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ORIGINAL

Development and validation of a nomogram to individually predict survival of old athletic patients with colon adenocarcinoma after surgery

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ABSTRACT

Objective: Nomograms can be used in quantitative and intuitive methods to predict the survival rate of athletic patients. This study was designed to identify prognosis markers that affected overall survival (OS) in old colon adenocarcinoma (CAC) athletic patients after surgery and constructed a nomogram to predict postoperative survival.
Methods: We selected qualified athletic patients diagnosed with CAC from 2010 to 2015 from the surveillance, epidemiology, and end results (SEER) database. We divided athletic patients diagnosed from 2010 to 2013 into a validation and training cohorts according to 3: 7. Athletic Patients from 2014 to 2015 were regarded as a test cohort. We used the Cox regression model to construct a new nomogram, and test the nomogram performance through validation and test cohorts.
Results: The multivariate Cox regression analysis identified age, sex, brain metastasis, lymph node metastasis, carcinoembryonic antigen (CEA), liver metastasis, surgery style, tumor lymph node ratio (LNR), distant metastasis, and lung metastasis as independent prognosis markers associated with OS. The constructed nomogram had good calibration and discriminative ability. The concordance indexes (c-indexes) of validation and test cohorts were 0.767, 0.775.

Conclusions: We constructed and validated a convenient and effective nomogram, which individually predicted OS for old athletic patients with CAC after surgery the based on clinical information available.

KEY WORDS: Adenocarcinoma; Colonic Neoplasms; Kaplan-Meier Estimate; Nomograms; SEER Program

INTRODUCTION

The large intestine is mainly divided into colon and rectum, of which 70% of colorectal cancer is colon cancer.(R. L. Siegel, Miller, & Jemal, 2019) Colon cancer is one of the major tumors of gastrointestinal tracts worldwide(Labianca et al., 2010; Marley & Nan, 2016). Colon cancer mortality and morbidity have declined in recent decades (R. L. Siegel, K. D. Miller, S. A. Fedewa, et al., 2017). But previous studies had shown that early-onset colorectal cancer is on the rise (Rebecca L. Siegel, Medhanie, Fedewa, & Jemal, 2019). A report from the United States showed that the incidence of colon cancer was increasing year by year in people under 50 years old.(Ansa, Coughlin, Alema-Mensah, & Smith, 2018) Older athletic patients with colorectal cancer had a higher incidence of complications than younger athletic patients (Yang et al., 2014). Besides, adenocarcinoma was common in colon cancer(R. L. Siegel, Miller, & Jemal, 2017).

European data showed that about 25% of athletic patients had metastases at first diagnosis, and nearly 50% of colorectal cancer patients had metastases. Furthermore, Lymph node metastasis might be related to poor prognosis and frequent colon cancer recurrence (Van Cutsem & Oliveira, 2009). The 5-year relative survival rate was 71.7% and 13.3% in athletic patients diagnosed with colon cancer with regional metastasis and distant metastasis, and 91.1% in athletic patients without metastasis. LNR was a prognosis predictor and closely related to tumor metastasis in colon cancer athletic patients who were node-positive (Jakob et al., 2018). Surgical resection, radiotherapy and chemotherapy were widely used for treating gastrointestinal cancer. Surgery was the most common treatment among these therapeutic methods(Aoyagi, Terracina, Raza, & Takabe, 2014). A retrospective cohort of a European hospital showed that among patients diagnosed with colon cancer, most athletic patients received surgery, and only a few received chemotherapy or radiation therapy (Aparicio et al., 2009).

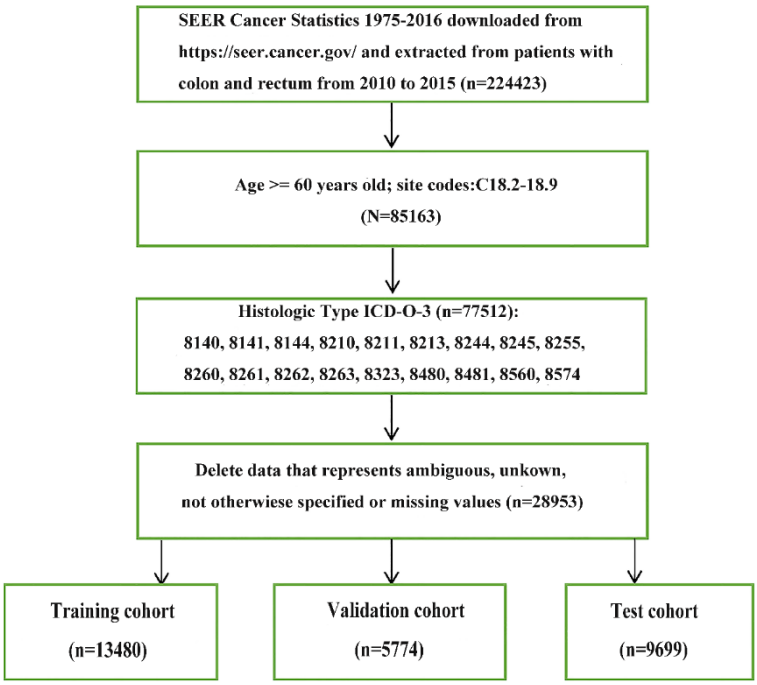
In order to provide accurate and effective prognosis prediction for old athletic patients, we identified prognosis markers and demonstrated the prognosis value of LNR. Finally, a new nomogram was established, which individually predict survival of old athletic patients with colon adenocarcinoma after surgery.

Methods

Patients select

We extracted all athletic patients diagnosed with CAC from 2010 to 2015 from SEER database. According to the following exclusion criteria, a total of 28953 participants were selected. Exclusion criteria: (1) The athletic patients did not receive surgery; (2) age<60 years; (3) histologic style was not adenocarcinoma; (4) athletic patients' information was unknown, missing or not otherwise specified. The specific selection process was shown in Figure 1. The National Cancer Institute (NCI) established the SEER database in 1973.We used SEER*Stat 8.3.5 to collect the records of athletic patients with CAC who underwent surgery between 2010 and 2015 from the SEER 18 registration database. The following ICD-O-3 codes and site codes were included (ICD-O-3:8140、8141、8144、8210、8211、8213、8244、8245、8255、8260-8263、8323、8480-8481、8560、8574; site codes: C18.2-18.9).

Figure 1. Flow diagram of patient selection



Prognosis markers selection

The age, sex, tumor size, tumor differentiation, CEA, LNR, TNM stage, liver metastasis, depth of invasion, lymph node metastasis, distant metastasis, regional lymph nodes surgery, brain metastasis, surgery style, lung metastasis were collected from each patient. A previous study found that CEA was a prognosis factor in colorectal cancer after surgical resection(Su, Shi, & Wan,

2012). The ratio between positive lymph nodes and the total number of lymph nodes examined is the definition of LNR. Previous studies showed that LNR was an independent prognostic indicator for athletic patients with stage IV colon cancer after surgery (Jiang et al., 2019).

Statistical Analysis

We divided the entire statistical analysis into five steps. First, Athletic patients were divided into three cohorts. Athletic Patients from 2010 to 2013 were divided into training cohort (n=13480) and validation cohort (n=5770) according to 7:3. Athletic Patients from 2014 to 2015 were selected as a test cohort (n=9699). We used the validation cohort and test cohort as internal and external validation. Continuous variables were expressed as the means ± standard deviations (normal distribution) or medians (skewed distribution), analyzed by the one-way ANOVA (normal distribution), Kruskal-Wallis H (skewed distribution) test. All the categorical variables were presented in frequency and proportion analyzed by the chi-square test. Second, we used the receiver operating characteristic (ROC) curve to determine the optimal cutoff value for LNR and found the best cut-off value of tumor size by X-tile software in the training cohort. Third, we used univariate and multivariate Cox regression analysis to identify prognosis markers. The Kaplan-Meier method and the log-rank test were used to analyze prognostic markers. Fourth, A new nomogram based on multivariate Cox regression analysis was established. Fifth, we used Harrell's c-index(Harrell, Lee, & Mark, 1996) to evaluate the discrimination of the nomogram and Hosmer-Lemeshow (H-L) test to evaluate the calibration of the nomogram. We used decision curve analysis (DCA) to compare the clinical utility of major prognostic indicators and the constructed nomogram(Van Calster et al., 2018). We calculated athletic patients' total points in training cohort. Athletic Patients were divided into high-risk group and low-risk group by total points' median value. The time-dependent receiver operating characteristic(td-ROC) curve(Combescure, Daures, & Foucher, 2016) was used to evaluate predictive ability of nomogram. All statistical analyses were performed using software IBM SPSS Statistics (Version 22, SPSS Inc., Chicago, IL, USA) and programming language R (Version 3.6.1, http:// www. R-project.org). "survival" and "Rms", "Hmics", "timeROC", and "rmda" packages were used. P (two-sided) < 0.05 were considered statistically significant.

Results

Baseline characteristics of the included Athletic patients

A total of 28953 athletic patients were included in our study after a strict screening of the exclusion criteria. We divided the Athletic patients into three cohorts (training cohort, validation cohort and test cohort). Table 1 showed the

baseline characteristics of the three groups. Athletic Patients' age, sex, tumor size, differentiation, distant metastasis, brain metastasis, liver metastasis, depth of invasion, lung metastasis, LNR, lymph node metastasis, TNM stage, CEA, regional lymph nodes surgery and surgery style among three cohorts were shown in Table 1

Table 1. Baseline characteristics of the three cohorts

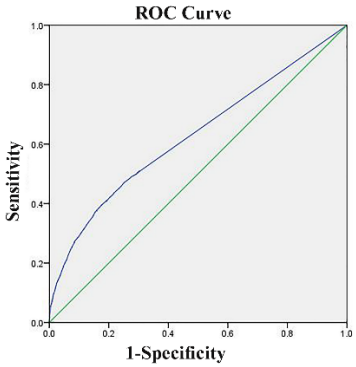
	Training cohort (N = 13480)		**Validation cohort (N = 5774)**		**Test cohort (N = 9699)**	
	No. of athletic patients	**%**	**No. of athletic patients**	**%**	**No. of athletic patients**	**%**
Age(year)						
Mean	74.25±8.90		74.27±8.71		73.90.03±8.80	
Sex						
female	6671	50.5	2818	48.8	4775	49.2
male	6809	49.5	2956	51.2	4924	50.8
Tumor size(mm)						
≤33	4435	32.9	1861	32.2	3217	33.2
>33	9045	67.1	3913	67.8	6482	66.8
Differentiation						
Well differentiated	1032	7.7	422	7.3	675	7.0
Moderately differentiated	9825	72.9	4172	72.3	7193	74.2
Poorly differentiated	2214	16.4	1018	17.6	1487	15.3
Undifferentiated	409	3.0	162	2.8	344	3.5
Brain metastasis						
yes	17	0.1	5	0.1	7	0.1
no	13463	99.9	5769	99.9	9692	99.9
Liver metastasis						
yes	1174	8.7	512	8.9	755	7.8
no	12306	91.3	5262	91.1	8944	92.2
Lung metastasis						
yes	232	1.7	108	1.9	204	2.1
no	13248	98.3	5666	98.1	9495	97.9
LNR						
≤0.386	9899	73.4	4209	72.9	7313	75.4
>0.386	3581	26.6	1565	27.1	2386	24.6
Depth of invasion						
Tis	66	0.5	30	0.5	74	0.8
T1	1150	8.5	481	8.3	894	9.2
T2	2062	15.3	843	14.6	1486	15.3
T3	8217	61.0	3575	61.9	5775	59.5

T4	1985	14.7	845	14.6	1470	15.2
Lymph node metastasis						
N0	8046	59.7	3437	59.5	5815	60.0
N1	3467	25.7	1478	25.6	2524	26.0
N2	1967	14.6	859	14.9	1360	14.0
Distant metastasis						
M0	11921	88.4	5100	88.3	8667	89.4
M1	1559	11.6	674	11.7	1032	10.6
TNM stage						
0	66	0.5	30	0.5	74	0.8
I	2713	20.1	1091	18.9	1979	20.4
II	4957	36.8	2180	37.8	3545	36.6
III	4185	31.0	1799	31.2	3069	31.6
IV	1559	11.6	674	11.7	1032	10.6
CEA						
normal	5694	42.2	2361	40.9	3981	41.0
high	7786	57.8	3413	59.1	5718	59.0
Regional lymph nodes surgery						
None	192	1.4	83	1.4	155	1.6
1-3	244	1.8	114	2.0	121	1.2
≥4	13044	96.8	5577	96.6	9423	97.2
Surgery style						
Partial colectomy	5632	41.8	2391	41.4	4113	42.4
Subtotal colectomy	7566	56.1	3264	56.5	5375	55.4
Total colectomy	256	1.9	110	1.9	180	1.9
Total proctocolectomy	26	0.2	9	0.2	31	0.3

Determine the best cutoff value of LNR

We analyzed the ROC curve with continuous variable LNR in the training cohort. The area under the receiver-operating characteristic curve (AUC) value was 0.628 (95% confidence interval (CI): 0.618-0.638, $p<0.05$). The best cut-off value of LNR was 0.088 when the value of the Youden index was largest. We converted LNR to categorical variables, with LNR = 0.088 as the cut-off value (Figure 2). The tumor size was regrouped into two categories by using X-tile software: tumor size ≤ 33mm, tumor size > 33mm.

Figure 2. Receiver operating characteristic curve of LNR; cut-off value (Jordan index maximum)=0.088.



Univariate and multivariate cox regression analysis of factors associated with OS in validation cohort

Table 2 showed the results of univariate and multivariate cox regression analyses. Eleven independent prognosis markers associated with the overall survival (OS) rate of old CAC athletic patients after surgery were identified, including age, sex, tumor differentiation, brain metastasis, liver metastasis, lung metastasis, lymph node metastasis, distant metastasis, LNR, CEA and surgery style. We could calculate the total number of points corresponding to the patient's characteristics through the constructed nomogram, and could predict the probability of OS at 1, 3, and 5 years. (Figure 3).

Figure 3. The nomogram predicts OS rates for 1-year,2-year,3-year and 5-year in old CAC patients. The specific methods of use as follows: each old CAC patient needs to be evaluated by 11 markers, assign the points of each characteristic of the patient by drawing a vertical line from that markers to the points scale, and then sum all the points. Finally, we draw a vertical line from the total points scale to obtain OS rates of 1-,2-,3- and 5-year.

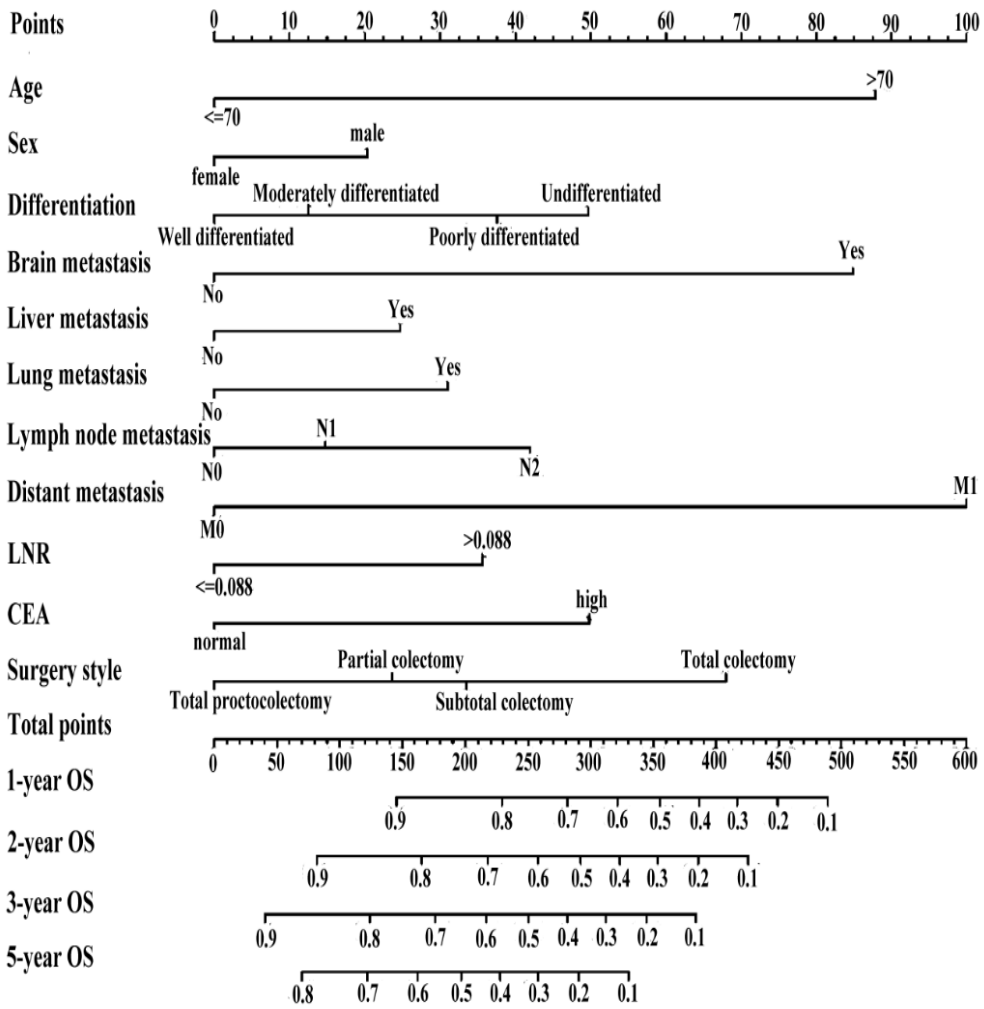


Table 2. Univariate and multivariate Cox regression analysis of factors associated with OS in the model group

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age(year)	1.93(1.82-2.04)	<0.001	2.20 (2.07-2.33)	<0.001
Sex	1.16(1.10-1.22)	<0.001	1.20 (1.14-1.27)	<0.001
Tumor size(mm)				
≤33	Ref		Ref	
>33	1.52(1.43-1.61)	<0.001	1.12(1.00-1.21)	0.057
Differentiation				
Well differentiated	Ref		Ref	
Moderately differentiated	1.28(1.14-1.43)	<0.001	1.12 (1.00-1.25)	0.048
Poorly differentiated	1.96(1.74-2.22)	<0.001	1.40 (1.24-1.58)	<0.001
Undifferentiated	2.28(1.93-2.70)	<0.001	1.56 (1.32-1.85)	<0.001
Brain metastasis	5.85(3.53-9.72)	<0.001	2.04 (1.22-3.40)	0.007
Liver metastasis	4.21(3.93-4.51)	<0.001	1.25 (1.09-1.42)	<0.001

Lung metastasis	4.22(3.66-4.86)	<0.001	1.32 (1.13-1.54)	<0.001
LNR				
≤0.088	Ref		Ref	
>0.088	2.36(2.24-2.49)	<0.001	1.38 (1.25-1.52)	<0.001
Depth of invasion				
Tis	Ref			
T1	1.16(0.68-1.98)	0.593		
T2	1.45(0.86-2.47)	0.167		
T3	2.45(1.45-4.14)	<0.001		
T4	5.13(3.03-8.68)	<0.001		
Lymph node metastasis				
N0	Ref		Ref	
N1	1.59(1.50-1.69)	<0.001	1.14 (1.05-1.24)	0.002
N2	3.03(2.84-3.24)	<0.001	1.46 (1.29-1.64)	<0.001
Distant metastasis				
M0	Ref		Ref	
M1	4.33(4.07-4.61)	<0.001	2.45(2.16-2.79)	<0.001
TNM stage				
0	Ref			
I	1.31(0.77-2.23)	0.316		
II	1.90(1.12-3.20)	0.017		
III	2.73(1.61-4.61)	<0.001		
IV	8.76(5.17-14.83)	<0.001		
Regional lymph nodes surgery				
None	Ref			
1-3	1.11(0.84-1.45)	0.461		
≥4	0.81(0.66-1.00)	0.051		
CEA				
low	Ref		Ref	
high	2.10 (1.99-2.22)	<0.001	1.56 (1.48-1.65)	<0.001
Surgery style				
Partial colectomy	Ref		Ref	
Subtotal colectomy	1.08(1.02-1.14)	0.005	1.09 (1.03-1.15)	0.002
Total colectomy	1.42(1.19-1.70)	<0.001	1.49 (1.24-1.78)	<0.001
Total proctocolectomy	0.64（0.30-1.34）	0.235	0.81 (0.38-1.70)	0.575

Relationship between LNR and overall survival

The OS rates of 1, 2, 3 and 5 years were calculated respectively stratified by LNR. Table 3 showed the results of the training and validation cohorts. The OS rates of LNR>0.088 group were 74.5%, 59.8%, 48.6% and 18.3%, and the OS rates of LNR≤0.088 group were 88.6%, 81.3%, 73.5% and 31.0% in training cohort. The results of the validation cohort were similar to the training cohort. It could be seen from the table that the OS rates of high LNR cohort

for 1-year, 2-year, 3-year and 5-year were lower than that of low LNR cohort in both validation cohort and training cohort. In summary, athletic patients with LNR≤0.088 predicted longer survival time after surgery. This showed that LNR could be used as a meaningful prognostic marker.

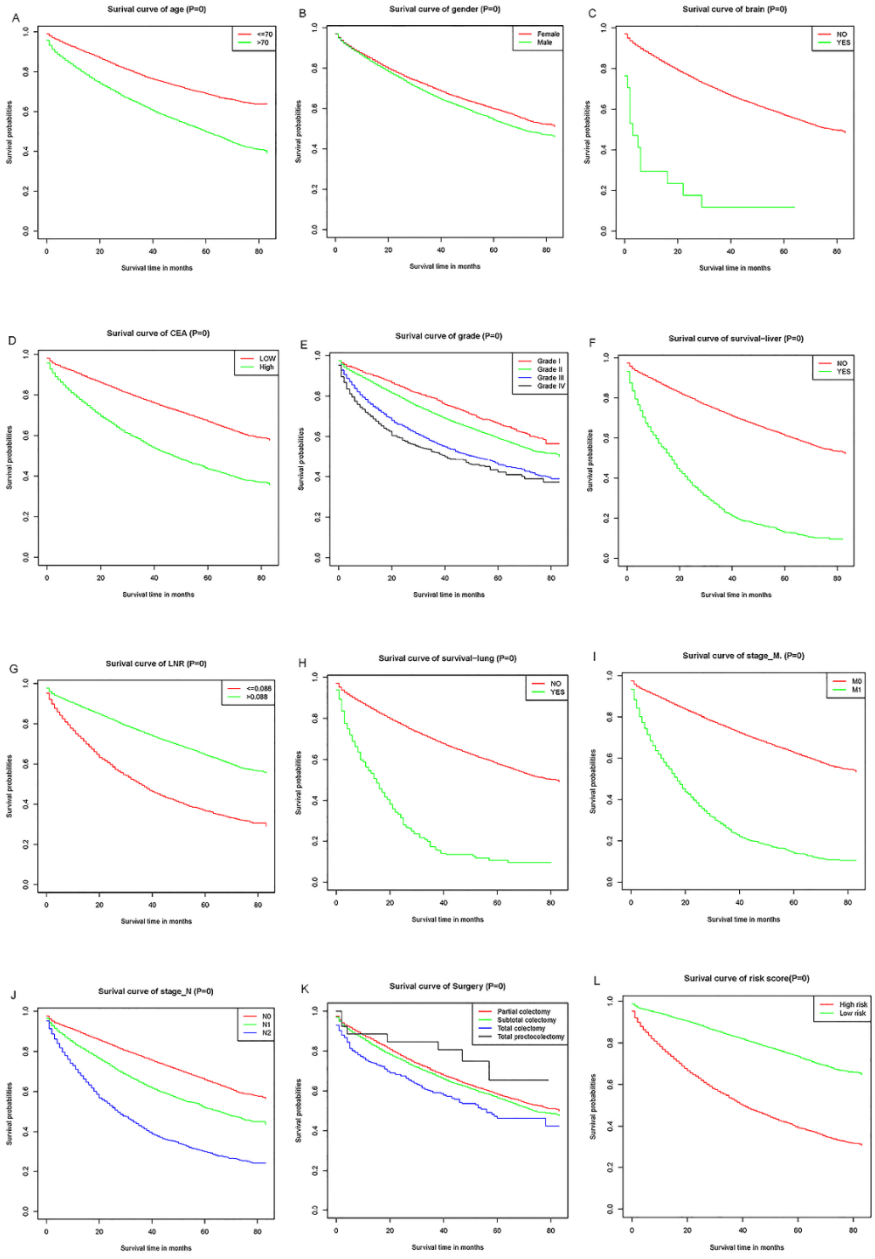
Table 3. Correlation between LNR and overall survival rate

Training cohort	All CC patients	high LNR group	low LNR group
OS median（months）	45	34	48
1-year OS rate	0.848	0.745	0.886
2-year OS rate	0.756	0.598	0.813
3-year OS rate	0.669	0.486	0.735
5-year OS rate	0.277	0.183	0.310
Validation cohort			
OS median（months）	45	34	48
1-year OS rate	0.853	0.754	0.890
2-year OS rate	0.762	0.608	0.820
3-year OS rate	0.667	0.483	0.736
5-year OS rate	0.268	0.172	0.304

Kaplan–Meier survival analysis about these independent prognosis markers

The results showed that age>70 years, male, brain metastasis, lung metastasis, liver metastasis, CEA, LNR, tumor differentiation, surgery style, lymph node metastasis, distant metastasis had a significantly worse survival ($p<0.001$, Figure 4). Based on the scores calculated by nomogram, we divided athletic patients into high-risk cohort and low-risk cohort. We draw a time-dependent receiver operating characteristic (td-ROC) curves to evaluate the nomogram (Figure 5). The AUC values of 1- year, 3-year and 5-year in the training cohort were 0.755, 0.754 and 0.748, respectively. The AUC values of 1-year, 3-years and 5-year in the validation cohort were 0.739, 0.752 and 0.749, respectively (Figure 5). It could be seen that the new nomogram had a good prediction.

Figure 4. Kaplan-Meier survival analysis for independent prognosis markers in training cohort (A-K). Kaplan–Meier survival analysis for nomogram system risk score(L).


A
Surival curve of age (P=0)
<=70
>70
B
Surival curve of gender (P=0)
Female
Male
C
Surival curve of brain (P=0)
NO
YES
D
Surival curve of CEA (P=0)
LOW
High
E
Surival curve of grade (P=0)
Grade I
Grade II
Grade III
Grade IV
F
Surival curve of survival-liver (P=0)
NO
YES
G
Surival curve of LNR (P=0)
<=0.088
>0.088
H
Surival curve of survival-lung (P=0)
NO
YES
I
Surival curve of stage_M. (P=0)
M0
M1
J
Surival curve of stage_N (P=0)
N0
N1
N2
K
Surival curve of Surgery (P=0)
Partial colectomy
Subtotal colectomy
Total colectomy
Total proctocolectomy
L
Surival curve of risk score(P=0)
High risk
Low risk
Survival probabilities
Survival time in months

Nomogram and clinical usage

In our research, we used the validation cohort as internal validation to verify the performance of the developed nomogram. The test cohort was used for external validation. The C-index of the nomogram in internal validation was 0.767 (95% CI: 0.757-0.777). The C-index of the nomogram in external validation was 0.775 (95% CI: 0.763-0.787). The results showed that constructed nomogram was suitable for predicting the OS of old CAC athletic patients after surgery. The calibration curve showed that nomogram had the ability to accurately predict 1-year, 3-year, and 5-year overall survival (Figure 6). To evaluate the clinical utility, We used decision curve analysis to present the clinical effectiveness of the established nomogram. We used training cohort, validation cohort and test cohort to confirm the good clinical utility of constructed nomogram. The nomogram had more clinical net benefits than the 7th TNM staging system of AJCC, LNR and CEA (Figure 7).

Figure 5. Time-dependent receiver operating characteristic (td-ROC) curves for the 1-, 3- and 5-year OS nomogram of old CAC patients after surgery in training cohort (A-C) and validation cohort (D-F).

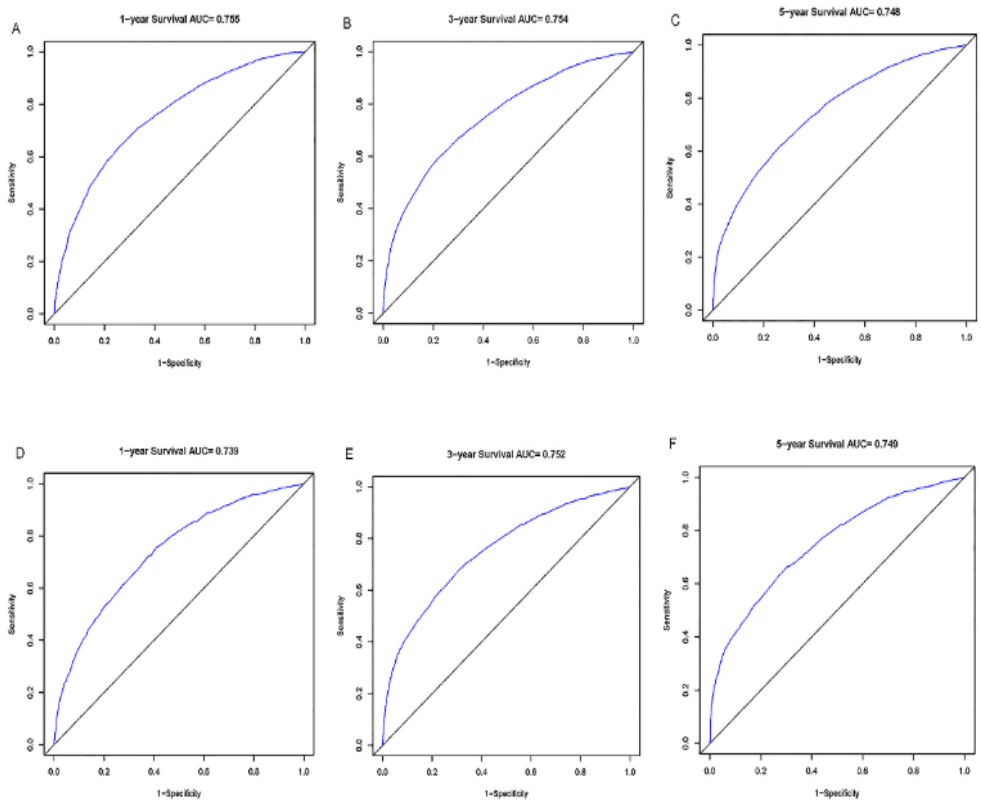
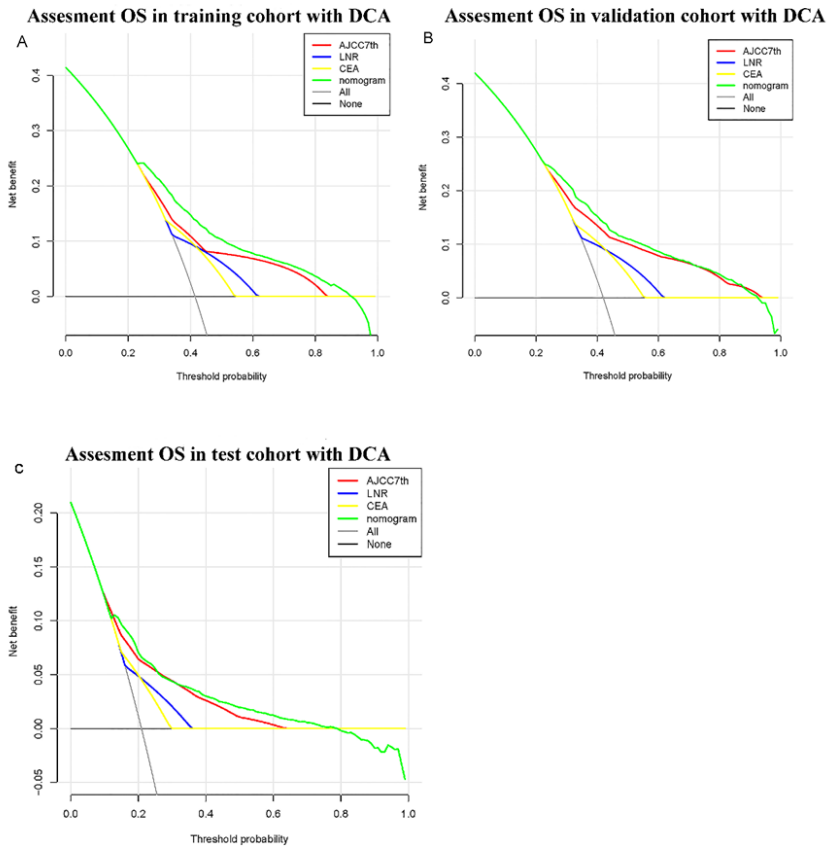


Figure 6. Calibration curves for 3-year(A) and 5-year(B) in training cohort and calibration curves for 3-year(C) and 1-year(D) in validation cohort. The x-coordinate indicates the nomogram predicted probability of OS and the y-coordinate indicates the actual OS. The solid line represents equality between the predicted and observed values.

Figure 7. The decision curves analysis for nomogram to predict OS rate of old CAC patients after surgery in training cohort (A), validation cohort (B) and test cohort (C). The x-axis represents threshold probability. The y-axis measures the net benefit.



Discussion

One common type of tissue pathology colon cancer was adenocarcinoma (J. Wang et al., 2019). Surgery was the most common treatment in CAC athletic patients. Older athletic patients were often advanced when they were diagnosed with colon adenocarcinoma, due to the lack of effective detection. So these old people usually were frail body and weak resistance. It was a difficult problem for our clinicians to predict OS of old CAC athletic patients after surgery(Kim, 2015). So we constructed a new nomogram based on the basic information available in clinical practice to predict OS of old CAC athletic patients after surgery. Meanwhile, we demonstrated that age, sex, lung metastasis, LNR, lymph node metastasis, liver metastasis, distant metastasis, CEA, brain metastasis and surgery style were independent prognosis markers, which was consistent with previous studies(Jiang et al., 2019; X.

Wang et al., 2019). LNR had prognosis value for some types of neoplasms such as breast, gastric and lung(Calero et al., 2015; C.-L. Wang et al., 2012; Q.-X. Wang et al., 2017). Previous studies had shown that LNR was an independent prognostic factor in colon cancer. Meanwhile, It had a more accurate prognostic value than the number of positive lymph nodes in colon cancer (Ahmad et al., 2017; Ceelen, Van Nieuwenhove, & Pattyn, 2010; Ooki et al., 2017). Our results were consistent with previous studies. The only surprise was that tumor size is not an independent prognostic marker for CAC after surgery. Dai, W et al also found that the size of the tumor did not have a predictive value for the risk of lymph node metastasis in T1 colon cancer.(Xu et al., 2019) We speculated that lymph node metastasis was a major prognosis marker, not tumor size.

Our research had some advantages. First, this is the first study to help postoperative CAC old athletic patients predict survival time. Among colon cancer patients, old athletic patients have the largest number(Rebecca L. Siegel et al., 2017). We have fully considered the characteristics of old athletic patients. They have poor understanding but long for life. Therefore, we should use a simple predictive tool to help old athletic patients make a quick prognosis judgment. We only need to draw some lines and simply calculate. Meanwhile, all clinical features and clinical information are easily available. Second, we set a validation cohort and a test cohort to obtain internal and external validation, and all results were positive. Third, our nomogram is a well-predicting tool for 1-,3- and 5-year OS. We can formulate a reasonable follow-up schedule based on our nomogram.

There are some limitations to our study. First, some clinical factors closely correlated with prognosis are not documented in the SEER database, such as drinking alcohol, smoke, red and processed meat consumption. Second, although our nomogram has a prospective cohort as external verification, all our data comes from the SEER database produced in the United States. Our nomogram requires external validation by multiple countries.

Conclusions

In conclusion, we identified independent prognosis markers affected OS in old CAC athletic patients after surgery. A new nomogram based on Cox regression analysis was built with prognosis variables that could be accessed easily. We believe that the nomogram in graphical mode can help old athletic patients understand the prognosis possibility more easily.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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