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Development and external validation of a nomogram for predicting the conditional probability of survival after D2 lymphadenectomy for gastric cancer: A multicentre study

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ABSTRACT

Background: Previous studies have elucidated that on average, long-term cancer survivors have better prognoses than newly diagnosed individuals. This study aimed to devise a nomogram to predict the conditional probability of cancer-specific survival (CPCS) in gastric cancer (GC) patients after D2 lymphadenectomy.

Methods: Clinicopathological data for 2,596 GC patients who underwent D2 lymphadenectomy in an Eastern institution (the training cohort) were retrospectively analysed. Cancer-specific survival (CSS) was predicted using Cox regression models. A nomogram was constructed to predict CPCS at 3 and 5 years post-gastrectomy. Two external validations were performed using a cohort of 2,198 Chinese patients and a cohort of 504 Italian patients.

Results: In the training cohort, the 5-year CPCS was 59.2% immediately post-gastrectomy and increased to 68.8%, 79.7%, and 88.8% at 1, 2, and 3 years post-gastrectomy, respectively. Multivariate Cox regression analyses showed that age; tumour site, size and invasion depth; numbers of examined and metastatic lymph nodes; and surgical margins were independent prognostic factors of CSS (all $P < 0.05$) and formed the nomogram predictor variables. Internal validation showed that the conditional nomogram exhibited good discrimination ability at 3 and 5 years post-gastrectomy (concordance index, 0.794 and 0.789, respectively). External validation showed a 3- and 5-year concordance index of 0.788 and 0.785, respectively, in the Chinese cohort, and 0.792 and 0.787, respectively, in the Italian cohort. Calibration of the nomogram predicted that survival corresponded closely with actual survival.

Conclusions: we developed a robust nomogram to predict CPCS after D2 lymphadenectomy for GC based on survival duration.

Introduction

The incidence of gastric cancer (GC) in China is much higher than that in any other country [1]. Moreover, in China, GC is the second leading cause of cancer-related death [2]. Gastrectomy with D2 lymph node (LN) dissection is the standard treatment for

Abbreviations: GC, Gastric cancer; AGC, advanced gastric cancer; CSS, Cancer-specific survival; CPCS, Conditional probability of cancer-specific survival; LN, Lymph node; Gx, Grade cannot be evaluated; CI, Confidence interval; SYSUCC, the Sun Yat-sen University Cancer Center; IMIGASTRIC, the International Study Group on Minimally Invasive Surgery for Gastric Cancer; AJCC TNM, American Joint Committee on Cancer Tumour Node Metastasis; FJUH, Fujian Medical University Union Hospital.

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curable GC in eastern Asia [3]. Recent reports revealed a trend towards improved cancer-specific survival (CSS) rates in patients who have undergone D2 lymphadenectomy, especially when lymphadenectomy was performed in a high-volume center [4–7].

Death risk assessments for GC patients are customarily based on the American Joint Committee on Cancer Tumour Node Metastasis (AJCC TNM) staging system or on more detailed nomograms [8,9]. Most reports evaluate the risk of death only from the time of surgery. However, recent studies have shown that the risk of death in patients with GC is not constant [10,11]. The conditional probability of CSS (CPCS) represents the probability of remaining life expectancy for a specific number of postoperative years based on the length of time that the patient has already survived. The benefits of CPCS estimates have already been demonstrated in various types of cancers [12–14]. For cancer survivors, CPCS estimates might allow patients to quantify improvements in their prognosis over time. CPCS estimates are equally necessary for clinicians because they might allow adjustment of the frequency and type of follow-up over time. In contrast to conventional survival estimates, CPCS estimates can provide cancer survivors and clinicians with a more accurate evaluation of the changes in the risk of death.

A nomogram is a useful tool for predicting the probability of survival of an individual patient with a simple way and for improving personalized decision-making in cancer treatment accordingly [15]. Recently, nomograms based on different databases have been constructed for predicting individual survival of GC [9,16,17]. Few studies have focused on the correlation of D2 lymphadenectomy to CSS; more importantly, these models cannot be applied to the prediction of CPCS. In assessing the prognosis of cancer survivors, CPCS estimates may drastically differ from baseline CSS predictions, especially after several years of cancer mortality-free follow-up.

Because of the high incidence of GC in eastern Asia, surgeons in these areas have accumulated substantial experience in GC-related surgical techniques, and gastrectomy with D2 lymphadenectomy is routinely performed with low morbidity and mortality rates [18,19]. The previously reported static GC nomograms did not provide an accurate prediction of the dynamic outcomes for cancer survivors because the prediction of the previous nomograms was only based on conventional CSS. Therefore, to date, the dynamic prognosis of GC patients who have undergone D2 lymphadenectomy has not been precisely predicted. Considering the sustainable surveillance requirement, this study aimed to construct a new conditional survival nomogram for predicting CPCS in GC patients from a large-volume institution after D2 lymphadenectomy. The performance of the nomogram model was validated using a cohort of 2,198 patients from China and another cohort of 504 patients from Italy.

Materials and methods

Population and covariates

We retrospectively collected data for 2,596 patients who underwent GC surgery between June 1, 2007, and December 31, 2013, in the Department of Gastric Surgery at Fujian Medical University Union Hospital (FJUH) and who satisfied the following inclusion criteria: the presence of primary gastric adenocarcinoma, the absence of combined malignancy, neoadjuvant therapy (neoadjuvant chemotherapy or radiotherapy or chemoradiotherapy), and distant metastasis, treatment with D2 lymphadenectomy according to the Japanese GC Association [3,20]. Exclusion criteria including: there was remnant GC, or when either the patient death or patient survival data had not been recorded. According to the Japanese gastric cancer treatment guidelines, all patients in the training cohort received a standard follow-up after surgery, including visits every 3–6 months for the first 2 years, every 6–12 months from year 3 to year 5, and once per year thereafter [3]. The final follow-up date was December 31, 2016, which ensured a minimum follow-up period of 3 years. All the cases were restaged according to the criteria described in the AJCC staging manual (7th edition) [8]. The patients were divided into five age groups ($\leq$44, 45–54, 55–64, 65–74 and $\geq$ 75 years), consistent with the international age-standardized survival classification categories [21]. The preoperative physical status was assessed based on the preoperative American Society of Anesthesiologists (ASA) score [22]. The tumour site was divided into four subsites based on the location of the lesion center: upper third, middle third, lower third and overlapping [23]. Adenocarcinoma of the oesophagogastric junction within the stomach was categorized as upper-third GC [24]. The histological grade was categorized as low grade (well and moderately differentiated), high grade (poorly differentiated and undifferentiated) or Gx (grade cannot be evaluated). Macroscopic types were classified into three types, namely, early GC, advanced GC with Borrmann type I to III tumours, and advanced GC with Borrmann type IV tumours. The severity of postoperative complications was assessed according to the Clavien-Dindo classification [25]. Fluorouracil-based adjuvant chemotherapy (e.g., tegafur, 80–120 mg/d, Taiho Pharmaceutical Co., Ltd. Tokyo, Japan) was recommended for patients with advanced GC in the FJUH cohort.

Statistical analysis

Deaths from GC were coded as disease-specific mortality. The kernel density smoothing method was used to plot the hazard curve for death. CPCS originates from the biostatistical concept of conditional probability [13,26] and can be calculated from life table data. The mathematical definition of CPCS can be expressed as follows: $CPCS\,(y|x) = CSS\,(y)/\,CSS\,(x)$, where $x < y$, $CPCS\,(y|x)$ is the CSS probability y years after surgery given that the patient has survived x years after surgery, $CSS\,(y)$ is the CSS probability y years after the operation, and $CSS\,(x)$ is the CSS probability x years after surgery [27]. For instance, a patient's 2-year CSS probability is 0.8, whereas her 5-year CSS probability is 0.4. The probability of surviving the first 5 years after surgery given that the patient has already survived the first 2 years is calculated as follows: $CPCS\,(5|2) = CSS\,(5)/\,CSS\,(2) = 0.5$ Thus, this patient's $CPCS\,(5|2)$ is 0.5, which is higher than the original 5-year CSS probability $(5|0)$ of 0.4. The variances of the conditional probabilities were evaluated using the formula from Davis et al. [28].

Within the training cohort, variables were selected by the backward stepwise selection method in the Cox proportional hazards regression analyses. Based on the predictive model with the identified prognostic factors, a nomogram was constructed for predicting 3- and 5-year CPCS. The conditional survival nomogram was validated in three independent analyses. First, an internal validation procedure using 200 bootstraps was applied to the multivariate Cox regression coefficients of the nomogram predictor variables. The second validation used the Sun Yat-sen University Cancer Center (SYSUCC) validation cohort between January 2000 to December 2012 ($n = 2, 198$), which satisfied the aforementioned inclusion criteria. The third validation used the International study group on Minimally Invasive Surgery for Gastric Cancer (IMIGASTRIC) validation cohort between January 2001 to December 2014 ($n = 504$), which was a large prospective cohort that also satisfied the aforementioned inclusion criteria. The performance of the nomogram included its discrimination and calibration. The discriminatory ability of the nomogram was quantified using Harrell's concordance index, which ranges from 0.5 to 1.0. Generally, a concordance index value greater than 0.75 is considered to

represent relatively good discrimination. We assessed the discriminatory ability of the nomogram at 3 and 5 years after gastrectomy. Furthermore, calibration plots were generated to evaluate the performance characteristics of the nomogram.

The institutional review boards of all the participating institutions approved the study (IRB: 2019KY007). The differences between cohorts were calculated by using variance analysis, or x 2 test as appropriate. All data were processed using SPSS 18.0 software (SPSS Inc, Chicago, IL, USA) and R software (version 3.4.3, Revolution Analytics, New Haven, CT, USA). All tests were two-tailed, with a significance level of $P < 0.05$.

Results

Clinicopathologic characteristics

The baseline clinicopathologic characteristics of the FJUH training cohort (n = 2,596), SYSUCC validation cohort (n = 2,198), and IMIGASTRIC validation cohort (n = 504) are provided in Table 1. The mean numbers of examined LNs were 31.3 ± 12.8, 24.6 ± 11.0 and 30.0 ± 11.3 in the FJUH training cohort, SYSUCC validation cohort, and IMIGASTRIC validation cohort, respectively.

Survival of study population

In the FJUH training cohort, the median follow-up time was 56.0 months (range 1–113 months). Of the 2,596 patients, 988 patients (38.1%) died of cancer. After the median follow-up time of 59.0 months (range, 1–182 months) in the SYSUCC validation cohort, 767 (34.9%) of the patients died, and 595 of these 767 deaths (77.6%) were attributed to GC. Of the 504 patients in the IMIGASTRIC validation cohort, 168 patients died of cancer after the median follow-up time of 63.0 months (range, 1–176 months). The CSS probabilities for the FJUH training cohort were 87.1%, 66.7%, and 59.2% at 1, 3, and 5 years after D2 lymphadenectomy, respectively. For the SYSUCC validation cohort, the CSS probabilities were 93.0%, 74.1%, and 68.7% at 1, 3, and 5 years after gastric resection, respectively. For the IMIGASTRIC validation cohort, the CSS probabilities were 89.0%, 72.3%, and 67.6% at 1, 3, and 5 years after gastrectomy, respectively. We also assessed the conditional CSS probability of the remaining life expectancy for a certain number of years after D2 lymphadenectomy based on the number of years that had elapsed since surgery (Fig. 1a, b, and c); this analysis showed obvious survival differences based on the time elapsed since surgery. In the training and validation cohorts, the likelihood of cancer-specific death was not uniform over time; most deaths in all cohorts occurred in the first 3 years after resection (Fig. 1d, e, and f).

The CPCS for the different age groups in the training cohort are listed in Supplemental Table 1. The results show that regardless of age group, CPCS showed an increasing trend with the prolongation of postoperative survival time. At the same time, the proportion of non-cancer-related death in older patients is higher than that in young patients (Supplemental Table 2). Cox regression analysis of age and non-cancer-related deaths also showed that older patients were more likely to have non-cancer-related deaths than in younger patients in three cohorts (Supplemental Table 3).

Changes in CPCS in the training cohort

Table 2 shows that CPCS improved with increasing postoperative survival time in the training cohort. The baseline 3-year CPCS of post-gastrectomy patients (3-year CSS) was 66.7%; this value increased to 77.5% (10.8%↑) and 89.7% (23.0%↑) at 1 and 2 years after gastrectomy, respectively. The 5-year CPCS of patients immediately after gastrectomy (5-year CSS) was 59.2%; this value increased to 68.8%, 79.7%, 88.8%, and 95.1% at 1, 2, 3 and 4 years after gastrectomy, respectively.

Predicting CPCS with the conditional nomogram

Within the FJUH training cohort, the parameters of preoperative physical status, clinicopathologic features and postoperative complications were included in the univariate and multivariate analysis. Table 3 provides the univariate and multivariate Cox regression analysis results for the prediction of CSS after gastrectomy. After stepwise backward variable selection, only the following variables remained in the final model: age, tumour site, tumour size, depth of tumour invasion, number of examined LNs, number of metastatic LNs and surgical margin ($P < 0.05$). The multivariate conditional survival nomogram (Fig. 2a) was based on the final regression analysis. The nomogram predictions are shown for the 3-year and 5-year time points. In Fig. 2b and c, the slanted lines denote the 3-year and 5-year CPCS, respectively. *Validation of the Conditional Nomogram.*

Within internal validation, the concordance index of the CPCS predictions was determined to be 0.794 [95% confidence interval (CI), 0.774–0.814] and 0.789 (95% CI, 0.771–0.808) at 3 and 5 years, respectively. For the SYSUCC validation cohort, the concordance index of the CPCS prediction nomogram was 0.788 (95% CI, 0.732–0.811) and 0.785 (95% CI, 0.763–0.807) at 3 and 5 years after gastrectomy, respectively. The external validation using the IMIGASTRIC cohort resulted in a concordance index of 0.792 (95% CI, 0.740–0.844) and 0.787 (95% CI, 0.738–0.836) at 3 and 5 years, respectively. Calibration of the nomogram demonstrated that the predicted 3- and 5-year CSS rates closely correspond with the actual survival rates within a 10% margin of error (Fig. 3).

Discussion

The increasing number of postsurgical GC survivors [29] has made the simple and accurate prediction of CSS in GC patients who have undergone D2 lymphadenectomy a clinically urgent problem. Therefore, in the interest of providing individualized and accurate CSS predictions for GC patients after surgery, different kinds of nomograms for the prediction of CSS have been constructed [16,30]. However, the present study showed that the likelihood of cancer-specific death in patients after D2 lymphadenectomy for GC was not constant over time and that the majority of the patients died in the first 3 years after resection. In both the training and validation cohorts, the prognosis for GC patients generally improved as survival time increased. Therefore, we developed and externally validated a robust nomogram that incorporates an adjustment for survival duration and thus is capable of dynamically predicting the individualized CPCS for GC patients who have undergone D2 lymphadenectomy.

After backward variable selection in the Cox proportional hazards regression, only 7 variables qualified for inclusion in the final model: age, tumour site, tumour size, depth of tumour invasion, number of examined LNs, number of metastatic LNs and surgical margin. Previous studies have demonstrated that combining the AJCC TNM staging system classification with other prognostic factors can provide highly accurate predictions of CSS [9,31–33]. In the current study, we applied conditional survival methodology to patients with stage I-III GC treated with D2 lymphadenectomy. The internal validation revealed that the predictive performance of the nomogram was good for time points 3 years and 5 years post-gastrectomy. However, internal validation has a theoretical probability of overinterpretation, and external validation is most stringent when a data cohort from another country is used [15]. Therefore, we also performed external validation analyses using

Table 1
Sociodemographic and clinicopathologic characteristics of the training and validation cohorts.

Variable	FJUH Training Cohort (n = 2,596)		SYSUCC Validation Cohort (n = 2,198)		IMIGASTRIC Validation Cohort (n = 504)		*p*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Size, mm							
Mean ± SD	49.2 ± 27.3		47.4 ± 25.9		42.0 ± 29.2		<0.001
Examined LNs, No.							
Mean ± SD	31.3 ± 12.8		24.6 ± 11.0		30.0 ± 11.3		<0.001
Sex							<0.001
Female	660	25.4	696	31.7	210	41.7	
Male	1936	74.6	1502	68.3	294	58.3	
Age y							<0.001
≤44	211	8.1	380	17.3	24	4.8	
45-54	472	18.2	490	22.3	66	13.1	
55-64	921	35.5	742	33.8	123	24.4	
65-74	704	27.1	475	21.6	151	30.0	
≥75	288	11.1	111	5.1	140	27.8	
ASA score							
I	1468	56.5					
II	1076	41.5					
III-IV	52	2.0					
Depth of invasion							<0.001
Mucosa/Submucosa	570	22.0	282	12.8	154	30.6	
Proper muscle	300	11.6	260	11.8	130	25.8	
Subserosa	600	23.1	418	19.0	138	27.4	
Serosa	971	37.4	1072	48.8	70	13.9	
Adjacent organ invasion	155	6.0	166	7.6	12	2.4	
Metastatic LNs, No.							<0.001
0	891	34.3	709	32.3	234	46.4	
1-2	355	13.7	365	16.6	92	18.3	
3-6	419	16.1	422	19.2	69	13.7	
7-15	554	21.3	467	21.2	82	16.3	
≥16	377	14.5	235	10.7	27	5.4	
Tumour Site							<0.001
Lower	1141	44.0	975	44.4	188	37.3	
Upper	456	17.6	725	33.0	134	26.6	
Middle	673	25.9	409	18.6	182	36.1	
Overlapping	326	12.6	89	4.0			
Macroscopic type							
EGC	603	23.2					
AGC,Borrmann 1-3	1665	64.1					
AGC,Borrmann 4	328	12.6					
Grade							
Low	1063	40.9					
High	1401	54.0					
Gx	132	5.1					
Lymphvascular invasion							
Negative	1954	75.3					
Positive	642	24.7					
Perineural invasion							
Negative	2294	88.4					
Positive	302	11.6					
Surgical margin							<0.001
Negative	2527	97.3	2101	95.6	473	93.8	
Positive	69	2.7	97	4.4	31	6.2	
Complications							
None	2169	83.6					
I-II[a]	324	12.5					
III-IV[a]	103	4.0					
Adjuvant chemotherapy							
No	1448	55.8					
Yes	1148	44.2					
Follow-up, month							
Median	56		59		63		
Range	1–114		1–182		1–176		

Abbreviations: FJUH, Fujian Medical University Union Hospital; SYSUCC, Sun Yat-sen University Cancer Center; IMIGASTRIC, International Study Group on Minimally Invasive Surgery for Gastric Cancer; SD, standard deviation; ASA, American Society of Anaesthesiologists; LNs, lymph nodes; Gx, Grade can't evaluate; EGC, early gastric cancer; AGC, advanced gastric cancer.
[a] Clavien-Dindo classification.

two cohorts from institutions in China and Italy, and the conditional nomogram performed well when the discriminatory ability for time points 3 years and 5 years post-gastrectomy was assessed. Moreover, the calibration curve confirmed that the model was highly stable in both Chinese and Italian populations. To the best of our knowledge, this model is the first conditional tool with proven accuracy that can be applied to stage I-III GC patients treated with D2 lymphadenectomy.

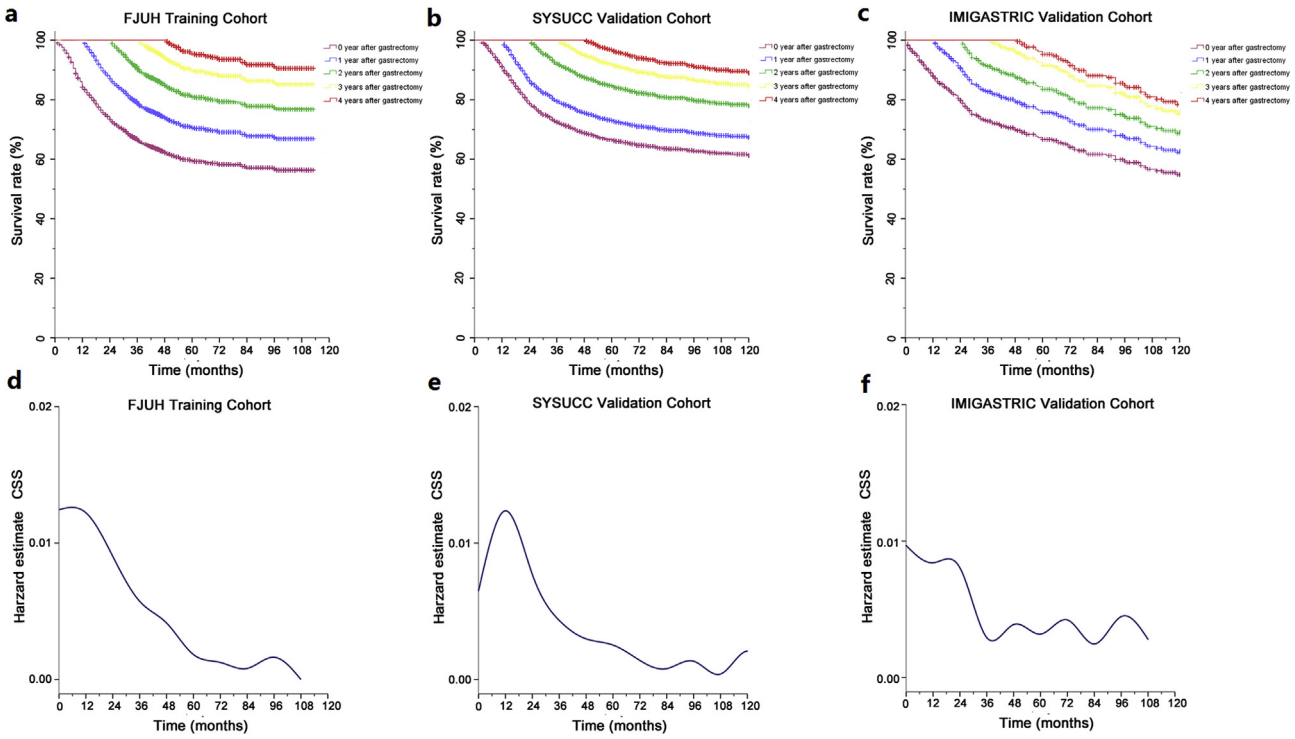

Fig. 1. Kaplan-Meier plots showing the CSS rates according to survival time after gastrectomy in the FJUH training cohort (a); the SYSUCC validation cohort (b); and the IMIGASTRIC validation cohort (c). Hazard curves showing the risk of death from GC for all patients in the FJUH training cohort (d); the SYSUCC validation cohort (e); and the IMIGASTRIC validation cohort (f).

Table 2
Conditional probabilities of cancer-specific survival at various time points in the training cohort (n = 2,596).

Alive (no deaths from gastric cancer)	3-year CPCS		5-year CPCS	
	%	95% CI (%)	%	95% CI (%)
Directly after surgery	66.7	63.9–69.5	59.2	55.8–62.7
1 year after surgery	77.5	75.2–79.8	68.8	65.7–71.9
2 years after surgery	89.7	88.1–91.3	79.7	77.1–82.3
3 years after surgery			88.8	86.8–90.9
4 years after surgery			95.1	93.7–96.6

Dikken et al. reported a conditional probability of survival nomogram for 1-, 2-, and 3-year survivors after an R0 resection for gastric cancer based on data from the United States and the Dutch [34]. The internal validation showed that the nomogram exhibits good discriminatory ability. However, Dikken's nomogram predicted the 5-year disease-specific survival only at 1, 2, and 3 years after surgery, while the new conditional survival nomogram established in this study predicted the 3- and 5-year cancer-specific survival at any time point after D2 lymphadenectomy for gastric cancer. Compared with the previous nomogram, the new conditional survival nomogram is more flexible and easier to implement in clinical practice. Furthermore, the new conditional survival nomogram has been validated by two external cohorts from China and Italy. At present, there are differences between East and West in the treatment of advanced gastric cancer (AGC) [3,35]. In East Asian countries including China, standard radical gastrectomy plus adjuvant chemotherapy has been the standard treatment for AGC for many years. European countries including Italy have more choices for neoadjuvant chemotherapy plus radical gastrectomy plus adjuvant chemoradiotherapy as a treatment model for AGC. Compared with patients with AGC in China, patients with AGC in Italy have received more neoadjuvant therapy. Since this study excluded patients receiving neoadjuvant therapy, some of the AGC patients in the Italian IMIGASTRIC cohort were excluded, so the proportion of early stage patients increased. The results of validation showed that the new nomogram has good stability and greatly enhances the universal applicability of the nomogram.

As survival time increases, the CPCS prediction model can provide clinicians and GC survivors with a more accurate prediction of prognosis than that estimated by conventional static survival approaches because CPCS takes into account a patient's changing likelihood of survival over time. By assessing the additional elapsed survival time at each follow-up period, patients may receive a survival estimate modified in real time. This estimation also merits a role in clinical practice as clinicians formulate strategies for future surveillance. Many clinicians taper the frequency of follow-up visits after 2–3 years, often without evidence to justify the appropriateness of this surveillance timeframe. However, the optimum frequency and duration of follow-up should ideally be based on the patient's death risk rather than solely on usual practice. If the prognostic evaluation is based on the postoperative CSS, then an overly pessimistic prognosis will be given to cancer survivors. Accordingly, excessively frequent follow-up may be recommended. We presumed that the frequency of follow-up can be reduced when CPCS exceeds 95%, which implies a mortality risk among cancer patients equal to that in the general population, as previously reported [36]. However, patients with a CPCS less than 90% should continue standard follow-up because these patients still have high risk of cancer-specific death. Our conditional nomogram can help clinicians determine the possibility of continued survival after a period of survival, to provide reference for an individualized follow-up strategy. At the same time, patients with a high risk of cancer-specific death should be considered for additional adjuvant chemotherapy, but further confirmation by prospective studies is

Table 3
Univariate and multivariate Cox regression analyses for the prediction of cancer-specific survival.

Variable	Univariate Analyses			Full Multivariate Cox Analyses			Reduced Multivariate Cox Analyses		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Tumour Size, mm			<0.001			0.012			0.006
Tumour Size	1.02	1.01–1.03	<0.001	1.00	1.00–1.01	0.012	1.00	1.00–1.01	0.006
No. of Examined LNs									
Examined LNs	0.99	0.99–1.00	0.010	0.97	0.97–0.98	<0.001	0.97	0.97–0.98	<0.001
Sex			0.014			0.520			
Female	Ref			Ref					
Male	1.24	1.04–1.31	0.014	1.05	0.91–1.22	0.520			
Age y			<0.001			<0.001			<0.001
≤44	Ref			Ref			Ref		
45-54	0.86	0.65–1.13	0.284	1.04	0.78–1.37	0.811	1.04	0.79–1.38	0.763
55-64	0.97	0.75–1.24	0.789	1.06	0.82–1.38	0.659	1.06	0.82–1.37	0.644
65-74	1.20	0.93–1.54	0.164	1.27	0.97–1.66	0.082	1.29	1.00–1.66	0.054
≥75	1.58	1.19–2.08	0.001	1.78	1.32–2.39	<0.001	1.78	1.34–2.36	<0.001
ASA score			0.001			0.451			
I	Ref			Ref					
II	1.19	1.04–1.35	0.010	0.96	0.84–1.10	0.579			
III	1.53	1.20–1.95	0.001	1.13	0.88–1.45	0.345			
Depth of invasion			<0.001			<0.001			<0.001
Mucosa/Submucosa	Ref			Ref			Ref		
Proper muscle	3.47	2.28–5.30	<0.001	4.07	2.05–8.07	<0.001	2.66	1.73–4.10	<0.001
Subserosa	7.68	5.35–11.02	<0.001	6.42	3.23–12.76	<0.001	4.04	2.73–5.98	<0.001
Serosa	14.50	10.25–20.5	<0.001	8.45	4.27–16.72	<0.001	5.38	3.65–7.94	<0.001
Adjacent organ invasion	22.23	15.1–32.72	<0.001	10.76	5.26–21.99	<0.001	6.99	4.52–10.79	<0.001
No. of Metastatic LNs			<0.001			<0.001			<0.001
0	Ref			Ref			Ref		
1-2	2.05	1.56–2.71	<0.001	1.24	0.93–1.65	0.149	1.23	0.93–1.64	0.155
3-6	3.62	2.86–4.58	<0.001	1.90	1.47–2.45	<0.001	1.90	1.47–2.45	<0.001
7-15	7.15	5.79–8.84	<0.001	3.29	2.57–4.2	<0.001	3.30	2.59–4.19	<0.001
≥16	11.73	9.43–14.59	<0.001	5.67	4.33–7.44	<0.001	5.73	4.40–7.46	<0.001
Tumour Site			<0.001			0.059			0.042
Lower	Ref			Ref			Ref		
Upper	1.69	1.42–2.02	<0.001	1.28	1.07–1.54	0.008	1.30	1.08–1.55	0.005
Middle	1.47	1.26–1.73	<0.001	1.13	0.95–1.33	0.161	1.13	0.96–1.33	0.138
Overlapping	2.34	1.95–2.82	<0.001	1.18	0.96–1.45	0.117	1.18	0.96–1.44	0.118
Grade			<0.001			0.590			
Low	Ref			Ref					
High	1.95	1.70–2.24	<0.001	1.06	0.92–1.23	0.417			
Gx	1.88	1.41–2.51	<0.001	1.14	0.85–1.54	0.381			
Macroscopic type			<0.001			0.128			
EGC	Ref			Ref					
AGC, Borrmann I-III	7.66	5.69–10.32	<0.001	0.62	0.35–1.11	0.109			
AGC, Borrmann IV	11.74	8.50–16.21	<0.001	0.69	0.38–1.26	0.232			
Adjuvant chemotherapy			<0.001			0.757			
No	Ref			Ref					
Yes	1.54	1.36–1.75	<0.001	1.02	0.89–1.17	0.757			
Lymphvascular invasion			<0.001			0.786			
Negative	Ref			Ref					
Positive	1.40	1.22–1.61	<0.001	1.03	0.85–1.24	0.786			
Complications			0.027			0.719			
None	Ref			Ref					
I-II[a]	1.26	1.05–1.51	0.012	1.08	0.90–1.30	0.418			
III-IV[a]	1.21	0.87–1.67	0.253	1.02	0.73–1.43	0.894			
Perineural invasion			0.001			0.408			
Negative	Ref			Ref					
Positive	1.36	1.13–1.64	0.001	0.90	0.71–1.15	0.408			
Surgical margin			<0.001			0.023			0.011
Negative	Ref			Ref			Ref		
Positive	3.82	2.90–5.03	<0.001	1.40	1.05–1.87	0.023	1.45	1.09–1.92	0.011

Abbreviations: ASA, American Society of Anaesthesiologists; LNs, lymph nodes; Gx, Grade can't evaluate; EGC, early gastric cancer; AGC, advanced gastric cancer.
[a] Clavien-Dindo classification.

needed. What's more, cancer survivors are faced with increased uncertainty about their future at a time when they need to make important life decisions [37]. Understanding the possibility of continued survival over time will help alleviate the anxiety of GC survivors and improve their quality of life, especially in those who are initially judged as having poor prognoses. This conditional nomogram is thus useful when GC survivors inquire about their prognosis after a prolonged postsurgical survival period.

Although the current study included a large number of patients with a long follow-up period and the CPCS prediction model was externally validated, we acknowledge that this study has limitations. First, our analysis was based on a retrospective study, and selection bias based on diagnoses, treatments, and follow-up is inevitable. It could not be denied that patients with GC will died of other reasons. However, due to the bias of retrospective data, other death records are still incomplete in our database. We look forward

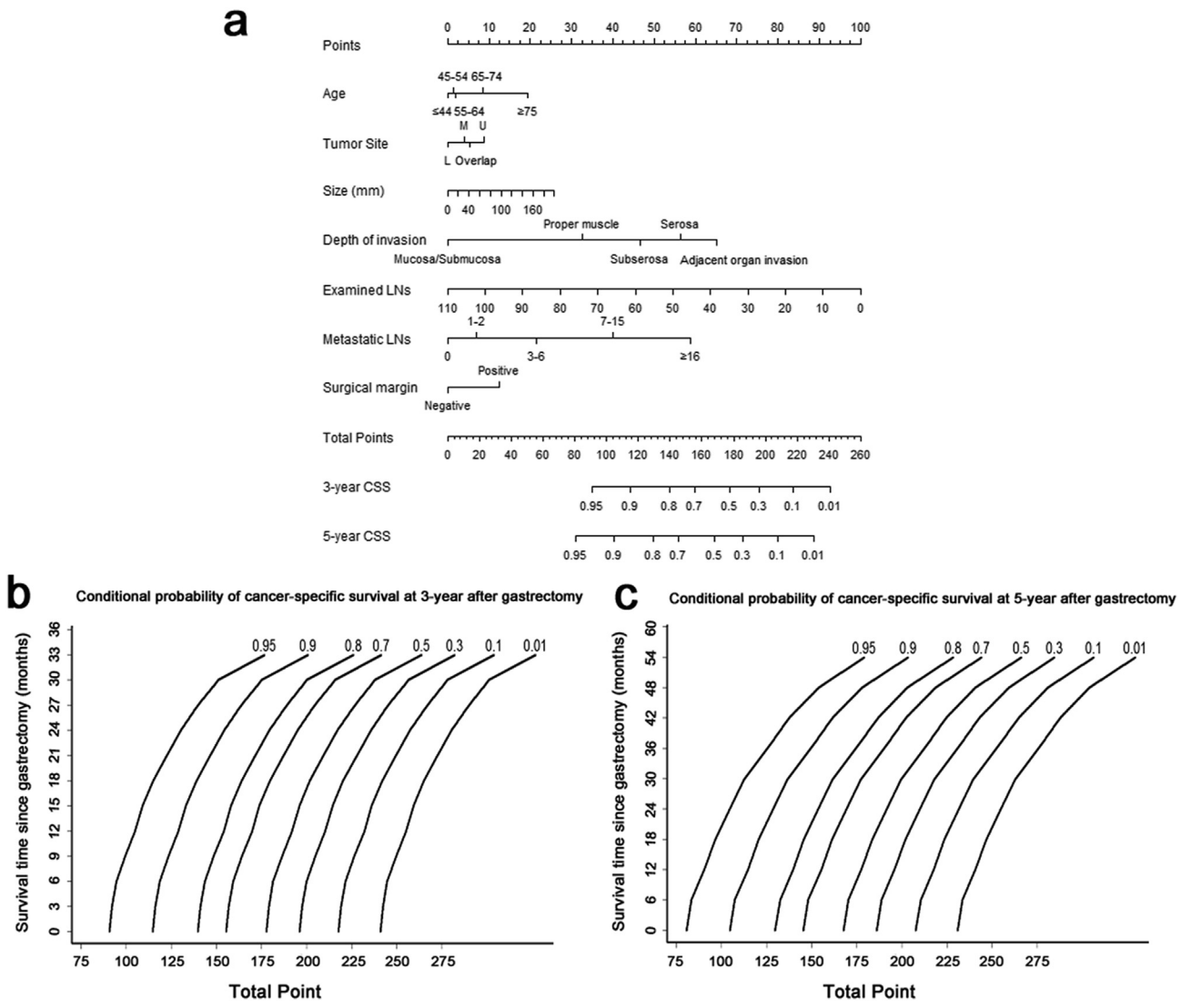

Fig. 2. Nomogram (a) and conditional probability plots (b and c) for the prediction of the individual probability of cancer-specific survival after gastrectomy are shown. To calculate CPCS on the nomogram, first, sum the points identified on the points scale for each variable. Next, choose the time point of interest after gastrectomy and draw a vertical line point on the x-axis corresponding to the total number of points. Then, draw a horizontal line from the value on the y-axis that corresponds to the survival time since gastrectomy. Finally, use the intersection of the two lines to identify a slanted line through the intersection to determine the probability of remaining free of disease-specific mortality at the prespecified number of years after gastrectomy (3 or 5 years). For example, for a patient with a total of 175 risk points calculated on the nomogram, the probability of CSS at 3 years is 53%. At 12 months after gastrectomy, the CPCS for this patient is 66%, and at 24 months after surgery, the 3-year CPCS for this patient increases to 82%.

to further establishing a CPS model for other causes of death through data from prospective studies. Second, although the current data allowed the examination of clinicopathologic factors in many patients who underwent D2 lymphadenectomy and who represent the Chinese treatment experience, we acknowledge that certain additional variables (e.g., biological markers or genes) might also provide potential prognostic information. However, these variables were not included in the nomogram because these data are not currently available at FJUH. Due to the limitations of a multicentre retrospective study, some of the institutional personnel in this study did not routinely collect detailed data about the Lauren classification; therefore, there were many missing data concerning this classification criteria. We did not include the Lauren classification in the analysis of this study because missing data would have reduced the statistical power. In addition, although the Lauren classification is of great prognostic value, the Lauren classification was also not included in the nomogram of gastric cancer established by Han et al. and Hirabayashi et al. [9,17]; the accuracy of these models has also been widely recognized [38,39]. We look forward to future prospective studies to further select more representative large-scale clinical gastric cancer data from more countries in the world, covering a wider range of clinicopathological data, including the Lauren classification and to establish a novel CPCS prediction model to better guide clinical practice. Because of the differences in treatment patterns between the East and the West, Chinese gastric cancer patients rarely receive preoperative adjuvant therapy compared with those in Europe and the United States. As is already known, preoperative adjuvant therapy has an adjuvant therapy-related downgrading effect. Postoperative pathological T stage (ypT) stage of gastric cancer patients after preoperative therapy may have different effects on prognosis compared with the same pathological T stage (pT) of patients without preoperative adjuvant therapy. The number of positive lymph nodes will also be affected by preoperative adjuvant therapy. To more accurately assess the independent prognostic factors for survival after D2 lymphadenectomy in patients with gastric cancer, the use

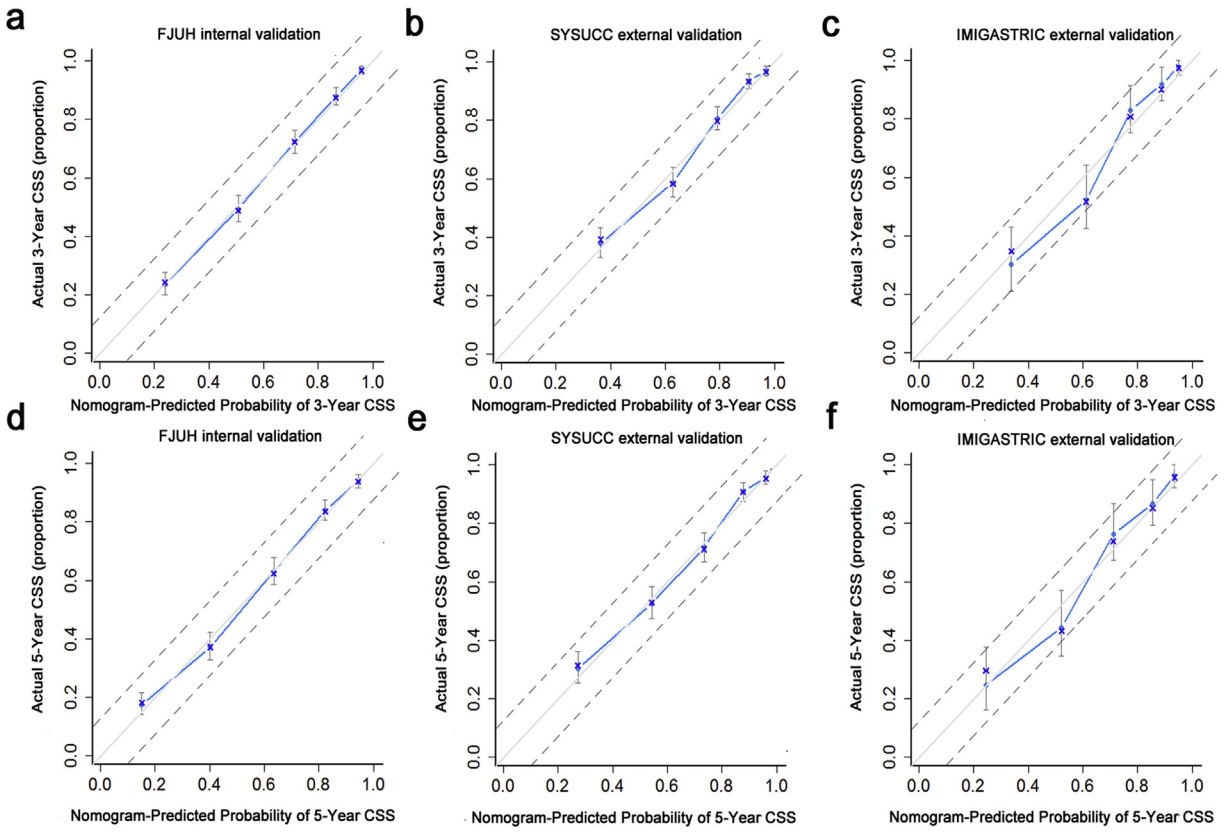

Fig. 3. Calibration of the nomogram using the training and validation cohorts is shown. The x-axis represents the nomogram-predicted CSS rate, and the y-axis represents the actual CSS rate. The 95% CIs were measured via a Kaplan–Meier analysis. All predictions lie within a 10% margin of error (within the dashed lines). The 3-year CSS rate is shown according to the FJUH internal validation cohort (a), the SYSUCC validation cohort (b); and the IMIGASTRIC validation cohort (c). The 5-year CSS rate is shown according to the FJUH internal validation cohort (d), the SYSUCC validation cohort (e) and the IMIGASTRIC validation cohort (f).

of preoperative adjuvant therapy was used as the exclusion criteria. In recent years, adjuvant chemotherapy has been recommended as a standard postoperative regimen for patients with stage II or stage III GC. [40,41] A large-scale randomized controlled trial demonstrated a survival benefit for adjuvant oral fluoropyrimidine (S-1) chemotherapy after gastrectomy with D2 lymphadenectomy [42]. However, in the current study, adjuvant chemotherapy was a nonsignificant covariate in the multivariate Cox regression model and was thus excluded from the nomogram. This may have been due to the retrospective nature of this study and since the patient cohort is relatively limited to a certain extent, this finding is not consistent with data from groundbreaking prospective clinical trials. We intend to conduct more stringent prospective studies in the future to assess the precise impact of (neo)adjuvant treatment on CSS in GC patients. What's more, data regarding adjuvant chemotherapy were not available in SYSUCC and IMIGASTRIC validation cohorts, and CPCS cannot be used to define indications to adjuvant treatments.

In summary, this study developed and externally validated a highly accurate nomogram for the prediction of CPCS in GC patients after D2 lymphadenectomy. The nomogram was supported by data from Chinese and Italian cohorts. Furthermore, this study describes the first nomogram capable of providing an individualized assessment of the conditional probability of survival for patients with GC by adjusting for survival duration after D2 resection. We believe that this nomogram will facilitate survival assessments and surveillance planning, especially in eastern Asia, where the incidence of GC is high and D2 lymphadenectomy is routinely performed.

Author contributions

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Data analysis and interpretation: Huang CM, Zhou ZW, Liu Zhi-Yu, Amilcare Parisi, Chen QY, Zhong Q, and Wang W;

Manuscript writing: Huang CM, Li P, Chen QY, and Zhong Q;

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Appendix A. Supplementary data

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Disclosure statement

None of the authors have any competing interests in the manuscript.

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