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A novel prognosis prediction model after completion gastrectomy for remnant gastric cancer: Development and validation using international multicenter databases

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ABSTRACT

Background: Examined lymph node counts of remnant gastric cancer patients are often insufficient, and the prognostic ability of tumor-node-metastasis staging is therefore limited. This study aimed to create a simple and universally applicable prediction model for RGC patients after completion of gastrectomy.
Methods: A 5-year overall survival prediction model for remnant gastric cancer patients was developed using a test dataset of 148 consecutive patients. Model coefficients were obtained based on the Cox analysis of clinicopathological factors. Prognostic performance was assessed with the concordance index (C-index) and decision curve analysis. For internal validation, the bootstrap method and calibration assessment were used. The model was validated using 2 external cohorts from China (First Affiliated Hospital of Fujian Medical University, $n = 46$) and the United States (Mayo Clinic, $n = 20$).
Results: Depth of tumor invasion, number of metastatic lymph nodes, distant metastasis, and operative time were independent prognostic factors. Our model's C-index (0.761) showed better discriminatory power than that of the eighth tumor-node-metastasis staging system (0.714, $P = .001$). The model calibration was accurate at predicting 5-year survival. Decision curve analysis showed that the model had a greater benefit, and the results were also confirmed by bootstrap internal validation. In external validation, the C-index and decision curve analysis showed good prognostic performances in patient datasets from 2 participating institutions. Moreover, we verified the reliability of the model in an analysis of patients with different examined lymph node counts (>15 or ≤15).
Conclusion: Utilizing clinically practical information, we developed a universally applicable prediction model for accurately determining the 5-year overall survival of remnant gastric cancer patients after completion of gastrectomy. Our predictive model outperformed tumor-node-metastasis staging in diverse international datasets regardless of examined lymph node counts.

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Introduction

Remnant gastric cancer (RGC) was first described by Balfour in 1922.[1] Although early studies of RGC focused on outcomes of patients who underwent gastrectomy for benign diseases,[2,3] the definition of RGC has been gradually used to define all cancers arising from the remnant stomach after partial gastrectomy regardless of history of prior gastrectomy for either benign or malignant diseases.[4–7] Owing to its rarity (incidence of ≈1%–2%[8]), there is limited prognostic information available to help guide the treatment of RGC patients.

The tumor-node-metastasis (TNM) staging system is the most important prognostic tool for gastric cancer. To ensure accuracy in staging, dissection of at least 16 lymph nodes (LNs) is recommended to avoid stage migration.[9] However, the examined lymph node (ELN) counts of RGC patients are lower than those of patients with primary gastric cancer (PGC) owing to the initial operation and meeting the requirement of at least 16 LNs is often difficult. Therefore, the TNM staging system has limited prognostic ability in RGC patients, and establishing a prognostic prediction model is thus necessary.

The purpose of this study was to (1) create a simple and universally applicable prediction model based on the clinicopathologic factors that significantly affect the prognosis of RGC patients to accurately predict their long-term survival after completion gastrectomy and (2) compare the prognostic abilities of the prediction model and the eighth edition of the American Joint Committee on Cancer (eighth the American Joint Committee on Cancer [AJCC]) TNM staging system in both internal and external validation datasets.

Patients and Methods

Datasets

Internal dataset

This study retrospectively analyzed the prospective databases of Fujian Medical University Union Hospital (FMUUH) in Fuzhou, China. We performed surgery on 4,405 patients with gastric cancer between January 2003 and June 2015. Patients with insufficient clinical or histopathologic data were excluded. Finally, we identified 148 patients who had undergone resection of the gastric remnant for RGC during that period in the test dataset. The patients received open or laparoscopic completion gastrectomy with either curative or palliative intent. The extent of resection and lymphadenectomy was based on the Japanese Classification of Gastric Cancer Guidelines[7] Neoadjuvant chemotherapy was recommended for patients with an esophageal invasion >3 cm and for unresectable patients with bulky lymphadenopathy. Patients with advanced GC usually received adjuvant chemotherapy based on a relatively uniform regimen of fluorouracil and platinum. The median follow-up was 75 months (range 37–147 months). The study was approved by the FMUUH Institutional Review Board.

External datasets

Two additional external validation datasets that satisfied the aforementioned inclusion and exclusion criteria were obtained from the First Affiliated Hospital of Fujian Medical University (FAHFMU), Fuzhou, China ($n = 46$), and the Mayo Clinic, Rochester, Minnesota ($n = 20$). The operation dates for the external validation sets were from January 2011 to June 2016 and from January 1994 to June 2014, respectively. The institutional review boards of the FAHFMU and the Mayo Clinic approved the study. The median follow-up periods of the 2 external validation datasets were 59 months and 114 months, respectively.

Data collection and term definitions

According to the Japanese Classification of Gastric Carcinoma (English edition, version 3),[7] RGC is defined as a carcinoma arising in the gastric remnant after gastrectomy regardless of disease at the time of initial surgery, the extent of resection, or the method of reconstruction. Patient demographics, tumor characteristics, and surgery information were collected from the database. Tumor classification, node classification, metastasis classification, and final staging were all conducted according to the eighth AJCC TNM classification.

Development of the prediction model

The prediction model was developed based on the Cox proportional hazards model. The model output was expressed as coefficients, which were used to calculate hazard ratios and predict survival. The prediction model for estimating the 5-year survival probability was as follows:

$$P_0^{\exp\ (\Sigma\beta iXi)},$$

where P0 is the baseline survival probability and β_i is the regression coefficient for the its predictor.

Statistical analysis

The characteristics of the different databases were analyzed by one-way analysis of variance, the Kruskal-Wallis test, or the χ^2 test. The Kaplan-Meier (K-M) method was used to calculate the survival rate, and differences were assessed with log-rank tests. Regression coefficients obtained from multivariate Cox analysis were used to develop the predictive model. Multivariate survival analysis was conducted using Cox proportional hazards regression. Significant variables in the univariate analysis ($P < .05$) were included in the multivariate Cox analysis. To assess and compare the prognostic ability of the prediction model with that of the eighth AJCC TNM classification, we performed concordance index (C-index) analysis and decision curve analysis (DCA). For the C-statistic analysis, survival times can be validly compared either when both patients have died or when one has died and the other's follow-up time has exceeded the survival time of the first. If both patients are still alive, who will live longer is unknown, and that pair of patients is not used in the analysis.[10] The bootstrap method and calibration assessment were used for internal validation. To do so, we used the bootstrap method to obtain a relatively unbiased estimate. The data were randomly drawn with replacement from the original data set, and the coefficients were recalculated. The C-statistic was then computed using the new coefficients in the bootstrap random samples.[11] Model calibration was examined by comparing the observed values with the predicted values in each of the subgroups, which were arranged in increasing order of patient risk. We used DCA to evaluate the clinical net benefit of the prediction models by summing the benefits (true positives) and subtracting the harms (false positives).[12,13] Finally, the prediction model was validated using the 2 external datasets mentioned earlier. All tests were 2-sided. The statistical analyses were performed with SPSS (SPSS, Chicago, IL, version 22.0) and R (Bell Laboratories, Murray Hill, NJ, version 3.4.0).

Table I
Patient, tumor, and surgery characteristics of the internal and external data sets

Variable	FMUUH (n = 148)		FAHFMU (n = 46)		Mayo Clinic (n = 20)		*P* value
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	
Age (y)	62.8 (10.5)		64.1 (10.2)		75.4 (9.5)		<.001
Sex							.299
Male	128	86.5	41	89.1	15	75.0	
Female	20	13.5	5	10.9	5	25.0	
Comorbidity							.722
No	76	51.3	25	54.3	—		
Yes	72	48.7	21	45.7	—		
Previous operation					—		.169
Benign	103	69.6	27	58.7	—		
Gastric cancer	45	30.4	19	41.3	—		
Reconstruction							.015
Billroth I	40	27.0	4	8.7	—		
Billroth II	100	67.5	37	80.4	—		
Other	8	5.5	5	10.9	—		
Chemoradiotherapy at the first operation							.525
No	122	82.4	36	78.3	—		
Yes	26	17.6	10	21.7	—		
Interval (y)	20.6 (14.6)		19.0 (15.4)				.506
Neoadjuvant chemotherapy							<.001
No	138	93.2	28	60.9	19	95.0	
Yes	10	6.8	18	39.1	1	5.0	
Tumor location							.001
Anastomosis site	76	51.3	36	78.3	—		
Nonanastomosis site	72	48.7	10	21.7	—		
Combined resection							.152
No	120	81.1	31	67.4	15	75.0	
Yes	28	18.9	15	32.6	5	25.0	
D2 lymphadenectomy							<.001
No	23	15.5	4	8.7	13	65.0	
Yes	125	84.5	42	91.3	7	35.0	
Palliative resections							<.001
No	118	79.7	40	87.0	19	95.0	
Yes	30	20.3	6	13.0	1	5.0	
Approach							<.001
Open	90	60.8	42	91.3	19	95.0	
Laparoscopic	58	39.2	4	8.7	1	5.0	
Operative time (min)	237.7 (76.1)		185.6 (56.5)		295.5 (71.2)		<.001
Histology							.04
Differentiated	55	37.2	22	47.8	3	15.0	
Undifferentiated	93	62.8	24	52.2	17	85.0	
Tumor size (cm)	4.8 (2.3)		4.8 (2.0)		5.8 (4.5)		.218
pT stage							.03
T1	15	10.1	6	13.0	2	10.0	
T2	20	13.5	0	0	2	10.0	
T3	35	23.6	7	15.2	6	30.0	
T4a	68	45.9	24	52.2	8	40.0	
T4b	10	6.9	9	19.6	2	10.0	
pN stage							.086
N0	55	37.2	13	28.3	10	50.0	
N1	23	15.5	16	34.8	3	15.0	
N2	32	21.6	11	23.9	3	15.0	
N3	38	25.7	6	13.0	4	20.0	
pM stage							.041
M0	126	85.1	33	71.7	19	95.0	
M1	22	14.9	13	28.3	1	5.0	
pTNM stage (8th AJCC)							.03
IA	15	10.1	5	10.8	2	10.0	
IB	10	6.7	1	2.2	2	10.0	
IIA	18	12.2	3	4.6	2	10.0	
IIB	20	13.5	6	13.0	4	20.0	
IIIA	33	22.3	12	26.1	6	30.0	
IIIB	24	16.2	5	10.8	1	5.0	
IIIC	6	4.1	1	2.2	2	10.0	
IV	22	14.9	13	30.3	1	5.0	
No. metastatic LN	4.2 (5.3)		2.5 (3.5)		3.7 (6.4)		.222
No. ELN	16.2 (11.0)		10.0 (8.1)		15.2 (13.0)		.008
ELN $\leq$15							.001
Yes	75	50.7	37	80.4	13	65.0	
No	73	49.3	9	19.6	7	35.0	
Adjuvant chemotherapy							<.001
No	63	42.6	20	43.5	19	95.0	
Yes	85	57.4	26	56.5	1	5.0	

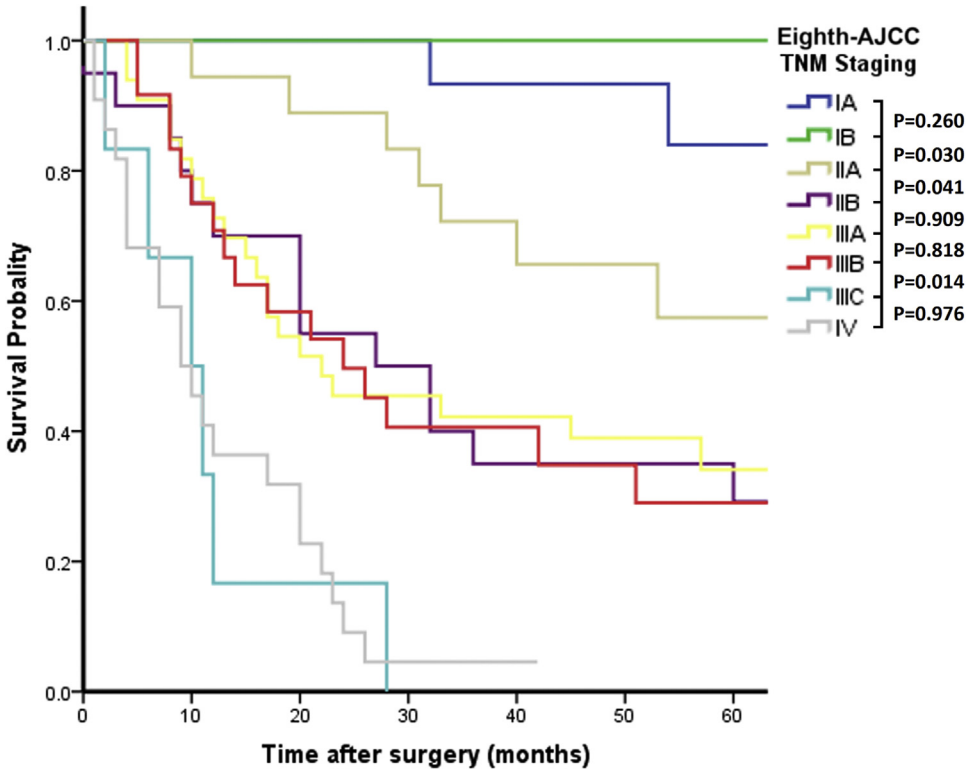

Fig 1. Kaplan-Meier survival curve of overall survival after completion gastrectomy for patients with remnant gastric cancer stratified by the eighth AJCC TNM staging system.

Results

Characteristics of the internal and external cohorts

In the internal training set, the mean age of the 148 patients was 62.8 ± 10.5 years, and 86.5% were male. Prior gastrectomy was performed on 103 patients (69.6%) owing to benign diseases, and 45 patients (30.4%) underwent lymphadenectomy for gastric cancer at the first operation. Billroth II anastomosis was performed in most patients (67.5%). The mean interval was 20.6 ± 14.6 years. Lesions were located at the anastomotic site in 76 patients (51.3%) and at the nonanastomotic site in 72 patients (48.7%). Forty-two patients (91.3%) underwent D2 lymph node dissection, and 6 patients (13.0%) underwent palliative resection. The number of patients with eighth TNM stages I, II, III, and IV were 25, 38, 63, and 22, respectively. The mean ELN was 16.2 ± 11.0, and 50.7% of the patients (75 out of 148) had an ELN ≤15. Lymph node dissection for gastric cancer at the first operation significantly decreased the ELN of RGC patients (9.0 ± 8.0 vs 19.4 ± 10.7, $P < 0$ .001). The baseline characteristics of all ($n = 148$) patients are shown in Table I.

In the external cohorts, the mean age of the 46 patients with RGC from the FAHFMU was 64.1 ± 10.2 years, including 41 male patients. The mean age of the 20 RGC patients from the Mayo Clinic was 75.4 ± 9.5 years, including 15 male patients. The clinicopathologic features of the internal training set and the external validation cohorts are shown in Table I. In addition, K-M survival analysis showed that the external cohorts were similar to the internal training set ($P = .752$; Supplemental Fig 1).

AJCC TNM staging in RGC

In the internal training set, the 5-year survival rates for each stage of the eighth AJCC TNM system were as follows: IA, 84.0%; IB, 100%; IIA, 57.4%; IIB, 29.2%; IIIA, 34.1%; IIIB, 29.0%; IIIC, 0%; and IV, 4.5%. K-M survival analysis shows that the survival curve of TNM substages was crossed (IA vs IB, $P = .260$; IIB vs IIIA, $P = .909$; IIIA vs IIIB, $P = .818$; IIIC vs IV, $P = .976$; Fig 1). The C-statistic of eighth AJCC TNM staging in RGC patients was 0.714 (95% confidence interval [CI], 0.665–0.764).

Development of the prediction model

Univariate Cox analysis showed that sex, pT stage, number of metastatic LNs, pM stage, operative time, combined resection, histology, tumor size, and adjuvant chemotherapy were associated with 5-year overall survival (OS), whereas age, comorbidity, previous operation (benign or gastric cancer), reconstruction, interval, neoadjuvant chemotherapy, tumor location and approach were not (Table II). Multivariate Cox analysis showed that pT stage ($P = .007$), number of metastatic LNs ($P = .002$), pM stage ($P = .003$), and operative time ($P = .02$) were independent prognostic factors, whereas sex, combined resection, histology, tumor size and adjuvant chemotherapy were not (Table III). Based on the results of the multivariate Cox analysis, pT stage, number of metastatic LNs, pM stage and operative time were included in the model development. The prediction model for estimating the 5-year survival probability was as follows:

$$P = 1 - P_0^A$$

where P is the 5-year survival probability, P_0 is the baseline survival probability, and

A = exp [(0.250 × T2) + (0.921 × T3) + (1.577 × T4a) + (1.922 × T4b) + (0.069 × No. of metastatic LNs) + (0.939 × M1) + (0.004 × operative time)].

The newly developed predictive model showed good discrimination, with a C-index of 0.761 (95% CI, 0.714–0.810). A calibration

Table II
Univariate analysis for 5-year overall survival of remnant gastric cancer

Predictor	*P* value	HR	95% CI	
Age (y)	.182	1.015	0.993	1.037
Sex				
Male		Ref.		
Female	.010	2.095	1.195	3.671
Comorbidity				
No		Ref.		
Yes	.549	0.879	0.577	1.340
Previous operation				
Benign		Ref.		
Gastric cancer	.912	1.026	0.651	1.616
Reconstruction				
Billroth I	.948	Ref.		
Billroth II	.948	1.016	0.627	1.645
Other	.747	1.173	0.446	3.085
Interval (y)	.363	1.007	0.992	1.021
Neoadjuvant chemotherapy				
No		Ref.		
Yes	.681	1.190	0.519	2.730
Tumor location				
Anastomosis site		Ref.		
Nonanastomosis site	.553	1.136	0.745	1.733
Combined resection				
No		Ref.		
Yes	.045	1.656	1.012	2.708
Approach				
Laparoscopic		Ref.		
Open	.072	0.662	0.422	1.038
Operative time (min)	.001	1.005	1.002	1.008
Histology				
Differentiated		Ref.		
Undifferentiated	.022	1.704	1.080	2.687
Tumor size (cm)	<.001	1.198	1.117	1.284
pT stage				
T1	<.001	Ref.		
T2	.361	2.147	0.416	11.070
T3	.046	4.483	1.030	19.512
T4a	<.001	12.517	3.043	51.494
T4b	<.001	15.578	3.351	72.429
No. LN retrieved	<.001	1.100	1.061	1.140
pM stage*				
M0		Ref.		
M1	<.001	4.351	2.601	7.278
No. LN retrieved	.363	0.991	0.972	1.010
ELN >15				
No		Ref.		
Yes	.878	1.033	0.679	1.574
Adjuvant chemotherapy				
No		Ref.		
Yes	.016	1.736	1.106	2.724

* Linear correlation was presented between palliative resections and pM staging, so palliative surgery was not included in the Cox analysis.

chart for predicted and observed survival was plotted. Calibration of the model seemed to yield accurate and useful 5-year survival predictions for RGC patients (Fig 2).

Internal validation of the prediction model

In the internal training set, the prognostic performance of the prediction model was significantly better than that of the eighth AJCC TNM staging system (C-index: 0.761 [0.714, 0.810] vs 0.714 [0.665, 0.764], $P = .001$). Figure 2 presents the decision curves showing the clinical usefulness of the prediction model and the eighth AJCC TNM classification to predict 5-year survival in the internal test dataset. The benefit of the prediction model was greater than that of the eighth AJCC TNM classification when the selected threshold was >40% (Fig 3).

Table III
Multivariate analysis of variables selected for the prediction model

Predictor	*P* value	HR	95% CI	
Sex				
Male		Ref.		
Female	.169	1.544	0.831	2.868
Tumor size (cm)	.261	1.050	0.965	1.142
pT stage				
T1	.007	Ref.		
T2	.769	1.284	0.242	6.817
T3	.232	2.511	0.554	11.385
T4a	.038	4.840	1.088	21.527
T4b	.02	6.834	1.345	37.724
No. metastatic LN	.002	1.072	1.026	1.119
pM stage				
M0		Ref.		
M1	.003	2.557	1.386	4.719
Operative time (min)	.02	1.004	1.001	1.008
Combined resection				
No		Ref.		
Yes	.339	0.761	0.435	1.332
Histology				
Differentiated		Ref.		
Undifferentiated	.502	0.842	0.510	1.391
Adjuvant chemotherapy				
Yes		Ref.		
No	.161	0.693	0.415	1.157

External validation of the prediction model

The prediction model also had high discriminatory ability in the external validation cohorts. In the FAHFMU cohort from China, the C-index of the prediction model was 0.828 (0.760, 0.896), which was significantly better than that of the 8th AJCC TNM staging system (0.756, [0.665, 0.848], $P = .032$; Table IV). In the Mayo Clinic cohort from the United States, the prediction model was also superior to that of the 8th AJCC TNM staging system (C-index: 0.706 [0.558, 0.854] vs 0.568 [0.440, 0.698]; Table IV). Model calibration demonstrated that the prediction model could accurately predict the 5-year survival of RGC patients (Supplemental Fig 2). In addition, DCA also showed that the clinical benefit of the prediction model was significantly better than that of the 8th AJCC TNM staging system when the selected threshold was >40% (Supplemental Fig 3).

Effect of examined lymph node counts on the prediction model

To further support our prediction model, prognostic performance with different ELN counts (>15 or ≤15) was also analyzed. The C-index of the prediction model (0.758 [0.694, 0.822]) was significantly higher than that of the 8th AJCC TNM staging system (0.698 [0.632, 0.764]) in 3 cohorts with ELN counts >15 ($P = .007$; Table V). In subgroups with ELN counts ≤15, the prediction model also showed better prognostic performance (0.765 [0.715, 0.814]) vs 0.709 (0.655, 0.762; $P < .001$; Table V). DCA showed that the clinical benefit of the prediction model was significantly better than that of the eighth AJCC TNM staging system regardless of ELN counts when the selected threshold was >40% (Supplemental Fig 1).

Effect of primary disease on the prediction model

We investigated the effect of primary disease (benign disease or gastric cancer) on the prediction model in the FMUUH and FAHFMU cohorts because the primary disease data were missing in the Mayo Clinic cohort. The prediction model (C-index, 0.745 [0.691, 0.800]) outperformed the eighth AJCC TNM staging

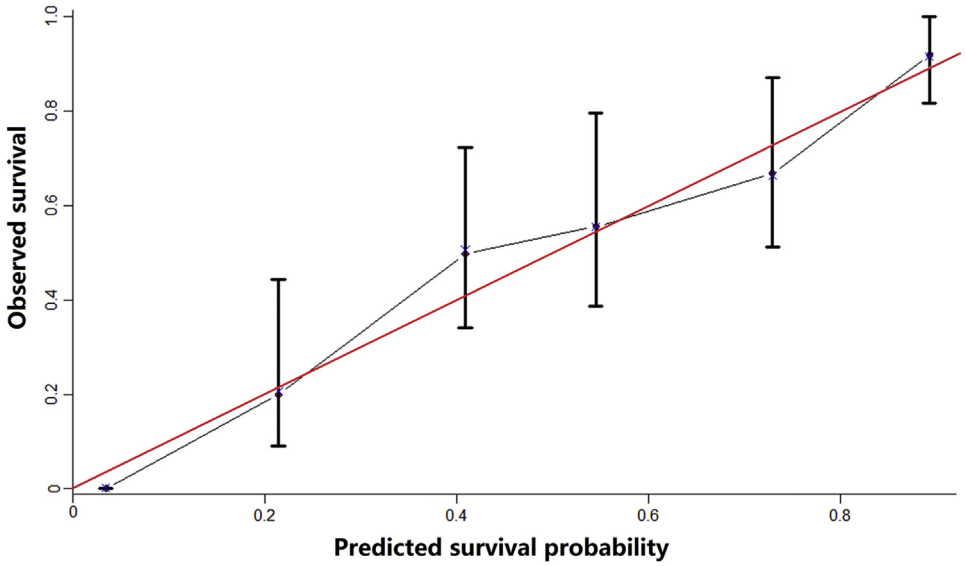

Fig 2. Model calibration curve. The x-axis represents the model-predicted survival, and the y-axis represents actual survival and 95% CI measured by Kaplan-Meier analysis. The model seems to yield accurate 5-year survival predictions.

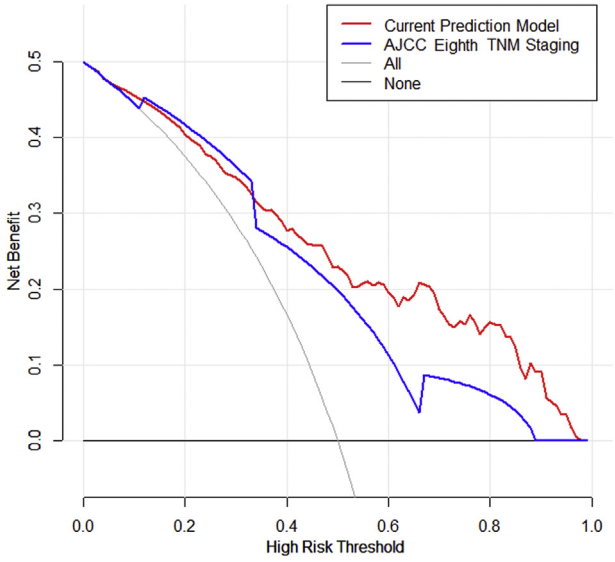

Fig 3. Decision curve analysis of 5-year survival. The x-axis depicts the risk threshold probability that changes from 0 to 1, and the y-axis shows the calculated net benefit for a given threshold probability. The red and blue curves depict the net benefit of the model-based selection strategy for screening, whereas the gray and black lines display the net benefits in the alternative strategies of screening all patients (gray) versus screening no patients (black) in the dataset.

system (C-index, 0.702 [0.644, 0.759]) for benign primary diseases ($P = .036$). For malignant primary diseases, the prediction model also had a better prognostic value (0.827 [0.765, 0.889] vs 0.762 [0.691, 0.833], $P = .005$). In addition, the clinical benefit of the prediction model was significantly better than that of the 8th AJCC TNM staging system regardless of the primary disease when the selected threshold was >30% (Supplemental Fig 2).

Discussion

Accurate prognostic assessment is essential for cancer patients and helps to provide individualized treatments for each patient. As a special tumor of the stomach, RGC results in poor prognosis for patients because of late diagnosis owing to symptoms remaining subclinical over a long period after onset of the original disease.[8,14] In addition, prognostic information that can be used to guide the treatment of RGC patients is limited because of the low incidence of RGC. Therefore, it is important to find a tool to accurately predict the prognosis of RGC patients.

Published guidelines suggest the definition of RGC and regional LNs and how to describe the disease but do not contain a description of RGC staging like that provided for PGC[7,15,16]; therefore, the TNM staging system is applied. However, RGC ELN counts are often lower than 16 owing to initial operation, especially in cases of initial malignant disease. In this study, the mean ELN count in the internal training set was 16.3, and 50.6% of the counts were <16. Insufficient LN dissection can lead to stage migration.[9,17] Therefore, the TNM staging system for PGC may not be appropriate for RGC.

To reduce the migration effect, the TRM staging system (using the ratio of the number of metastatic LNs to the number of ELNs) as an alternative to the TNM staging system has attracted the attention of scholars. Some studies have demonstrated that the TRM staging system can more accurately predict the prognosis of PGC patients regardless of the ELN counts.[9,17-19] However, by analyzing the data of 164 RGC patients, Son et al showed that the prognostic ability of the TRM staging system in RGC patients was not improved compared with that of the TNM staging system.[20] Nakagawa et al also confirmed that the LN ratio was not superior to the pN stage for prognostic classification.[6] Therefore, TRM staging may not be an ideal prognostic tool for patients with RGC. Although our previous studies have shown that the modified TNM staging system based on tumor size can better predict the prognosis of patients with RGC,[21] the effect of tumor size on RGC prognosis remains controversial. Currently, several studies have found that using a combination of multiple prognostic factors to establish a prediction model can improve the accuracy of prognostic prediction.[22–24] However, thus far, a prediction model for RGC has not been reported.

Therefore, a simple and universally applicable prediction model was created by combining independent prognostic factors of RGC. This prediction model can accurately predict the long-term survival of RGC patients after completion gastrectomy and is significantly

Table IV
C-index of the current novel prediction model for the 2 external validation cohorts compared with the corresponding C-index for the eighth TNM staging system

Data set	N	Current prediction model			AJCC eighth TNM staging			*P* value
		C-index	95% CI		C-index	95% CI		
FAHFMU cohort	46	0.828	0.760	0.896	0.756	0.665	0.848	.032
Mayo clinic cohort	20	0.706	0.558	0.854	0.568	0.440	0.698	.026

Table V
Comparison of the C-index with different ELN counts in the FMUUH cohort and external validation cohorts

Data Set	ELN >15				ELN ≤15			
	N	Current prediction model	AJCC eighth TNM staging	*P* value	N	Current prediction model	AJCC eighth TNM staging	*P* value
FMUUH+FAHFMU+Mayo clinic Cohort	89	0.758 (0.694, 0.822)	0.698 (0.632, 0.764)	.007	125	0.765 (0.715, 0.814)	0.709 (0.655, 0.762)	<.001

superior to the eighth AJCC TNM staging system. To develop this model, we analyzed the number of metastatic LNs as a continuous variable because this factor exhibits prognostic characteristics more ideally expressed by gradual increases. This is an important difference from the TNM staging system because the prognosis of patients with 3 metastatic LNs is significantly better than that of patients with 6 metastatic LNs (with the same pN staging), especially for RGC patients with insufficient LNs. To some extent, this factor increased the strength and high degree of discriminatory power of the model to predict the prognosis of RGC patients. The operation time was shown to be affected by patient and tumor characteristics, such as body mass index and LN metastasis.[25,26] Long operative times tend to be required for patients with more advanced tumors that therefore require a higher scope of surgery (combined organ resection), thus leading to their prognosis being poorer than those of patients at lower stages of disease. Furthermore, completion gastrectomy for RGC is even more technically complex, and surgeons lack experience because of its low incidence and anatomic factors, such as adhesions to adjacent organs, displacement of anatomic structures, and changes in lymphatic flow triangulation. Therefore, operation time was used as an independent prognostic factor to understand the correlation between the learning process and patient survival.[27]

Although R0 resection is the only chance for a cure, palliative resection can also provide survival benefits for specific patients. The influence of nonradical surgical resection on the prognosis of cancer patients becomes increasingly important with more effective adjuvant treatments.[28–30] Our prediction model is important for RGC patients. First, many RGC patients are at advanced stages of disease because of late diagnosis,[8,14] and numerous patients undergo nonradical resection. This model includes not only RGC patients undergoing R0 resection, but also M1 patients with palliative resection, which increases the clinical practicability of the model. Second, this model overcomes the limitation that TNM staging requires the dissection of more than 15 ELN counts, showing good prognostic performance for RGC patients with insufficient ELN counts. Therefore, the model meets the need for the accurate assessment of patients without R0 resection or <16 ELN counts. Moreover, our prediction model was externally validated by 2 datasets from Eastern and Western countries, which was necessary because both the Eastern and Western cohorts, which had significantly different patients, tumors, and surgical factors, showed good prognostic performance, proving that our model is universal and accurate in evaluating the prognosis of different patient populations.

This study has some limitations. First, it is a retrospective study, and the results need to be confirmed by a larger multicenter prospective study. Second, RGC is a rare disease, and although this study has a large RGC sample size, the limited number of cases may still bias the outcome. Third, because our prediction model assesses OS as the end point, assessing disease-specific survival or disease-free survival is not possible with our model; however, a large number of studies have demonstrated that OS has an important significance in evaluating the prognosis of cancer patients.[22–24,31] In addition, because this was a multi-institutional study that included data from 3 different medical centers, the mode of treatment for RGC may have been variable, and the Mayo Clinic cohort included patients for which some data were missing from 1994, a full decade before patients in the primary cohort underwent surgery, making the groups not totally comparable. Nevertheless, a simple and universally applicable prediction model for RGC was created for the first time; this model was shown to accurately predict the long-term survival of RGC patients after completion gastrectomy and was verified by external Eastern and Western cohorts.

In conclusion, we developed a simple and universally applicable prediction model for RGC that can accurately predict the long-term survival of RGC patients after completion gastrectomy. The prognostic performance of the model is superior to that of the eighth AJCC TNM staging system and verified in Eastern and Western datasets. In addition, its accuracy is not affected by the ELN counts. We hope that the prediction model can be validated in more cases and becomes an important tool for evaluating the prognosis of patients with RGC.

Disclosure

All authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.05.004.

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