Original Article

The incidence, risk factors and predictive nomograms for early death among patients with stage IV gastric cancer: a population-based study

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Background: Although advances in the treatment of stage IV gastric cancer (GC) patients, some patients were observed to die within 3 months of initial diagnosis. The present study aimed to explore the early mortality and risk factors for stage IV GC and further develop nomograms.

Methods: A total of 2,174 eligible stage IV GC patients were selected from the Surveillance, Epidemiology, and End Results database. Logistic regression analyses were used to determine the risk factors and develop the nomograms to predict all-cause early death and cancer-specific early death. The predictive performance of the nomograms was assessed by receiver operating characteristic curves (ROC), calibration plots and decision curve analyses (DCA) in both training and validation cohorts.

Results: Of 2,174 patients enrolled, 708 died within 3 months of initial diagnosis (n=668 for cancer-specific early death). Early mortality remained stable from 2010–2015. Non-Asian or Pacific Islander (API) race, poorer differentiation, middle sites of the stomach, no surgery, no radiotherapy, no chemotherapy, lung metastases and liver metastases were associated with high risk of both all-causes early death and cancer-specific early death. The nomograms constructed based on these factors showed favorable sensitivity, with the area under the ROC range of 0.816–0.847. The calibration curves and DCAs also exhibited adequate fit and ideal net benefit in prediction and clinical application.

Conclusions: Approximately one-third of stage IV GC patients experienced early death. These associated risk factors and predictive nomograms may help clinicians identify the patients at high risk of early death and be the reference for treatment choices.

Keywords: Gastric cancer (GC); stage IV; Surveillance, Epidemiology, and End Results (SEER); early death; nomogram

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Introduction

Gastric cancer (GC) ranks as the fifth most frequent malignancy worldwide, with over 1.03 million newly diagnosed GC cases in 2018 (1). More than 30% of GC patients are diagnosed with synchronous distant metastasis (2). GC patients with distant metastatic disease have the poor prognosis, with the 5-year survival rate of <5% and the median survival of 11–18 months (3-6).

Despite advances in treatment, and the prognosis of GC patients with metastatic disease improving in recent decades (6-9), some GC patients with distant metastatic disease die within 3 months of initial diagnosis. Understanding the risk

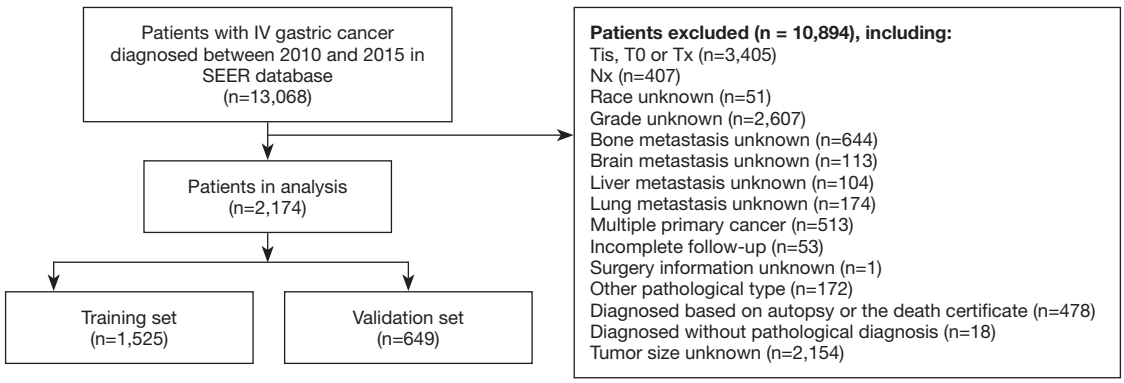

Figure 1 Flowchart of data selection from Surveillance, Epidemiology, and End Results (SEER) database.

factors associated with early mortality for GC patients with distant metastatic disease is crucial, and may assist clinicians in identifying the patients at high risk of early death as well as provide insight into treatment plan options. However, data on early death in GC patients with metastatic disease has not been well documented.

Therefore, in the present study, we used a large population-based database to evaluate the early mortality in GC patients with metastatic disease and identify the risk factors. Furthermore, based on these associated factors, nomograms were developed and validated to predict the risk of early death. We presented the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-217).

Methods

Database and patient selection

This was a retrospective study using the Surveillance, Epidemiology, and End Results (SEER) database, which covers more than 28% of the US population. The stage IV GC patients who were pathologically confirmed diagnosed from 2010 to 2015 were identified in the present study. The International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) was used to limit pathology types (8010–8231, 8255–8576) and tumor sites (C16.0–C16.6, C16.8–C16.9). The exclusion criteria were: (I) stage Tis, T0, Tx or NX; (II) unknown histological grade; (III) unknown race; (IV) unknown tumor size; (V) unknown information of distant metastases; (VI) incomplete follow-up; (VII) no primary cancer; (VIII) unknown surgery information; (IX) diagnosed based on autopsy or the death certificate; (X) other pathological types; (XI) diagnosed without the pathological diagnosis. Finally, 2,174 stage IV GC patients were included in the study and randomly divided into two cohorts (7:3): the training cohort (1,525 patients) and the validation cohort (649 patients). The process for patient selection is shown in *Figure 1*. The SEER database is an open-access cancer database that only contains de-identified patient data. Therefore, this study was exempted from the approval by the institutional review board of the First Affiliated Hospital of Soochow University.

Variables and definition of early death

Data on patients' demographic characteristics (age at diagnosis, sex, race, and year of diagnosis), tumor and treatment characteristics (tumor grade, histology type, primary tumor site, distant metastatic site, depth of invasion, lymph node metastasis, radiotherapy, chemotherapy, and surgery), and survival data (follow-up time, survival status and cause of death) were included in the analysis. All Patients were followed up for 3 months, or the date of death recorded. Age, as a continuous variable, was divided into three categories (<50, 50–70 and ≥70). Race was categorized as Asian or Pacific Islander (API) and non-API. We classified primary tumor sites into four groups: cardia (C16.0), middle site (C16.1, C16.2, C16.5 and C16.6), distal site (C16.3 and C16.4), and overlapping or not otherwise specified (NOS) (C16.8 and C16.9). The pathology types were classified into diffuse type (8020–8022, 8142, 8145 and 8490), intestinal type (8140, 8144, 8210–8211, 8260 and 8480–8481), and other. The outcomes were all-causes early death and cancer-specific early death. Early death was defined as death within 3 months following the time of initial diagnosis, according to the previous studies (10-12).

Statistical analysis

Early mortality among stage IV GC patients was calculated and stratified by year of diagnosis, and metastatic site and number of metastatic organs. Univariate and multivariate logistic regression analyses were used to determine the risk factors in the training cohort. Variables statistically significantly associated with early death on multivariate analyses were used to develop nomograms.

Based on the results of the multivariate logistic regression analyses, two nomograms were developed to separately predict the risk of all-causes and cancer-specific early death. The predictive performance of these nomograms, including their predictive accuracy and calibration, were evaluated in the training and validation cohort. Receiver operating characteristic (ROC) curves were used to measure discrimination. Calibration was assessed graphically by calibration curves, which represented the agreement between observed outcome and predicted probabilities. Decision curve analysis (DCA) was used to evaluate the clinical usefulness in all patients, which quantified the net benefits at different threshold probabilities.

Data was extracted using SEER*Stat software (version 8.3.5; http://seer.cancer.gov/seerstat/). All statistical analyses were performed using R software (version 3.5.2; http://www.r-project.org) and SPSS statistics software (version 21; IBM Corp, Armonk, NY, USA). Two-tailed P value <0.05 was considered as the level for all statistics.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Demographic and clinical characteristics

According to our inclusion and exclusion criteria (*Figure 1*), a total of 2,174 eligible patients, who were diagnosed with stage IV GC from 2010 to 2015 in the SEER database, were finally included in the study. The mean age of patients was 63.16±14.007 years. Of the patients, 65.32% of patients (N=1,420) were male. The most common site of metastasis was the liver (40.57%), followed by the brain (1.15%), lungs (12.24%), and bones (9.48%). *Table 1* shows the patients' characteristics.

Mortality and cause of early death

Among the 2,174 stage IV GC patients, 708 (32.57%) experienced all-cause early death. Of these patients, 668 patients had cancer-specific early death and 40 died from non-cancer-related causes (*Figure 2A*). Patients with non-cancer early death died from heart disease (30.00%), chronic obstructive pulmonary disease and allied conditions (10.00%), cerebrovascular disease (7.50%), septicemia (7.50%) and diabetes mellitus (5.00%) (*Figure 2B*). All-causes early mortality remained stable between 2010 and 2015 (*Figure 3A*). All-cause early mortality was highest among patients with brain metastasis (52.00%), followed by patients with lung metastasis (48.87%), liver metastasis (39.68%), and bone metastasis (39.32%) (*Figure 3B*). The risk of early mortality increased with the number of metastatic organ sites (*Figure 3C*).

Risk factors for early death

Using random assignment, 1,525 patients were enrolled into the training cohort and 649 into the validation cohort. The clinical data of these two cohorts are shown in *Table 2*. According to the univariate logistic regression analyses for the training cohort, advanced age, non-API race, poorer differentiation, middle sites of the stomach, deeper invasion, lymph node metastasis, no surgery, no radiotherapy, no chemotherapy, lung metastases, and liver metastases were significantly associated with all-causes and cancer-specific early death (*Table 3*). Besides, histological type was also observed to be significantly associated with cancer-specific early death (*Table 3*). These risk factors associated with all-causes and cancer-specific early mortality, identified in the univariate logistic regression analyses, were included in the multivariate logistic analyses, which found that non-API race, poorer differentiation, middle sites of the stomach, no surgery, no radiotherapy, no chemotherapy, lung metastases, and liver metastases were significantly associated with all-cause and cancer-specific early death (*Table 4*).

Nomogram development

Based on the results of the multivariate logistic analyses, two nomograms were developed to predict the risk of all-causes early death (*Figure 4A*) and cancer-specific early death (*Figure 4B*). The relative risk score for each risk factor is shown in *Table 5*. The steps for using the nomograms are as follows: (I) draw a straight line upwards from each predictor to the top point reference line to determine the patient's value; (II) tally up the predictive variables points; and (III) locate the final score on the total points reference line, draw a straight line to the bottom probability line

Table 1 The early death in patients with stage IV gastric cancer

Characters	Total patients (n=2,174)		No early death (n=1,466)		All-cause early death (n=708)		Cancer-specific early death (n=668)		Non-cancer-specific early death (n=40)	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Age (years)										
<50	360	16.56	282	19.24	78	11.02	73	10.93	5	12.50
50–70	1,062	48.85	767	52.32	295	41.67	278	41.62	17	42.50
≥70	752	34.59	417	28.44	335	47.32	317	47.46	18	45.00
Sex										
Male	1,420	65.32	953	65.01	467	65.96	440	65.87	27	67.50
Female	754	34.68	513	34.99	241	34.04	228	34.13	13	32.50
Race										
Non-API	1,841	84.68	1225	83.56	616	87.01	578	86.53	38	95.00
API	333	15.32	241	16.44	92	12.99	90	13.47	2	5.00
Size										
<1 cm	19	0.87	14	0.95	5	0.71	5	0.75	0	0.00
1–2 cm	95	4.37	60	4.09	35	4.94	34	5.09	1	2.50
2–3 cm	165	7.59	120	8.19	45	6.36	43	6.44	2	5.00
3–4 cm	273	12.56	191	13.03	82	11.58	76	11.38	6	15.00
4–5 cm	305	14.03	204	13.92	101	14.27	94	14.07	7	17.50
≥5 cm	1,317	60.58	877	59.82	440	62.15	416	62.28	24	60.00
Differentiation										
Well differentiated	46	2.12	36	2.46	10	1.41	10	1.50	0	0.00
Moderately differentiated	478	21.99	340	23.19	138	19.49	127	19.01	11	27.50
Poorly differentiated	1,599	73.55	1,060	72.31	539	76.13	512	76.65	27	67.50
Non-differentiated	51	2.35	30	2.05	21	2.97	19	2.84	2	5.00
Tumor subsites										
Cardia	729	33.53	525	35.81	204	28.81	188	28.14	16	40.00
Middle	586	26.95	378	25.78	208	29.38	195	29.19	13	32.50
Distal	433	19.92	287	19.58	146	20.62	143	21.41	3	7.50
Overlapping/NOS	426	19.60	276	18.83	150	21.19	142	21.26	8	20.00
Histological type										
Diffuse	567	26.08	399	27.22	168	23.73	159	23.80	9	22.50
Intestinal	1,462	67.25	976	66.58	486	68.64	457	68.41	29	72.50
Other	145	6.67	91	6.21	54	7.63	52	7.78	2	5.00

Table 1 (*continued*)

Table 1 (*continued*)

Characters	Total patients (n=2,174)		No early death (n=1,466)		All-cause early death (n=708)		Cancer-specific early death (n=668)		Non-cancer-specific early death (n=40)	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Depth of invasion										
T1, T2	689	31.69	437	29.81	252	30.59	235	35.18	17	42.50
T3, T4	1,485	68.31	1029	70.19	456	64.40	433	64.82	23	57.50
Lymph node metastasis										
N0	648	29.81	385	26.26	263	37.15	247	36.98	16	40.00
N1	869	39.97	581	39.63	288	40.68	269	40.27	19	47.50
N2	272	12.51	209	14.26	63	8.90	62	9.28	1	2.50
N3	385	17.71	291	19.85	94	13.28	90	13.47	4	10.00
Surgery										
No	1,451	66.74	902	61.53	549	77.54	519	77.69	30	75.00
Yes	723	33.26	564	38.47	159	22.46	149	22.31	10	25.00
Radiotherapy										
No	1,697	78.06	1,084	73.94	613	86.58	579	86.68	34	85.00
Yes	477	21.94	382	26.06	95	13.42	89	13.32	6	15.00
Chemotherapy										
No	748	34.41	255	17.39	493	69.63	463	69.31	30	75.00
Yes	1,426	65.59	1,211	82.61	215	30.37	205	30.69	10	25.00
Brain metastases										
No	2,149	98.85	1,454	99.18	695	98.16	655	98.05	40	100.00
Yes	25	1.15	12	0.82	13	1.84	13	1.95	0	0.00
Bone metastases										
No	1,968	90.52	1,341	91.47	627	88.56	591	88.47	36	90.00
Yes	206	9.48	125	8.53	81	11.44	77	11.53	4	10.00
Lung metastases										
No	1,908	87.76	1,330	90.72	578	81.64	546	81.74	32	80.00
Yes	266	12.24	136	9.28	130	18.36	122	18.26	8	20.00
Liver metastases										
No	1,292	59.43	934	63.71	358	50.56	335	50.15	23	57.50
Yes	882	40.57	532	36.29	350	49.44	333	49.85	17	42.50

API, Asian or Pacific Islander.

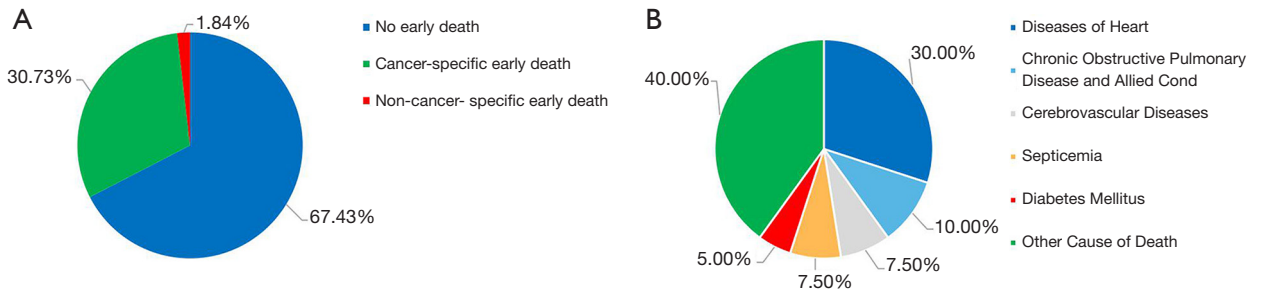

Figure 2 Distribution of the incidence of cancer-specific early death (A) and all-cause early death (B) among stage IV gastric cancer patients.

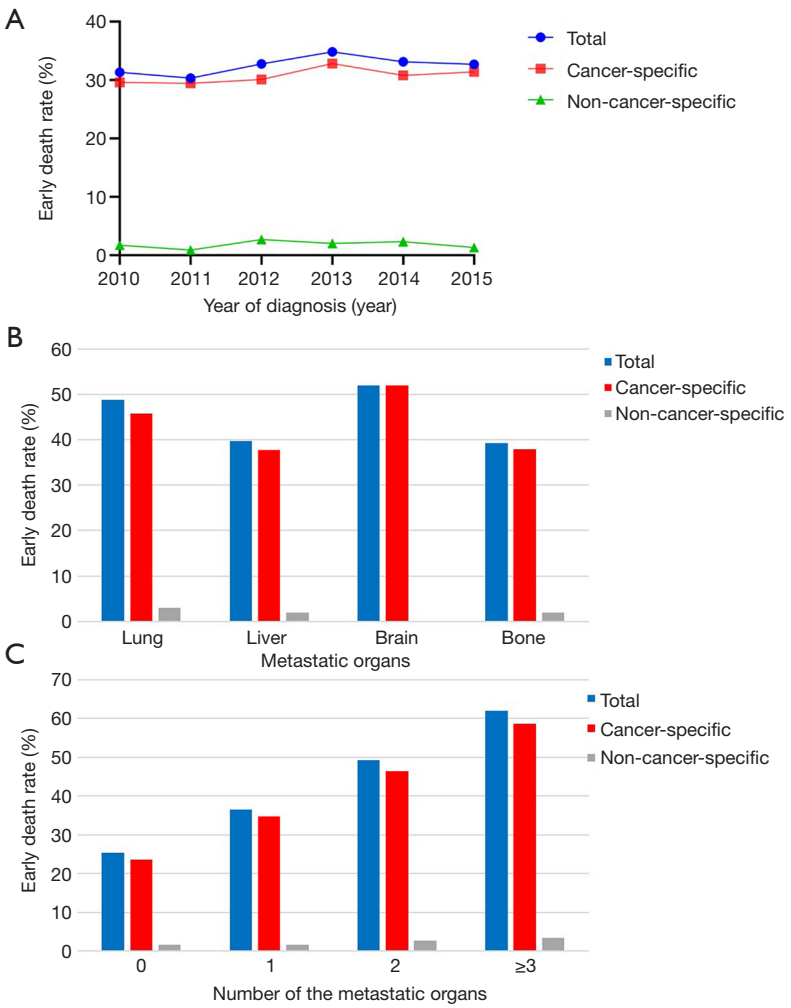

Figure 3 Distribution of early death among stage IV gastric cancer patients stratified by year of diagnosis (A), metastatic site (B) and number of the metastatic organs (C).

Table 2 The baseline characteristics of the training and validation cohorts

Characteristics	Training cohort (n=1,525)		Validation cohort (n=649)	
	No. of patients	%	No. of patients	%
Age (years)				
<50	257	16.85	103	15.87
50–70	757	49.64	305	47.00
≥70	511	33.51	241	37.13
Sex				
Male	1,003	65.77	417	64.25
Female	522	34.23	232	35.75
Race				
Non-API	1,299	85.18	542	83.51
API	226	14.82	107	16.49
Size				
<1 cm	15	0.98	4	0.62
1–2 cm	71	4.66	24	3.70
2–3 cm	116	7.61	49	7.55
3–4 cm	196	12.85	77	11.86
4–5cm	207	13.57	98	15.10
≥5 cm	920	60.33	397	61.17
Differentiation				
Well differentiated	34	2.23	12	1.85
Moderately differentiated	336	22.03	142	21.88
Poorly differentiated	1,118	73.31	481	74.11
Non-differentiated	37	2.43	14	2.16
Tumor subsites				
Cardia	497	32.59	232	35.75
Middle	419	27.48	167	25.73
Distal	299	19.61	134	20.65
Overlapping/NOS	310	20.33	116	17.87
Histological type				
Diffuse	407	26.69	160	24.65
Intestinal	1,016	66.62	446	68.72
Other	102	6.69	43	6.63
Depth of invasion				
T1, T2	481	31.54	208	32.05
T3, T4	1,044	68.46	441	67.95

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Training cohort (n=1,525)		Validation cohort (n=649)	
	No. of patients	%	No. of patients	%
Lymph node metastasis				
N0	443	29.05	205	31.59
N1	623	40.85	246	37.90
N2	192	12.59	80	12.33
N3	267	17.51	118	18.18
Surgery				
No	1,023	67.08	428	65.95
Yes	502	32.92	221	34.05
Radiotherapy				
No	1,192	78.16	505	77.81
Yes	333	21.84	144	22.19
Chemotherapy				
No	520	34.10	228	35.13
Yes	1,005	65.90	421	64.87
Brain metastases				
No	1,507	98.82	642	98.92
Yes	18	1.18	7	1.08
Bone metastases				
No	1,388	91.02	580	89.37
Yes	137	8.98	69	10.63
Lung metastases				
No	1,342	88.00	566	87.21
Yes	183	12.00	83	12.79
Liver metastases				
No	907	59.48	385	59.32
Yes	618	40.52	264	40.68

API, Asian or Pacific Islander.

to determine the patient's likelihood of metastasis. The prediction websites of the nomograms predicting the risk of all-causes of early death and cancer-specific early death are https://yyangyi.shinyapps.io/IVGC_ED_AC/ and https://yyangyi.shinyapps.io/IVGC_ED_CS/.

Nomogram evaluation

The area under the ROC curve (AUC) for the nomograms to separately predict the risk of all-causes early death and cancer-specific early death were 0.847 and 0.825, respectively, in the training cohort, and 0.835 and 0.816, respectively, in the validation cohort (*Figure 5*). Calibration curves for the two nomograms showed great agreement between predictions and observations in both training cohort and validation cohort (*Figure 6*). Additionally, the DCAs exhibited the ideal net benefits for all patients when predicting all-causes early death and cancer-specific early

Table 3 Univariate logistic regression for analyzing the risk factors for early death

Variable	All-cause early death			Cancer-specific early death		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)						
<50	1 (ref.)			1 (ref.)		
50–70	1.230	0.882–1.714	0.223	1.228	0.876–1.723	0.234
≥70	2.747	1.957–3.855	<0.001	2.671	1.893–3.768	<0.001
Sex						
Male	1 (ref.)			1 (ref.)		
Female	0.93	0.741–1.167	0.532	0.897	0.712–1.131	0.358
Race						
Non-API	1 (ref.)			1 (ref.)		
API	0.634	0.458–0.878	0.006	0.674	0.486–0.934	0.018
Size						
<1 cm	1 (ref.)			1 (ref.)		
1–2 cm	1.495	0.431–5.184	0.527	1.404	0.404–4.880	0.593
2–3 cm	1.093	0.325–3.679	0.885	1.003	0.297–3.384	0.996
3–4 cm	1.243	0.380–4.059	0.719	1.128	0.345–3.689	0.842
4–5 cm	1.316	0.404–4.287	0.648	1.231	0.378–4.012	0.731
≥5 cm	1.344	0.424–4.255	0.615	1.247	0.394–3.949	0.708
Differentiation						
Well differentiated	1 (ref.)			1 (ref.)		
Moderately differentiated	1.682	0.674–4.196	0.265	1.507	0.603–3.766	0.381
Poorly differentiated	2.393	0.982–5.830	0.055	2.235	0.917–5.445	0.077
Non-differentiated	4.421	1.483–13.179	0.008	3.967	1.329–11.838	0.014
Tumor subsites						
Cardia	1 (ref.)			1 (ref.)		
Middle	1.451	1.096–1.919	0.009	1.417	1.066–1.883	0.016
Distal	1.174	0.858–1.607	0.315	1.203	0.876–1.653	0.254
Overlapping/NOS	1.451	1.071–1.967	0.016	1.431	1.051–1.948	0.023
Histological type						
Diffuse	1 (ref.)			1 (ref.)		
Intestinal	1.083	0.845–1.389	0.529	1.07	0.832–1.378	0.597
Other	1.534	0.979–2.402	0.062	1.58	1.006–2.482	0.047
Depth of invasion						
T1, T2	1 (ref.)			1 (ref.)		
T3, T4	0.713	0.568–0.895	0.004	0.717	0.570–0.903	0.005

Table 3 (*continued*)

Table 3 (*continued*)

Variable	All-cause early death			Cancer-specific early death		
	OR	95% CI	P value	OR	95% CI	P value
Lymph node metastasis						
N0	1 (ref.)			1 (ref.)		
N1	0.756	0.588–0.972	0.029	0.736	0.571–0.949	0.018
N2	0.377	0.254–0.561	<0.001	0.394	0.264–0.588	<0.001
N3	0.372	0.262–0.529	<0.001	0.383	0.268–0.547	<0.001
Surgery						
No	1 (ref.)			1 (ref.)		
Yes	0.374	0.290–0.483	<0.001	0.374	0.288–0.486	<0.001
Radiotherapy						
No	1 (ref.)			1 (ref.)		
Yes	0.455	0.339–0.609	<0.001	0.445	0.329–0.601	<0.001
Chemotherapy						
No	1 (ref.)			1 (ref.)		
Yes	0.099	0.077–0.127	<0.001	0.112	0.088–0.144	<0.001
Brain metastases						
No	1 (ref.)			1 (ref.)		
Yes	1.691	0.663–4.311	0.271	1.827	0.716–4.658	0.207
Bone metastases						
No	1 (ref.)			1 (ref.)		
Yes	1.273	0.885–1.833	0.193	1.247	0.862–1.804	0.241
Lung metastases						
No	1 (ref.)			1 (ref.)		
Yes	2.774	2.028–3.795	<0.001	2.675	1.955–3.659	<0.001
Liver metastases						
No	1 (ref.)			1 (ref.)		
Yes	1.590	1.280–1.977	<0.001	1.593	1.278–1.986	<0.001

OR, odds ratio; ref., reference; API, Asian or Pacific Islander.

death, which showed that these nomograms had favorable clinical value (*Figure 7*).

Discussion

GC is a major cause of cancer mortality worldwide (1), and the clinical stage is one of the key factors affecting the prognosis (13-15). Although many previous studies have investigated the prognosis of patients with stage IV GC (9,16-19), little is known about early death. To the best of our knowledge, the present study is the first to explore the early mortality and associated factors among stage IV GC patients.

In the present study, we observed that 32.57% stage IV GC patients died within 3 months after the initial diagnosis, and most of these deaths were cancer specific.

Table 4 Multivariate logistic regression for analyzing the risk factors for early death

Variable	All-cause early death			Cancer-specific early death		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)						
<50	1 (ref.)			1 (ref.)		
50–70	0.814	0.544–1.217	0.316	0.835	0.557–1.252	0.384
≥70	1.130	0.741–1.723	0.571	1.147	0.750–1.756	0.527
Race						
Non-API	1 (ref.)			1 (ref.)		
API	0.606	0.401–0.915	0.017	0.666	0.444–1.000	0.050
Differentiation						
Well differentiated	1 (ref.)			1 (ref.)		
Moderately differentiated	1.868	0.623–5.599	0.264	1.575	0.537–4.621	0.408
Poorly differentiated	4.333	1.480–12.683	0.007	3.588	1.250–10.298	0.018
Non-differentiated	9.665	2.551–36.611	0.001	7.294	1.968–27.027	0.003
Tumor subsites						
Cardia	1 (ref.)			1 (ref.)		
Middle	1.620	1.125–2.332	0.009	1.539	1.071–2.213	0.020
Distal	1.433	0.924–2.221	0.108	1.467	0.949–2.266	0.084
Overlapping/NOS	1.675	1.113–2.522	0.013	1.597	1.060–2.405	0.025
Histological type						
Diffuse	1 (ref.)			1 (ref.)		
Intestinal	NA	NA	NA	0.958	0.675–1.360	0.809
Other	NA	NA	NA	1.270	0.719–2.244	0.410
Depth of invasion						
T1, T2	1 (ref.)			1 (ref.)		
T3, T4	1.12	0.819–1.531	0.477	1.111	0.815–1.515	0.506
Lymph node metastasis						
N0	1 (ref.)			1 (ref.)		
N1	0.947	0.687–1.306	0.742	0.895	0.651–1.230	0.495
N2	0.836	0.504–1.386	0.487	0.873	0.529–1.441	0.595
N3	0.769	0.474–1.250	0.290	0.817	0.504–1.326	0.414
Surgery						
No	1 (ref.)			1 (ref.)		
Yes	0.22	0.147–0.329	<0.001	0.226	0.151–0.337	<0.001

Table 4 (*continued*)

Table 4 (*continued*)

Variable	All-cause early death			Cancer-specific early death		
	OR	95% CI	P value	OR	95% CI	P value
Radiotherapy						
No	1 (ref.)			1 (ref.)		
Yes	1.491	1.032–2.154	0.034	1.55	1.071–2.243	0.020
Chemotherapy						
No	1 (ref.)			1 (ref.)		
Yes	0.078	0.057–0.106	<0.001	0.094	0.070–0.127	<0.001
Lung metastases						
No	1 (ref.)			1 (ref.)		
Yes	1.450	1.096–1.918	0.009	2.523	1.703–3.737	<0.001
Liver metastases						
No	1 (ref.)			1 (ref.)		
Yes	2.704	1.811–4.036	<0.001	1.451	1.088–1.936	0.011

OR, odds ratio; ref., reference; API, Asian or Pacific Islander.

Only 1.84% of early deaths were not cancer-specific, with heart disease being the main cause of non-cancer early death. This finding is in agreement with a Swedish study by Xie *et al.*, which found that disease of heart was one of the major causes of non-cancer death (20). Similar results have also been observed in other types of cancer, such as liver cancer, bladder cancer and breast cancer (21-24). In a recent study, Herrmann found that heart disease often occurred in the first year after the initial diagnosis (25). This might be due to the interaction between the acute cancer phase and pre-existing cardiovascular (CV) diseases, including CV risk associated with the tumor burden and potential CV toxicities of cancer therapies (25). These findings may suggest that the monitoring of heart disease in patients with stage IV GC should be improved.

We found that the early mortality of stage IV GC patients increased with the number of metastatic organ sites. Zhang *et al.* reported a similar result in GC (26). The similar result was also observed in other tumors (12,27). The prognostic significance of the number of metastatic organ sites has been linked to resistance among patients with a larger tumor burden (28). However, the SEER database only contains information on liver, lung, bone, and brain metastatic sites, and the lack of data on other metastatic sites may impair the accuracy of our findings. Therefore, our results are only preliminary and need to be interpreted with caution. Futures studies with larger sample sizes are warranted.

Although the prognosis of GC patients has been improved in recent years (8,9), we found that the early mortality remained stable during 2010–2015, which suggests that we need to pay more attention to early death and its related factors to reduce the risk of early death. Several characteristics and treatment modalities were found to be independent risk factors associated with all-cause early death and cancer-specific early death in our study, including non-API, poorer differentiation, middle sites of stomach, lung metastases, liver metastases, no surgery, no radiotherapy, and no chemotherapy.

We found that API races had a lower risk of death compared to other race, which has also been proved in many earlier studies (29-31). Jin *et al.* indicated that regular screening and earlier diagnosis among the API population might partially account for this survival advantage (32). Compared to patients of other races, API patients were considered to have a more positive attitude toward treatment (33,34). Zhang *et al.* and Ulanja *et al.* reported that the API had a higher rate of surgery and radiation than patients of other races (33,34). Aggressive treatment could effectively reduce the risk of early death (18). More researches are needed to explore the reasons behind survival differences between different races in the future.

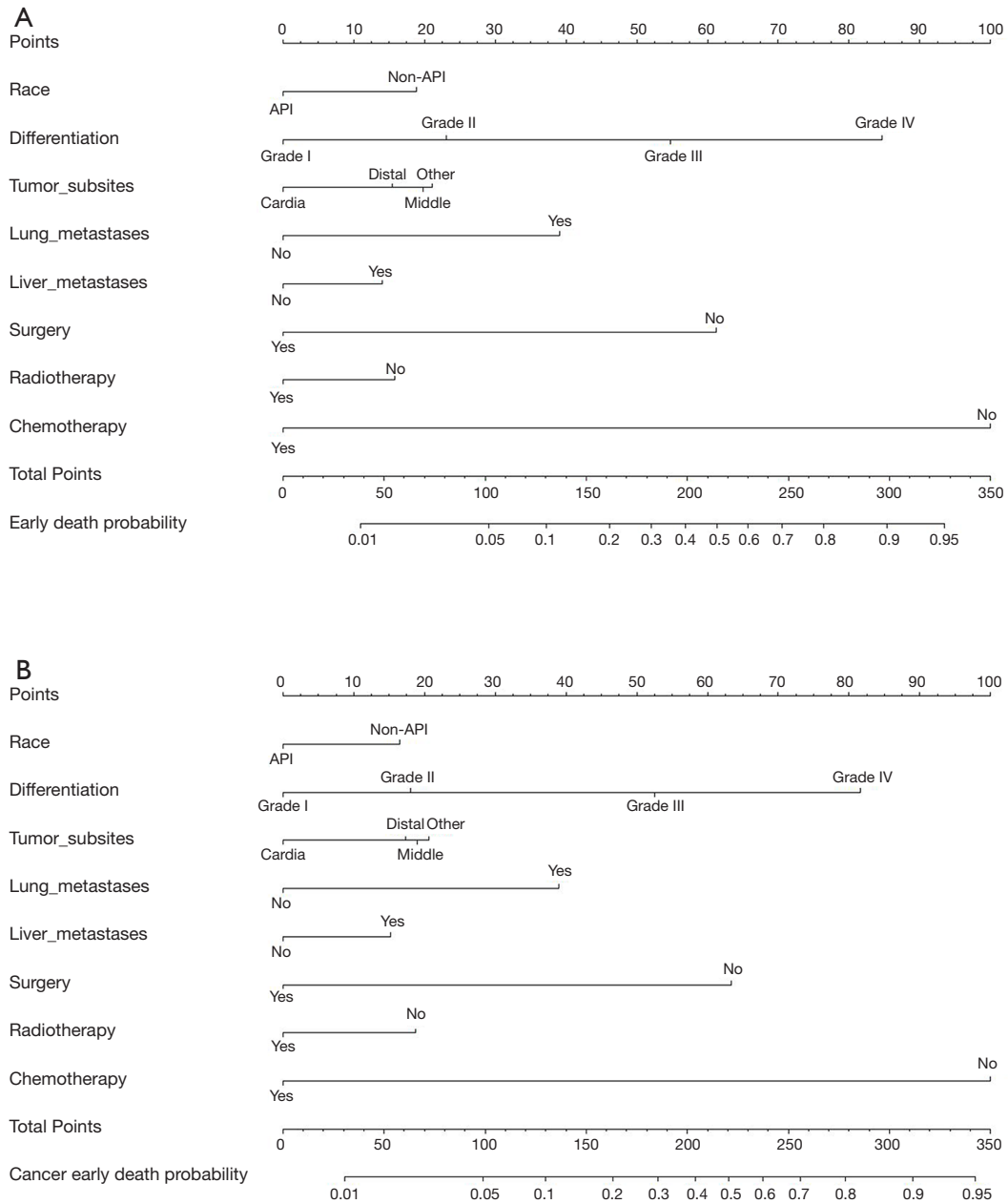

Figure 4 Nomograms for predicting all-causes (A) and cancer-specific early death (B). Other, overlapping/NOS.

The impact of surgery on the prognosis of stage IV GC patients remains controversial (3,35-39). Previous studies have reported that patients with stage IV GC could have survival benefit from the surgery (36-38). The disadvantages of surgery that can seriously affect survival, including chemotherapy delay and the increased risk of surgical-related complications, also need to be considered. The findings of the present study showed that patients who had undergone surgery could have potential survival benefits and a lower risk of early death, even with the risk of postoperative complications. However, as our study was retrospective, selection bias could exist. More prospective researches are needed to confirm this conclusion in the future.

Table 5 Point assignments and predictive scores for each variable in two nomograms

Variables	All-cause early death		Cancer-specific early death	
	Classification	Score	Classification	Score
Race	API	0	API	0
	Non-API	19	Non-API	17
Differentiation	Grade I	0	Grade I	0
	Grade II	23	Grade II	18
	Grade III	55	Grade III	53
	Grade IV	85	Grade IV	82
Tumor subsites	Cardia	0	Cardia	0
	Distal	15	Distal	17
	Middle	20	Middle	19
	Other (overlapping/NOS)	21	Other (overlapping/NOS)	21
Lung metastases	No	0	No	0
	Yes	39	Yes	39
Liver metastases	No	0	No	0
	Yes	14	Yes	15
Surgery	No	61	No	63
	Yes	0	Yes	0
Radiotherapy	No	16	No	19
	Yes	0	Yes	0
Chemotherapy	No	100	No	100
	Yes	0	Yes	0

In addition to race and surgery, other factors were also reported to be associated with prognosis in the previous studies (17,40). Ma *et al.* developed a nomogram to predict survival in patients with metastatic gastric adenocarcinoma who underwent palliative gastrectomy, based on age, tumor size, location, tumor grade, T stage, N stage, metastatic site, scope of gastrectomy, number of examined lymph nodes, chemotherapy, and radiotherapy (17). Gao *et al.* developed a nomogram for prediction of stage III/IV GC outcome after surgery based on the tumor size, age, N stage, tumor grade, and distant metastases (41). Some variables included in the nomograms in previous study were not statistically significant on multivariate analysis in our study, including age. Although age was an important clinical prognostic factor for patients with stage IV GC after surgery in the two previously mentioned studies, some studies found that age is not an independently associated factor for cancer-specific mortality in patients with stage IV GC (42). Differences among these results could be due to relatively higher perioperative mortality of the elder patients after the surgical treatment. The applicable people and the outcome which nomograms in previous studies were fit for and used to predict were different from our study, which may lead to the difference of risk factors. Considering these different variables have not been identified to be associated with the early death in GC, we did not include these variables in our nomograms.

Although several previous studies have constructed nomograms to predict the prognosis of patients with stage IV GC (17,40,41,43,44), to the best of our knowledge, no studies have developed nomograms to predict early death in patients with stage IV GC. In the present study, we developed two nomograms to predict the risk of all-cause early death and cancer-specific early death. These

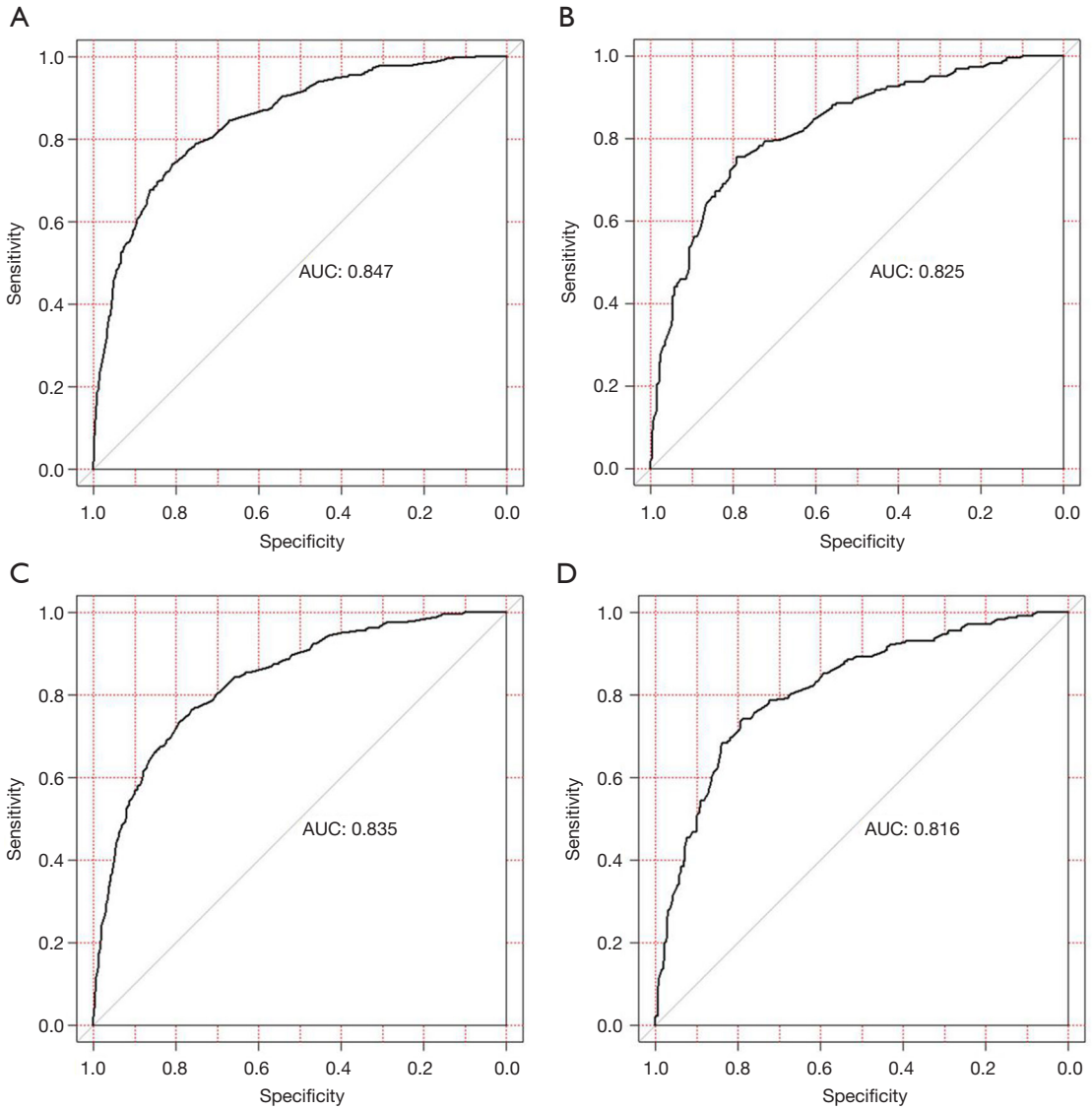

Figure 5 Receiver operating characteristic (ROC) curves for discrimination of the nomograms in predicting all-causes and cancer-specific early death in the training cohort (A, B) and the validation cohort (C, D).

nomograms were evaluated in the training and validation cohorts. Taking into account the AUCs and the calibration plots in the training and validation cohorts, these nomograms showed reliable discrimination and calibration ability. Moreover, these nomograms also showed good clinical value, as indicated by DCAs.

These nomograms are quantitative and intuitive, which are convenient to use. These simple-to-use nomograms can be used to predict real-time risk of early death in GC patients, including the patients not receiving any treatment at the time of diagnosis and patients who were currently receiving treatment. The predicted risk of early death is changed with the current treatments. Besides, these nomograms can be used to predict the risk of early death of patients if they will receive some treatments, which can assist in determining suitable treatment options. These nomograms can also improve communication of prognosis with patients and enable informed decision making. In addition, these nomograms can provide insight into the disease management and be the reference for the follow-up

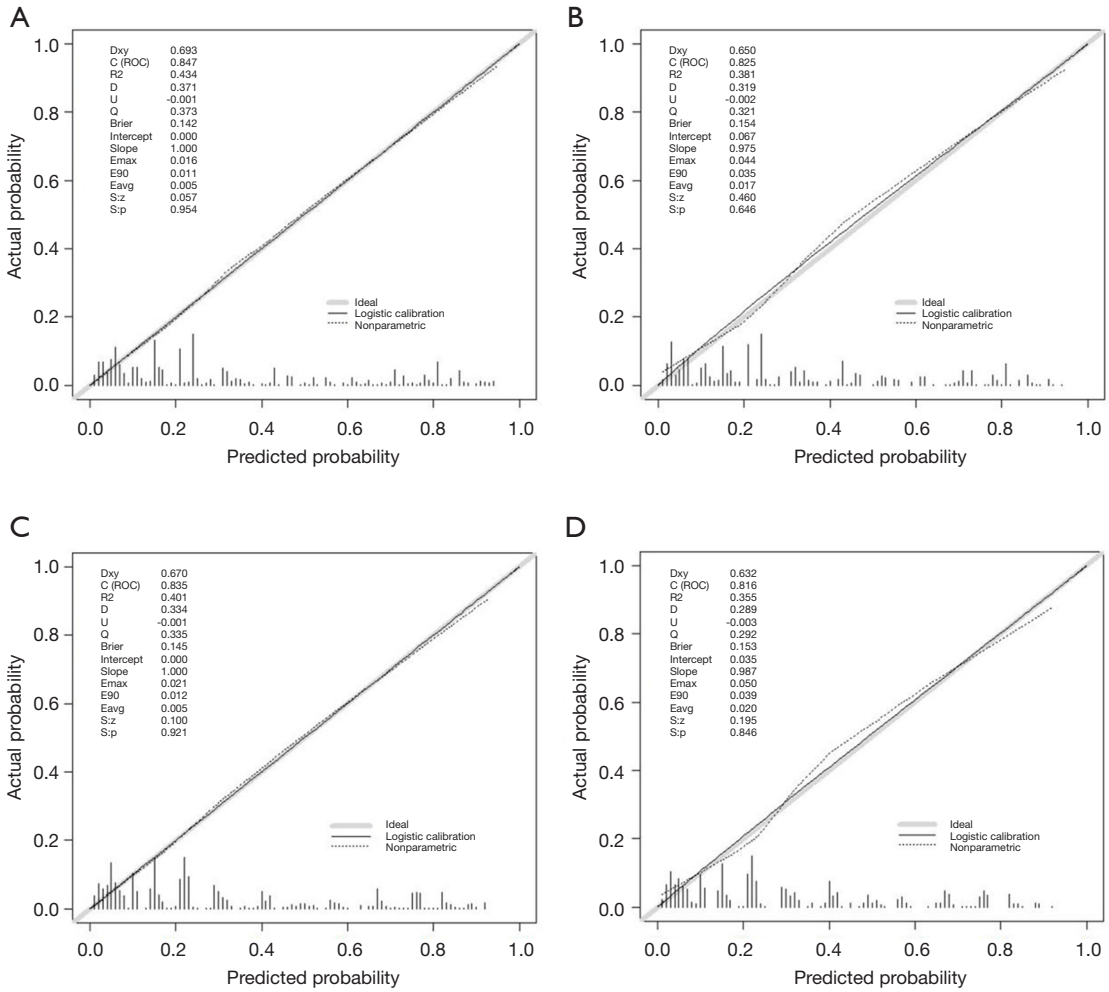

Figure 6 Calibration curves for assessing the calibration of the nomogram in predicting all-causes and cancer-specific early death in the training cohort (A, B) and the validation cohort (C, D).

schedule. To facilitate the use of these models, we developed the nomograms associated with web-based calculators.

Despite the advantages of our study, several potential limitations should also be considered. Firstly, detailed information on some factors that may influence the risk of early death, such as physical conditions and peritoneal metastasis, was not reported in the SEER database. Second, the present study was retrospective, and selection bias might exist. Third, we only included GC patients who were diagnosed with metastatic disease at initial diagnosis. We could not analyze the impact of metachronous metastasis on early death, which was not recorded in the SEER database. Therefore, more future studies may be needed to verify our results.

Conclusions

Approximately one-third of the stage IV GC patients died within three months. The early mortality remained stable during 2010–2015. A series of factors were found to be the independent risk factors associated with all-cause early death and cancer-specific early death in our study, including non-API race, poorer differentiation, middle sites of the stomach, lung metastases, liver metastases, no radiotherapy, no chemotherapy and no surgery. Two reliable nomograms were further developed to predict the risk of all-cause early death and cancer-specific early death. These risk factors and nomograms may be useful to assist clinicians in identifying the patients with the high risk of early death and provide

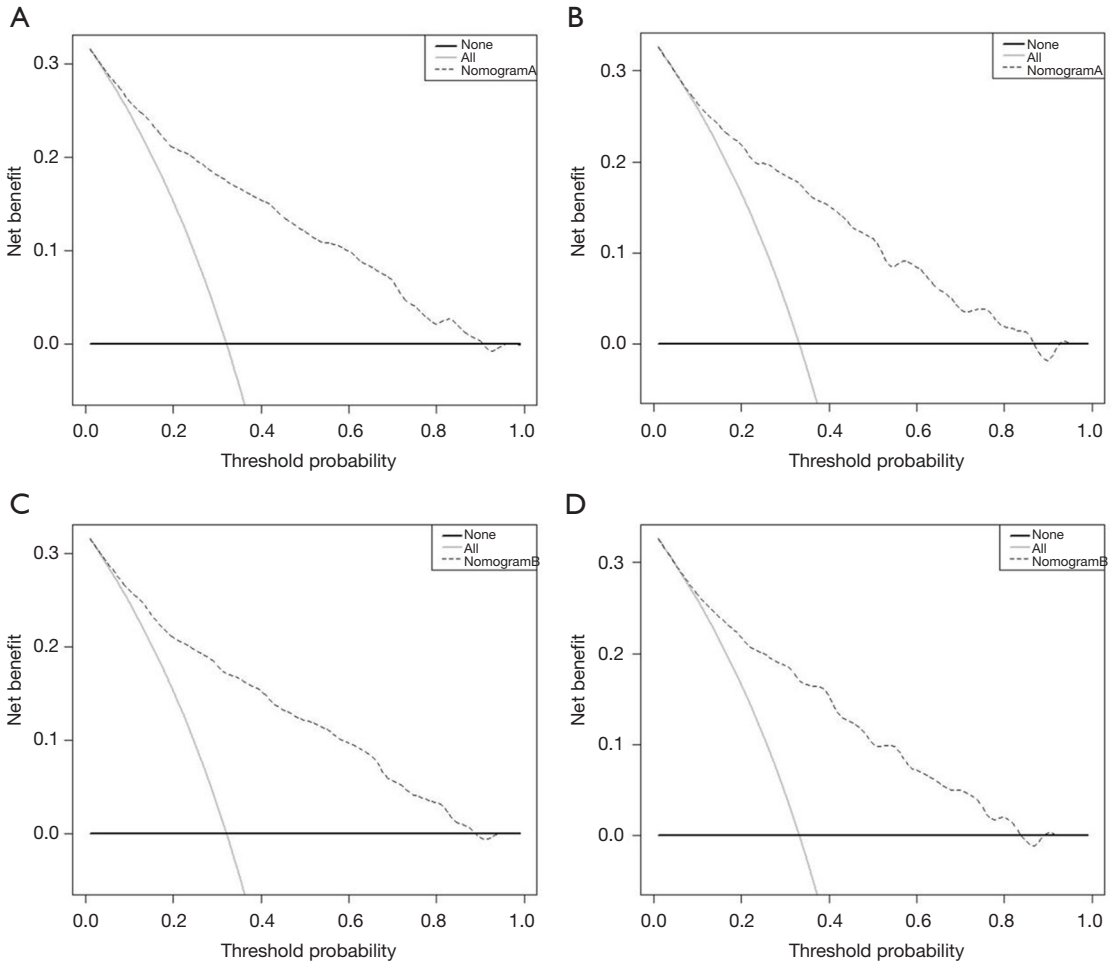

Figure 7 Decision curve analyses (DCAs) for the nomograms in predicting all-causes early death and cancer-specific early death in the training cohort (A, B) and the validation cohort (C, D).

insight into the clinical judgment and treatment plan options.

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Footnote

Reporting Checklist: The authors present the study in accordance with the TRIPOD reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-217

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-217). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The SEER database is an open-access cancer database that only contains de-identified patient data. Therefore, this study was exempted from the approval by the institutional review board of the First Affiliated Hospital of Soochow University. The

study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Jim MA, Pinheiro PS, Carreira H, et al. Stomach cancer survival in the United States by race and stage (2001-2009): Findings from the CONCORD-2 study. Cancer 2017;123 Suppl 24:4994-5013.
3. Chang YR, Han DS, Kong SH, et al. The value of palliative gastrectomy in gastric cancer with distant metastasis. Ann Surg Oncol 2012;19:1231-9.
4. Yamaguchi K, Yoshida K, Tanahashi T, et al. The long-term survival of stage IV gastric cancer patients with conversion therapy. Gastric Cancer 2018;21:315-23.
5. Zhao L, Li J, Bai C, et al. Multi-Modality Treatment for Patients With Metastatic Gastric Cancer: A Real-World Study in China. Front Oncol 2019;9:1155.
6. Ajani JA, Lee J, Sano T, et al. Gastric adenocarcinoma. Nat Rev Dis Primers 2017;3:17036.
7. Yoshida K, Yamaguchi K, Okumura N, et al. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. Gastric Cancer 2016;19:329-38.
8. Ebinger SM, Warschkow R, Tarantino I, et al. Modest overall survival improvements from 1998 to 2009 in metastatic gastric cancer patients: a population-based SEER analysis. Gastric Cancer 2016;19:723-34.
9. Abdel-Rahman O. A 10-year review of survival among patients with metastatic gastrointestinal cancers: a population-based study. Int J Colorectal Dis 2020;35:911-20.
10. Jochems A, El-Naqa I, Kessler M, et al. A prediction model for early death in non-small cell lung cancer patients following curative-intent chemoradiotherapy. Acta Oncol 2018;57:226-30.
11. Inoue T, Tamiya M, Tamiya A, et al. Analysis of Early Death in Japanese Patients With Advanced Non-small-cell Lung Cancer Treated With Nivolumab. Clin Lung Cancer 2018;19:e171-6.
12. Wang X, Mao M, Xu G, et al. The incidence, associated factors, and predictive nomogram for early death in stage IV colorectal cancer. Int J Colorectal Dis 2019;34:1189-201.
13. Lin JX, Desiderio J, Lin JP, et al. Multicenter Validation Study of the American Joint Commission on Cancer (8th Edition) for Gastric Cancer: Proposal for a Simplified and Improved TNM Staging System. J Cancer 2020;11:3483-91.
14. Brierley J, Gospodarowicz M, O'Sullivan B. The principles of cancer staging. Ecancermedicalscience 2016;10:ed61.
15. Son T, Sun J, Choi S, et al. Multi-institutional validation of the 8th AJCC TNM staging system for gastric cancer: Analysis of survival data from high-volume Eastern centers and the SEER database. J Surg Oncol 2019;120:676-84.
16. Ge XY, Ge F, Wang Z, et al. Analysis of risk factors of stage IV gastric cancer from the SEER database. Ann R Coll Surg Engl 2020;102:355-62.
17. Ma T, Wu ZJ, Xu H, et al. Nomograms for predicting survival in patients with metastatic gastric adenocarcinoma who undergo palliative gastrectomy. BMC Cancer 2019;19:852.
18. Min SH, Won Y, Lee K, et al. Laparoscopic gastrectomy and metastasectomy for stage IV gastric cancer. Surg Endosc 2020. [Epub ahead of print].
19. Liang C, Chen H, Yang Z, et al. Risk factors and prognosis of bone metastases in newly diagnosed gastric cancer. Future Oncol 2020;16:733-48.
20. Xie SH, Chen H, Lagergren J. Causes of death in patients diagnosed with gastric adenocarcinoma in 1970-2014 in Sweden: A population-based study. Cancer Sci 2020;111:2451-9.
21. Afifi AM, Saad AM, Al-Husseini MJ, et al. Causes of death after breast cancer diagnosis: A US population-based analysis. Cancer 2020;126:1559-67.
22. Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J 2019;40:3889-97.
23. Kong J, Diao X, Diao F, et al. Causes of death in long-term bladder cancer survivors: A population-based study. Asia Pac J Clin Oncol 2019;15:e167-74.
24. Gad MM, Saad AM, Al-Husseini MJ, et al. Temporal trends, ethnic determinants, and short-term and long-term

risk of cardiac death in cancer patients: a cohort study. Cardiovasc Pathol 2019;43:107147.
25. Herrmann J. From trends to transformation: where cardio-oncology is to make a difference. Eur Heart J 2019;40:3898-900.
26. Zhang Y, Lin Y, Duan J, et al. A Population-Based Analysis of Distant Metastasis in Stage IV Gastric Cancer. Med Sci Monit 2020;26:e923867.
27. Taniguchi Y, Tamiya A, Nakahama K, et al. Impact of metastatic status on the prognosis of EGFR mutation-positive non-small cell lung cancer patients treated with first-generation EGFR-tyrosine kinase inhibitors. Oncol Lett 2017;14:7589-96.
28. Goldie JH, Coldman AJ. The genetic origin of drug resistance in neoplasms: implications for systemic therapy. Cancer Res 1984;44:3643-53.
29. Wu C, Wang N, Zhou H, et al. Development and validation of a nomogram to individually predict survival of young patients with nonmetastatic gastric cancer: A retrospective cohort study. Saudi J Gastroenterol 2019;25:236-44.
30. Rana N, Gosain R, Lemini R, et al. Socio-Demographic Disparities in Gastric Adenocarcinoma: A Population-Based Study. Cancers (Basel) 2020;12:157.
31. Abdel-Rahman O. Asian Americans have better outcomes of non-metastatic gastric cancer compared to other United States racial groups: A secondary analysis from a randomized study. World J Gastrointest Oncol 2019;11:1151-60.
32. Jin H, Pinheiro PS, Callahan KE, et al. Examining the gastric cancer survival gap between Asians and whites in the United States. Gastric Cancer 2017;20:573-82.
33. Zhang G, Zhao X, Li J, et al. Racial disparities in stage-specific gastric cancer: analysis of results from the Surveillance Epidemiology and End Results (SEER) program database. J Investig Med 2017;65:991-8.
34. Ulanja MB, Beutler BD, Rishi M, et al. Influence of race and geographic setting on the management of gastric adenocarcinoma. J Surg Oncol 2019;120:270-9.
35. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016;17:309-18.
36. Kulig P, Sierzega M, Kowalczyk T, et al. Non-curative gastrectomy for metastatic gastric cancer: rationale and long-term outcome in multicenter settings. Eur J Surg Oncol 2012;38:490-6.
37. Yazıcı O, Ozdemir N, Duran AO, et al. The effect of the gastrectomy on survival in patients with metastatic gastric cancer: a study of ASMO. Future Oncol 2016;12:343-54.
38. Hsu JT, Liao JA, Chuang HC, et al. Palliative gastrectomy is beneficial in selected cases of metastatic gastric cancer. BMC Palliat Care 2017;16:19.
39. Sun J, Song Y, Wang Z, et al. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis. BMC Cancer 2013;13:577.
40. Narita Y, Kadowaki S, Oze I, et al. Establishment and validation of prognostic nomograms in first-line metastatic gastric cancer patients. J Gastrointest Oncol 2018;9:52-63.
41. Gao Z, Ni J, Ding H, et al. A nomogram for prediction of stage III/IV gastric cancer outcome after surgery: A multicenter population-based study. Cancer Med 2020;9:5490-9.
42. Wani S, Drahos J, Cook MB, et al. Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population-based study. Gastrointest Endosc 2014;79:224-32.e1.
43. Wang J, Yang B, Li Z, et al. Nomogram-based prediction of survival in unresectable or metastatic gastric cancer patients with good performance status who received first-line chemotherapy. Ann Transl Med 2020;8:311.
44. Kim SY, Yoon MJ, Park YI, et al. Nomograms predicting survival of patients with unresectable or metastatic gastric cancer who receive combination cytotoxic chemotherapy as first-line treatment. Gastric Cancer 2018;21:453-63.

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