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Nomogram to predict overall survival and disease-specific survival with appendiceal mucinous adenocarcinoma

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Abstract

To predict the survival of appendiceal mucinous adenocarcinoma (AMA) by prognostic nomogram.

A total of 3234 patients with AMA were collected from the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2015. Univariate and multivariate Cox proportional hazards (PH) regression analyses were used to generate independent prognostic factors. These variables were included in the nomogram to predict overall survival (OS) and disease-specific survival (DSS) at 1-, 3-, and 5- years. These data are validated both internally and externally. The consistency index (C-index) and calibration chart were used to estimate the accuracy of the nomogram.

The study cohort was randomly divided into the training (n = 2155) and validation group (n = 1799). According to univariate and multivariate analyses, age at diagnosis, marital status, sex, histological differentiation, SEER extent of disease, number of local lymph nodes examined, whether they were positive, and surgical methods were independent prognostic factors for OS and DSS. These factors were incorporated into the nomogram. Internal validation in the training cohort showed that the C-index values for nomogram predictions of OS and DSS were 0.73 (95% CI 0.70–0.76) and 0.77 (95% CI 0.73–0.81), respectively. Similarly, the corresponding C-index values in the external validation cohort were 0.76 (95% CI 0.70–0.81) and 0.75 (95% CI 0.71–0.80). The Calibration plots revealed that the actual survival and nomogram prediction had a good consistency.

Build a nomogram in the SEER database to predict OS and DSS in patients with AMA. It can provide accurate and personalised survival prediction for clinicians and patients.

Abbreviations: AJCC = American Joint Committee on Cancer, AMA = appendiceal mucinous adenocarcinoma, CEA = carcinoembryonic antigen, CI = confidence interval, C-index = consistency index, CSS/DSS = cancer-specific survival/disease-specific survival, HR = hazard ratio, OS = overall survival, PH = proportional hazards, SEER = Surveillance, Epidemiology, and End Results.

Keywords: appendiceal mucinous adenocarcinoma, cancer-specific survival, nomogram, overall survival, SEER database

1. Introduction

Tumor of the Appendix is a rare malignancy, with an age-adjusted incidence being 0.12 cases per 100,000 people in the population represented by the Surveillance, Epidemiology, and End Results (SEER) program from 1973 to 1998.[1] Compared with other solid tumors, the prevalence of appendiceal cancer is very low, but its incidence and mortality have been on the rise.[2,3] Meanwhile, the burden it brings to the country cannot be ignored.[4] Appendiceal tumors include many histologic subtypes, the most common of which is appendiceal mucinous adenocarcinoma (AMA) that originate from epithelial tissue.[5–7] Most patients with AMA had no typical clinical manifestations. Hence, these rare tumors are rarely suspected before surgery, and most of them are found during or after surgery.[8] AMA has unique biological characteristics and rarely has extraperitoneal metastasis. The only way to metastasis in most patients is intraperitoneal dissemination.[9] Surgery is the primary treatment for AMA, with right hemicolectomy being the most common.[10]

Previous[10–13] studies have identified a number of prognostic factors affecting patients with AMA, including stage, grade, degree of SEER disease, surgical procedure, number of regional nodes examined, and so on. However, these variables are only used as a single indicator to evaluate the prognosis, which has excellent limitations and affects the accurate, individualized survival prediction of AMA patients. In our study, we constructed a nomogram to predict the individual survival for patients with AMA thoroughly by integrating all the independent factors. As a statistical prognostic model, the nomogram can be used to predict the overall survival or death of a given individual,[14] and it can

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improve the prediction accuracy of individual prognosis, which has been widely used in the forecast of cancer.[15] However, there is no nomogram for predicting overall survival (OS) and disease-specific survival (DSS) of patients with AMA at present.

In this study, we collected data from SEER databases on patients diagnosed with AMA from 1973 to 2015. This database is a population-based cancer data set for the United States, collecting information on cancer patients in [18] registries across the United States, covering about 30% of the total US population. Our purpose is to develop validated prognostic nomogram, including demographic variables (age at diagnosis, sex, race, marital status), clinical pathologic information (tumor size, SEER extent of disease, TNM stage, carcinoembryonic antigen (CEA) levels, number of regional lymph nodes, and whether they were positive), and treatment information (surgery type, radiotherapy, chemotherapy) used to predict the survival situation in patients with OS and DSS.

2. Materials and methods

2.1. Patient eligibility and variables

Our study did not seek approval from an ethics committee because the data provided in the SEER database does not contain patient personal information. All work is under the provisions of the Declaration of Helsinki. Based on our research purposes, we screened the data, and the specific screening process is shown in Fig. 1. According to the International Classification of Diseases for Oncology (ICD.O3),[16] the pathological types codes of patients with AMA are 8470, 8471, 8472, 8480, and 8481. For some blank information in the data set, we chose to keep it due to its importance but decided to adopt the missing value processing method in the process of making the nomogram.

In our research, the necessary information about the patient with AMA including age at diagnosis, sex, race, marital status, TNM stage, SEER extent of disease, tumor size, CEA level,

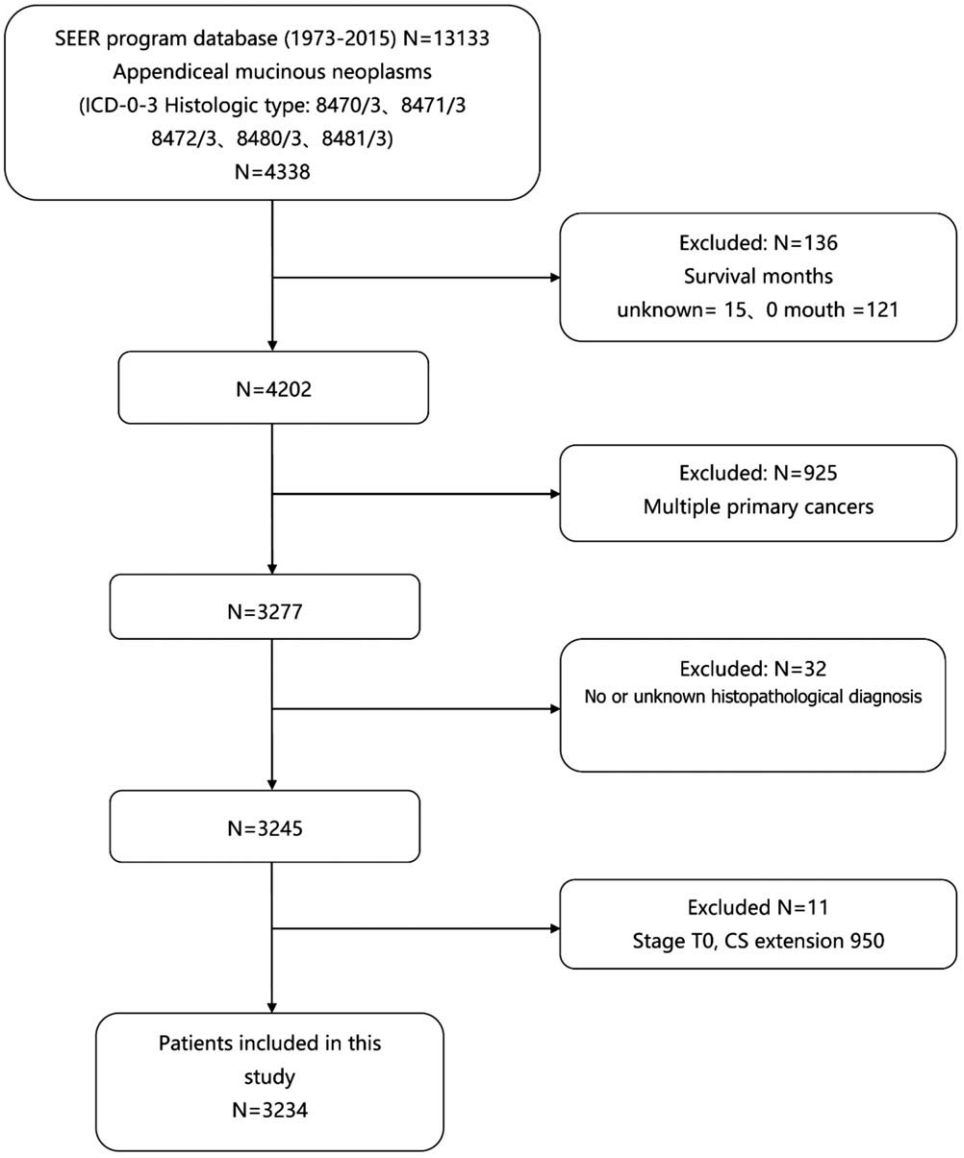

Figure 1. A flow diagram of the selection process for the study.

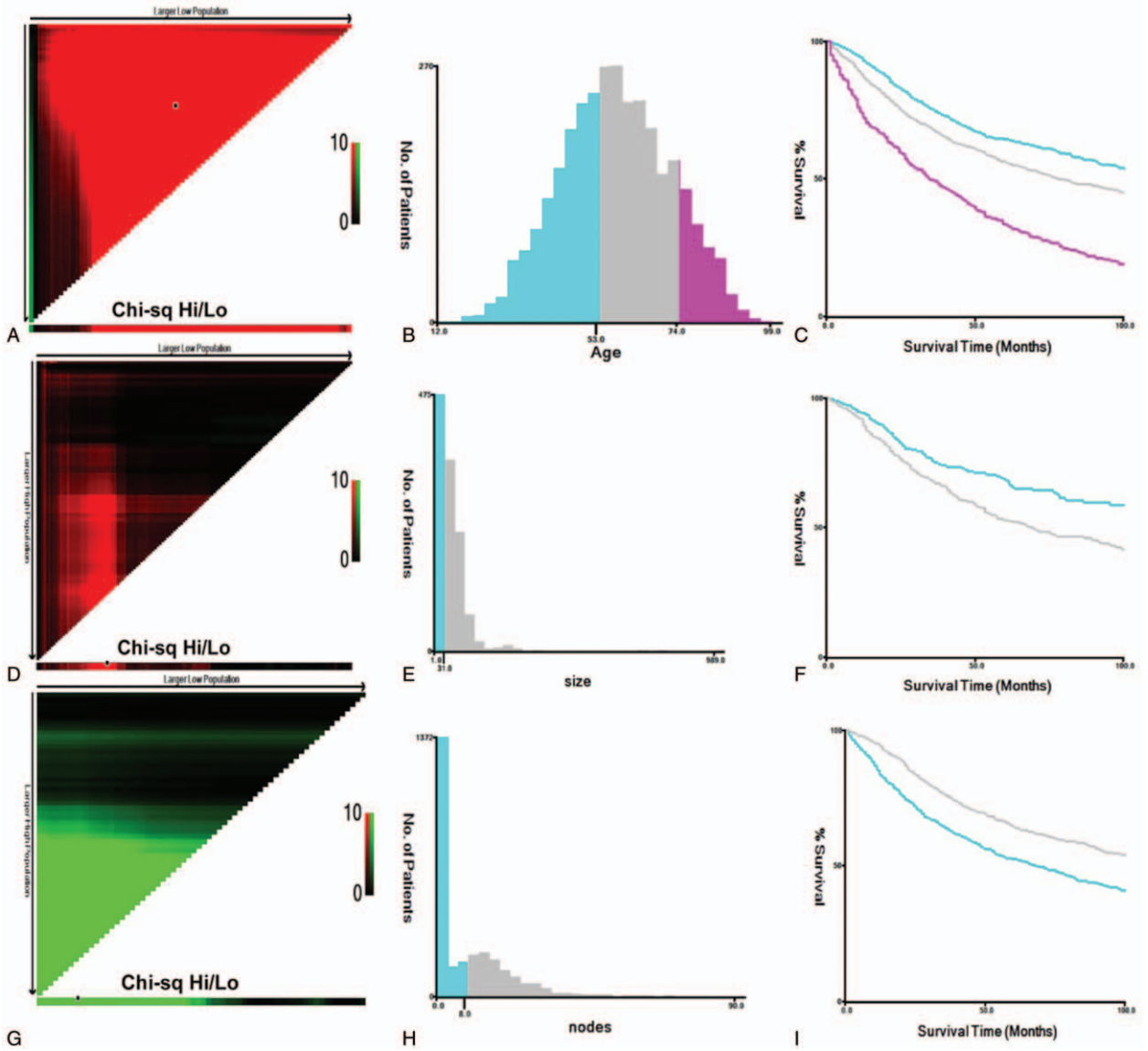

Figure 2. Identification of optimal cutoff values of age of diagnosis (A–C), tumor size (D–F), and number of regional examined (G–I) via X-tile analysis. Notes: Optimal cutoff values of age were identified as 53 and 74 years based on overall survival. Optimal cutoff values of tumor size were identified as 31 mm based on overall survival. Optimal cutoff values of number of regional examined were identified as 8 based on overall survival. Histogram and Kaplan–Meier analysis were developed based on these cutoff values.

number of regional examined and whether they were positive, surgery type, chemotherapy, and radiotherapy was collected. Continuous data such as tumor size, age at diagnosis, number of regional examined were grouped by X-tile software (Yale University, New Haven, CT).[17] The optimal age cutoffs were 53 and 74 years (Fig. 2A–C), so patients were divided into 3 age groups (0–53 years, 53–74 years, or >74 years). Tumor size and number of regional nodes examined both were classified into 2 groups, and the optimum cut-off value was 31 mm and 8 mm, respectively (Fig. 2D–I).

2.2. Statistical analysis

Using the randomized grouping function of SPSS 24.0 (Chicago, IL), AMA patients who met the inclusion and exclusion criteria were randomly assigned to a training group (n = 2155) or a validation group (n = 1097) to construct and verify the nomogram. The χ^2 test was used to compare differences in clinical characteristics between the 2 groups. Continuous variables such as age at diagnosis, tumor size, and the number of regional nodes examined were analyzed by the software X-tile, which can help us calculate the cut-off values of them based on the overall survival information. Univariate and multivariate Cox proportional hazards (PH) regression analysis with SPSS 24.0 software was used to assess the prognostic factors. The variables were calculated by the hazard ratio (HR) and the corresponding 95% CI. We have 2 primary endpoints, including OS and DSS, also known as cancer-specific survival (CSS). The time interval from the time of diagnosis to death because of any cause or the time of the last follow-up was OS and DSS was defined as the interval between the time of diagnosis and the time of death due to the tumor itself. According to the univariate and multivariate

Cox analysis results, we constructed the 1-, 3-, and 5-year OS and DSS nomogram with the rms Package in R software (version 3.5.3). In the meantime, the internal and external validations of the prognostic nomogram were performed. Harrell's concordance index (C-index) was used to evaluate the discrimination of nomogram. Calibration curves were constructed to compare consistency between predicted and observed survivals. In essence, C-index estimates the probability that the predicted results are consistent with the actual observed results, that is, the proportion of the predicted results that are consistent with the actual results in all patient pairs in the data. It is kind of like the area under the ROC curve.[14] In practical applications, it is difficult to find an utterly consistent prediction model. The C-index ranges from 0.5 to 1.0, and previous studies[18] have shown that a c-index of 0.50 to 0.70 is of low accuracy, and a c-index of 0.71 to 0.90 is of medium accuracy. Higher than 0.90 indicates high efficiency.

3. Results

3.1. Patient baseline characteristics

The primary characteristics of the 2 study cohorts are shown in Table 1. Patients diagnosed with AMA at 1973 to 2015 in the SEER database were contained in this study. A total of 3234 patients were included in this study, including 2155 patients in the training cohort and 1079 patients in the validation group. The training group and the validation group were used for internal and external validation, respectively, and the nomogram was constructed. Specific information included age at diagnosis, sex, race, marital status, histological grade, TNM stage, SEER extent of disease, number of regional lymph nodes examined and whether they were positive, surgical type, radiotherapy, and chemotherapy, etc. In this cohort study, 1037 people died in the training group, and 857 people died from tumors, while 505 patients died in the validation group, and 410 patients died from tumors.

3.2. Prognostic factors for OS and DSS

In the univariate analysis, except for race and radiation therapy, the remaining elements were associated with OS. All the items were associated with DSS in addition to sex and radiotherapy. These significant variables were further included in the multivariate analysis to control the confounding variables, and because TNM staging was consistent with tumor infiltration depth, lymph node, and distant metastasis, it was not included in multivariate analysis. Finally, as is shown in Tables 2 and 3, in multivariate analysis, the age at diagnosis, marital status, sex, histological grade, SEER extent of disease, number of regional lymph nodes examined, and whether they were positive, the surgical approach were independent prognostic factors for OS. Age at diagnosis, histological grade, SEER extent of disease, number of regional lymph nodes examined, the surgery type, and chemotherapy were independent prognostic factors for DSS.

3.3. Construction and validation of the OS and DSS nomograms

The significant independent factors including age, marital status, sex, histology grade, SEER extent of disease, number of regional nodes examined, and whether they were positive, surgery type were incorporated to create the prognostic nomograms for estimating the1-, 3-, and 5-year OS. Age at diagnosis, histology grade, SEER extent of disease, lymph node metastasis, number of regional nodes examined, chemotherapy, and surgery type were used to estimate the 1-, 3-, and 5-year DSS (Fig. 3). The nomogram gives every prognostic variable a score on the point scale (Table 4). Adding these scores to the total score of the scale predicted 1-, 3-, and 5- years of OS and DSS in AMA patients to construct the predictive nomogram of internal verification. To predict the nomogram of internal and external verification. Internal validation of the training cohort showed that the index of the OS and DSS nomograms predicted 0.73 (95% CI 0.70–0.76) and 0.77 (95% CI 0.73–0.81), respectively. Similarly, the corresponding c-index in the external validation cohort was 0.76 (95% CI 0.70–0.81) and 0.75 (95% CI 0.71–0.80). These results confirm that our prognostic nomograms are reasonably accurate. The calibration chart (Fig. 4) shows that the actual survival rate is in good agreement with the nomogram prediction.

In summary, we constructed and validated nomogram to estimate 1-, 3-, and 5-year OS and DSS in AMA patients. Based on the prognostic factors of individual AMA patients, we can obtain

Table 1

Basic demographic and clinical characteristics of patients with appendiceal mucinous adenocarcinoma.

Variables	Training cohort (n = 2155), n, %		Validation cohort (n = 1079), n, %		Total (n = 3234)		P
Age at diagnosis	57.86 ± 14.11		57.37 ± 14.52		57.69 ± 14.25		.36
≤53	812	37.7	453	42	1265	39.1	
53–74	1060	49.2	474	43.9	1534	47.4	
>74	283	13.1	152	14.1	435	13.5	
Marital status							.652
Married (including common law)	1359	63.1	682	63.2	2041	63.1	
Single (never married/divorced/separated/widowed)	725	33.6	355	32.9	1080	33.4	
Unknown	71	3.3	42	3.9	113	3.5	
Sex							.966
Female	1241	56.3	607	56.3	1821	56.3	
Male	941	43.7	472	43.7	1413	43.7	
Ethnicity							.938
White	1786	82.9	888	82.3	2674	82.7	
Black	181	8.4	93	8.6	274	8.5	
Other (American Indian/AK Native, Asian/Pacific Islander)	179	8.3	92	8.5	271	8.4	
Unknown	9	0.4	6	0.6	15	0.5	

(*continued*)

Table 1

(continued).

Variables	Training cohort (n = 2155), n, %		Validation cohort (n = 1079), n, %		Total (n = 3234)		*P*
Histologic grade							.819
Well differentiated; Grade I	719	33.4	360	33.4	1079	33.4	
Moderately differentiated; Grade II	591	27.4	309	28.6	900	27.8	
Poorly differentiated; Grade III	192	8.9	88	8.2	280	8.7	
Undifferentiated; anaplastic; Grade IV	34	1.6	13	1.2	47	1.5	
Unknown	619	28.7	309	28.6	928	28.7	
SEER extent of disease							.312
Distant	1189	55.2	582	53.9	1771	54.8	
Localized	532	24.7	265	24.6	797	24.6	
Regional	376	17.4	190	17.6	566	17.5	
Unknown/unstaged	58	2.7	42	3.9	100	3.1	
AJCC Stage, 7th ed							.263
I/II	277	12.9	160	14.8	437	13.5	
III/IV	510	23.7	241	22.3	751	23.2	
Unknown/UNK stage	1368	63.5	678	62.8	2046	63.3	
Primary tumor (T)							.86
T1	43	2	26	2.4	69	2.1	
T2	33	1.5	15	1.4	48	1.5	
T3	136	6.3	75	7	211	6.5	
T4	520	24.1	252	23.4	772	23.9	
Other	1423	66	711	65.9	213	66	
Regional lymph nodes (N)							.789
N0	624	29	329	32.5	953	29.5	
N1	80	3.7	38	3.5	118	3.6	
N2	34	1.6	19	1.5	53	1.6	
Other	1417	65.8	693	64.2	2110	65.2	
Distant metastases (M)							.344
M0	365	16.9	205	19	570	17.6	
M1	450	20.9	217	20.1	667	20.6	
Other	1340	62.2	657	60.9	1997	61.8	
Tumor size							.39
≤31 mm	263	12.2	148	13.7	411	12.7	
>31 mm	497	23.1	255	23.6	752	23.3	
unknown	1395	64.7	676	62.7	2071	64	
CEA							.575
Negative/normal; within normal limits	227	10.5	102	9.5	329	10.2	
Positive/elevated	384	17.8	188	17.4	572	17.7	
Borderline/unknown	1544	71.6	789	73.1	2333	72.1	
Regional nodes examined							.787
Less than 8	1085	50.3	557	51.6	1642	50.8	
More than 8	837	38.8	407	37.7	1244	38.5	
Other	233	10.8	115	10.7	348	10.8	
Regional nodes positive							.927
All nodes examined negative	1140	52.9	563	52.2	1703	52.7	
Regional lymph nodes examined positive	14	0.6	7	0.6	21	0.6	
Other	1001	46.5	509	47.2	1510	46.7	
Surgery type							.51
No cancer-directed surgery of primary site	164	7.6	91	8.4	255	7.9	
Local surgery (excision/destruction/curettage)	62	2.9	37	3.4	99	3.1	
Appendectomy	553	25.7	262	24.3	815	25.2	
segmental colectomy	208	9.7	115	10.7	323	10	
colectomy plus resection of contiguous organ	756	35.1	354	32.8	1110	34.3	
Unknown	412	19.1	220	22.4	632	19.5	
Radiotherapy							.165
Yes	64	3	42	3.9	106	3.3	
No	2091	97	1037	96.1	3128	96.7	
Chemotherapy							.594
Yes	1020	47.3	500	46.3	1520	47	
No	1135	52.7	579	53.7	1714	53	

Table 2

Univariate and multivariate analyses of overall survival in the training cohort.

	Univariate analysis	Multivariate analysis		
Characteristics	***P***	**HR**	**95% CI**	***P***
Age at diagnosis				
≤53	0	Reference		
53–74		1.501	1.301–1.732	0
>74		2.885	2.367–3.443	0
Marital status				
Married (including common law)	.002	Reference		
Single (never married/divorced/separated/widowed)		1.179	1.029–1.350	.018
Unknown		1.15	0.803–1.648	.446
Sex				
Female	.019	Reference		
Male		1.291	1.135–1.469	0
Ethnicity				
White	.061		NA	
Black				
Other (American Indian/AK Native, Asian/Pacific Islander)				
Unknown				
Histologic grade				
Well differentiated; Grade I	0	Reference		
Moderately differentiated; Grade II		1.350	1.131–1.613	.001
Poorly differentiated; Grade III		2.259	1.789–2.852	0
Undifferentiated; anaplastic; Grade IV		2.162	1.269–3.684	.005
Unknown		1.247	1.056–1.474	.009
SEER extent of disease				
Distant	0	Reference		
Localized		0.482	0.395–0.588	0
Regional		0.566	0.469–0.684	0
Unknown/unstaged		0.694	0.464–1.036	.074
AJCC Stage, 7th ed				
I/II	0	Reference		
III/IV		0.531	0.253–1.113	.094
Unknown/UNK stage		0.777	0.277–2.180	.632
Primary tumor (T)				
T1	0	Reference		
T2		0.684	0.132–3.552	.651
T3		1.647	0.624–4.344	.313
T4		1.905	0.769–4.720	.164
Other		1.738	0.641–4.711	.277
Regional lymph nodes (N)				
N0	0	Reference		
N1		1.418	0.864–2.328	.167
N2		1.786	0968–3.297	.064
Other		1.935	1.268–2.955	.002
Distant metastases (M)				
M0	0	Reference		
M1		1.633	0.861–3.098	.133
Other		0.802	0.316–2.040	.644
Tumor size				
≤31 mm	0	Reference		
>31 mm		1.033	0.777–1.374	.822
unknown		1.151	0.883–1.499	.298
CEA				
Negative/normal; within normal limits	.001	Reference		
Positive/elevated		1.199	0.896–1.603	.223
Borderline/ Unknown		1.046	0.808–1.354	.733
Regional nodes examined				
Less than 8	0	Reference		
More than 8		0.756	0.620–0.922	.006
Other		1.019	0.838–1.239	.851
Regional nodes positive				
All nodes examined negative	0	Reference		
Regional lymph nodes examined positive		2.375	1.889–2.987	0
Other		1.116	0.911–1.365	.289
Surgery type				
No cancer-directed surgery of primary site	0	Reference		
Local surgery		0.709	0.456–1.103	.128
Appendectomy		0.588	0.454–0.763	0
segmental colectomy		0.613	0.442–0.850	.003
colectomy plus resection of contiguous organ		0.556	0.425–0.728	0
Unknown		0.747	0.578–0.965	.026
Radiotherapy				
Yes	.63		NA	
No				
Chemotherapy				
Yes	0	Reference		
No		1.13	0.983–1.299	.085

Table 3

Univariate and multivariate analyses of cancer-specific survival in the training cohort.

	Univariate analysis	Multivariate analysis		
Characteristics	***P***	**HR**	**95% CI**	***P***
Age at diagnosis				
≤53	0	Reference		
53–74		1.266	1.088–1.474	.002
>74		1.845	1.487–2.289	0
Marital status				
Married (including common law)	.046	Reference		
Single (never married/divorced/separated/widowed)		1.153	0.993–1.338	.062
Unknown		1.141	0.768–1.694	.515
Sex				
Female	.092		NA	
Male				
Ethnicity				
White	.049	Reference		
Black		1.171	0.921–1.489	.198
Other (American Indian/AK Native, Asian/Pacific Islander)		0.77	0.590–1.007	.056
Unknown		0	0–2.127E+57	.89
Histologic grade				
Well differentiated; Grade I	0	Reference		
Moderately differentiated; Grade II		1.509	1.239–1.837	0
Poorly differentiated; Grade III		2.436	1.884–3.151	0
Undifferentiated; anaplastic; Grade IV		2.529	1.453–3.400	.001
Unknown		1.362	1.129–1.644	.001
SEER extent of disease				
Distant	0	Reference		
Localized		0.341	0.267–0.436	0
Regional		0.529	0.429–0.653	0
Unknown/upstaged		0.503	0.314–0.806	.004
AJCC Stage, 7th ed				
I/II	0	Reference		
III/IV		0.462	0.207–1.032	.06
Unknown/UNK Stage		1.195	0.397–3.592	.752
Primary tumor (T)				
T1	0	Reference		
T2		0.45	0.05–4.072	.478
T3		1.642	0.552–4.882	.372
T4		2.006	0.731–0.506	.177
Other		1.695	0.565–5.087	.346
Regional lymph nodes (N)				
N0	0	Reference		
N1		1.659	0.998–2.758	.051
N2		2.06	1.098–3.866	.024
Other		2.279	1.479–3.512	0
Distant metastases (M)				
M0	0	Reference		
M1		1.633	0.861–3.098	.133
Other		0.802	0.316–2.040	.644
Tumor size				
≤31 mm	0	Reference		
>31 mm		1.819	0.923–3.585	.084
unknown		0.504	0.193–3.314	1.161
CEA				
Negative/normal; within normal limits	.001	Reference		
Positive/elevated		1.26	0.896–1.603	.416
Borderline/ unknown		1.071	0.808–1.354	.631
Regional nodes examined				
Less than 8	0	Reference		
More than 8		0.756	0.923–1.721	.006
Other		1.019	0.809–1.419	.851
Regional nodes positive				
All nodes examined negative	0	Reference		
Regional lymph nodes examined positive		0.854	0.683–1.086	.166
Other		1.058	0.849–1.317	.616
Surgery type				
No cancer-directed surgery of primary site	0	Reference		
Local surgery (excision/destruction/curettage)		0.596	0.360–0.986	.044
Appendectomy		0.532	0.405–0.700	0
segmental colectomy		0.558	0.396–0.785	.001
colectomy plus resection of contiguous organ		0.526	0.396–0.698	0
Unknown		0.707	0.539–0.927	.012
Radiotherapy				
No	.49		NA	
Yes				
Chemotherapy				
No	0	Reference		
Yes		1.215	1.044–1.413	.012

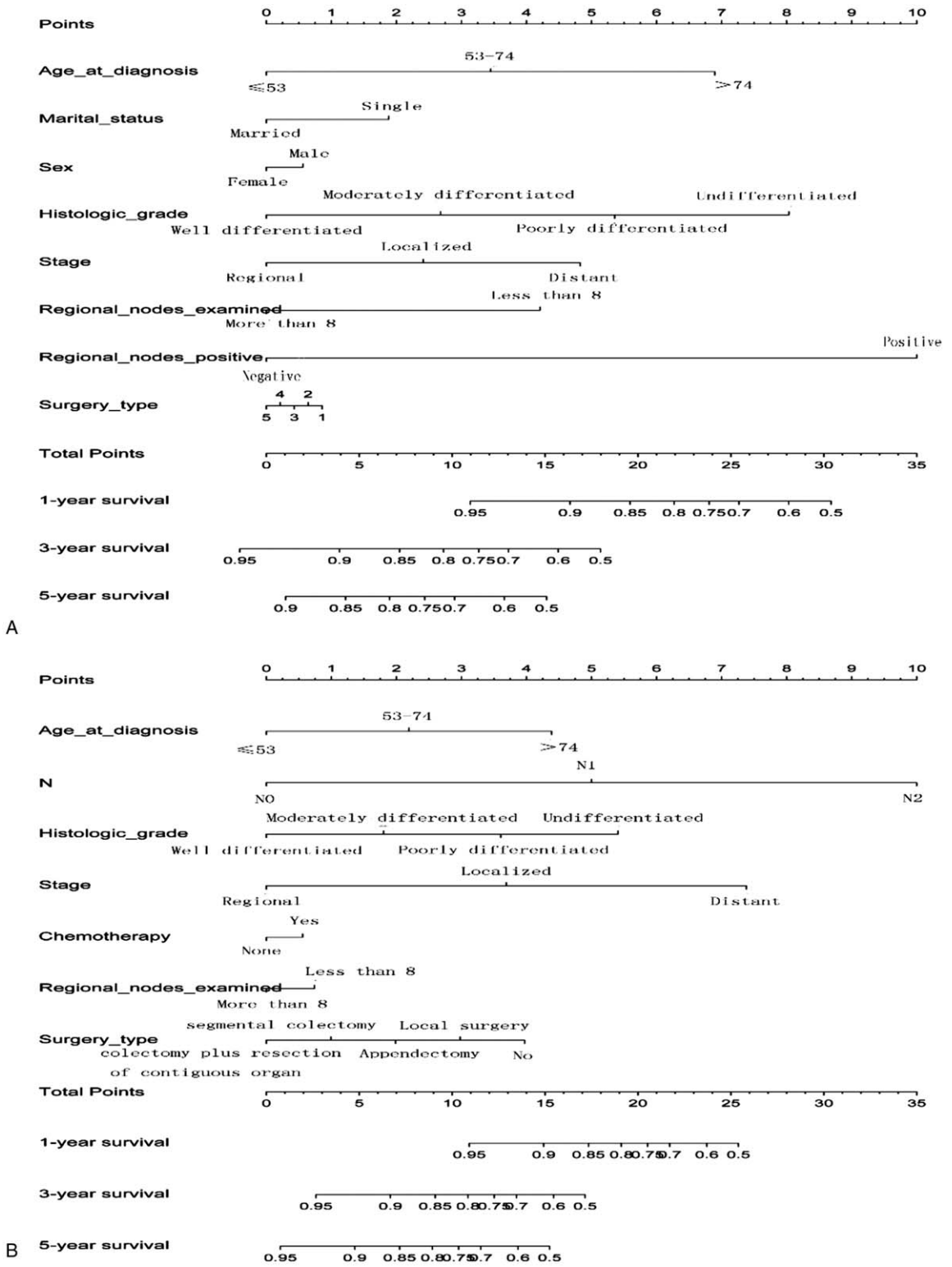

Figure 3. Nomograms to predict 1-, 3-, and 5-year overall survival (A) and disease-specific survival (B) of AMA patients. Notes: Points of each variable were obtained via a vertical line between each variable and the point scale. The predicted survival rate was correlated with the total points by drawing a vertical line from the Total Points scale to the overall survival or disease-specific survival. AMA = appendiceal mucinous adenocarcinoma.

a score associated with each prognostic factor on the nomogram point scale and calculate the total score. Then, we can estimate the survival probability of 1-, 3-, and 5-years by projecting the complete count to the overall score of the nomogram.

4. Discussion

The purpose of our research aims to investigate the factors that influence the prognosis of patients with AMA. Many factors can affect the prognosis of AMA. Hence, we have created nomograms

Table 4

Detailed scores of prognostic factors in the overall and cancer-specific survival nomograms.

Characteristic	OS nomogram	CSS nomogram
Age at diagnosis		
≤53	0.000	0.000
53–74	3.450	2.190
>74	6.900	4.390
Marital status		NA
Married (including common law)	0.000	
Single	1.880	
Gender		NA
Female	0.000	
Male	0.560	
Histologic grade		
Well differentiated; Grade I	0.000	0.000
Moderately differentiated; Grade II	2.680	1.800
Poorly differentiated; Grade III	5.360	3.600
Undifferentiated; Grade IV	8.040	5.410
SEER extent of disease		
Distant	4.830	7.380
Localized	2.410	3.690
Regional	0.000	0.000
Regional Lymph Nodes (N)		NA
N0		0.000
N1		5.000
N2		10.000
Regional nodes examined		
Less than 8	4.210	0.740
More than 8	0.000	0.000
Regional nodes positive		NA
All nodes examined negative	0.000	
Regional lymph nodes examined positive	10.000	
Surgery type		
No surgery of primary site	0.860	3.970
Local surgery	0.640	2.990
Appendectomy	0.430	1.990
segmental colectomy	0.210	0.990
colectomy plus resection of contiguous organ	0.000	0.000
Chemotherapy	NA	
No		0.000
Yes		0.560

to predict individualized patients. By analyzing patients diagnosed with AMA in the SEER database from 1973 to 2015, we randomly divided the study cohort into a training cohort and a validation cohort. First, the training cohort was analyzed by univariate analysis. The results showed that age at diagnosis, sex, marital status, TNM stage, histological grade, SEER extent of disease, CEA level, number of regional lymph nodes and whether they were positive, surgical methods, radiotherapy, and chemotherapy were all factors that are affecting OS or DSS. We further included these factors into a multivariate Cox analysis. The outcomes showed that age at diagnosis, sex, marital status, histological grade, SEER extent of disease, number of regional lymph nodes examined and whether they were positive, surgery type were the independent prognostic factors for OS. Age at diagnosis, number of lymph nodes metastases, histological grade, SEER extent of disease, chemotherapy, number of regional lymph nodes examined, and surgical procedures were independent prognostic factors for DSS. Finally, we validate the accuracy of this model using the data from the validation group and plot the calibration curve to determine the accuracy of the prediction. The consistency C-index of the OS was 0.73 (95% CI 0.70–0.76) and 0.76 (95% CI 0.70–0.81) in the training group and the validation group, respectively. The C-index of DSS was 0.77 (95% CI 0.73–0.81), 0.75 (95% CI 0.71–0.80), respectively. The C-index is greater than 0.7, indicating that the prognostic performance is acceptable.

In this study, age at diagnosis was an independent prognostic risk factor for both OS and DSS, and increased age was associated with a worse prognosis in patients with AMA. Sex and marital status were associated with OS, but not DSS. Shaib et al[3] observed no significant change in sex ($P = .69$) in patients with appendiceal mucinous neoplasms. The relationship between marital status and AMA survival has not been discussed. Histological grade and SEER extent of disease are 2 critical factors affecting AMA patients, which are also related to OS and DSS. At present, many studies[7,11] have discussed the correlation between the 2 elements and AMA, which is consistent with our conclusions.

Our study suggests that poor or undifferentiated histology is associated with poorer prognosis. The regional disease had the best forecast in OS and DSS, and the distant disease had the worst outcomes. Overman et al[11] investigated the impact of these 2 factors on DSS and the interactions between them, and the effect of histologic grade on the prognosis of mucinous adenocarcinoma was mainly limited to stage IV disease. Neither this study nor our data support the 3-stage classification scheme in the recent American Joint Committee on Cancer (AJCC) 7th edition.[19]

Concerning the number of regional lymph nodes examined and whether they were positive, the former affects the prognosis of OS and DSS, while the latter only affects the prognosis of OS. We used x-tile software to select the best cut-off point for the number of local lymph node examinations and found that the amount greater than 8 was associated with better prognosis. A positive local lymph node is associated with a worse prognosis. However, Gonza' lez-Moreno et al[20] studied 501 patients with appendiceal malignancies and were surprised to find that lymph node status had no significant effect on patient survival. Although median survival was indeed shorter in patients with lymph node involvement than in other patients, this was not statistically significant. Fleischmann et al[12] studied the date between 2004 and 2012 in the SEER database including 1046 patients with primary carcinoma of the appendix, and the results showed that with 12 or more of regional lymph nodes removed, a significant advantage concerning OS and DSS emerged.

TNM was analyzed by the AJCC 7th staging system. Although there are more missing data in the 7th edition, the classification of T, N, and M is more detailed, so the seventh edition is adopted for our analysis.[21] In the TNM stage, the number of lymph node metastasis was closely related to DSS. The prognosis is worse if the number of lymph node metastases is greater than 3 than 1 to 3, and the prediction is best without lymph node metastasis. Nash et al[22] proved that lymph node metastasis strongly predicted recurrence. The study of Ihemelandu et al showed that lymph node metastasis was an essential predictor of OS, which was consistent with our findings.

Considering the treatment of patients with AMA, right hemicolectomy with lymph node dissection, and an ileocolic anastomosis are relatively conventional at present.[10,23,24] However, in 2004, Gonzalez-Moreno and Sugarbaker[23] reported that in peritoneally disseminated mucinous appendiceal tumor, right colectomy with ileocolonic lymph node dissection did not have a survival advantage over appendectomy alone. Turaga et al[10] proved that the correct hemicolectomy should be performed when the tumor cannot be removed, meaning that not

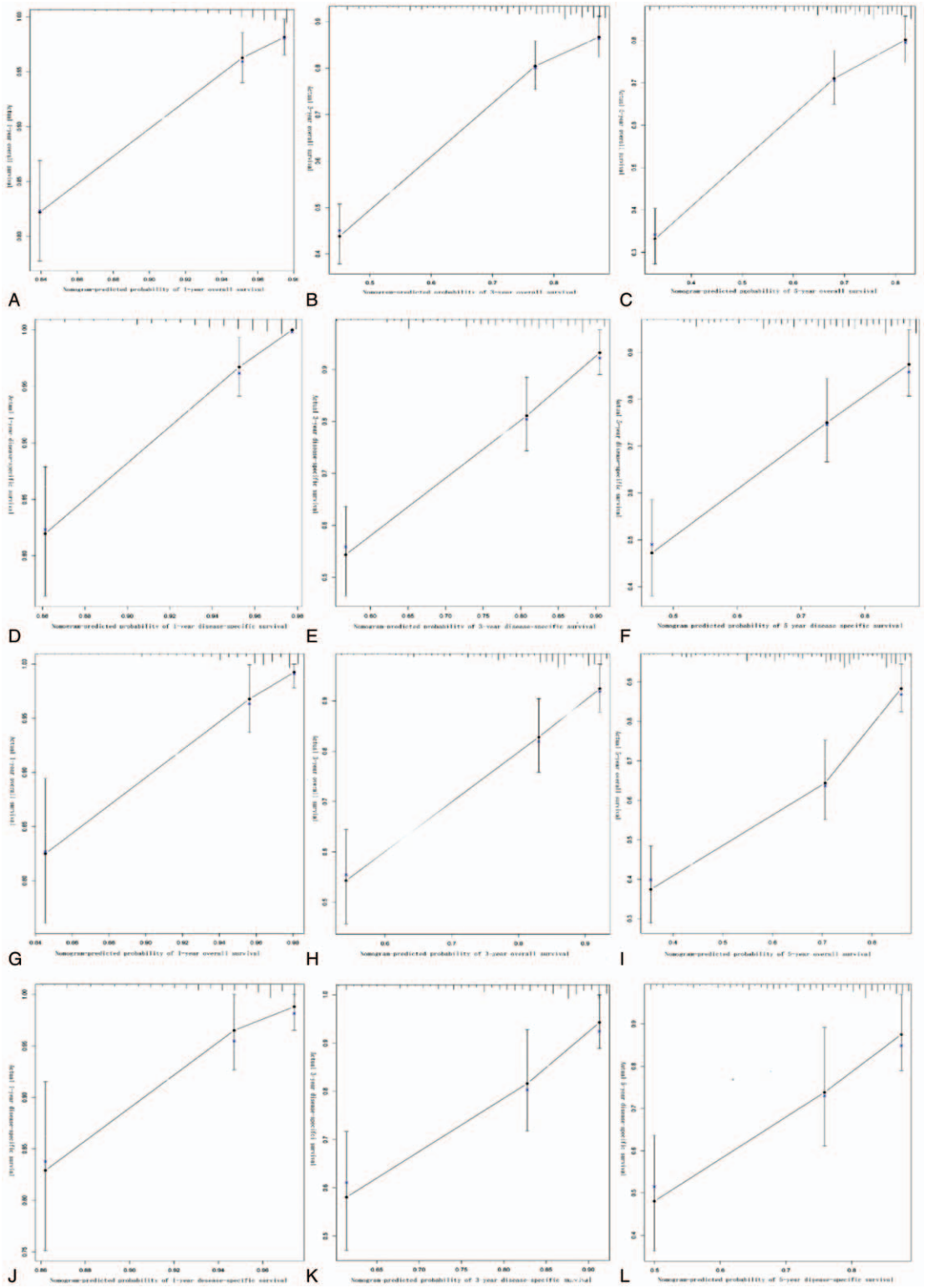

Figure 4. External calibration plots of 1-year (A), 3-year (B), and 5-year (C) overall survival nomogram calibration curves; 1-year (D), 3-year (E), and 5-year (F) cancer-specific survival nomogram calibration curves. Notes: The dashed line represents an excellent match between actual survival outcome (Y-axis) and nomogram prediction (X-axis). Closer distances between the dashed line and points indicate higher prediction accuracy.

all the benefits of right hemicolectomy are most significant. In our study, surgical methods are closely related to OS and DSS in patients with AMA. Our study demonstrated that patients without surgery have the worst prognosis, and patients receiving colectomy plus resection of the contiguous organ have the best prognosis. The prognosis of colectomy is better than an appendectomy in OS and DSS. Because the SEER database does not provide specific information about the surgery or its

combination with other treatments, our results may differ from previous studies. At the same time, because we set the missing value in the process of making the nomogram, the result of multifactor COX may be slightly different from that of the nomogram. Previous studies[13] have shown that the use of chemoradiotherapy does not bring benefits to the survival of patients with AMA. This is basically consistent with our findings. At the same time, our study also showed that in DSS, the use of chemotherapy increased the risk by 21.5%.

Based on the independent prognostic factors of OS and DSS, we constructed a nomogram to predict 1-, 3-, and 5-year survival. For instance, an 80-year-old never-married man was diagnosed with AMA, a localized disease with no lymph nodes and distant metastasis, a tumor size of 70 mm, and underwent appendectomy without chemoradiotherapy. He scored 12.1 on OS and 10.07 on DSS. Accordingly, he estimated that OS and DSS for 1, 3, and 5 years were 94.2%, 72.9%, 62.9% and 95.6%, 82.3%, and 76.0% respectively.

The study currently has the following limitations. First, there is only a normal or elevated classification of CEA serum levels, and no specific levels of CEA are recorded in the SEER database, which would lead to a bias in prognosis. Second, the treatment information is not comprehensive, and there is no record of the frequency and time of the operation. There is no specific plan and time record for radiotherapy and chemotherapy, and the treatment strategy of the patient will not be evaluated. Third, the TNM stage is the seventh edition of the AJCC staging. There are more missing data, resulting in less research on the actual inclusion of the nomogram. Fourth, the research data represents only the US population. Without external verification, it will be impossible to judge whether these data are universally applicable. More external data are expected to confirm this conclusion in the future. Despite these shortcomings, our nomogram can still be considered a useful prognostic model.

5. Conclusion

Our results indicate that age at diagnosis, sex, marital status, histological grade, SEER extent of disease, number of regional lymph nodes examined, whether or not they were positive, surgical approach were independent prognostic factors for OS. Age at diagnosis, number of lymph nodes metastases, histological grade, SEER extent of disease, chemotherapy, number of regional lymph nodes examined, and surgical procedures were independent prognostic factors for DSS. Besides, we developed a nomogram to effectively visualize OS and DSS for 1-, 3-, and 5-years in patients with AMA.

Author contributions

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References

[1] McCusker ME, Cote TR, Clegg LX, et al. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end results program, 1973–1998. Cancer 2002;94:3307–12.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
[3] Shaib WL, Goodman M, Chen Z, et al. Incidence and survival of appendiceal mucinous neoplasms: a SEER analysis. Am J Clin Oncol 2017;40:569–73.
[4] DeSantis CE, Kramer JL, Jemal A. The burden of rare cancers in the United States. CA Cancer J Clin 2017;67:261–72.
[5] Marmor S, Portschy PR, Tuttle TM, et al. The rise in appendiceal cancer incidence: 2000–2009. J Gastrointest Surg 2015;19:743–50.
[6] Xie GD, Liu YR, Jiang YZ, et al. Epidemiology and survival outcomes of mucinous adenocarcinomas: a SEER population-based study. Sci Rep 2018;8:6117.
[7] Turaga KK, Pappas SG, Gamblin T. Importance of histologic subtype in the staging of appendiceal tumors. Ann Surg Oncol 2012;19:1379–85.
[8] Yilmaz M, Akbulut S, Kutluturk K, et al. Unusual histopathological findings in appendectomy specimens from patients with suspected acute appendicitis. World J Gastroenterol 2013;19:4015–22.
[9] Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. Cancer 2010;116:316–22.
[10] Turaga KK, Pappas S, Gamblin TC. Right hemicolectomy for mucinous adenocarcinoma of the appendix: just right or too much? Ann Surg Oncol 2013;20:1063–7.
[11] Overman MJ, Fournier K, Hu CY, et al. Improving the AJCC/TNM staging for adenocarcinomas of the appendix: the prognostic impact of histological grade. Ann Surg 2013;257:1072–8.
[12] Fleischmann I, Warschkow R, Beutner U, et al. Improved survival after retrieval of 12 or more regional lymph nodes in appendiceal cancer. Eur J Surg Oncol 2017;43:1876–85.
[13] Asare EA, Compton CC, Hanna NN, et al. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: analysis of the National Cancer Data Base. Cancer 2016;122:213–21.
[14] Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015;16:e173–80.
[15] Iasonos A, Schrag D, Raj GV, et al. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 2008;26:1364–70.
[16] Fritz APC, Jack A. International Classification of Disease for Oncology. 3rd edGeneva, Switzerland: World Health Organization; 2000.
[17] Camp RL, Rimm DL, Dolled-Filhart M. X-Tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004;10:7252–9.
[18] Valentini V, van Stiphout RG, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011;29:3163–72.
[19] Umetsu SE, Shafizadeh N, Kakar S. Grading and staging mucinous neoplasms of the appendix: a case series and review of the literature. Hum Pathol 2017;69:81–9.
[20] Gonza' lez-Moreno S, Brun E, Sugarbaker PH. Lymph node metastasis in epithelial malignancies of the appendix with peritoneal dissemination does not reduce survival in patients treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2005; 12:72–80.
[21] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. Ann Surg Oncol 2010;17:1471–4.
[22] Nash GM, Smith JD, Tang L, et al. Lymph node metastasis predicts disease recurrence in a single-center experience of 70 stages 1-3 appendix cancers: a retrospective review. Ann Surg Oncol 2015;22:3613–7.
[23] Gonzalez-Moreno S, Sugarbaker PH. Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. Br J Surg 2004;91:304–11.
[24] Nitecki SS, Wolff BG, Schlinkert R, et al. The natural history of surgically treated primary adenocarcinoma of the appendix. Ann Surg 1994;219:51–7.