Cohort Study

ANNALS OF MEDICINE & SURGERY

OPEN

Individualized prediction of conditional survival for colorectal signet-ring cell carcinoma patients

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Background: Conditional survival (CS) considers the time already survived after surgery and may provide additional survival information. The authors sought to construct and validate novel conditional survival nomograms for the prediction of conditional overall survival (OS) and cancer-specific survival (CSS) of colorectal signet-ring cell carcinoma (SRCC) patients.

Methods: Patients diagnosed with stage I–III SRCC between 2010 and 2019 were identified from the Surveillance, Epidemiology, and End Results database. The formula calculating CS was: CS(x|y) = S(x + y)/S(x), where S(x) represents the survival at x years. CS nomograms were then constructed to predict the 5-year conditional OS and CSS, followed by internal validation.

Results: A total of 944 colorectal SRCC patients were finally identified in this study. The 5-year OS and CSS improved gradually with additional survival time. Univariate and multivariate Cox regression analysis conducted in training set revealed that age, race, T stage, LNR, and perineural invasion were independent risk factors for both OS and CSS. Two nomograms with considerable predictive ability were successfully constructed [area under the curve (AUC) for OS: 0.788; AUC for CSS: 0.847] and validated (AUC for OS: 0.773; AUC for CSS: 0.799) for the prediction of 5-year OS and CSS, based on the duration of 1–4 years post-surgery survival.

Conclusions: The probability of achieving 5-year OS and 5-year CSS in colorectal SRCC patients improved gradually with additional time. Conditional nomograms considering survival time will be more reliable and informative for risk stratification and postoperative follow-up.

Keywords: cancer-specific survival, colorectal signet-ring cell carcinoma, conditional survival, nomogram, overall survival

Introduction

Colorectal signet-ring cell carcinoma (SRCC) is a rare type of adenocarcinoma (AC) and only accounts for ~1% of colorectal cancer[1–3]. Compared with other common adenocarcinoma, SRCC patients are characterized by extremely shorter relapse-free survival, lower response to chemotherapy and poorer prognosis[4–6]. Consequently, more prognostic factors and reliable predictive models should be identified to facilitate risk evaluation for SRCC patients.

HIGHLIGHTS

- For the first time, we developed novel conditional survival nomograms with high predictive accuracy in signet-ring cell carcinoma (SRCC) patients.
- The probability of achieving 5-year overall survival (OS) and 5-year cancer-specific survival (CSS) in colorectal SRCC patients improved gradually with additional time.
- Conditional nomograms considering survival time will be more reliable and informative for individualizing risk stratification and postoperative follow-up.

With the identification of additional prognostic factors such as lymph node ratio (LNR), primary tumour location and perineural invasion (PI) status, prognostic nomograms incorporating all independent factors have been developed to enhance survival prediction for colorectal SRCC[7–9]. However, apart from the aforementioned prognostic clinicopathological factors, the survived time after surgery is another overlooked factor influencing prognosis, and the risk of death changes with time after surgery. Conventional survival analysis is based on calculations from the day of diagnosis or surgery. Conditional survival (CS) represents the probability of surviving for additional years after already surviving for certain years. CS assessments provide important quantitative information about the probability of survival over time and should be regarded as a more precise tool for prognosis analysis[10–12].

To date, no previous studies have attempted to develop nomograms to predict the CS of colorectal SRCC patients. In this present study, we first sought to define CS among patients with colorectal SRCC, and then to construct and validate nomograms

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:2524–2530

Received 29 December 2023; Accepted 6 March 2024

Published online 25 March 2024

http://dx.doi.org/10.1097/MS9.0000000000001982

for predicting the conditional probability of survival based on the Surveillance, Epidemiology and End Results (SEER) database.

Patients and methods

Patients' selection

The SEER database of National Cancer Institute is a public source for researchers that collects demographic, diagnostic, therapeutic, and prognostic information of patients from 18 cancer registries, approximately covering one-third of the total population in the United States. Patients pathologically diagnosed with colorectal SRCC were extracted from SEER database between 2010 and 2019 in our study. Clinicopathological features, overall survival (OS) and cancer-specific survival (CSS) were collected. Patients who met the following criteria were included: (a) pathologically diagnosed colorectal SRCC; (b) AJCC TNM stage I–III; (c) colorectal SRCC was the only primary tumour; (d) patients with complete follow-up information. Patients with incomplete records of follow-up information were excluded.

Statistical analysis

Metric variables are displayed as median with interquartile range (IQR), while categorical variables are presented as frequency with percentage. Independent predictors associated with survival were identified using the multivariate Cox proportional hazards models. CS analysis was used to depict the exactly survival for patients who have survived for specific years. CS was calculated in the formula: $CS(x|y) = S(x+y)/S(x)$, which means CS for y years among patients who have already survived for x years from the date of diagnosis[13]. CS nomograms were fitted to estimate 5-year conditional OS and CSS of SRCC patients based on independent variables selected by multivariate Cox regression analysis. Survival receiver operating curves (ROC) and area under the curve (AUC) were used to evaluate the discrimination of nomograms. Analysis was carried out using R version 3.4.1. All analyses were two-sided, and results of P less than 0.05 were considered statistically significant. This study has been reported in line with the STROCSS criteria[14].

Results

Demographic and clinicopathological characteristics

A total of 944 SRCC patients were finally included in this study. The mean age of all patients was 66.5, with IQR of 57–80. 50.4% of patients were female, and most patients were white people (n = 782, 82.8%). Only 6.8% (n = 64) were categorized into I/II in histological grade, and the majority of patients were poor differentiation or undifferentiation. 30.8% of patients showed elevated CEA level, and 23.5% had PI. The basic clinicopathological features of patients are shown in Table 1.

Estimation of conditional overall survival and cancer-specific survival

The 5-year OS and CSS of SRCC patients identified in this study were 42% and 52%, respectively. The non-cancer-caused death accounted for about 10%. The conditional probability of OS and CSS were shown in Table 2, and the conditional survival curves in Fig. 1. The condition probability of OS and CSS increased with each additional year survived, and the more years patients had

Table 1

Baseline features of colorectal signet-ring cell carcinoma in SEER database

	N (%)
Age (IQR)	66.5 (57–80)
Sex	
Female	477 (50.5)
Male	467 (49.5)
Race	
White	782 (82.8)
Black	80 (8.5)
Other	82 (8.7)
Site	
Right	300 (31.8)
Left	517 (54.8)
Trans	127 (13.5)
Grade	
I/II	112 (11.9)
III	640 (67.8)
IV	192 (20.3)
T stage	
T1	45 (4.8)
T2	67 (7.1)
T3	500 (53.0)
T4	324 (34.3)
N stage	
N0	318 (33.7)
N1	209 (22.1)
N2	417 (44.2)
LNR (IQR)	0.272 (0.0–0.475)
CEA	
No	289 (30.6)
Yes	291 (30.8)
Unknown	364 (38.6)
PI	
No	722 (76.5)
Yes	222 (23.5)

IQR, interquartile range; LNR, lymph node ratio; PI, perineural invasion; SEER, Surveillance, Epidemiology and End Results.

Table 2

Conditional overall and cancer-specific survival estimates

		Overall survival for patients surviving				
OS (year)	**Actuarial survival**	**1**	**2**	**3**	**4**	**5**
1	0.76					
2	0.59	0.78				
3	0.51	0.66	0.85			
4	0.46	0.60	0.77	0.91		
5	0.42	0.55	0.71	0.83	0.91	
6	0.40	0.52	0.67	0.78	0.86	0.94
		Cancer-specific survival for patients surviving				
CSS (year)	Actuarial survival	1	2	3	4	5
1	0.81					
2	0.66	0.82				
3	0.58	0.72	0.87			
4	0.55	0.68	0.83	0.95		
5	0.52	0.65	0.79	0.90	0.95	
6	0.51	0.63	0.77	0.87	0.92	0.97

CSS, cancer-specific survival; OS, overall survival.

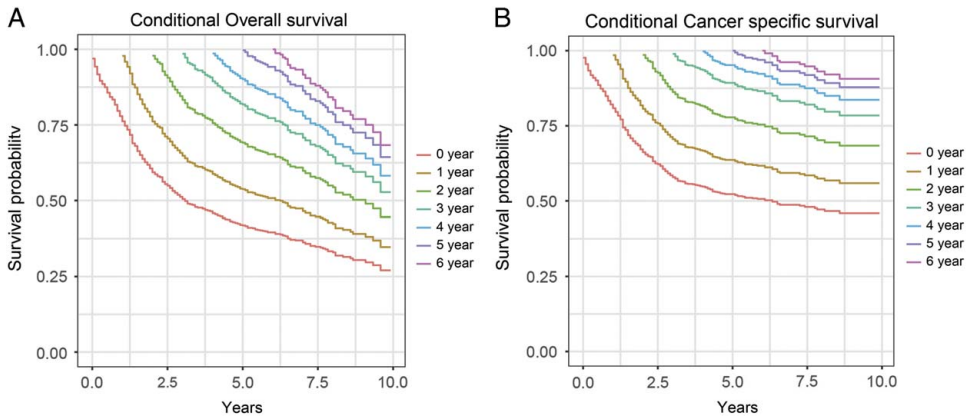

Figure 1. Kaplan–Meier estimates of survival after surgery (0 years) and conditional survival according to years already survived after surgery (1–6 years). (A) Overall survival; (B) Cancer-specific survival.

already survived, the better the chances of achieving a high rate of survival. The postoperative 5-year OS increased from 42% to 55%, 71%, 83% and 91% given 1–4 years survived already, and 5-year CSS increased from 52% to 65%, 79%, 90% and 95% (Table 2).

Construction of conditional survival nomograms

To construct and validate the CS nomograms, we randomly divided patients into training and validation sets. Univariate and multivariate Cox regression analysis were then performed in the training set. The basic clinicopathological information of patients in training and validation sets is shown in Table 3. In the univariate analysis, T stage, N stage, LNR, grade, CEA status and PI status were risk factors for both OS and CSS. After balancing all these variables in multivariable analysis, N stage, grade and CEA status lost their prognostic value, while T stage, LNR, PI status, age and race were verified as independent risk factors of OS and CSS (Table 4). Based on the multivariate analysis, T stage, LNR, PI status, age and race were included in the nomogram, which predicts the probability of reaching 5-year conditional OS given 1-4 years survival (Fig. 2A). The nomogram for 5-year conditional CSS given 1-4 years was shown in Fig. 2B. For example, for the patients with 170 points, the 5-year OS was only 30%; however, their 5-year conditional OS increased to 72% given 3 years already survived.

Performance of conditional survival nomograms

Survival ROC analysis was performed in both training and validation sets to test and validate the prognostic accuracy of developed nomograms. The result showed that the developed nomograms exhibited outstanding predictive ability and performed better than any other clinicopathological features alone in predicting 5-year conditional OS (nomogram AUC = 0.788, Fig.3A) and 5-year conditional CSS (nomogram AUC = 0.847, Fig.3B) in the training set. Consistent with the result in the training set, it was successfully validated in the validation set, and the 5-year AUC reached 0.773 and 0.799 when predicting OS (Fig.4A) and CSS (Fig.4B).

Discussion

CRC is a major disease threatening human health and causes a heavy burden on society in consideration of the high level of incidence and mortality. Although SRCC is a rare type of CRC, the prognosis of colorectal SRCC is extremely poor. Similar to the common type of adenocarcinoma, surgery followed by chemotherapy is still the

Table 3

Baseline features of colorectal signet-ring cell carcinoma patients in training and validation set

	Training set *N* (%)	Validation set *N* (%)
Age (IQR)	66.6 (57–80)	66.5 (57–80)
Sex		
Female	236 (50.0)	241 (51.1)
Male	236 (50.0)	231 (48.9)
Race		
White	392 (83.1)	390 (82.6)
Black	43 (9.1)	37 (7.8)
Other	37 (7.8)	45 (9.5)
Site		
Left	148 (31.4)	152 (32.2)
Right	262 (55.5)	255 (54.0)
Trans	62 (13.1)	65 (13.8)
Grade		
I/II	27 (5.7)	37 (7.8)
III	310 (65.7)	330 (69.9)
IV	110 (23.3)	82 (17.4)
T stage		
T1	18 (3.8)	27 (5.8)
T2	32 (6.8)	35 (7.5)
T3	252 (53.8)	248 (53.0)
T4	166 (35.5)	158 (33.8)
N stage		
N0	153 (32.4)	165 (35.0)
N1	103 (21.8)	106 (22.5)
N2	216 (45.8)	201 (42.6)
LNR (IQR)	0.274 (0.0–0.440)	0.274 (0.0–0.50)
CEA		
NO	155 (32.8)	134 (28.4)
Yes	139 (29.4)	152 (32.2)
Unknown	178 (37.7)	186 (39.4)
PI		
NO	356 (75.4)	366 (77.5)
Yes	116 (24.6)	106 (22.5)

IQR, interquartile range; LNR, lymph node ratio; PI, perineural invasion.

Table 4

Univariate and multivariate Cox regression analysis for OS and CSS in training set.

	OS								CSS							
	Univariate				Multivariate				Univariate				Multivariate			
		95% CI				95% CI				95% CI				95% CI		
Variables	HR	Lower	Upper	*P*	HR	Lower	Upper	*P*	HR	Lower	Upper	*P*	HR	Lower	Upper	*P*
Age	1.012	1.006	1.018	< 0.001	1.023	1.017	1.030	< 0.001	1.001	0.995	1.007	0.826	1.014	1.007	1.021	< 0.001
Sex				0.890				0.322				0.377				0.278
Female	1.000				1.000				1.000				1.000			
Male	1.011	0.861	1.188		1.092	0.918	1.298		1.089	0.902	1.314		1.118	0.914	1.368	
Race				0.609				0.008				0.966				0.048
White	1.000				1.000				1.000				1.000			
Black	1.120	0.844	1.487		1.461	1.090	1.959		1.029	0.730	1.449		1.308	0.920	1.860	
Other	0.923	0.688	1.238		0.781	0.571	1.070		0.968	0.693	1.352		0.711	0.498	1.016	
Site				0.960				0.427				0.639				0.222
Left	1.000				1.000				1.000				1.000			
Right	1.010	0.844	1.208		1.023	0.837	1.249		0.905	0.737	1.113		1.056	0.838	1.331	
Trans	0.974	0.748	1.269		1.197	0.900	1.592		0.946	0.699	1.281		1.328	0.957	1.844	
Grade				0.006				0.239				0.024				0.701
I/II	1.000				1.000				1.000				1.000			
III	1.960	1.294	2.968		1.428	0.937	2.176		1.988	1.214	3.255		1.241	0.751	2.052	
IV	1.742	1.180	2.572		1.296	0.874	1.923		1.801	1.132	2.863		1.195	0.746	1.914	
T stage				< 0.001				< 0.001				< 0.001				< 0.001
T1	1.000				1.000				1.000				1.000			
T2	0.909	0.469	1.763		0.684	0.339	1.382		0.457	0.174	1.200		0.358	0.124	1.037	
T3	2.229	1.327	3.746		1.316	0.742	2.333		2.229	1.181	4.207		1.223	0.591	2.533	
T4	4.233	2.512	7.135		1.873	1.039	3.375		5.047	2.674	9.526		1.859	0.885	3.904	
N stage				< 0.001				0.620				< 0.001				0.05
N0	1.000				1.000				1.000				1.000			
N1	1.653	1.300	2.103		1.124	0.862	1.467		2.385	1.744	3.262		1.540	1.085	2.186	
N2	2.753	2.254	3.362		1.024	0.754	1.390		4.584	3.516	5.978		1.453	0.994	2.125	
LNR	6.013	4.709	7.678	< 0.001	5.501	3.685	8.211	< 0.001	9.651	7.327	12.713	< 0.001	6.252	4.045	9.665	< 0.001
CEA				0.03				0.953				0.031				0.289
No	1.000				1.000				1.000				1.000			
Yes	1.255	1.022	1.540		1.033	0.831	1.283		1.294	1.023	1.637		1.144	0.892	1.467	
PI				< 0.001				< 0.001				< 0.001				< 0.001
No	1.000				1.000				1.000				1.000			
Yes	2.045	1.716	2.438		1.353	1.108	1.651		2.542	2.088	3.096		1.435	1.151	1.789	

CSS, cancer-specific survival; HR, hazard ratio; IQR, interquartile range; LNR, lymph node ratio; OS, overall survival; PI, perineural invasion.

standard treatment for resectable SRCC. However, as reported by Inamura *et al.*[15], the prognosis of SRCC is clearly poorer than that of adenocarcinoma. Therefore, a more tailored approach to risk assessment and treatment is essential for colorectal SRCC patients.

Conventional survival analysis in clinical research investigates the distribution of patients' survival time from the date of diagnosis or the start of treatment. Estimates of survival based on fixed time points will probably influence the death rate and can mislead both physician and patients. Thus, it becomes important to know how the prognosis will change over time, taking the patient's current survival time into account. As the survival time extends, the long-term prognosis of the patient may correspondingly improve. Estimation of conditional survival provides a dynamic assessment of long-term oncological outcomes for patients given periods of time already survived[16,17]. Conditional survival has been applied for evaluating patients' survival with several types of tumours, such as hepatocellular carcinoma, oesophageal cancer, pancreatic cancer[13,18–20].

In this study, we focused on patients with SRCC and demonstrated that the probability of conditional OS increases with each additional year survived. Of note, the more years patients had already survived, the better the chances of achieving a high rate of survival. The probability of achieving 5-year survival even increased from 42% directly to 91%, given that it already survived for 4 years.

Univariate and multivariate Cox regression analysis revealed that age, race, T stage, LNR and PI were verified as significantly independent risk factors of OS and CSS in SRCC patients. Consistent with our results, previous studies have shown that the advanced T stage and PI were related to poor survival[21,22]. By graphically showing the effect of predictors on the outcome, the nomogram gives a more tangible interpretation of predictors' impact on the outcome and is a usable model for clinicians to estimate the survival rate based on some significant clinicopathologic predictors. The independent predictors determined in Cox analysis, which are age, race, T stage, LNR and PI, were included in the nomogram, which predicts the probability of reaching 5-year OS and 5-year conditional OS given 1, 2 and 3 years.

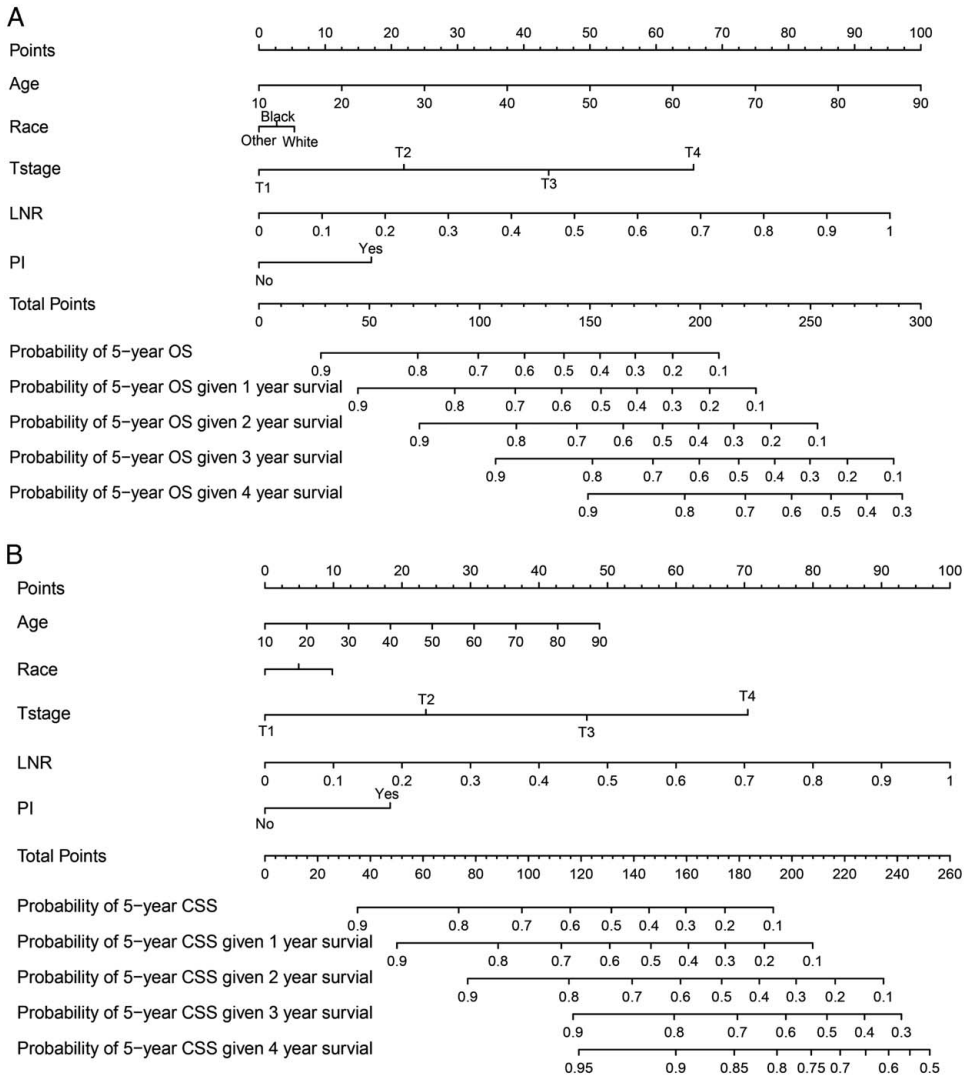

Figure 2. Conditional nomograms for the prediction of the conditional 5-year probability of overall survival (OS) (A) and cancer-specific survival (CSS) (B).

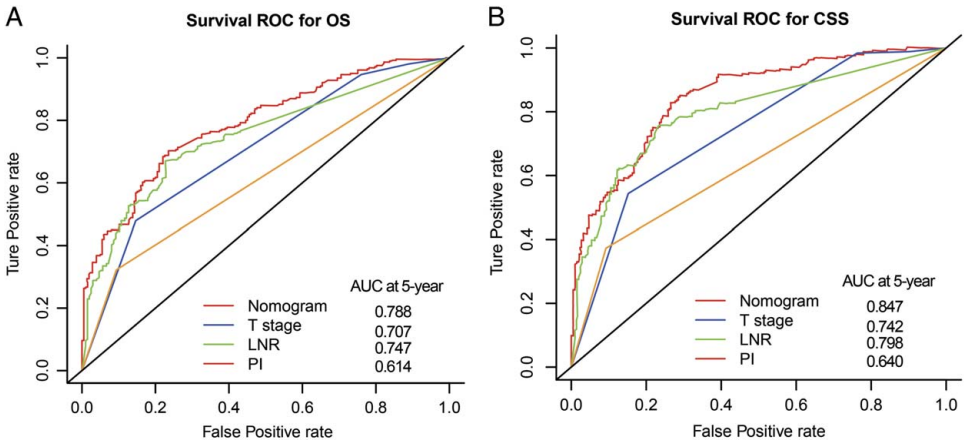

Figure 3. Survival receiver operating curve (ROC) curves of nomograms and other risk factors for overall survival (OS) (A) and cancer-specific survival (B) prediction in training set.

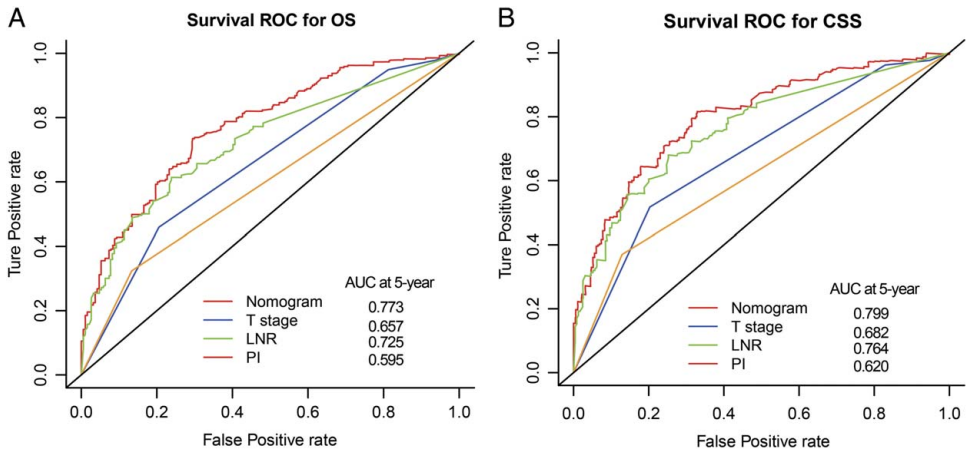

Figure 4. Survival receiver operating curve (ROC) curves of nomograms and other risk factors for overall survival (OS) (A) and cancer-specific survival (CSS) (B) prediction in validation set. AUC, area under the curve.

We must admit that there were several limitations to our study. Firstly, the SEER database, while a valuable resource, lacks certain key variables that could influence survival outcomes, such as tumour differentiation, surgical resection outcomes (R0 or not), and postoperative morbidity. Secondly, due to the retrospective nature of the study, there may be inherent biases and confounding factors that were not accounted for in the analysis. Additionally, the generalizability of our findings may be limited by the specific population and timeframe included in the SEER database. Furthermore, as with any observational study, causality cannot be inferred, and there may be unmeasured variables that could impact the results. Additional research endeavours are imperative to comprehensively address these identified limitations.

Conclusions

Patients with colorectal SRCC acquired a substantial increase in CS over time. Nomograms constructed with consideration of survival time can be more precise for prognosis analysis in patients with colorectal SRCC.

Ethical approval

As all the data were obtained from public database, the ethical approval is not applicable for this study.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Source of funding

None.

Author contributions

J.G., L.Z. and Y.Z. wrote the main manuscript text. All authors prepared Figures 1–3 and Tables 1–4. All authors reviewed the manuscript.

Conflicts of interest disclosure

The authors have no conflicts of interest.

Research Registration Unique Identifying Number (UIN)

1. Name of the registry: Research Registry.
2. Unique Identifying number or registration ID: research registry9846.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://researchregistry.knack.com/research-registry#home/registrationdetails/658792967872bb00289b721a/.

Guarantor

Lifeng Yao.

Data availability statement

All data used in this study were downloaded from public SEER database.

Provenance and peer review

No. This paper was not invited.

Acknowledgements

The authors thank the SEER database for providing the valuable data.

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