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Application of Survival Quilts for prognosis prediction of gastrectomy patients based on the Surveillance, Epidemiology, and End Results database and China National Cancer Center Gastric Cancer database

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ABSTRACT

Objective: Accurate prognosis prediction is critical for individualized-therapy making of gastric cancer patients. We aimed to develop and test 6-month, 1-, 2-, 3-, 5-, and 10-year overall survival (OS) and cancer-specific survival (CSS) prediction models for gastric cancer patients following gastrectomy.

Methods: We derived and tested Survival Quilts, a machine learning-based model, to develop 6-month, 1-, 2-, 3-, 5-, and 10-year OS and CSS prediction models. Gastrectomy patients in the development set (n = 20,583) and the internal validation set (n = 5,106) were recruited from the Surveillance, Epidemiology, and End Results (SEER) database, while those in the external validation set (n = 6,352) were recruited from the China National Cancer Center Gastric Cancer (NCCGC) database. Furthermore, we selected gastrectomy patients without neoadjuvant therapy as a subgroup to train and test the prognostic models in order to keep the accuracy of tumor-node-metastasis (TNM) stage. Prognostic performances of these OS and CSS models were assessed using the Concordance Index (C-index) and area under the curve (AUC) values.

Results: The machine learning model had a consistently high accuracy in predicting 6-month, 1-, 2-, 3-, 5-, and 10-year OS in the SEER development set (C-index = 0.861, 0.832, 0.789, 0.766, 0.740, and 0.709; AUC = 0.784, 0.828, 0.840, 0.849, 0.869, and 0.902, respectively), SEER validation set (C-index = 0.782, 0.739, 0.712, 0.698, 0.681, and 0.660; AUC = 0.751, 0.772, 0.767, 0.762, 0.766, and 0.787, respectively), and NCCGC set (C-index = 0.691, 0.756, 0.751, 0.737, 0.722, and 0.701; AUC = 0.769, 0.788, 0.790, 0.790, 0.787, and 0.788, respectively). The model was able to predict 6-month, 1-, 2-, 3-, 5-, and 10-year CSS in the SEER development set (C-index = 0.879, 0.858, 0.820, 0.802, 0.784, and 0.774; AUC = 0.756, 0.827, 0.852, 0.863, 0.874, and 0.884, respectively) and SEER validation set (C-index = 0.790, 0.763, 0.741, 0.729, 0.718, and 0.708; AUC = 0.706, 0.758, 0.767, 0.766, 0.766, and 0.764, respectively). In multivariate analysis, the high-risk group with risk score output by 5-year OS model was proved to be a strong survival predictor both in the SEER development set (hazard ratio [HR] = 14.59, 95% confidence interval [CI]: 1.872–2.774, $P < 0.001$), SEER validation set (HR = 2.28, 95% CI: 13.089–16.293, $P < 0.001$), and NCCGC set (HR = 1.98, 95% CI: 1.617–2.437, $P < 0.001$). We further explored the prognostic value of risk score resulted 5-year CSS model of gastrectomy patients, and found that high-risk group remained as an independent CSS factor in the SEER development set (HR = 12.81, 95% CI: 11.568–14.194, $P < 0.001$) and SEER validation set (HR = 1.61, 95% CI: 1.338–1.935, $P < 0.001$).

Conclusion: Survival Quilts could allow accurate prediction of 6-month, 1-, 2-, 3-, 5-, and 10-year OS and CSS in gastric cancer patients following gastrectomy.

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1. Introduction

Gastric cancer is the fourth leading cause of cancer-related mortality and the sixth most common type of cancer globally.[1] Due to the lack of specific screening programs, more than half of gastric cancer are diagnosed as locally advanced or advanced disease.[2] Surgery represents the main approach for locally advanced gastric cancer patients; however, the prognosis remains poor due to the effect limitations of radiotherapy and chemotherapy and high rate of disease relapse.[2] Thus, how to predict gastric cancer patients' prognosis accurately is critical for individualized-therapy making, including expensive and painful adjuvant treatments.

Previous studies have reported that clinicopathological characteristics and computed tomography (CT) imaging features could be used to develop survival prediction models,[3-9] but their power is limited. Firstly, the risk scores of the clinicopathological characteristics in these studies were not consistent across all reports. Secondly, most of them were single-center studies with small sample sizes and traditional statistical modeling, lacking effective proof to validate the robustness of the models. Thirdly, some studies only focused on the subgroups of gastric cancer patients, such as stage IV patients. In this context, machine learning methods combined with a large sample population could be crucial in developing superior predictive models for gastric cancer patients. Survival Quilts,[10] a powerful machine learning algorithm for survival analysis developed by Changhee Lee, combines the collective intelligence of different survival models and provides significant performance gains on various real-world survival datasets, including cancer.[11] It offers new insights for prognosis prediction in gastric cancer patients.

Given the strong capability of Survival Quilts to automatically select and fine-tune ensembles of survival models using clinicopathological variables, we utilized this algorithm to create prediction models for 6-month, 1-, 2-, 3-, 5-, and 10-year overall survival (OS) and cancer-specific survival (CSS) in gastrectomy patients based on the Surveillance, Epidemiology, and End Results (SEER) database. Additionally, we validated the performance of the prognosis prediction models using the China National Cancer Center Gastric Cancer (NCCGC) database.

2. Methods

2.1. Data source and study population

This study was based on data abstracted from SEER Program (https://seer.cancer.gov/), and patients diagnosed with gastric cancer between 2000 and 2019 were selected from the "SEER 18 Regs Custom Data (with additional treatment fields) Nov 2019 Sub (1975–2019 varying)" database using the "case listing session". SEER, maintained by the National Cancer Institute (NCI), is a cancer registry database that compiles data on cancer cases from various locations and sources across the United States (US). The inclusion criteria were as follows: (1) patients diagnosed with gastric cancer (site recodes of ICD-O-3/WHO2008: C160-C169); (2) aged more than 20 years; (3) complete information on age at diagnosis, sex, race code, tumor location, grade, signet ring cell, regional nodes examined, T stage, N stage, M stage, neoadjuvant therapy, adjuvant radiation, and adjuvant chemotherapy; (4) patients following gastrectomy; (5) complete survival data and follow-up data. After data selection, a total of 25,689 gastrectomy patients were included in this study and were randomly divided into a development set (n = 20,583) and a validation set (n = 5,106) at an 8:2 ratio.

In addition, 6,352 gastrectomy patients from the NCCGC database,[12,13] were used for external verification. The NCCGC database, a large bidirectional cohort on gastric cancer, originated from the China National Cancer Center, a single but large-scale institution, and included more than 20,000 patients from across China from 1997 to 2019. The inclusion criteria were the same as those for the SEER database.

We also stratified the gastrectomy patients who did not receive neoadjuvant therapy as a subgroup to ensure the accuracy of the tumor-node-metastasis (TNM) staging. The SEER dataset included 20,711 patients who did not receive neoadjuvant therapy, while the NCCGC dataset comprised 5,898 such patients. Then, those patients from the SEER database were randomly divided into the development set and the validation set at an 8:2 ratio.

2.2. Model development and validation

We derived Survival Quilts[10,11] to conduct the 6-month, 1-, 2-, 3-, 5-, and 10-year OS and CSS prediction models of the SEER development set by incorporating the following parameters: age at diagnosis, sex, year of diagnosis, race code, tumor location, grade, signet ring cell, regional nodes examined, T stage, N stage, M stage, neoadjuvant therapy, adjuvant radiation, and adjuvant chemotherapy. Survival Quilts, creating time-varying ensembles of four existing survival models, including Cox proportional hazards, random survival forest, conditional inference survival forest, and the DeepHit model, is a novel algorithm for configuring the weights sequentially over a grid of time intervals. The number of time-horizons for temporal quilting in this study is 10 (K = 10). Then, we tested the OS and CSS models independently in the internal and external sets.

2.3. Performance evaluation of OS and CSS prediction models

In this study, OS was defined as the time from diagnosis to death from any cause, while CSS was defined as the time from diagnosis to death specifically attributable to gastric cancer. The prognostic performance of both OS and CSS models was evaluated using the Concordance Index (C-index) and area under the curve (AUC) values, along with a 95% confidence interval (CI). The C-index was employed to estimate the predictive accuracy of each model, with a higher C-index indicating better prognostic accuracy. The receiver operating characteristic (ROC) curve, represented by the time-dependent AUC, was utilized to assess the discrimination ability of the models.

According to the Survival Quilts formula, each patient in each prediction model was assigned an OS or CSS risk score. Subsequently, gastrectomy patients were categorized into high-risk and low-risk groups (50% vs. 50%) using the median of the risk score as the cut-off criterion, which optimized the sum of sensitivity and specificity for each prediction model. Furthermore, the OS and CSS curves between these two risk groups were generated according to the Kaplan-Meier method and compared with the log-rank test. Then, multivariate Cox proportional hazards models were finished to explore the prognostic value of risk score resulted 5-year OS model after adjusting age at diagnosis, sex, race code, tumor location, grade, signet ring cell, regional nodes examined, T stage, N stage, M stage, adjuvant radiation, and adjuvant chemotherapy.

2.4. Statistical analysis

All statistical analyses were conducted using Python (version 3.6.5) and R (version 4.1.0). Group comparisons for continuous variables were performed using the t-test, while categorical variables were assessed with the chi-square test. A P-value of less than 0.05 was deemed statistically significant, and all tests were two-sided.

3. Results

After removing 90,658 rows with any empty labels of clinicopathological characteristics in gastric cancer patients, a total of 25,689 patients were included in this study using the SEER database. Subsequently, these gastric cancer patients were randomly divided into a development set (n = 20,583) and a validation set (n = 5,106) at an 8:2

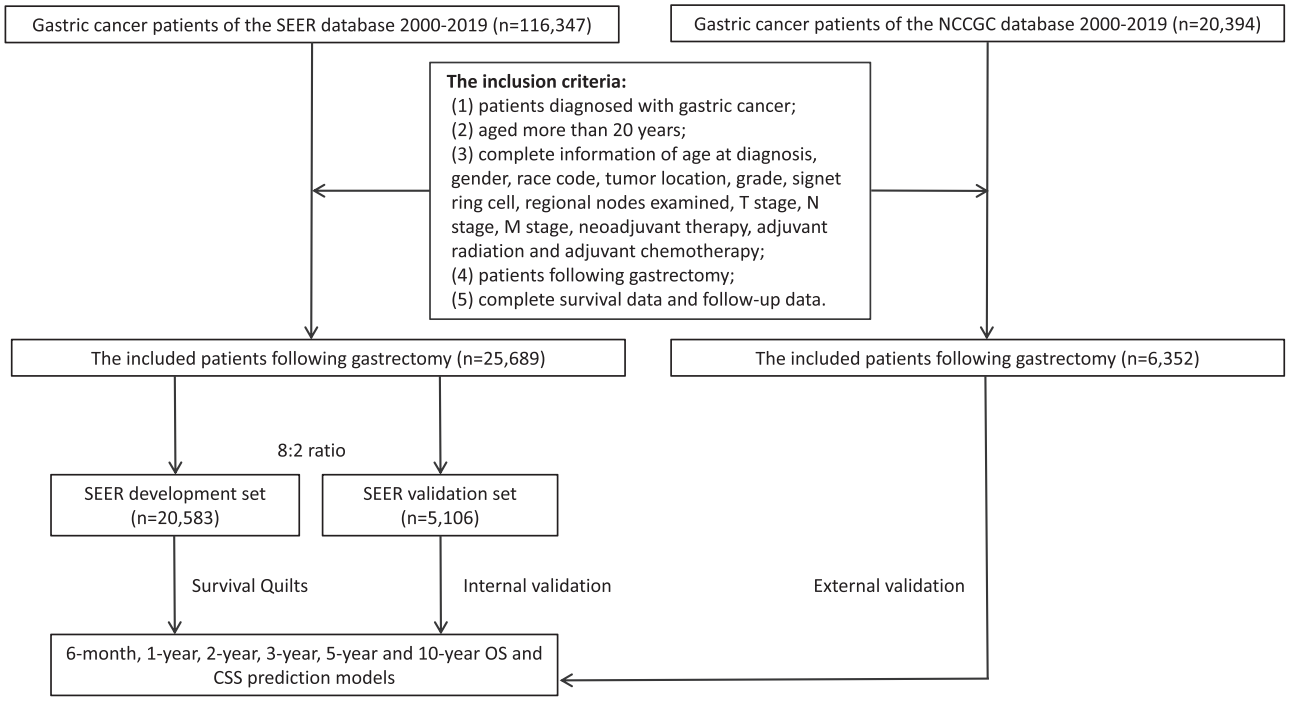

Fig. 1. Flow diagram illustrating recruitment of gastrectomy patients. CSS, cancer specific survival; NCCGC, National Cancer Center Gastric Cancer; SEER, Surveillance, Epidemiology, and End Results; OS, overall survival.

ratio (Fig. 1). No significant differences in clinicopathological characteristics were observed between the SEER development set and validation set (Table 1, all $P > 0.05$). In comparison to the SEER set, gastric cancer patients in the NCCGC set ($n = 6,352$) exhibited a higher percentage of regional nodes examined (nodes ≥30, $n = 2,098$, 33.0%), M0 ($n = 6,251$, 98.4%), and adjuvant chemotherapy ($n = 4,166$, 65.6%), but a lower rate of neoadjuvant therapy ($n = 454$, 7.1%).

When considering the impact of neoadjuvant therapy on TNM staging, we conducted further stratification specifically for patients who did not receive neoadjuvant therapy. The detailed clinicopathological characteristics of these patients without neoadjuvant therapy in the SEER development set ($n = 16,559$), SEER validation set ($n = 4,152$), and NCCGC set ($n = 5,898$) were listed in the Supplementary Table 1. No statistical difference was found in the SEER development set and validation set of clinicopathological characteristics between the two groups (all $P > 0.05$).

Next, we presented the OS and CSS outcomes through Kaplan-Meier curves for gastrectomy patients in the SEER development set (Supplementary Fig. 1A), SEER validation set (Supplementary Fig. 1B), and NCCGC set (Supplementary Fig. 1C), as well as for the subgroup of gastrectomy patients without neoadjuvant therapy (Supplementary Fig. 1D-F).

The C-index and AUC values for each OS or CSS model in the SEER development set, SEER validation set, and NCCGC set are presented in Table 2. For gastrectomy patients from the SEER development set, the C-index of 6-month, 1-, 2-, 3-, 5- and 10-year OS models were 0.861 (0.843–0.880), 0.832 (0.818–0.848), 0.789 (0.777–0.803), 0.766 (0.753–0.780), 0.740 (0.728–0.755) and 0.709 (0.696–0.726), respectively. In the SEER validation set, the C-index of 6-month, 1-, 2-, 3-, 5- and 10-year OS models were 0.782 (0.763–0.805), 0.739 (0.722–0.757), 0.712 (0.695–0.727), 0.698 (0.685–0.712), 0.681 (0.668–0.693) and 0.660 (0.649–0.673), respectively. The high accuracy was also found in the NCCGC set of 6-month, 1-, 2-, 3-, 5- and 10-year OS models with the C-index being 0.691 (0.612–0.770), 0.756 (0.722–0.788), 0.751 (0.733–0.771), 0.737 (0.721–0.755), 0.722 (0.706–0.740) and 0.701 (0.685–0.715), respectively.

The time-independent ROC analysis of each OS model was presented with AUC values of the SEER development set (Fig. 2A), SEER validation set (Fig. 2B), and NCCGC set (Fig. 2C). In SEER development set of gastrectomy patients, the AUC values for 6-month, 1-, 2-, 3-, 5- and 10-year OS models were 0.784 (0.766–0.803), 0.828 (0.812–0.846), 0.840 (0.823–0.856), 0.849 (0.832–0.865), 0.869 (0.853–0.883) and 0.902 (0.890–0.915), respectively. In the SEER validation set, the AUC values of 6-month, 1-, 2-, 3-, 5- and 10-year OS models were 0.751 (0.734–0.769), 0.772 (0.753–0.788), 0.767 (0.750–0.782), 0.762 (0.747–0.778), 0.766 (0.749–0.780) and 0.787 (0.771–0.803), respectively. The excellent performance was also found in NCCGC set of 6-month, 1-, 2-, 3-, 5- and 10-year OS models with the AUC values were 0.769 (0.753–0.783), 0.788 (0.771–0.802), 0.789 (0.773–0.803), 0.780 (0.774–0.804), 0.787 (0.771–0.802) and 0.788 (0.770–0.804), respectively.

As for CSS prediction models of gastrectomy patients, we trained and tested the Survival Quilts using SEER development set and SEER validation set only (Table 2 and Fig. 2D-2E). The 6-month, 1-, 2-, 3-, 5- and 10-year CSS prediction models showed excellent accuracy and discrimination with high C-index and AUC values. The AUCs for CSS models in the SEER development set were 0.756 (0.734–0.777) for 6-month, 0.827 (0.810–0.845) for 1-year, 0.852 (0.838–0.868) for 2-year, 0.863 (0.847–0.878) for 3-year, 0.874 (0.860–0.888) for 5-year and 0.884 (0.871–0.898) for 10-year CSS. The AUC values in the SEER validation set of 6-month, 1-, 2-, 3-, 5- and 10-year OS prediction model were 0.706 (0.688–0.722), 0.758 (0.743–0.774), 0.767 (0.752–0.784), 0.766 (0.748–0.781), 0.766 (0.748–0.781) and 0.764 (0.746–0.779), respectively (Fig. 2E).

Then, we selected a subgroup of gastrectomy patients without neoadjuvant therapy for analysis to maintain the accuracy of TNM stage in prognosis models. Supplementary Table 2 presents the C-index and AUC values for the 6-month, 1-, 2-, 3-, 5-, and 10-year OS models in the SEER development set, SEER validation set, and NCCGC set, as well as CSS prediction models in the SEER development set and SEER validation set.

The Survival Quilts method assigned a risk score to each gastrectomy patient in each OS or CSS model, and we categorized the gastrectomy

Table 1
Clinicopathological characteristics of gastrectomy patients in SEER development set, SEER validation set and NCCGC set.

Characteristics	SEER development set (n = 20,583)	SEER validation set (n = 5,106)	*P* value	NCCGC set (n = 6,352)
Age at diagnosis, n (%), years				
20–24	29 (0.1)	9 (0.2)	0.134	13 (0.2)
25–29	62 (0.3)	10 (0.2)		62 (1.0)
30–34	165 (0.8)	33 (0.6)		142 (2.2)
35–39	320 (1.6)	93 (1.8)		237 (3.7)
40–44	562 (2.7)	153 (3.0)		423 (6.7)
45–49	990 (4.8)	240 (4.7)		660 (10.4)
50–54	1,477 (7.2)	395 (7.7)		916 (14.4)
55–59	2,020 (9.8)	460 (9.0)		1,178 (18.5)
60–64	2,517 (12.2)	593 (11.6)		1,125 (17.7)
65–69	2,970 (14.4)	743 (14.6)		873 (13.7)
70–74	3,157 (15.3)	745 (14.6)		506 (8.0)
75–79	2,767 (13.4)	708 (13.9)		183 (2.9)
80–84	2,097 (10.2)	574 (11.2)		31 (0.5)
85+	1,450 (7.0)	350 (6.9)		3 (0)
Sex, n (%)				
Male	13,032 (63.3)	3,301 (64.6)	0.076	4,659 (73.3)
Female	7,551 (36.7)	1,805 (35.4)		1,693 (26.7)
Race code, n (%)				
American Indian/Alaska Native	168 (0.8)	33 (0.6)	0.314	0 (0)
Asian or Pacific Islander	3,998 (19.4)	1,012 (19.8)		6,352 (100.0)
Black	2,424 (11.8)	607 (11.9)		0 (0)
White	13,947 (67.8)	3,436 (67.3)		0 (0)
Others	46 (0.2)	18 (0.4)		0 (0)
Tumor location*, n (%)				
Proximal	6,747 (32.8)	1,674 (32.8)	0.801	2,060 (32.4)
Body	5,625 (27.3)	1,402 (27.5)		0 (0.0)
Distal	6,558 (31.9)	1,641 (32.1)		4,077 (64.2)
Total stomach	1,653 (8.0)	389 (7.6)		215 (3.4)
Grade, n (%)				
Well differentiated	1,346 (6.5)	341 (6.7)	0.601	204 (3.2)
Moderately differentiated	5,838 (28.4)	1,415 (27.7)		1,391 (21.9)
Poorly differentiated	12,870 (62.5)	3,230 (63.3)		4,756 (74.9)
Undifferentiated	529 (2.6)	120 (2.4)		1 (0)
Signet ring cell, n (%)				
Yes	3,810 (18.5)	945 (18.5)	0.996	37 (0.6)
No	16,773 (81.5)	4,161 (81.5)		6,315 (99.4)
Regional nodes examined, n (%)				
0	1,731 (8.4)	466 (9.1)	0.336	64 (1.0)
1–15	9,593 (46.6)	2,380 (46.6)		1,306 (20.6)
16–29	6,773 (32.9)	1,669 (32.7)		2,884 (45.4)
≥30	2,486 (12.1)	591 (11.6)		2,098 (33.0)
T stage, n (%)				
T0	2 (0.0)	0 (0.0)	0.650	8 (0.1)
T1	5,090 (24.7)	1,309 (25.6)		1,880 (29.6)
T2	8,587 (41.7)	2,091 (41.0)		641 (10.1)
T3	4,961 (24.1)	1,229 (24.1)		1,425 (22.4)
T4	1,943 (9.4)	477 (9.3)		2,398 (37.8)
N stage, n (%)				
N0	8,647 (42.0)	2,187 (42.8)	0.694	2,623 (41.3)
N1	7,246 (35.2)	1,764 (34.5)		947 (14.9)
N2	3,164 (15.4)	788 (15.4)		1,098 (17.3)
N3	1,526 (7.4)	367 (7.2)		1,684 (26.5)
M stage, n (%)				
M0	18,541 (90.1)	4,616 (90.4)	0.487	6,251 (98.4)
M1	2,042 (9.9)	490 (9.6)		101 (1.6)
TNM stage, n (%)				
I	7,873 (38.3)	1,991 (39.0)	0.676	2,068 (32.6)
II	7,659 (37.2)	1,869 (36.6)		1,333 (21.0)
III	3,009 (14.6)	756 (14.8)		2,850 (44.9)
IV	2,042 (9.9)	490 (9.6)		101 (1.6)
Neoadjuvant therapy, n (%)				
Yes	4024 (19.6)	954 (18.7)	0.161	454 (7.1)
No	16,559 (80.4)	4152 (81.3)		5,898 (92.9)
Adjuvant radiation, n (%)				
Yes	6,472 (31.4)	1,640 (32.1)	0.353	257 (4.0)
No	14,111 (68.6)	3,466 (67.9)		6,095 (96.0)
Adjuvant chemotherapy, n (%)				
Yes	10,184 (49.5)	2,577 (49.5)	0.987	4,166 (65.6)
No	10,399 (50.5)	2,579 (50.5)		2,186 (34.4)
5–year OS rate (95% CI), %	39.9 (39.2–40.6)	41.3 (39.9–42.7)	0.200	59.2 (58.0–60.3)

* In the NCCGC set, the tumor location was divided into Proximal, Distal and Total stomach.
Abbreviations: CI, confidence interval; NCCGC, National Cancer Center Gastric Cancer; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.

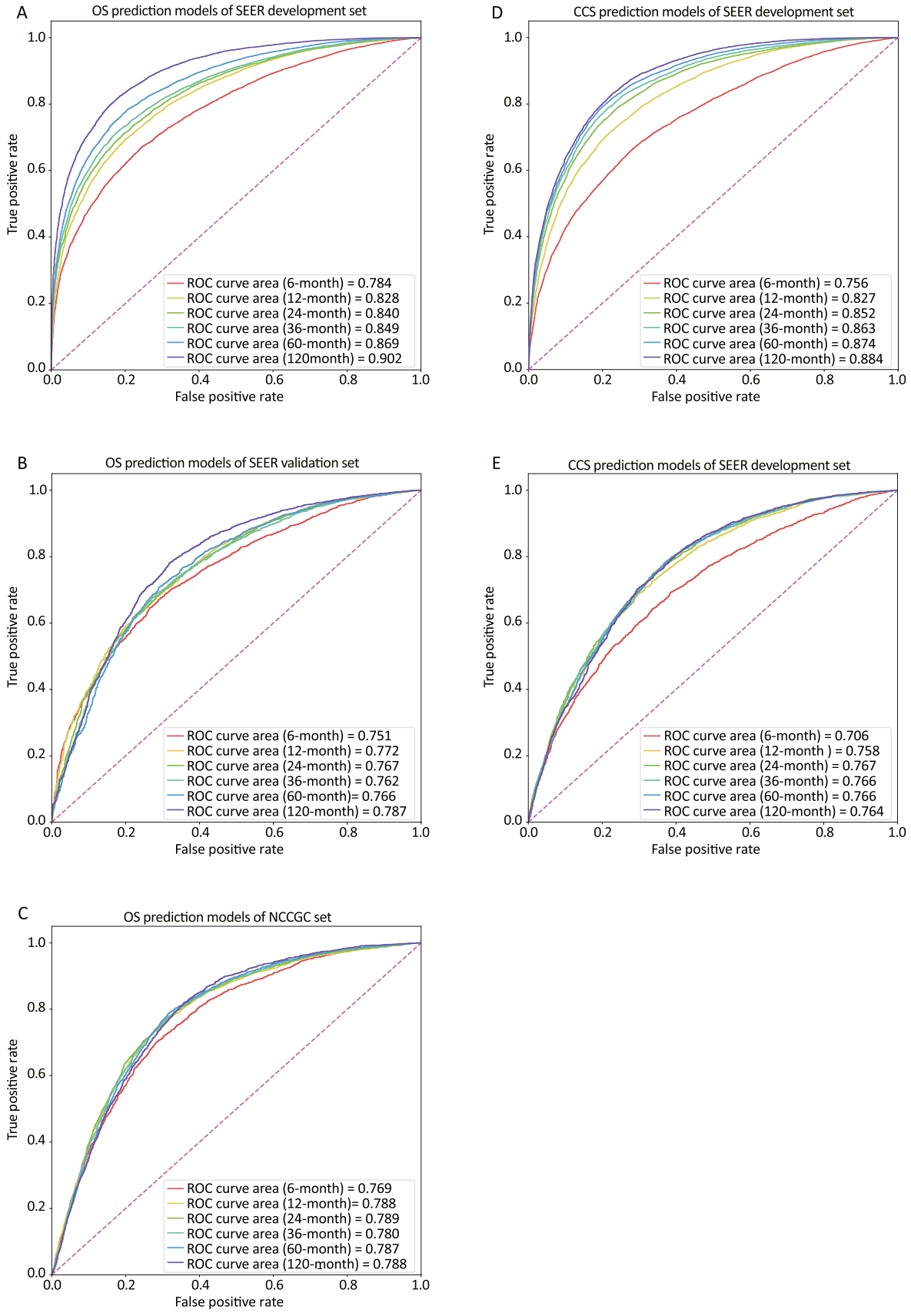

Fig. 2. Time-dependent AUC values and ROC curves for each OS or CSS prediction model of gastrectomy patients. The OS models in (A) SEER development set, (B) SEER validation set, and (C) NCCGC set; CSS models in (D) SEER development set and (E) SEER validation set. AUC, area under the curve; CSS, cancer-specific survival; NCCGC, National Cancer Center Gastric Cancer; OS, overall survival; ROC, receiver operating characteristic; SEER, Surveillance, Epidemiology, and End Results .

Table 2
Accuracy and discrimination of OS and CSS prediction models of gastrectomy patients in SEER development set, SEER validation set and NCCGC set.

OS prediction models	C-index (95% CI)	AUC (95% CI)	CSS prediction models	C-index (95% CI)	AUC (95% CI)
SEER development set			SEER development set		
6-month	0.861 (0.843–0.880)	0.784 (0.766–0.803)	6-month	0.879 (0.856–0.902)	0.756 (0.734–0.777)
1-year	0.832 (0.818–0.848)	0.828 (0.812–0.846)	1-year	0.858 (0.842–0.877)	0.827 (0.810–0.845)
2-year	0.789 (0.777–0.803)	0.840 (0.823–0.856)	2-year	0.820 (0.807 0.836)	0.852 (0.838–0.868)
3-year	0.766 (0.753–0.780)	0.849 (0.832–0.865)	3-year	0.802 (0.789–0.816)	0.863 (0.847–0.878)
5-year	0.740 (0.728–0.755)	0.869 (0.853–0.883)	5-year	0.784 (0.770–0.797)	0.874 (0.860–0.888)
10-year	0.709 (0.696–0.726)	0.902 (0.890–0.915)	10-year	0.774 (0.760–0.789)	0.884 (0.871–0.898)
SEER validation set			SEER validation set		
6-month	0.782 (0.763–0.805)	0.751 (0.734–0.769)	6-month	0.790 (0.765–0.814)	0.706 (0.688–0.722)
1-year	0.739 (0.722–0.757)	0.772 (0.753–0.788)	1-year	0.763 (0.745–0.778)	0.758 (0.743–0.774)
2-year	0.712 (0.695–0.727)	0.767 (0.750–0.782)	2-year	0.741 (0.728–0.754)	0.767 (0.752–0.784)
3-year	0.698 (0.685–0.712)	0.762 (0.747–0.778)	3-year	0.729 (0.717–0.741)	0.766 (0.748–0.781)
5-year	0.681 (0.668–0.693)	0.766 (0.749–0.780)	5-year	0.718 (0.707–0.731)	0.766 (0.748–0.781)
10-year	0.660 (0.649–0.673)	0.787 (0.771–0.803)	10-year	0.708 (0.697–0.720)	0.764 (0.746–0.779)
NCCGC set					
6-month	0.691 (0.612–0.770)	0.769 (0.753–0.783)			
1-year	0.756 (0.722–0.788)	0.788 (0.771–0.802)			
2-year	0.751 (0.733–0.771)	0.790 (0.773–0.803)			
3-year	0.737 (0.721–0.755)	0.790 (0.774–0.804)			
5-year	0.722 (0.706–0.740	0.787 (0.771–0.802)			
10-year	0.701 (0.685–0.715)	0.788 (0.770–0.804)			

Abbreviations: AUC, area under the curve; CI, confidence interval; CSS, cancer specific survival; NCCGC, National Cancer Center Gastric Cancer; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.

patients into high-risk and low-risk score groups (50% vs. 50%) for each model. Then, we adopted Kaplan-Meier plots to assess and test the association between risk score and prognosis outcomes, including OS and CSS, among gastrectomy patients from the SEER development set, SEER validation set and NCCGC set. Compared with the high-risk group, the low-risk group from the 6-month, 1-, 2-, 3-, 5- and 10-year OS models showed better OS outcomes in SEER development set (all $P < 0.001$, Fig. 3A-F), SEER validation set (all $P < 0.001$, Fig. 3G-L) and NCCGC set (all $P < 0.001$, Fig. 3M-R). When it comes to 6-month, 1-, 2-, 3-, 5- and 10-year CSS models, similar results were observed in the SEER development set (all $P < 0.001$, Fig. 4A-F) and SEER validation set (all $P < 0.001$, Fig. 4G-L). The same work was finished for the subgroup analysis with gastrectomy patients without neoadjuvant therapy (Supplementary Fig. 2-3).

We next did multivariate Cox regression analysis to explore the prognostic value of risk score resulted 5-year OS model of gastrectomy patients. The clinicopathological characteristics of the low-risk group and high-risk group were shown in Supplementary Table 3. After adjusting age at diagnosis, sex, race code, tumor location, grade, signet ring cell, regional nodes examined, T stage, N stage, M stage, adjuvant radiation and adjuvant chemotherapy, the high-risk group was a strong independent OS factor in the SEER development set (HR = 14.59, 95% CI: 13.089–16.293, $P < 0.001$), SEER validation set (HR = 2.28, 95% CI: 1.872–2.774, $P < 0.001$) and NCCGC set (HR = 1.99, 95% CI: 1.617–2.438, $P < 0.001$) (Supplementary Table 4 and Fig. 5). We further explored the prognostic value of risk score resulted 5-year CSS model of gastrectomy patients (Supplementary Table 5–6 and Fig. 6), and found that the high-risk group remained as an independent CSS factor in the SEER development set (HR = 12.81, 95% CI: 11.568–14.194, $P < 0.001$) and SEER validation set (HR = 1.61, 95% CI: 1.338–1.935, $P < 0.001$).

4. Discussion

In this study, we developed and tested 6-month, 1-year, 2-year, 3-year, 5-year, and 10-year OS and CSS prediction models for 32,041 gastrectomy patients from the SEER and NCCGC databases using Survival Quilts. Encouragingly, the OS models demonstrated excellent performance in the SEER development set, SEER validation set, and NCCGC set, with high C-index and AUC values. Similarly, the CSS prediction models performed well in the SEER development set and SEER validation set. To our knowledge, this represents the largest study targeting OS and CSS prediction models for gastrectomy patients and marks the first application of Survival Quilts in prognosis prediction for patients with gastric cancer. Its widespread application could establish a robust foundation for personalized treatment approaches in future management of gastric cancer.

There were a few studies in prognosis prediction of gastric cancer patients; however, these studies were with small sample sizes and traditional statistical modeling. With its extensive dataset, SEER, as a cancer registry database collecting information on cancer cases from diverse locations and sources across the US, offers a public repository of data for the analysis of more than 120,000 gastric cancer patients. Hu et al.[14] used the SEER database to develop nomograms of predicting the prognosis of gastric cancer patients with different grades using the traditional Cox regression methods only. Recently, Wang et al.[9] conducted prognostic models for predicting the survival of gastric cancer with multi-organ metastases based on the SEER database, but it has not yet been externally validated. In this context, increasing evidences have been accumulated to predict the prognosis for gastric cancer patients using machine learning or deep learning methods based on clinicopathological variations and even CT and pathological images.[15-18] However, these studies applied a large number of technological annotations to train and test the models, which would consume a lot of time and effort of pathologists and radiologist when applying them in the clinical practices.

Survival Quilts could combine optimal attributes from four survival prediction models autonomously and incorporate more clinicopathological variables. A previous study showed that the application of Survival Quilts for predicting non-metastatic prostate cancer-specific mortality got great performance.[11] Similar to the study, we demonstrated that Survival Quilts allowed accurate prediction of 6-month, 1-, 2-, 3-, 5- and 10-year OS and CSS outcomes in gastric cancer patients following gastrectomy from the SEER and NCCGC databases.

5-year survival rate is the most commonly used indicator to evaluate the prognosis of gastric cancer patients in clinical practice.[19] Here, we utilized Kaplan-Meier plots and multivariable Cox models to evaluate the association between the risk scores derived from the 5-year OS and CSS models and the prognosis of gastrectomy patients. Our findings indicated that the high-risk group emerged as a robust independent prognos-

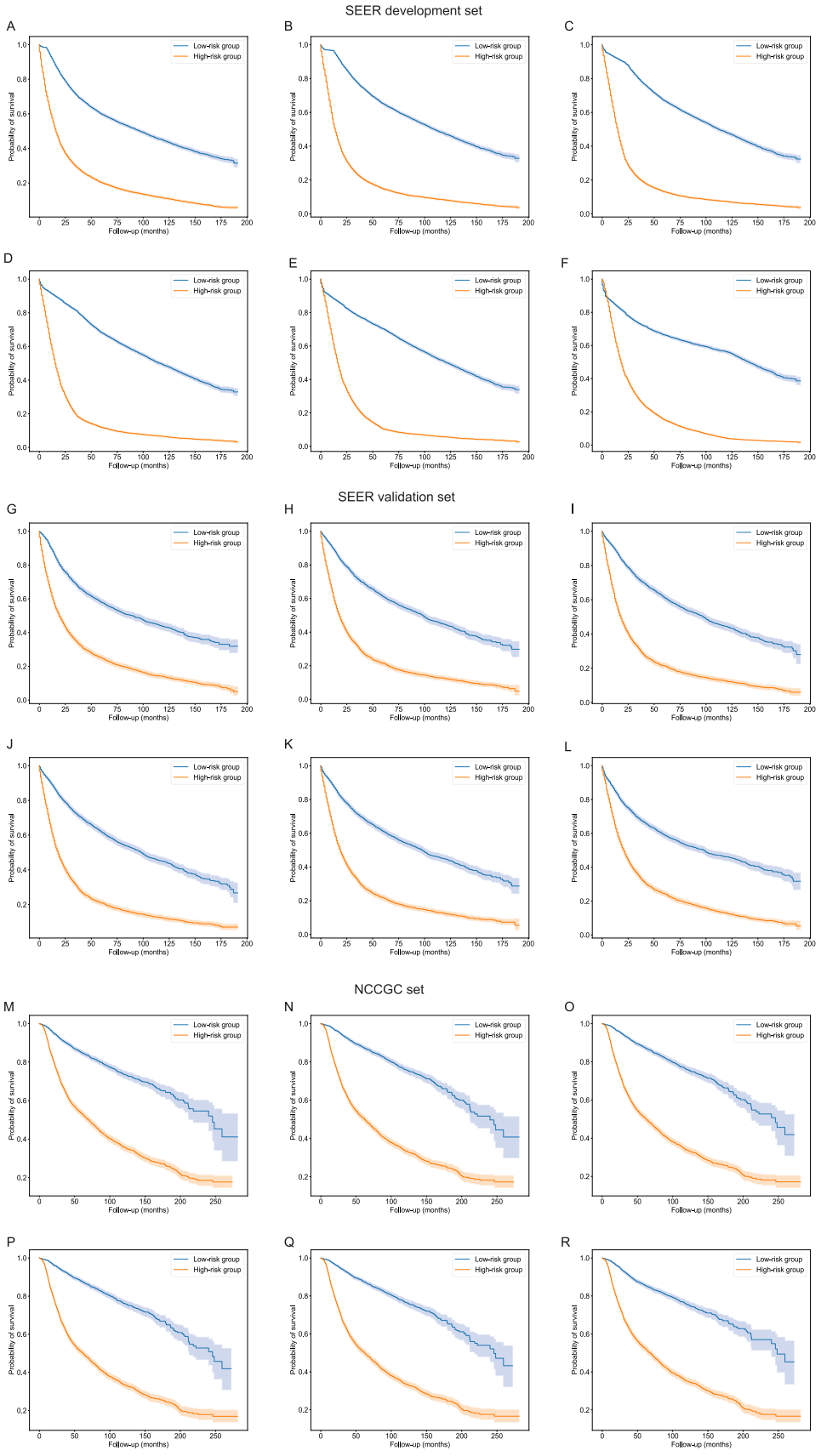

Fig. 3. The Kaplan-Meier curves of high-risk and low-risk groups with risk score resulted 6-month, 1-, 2-, 3-, 5- and 10-year OS prediction models. The curves of two groups in SEER development set (A-F), SEER validation set (G-L) and NCCGC set (M-R), and all $P < 0.001$. NCCGC, National Cancer Center Gastric Cancer; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.

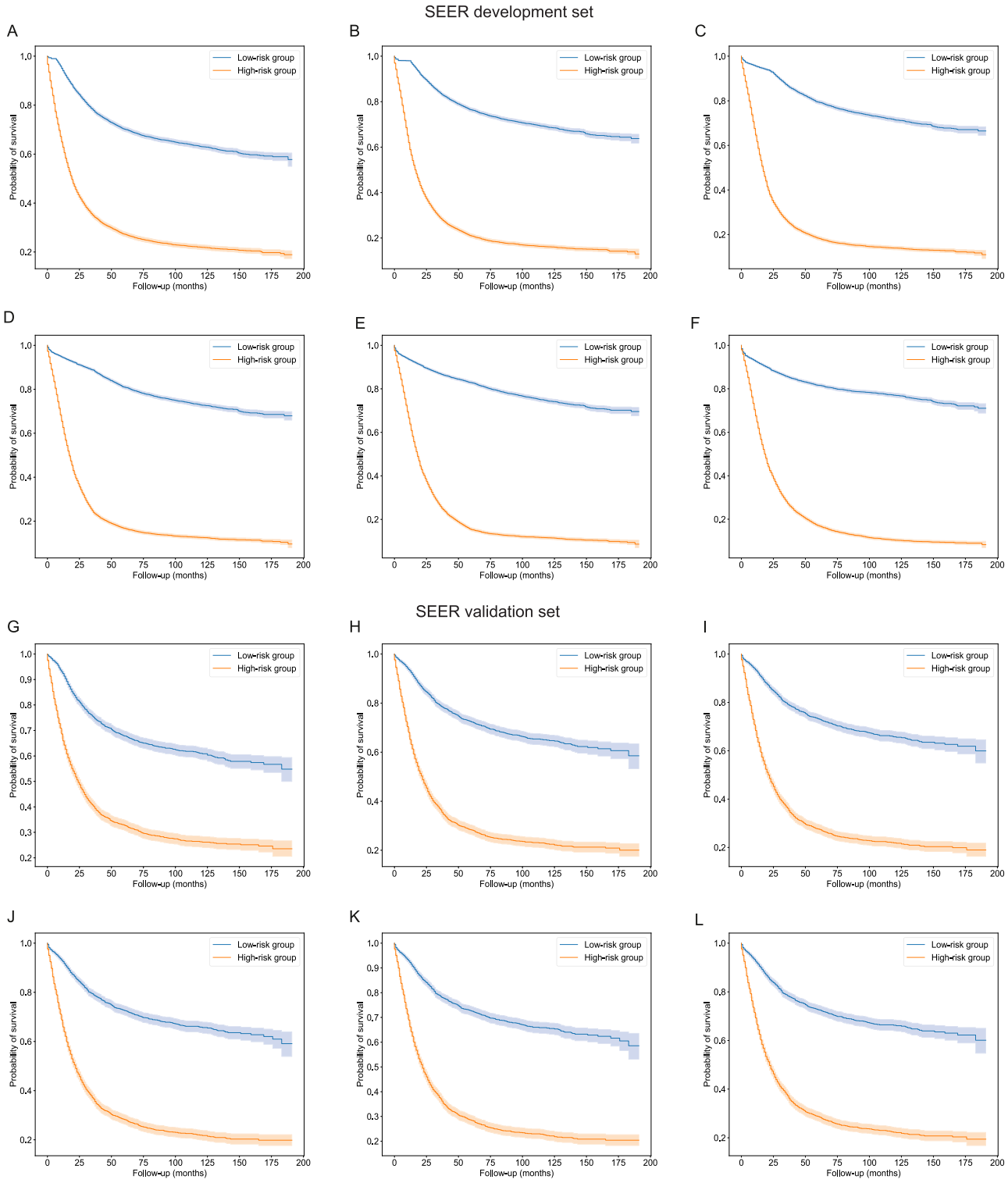

Fig. 4. The Kaplan-Meier curves of high-risk and low-risk groups with risk score resulted 6-month, 1-, 2-, 3-, 5- and 10-year CSS prediction models. The curves of two groups in SEER development set (A-F) and SEER validation set (G-L), and all $P < 0.001$. CSS, cancer-specific survival; SEER, Surveillance, Epidemiology, and End Results.

tic factor for both OS and CSS. The results suggested that our prognostic model, built on the Survival Quilts algorithm, demonstrated the capability to predict the OS and CSS of gastrectomy patients, and thereby potentially offering valuable insights for treatment decision-making.

Neoadjuvant therapy has been considered a standard treatment for locally advanced gastric cancer with down-staging tumor.[20-23] However, this post-treatment TNM stage would affect the accuracy of prognosis prediction models. Thus, we identified 26,609 gastrectomy patients without neoadjuvant therapy as a subgroup to train and test the 6-month, 1-year, 2-year, 3-year, 5-year and 10-year OS and CSS prediction models based on Survival Quilts methods. Interestingly, we found that the C-index and AUC values of 6-month, 1-year, 2-year, 3-year, 5-year and 10-year OS and CSS prediction models were comparable with that of all gastrectomy patients, suggesting our prognostic models were suit-

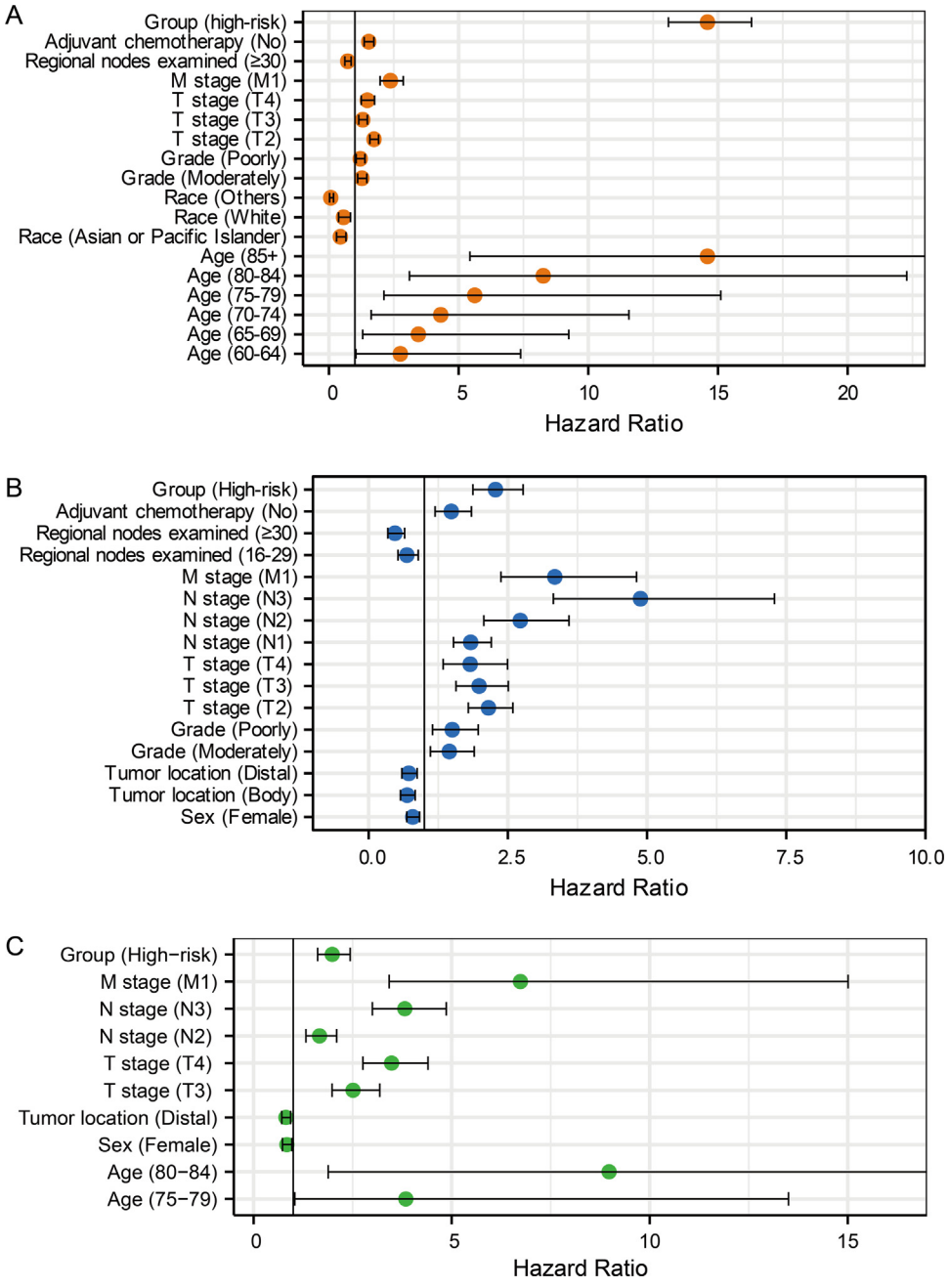

Fig. 5. The OS multivariate analysis of high-risk group in the SEER development set (A), SEER validation set (B), and NCCGC set (C). NCCGC, National Cancer Center Gastric Cancer; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.

able for gastrectomy patients regardless of neoadjuvant therapy status. The results demonstrated the advantages of Survival Quilts algorithm with excellent ability of self-training and flexibility for input variables to evolve.

Regional and racial disparities in survival outcomes for patients with gastric cancer between the US and China have been demonstrated in our previous study,[24] while Chinese patients with gastric cancer have a better survival outcome than those in the US. Here, we conducted and tested the OS and CSS models from two sets of different regions; the SEER database was from the US and the external validation set, NCCGC database, was from China. Though the clinicopathological characteristics and prognosis differences were observed in the published studies,[25-27] our study demonstrated high accuracy and discrimination in the external validation set across the 6-month, 1-, 2-, 3-, 5-, and 10-year OS prediction models, significantly enhancing the applicability of the survival models. A potentially crucial factor contributing to this success was the inclusion of race code as a variable in our OS and CSS models using the Survival Quilts algorithm.

This study had some limitations. Firstly, both the SEER database and the NCCGC database were retrospective cohorts, which might have some inherent biases and unknown confounders. Secondly, the SEER database did not select all prognostic dictators, such as environmental exposures, lifestyle factors, type of surgery, surgical margins, Charleson-Deyo comorbidity score, and so on, which have been proved to be related to the prognosis of gastric cancer.[28-30] Thirdly, the NCCGC database did not provide the CSS information, and thus the CSS models developed from the SEER set in this study had not been validated using an external set. Fourthly, gastric cancer patients diagnosed during 2000–2019, spanning nearly 20 years, were included in this study. During this long period, the cancer treatment, diet and potentially environmental factors changed a lot, not only in the US, but also in China, which could affect the accuracy of the prediction models. Despite all these limitations, this

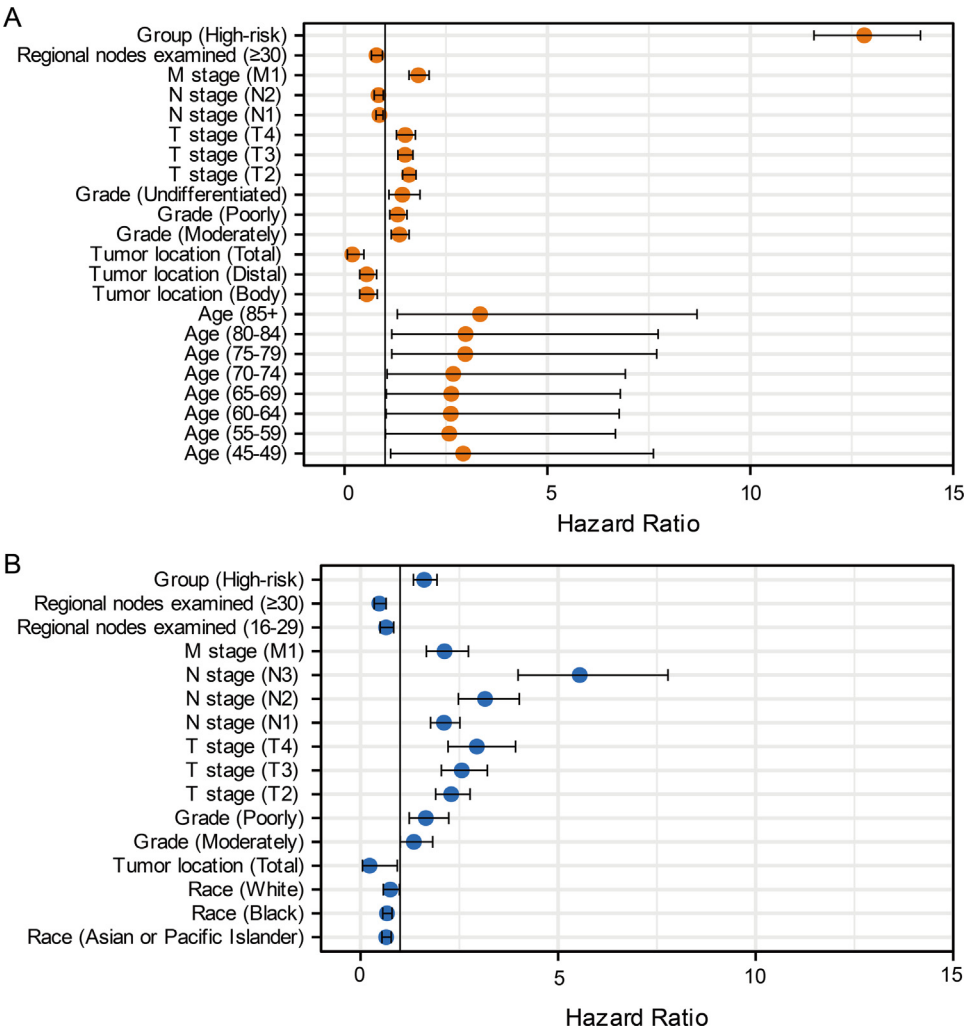

Fig. 6. The CSS multivariate analysis of high-risk group in the SEER development set (A) and SEER validation set (B). CSS, cancer-specific survival; SEER, Surveillance, Epidemiology, and End Results.

large population-based study conducted and tested excellent prognosis prediction models of gastrectomy patients using Survival Quilts, and C-index and AUCs values were much higher than the models based on the SEER database in previous studies.[9,14]

5. Conclusion

Survival Quilts could allow accurate prediction of 6-month, 1-, 2-, 3-, 5- and 10-year OS and CSS outcomes in gastric cancer patients following gastrectomy. Future additional integrated imaging or pathological data might improve the performance and accuracy of personalized prediction models.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement

This study was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval number: 17-156/1412).

Data availability

Data for this study were made available through application to the SEER database, while the NCCGC database generated during this study was included in this published article. The source code for the analysis is available at https://github.com/yingtaichen/Survival_Quilts_of_Gastric_Cancer.

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Author contributions

L.Z. and Y.C. contributed to the conceptualisation, data curation and verification, formal analysis, investigation, methods, project administration, validation, and drafting of the manuscript. W.W. and P.N. contributed to the literature review. X.L. and X.H. were involved in data curation. D.Z., J.G. and Y.Z. revised the manuscript for final submission. All authors contributed to writing the manuscript and editing and approved the final manuscript. L.Z. and Y.C. accessed and verified the

raw data of the SEER and NCCGC databases. There was no funder organization involved in data access, curation, or verification.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2024.01.007.

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