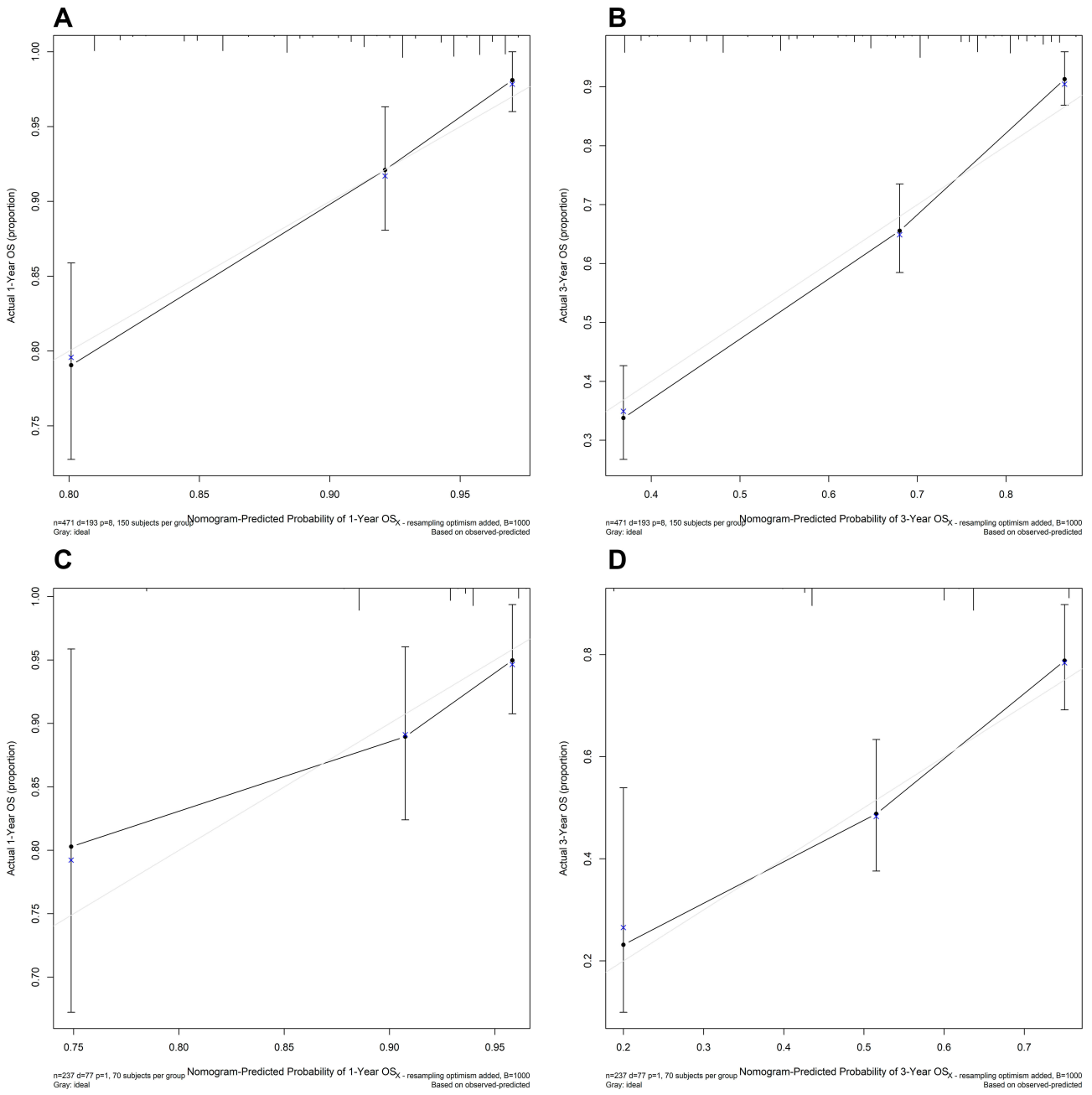

Figure 2 Calibration curve of the nomogram for (**A**) 1-year OS in training cohort (**B**) 3-year OS in training cohort (**C**) 1-year OS in validation (**D**) 3-year OS in validation cohort. The x-axes represent the survival estimated by the nomogram, the y-axes are survival calculated by the Kaplan–Meier method.

factors and predicts survival more accurately than the AJCC TNM staging system.

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Disclosure

The authors report no conflicts of interest in this work.

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