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ORIGINAL ARTICLE

Clinical and Translational Research

Nomogram predicting the cardiovascular disease mortality for older patients with colorectal cancer: A real-world population-based study

Jia-Yu Tan, Shuo-Hao Shen

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Abstract

BACKGROUND

Cardio-oncology has received increasing attention especially among older patients with colorectal cancer (CRC). Cardiovascular disease (CVD)-specific mortality is the second-most frequent cause of death. The risk factors for CVD-specific mortality among older patients with CRC are still poorly understood.

AIM

To identify the prognostic factors and construct a nomogram-based model to predict the CVD-specific mortality among older patients with CRC.

METHODS

The data on older patients diagnosed with CRC were retrieved from The Surveillance, Epidemiology, and End Results database from 2004 to 2015. The prognostic factors and a nomogram-based model predicting the CVD-specific mortality were assessed using least absolute shrinkage and selection operator and Cox regression.

RESULTS

A total of 141251 eligible patients with CRC were enrolled, of which 41459 patients died of CRC and 12651 patients died of CVD. The age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy were independent prognostic factors associated with CVD-specific mortality among older patients with CRC. We used these variables to develop a model to predict CVD-specific mortality. The calibration curves for CVD-specific mortality probabilities showed that the model was in good agreement with actual observations. The C-index value of the model in the training cohort and testing cohort for predicting CVD-

specific mortality was 0.728 and 0.734, respectively.

CONCLUSION
The proposed nomogram-based model for CVD-specific mortality can be used for accurate prognostic prediction among older patients with CRC. This model is a potentially useful tool for clinicians to identify high-risk patients and develop personalized treatment plans.

Key Words: Older patients; Colorectal cancer; Cardio-oncology; Nomogram; Outcome

Core Tip: For older patients with colorectal cancer (CRC), cardiovascular disease (CVD)-specific mortality is the second-most frequent cause of death. Herein, we analyzed data from the Surveillance, Epidemiology, and End Results program. The age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy were independent prognostic factors associated with CVD-specific mortality among older patients with CRC. Six variables were independent prognostic factors. Subsequently, we proposed a nomogram-based model of the CVD-specific mortality that could be used for accurate prognostic prediction of older patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the third-most deadly cancer worldwide. In 2020, there were 1.9 million new CRC cases[1,2]. Moreover, the incidence rates of CRC have been steadily increasing; the projected increase by 2035 is 2.5 million[2,3]. Cancer-specific mortality is known to be the most common cause for CRC patients[1,3]. With improved treatment options such as endoscopy, surgical local excision, radiotherapy, systemic therapy, chemotherapy, targeted therapy, immunotherapy[1], altered CRC risk factor patterns, and screening, the CRC mortality rates have declined[4]. Thus, the non-cancer causes of death among CRC patients have increased with increasing survival time. Many researchers have been increasingly concerned regarding non-cancer deaths, especially due to cardiovascular disease (CVD)[5-8]. Cardio-oncology has developed as a relatively new discipline and received increasing attention in clinical treatment. Baraghoshi *et al*[9] showed CRC survivors had almost double the risk of CVD than the general population. Among older patients with CRC, deaths due to cancer and CVD-specific factors were the first and second-most frequent cause of deaths, respectively[8,10].

Therefore, risk factors for cancer-specific mortality and CVD-specific mortality among older patients with CRC merits further analysis. Until now, the risk factors and cardio-oncological factors in older patients with CRC have been poorly understood. Furthermore, there is no predictive model yet that can estimate the CVD risk in older patients with CRC. In this study, we characterized the risk factors for cancer-specific mortality and CVD-specific mortality and established a risk predictive model for CVD-specific mortality, aiming to provide a contemporary and valuable resource for cardiologists and oncologists in their follow-up care of older patients with CRC.

MATERIALS AND METHODS

Patient selection

In this retrospective study, we used data from The Surveillance, Epidemiology, and End Result (SEER) program which is a public tumor registry that covers 34.6% of the US population with cancer.

In total, the clinical data of patients diagnosed with CRC in the SEER program from January 1, 2004 to December 31, 2015 were retrospectively included in this study. All patients aged > 60 years with complete follow-up data and positive malignant histological examination were included. Patients whose clinicopathological information was incomplete were excluded. To further decrease the potential bias, we also excluded patients with < 30 days of follow-up and patients with more than one lifetime history of cancer. Finally, 141251 patients were enrolled in the study (Figure 1).

This observational study used de-identified and publicly available data from the SEER registry and thus did not require formal consent or institutional review board approval. This study was conducted in accordance with the tenets of the Helsinki Declaration.

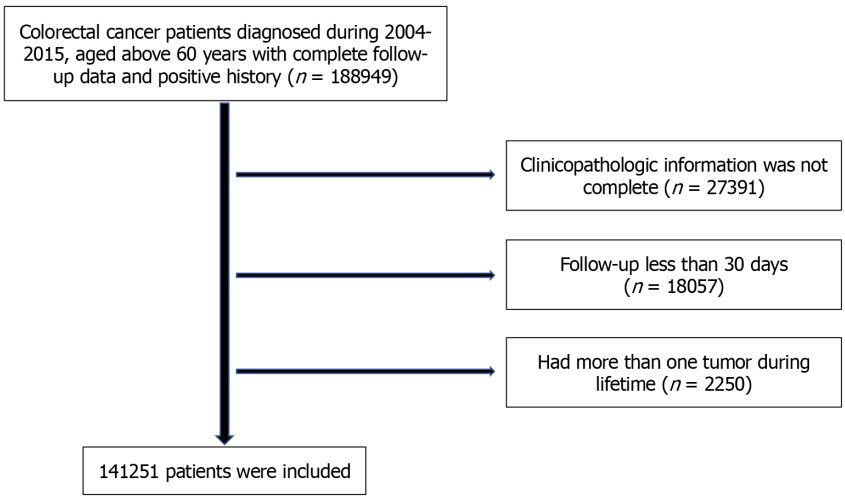

Figure 1 Cohort selection criteria.

Information collection

We collected the basic information of patients, namely age at diagnosis; sex; marital status (single, married, or others); race (White, Black, or others); year of diagnosis; insurance status; primary site (right half colon, left half colon, or rectum); TNM stage; histological grade (well, moderate, poorly, or undifferentiated); histology type (adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma, or others); surgery; radiotherapy; and chemotherapy.

The cause of death classification was recorded from the variable "COD to site recode" in the SEER database. Cancer-specific mortality was defined by the cause of death recorded as CRC. We considered deaths due to heart disease, atherosclerosis, aortic aneurysm and dissection, cerebrovascular disease, hypertension without heart disease, and the diseases of arteries, arterioles, and capillaries as CVD-specific mortality.

Statistical analysis

Univariate and multivariate Cox regression analyses were used to determine the survival risk factors of cancer-specific mortality and CVD-specific mortality in the training cohort. Least absolute shrinkage and selection operator (LASSO) method is a commonly used method for regression with high-dimensional predictors[11]. The LASSO Cox regression model was used to select the most valuable prognostic variables of all CRC and CVD-specific mortality in our study. We constructed the nomogram of CVD-specific mortality according to the LASSO results.

The C-index, calibration curves, and prognostic decision curve analysis (DCA) were created to assess the predictive accuracy and discriminative ability of the nomogram-based model in the training and testing cohorts. R software (version 3.6.1) was used for statistical analysis. $P < 0.05$ was considered to indicate statistically significant differences.

RESULTS

Patient characteristics

A total of 141251 patients with CRC (48.7% male and 51.3% female) were included in this study. The proportion of patients aged 60-69 years was 38.2%, that of patients aged 70-79 years was 34.1%, and that of patients aged ≥ 80 years was 27.7%. In the entire cohort, 41459 patients died of CRC, 12651 patients died of CVD, 73035 patients were alive, and 14106 patients died of other causes. The clinicopathologic characteristics of patients with CRC are summarized in Table 1.

Analysis on the cancer-specific mortality and CVD-specific mortality

Patients were randomly divided into a training cohort (98876 patients) and a test cohort (42375 patients) in a ratio of 7:3 based on the "caret" package on the outcome of "dead." Univariate analysis on the cancer-specific mortality and CVD-specific mortality was performed in the training cohort.

As shown in Table 2, univariate analysis revealed that age was both associated with cancer-specific mortality and CVD-specific mortality. The risk of cancer-specific mortality in patients aged ≥ 80 years was 1.63-times that of patients aged 60-69 years, while the risk of CVD-specific mortality in patients aged ≥ 80 years was 7.31-times that of patients aged 60-69 years. TNM stage was positively associated with cancer-specific mortality. However, the TNM stage was negatively associated with CVD-specific mortality, and the risk of CVD-specific mortality in TNM stage IV was 0.73-times that of TNM stage I. Absence of chemotherapy was associated with cancer-specific mortality, but presence of chemotherapy was associated with CVD-specific mortality.

On multivariate analysis, we found that the age at diagnosis (≥ 80 years *vs* 60-69, HR: 6.43;70-79 *vs* 60-69, HR: 2.44); sex (male *vs* female, HR: 1.58); marital status (married *vs* single, HR: 0.68); year of diagnosis (2008-2011 *vs* 2004-2007, HR: 0.89; 2012-2015 *vs* 2004-2007, HR: 0.79); surgery (no *vs* yes, HR: 2.07); and chemotherapy (no *vs* yes, HR: 0.51) was associated

Table 1 Clinicopathologic characteristics of patients with different outcomes, *n* (%)

Variables	Cancer-specific mortality (*n* = 41459)	CVD-specific mortality (*n* = 12651)	Others-specific mortality (*n* = 14106)	Survivors (*n* = 73035)	Total (*n* = 141251)
Age at diagnosis (years)					
60-69	14188 (34.2)	1911 (15.1)	2750 (19.5)	35112 (48.1)	53961 (38.2)
70-79	13969 (33.7)	3971 (31.4)	4895 (34.7)	25384 (34.8)	48219 (34.1)
≥ 80	13302 (32.1)	6769 (53.5)	6461 (45.8)	12539 (17.1)	39071 (27.7)
Sex					
Female	21112 (50.9)	6395 (50.5)	7294 (51.7)	37631 (51.5)	72432 (51.3)
Male	20347 (49.1)	6256 (49.5)	6812 (48.3)	35404 (48.5)	68819 (48.7)
Marital status					
Single	4908 (11.8)	1296 (10.2)	1431 (10.1)	7802 (10.7)	15437 (10.9)
Married	19950 (48.1)	5414 (42.8)	6312 (44.7)	41601 (57)	73277 (51.9)
Others	16601 (40.1)	5941 (47)	6363 (45.2)	23632 (32.3)	52537 (37.2)
Race					
White	33337 (80.4)	10670 (84.3)	11818 (83.8)	58562 (80.2)	114387 (81)
Black	4928 (11.9)	1232 (9.8)	1318 (9.3)	7158 (9.8)	14636 (10.4)
Others	3197 (7.7)	749 (5.9)	970 (6.9)	7315 (10)	12228 (8.6)
Year of diagnosis					
2004-2007	16825 (40.6)	6651 (52.6)	7135 (50.6)	16055 (22)	46666 (33)
2008-2011	14971 (36.1)	4215 (33.3)	4873 (34.5)	23245 (31.8)	47304 (33.5)
2011-2016	9663 (23.3)	1785 (14.1)	2098 (14.9)	33735 (46.2)	47281 (33.5)
Insurance status					
Insured	27713 (66.8)	7290 (57.6)	8303 (58.9)	59691 (81.7)	102997 (72.9)
Uninsured	576 (1.4)	45 (0.4)	78 (0.6)	1030 (1.4)	1729 (1.2)
Unknown	13170 (31.8)	5316 (42)	5725 (40.5)	12314 (16.9)	36525 (25.9)
Primary site					
Right half colon	20201 (48.7)	6787 (53.6)	7596 (53.8)	35512 (48.6)	20096 (49.6)
Left half colon	10320 (24.9)	3254 (25.7)	3530 (25)	19442 (26.6)	36546 (25.9)
Rectum	10938 (26.4)	2610 (20.6)	2980 (21.2)	18081 (24.8)	34609 (24.5)
TNM stage					
I	3391 (8.2)	4101 (32.4)	4414 (31.3)	24426 (33.4)	36332 (25.7)
II	7956 (19.2)	4755 (37.6)	5207 (36.9)	25190 (34.5)	43108 (30.5)
III	14313 (34.5)	3216 (25.4)	3657 (25.9)	20502 (28.1)	41688 (29.5)
IV	15799 (38.1)	579 (4.6)	828 (5.9)	2917 (4)	20123 (14.3)
Grade					
Well	2399 (5.8)	1314 (10.4)	1459 (10.3)	8479 (11.6)	13651 (9.7)
Moderate	26863 (64.8)	9080 (71.8)	10068 (71.4)	53387 (73.1)	99398 (70.4)
Poorly	10709 (25.8)	2043 (16.1)	2297 (16.3)	9734 (13.3)	24783 (17.5)
Undifferentiated	1488 (3.6)	214 (1.7)	282 (2)	1435 (2)	3419 (2.4)
Histology					
Adenocarcinoma	32932 (79.4)	9709 (76.7)	10920 (77.4)	56050 (76.7)	109611 (77.6)
Mucinous adenocarcinoma and	4075 (9.8)	1073 (8.5)	112 (7.9)	5174 (7.1)	11434 (8.1)

signet-ring cell carcinoma					
Others	4452 (10.8)	1869 (14.8)	2074 (14.7)	11811 (16.2)	20206 (14.3)
Surgery					
Yes	36485 (88)	12112 (95.7)	13507 (95.8)	71367 (97.7)	133471 (94.5)
No	4974 (12)	539 (4.3)	599 (4.2)	1668 (2.3)	7780 (5.5)
Radiotherapy					
Yes	6094 (14.7)	929 (7.3)	1202 (8.5)	9064 (12.4)	17289 (12.2)
No	35365 (85.3)	11722 (92.7)	12769 (91.5)	63971 (87.6)	123962 (87.8)
Chemotherapy					
Yes	19038 (45.9)	2036 (16.1)	2593 (18.4)	24410 (33.4)	48077 (34)
No	22421 (54.1)	10615 (83.9)	11513 (81.6)	48625 (66.6)	93174 (66)

CVD: Cardiovascular disease.

with CVD-specific mortality (Table 2).

Prognostic nomogram-based model construction

We performed LASSO regression analysis to reduce the risk of over-fitting of our model by compressing the partial factorial regression coefficient to zero[12]. After primary filtration, we used penalty parameter tuning performed *via* 10-fold cross-validation to further narrow the variables, which requires the selected variables to appear more than 900 times in a total of 1000 times 10-fold cross-validation repetitions (Figure 2).

Finally, six variables-age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy-were selected to construct the nomogram-based model, which was used to estimate the 3-year and 5-year CVD-specific mortality (Figure 3).

Validating the nomogram-based model

In the training cohort, the C-index of the nomogram for predicting CVD-specific mortality was 0.728 (95%CI: 0.722-0.734), indicating good discrimination. Figure 4A and B show a corrected graph of the prediction accuracy of the nomogram, which shows good consistency between the actual and predicted 3- and 5-year CVD-specific mortality, with a slope of nearly 45°.

Similarly, in the testing cohort, the C-index of the nomogram for CVD-specific mortality was 0.734 (95%CI: 0.725-0.743). Figure 4C and D show the corrected graph of the prediction accuracy of the nomogram, which showed good consistency between the actual and predicted 3- and 5-year cardiovascular mortality rates, with a slope of nearly 45°.

The DCA was plotted to evaluate how clinical benefits affected patients (Figure 5). According to the DCA, our nomogram had a positive net benefit in the training and testing cohorts, with a wide threshold probability range.

DISCUSSION

According to previous studies, older patients with CRC had a significantly higher risk of CVD morbidity and CVD-specific mortality than the general population[5]. Researchers have analyzed various causes of death in patients with different types of cancer and have emphasized that CVD was the most prevalent cause of non-cancer death in patients with cancer[13,14]. In recent years, a new international discipline called cardio-oncology has emerged that integrates cardiology and oncology organically and is receiving extensive attention. Cardio-oncology as a new discipline has now become a research hotspot. In a Canadian study, researchers found that CVD was the leading non-cancer cause of death among older patients with CRC[15]. Our findings were consistent with this Canadian study. In our study, we focused on the cardio-oncological health of older patients with CRC and found that the CVD-specific mortality was 8.96% among older patients with CRC, the second-leading cause of death, after CRC-specific mortality (29.35%). Therefore, it is very important to explore the prognostic factors of CVD-specific mortality in older patients with CRC.

To our best knowledge, the prognostic factors of CVD-specific mortality for older patients with CRC have not yet been completely elucidated, there is no constructed nomogram model for CVD-specific mortality in older patients with CRC. Therefore, our study focused on identifying the prognostic risk factors for CVD-specific mortality among older patients with CRC. In this study, we performed LASSO regression analysis to reduce the risk of over-fitting the model and suggested that the age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy were the key prognostic factors associated with CVD-specific mortality among older patients with CRC. We synthesized a variety of analysis methods to construct a nomogram-based prognostic evaluation model with these six key prognostic factors, and validated the prognostic model with a testing cohort. By using comprehensive analysis and further verification, we found good predictive effect and high reliability. To our knowledge, this is the largest contemporary cohort of CVD-specific

Table 2 Competing risk analysis on the cancer-specific mortality and cardiovascular mortality

Variables	Univariate analysis (cancer-specific mortality)			Univariate analysis (CVD-specific mortality)			Multivariate analysis (cancer-specific mortality)			Multivariate analysis (CVD-specific mortality)		
	HR	95%CI	*P* value	HR	95%CI	*P* value	HR	95%CI	*P* value	HR	95%CI	*P* value
Age at diagnosis (years)												
60-69	Reference			Reference			Reference			Reference		
70-79	1.17	1.14-1.2	< 0.001	2.52	2.36-2.69	< 0.001	1.34	1.3-1.37	< 0.001	2.44	2.29-2.61	< 0.001
≥ 80	1.63	1.58-1.67	< 0.001	7.31	6.88-7.77	< 0.001	1.94	1.88-2	< 0.001	6.43	6.02-6.85	< 0.001
Sex												
Female	Reference						Reference			Reference		
Male	1.03	1.1-1.05	< 0.01	1.07	1.02-1.11	< 0.01	1.16	1.13-1.19	< 0.001	1.58	1.51-1.65	< 0.001
Marital status												
Single	Reference			Reference			Reference			Reference		
Married	0.77	0.74-0.80	< 0.001	0.72	0.67-0.77	< 0.001	0.83	0.80-0.86	< 0.001	0.68	0.63-0.73	< 0.001
Others	0.98	0.94-1.02	0.31	1.28	1.19-1.38	< 0.001	0.98	0.94-1.01	0.21	0.93	0.87-1.00	0.06
Race												
Black	Reference			Reference			Reference			Reference		
White	0.82	0.79-0.85	< 0.001	1.05	0.98-1.12	0.2	0.84	0.81-0.88	< 0.001	0.89	0.83-0.96	< 0.001
Others	0.71	0.68-0.75	< 0.001	0.66	0.50-0.74	< 0.001	0.73	0.69-0.77	< 0.001	0.63	0.57-0.71	< 0.001
Year of diagnosis												
2004-2007	Reference			Reference			Reference			Reference		
2008-2011	0.92	0.9-0.95	< 0.001	0.86	0.82-0.91	< 0.001	0.89	0.87-0.91	< 0.001	0.89	0.85-0.94	< 0.001
2012-2015	0.85	0.83-0.88	< 0.001	0.73	0.68-0.78	< 0.001	0.82	0.8-0.85	< 0.001	0.79	0.74-0.85	< 0.001
Primary site												
Right half colon	Reference			Reference			Reference			Reference		
Left half colon	0.93	0.9-0.95	< 0.001	0.84	0.80-0.89	< 0.001	0.99	0.96-1.02	0.39	1.02	0.97-1.07	0.44
Rectum	1.07	1.04-1.1	< 0.001	0.76	0.72-0.80	< 0.001	1.08	1.04-1.12	< 0.001	1.06	0.99-1.13	0.08
TNM stage												

I	Reference			Reference			Reference			Reference		
II	2.09	1.99-2.19	< 0.001	1.05	1.00-1.11	0.05	1.39	1.29-1.49	< 0.001	1.03	0.98-1.09	0.26
III	4.39	4.19-4.59	< 0.001	0.86	0.81-0.90	< 0.001	2.46	2.28-2.65	< 0.001	0.78	0.63-0.98	0.04
IV	18.42	17.61-19.27	< 0.001	0.73	0.65-0.81	< 0.001	9.26	8.61-9.95	< 0.001	0.87	0.72-1.06	0.17
Grade												
Well	Reference			Reference			Reference			Reference		
Moderate	1.64	1.56-1.72	< 0.001	1.05	0.98-1.13	0.14	1.26	1.2-1.33	< 0.001	1.05	0.99-1.13	0.15
Poorly	3.11	2.95-3.28	< 0.001	1.14	1.05-1.24	< 0.001	1.65	1.56-1.74	< 0.001	1.08	0.98-1.13	0.07
Undifferentiated	3.48	3.22-3.76	< 0.001	1.11	0.93-1.31	0.25	1.81	1.68-1.96	< 0.001	1.11	0.93-1.32	0.26
Histology												
Adenocarcinoma	Reference			Reference			Reference			Reference		
Mucinous adenocarcinoma and signet-ring cell carcinoma	1.26	1.21-1.31	< 0.001	1.14	1.06-1.23	< 0.001	1.05	1.01-1.09	0.01	1.13	1.05-1.22	< 0.01
Others	0.71	0.68-0.74	< 0.001	1	0.94-1.06	0.95	1.01	0.97-1.04	0.77	1.01	0.95-1.07	0.77
Surgery												
Yes	Reference			Reference			Reference			Reference		
No	4.24	4.09-4.4	< 0.001	1.74	1.57-1.94	< 0.001	3.46	3.32-3.62	< 0.001	2.07	1.86-2.32	< 0.001
Radiotherapy												
Yes	Reference			Reference			Reference			Reference		
No	1.22	1.18-1.26	< 0.001	0.57	0.52-0.61	< 0.001	1.17	1.12-1.22	< 0.001	0.99	0.89-1.10	0.9
Chemotherapy												
Yes	Reference			Reference			Reference			Reference		
No	1.66	1.62-1.7	< 0.001	0.39	0.37-0.41	< 0.001	1.66	1.64-1.68	< 0.001	0.51	0.47-0.55	< 0.001

CVD: Cardiovascular disease.

mortality and construction of nomogram-based prognostic evaluation model for older patients with CRC.

Our results indicated that the risk of CRC-specific mortality and CVD-specific mortality were both negatively associated with age at diagnosis. Previous studies have reported that patients with cancer perpetually have a higher risk of dying from CVD than the general population in the United States, and the incidence of any CVD increased with age[16, 17]. Meanwhile, age was also identified as a risk factor for anthracycline-induced cardiotoxicity in CRC patients[17].

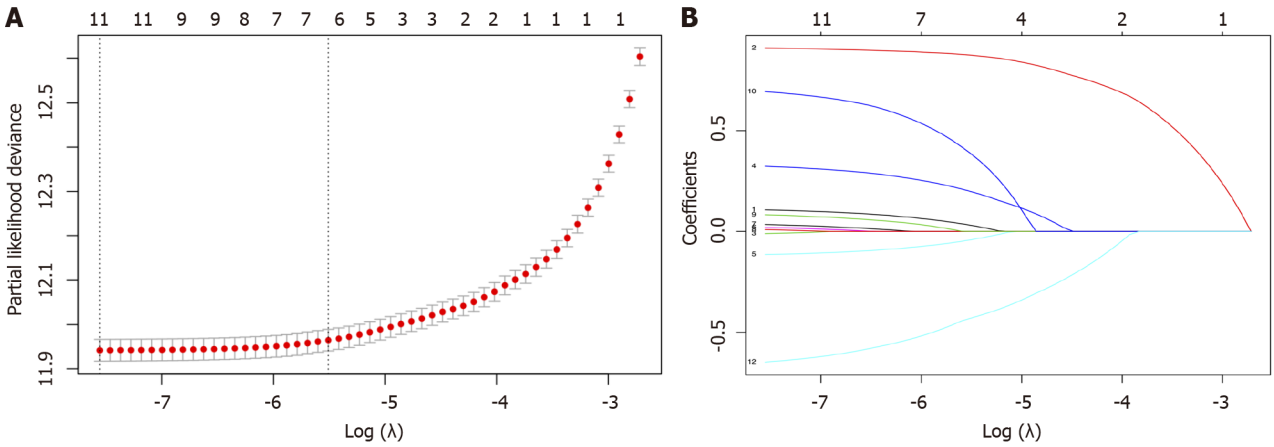

Figure 2 Lasso regression to determine the variables included in the model. A: Lasso regression search for the optimal coefficient; B: A 10x cross-validation approach used to determine lambda at the least partial likelihood deviance.

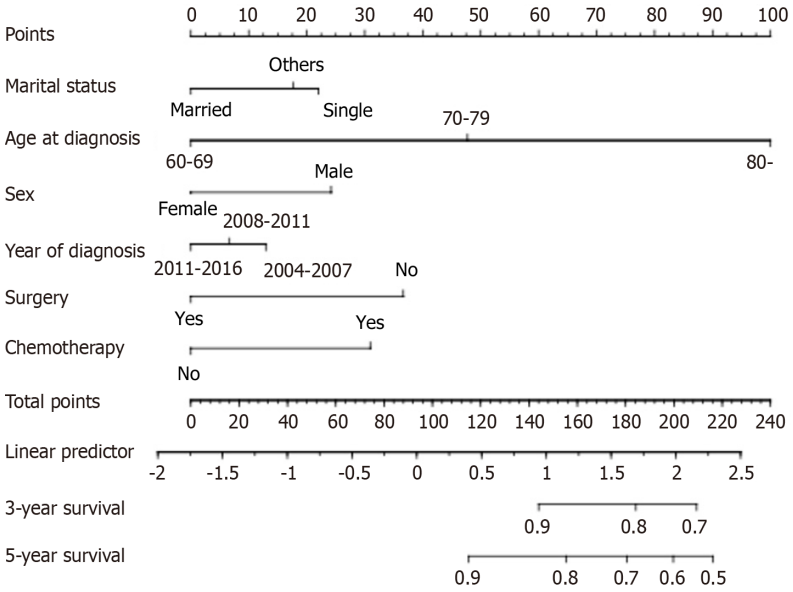

Figure 3 Nomogram to predict the 3- and 5-year cardiovascular disease survival of older patients of colorectal cancer.

Our results suggested that male patients had a positive correlation with the risk of CVD-specific mortality. Because estrogen lowers a woman's risk of CVD, they are typically protected by estrogen. Increased levels of oxidative stress may interfere with the mechanisms of DNA repair and was associated with higher rates of CRC and CVD[18]. Men are less resilient to oxidative stress than women and also have a higher risk of myocardial infarctions than women[19-21]. In addition, in our study, married status was also associated with reduced CVD-specific mortality in older patients with CRC. Married patients generally had better outcomes than single patients, which may be partly related to a favorable family environment[22].

An increasing number of older patients with CRC undergo surgery, chemotherapy, and/or radiotherapy. The improved anti-tumor systemic treatments resulted in longer survival time of patients with CRC[23]. However, the chemotherapeutic agents for CRC, such as oxaliplatin, 5-fluorouracil, cetuximab, and bavacizumab exhibit potential cardiotoxicity that may lead to a progressive increase in CVD deaths. Some studies have reported that a significant number of patients with CRC suffered CVD events following treatment with capecitabine, oxaliplatin, and bevacizumab [24-26]. Unfortunately, there are no specific chemotherapy regimens for patients with cancer in the SEER database, so we were unable to draw conclusions about the effects of specific chemotherapy regimens on CVD-specific mortality in this study. In the future, we aim to collect relevant data from other research centers for analysis to obtain more accurate results.

We developed a nomogram-based model for predicting the CVD-specific mortality in older patients with CRC based on six key prognostic variables, which is the first for CRC patients > 60 years old based on the SEER database. The model could be well applied in clinical work. This nomogram provides a visual and convenient assessment tool not only for the follow-up management of patients with cancer but also to ensure early intervention measures for such a high-risk population to improve the prognosis of patients and reduce the burden on healthcare resources. The nomogram-based

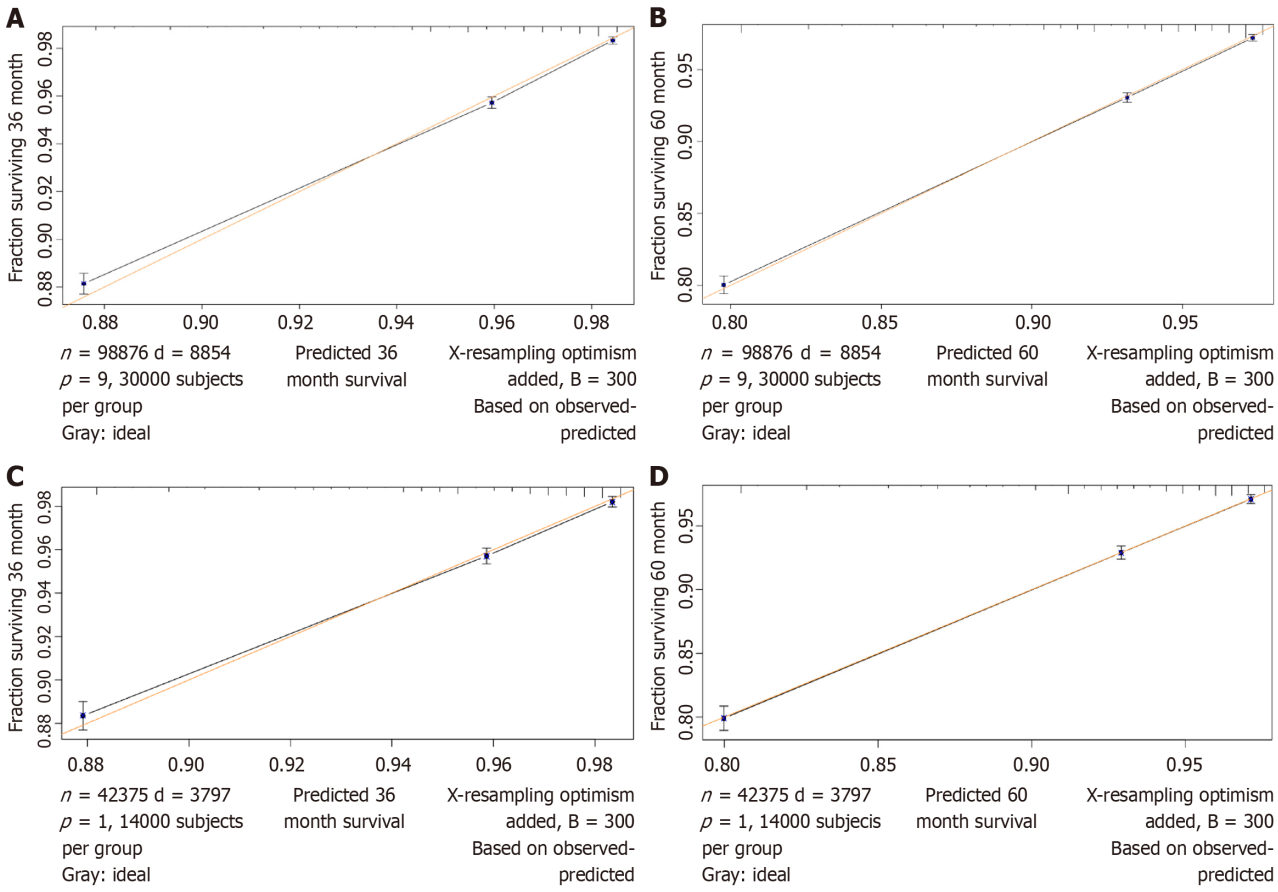

Figure 4 Calibration curves for the 3-year and 5-year cardiovascular disease survival. A and B: Training cohort; C and D: Testing cohort.

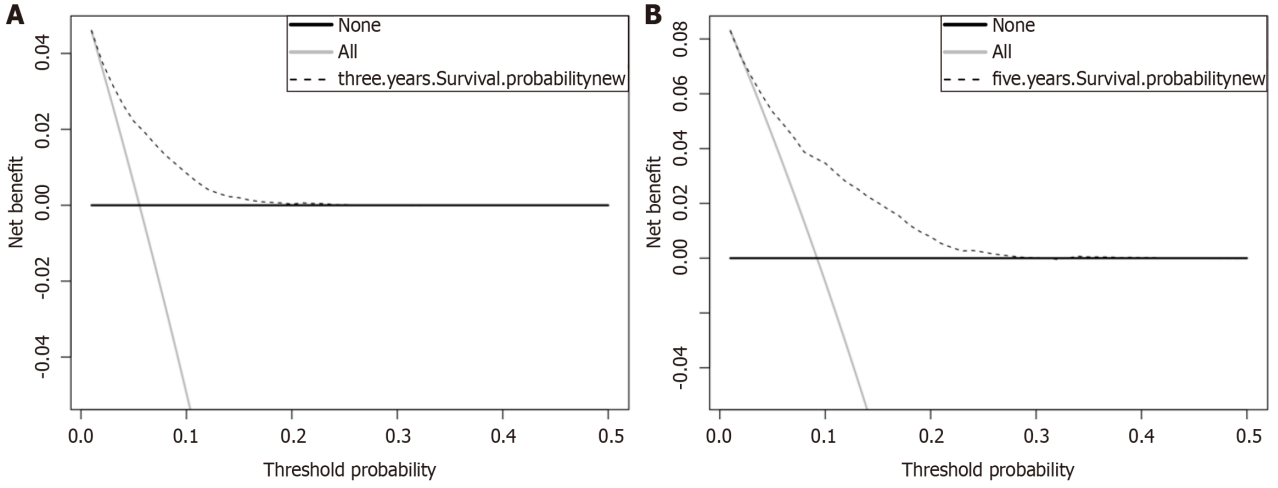

Figure 5 Decision curve analysis for the nomogram-based model. A and B: Predicting the prognosis of 3-year (A) and 5-year (B) cardiovascular disease survival in the testing cohort.

model emphasized the contributions of age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy. The nomogram-based model was verified by a training (C-index: 0.728) and testing (C-index: 0.734) cohort, indicating great diagnostic accuracy of the model. In addition, the DCA suggested that the estimated CVD-specific mortality threshold probability of a patient had a positive net benefit.

Older patients with CRC have a better cancer-specific prognosis, but the risk of CVD-specific death is still higher. Antitumor therapy could directly lead to CVD or increase the risk of CVD, which had a serious impact on the quality of life and health of patients with cancer. There is growing evidence showing the shared pathophysiology and overlapping risk factors between CRC and CVD in the field of cardio-oncology[27-29]. Cardio-oncology has explored an optimal approach to manage these patients *via* the active collaboration between oncologists and cardiologists[30]. Patients with CRC maybe benefit from clinical intervention, which could reduce the CVD events. In addition, this study also emphasizes the need

for continuous and active surveillance during patient survival. This finding supports the early intervention of cardiologists, and they are especially important in that future research will focus on early heart disease assessment and how active heart diseases care should be in older patients.

This study has some limitations. First, the SEER database lacked many important variables such as blood lipid data, height, weight, medical history, and chemotherapy regimens. Second, the SEER database includes data from many medical centers, and the data were hence heterogeneous. We have adopted strict inclusion and exclusion of indicators to reduce heterogeneity. Third, our nomogram currently lacks an external cohort for predictive efficacy. In the future, we aim to incorporate external cohorts to validate our nomogram.

CONCLUSION

The age at diagnosis, sex, marital status, year of diagnosis, surgery, and chemotherapy were independent prognostic factors associated with CVD-specific mortality in older patients with CRC. The proposed nomogram-based model of the CVD-specific mortality could be used to predict the accurate prognosis for older patients with CRC and could be adopted to assist clinicians including oncologists and cardiologists to provide screening recommendations and choose an optimum treatment regimen.

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FOOTNOTES

Author contributions: Shen SH and Tan JY designed the research study; Shen SH and Tan JY performed the research. Shen SH and Tan JY analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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