Establishment of a novel survival assessment and prediction model for advanced gastric cancer patients receiving immunotherapy

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Abstract. Currently, there are only a few risk assessment tools that provide predictions of survival duration for patients with gastric cancer (GC) receiving immunotherapy. The purpose of the present study was to develop and validate a nomogram that uses statistical data to predict survival and make risk assessments for patients with advanced staged GC. A total of 1,013 patients consisting of a development cohort (n=501) and validation cohort (n=512) collected during the time interval between January 2018 and June 2022 were included in the present study. The analysis consisted of the discrimination index, calibration plots and decision curve of the nomogram model. A total of 167 (33.33%) patients from the development cohort, and 158 (30.85%) from the validation cohort died during the observation period. The median overall survival (OS) of female patients was higher at 980 days (95% CI, 613-NA) compared with that of male patients, which was 748 days (95% CI, 597-NA; P=0.24). The median survival of patients with domestic immunotherapy was 789 (95% CI, 597-NA) days, which was lower compared with the imported immunotherapy group who had a median OS of 980 days (95% CI, 582-NA; P=0.22). A total of four independent predictors, age (HR=1.012; P=0.0245), histological grade (HR=1.395; P=0.016), immunotherapy cycles (HR=0.932; P=0.028) and line of first immunotherapy (HR=1.693; P=0.0003), were identified. The C-index was 0.64 and 0.67 for the development and validation cohorts, respectively. Patients who received more cycles of immunotherapy as the first-line treatment with highly differentiated tumor led to increase in the survival time of the patients. Thus, this nomogram could be used to determine the benefit of immunotherapies on patients at various stages of treatment of GC.

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Key words: survival assessment, prediction model, development cohort, validation cohort, advanced gastric cancer, received immunotherapy

Introduction

Gastric cancer (GC) is the fifth most common cancer in the world, with ~952,000 newly diagnosed cases per year and 1,089,103 diagnosed cases in 2020 (1). It is the third leading cause of cancer-associated mortality, with ~723,000 patients dying from the disease each year. Although the morbidity of GC is higher in East Asian countries compared with Western countries, the histological types of GC are similar in Asian and Western countries, with adenocarcinoma being the most common (2-4). Regardless of stage, the 5-year overall survival (OS) rate in the United States (US) is <30%. Known risk factors for developing GC include high salt intake, smoking, *Helicobacter pylori infection* (2,3) and advanced age (5,6). The risk index of GC survival outcome involves age, sex, clinical tumor size, body mass index, histology, clinical stages and tumor location (7-9).

According to the 2020 Chinese Society of Clinical Oncology Guidelines for diagnosis and treatment of GC (10), second- or third-line drugs for advanced metastatic or recurrent gastric or gastroesophageal junction adenocarcinomas have poor efficacy and limited options. The benefit of chemotherapy for advanced GC is limited (11). With the launch of biological products such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) monoclonal antibodies and anti-angiogenic factors, more and more patients with GC benefit from immunotherapy (12,13). Therefore, apart from biomarkers, investigations into parameters or indexes that are independent risk factors that affect the prognosis of immunotherapy need to be performed. For example, the number of patients receiving second-line immunotherapy varies in clinical trials in CHECKMATE-649 (14); the proportion of patients receiving second-line immunotherapy is 8%, and in the KEYNOTE-062 (15) clinical trial, the proportion of patients receiving second line immunotherapy is 15%. Whether immunotherapy intervention be performed after the failure of first-line and second-line standard treatments remains to be investigated, as the time point of immunotherapy intervention may be an independent risk factor for the survival and prognosis of patients receiving immunotherapy. According to

CHECKMATE-649 (14) or KEYNOTE-061/062 (15), there is little data on Asian patients with GC. The analysis of prognosis after immunotherapy is insufficient, therefore, there is a lack of systematic tools for predicting individual survival outcomes in patients with GC before immunotherapy.

At present, the common clinical prognostic evaluation is mainly based on the American Joint Committee on Cancer (AJCC) staging guidelines, which mainly include the depth of tumor invasion, lymph node metastasis data, hematogenous metastasis, location of the tumor in the stomach, histological grade and lymphovascular invasion (16,17). However, factors such as age, sex, marital status, degree of tumor differentiation, number of primary tumors and immunotherapy cycle, which may be of great significance for the prediction of individual survival, have not yet been fully considered. Therefore, its guiding value for the individualized prognosis of patients is limited to a certain extent. One study has stated that the prognosis is improved in younger patients (18), whereas another has reported it being improved in the elderly (19). Women are more likely to have cancer of certain organs such as the breast, uterine corpus, colon and rectum (20), while similar can be said in men for some carcinomas, such as prostate and bladder cancer (21). Similarly, degree of tumor differentiation and number of primary tumors have their own varying significance (22). Prognostic factors and survival models for advanced patients with GC undergoing immunotherapy are to be explored.

Therefore, the present study was designed to develop a novel GC nomogram, which was built using only clinically available variables, to determine the clinical prognosis of patients with GC receiving immunotherapy through risk prediction. In addition to further exploring whether there are novel targets that could be used to guide further immunotherapy.

Materials and methods

Study cohorts. From the perspective of evidence-based medicine, aiming at the aforementioned problems, prospective methods were used to establish the prognosis model of GC. The prognostic model was based on a cohort study and cluster sampling method (Fig. 1).

As the goal of the prediction model research is an application, the study objects have as few exclusion criteria as possible in addition to the inclusion criteria, so as to ensure that the study population is as consistent as possible with the target population. Although randomized controlled trials (RCTs) are typical representatives of high-quality research data, too high a number of exclusion criteria in the RCT scheme leads to inconsistency between the research population and the population served in clinical practice. Selective bias leads to inconsistency between the prediction model and the real situation, a poor prediction effect and low research quality (23). Therefore, the data sources in the present scheme were patients with advanced gastric or gastroesophageal junction tumors who received immunotherapy at two clinical sites (Fig. 1).

Research subjects. To develop a nomogram, the development cohort consisted of patients with GC who received immunotherapy between January 2018 and June 2022, in The First Affiliated Hospital of Nanjing Medical University (Nanjing, China), which was a tertiary teaching hospital and ranked in the top 20 in Science and Technology Evaluation Metrics China. The mean age was 62.27 (SD±11.27) years and 366 (73.05%) patients were male. Patients in the validation cohort were selected from Drum Tower Hospital (Nanjing, China), another high-level clinical facility (Fig. 1). The mean age was 62.11 (SD±11.51) years and 364 (71.09%) patients were male.

The inclusion criteria were as follows: Patients with clinically confirmed advanced gastric cancer, adenocarcinomas of the stomach or gastroesophageal junction (based on pathology, cytology and imaging diagnosis) who received immunotherapy between January 2018 and June 2022. The immunotherapy was anti-PD-1 and anti-PD-L1 monoclonal antibodies, including Camrelizuma, Tislelizumab, Sintilimab, Toripalimab, Nivolumab, Pembrolizumab, Penpulimab and Envafolimab for injection. The exclusion criteria were as follows: i) Patients with critical organ dysfunction, such as heart failure, respiratory failure, liver failure and renal failure; and ii) pregnant women.

Predictive indicators. i) Demographics, including age and marital status.

ii) Disease characteristics. Histological grade and primary stage of the tumor at first diagnosis according to the AJCC. Tumor node metastasis (TNM), including primary tumor (T), regional lymph node (N) and distant metastasis (M). The clinical stage was based on the CT and histopathology findings, tumor location, macroscopic type and histological differentiation based on endoscopic biopsy. The primary tumor T stages were classified as T1, T2, T3, T4a and T4b, and the clinical N stages were classified as N0 and Nx.

iii) Pathological features. Microsatellite stable (MSS), microsatellite unstable (MSI) or mismatch repair deficient (dMMR); human herpesvirus type 4; Epstein-Barr virus; human epidermal growth factor receptor-2 (HER2); PD-L1. Previous and current treatment regimens were collected, as well as the survival status of the subjects after immunotherapy. For a dichotomous variable, all negative data records were '0' and all positive data records were '1'.

Survival follow-up. The cut-off point for follow-up was September 2022. A telephone follow-up was conducted to verify the post-discharge treatment, genetic testing results and OS conditions. The data of patients who could not be contacted was eliminated.

Ethical approval. This research was approved by Ethic Review Board of The First Affiliated Hospital of Nanjing Medical University. All the necessary formalities for the informed consent of the patients were fulfilled according to the local regulation and Declaration of Helsinki.

Statistical analysis. A Cox proportional hazards regression model (Cox model) was performed to estimate the OS risk and predictor using stepwise regression method for variable selection; sls=0.1 and sle=0.1 indicate that both inclusion and exclusion criteria are 0.1. The Kaplan-Meier method combined with the two-stage test was used for survival analysis with survival curves. The development cohort was divided into two groups by sex and by immunotherapy manufacture separately. For the comparison of baseline categorical variables, the wald χ^2 statistic for hypothesis testing of regression parameters in

the COX model. The survival prediction model used a nomogram based on the results of regression modeling. To evaluate the internal and external discrimination performance of the nomogram, bootstrapping validation was performed on both the developmental and validation cohorts with the concordance index (Harrell's C-index and Uno C). The criteria of discrimination, calibration and decision curve analysis were used to evaluate the clinical utility of the prediction model. All analyses were performed using R software version 4.1.1 (24). P<0.05 was considered to indicate a statistically significant difference.

Results

Patients and demographics. Both datasets consisted of patients who underwent immunotherapy for GC, and the therapeutic strategy was determined by the appropriate protocol and guidelines. Patients in both datasets were followed up regularly by physical examinations, laboratory tests, endoscopy and CT. Table I presents the descriptive statistics of both the developmental (n=501) and validation (n=512) cohorts. As displayed in Table I, the majority of patients in the two cohorts were in Stage III-IV (n=410, 90.11%; and n=389, 75.98%). The mean ages were 62.27 (SD±11.27) and 62.11 (SD±11.51). A total of 366 men (73.05%) in the development set and 364 men (71.09%) in the validation set were included. A total of 235 (48.55%) and 290 (60.54%) patients underwent surgery. The number of patients who received all three interventions in the sequence were 177 (43.07%) and 174 (52.73%); the number of patients treated with chemotherapy as first- or second-line and immunotherapy + chemotherapy after were 173 (42.09%) and 103 (31.21%); and the number of patients treated with immunotherapy + chemotherapy only were 61 (14.84%) and 53 (16.06%) in the development and validation sets, respectively. The mean number of immunotherapy cycles patients received was 4.34 (SD±4.03) vs. 4.91 (SD±4.26) in the development and validation sets. A total of six tumor markers, including HER2, MSS/MSI, MMR, PD-L1, TMB and EBER, were designed as independent indices, but most of them have not been tested based on their medical records.

Risk factors for survival outcomes and nomogram construction. A total of 167 (33.33%) patients from the development cohort and 158 (30.85%) from the validation cohort died during the observation period. Cox proportional hazards regression had been used to select independent risk factors for survival. To estimate the lifetime of the development cohort, the Kaplan-Meier method was conducted with a mean OS of 677.53 (SD±21.88) days. The survival status for the development set was 342 (77.38%) during the observation period. The predicted probability of OS was shown in Fig. 1. Overall, 50% of patients remained alive in 794 days. According to Fig. 2A, the mean survival outcome of patients with domestic immunotherapy was 570.28 (SD±18.55) days inferior to the imported immunotherapy group with a mean OS of 720 (SD±40.65). The median survival outcome of patients with indigenously manufactured medicine immunotherapy was 789 (95% CI, 597-NA) days, which was lower compared with the multinational medicine immunotherapy group with a median OS of 980 (95% CI, 582-NA) days. Fig. 2B revealed that the mean OS of female patients was 739.12 (SD±43.27), which was

Table I. Clinicopathological characteristics of the development and validation sets.

Variables	Development set (n=501)	Validation set (n=512)
Age, years		
Mean (SD)	62.27 (11.27)	62.11 (11.51)
Median	63.87	64.59
Q1, Q3	56.02,70.29	55.94,69.44
Min, Max	24.74,120.90	21.65,84.82
Sex, n (%)		
Male	366 (73.05)	364 (71.09)
Female	135 (26.95)	148 (28.91)
Marital status, n (%)		
Unmarried	3 (0.68)	196 (38.28)
Married	484 (96.61)	311 (60.74)
Divorced	10 (2.26)	2 (0.39)
Widowed	4 (0.90)	3 (0.59)
History of chronic diseases, n (%)		
1	218 (46.88)	203 (41.86)
0	247 (48.41)	282 (58.14)
Histological grade, n (%)		
Highly differentiated	18 (4.69)	4 (0.88)
Medium differentiation	125 (32.55)	200 (43.86)
Low differentiation	241 (62.76)	252 (55.26)
Borrmann, n (%)		
I	9 (2.01)	9 (2.24)
II	48 (10.71)	30 (7.46)
III	114 (25.45)	256 (63.68)
IV	277 (61.83)	107 (26.62)
LAUREN, n (%)		
Intestinal type	89 (34.63)	119 (40.48)
Diffuse type	99 (38.52)	105 (35.71)
Mixed type	69 (26.85)	70 (23.81)
Primary tumor stage, n (%)		
T1	16 (3.19)	24 (4.69)
T2	22 (4.39)	24 (4.69)
T3	91 (18.16)	112 (21.88)
T4	206 (41.12)	162 (31.64)
Tx	166 (33.13)	192 (37.5)
Lymph node metastasis, n (%)		
N0	34 (11.18)	50 (19.61)
N1	50 (16.45)	34 (12.94)
N2	77 (25.33)	55 (21.57)
N3	144 (28.74)	177 (22.85)
Nx	196 (39.12)	257 (22.85)
Distant metastasis, n (%)		
M0	155 (34.91)	197 (43.97)
M1	289 (65.09)	251 (56.03)

Table I. Continued.

Variables	Development set (n=501)	Validation set (n=512)
Stage, n (%)		
I	9 (1.98)	18 (3.52)
II	36 (7.91)	48 (9.38)
III	109 (23.96)	138 (26.95)
IV	301 (66.15)	251 (49.02)
Surgery, n (%)		
0	249 (51.45)	186 (38.83)
1	235 (48.55)	290 (60.54)
Chemotherapy, n (%)		
0	107 (22.86)	148 (33.18)
1	361 (77.14)	297 (66.59)
Immunotherapy cycles, n		
Mean (SD)	4.34 (4.03)	4.91 (4.26)
Median	3	4
Q1,Q3	2.6	2.6
Min, Max	1.27	1.36
Treatment, n (%)		
Surgery + Chemo + (Immuno + Chemo)	177 (43.07)	174 (52.73)
Chemo + (Immuno + Chemo)	173 (42.09)	103 (31.21)
Immuno + Chemo	61 (14.84)	53 (16.06)
HER2, n (%)		
0	118 (20.81)	182 (50.14)
1+	50 (22.52)	77 (21.21)
2+	36 (16.22)	53 (14.60)
3+	18 (8.11)	51 (14.05)
Signet ring cell, n (%)		
0	449 (89.62)	458 (89.11)
1	52 (10.38)	56 (10.89)
Immunotherapy manufacturers, n (%)		
Indigenous	356 (72.95)	305 (59.45)
Multinational	132 (27.05)	208 (40.55)
Line of first immunotherapy, n (%)		
1	211 (42.12)	302 (58.98)
2	241 (48.1)	147 (28.71)
3	42 (8.38)	34 (6.64)
4	2 (0.40)	14 (2.73)

superior compared with the male patients 577.02 (SD±17.56). Median OS of female patients was 980 (95% CI, 613-NA), which was greater compared with the male patients 748 (95% CI, 597-NA). However, no statistical significance was found

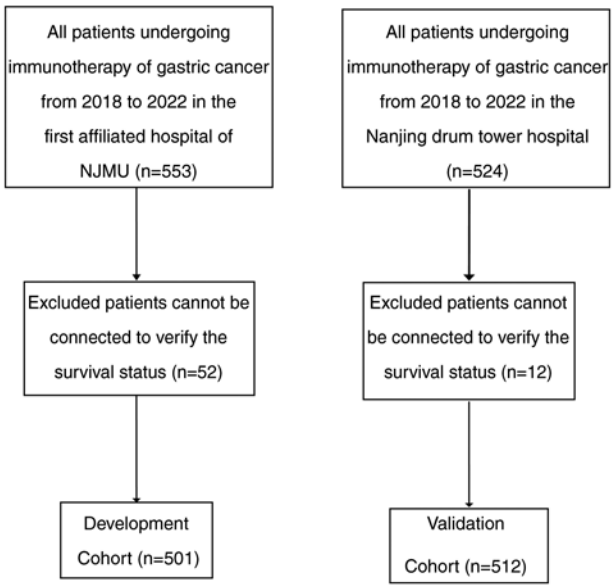

Figure 1. Basic research model used in the present study. NMU, Nanjing Medical University.

The hazard ratio (HR) of all the variables are plotted in Table II. All predictors were entered into the model after multivariate analysis: The difference between the two groups of immunotherapy manufacturers (HR=1.419; P=0.0078), Borrmann (P=0.0287), histological grade (HR=1.395; P=0.0151), immunotherapy cycles (HR=0.932; P=0.028), the line of first immunotherapy (HR=1.693, P=0.0003) and age (HR=1.012; P=0.0245). However, only histological grade, immunotherapy cycle, line of first immunotherapy and age entered the model and may be the predictors (Fig. 3). With the potential prediction index, a nomogram (Fig. 3) was used, allowing clinicians to discuss future treatmet options with individual patients based on their previous medical records. It appears that patients who received immunotherapy 10 cycles earlier as the first-line treatment and whose tumors were highly differentiated at a younger age led to an increase in survival time (Fig. 3).

Nomogram discrimination and calibration. The Harrel C-index for the present nomogram was 0.64 (95% CI 0.58-0.7), and the bias-corrected Harrell C-index was 0.62; Uno C was 0.61 after bootstrapping (n=1,013) internal validation. In the external validation cohort, the C-identification power calibration plots with external verification for the developmental set were 0.67 (95% CI, 0.63-0.72), indicating that the nomogram maintained a certain discrepancy as presented by each year in Fig. 4. The mean calibration of 1-year survival was observed expected ratio (OE)=0.95 (95% CI, 0.77-1.16), as revealed in Fig. 4C. The mean calibration of 2-year survival was OE=0.86 (95% CI, 0.72-1.03), as shown in Fig. 5. The 3-year mean calibration survival was OE=0.86 (95% CI, 0.72-1.02) in Fig. 4A. To combine all the timelines, the mean calibration in the large was slope was 0.95, and the interquartile range was (0.798-1.12). The present monogram consistently showed favorable net benefits across a wide range of threshold probabilities in both the developmental and validation cohorts (Fig. 5).

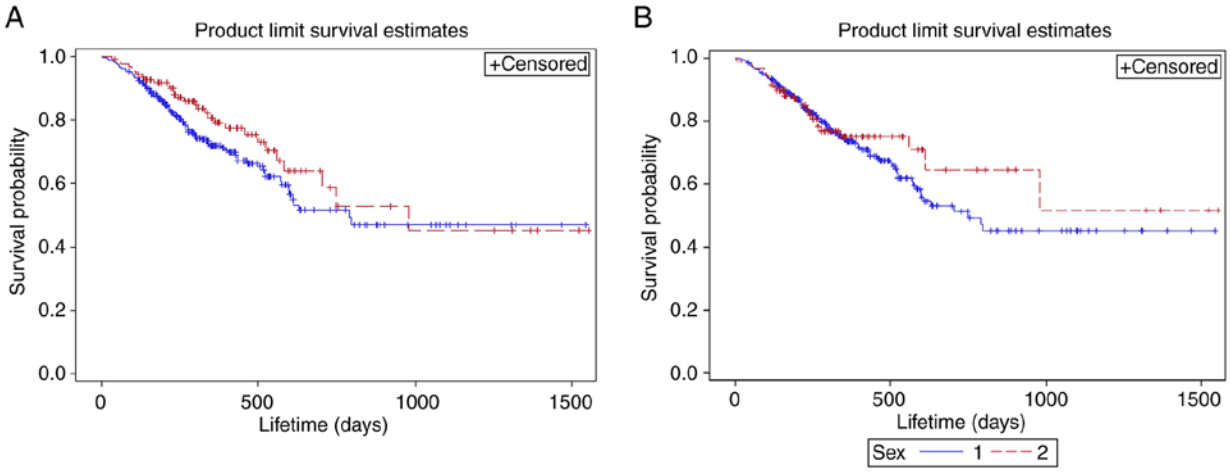

Figure 2. (A) Kaplan-Meier survival curve of OS on immunotherapy manufacturers. The blue line represents patients with immunotherapy produced by domestic manufactures; the red line means patients received imported immunotherapy. (B) Kaplan-Meier survival curve of OS on sex. 1=male, 2=female. OS, overall survival.

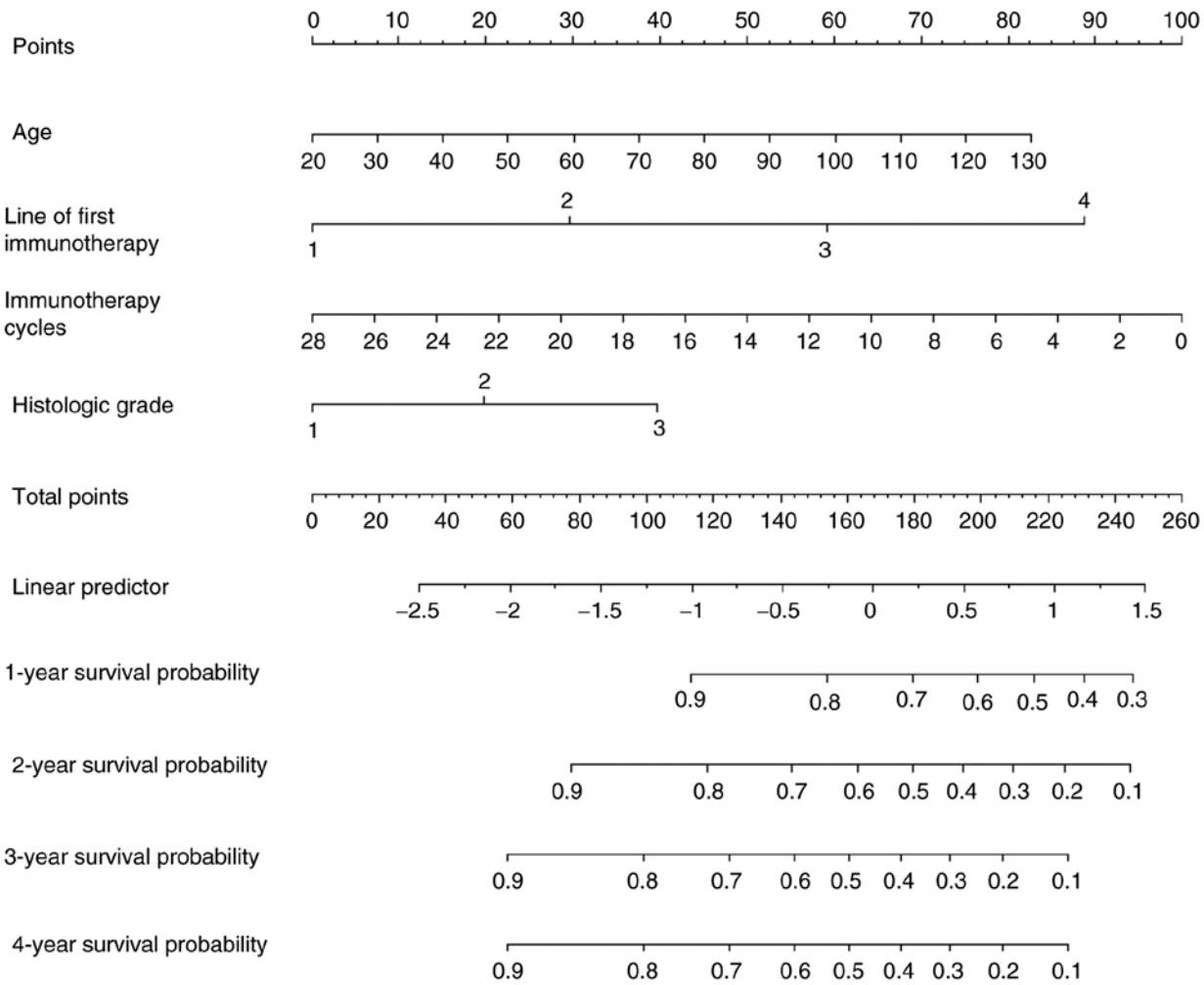

Figure 3. Nomogram was constructed with four variables from the Cox model, and was evaluated internally and externally. The total points of each patient were calculated using the monogram in the development set.

Discussion

The present study developed a novel nomogram for survival assessment and prediction of immunotherapy for patients with advanced GC. There have been numerous nomograms to assess the survival of patients with GC. Previously, Eom *et al* (25) developed a nomogram for undergoing curative resection for GC, predicting that age,

Table II. Multi-variable cox proportion hazards model of the development cohort.

Variables	Wald χ^2	Hazard ratio	d.f.	95% CI		Pr>χ^2
				Lower	Upper	
Age	5.0568	1.012		0.996	1.029	0.0245
Sex	0.6009		1			0.4382
Male	0.6009	1.178		0.790	1.814	
Female				Reference		
History of chronic diseases	0.0493	1.042	1			0.8242
Yes				0.725	1.493	
No				Reference		
Histological grade	3.1897	1.395	2			0.0151
Highly differentiated	0.3057	0.774		0.271	1.736	
Medium differentiation	4.4034	0.611		0.378	0.954	
Low differentiation				Reference		
LAUREN	3.6707		2			0.1596
Intestinal type	0.0014	1.013		0.528	1.995	0.9701
Diffuse type	2.2786	1.611		0.883	3.076	0.1312
Mixed type				Reference		
Borrmann	9.0417		3			0.0287
I	0.6659	1.521		0.463	3.669	0.4145
II	1.2826	0.704		0.364	1.242	0.2574
III	7.2571	0.487		0.279	0.801	0.0071
IV				Reference		
Primary tumor stage	4.0937		4			0.3935
T1	0.0005	0.989		0.298	2.433	0.9825
T2	0.0075	1.036		0.427	2.149	0.9309
T3	2.9429	0.608		0.334	1.050	0.0863
T4	0.1113	1.069		0.722	1.591	0.7386
Tx				Reference		
Lymph node metastasis	6.5785		4			0.1599
N0	4.1054	0.390		0.136	0.877	0.0427
N1	0.0023	1.014		0.544	1.765	0.9617
N2	0.0000	1.001		0.588	1.633	0.9980
N3	2.6430	0.689		0.434	1.068	0.1040
Nx				Reference		
Distant metastasis	1.8407		1			0.1749
M0	1.8407	0.768		0.519	1.115	0.1749
M1						
P-stage	2.6580		3			0.4474
I	0.2012	0.726		0.119	2.296	0.6538
II	1.5306	0.615		0.258	1.235	0.2160
III	1.3421	0.769		0.483	1.180	0.2467
IV					Reference	
Signet ring cell	1.2166					0.2700
0	1.2166	0.737		0.443	1.321	0.2700
1				Reference		
HER2	0.6298		3			0.8896
0	0.0007	1.013		0.425	2.989	
1+	0.1376	1.210		0.472	3.711	
2+	0.2218	1.302		0.448	4.248	
3+				Reference		

Table II. Continued.

Variables	Wald χ^2	Hazard ratio	d.f.	95% CI		Pr>χ^2
				Lower	Upper	
Surgery	1.8390		1			0.1751
0	1.8390	1.275		0.899	1.819	0.1751
1				Reference		
Chemotherapy	1.3038		1			0.2535
0	1.3038	0.759		0.460	1.193	0.2535
1				Reference		
Treatment	0.7154					0.6993
Surgery + Chemo + Immuno	0.0218	1.046		0.590	1.976	0.8827
Chemo + Immuno	0.4121	1.216		0.688	2.293	0.5209
Immuno						
Line of first immunotherapy	10.9980		3			0.0117
1	0.0007	52219.83		0.154		0.9791
2	0.0007	62171.62		0.184		0.9788
3	0.0008	120253.2		0.348		0.9775
4				Reference		
Immunotherapy manufacturers	7.0682	1.419	1			0.0078
Indigenous	2.2802	1.372		0.922	2.102	0.1310
Multinational				Reference		
Immunotherapy cycles	4.8301	0.932	1	0.885	0.975	0.028

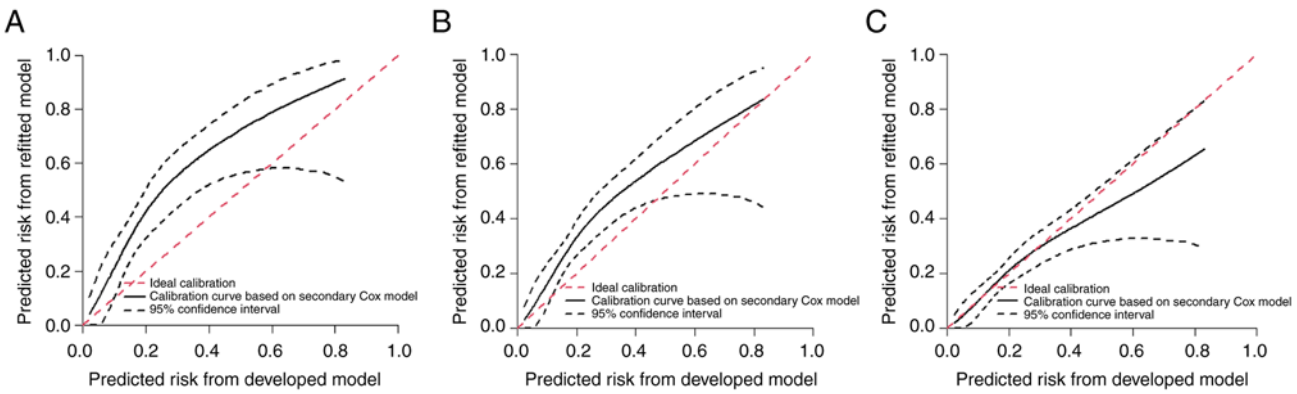

Figure 4. (A) Calibration plots for predicting 3-year DSS. Calibration plots after external validations (slope, 0.86; interquartile range, 0.72-1.02). (B) Calibration plots for predicting 2-year DSS. Calibration plots after external validations (slope, 0.86; interquartile range, 0.72-1.03). (C) Calibration plots for predicting 1-year DSS. The red line is ideal calibration. Calibration plots after external validations (slope, 0.94; interquartile range, 0.77-1.16). DSS, disease-specific survival.

tumor size, lymphovascular invasion, depth of invasion and metastatic lymph nodes were significant prognostic factors for OS. Han *et al* (26) selected patients with GC after D2 gastrectomy to predict the long-term survival outcome. The multivariate Cox model identified age at diagnosis, sex, location, depth of invasion, number of metastatic lymph nodes and number of examined lymph nodes as covariates to be associated with survival. Hou *et al* (27) established a prognostic model of liver metastasis in GC based on the SEER database. Ethnicity, grade, marital status, tumor size, TNM stage, T stage and M stage are independent risk factors for GC, and GC bone metastasis is an independent risk factor that affects the prognosis of patients with GC. Song *et al* (17) built a survival prediction model for radical surgery that only included patients with lymph node metastases. Shin *et al* (28) used preoperative data to select the high-risk patients without considering the treatment they received; eight independent predictors, including age, sex, clinical tumor size, macroscopic features, body mass index, histology, clinical stages and tumor location, were considered for the preoperative nomogram of patients with GC. The present study has different research subjects and prospective cohorts.

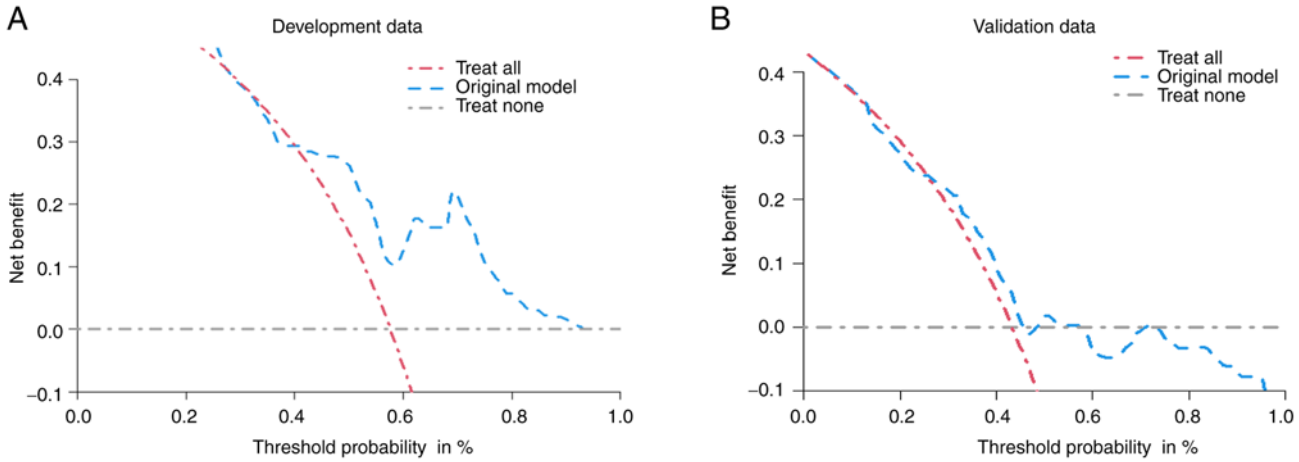

Figure 5. (A) Decision curve analysis on development cohort. (B) Decision curve analysis on validation cohort.

The current study developed a novel nomogram by considering the most common and significant parameters as aforementioned that could help identify high-risk patients before immunotherapy and help clinicians make appropriate decisions for patients. In the present study, the depth of invasion, called the T stage, and metastatic lymph nodes, also known as the N stage, did not enter the model due to their progressive status distribution. Survival time increased with an increase in patient age, and vice versa. The aforementioned studies reveal that as the age of the patient and the age of diagnosis rise, the survival period falls. The present study showed that the higher number of cycles of immunotherapy taken by the patients and the higher the immunotherapy intervention, the higher the survival. The histological grade is also a risk factor for GC; patients with a poorly differentiated tumour are associated with a lower survival rate. As a result, immunotherapy should be applied in advance as the first-line treatment for stage III-IV patients with cancer with chemotherapy.

The present study developed a novel nomogram and validated it both internally and externally using a data set from multicenter studies. There have been numerous nomograms to assess the survival of patients with GC, but they cannot be applied to advanced patients with GC who have received immunotherapy.

The current study had several strengths. First, all the factors used in the nomogram are easy and convenient to obtain and are objective; thus, they could be widely applicable to physicians. Additionally, based on careful statistical calculation, a novel significant indicator was identified: The line of first-line immunotherapy in both the developmental and validation datasets, elevating early intervention in immunotherapy with chemotherapy as the first-line treatment. And no matter which line of immunotherapy was involved, the more cycles patients received, their survival condition improved; thus, they could be widely applicable to physicians. Therefore, more careful clinical consideration may be required to select a therapeutic approach. Moreover, the difference in GC survival outcome between domestic immunotherapy and imported immunotherapy had no statistical significance. It seems female OS tended to be higher compared with male OS in immunotherapy; however, longer observation is needed. Signet ring cells are usually considered to have a poor prognosis for GC; however, they were not included in the present nomogram.

The current study demonstrated not so good discrimination but a good calibration, and there were several limitations. First, the present nomogram was developed and validated only in Asian patients who underwent immunotherapy; therefore, further validation is needed for the application of our nomogram in a more diverse population. Secondly, the present study attempted to search for as much preoperative information as possible; however, there were unavoidable missing values that needed to be imputed using statistical methods, such as tumor markers, which patients would not be required to test. In addition, patients without surgery lack data on Borrmann and Lauren grades. Thirdly, in cases of diffuse types of cancer, such as Borrmann type 4, more careful application would be needed. Finally, the present nomogram did not include frailty or patient psychology-related variables, such as the Self-Rating Anxiety Scale. Frailty and psychological conditions are important clinical factors and are not included in the nomogram. This could be a potential confounding source. Despite advances in treatment techniques, there is no recommended method to establish a risk factor system for immunotherapy patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MS and JZ carried out the conception and design of this study. Acquisition of data was conducted by MS and YY.

MS conducted the statistical analysis, data interpretation and drafted the manuscript, that was later revised by JZ. The funding was obtained by JZ. MS, JZ and YY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethical approval and consent to participate

This research was approved by Ethic Review Board of The First Affiliated Hospital with Nanjing Medical University. All the necessary formalities for the informed consent of the patients were fulfilled according to the local regulation and Declaration of Helsinki.

Patient consent for publication

All the patients involved in this study provided written informed consent for the publication of any data and/or accompanying images.

Competing interests

The authors declare that they have no competing interests.

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