

# A nomogram to predict prognosis for gastric cancer with peritoneal dissemination

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## Abstract

**Objective:** To identify independent prognostic factors to be included in a nomogram to predict the prognosis of gastric cancer patients with peritoneal dissemination.

**Methods:** This is a retrospective study on 684 patients with a histological diagnosis of gastric cancer with peritoneal dissemination from the Sun Yat-sen University Cancer Center as the development set, and 62 gastric cancer patients from the Sixth Affiliated Hospital of Sun Yat-sen University as the validation group. Chi-square test and Cox regression analysis were used to compare the clinicopathological variables and the prognosis of gastric cancer patients with peritoneal dissemination. The Harrell's concordance index (C-index) and calibration curve were determined for comparisons of predictive ability of the nomogram.

**Results:** Univariate and multivariate analyses showed that serum carcinoembryonic antigen (CEA) level ( $P=0.032$ ), ascites grading ( $P=0.008$ ), presence of extraperitoneal metastasis ( $P<0.001$ ), seeding status ( $P=0.016$ ) and performance status ( $P=0.009$ ) were independent prognostic factors for gastric cancer patients with peritoneal dissemination in the development set. The nomogram model was constructed using these five factors. Internal validation showed that the C-index of the model was 0.641. For the external validation, the C-index of this model was 0.709.

**Conclusions:** We developed and validated a nomogram to predict the prognosis for gastric cancer patients with peritoneal dissemination. This nomogram may play an important clinical role in guiding palliative therapy for these types of patients, although it may need more data for optimization.

**Keywords:** Gastric cancer; prognosis; peritoneal dissemination; nomogram

Submitted Feb 25, 2018. Accepted for publication Aug 06, 2018.

doi: 10.21147/j.issn.1000-9604.2018.04.08

View this article at: <https://doi.org/10.21147/j.issn.1000-9604.2018.04.08>

## Introduction

Despite the decrease in the incidence of gastric cancer over the past few decades, it remains the second most common

cause of cancer-related death among carcinomas in the world, with 738,000 deaths globally, mainly in Latin America, Eastern Europe and Eastern Asia (1-4). In many countries, including China, gastric cancer patients are

diagnosed at a relatively advanced stage (5). In addition, 30%–60% of gastric cancer patients were found to have peritoneal dissemination at the time of diagnosis and have a median survival time of only 3–6 months (6).

Despite the progress in surgery, chemotherapy and radiotherapy, the prognosis of gastric cancer is still unsatisfactory (7). Recently, the molecular targeting of genes, such as human epidermal growth factor receptor 2 (*Her2*), has been the focus of many gastric cancer investigations, and several molecular targeting agents have been approved for use in clinic practice due to their beneficial effects on the short-term survival of gastric cancer patients with or without peritoneal dissemination (8,9). However, the effects of Trastuzumab on the subgroup of patients with peritoneal dissemination have been unclear.

In the clinical setting, the 7th version of the TNM Staging System of the American Joint Committee on Cancer (AJCC) is used to stage gastric cancer patients and predict their prognosis. However, other important clinicopathological features, including the gross type and patient age, among others, are not taken into consideration in this system. We and other investigators have found that gastric cancer patients may have a different prognosis even when they are classified in the same stage. Above all, a more reliable tool is needed to predict the prognosis of patients so better treatments can be administered. A nomogram is an efficient tool to quantify risks by combining all known prognostic factors using statistical software and has demonstrated practical use in the diagnosis of several diseases. There are already a few nomograms that have been developed to estimate the prognosis of gastric cancer, for example, the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram for gastric cancer, which is used to predict the 5-year and 9-year disease-specific survival (DSS) after an R0 resection without any other therapy, has been widely validated and proven to be accurate (10–21). We have observed that some patients with gastric cancer with peritoneal dissemination (GCPD) achieved a better prognosis after receiving palliative gastrectomy, chemotherapy or hyperthermic intraperitoneal chemotherapy (HIPEC). However, it is difficult to identify these patients clinically. In this study, we tried to develop a nomogram model to predict the prognosis of gastric cancer patients with peritoneal dissemination by months of survival, for the purpose of screening out appropriate patients for more aggressive treatment.

## Materials and methods

### *Ethics statement*

All the patients provided written informed consent for their information to be stored in the hospital database of the Sixth Affiliated Hospital of Sun Yat-sen University and the Sun Yat-sen University Cancer Center. We obtained separate consent for the use of this information for research. Study approval was obtained from the independent Ethics Committees of the Sixth Affiliated Hospital of Sun Yat-sen University and the Sun Yat-sen University Cancer Center. This study was performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

### *Patient inclusion and exclusion criteria*

The inclusion criteria were as follows: 1) histologically proven adenocarcinoma of the stomach with synchronous peritoneal dissemination at the time of surgery or biopsy; and 2) no other synchronous or metachronous cancers. The exclusion criteria were as follows: 1) incomplete or important data censored; 2) patients with mental disorders or severe dysfunction of the liver and/or kidneys; or 3) no pathological diagnosis of peritoneal dissemination.

### *Peritoneal seeding status*

We classified peritoneal seeding status according to the first English edition of the Japanese Classification of Gastric Carcinoma (22). The classification was as follows: P0, no peritoneal seeding; P1, disseminated metastasis to the region directly adjacent to the peritoneum of the stomach (above the transverse colon, including the greater omentum); P2, several scattered metastases to the distant peritoneum and ovarian metastasis only; and P3, numerous metastases to the distant peritoneum.

### *Follow-up*

After treatment, the patients were monitored every month for the first year, every 3 months for the second year, and every 6 months thereafter, with regular follow-up assessments. We always followed up using telephone interviews, a follow-up letter, a short message platform and an email.

### *End points*

In our research, the end point is the overall survival of

patients with peritoneal dissemination. We followed up all the patients until June 2017 or the death of patients.

**Statistical analysis**

All data were analyzed using IBM SPSS Statistics (Version 20.0; IBM Corp., New York, USA) and R software (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria). The clinicopathological parameters between the development cohort and the validation cohort were analyzed using a Chi-square test or Fisher’s exact test. Then, we performed a Kaplan-Meier analysis and Cox regression analysis to evaluate the independent prognostic factors for overall survival of the gastric cancer patients with peritoneal dissemination.

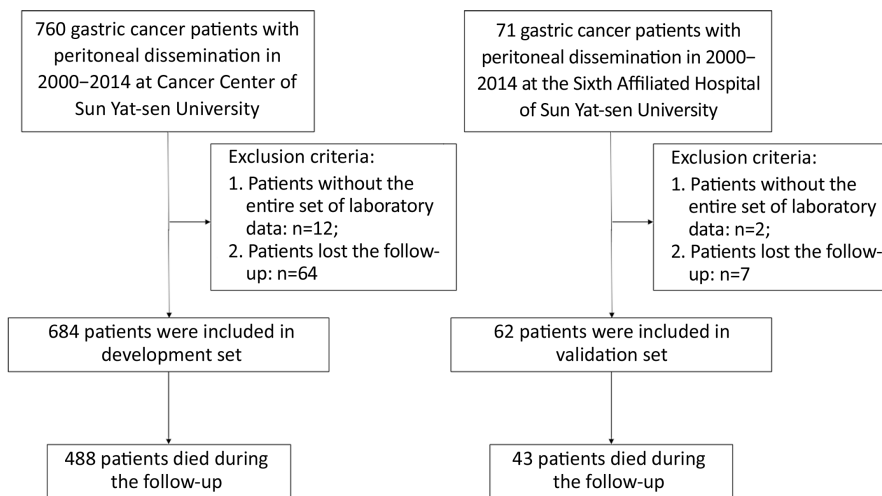
A nomogram was developed as a tool to predict the prognosis of gastric cancer patients with peritoneal dissemination by the months of survival. It graphically presents the patient prognosis. The nomogram and the calibration curve were displayed using the package of Regression Modeling Strategies in R. The predictive performance of this model was evaluated in the test group using the concordance index (C-index) (11).  $P < 0.05$  was considered statistically significant.

**Results**

**Patient characteristics**

From January 2000 to December 2014, a total of 746 patients with histologically diagnosed GCPD were included in the present study: 684 consecutive patients from Sun Yat-sen University Cancer Center comprised the

development cohort, and the other 62 consecutive patients from the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China comprised the validation cohort. The flow chart is shown in *Figure 1*. All cases of peritoneal dissemination were proven clinicopathologically at surgery. The clinicopathological factors for the development set and validation set are shown in *Table 1*. Among the 684 patients from Sun Yat-sen University Cancer Center, 31 patients received gastrectomy + perioperative chemotherapy; 195 patient received gastrectomy + postoperative chemotherapy; 70 patients received gastrectomy only; 31 patients received bypass surgery + postoperative chemotherapy; 37 patients received bypass surgery only; another 226 patients received palliative chemotherapy only, and the remaining 94 patients did not receive any therapy. In addition, among the 62 patients from the Sixth Affiliated Hospital of Sun Yat-sen University, 3 patients received gastrectomy + perioperative chemotherapy; 45 patient received gastrectomy + postoperative chemotherapy; 3 patients received bypass surgery only; another 3 patients received palliative chemotherapy only; and the remaining 8 patients did not receive any therapy. Regarding hyperthermic intraperitoneal perfusion, 24 patients in the development group and 16 patients in the validation group accepted this treatment after surgery. None of the patients received targeted chemotherapy according to our records. Patient survival was measured from the diagnosis of peritoneal dissemination. The median follow-up time and median survival for all patients were 12.5 (range: 1–152) months and 11.5 [95% confidence interval (95% CI): 10.4–12.6] months, respectively.



**Figure 1** Flow chart of patient selection.

**Table 1** Clinical pathological data of gastric cancer patients (N=746)

Variables	Development set (N=684)		Validation set (N=62)		P
	n	%	n	%	
Age					0.121
≥65 years	120	17.5	16	25.8	
Sex					0.790
Male	370	54.1	32	51.6	
Tumor location					0.146
Gastric cardia	195	28.5	25	40.3	
Middle	220	32.2	16	25.8	
Antrum	269	39.3	21	33.9	
Tumor size					0.188
<5 cm	202	29.5	13	21.0	
CEA level					0.884
<5 µg/mL	485	70.9	45	72.6	
Pathological staging					0.131
Well	12	1.8	3	4.8	
Moderate	44	6.4	7	11.3	
Poor	628	91.8	52	83.9	
Signet ring cell carcinoma					<0.001
Yes	248	36.3	9	14.5	
No	431	63.0	42	67.7	
Undefined	5	0.7	11	17.7	
Peritoneal seeding					<0.001
1	136	19.9	27	43.5	
2	211	30.8	9	14.5	
3	337	49.3	26	41.9	
Ascites grading*					0.448
0	372	54.4	40	64.5	
1	136	19.9	11	17.7	
2	76	11.1	5	8.1	
3	100	14.6	6	9.7	
Extraperitoneal metastasis					0.008
Without	438	64.0	50	80.6	
Performance status**					0.031
0	137	20.0	10	16.1	
1	367	53.7	25	40.3	
2	148	21.6	21	33.9	
3	32	4.7	6	9.7	
Pathological T staging***					0.154
T3	114	38.5	24	50.0	
T4a/b	182	61.5	24	50.0	

**Table 1** (continued)

Table 1 (continued)

Variables	Development set (N=684)		Validation set (N=62)		P
	n	%	n	%	
Pathological N staging***					0.382
N1	7	2.4	0	0	
N2	152	51.4	22	45.8	
N3a/b	137	46.3	26	54.2	
Palliative chemotherapy					0.030
Yes	483	70.6	35	56.5	
No	201	29.4	27	43.5	

CEA, carcinoembryonic antigen; \*, standard of the ascites grading was as followed: Grade 0, no ascites; Grade 1, mild, only visible on ultrasound and CT; Grade 2, detectable with flank bulging and shifting dullness; Grade 3, directly visible, confirmed with the fluid wave/thrill test; \*\*, standard of the performance status was as followed: 0, asymptomatic (fully active, able to carry on all pre-disease activities without restriction); 1, symptomatic but completely ambulatory; 2, symptomatic, <50% in bed during the day; 3, symptomatic, >50% in bed, but not bedbound; 4, bedbound (completely disabled, cannot carry on any self-care); \*\*\*, only 344 patients received palliative gastrectomy, including 296 in the Cancer Center of Sun Yat-sen University and 48 in the Sixth Affiliated Hospital of Sun Yat-sen University.

#### *Univariate and multivariate analyses (Cox's regression) of gastric cancer patients in development set*

Univariate analysis showed that tumor size, serum carcinoembryonic antigen (CEA) level, ascites grading, presence of extraperitoneal metastasis, seeding status and performance status were prognostic factors for these patients. We included these clinicopathological factors identified as prognostic factors in the univariate analysis ( $P < 0.05$ ) for the Cox regression model. Multivariate analysis showed that serum CEA level, ascites grading, presence of extraperitoneal metastasis, seeding status and performance status were independent prognostic factors for gastric cancer patients with peritoneal dissemination in the development set. The results of the univariate and multivariate analyses are shown in Table 2.

#### *Development and internal validation of nomogram model to predict prognosis of gastric cancer patients with peritoneal dissemination*

Along with the visualized tool provided by the nomogram, we then used the Cox regression model to predict the prognosis by months of survival of the gastric cancer patients with peritoneal dissemination. The nomogram model is shown in Figure 2.

We performed an internal validation to validate this nomogram and found that the concordance index was 0.641, which closely corresponded to the actual survival. The internal calibration curves for half-, 1- and 2-year survival are shown in Figure 3. As shown in Figure 3, the black line represents the predicted values of the nomogram,

while the gray line represents the actual values. The less discrepant they are, the more precise the predictive capability of the model is. For the internal calibration, the black lines fluctuated above and below the gray lines, to identify a reliable predictive capability of the nomogram.

#### *External validation of nomogram model of gastric cancer patients from the Sixth Affiliated Hospital of Sun Yat-sen University*

We used an external validation set, consisting of 62 gastric cancer patients from the Sixth Affiliated Hospital of Sun Yat-sen University, to characterize the discrimination of the newly developed nomogram model. The C-index was 0.709, and the external calibration curves for half-, 1- and 2-year survival are shown in Figure 4. As shown in Figure 4, the goodness of fit indicated relatively satisfactory predictive values in the external validation, even though the predicted half-year survival and the predicted 2-year survival were not as fit as the predicted 1-year survival.

## Discussion

Peritoneal dissemination is one of the most common forms of metastasis for gastric cancer. Palliative chemotherapy has been the main treatment administered to gastric cancer patients with peritoneal dissemination. In the past few decades, researchers have devoted efforts toward the development of new treatments for gastric cancer patients with peritoneal dissemination, including radiotherapy, chemotherapy, and molecular targeted drugs (23).

**Table 2** Univariate and multivariate analysis of gastric cancer patients in development cohort (N=684)

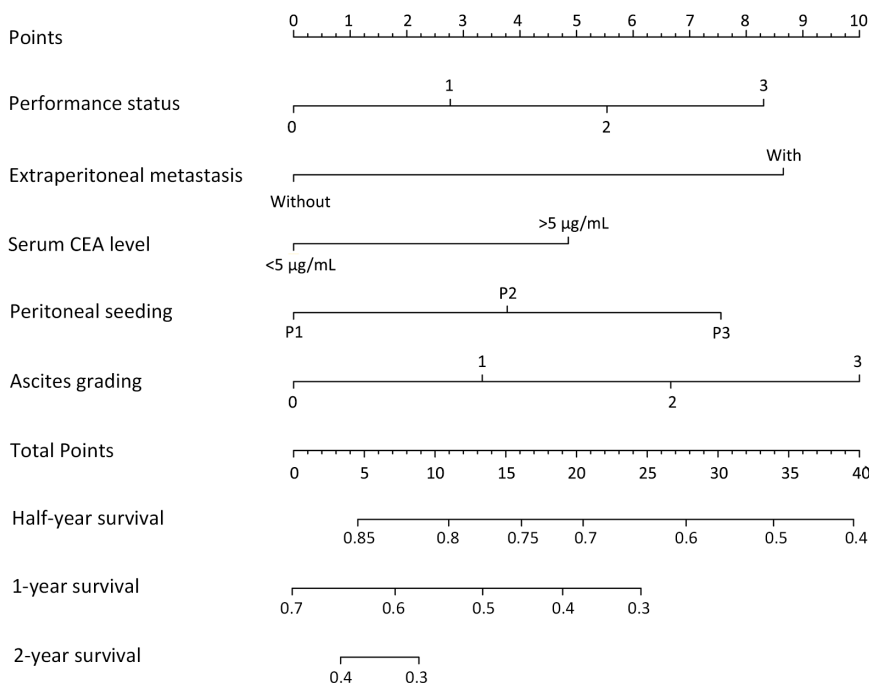
Variables	Univariate analysis			Multivariate analysis				
	n	Median survival (95% CI)	P	HR	95% CI	P		
Sex								
Male	370	10.97 (9.33–12.60)	0.684					
Female	314	11.33 (9.65–13.01)						
Tumor location								
Upper	195	10.20 (8.44–11.96)	0.107					
Middle	220	11.27 (8.82–13.72)						
Antrum	269	12.10 (10.33–13.87)						
Tumor size (cm)								
<5	202	13.23 (10.68–15.78)	0.020	1.203	0.984–1.471	0.072		
≥5	482	10.17 (8.82–11.51)						
CEA level (μg/mL)								
<5	485	12.43 (10.99–13.87)	0.002	1.239	1.019–1.507	0.032		
≥5	199	8.97 (7.29–10.65)						
Signet ring cell carcinoma								
Yes	248	10.37 (9.02–11.71)	0.211					
No	431	12.43 (10.79–14.08)						
Undefined	5	9.03 (5.34–12.72)						
Peritoneal seeding								
1	136	15.07 (11.09–19.05)	<0.001	1		0.016		
2	211	13.53 (11.38–15.68)					0.853–1.435	0.446
3	337	8.57 (7.28–9.85)					1.093–1.819	0.008
Ascites grading								
0	372	14.27 (12.39–16.14)	<0.001	1		0.008		
1	136	9.73 (7.63–11.83)					0.918–1.489	0.204
2	76	6.73 (5.76–7.71)					1.050–1.921	0.023
3	100	8.10 (6.52–9.68)					1.182–2.141	0.002
Extraperitoneal metastasis								
Without	438	13.23 (11.42–15.04)	<0.001	1.506	1.246–1.819	<0.001		
With	246	8.17 (6.72–9.62)						
Performance status								
0	137	11.30 (8.90–13.70)	<0.001	1		0.009		
1	367	12.36 (10.77–13.96)					0.875–1.104	0.261
2	148	9.30 (7.57–11.03)					0.910–1.564	0.201
3	32	9.37 (9.96–12.24)					0.983–2.465	0.059

CEA, carcinoembryonic antigen; 95% CI, 95% confidence interval; HR, hazard ratio.

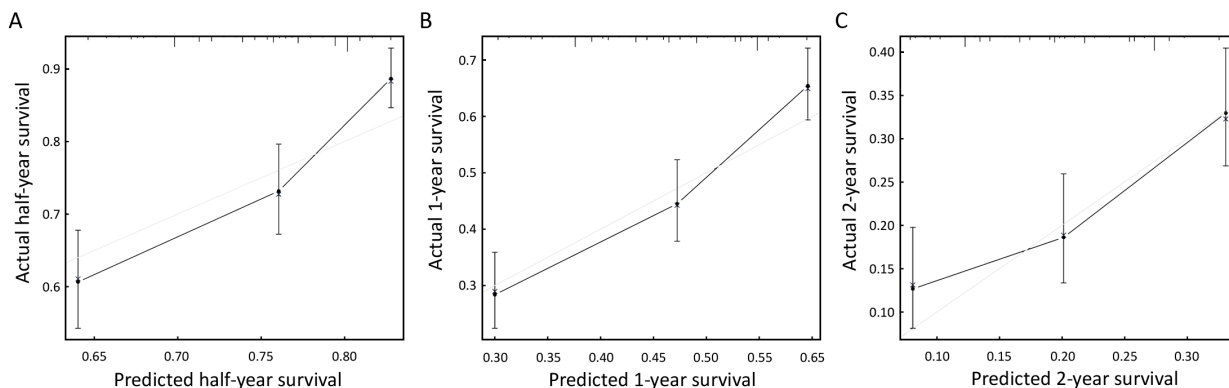
Unfortunately, the results of clinical trials have been unsatisfactory, although some patients were reported to experience prolonged survival after they received intraperitoneal perfusion of chemotherapy or combination treatment with chemoradiotherapy (24). Clinically, it is important to predict the prognosis of gastric cancer

patients with peritoneal dissemination to ensure that they receive the most optimal treatment.

Currently, the 7th Edition of the AJCC Staging System is used clinically to predict the survival of gastric cancer patients. However, this system places all the gastric cancer patients with peritoneal dissemination into stage IV. In a



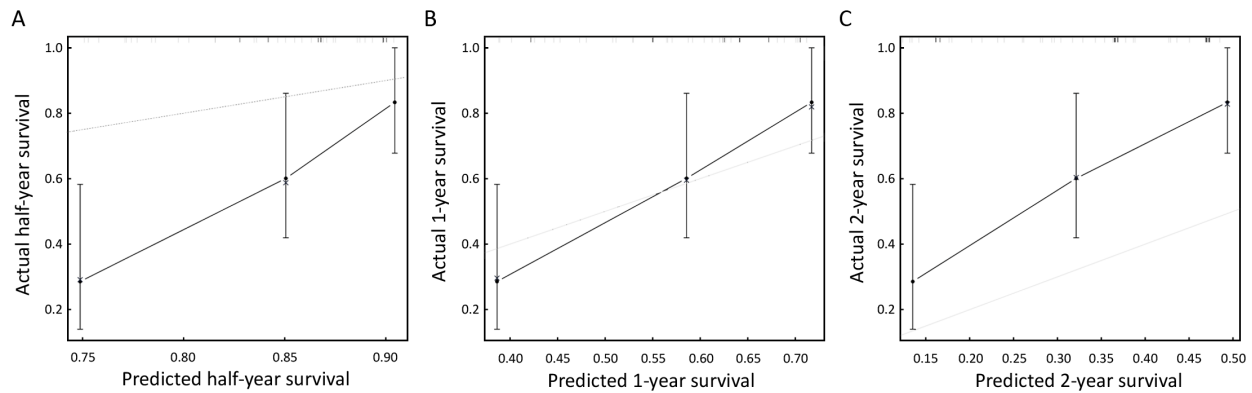
**Figure 2** Nomogram predicting half-, 1- and 2-year overall survival for gastric cancer patients with peritoneal dissemination (GCPD). The nomogram is used by adding up the points identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of half-, 1- and 2-year survival. Serum carcinoembryonic antigen (CEA) level: 0, negative; 1, positive; extraperitoneal metastasis: 0, without; 1, with.



**Figure 3** Internal calibration curve to validate nomogram model for which C-index was 0.641.

previous report, it was found that the patient age, tumor location, total number of lymph nodes retrieved, postoperative recurrence, adjuvant radio/chemotherapy, the Lauren classification, etc. were related to the prognosis of gastric cancer patients (10-14,16-18,25-27). In our present study, we identified serum CEA level, ascites grading, presence of extraperitoneal metastasis, seeding status, and performance status as independent prognostic risk factors for GCPD patients by a Cox regression model.

In our research, all the patients were gastric cancer patients with synchronous peritoneal dissemination. The prognostic influence of some proven clinicopathological factors, Lauren type, lymph node metastasis, lymphovascular and perineural invasion might be inconsequential in the presence of distant metastasis. In our previous study, we found that palliative gastrectomy can prolong the survival of GCPD patients without extraperitoneal metastasis when combined with more than five cycles, and particularly more



**Figure 4** External calibration curve to validate nomogram model for which C-index was 0.709.

than eight cycles, of first-line chemotherapy (28-37). In another study, it was shown that preoperative or postoperative chemotherapy on the basis of S-1, alone or combined with other chemotherapeutic agents such as cisplatin (SP therapy), paclitaxel or oxaliplatin as first-line chemotherapy can prolong patient survival, with one patient still alive three years after chemotherapy (38-40).

In support of the practicality of our model, the C-indexes were 0.641 and 0.709 in the internal and external validation subsets. This finding means that the model was still not precise enough and needed to be optimized, which might be related to the following reasons. First, the treatment strategies in this group of patients were complex. As aforementioned, there were 6 treatment strategies in our data: 1) gastrectomy + perioperative chemotherapy; 2) gastrectomy + postoperative chemotherapy; 3) gastrectomy only; 4) bypass surgery + postoperative chemotherapy; 5) bypass surgery + postoperative chemotherapy; 6) palliative chemotherapy only; and 7) no therapy. In addition, some patients received HIPEC. Different treatments may affect the prognoses of the patients. Second, we only included the preoperative variables to construct the model to make it fit clinically. However, the effects of the treatments were disregarded in the model. Finally, this study had bias because it was a retrospective study; moreover, for the validation group, more patients from multiple centers will be needed for external validation to fully examine this model. However, the calibration was unsatisfactory, which we believe may be related to the different treatment strategies accepted in the validation group compared with those in the development group. The percentage of patients in the validation group who received chemotherapy was lower than that of the development group. This observation may account for the lower fitness of the

predicted half-year survival and of the predicted 2-year survival. In addition, the number of patients in the validation group is too small, which also may have caused bias in the calibration curve. In conclusion, we have reasons to believe that the nomogram we constructed has prognostic potential accordingly.

We therefore believe that this model can be used to predict the prognosis of GCPD. Chemotherapy is currently the mainstay of treatment for GCPD patients. However, some of these patients were shown to have a better prognosis under comprehensive therapy that included surgery and other approaches. This model could be practical for suggesting the optimal clinical treatment for these patients. For example, for the patients predicted to have a better prognosis, aggressive treatments including surgery or HIPEC should be considered. For the patients predicted to have a poor prognosis, only palliative therapy should be administered. We are the first to identify possible risk factors for patients with peritoneal dissemination in a nomogram and believe that this model should permit individualized survival prediction and provide better treatment allocation than the existing systems. We believe that our nomogram may assist surgeons in selecting the appropriate treatment for gastric cancer patients with regard to the probability of a survival benefit.

As shown in *Table 1*, there were several clinicopathological factors that differed significantly between the development group and the validation group, such as signet-ring cell carcinoma, peritoneal seeding, extraperitoneal metastasis, performance status, and palliative chemotherapy. Among them, peritoneal seeding, extraperitoneal metastasis and performance status were included in the nomogram model, which may demonstrate the validity of the model for two different groups of patients. However, the ratio of the



palliative chemotherapy group may cause a deviation of the prediction from the model because different treatment strategies may cause survival differences. Another group of patients who had treatment strategies similarly proportional to those of the development group may be needed to validate the accuracy of the model.

There are some limitations associated with our study. First, although we constructed a robust nomogram model for prognostic prediction, more patients from multiple centers will be needed for external validation to fully examine this model. In addition, we removed some patients who had been lost to follow-up or discontinued follow-up for various reasons. Other patients were also removed because of missing data, such as tumor size, precise pathological staging and performance status. Second, the findings may not be generalizable to gastric cancer in Western countries.

## Conclusions

We have constructed a nomogram to estimate the survival of gastric cancer patients with peritoneal dissemination. The internal and external validations showed that this model can effectively predict the prognosis of gastric cancer patients with peritoneal dissemination. However, the number of subjects included in the external validation set was too small. More data are needed to validate and modify this model.

## Acknowledgements

This work was supported in part by a major special project grant from Guangzhou Health and Medical Collaborative Innovation (No. 15570006) and the Tianhe District Science and Technology Project, Guangdong, China (No. 201434KW020).

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Chen S, Chen X, Nie R, Ou Yang L, Liu A, Li Y, Zhou Z, Chen Y, Peng J. A nomogram to predict prognosis for gastric cancer with peritoneal dissemination. *Chin J Cancer Res* 2018;30(4):449-459. doi: 10.21147/j.issn.1000-9604.2018.04.08