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Prognostic Nomograms for Predicting Survival in Gastric Carcinoma Patients with History of a Prior Malignancy

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Abstract

Objective: Prior malignancy is a frequent exclusion criterion in gastric carcinoma (GC) trials. However, the impact of prior malignancy on GC prognosis is not known. We aim to investigate the impact of history of a prior malignancy on overall survival (OS) and cancer-specific survival (CSS) in patients with GC, and develop nomograms for prognostic prediction of these patients using SEER database.

Methods: A total of 12676 histologically confirmed GC patients were obtained from the SEER database. Propensity-score matching (PSM) was performed to reduce potential selective bias. All matched patients were randomly divided into development (n=1155) and validation (n=1155) cohorts. We used univariate and multivariate analyses to identify the independent variables for OS and CSS. A nomogram was established based on independent prognostic factors. The prognostic performances of nomograms were validated using the concordance index (C-index) and calibration plots both internally and externally. The clinical usefulness of nomograms was compared using decision curve analysis (DCA) between nomograms and American Joint Committee on Cancer (AJCC) 7th staging system.

Results: Two nomograms were built based on the independent variables. In the development cohort, the C-indexes for the constructed nomogram to predict OS and CSS were 0.699 and 0.744, respectively. The nomograms achieved favorable discriminative ability in the validation cohort to predict OS and CSS, with C-indexes of 0.698 and 0.744, respectively, which were higher than C-indexes of the AJCC 7th staging system. The calibration plots displayed good agreement between nomogram-predicted survival probability and the actual observed outcomes. Furthermore, DCA indicated that the nomograms offered advantage over the AJCC staging system with bringing more clinical net benefit.

Conclusions: The novel proposed nomograms based on history of a prior malignancy can more effectively prediction the individualized probability of OS and CSS in patients with GC than the AJCC staging system, and the predictive power can help clinicians formulate suitable individual treatment and conduct personalized prognostic evaluation.

Keywords: nomogram; prior malignancy; gastric carcinoma; survival

1. Introduction

Gastric carcinoma (GC) is remains the fifth most commonly diagnosed malignancies and second dominant cause of cancer-related death in the world, and its incidence and mortality are increasing yearly[1]. Every year, around one million newly diagnosed cancer cases occur and nearly 7,00,000 individuals die of GC[2].

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Despite the rapid advances in surgical techniques and chemotherapy regimens, patients with GC still suffer from a poor 5-year OS of 28% depending on the depth of tumor invasion and nodal metastasis[3]. Therefore, the accuracy of survival prediction for patients with GC is crucial for treatment decisions and surveillance. GC is a heterogeneous disease, and many prognostic factors influence the prognosis of the cancer including tumor stage, tumor size, grade, and patients' performance status. The presence of prior cancer may influence the outcome of the disease[4]. In cancer clinical trials, a history of prior malignancy is a common

exclusion criterion5-7. Most clinical trials involving GC patients consider a "history of a prior malignancy" as an exclusion criterion8-10. Therefore, patients of this population are usually underrepresented in clinical trials. The exclusion of patients with prior malignancy from clinical trials mainly expresses concerns that a prior malignancy could influence study perform or prognosis. However, there are no available studies investigating OS and CSS in GC patients with a prior malignancy, and formulating new prognostic models.

Thus, in the present study, we use data derived from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, which is an open registry database that records recent incidence, prevalence, mortality, and survival cancer statistics, to investigate the impact of history of a prior malignancy on OS and CSS in GC patients, and to formulate new prognostic models through developing and validating nomograms. Then, according to the established nomograms, a comparison with the AJCC 7th staging system was performed.

2. Methods

Study population and inclusion criteria

The SEER database is a national cancer collaboration program, which comprises 18 population-based cancer registries and covers about 28% of US population across different geographic regions11. The study population was composed of patients diagnosed with GC between 2004 and 2015 from the SEER database. National Cancer Institute SEER*Stat software (version 8.3.5) was used to identify eligible patients. The SEER database was searched identifying ICD-0-3 site recode for "stomach", and the histological type codes was limited to 8140-8389 (adenomas and adenocarcinomas) for GC. Prior cancer was identified using the SEER variable sequence number. We excluded cases that had the following criteria: (1) with a history of more than one primary malignancy before GC, a history of another primary gastrointestinal malignancy ; (2) a history of a prior cancer diagnosed within 6 months before GC; (3) the diagnosis was not histologically confirmed; (4) the patients were <18 years; (5) exact nodes examined and regional nodes positive status unknown; (6) surgery status unknown; (7) cause of death unknown; (8) follow-up time less than one month; (9) complete information of race, grade, SEER stage, TNM stage, tumor size, AJCC stage. Finally, the final cohort consisted of 12676 patients. Institutional review board approval was not necessary in the present study since the SEER research data is publicly available for free use at https://seer.cancer.gov/.

Prognostic variables

The following information was collected for each patient: age at diagnosis, gender, race, marital status, SEER stage, tumor size, surgery status, histological grade, primary T category, primary N category, primary M category, AJCC stage, number of nodes examined and regional nodes positive, follow-up information and cause of death. Due to changes in AJCC 7th TNM staging coding, AJCC 6th staging was recoded accordingly. Log odds of positive lymph nodes (LODDS) has been confirmed as an independent prognostic factor in GC, which was calculated by log[(regional nodes positive + 0.5)/(total lymph nodes − regional nodes positive negative + 0.5)12,13. Lymph node ratio (LNR) was defined as the ratio of positive retrieved lymph nodes to total number of retrieved lymph nodes14. Patient age, tumor size, LNR, and LODDS were stratified into different groups (Figure 1), using the X-tile program to achieve the optimal cut-off points15. The identified cut-off value of LODDS was -0.86 and 0.16 via the X-tile. The LNR was divided into three groups, <0.09, 0.09-0.59, ≥0.6. And the age was divided into three groups, <69 years, 70 to 80 years, and>81 years. The identified cut-off value of tumor size was 26 and 43mm. The primary endpoints were overall survival (OS) and cancer-specific survival (CSS). OS referred to the time interval from the initially diagnosis to death from all possible causes. CSS was measured as the time from diagnosis to death attributed to GC in the absence of other causes. Censored events referred to patients who were still alive at the time of last follow-up.

Statistical analyses

Categorical variables are presented as number and compared with Chi-square test or Fisher's exact test. Kaplan-Meier method and log-rank test were used to perform univariate prognostic analysis for OS and CSS, respectively. The hazard ratio (HR) of each factor was also calculated with its 95% confidence interval (CI). The variables determined by univariate logistic regression analysis with P<0.05 were considered as candidates for the multivariate logistic analysis. In an observational study, selection bias is a common concern. Propensity-score matching (PSM) helps to heighten causal arguments in retrospective data by reducing the inherent selection bias16,17. Previous study revealed that a PSM using 1:1 nearest

neighbor matching can contributes to reduce bias and high accuracy18. In this study, PSM was used to adjust for age at diagnosis, sex, race, marital status, SEER stage, surgery status, histological grade, LODDS, LNR, and tumor size within the caliper of 0.001. Since N stage and AJCC staging system are associated with LODDS, thereby did not included in PSM. After PSM, the match cohort was randomly divided two cohorts in a 1-to-1 ratio, forming a development cohort and a validation cohort, to build and validate the nomograms predicting 1-, 3-, 5-, and 10 year OS and CSS, respectively. The nomogram was 1000-bootstrapped validated by measuring discrimination and calibration curves both in development and validation cohorts. The concordance index (C-index), which measures the differences in predictive ability between observed and nomogram-predicted result, was used to evaluate the discrimination of nomograms. The DCA, which is a novel method that evaluates predictive models from the perspective of clinical consequences, was performed to evaluate the clinical useless of the models. The threshold probability is where the expected benefit of treatment balances the expected benefit of avoiding treatment. Statistical analyses were all performed using R software (v3.5.1, http://www.r-project.org). A two-tailed P-value < 0.05 was considered statistically significant.

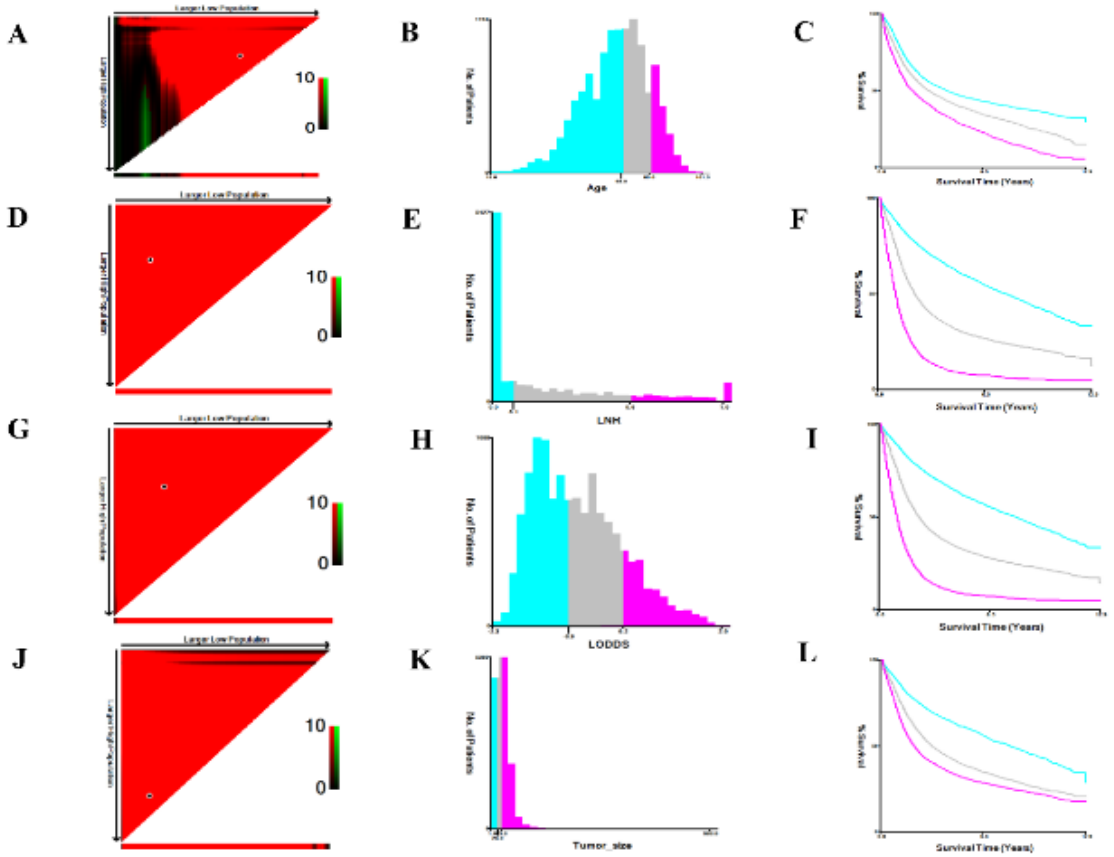

Figure 1. **The graphs show defining the optimal cutoff values of LODDS, LNR, age, and tumor size via X-tile analysis. The black dot demonstrates that optimal cut-off values have been identified (A, D, G, J). A histogram (B, E, H, K) and Kaplan–Meier (C, F, I, L) were built according to the identified cut-off values. Abbreviations: LODDS, the log odds of positive lymph nodes; LNR, lymph node ratio**

3. Results

Clinical characteristics

The study identified 12,676 patients with GC. Patients with a prior malignancy were present in 1157(9.13%) among patients with GC. The matched population analysis comprised 2310 patients, 1155 with a prior malignancy and 1155 patients without a prior malignancy. Baseline characteristic of all GC patients as well as of the matched cohorts are in Table 1. There was significant difference between two groups with respect to age, sex, marital status, SEER stage, Grade, AJCC stage, TNM classification, LODDS, LNR, and tumor size (all P<0.05). The baseline characteristics between two groups after

PSM were balanced in all factors, except for T and N classification. The matched cohort was then divided into the development cohort (1155 patients) and the validation cohort (1155 patients). The demographic features and clinicopathological characteristics between the two groups were comparable (Table 2).

Prognostic factors and Nomograms construction

The univariate and multivariate Cox regression analysis were performed to identify prognostic factors of OS and CSS in the development cohort. Initially, except for sex, all factors were significantly correlated with OS in the univariate analysis (P<0.01, Table 3). After adjusting for other risk factors, the multivariate Cox analysis revealed that age at diagnosis, marital status, T stage, grade, LNR, surgery status, and prior malignancy all remained independently associated with OS. Particularly, the OS statistically differs in patients with a prior malignancy (hazard ratio [HR] = 0.6285, 95%CI = 0.53565–0.7374, P =1.22E-08) compared to those without a history of prior malignancy. Moreover, CSS was also better in patients with a prior malignancy (HR = 0.5457, 95% CI = 0.4455–0.6686, P =4.99E-09) compared to those without a prior malignancy. Then nomograms for predicting 1-, 3- , 5- and 10-year OS were built based on these risk factors in the development cohort (Figure 2A). Nine variables

Table 1. **Baseline characteristics of the entire and matched propensity score–matched cohort according to prior malignancy**

	Entire cohort (N=12676)			Propensity score–matched cohort (N=2310)		
Characteristics	Patients without a prior malignancy(N=11519)	Patients with a prior malignancy(N=1157)	P-value	Patients without a prior malignancy(N=1155)	Patients with a prior malignancy(N=1155)	P-value
Age			<0.001			0.20291
≤69 years	6341	559		583	559	
70-80 years	3482	441		400	440	
≥81 years	1696	157		172	156	
Race			0.1137			0.78114
Black	1483	160		160	159	
White	7479	770		755	769	
Other	2557	227		240	227	
Sex			0.0297			0.82306
Female	4001	365		369	364	
Male	7518	792		786	791	
Marital status			0.0068			0.72156
Unmarried	4195	375		366	374	
Married	7324	782		789	781	
SEER stage			<0.001			0.91302
Localized	3377	509		513	507	
Regional	6756	590		588	590	
Distant	1386	58		54	58	
T stage			<0.001			0.00281
T1	2377	369		307	367	
T2	3745	424		403	424	
T3	2263	178		213	178	
T4	3134	186		232	186	
N stage			<0.001			0.00301
N0	4287	583		606	581	
N1	3789	383		314	383	
N2	2003	129		143	129	
N3	1440	62		92	62	
M stage			<0.001			0.91647
M0	10357	1112		1109	1110	
M1	1162	45		46	45	
Histological grade			0.00001			0.1671
Grade I	709	93		98	92	

Grade II	3776	440		411	440	
Grade III	6787	611		621	610	
Grade IV	247	13		25	13	
AJCC stage			<0.001			0.13307
I	3395	526		487	524	
II	2892	304		289	304	
III	3952	278		324	278	
IV	1280	49		55	49	
Tumor size (mm)			<0.001			0.47592
≤25mm	2938	380		385	379	
26-65mm	2960	307		282	307	
≥66mm	5621	470		488	469	
LODDS			<0.001			0.8711
<-0.86	5282	672		676	671	
-0.86~0.16	4316	389		378	388	
≥0.16	1921	96		101	96	
LNR			<0.001			0.86114
<0.09	5632	727		732	725	
0.09~0.59	3943	332		321	332	
≥0.6	1944	98		102	98	
Surgery			0.0173			1
None	109	3		3	3	
Yes	11410	1154		1152	1152	

ere also independent predictive variables for CSS. These prognostic factors were age, marital status, T stage, N stage, grade, LNR, surgery status, and prior malignancy (Table 4). A nomogram for predicting 1-, 3- , 5- and 10-year CSS was established based on the nine risk factors (Figure 2B). By adding the scores for each selected variable, the risk of patient individual survival can be easily calculated.

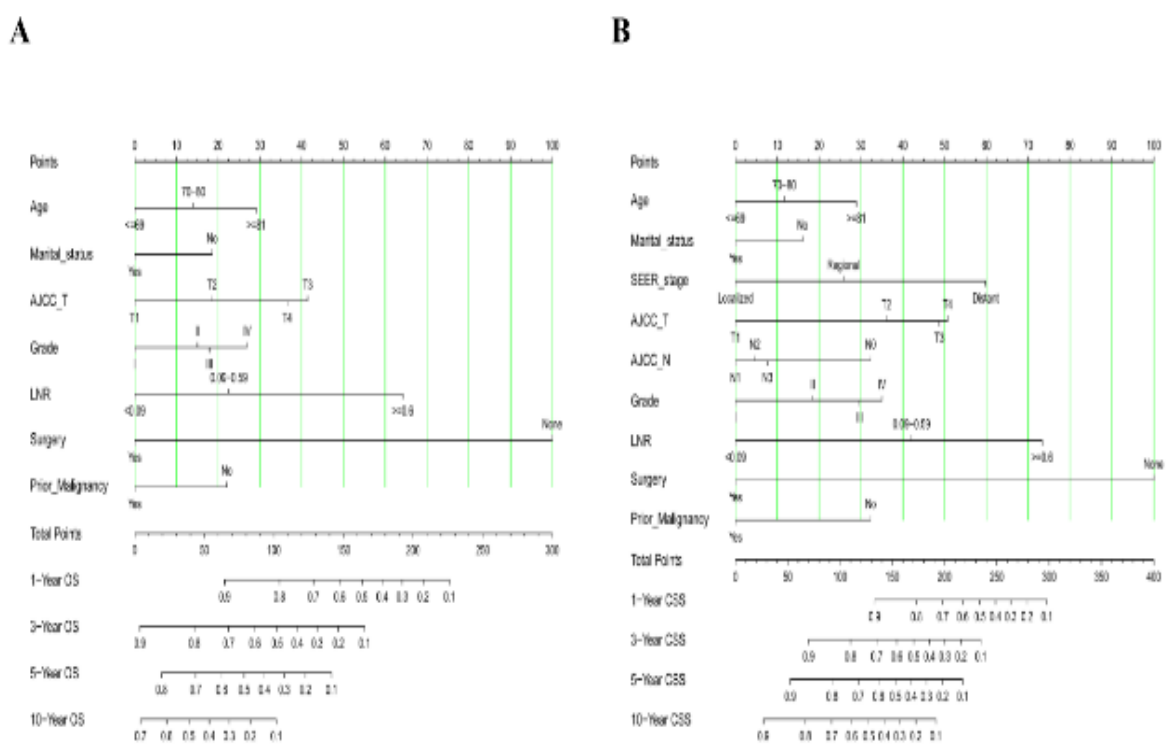

Figure 2. **Nomogram for predicting 1-, 3-, 5- and 10-year overall survival (A) cancer-specific survival (B) of patients with gastric carcinoma.**

Table 2. **Clinicopathological characteristics of gastric cancer patients in the development cohort and validation cohort**

Characteristics	Development cohort (N=1155)	Validation cohort (N=1155)	P value
Age			0.05522
≤69 years	569	573	
70-80 years	403	437	
≥81 years	183	145	
Race			0.20608
Black	163	156	
White	743	781	
Other	249	218	
Sex			0.84747
Female	369	365	
Male	786	791	
Marital status			0.78845
Unmarried	367	373	
Married	788	782	
SEER stage			0.42999
Localized	514	506	
Regional	579	599	
Distant	62	50	
T stage			0.17836
T1	355	319	
T2	409	418	
T3	199	192	
T4	192	226	
N stage			0.39956
N0	606	593	
N1	314	348	
N2	143	133	
N3	92	81	
M stage			0.33564
M0	1105	1114	
M1	50	41	
Histological grade			0.5212
Grade I	94	96	
Grade II	410	441	
Grade III	630	601	
Grade IV	21	17	
AJCC stage			0.26658
I	514	497	
II	293	300	
III	288	314	
IV	60	44	
Tumor size (mm)			0.77724
≤25mm	390	374	
26-65mm	292	297	
≥66mm	473	484	
LODDS			0.76759
<-0.86	665	682	
-0.86-0.16	389	377	
≥0.16	101	96	

LNR			0.95409
<0.09	728	729	
0.09-0.59	325	328	
≥0.6	102	98	
Surgery			0.102
None	5	1	
Yes	1150	1154	
Prior malignancy			0.22757
No	563	592	
Yes	592	563	

Table 3. **Univariate and multivariate analyses of prognostic characteristics associated with overall survival of patients with gastric carcinoma in the development cohort**

	Univariate analysis		**Multivariate analysis**	
Variables	**HR(95%CI)**	**P value**	**HR(95%CI)**	**P value**
Age				
≤69 years	1(Reference)		1(Reference)	
70-80 years	1.209(1.018-1.435)	3.03E-02	1.3365(1.12086-1.5938)	0.00124
≥81 years	1.768(1.436-2.177)	7.91E-08	1.8683(1.49093-2.3413)	5.66E-08
Race				
Black	1(Reference)		1(Reference)	
White	0.8971(0.7224-1.1141)	0.326	1.0186(0.81317-1.2759)	0.87271
Other	0.7195(0.5523-0.9372)	1.47E-02	0.8666(0.65753-1.1421)	0.30938
Sex				
Female	1(Reference)			
Male	1.053(0.8924-1.242)	0.543		
Marital status				
Unmarried	1(Reference)		1(Reference)	
Married	0.7289(0.621-0.8555)	0.000109	0.6759(0.56436-0.8095)	2.07E-05
SEER stage				
Localized	1(Reference)		1(Reference)	
Regional	1.843(1.565-2.170)	2.40E-13	1.1420(0.77799-1.6762)	0.49782
Distant	3.656(2.677-4.995)	3.76E-16	2.1731(0.95713-4.9339)	0.06356
T stage				
T1	1(Reference)		1(Reference)	
T2	1.669(1.362-2.045)	7.81E-07	1.2863(0.99567-1.6617)	0.05401
T3	2.585(2.000-3.341)	4.08E-13	1.6479(1.11647-2.4323)	0.01192
T4	2.864(2.270-3.612)	<2E-16	1.5607(1.04878-2.3224)	0.02818
N stage				
N0	1(Reference)		1(Reference)	
N1	1.512(1.268-1.804)	4.34E-06	0.6619(0.43606-1.0048)	0.05267
N2	2.373(1.888-2.984)	1.34E-13	0.7096(0.41116-1.2247)	0.21794
N3	3.35(2.478-4.528)	3.77E-15	0.8428(0.47137-1.5070)	0.56414
M stage				
M0	1(Reference)		1(Reference)	
M1	2.652(1.924-3.654)	2.49E-09	0.6997(0.23598-2.0744)	0.51953
Histological grade				
Grade I	1(Reference)		1(Reference)	
Grade II	1.5(1.055-2.132)	0.0239	1.4166(0.9871-2.0331)	0.05882
Grade III	1.988(1.412-2.798)	8.22E-05	1.532(1.0694-2.1947)	0.02003
Grade IV	2.657(1.381-5.114)	3.43E-03	1.6104(0.82177-3.1559)	0.16511
AJCC stage				

I	1(Reference)		1(Reference)	
II	1.671(1.373-2.034)	3.12E-07	1.2688(0.87018-1.8500)	0.21598
III	2.521(2.083-3.052)	<2E-16	1.4283(0.83503-2.4431)	0.19302
IV	3.895(2.861-5.303)	<2E-16	1.6432(0.71414-3.7807)	0.24278
Tumor size (mm)				
≤25mm	1(Reference)		1(Reference)	
26-65mm	1.421(1.152-1.752)	1.02E-03	1.0455(0.83242-1.3132)	7.02E-01
≥66mm	1.646(1.369-1.979)	1.15E-07	1.0008(0.80759-1.2402)	0.99434
LODDS				
<-0.86	1(Reference)		1(Reference)	
-0.86~0.16	1.719(1.457-2.027)	1.28E-10	1.1823(0.87743-1.5931)	0.27109
≥0.16	3.929(3.091-4.995)	<2E-16	0.1444(0.01809-1.1534)	0.06795
LNR				
<0.09	1(Reference)		1(Reference)	
0.09~0.59	1.818(1.536-2.152)	3.71E-12	1.3949(0.93062-2.0908)	0.10701
≥0.6	3.919(3.094-4.964)	<2E-16	21.8418(2.70455-176.3936)	0.00381
Surgery				
None	1(Reference)		1(Reference)	
Yes	0.07275(0.02971-0.1782)	9.73E-09	0.1627(0.06452-0.4104)	0.00012
Prior malignancy				
No	1(Reference)		1(Reference)	
Yes	0.6944(0.5954-0.8099)	3.37E-06	0.6285(0.53565-0.7374)	1.22E-08

Table 4. **Univariate and multivariate analyses of prognostic characteristics associated with cancer-specific survival of patients with gastric carcinoma in the development cohort**

	Univariate analysis		**Multivariate analysis**	
Variables	**HR(95%CI)**	**P value**	**HR(95%CI)**	**P value**
Age				
≤69 years	1(Reference)		1(Reference)	
70-80 years	1.168(0.9426-1.448)	1.55E-01	1.2711(1.0176-1.5877)	0.034557
≥81 years	1.645(1.244-2.176)	4.81E-04	1.7161(1.2702-2.3184)	4.35E-04
Race				
Black	1(Reference)		1(Reference)	
White	0.8934(0.6769-1.179)	0.4261	1.0575(0.7956-1.4056)	0.700308
Other	0.6659(0.4744-0.9348)	1.88E-02	0.8270(0.5814-1.1764)	0.290816
Sex				
Female	1(Reference)			
Male	1.102(0.8918-1.362)	0.369		
Marital status				
Unmarried	1(Reference)		1(Reference)	
Married	0.7643(0.6205-0.9413)	0.0114	0.7407(0.5934-0.9244)	7.93E-03
SEER stage				
Localized	1(Reference)		1(Reference)	
Regional	2.716(2.164-3.410)	<2E-16	1.4973(0.9112-2.4606)	0.111205
Distant	5.687(3.941-8.206)	<2E-16	3.2028(1.3196-7.7740)	0.010086
T stage				
T1	1(Reference)		1(Reference)	
T2	2.594(1.912-3.518)	8.81E-10	1.8157(1.2537-2.6297)	0.001598
T3	3.701(2.627-5.215)	7.38E-14	2.0968(1.2773-3.4423)	0.003416
T4	5.213(3.780-7.190)	<2E-16	2.2344(1.3528-3.6907)	0.001689

N stage				
N0	1(Reference)		1(Reference)	
N1	1.995(1.581-2.516)	5.64E-09	0.5203(0.3116-0.8686)	0.012473
N2	3.193(2.420-4.214)	2.32E-16	0.5034(0.2636-0.9614)	0.037583
N3	4.225(3.010-5.931)	<2E-16	0.5361(0.2718-1.0576)	0.072127
M stage				
M0	1(Reference)		1(Reference)	
M1	3.196(2.225-4.589)	3.14E-10	0.5645(0.1743-1.8283)	0.340281
Histological grade				
Grade I	1(Reference)		1(Reference)	
Grade II	1.663(1.012-2.734)	0.04474	1.4278(0.8570-2.3789)	0.171528
Grade III	2.748(1.705-4.43)	3.34E-05	1.7965(1.0908-2.9588)	0.021374
Grade IV	3.337(1.539-7.236)	2.27E-03	1.8463(0.8299-4.1076)	0.132877
AJCC stage				
I	1(Reference)		1(Reference)	
II	2.257(1.729-2.945)	2.06E-09	1.0792(0.6593-1.7664)	0.761837
III	3.732(2.899-4.805)	<2E-16	1.3486(0.6970-2.6092)	0.374494
IV	6.163(4.257-8.922)	<2E-16	1.8007(0.6714-4.8295)	0.242639
Tumor size (mm)				
≤25mm	1(Reference)		1(Reference)	
26-65mm	1.737(1.32-2.287)	8.24E-05	1.1231(0.8371-1.5068)	4.39E-01
≥66mm	2.137(1.674-2.728)	1.11E-09	1.1196(0.8501-1.4745)	0.4214
LODDS				
<-0.86	1(Reference)		1(Reference)	
-0.86~0.16	2.324(1.880-2.872)	5.91E-15	1.3169(0.8784-1.9743)	0.182775
≥0.16	5.193(3.882-6.945)	<2E-16	0.1496(0.0180-1.2466)	0.079049
LNR				
<0.09	1(Reference)		1(Reference)	
0.09~0.59	2.558(2.070-3.161)	<2E-16	1.7688(1.0468-2.9888)	0.033097
≥0.6	5.254(3.948-6.991)	<2E-16	26.4187(3.1114-224.3191)	0.002699
Surgery				
None	1(Reference)		1(Reference)	
Yes	0.07438(0.0302-0.1829)	1.52E-08	0.1643(0.0644-0.4187)	0.000155
Prior malignancy				
No	1(Reference)		1(Reference)	
Yes	0.6031(0.4954-0.7341)	4.64E-07	0.5457(0.4455-0.6686)	4.99E-09

Calibration and Validation of the Nomograms

We validated the performance of nomograms via the development cohort and the nomogram for OS yielded a C-index of 0.699(95%CI: 0.678-0.720). Internal validation via the development cohort demonstrated that the C-index of the nomograms for CSS was 0.672 (95%CI: 0.657–0.687). As for external validation cohort, C-index for the nomogram to predict OS was 0.698 (95%CI: 0.676–0.720). Moreover, C-indexes for the nomogram to predict CSS were 0.744 (95%CI: 0.720–0.768) both in the development and validation cohorts. A calibration plot along the 45-degree line in both development cohort and validation cohort would demonstrate a perfect calibration model between the bootstrap-predicted probabilities and the actual outcomes. At the same time, the calibration plots for the OS and CSS nomograms in the development cohort (Figure 3A, C) and validation cohort (Figure 3B, D) demonstrated an excellent agreement between the nomogram prediction and observed estimates for 1-, 3-, 5-, and 10-year survival. In addition, we compared the discrimination of the nomograms with that of the AJCC staging system in the development cohort. In the development cohort, the C-indexes of the AJCC stages alone for predicting OS and CSS were 0.624 (95% CI: 0.602–0.646), 0.681 (95% CI: 0.656–0.706),

respectively, which were significantly lower than the present nomograms did. Furthermore, there was still the same distinction ability in the validation cohort with C-index of 0.621 (95% CI: 0.598–0.644) for OS and C-index of 0.69 (95% CI: 0.664–0.716) for CSS. The results revealed that the nomograms discrimination for OS and CSS yielded superiority over the AJCC staging system.

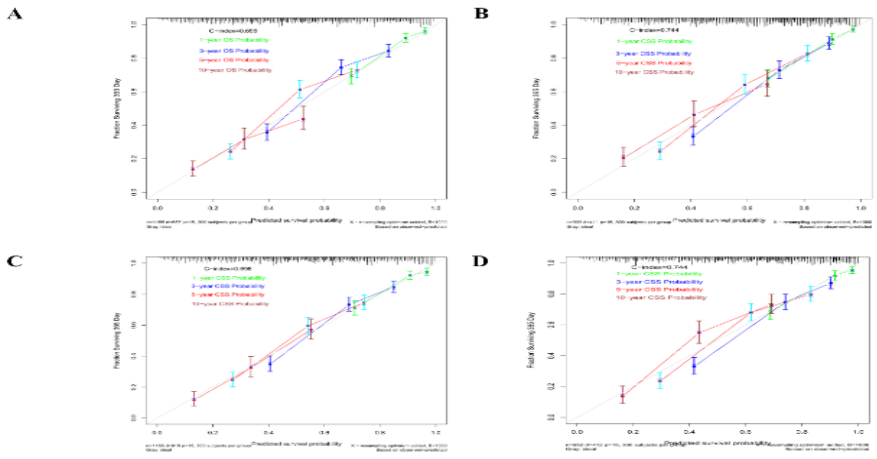

Figure 3. **Calibration curves for predicting 1-, 3- 5- and 10-year OS (A) and CSS (B) in the development cohort and validation cohort (C, D). Bootstrap-predicted survival is plotted on the x-axis, and actual outcome is plotted on the y-axis. Vertical bars indicate 95% CIs measured by Kaplan-Meier analysis. Gray lines along the 45° line through the origin point denote a perfect calibration model.**

Decision curve analysis

The clinical usefulness of nomograms was estimated using DCA by quantifying the net benefits for a range of threshold probabilities in combined development and validation cohorts[19]. In DCA, the established nomogram yielded preferable net benefit together with a wider range of threshold probability compared to the TNM staging system of the AJCC 7th edition and LNR (Figure 4), which demonstrated more robust predictive power for predicting OS and CSS at 1, 3, 5, and 10 years.

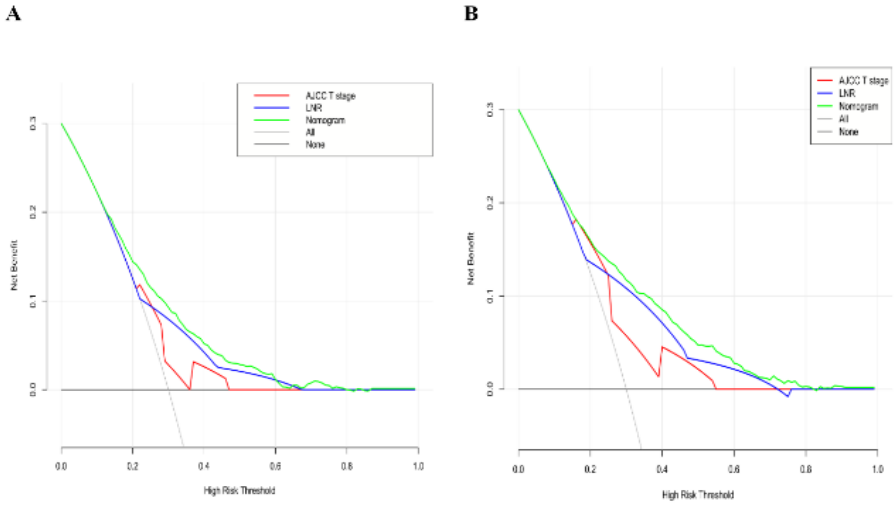

Figure 4. **Decision curve analysis of nomograms and AJCC staging system in terms of overall survival (A) and cancer-specific survival (B). The x-axis represents the threshold probability. The y-axis measures the net benefit. The threshold probability is where the expected benefit of treatment balances the expected benefit of avoiding treatment. The nomograms revealed superior net benefit to the AJCC staging system and LNR with a wide range of threshold probabilities. Abbreviations: AJCC staging system, American Joint Committee on Cancer staging system; LNR, lymph node ratio**

Survival analysis

Notably, the Kaplan-Meier curves demonstrated statistically clearly different OS and CSS (all P < 0.001) between patients with and without a prior cancer both in the development cohort and the validation cohort, demonstrating a favorable effect of prior malignancy on all-cause and gastric cancer–specific survival (Figure 5).

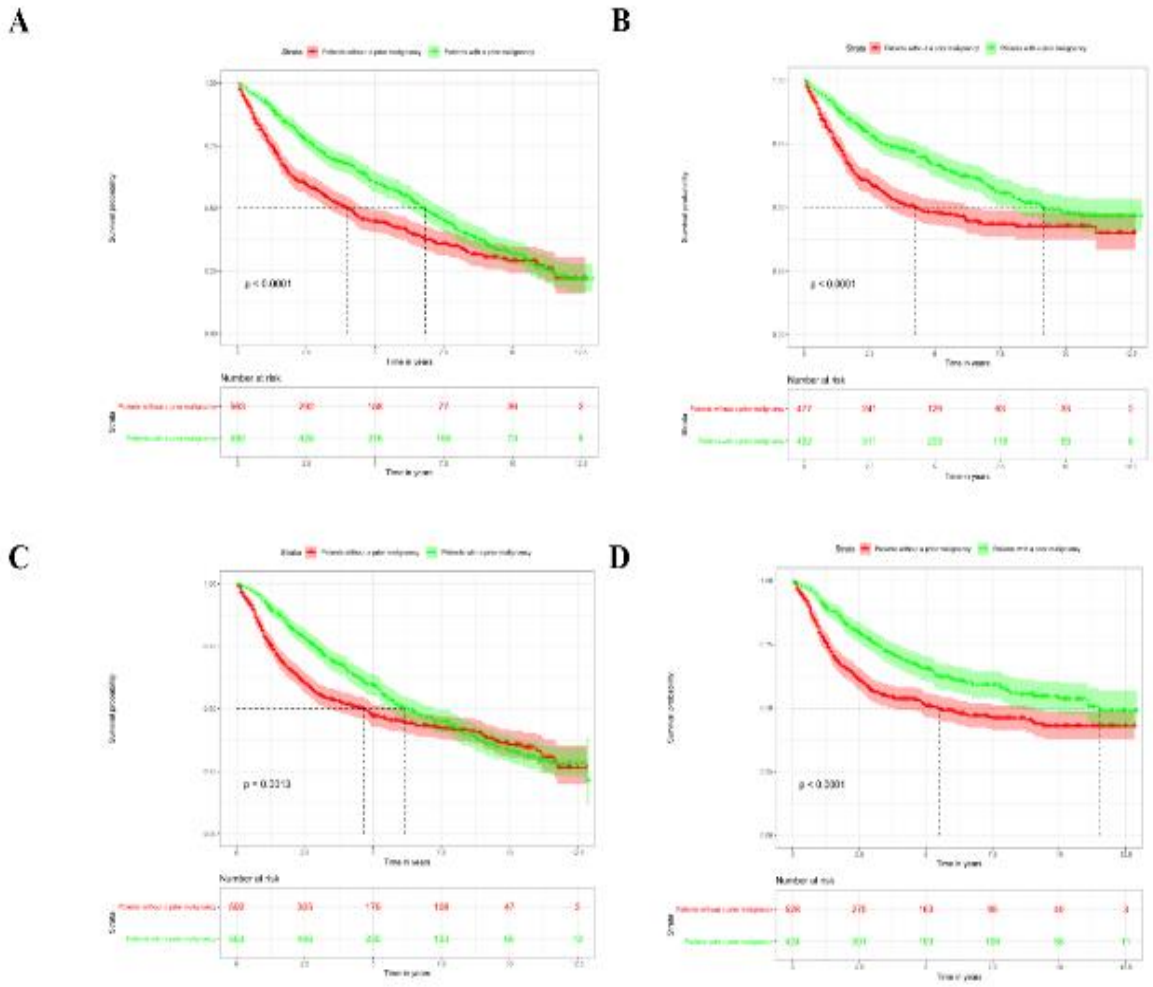

Figure 5. **Kaplan-Meier curves for OS and CSS according to history of a prior malignancy. Gastric cancer patients with history of a prior malignancy yielded good OS in the development cohort (A) and in the validation cohort (C).**

A prior cancer was associated with a better CSS in the development cohort (B) and in the validation cohort (D). Abbreviations: CSS, cancer-specific survival; OS, overall survival. Gastric overall survival and cancer-specific survival were better among GC patients with a prior malignancy.

4. Discussion

The assumption that a prior malignancy diagnosis may interfere with study conduct or outcomes has resulted in widespread exclusion of patients with prior malignancy from clinical trials across various cancer types20. In the field of gastric cancer research, studies have indicated that researchers usually exclude patients with a previous history of cancer in related clinical trials with no scientific evidence supporting this practice. In this SEER-based study of more than 12,000 gastric cancer patients, 9.13% of the patients had a history of a prior malignancy. Our results showed that such medical history did have a significant effect on the overall and cancer-specific survival of GC patients. Based on the multivariate analyses and Kaplan-Meier curves, we found that a prior malignancy was associated with an increase gastric cancer-specific survival (HR=0.6285, 95%CI = 0.53565–0.7374, P<0.001) and overall survival (HR= 0.5457, 95% CI = 0.4455–0.6686, P <0.001). These

results are consistent with a previous paper that studied stage IV pancreatic adenocarcinoma with prior malignancy21. It showed a better pancreatic cancer-specific survival for patients with a history of prior malignancy, while it did not cause obvious difference in overall survival (HR=0.938, 95%CI=0.880–1.000, P=0.052). A clinical trial in UK studied 697 gastrointestinal cancers (colorectal, pancreatic, hepatocellular, and esophagogastric cancer). However, it reported that overall and gastrointestinal CSS were comparable for gastrointestinal cancer patients with/without a prior malignancy5. For GC, such study was still missing. The findings of our study concluded opposed view in GC. This can be ascribed to that patients with a past medical history tend to more cautious about their health or obtaining a more strict screening and care. The past treatments that patients may have received while treating their first cancer might interfere and probably affect the effectiveness of the subsequent treatment. However, more studies are needed to confirm this result and objectively explore the underlying causes.

The present study found that a previous history of cancer was an independent prognostic factor for patients with GC, and we established two nomograms incorporating history of prior cancer to predict 1-, 3-, 5-, and 10 year OS and CSS for GC patients. It demonstrated superior predictive ability compared to the AJCC staging system alone. Discrimination and calibration of the nomograms were verified both internally and externally, and the results showed that the prognostic models have considerable performance. Furthermore, DCA and model comparison illustrated that the nomograms obtaining more clinical net benefit were superior to the AJCC staging system across a wide range of threshold probability, which provided beneficial prognostic tools for guiding and potentially design therapeutic strategies.

It was known that nomograms are commonly used as prognostic tools in oncology and medicine. It provided individual predicts of future clinical outcomes by combining the effects of various variables associated with these events. As far as we know, this is the first clinical prediction model incorporated history of a prior malignancy to predict GC survival. Recently, it was revealed that the current AJCC TNM staging system gradually lose its advantage in prognosis prediction22. Many practical and reliable alternative nodal scoring models have been proposed aiming to predict the survival of patients with GC. A recent study performed in China compared the prognostic abilities of TNM staging system, LNR, and LODDS. It was revealed that all the three staging systems were independent prognostic factors for GC patients, and LODDS seemed to be the best predictor of overall survival23, which was similar to our results in GC patients with history of a prior malignancy.

The present analysis is based on the data collected from the SEER database, which is a population-based surveillance system that limits the possibility of selection bias. Moreover, we performed PSM to reduce potential selective bias. Besides, SEER database provides data in many clinical variables including tumor size, grade, histology, AJCC stage, surgery status, and lymph node status that allow for further analysis of potential risk factors and prediction of cancer-specific survival. Although the nomograms have good performance, several limitations also deserved mention. First, the study was limited by the availability of data in the registries. For instance, systemic therapies, treatment regimens, and information chemotherapy are not well covered in the database. Another limitation is the absence of necessary information to determine whether previous cancers were treated, untreated, or incompletely treated before the gastric malignancy.

5. Conclusion

In summary, history of a prior malignancy is an independent prognostic factor for patients with GC. A prior malignancy was associated with an increase gastric overall and cancer-specific survival. The nomograms based on prior malignancy history demonstrated an accurate and powerful predictive ability than the AJCC staging system for predicting OS and CSS in patients with GC. These nomograms can contribute to clinicians formulate suitable individual treatments and conduct personalized prognostic evaluation.

Data statement

The raw data of this study are derived from the SEER database, which is a publicly available database. All detailed data included in the study are available at https://seer.cancer.gov/

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Institutional review board approval was not necessary in the present study since the SEER

research data is publicly available for free use at https://seer.cancer.gov/

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References

[1] Fitzmaurice C, Dicker D, Pain A, et al. The Global Burden of Cancer 2013. JAMA oncology. 2015;1(4):505-527.

[2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA: a cancer journal for clinicians. 2016;66(2):115-132.

[3] Posteraro B, Persiani R, Dall'Armi V, et al. Prognostic factors and outcomes in Italian patients undergoing curative gastric cancer surgery. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2014;40(3):345-351.

[4] Saad AM, Al-Husseini MJ, Elgebaly A, Aboshady OA, Salahia S, Abdel-Rahman O. Impact of prior malignancy on outcomes of stage IV esophageal carcinoma: SEER based study. Expert review of gastroenterology & hepatology. 2018;12(4):417-423.

[5] Smyth EC, Tarazona N, Peckitt C, et al. Exclusion of Gastrointestinal Cancer Patients With Prior Cancer From Clinical Trials: Is This Justified? Clinical colorectal cancer. 2016;15(2):e53-59.

[6] Gerber DE, Laccetti AL, Xuan L, Halm EA, Pruitt SL. Impact of prior cancer on eligibility for lung cancer clinical trials. Journal of the National Cancer Institute. 2014;106(11).

[7] Tournoux C, Katsahian S, Chevret S, Levy V. Factors influencing inclusion of patients with malignancies in clinical trials. Cancer. 2006;106(2):258-270.

[8] Arroyo-Martinez Q, Han WH, Eom BW, et al. The distribution pattern of metastatic lymph nodes after non-curative endoscopic resection in early gastric cancer. Journal of surgical oncology. 2018;118(8):1257-1263.

[9] Kurokawa Y, Doki Y, Mizusawa J, et al. Bursectomy versus omentectomy alone for resectable gastric cancer (JCOG1001): a phase 3, open-label, randomised controlled trial. The lancet Gastroenterology & hepatology. 2018;3(7):460-468.

[10] Zhou YX, Yang LP, Wang ZX, et al. Lymph node staging systems in patients with gastric cancer treated with D2 resection plus adjuvant chemotherapy. Journal of Cancer. 2018;9(4):660-666.

[11] Cronin KA, Ries LA, Edwards BK. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Cancer. 2014;120 Suppl 23:3755-3757.

[12] Wang J, Hassett JM, Dayton MT, Kulaylat MN. The prognostic superiority of log odds of positive lymph nodes in stage III colon cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2008;12(10):1790-1796.

[13] Kilic MO, Gundogdu SB, Ozden S, Saylam B, Tez M. The prognostic value of different node staging systems in patients with </=15 lymph nodes following surgery for gastric adenocarcinoma. Acta chirurgica Belgica. 2018;118(1):1-6.

[14] Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. Annals of surgery. 2008;247(2):365-371.

[15] Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clinical cancer research : an official journal of the American Association for Cancer Research. 2004;10(21):7252-7259.

[16] Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. Annual review of public health. 2000;21:121-145.

[17] D'Agostino RB, Jr., D'Agostino RB, Sr. Estimating treatment effects using observational data. Jama. 2007;297(3):314-316.

[18] Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biometrical journal Biometrische Zeitschrift. 2009;51(1):171-184.

[19] Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Medical decision making : an international journal of the Society for Medical Decision Making. 2006;26(6):565-574.

[20] Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual. Journal of the National Cancer Institute. 2015;107(4).

[21] Al-Husseini MJ, Saad AM, Turk T, Tabash MA, Abdel-Rahman O. Impact of Prior Malignancy on

Survival Outcomes of Stage IV Pancreatic Adenocarcinoma: SEER-Based Cohort. Journal of gastrointestinal cancer. 2018.

[22] Charlton ME, Adamo MP, Sun L, Deorah S. Bladder cancer collaborative stage variables and their data quality, usage, and clinical implications: a review of SEER data, 2004-2010. Cancer. 2014;120 Suppl 23:3815-3825.

[23] Jian-Hui C, Shi-Rong C, Hui W, et al. Prognostic value of three different lymph node staging systems in the survival of patients with gastric cancer following D2 lymphadenectomy. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2016;37(8):11105-11113.