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 personalized survival prediction for clinicians and patients.

Abbreviations: AJCC = American Joint Committee on Cancer, AMA = appendiceal mucinous adenocarcinoma, CEA = carciioembryonic 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
improve the prediction accuracy of individual prognosis, which has been widely used in the forecast of cancer. 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 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), 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,
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 cutoff 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 \( \chi^2 \) 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. 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 have shown that a c-index of 0.50 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 the 1-, 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

| Variables                              | Training cohort      | Validation cohort     | Total                  |
|----------------------------------------|----------------------|-----------------------|------------------------|
|                                        | (n = 2155), n, %     | (n = 1079), n, %      | (n = 3234)             |
| Age at diagnosis                       | 57.86 ± 14.11        | 57.37 ± 14.52         | 57.69 ± 14.25          | .36 |
| ≤53                                    | 812                  | 453                   | 1265                   | .91 |
| 53-74                                  | 1060                 | 474                   | 1534                   | .74 |
| >74                                    | 283                  | 152                   | 435                    | 13.5 |
| Marital status                         |                      |                       |                        | .652 |
| Married (including common law)         | 1359                 | 682                   | 2041                   | .51 |
| Single (never married/divorced/separated/widowed) | 725                 | 355                   | 1080                   | 33.4 |
| Unknown                                | 71                   | 42                    | 113                    | 3.5 |
| Sex                                    |                      |                       |                        | .966 |
| Female                                 | 1241                 | 607                   | 1821                   | 56.3 |
| Male                                   | 941                  | 472                   | 1413                   | 43.7 |
| Ethnicity                              |                      |                       |                        | .938 |
| White                                  | 1786                 | 888                   | 2674                   | 82.7 |
| Black                                  | 181                  | 93                    | 274                    | 8.5 |
| Other (American Indian/AK Native, Asian/Pacific Islander) | 179                  | 92                    | 271                    | 8.4 |
| Unknown                                | 9                    | 6                     | 15                     | 0.5 |

(continued)
| Variables | Training cohort | Validation cohort | Total | P |
|-----------|----------------|------------------|-------|---|
|           | (n = 2155), n, % | (n = 1079), n, % | (n = 3234) |   |
| Histologic grade | | | | .819 |
| Well differentiated; Grade I | 719 (33.4) | 360 (33.4) | 1079 (33.4) |   |
| Moderately differentiated; Grade II | 591 (27.4) | 309 (26.6) | 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 | 56 (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 | | | | .504 |
| 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.

| Characteristics | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|-----------------------|
|                 | P                   | HR 95% CI              | P         |
| Age at diagnosis|                     |                       |           |
| <53             | 0                   | Reference             |           |
| 53–74           | 2.889               | 2.367–3.443           | 0         |
| >74             |                    |                       |           |
| 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 | 1.247 | 1.056–1.474 | .009 |
| 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 | 1.269–3.884 | .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 |       |                       |           |
| T1              | 0.684               | 0.132–3.552           | .651      |
| T2              | 1.647               | 0.624–4.344           | .313      |
| T3              | 1.905               | 0.769–4.720           | .164      |
| T4              | 1.738               | 0.641–4.711           | .277      |
| Other           | 1.835               | 1.268–2.655           | .002      |
| Regional lymph nodes (N) |     |                       |           |
| N0              | 1.418               | 0.864–2.328           | .167      |
| N1              | 1.786               | 0.988–3.297           | .064      |
| N2              | 1.535               | 1.268–2.955           | .002      |
| Other           |                     |                       |           |
| Distant metastases (M) |     |                       |           |
| M0              | 1.633               | 0.861–3.098           | .133      |
| M1              | 0.802               | 0.316–2.040           | .644      |
| Other           |                     |                       |           |
| Tumor size      |                     |                       |           |
| ≤31 mm          | 1.033               | 0.777–1.374           | .822      |
| >31 mm          | 1.151               | 0.883–1.499           | .298      |
| Unknown         |                     |                       |           |
| CEA             | .001                | Reference             |           |
| Negative/normal; within normal limits | 1.199 | 0.896–1.603 | .223 |
| Positive/elevated| 1.046               | 0.808–1.354           | .733      |
| Regional nodes examined |       |                       |           |
| Less 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 |                       | .299 |
| Regional lymph nodes examined positive | 2.375 | 1.889–2.987 | 0   |
| Other           | 1.116               | 0.911–1.365           | .299      |
| Surgery type    |                     |                       |           |
| No cancer-directed surgery of primary site | 0 | Reference |                       | .299 |
| Local surgery   | 0.709               | 0.456–1.103           | .128      |
| Appendectomy    | 0.589               | 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               | 0.576–0.965           | .026      |
| Radiotherapy    | .63                 | NA                    |           |
| Yes             |                     |                       |           |
| No              |                     |                       |           |
| Chemotherapy    |                     |                       |           |
| Yes             | 0                   | Reference             | .085      |
| No              |                     |                       |           |
| Characteristics                              | Univariate analysis | Multivariate analysis |
|---------------------------------------------|---------------------|-----------------------|
|                                             | $P$                 | HR                    | 95% CI      | $P$     |
| Age at diagnosis                            | 0                   | Reference             |            |        |
| <53                                          |                     | 1.266                 | 1.088–1.474 | .002    |
| 53–74                                        |                     | 1.845                 | 1.487–2.289 | 0       |
| >74                                          |                     | 1.845                 | 1.487–2.289 | 0       |
| Marital status                              |                     | Reference             |            |        |
| Married (including common law)               | .046                | 1.153                 | 0.993–1.338 | .062    |
| Single (never married/divorced/separated/widowed) |       | 1.141                 | 0.768–1.694 | .515    |
| Unknown                                     |                     |                       |            |        |
| Sex                                         | .092                | NA                    |            |        |
| Male                                        |                     |                       |            |        |
| Ethnicity                                   | .049                | Reference             |            | .198    |
| Black                                       | 1.171               | 0.921–1.469           |            | .002    |
| Other (American Indian/AK Native, Asian/Pacific Islander) | | 0.77                  | 0.590–1.007           | .056    |
| Unknown                                     | 0                   | 0–2.12E+57            |            | .002    |
| Histologic grade                            |                     | Reference             |            |        |
| Well differentiated; Grade I                | 0                   | 1.509                 | 1.239–1.837 | 0       |
| Moderately differentiated; Grade II         |                     | 2.436                 | 1.884–3.151 | 0       |
| Poorly differentiated; Grade III            |                     | 2.529                 | 1.453–3.400 | .001    |
| Undifferentiated; anaplastic; Grade IV      |                     | 1.362                 | 1.129–1.644 | .001    |
| SEER extent of disease                      |                     | Reference             |            |        |
| Distant                                     | 0                   | 0.341                 | 0.267–0.436 | 0       |
| Localized                                   | 0.623               | 0.429–0.653           |            | .004    |
| Regional                                    | 0.529               | 0.314–0.806           |            | .004    |
| Unknown/upstaged                            | 0.503               | 0.314–0.806           |            | .004    |
| AJCC Stage, 7th ed                          |                     | Reference             |            |        |
| T1                                          | 0                   | 0.45                  | 0.05–4.072  | .478    |
| T2                                          | 1.642               | 0.552–4.882           |            | .372    |
| T3                                          | 2.006               | 0.731–5.506           |            | .177    |
| T4                                          | 1.695               | 0.565–5.087           |            | .346    |
| Primary tumor (T)                           |                     | Reference             |            |        |
| Regional lymph nodes (N)                    |                     | Reference             |            |        |
| N0                                          | 0                   | 1.659                 | 0.998–2.758 | .051    |
| N1                                          | 2.06                | 1.098–3.866           |            | .024    |
| N2                                          | 2.279               | 1.479–3.512           |            |        |
| Other                                       |                     |                       |            |        |
| Distant metastases (M)                      |                     | Reference             |            |        |
| M0                                          | 0                   | 0.802                 | 0.316–2.040 | .644    |
| M1                                          | 1.633               | 0.861–3.098           |            | .133    |
| Other                                       | 0.802               | 0.316–2.040           |            | .644    |
| Tumor size                                  |                     | Reference             |            |        |
| $\leq$ 31 mm                                | 0                   | 1.819                 | 0.923–3.585 | .084    |
| $>$ 31 mm                                   |                     | 0.504                 | 0.193–3.314 | 1.161   |
| CEA                                         |                     | Reference             |            |        |
| Positive/elevated                           | 1.26                | 0.896–1.603           |            | .416    |
| Borderline/ unknown                         | 1.071               | 0.803–1.354           |            | .631    |
| Regional nodes examined                     |                     | Reference             |            |        |
| Less than 8                                 | 0                   | 0.756                 | 0.923–1.721 | .006    |
| Other                                       | 1.019               | 0.809–1.419           |            | .851    |
| Regional nodes positive                     |                     | Reference             |            |        |
| All nodes examined negative                 | 0                   | 0.854                 | 0.633–1.086 | .166    |
| Other                                       | 1.058               | 0.849–1.317           |            | .616    |
| Surgery type                                |                     | Reference             |            |        |
| No cancer-directed surgery of primary site  | 0                   | 0.532                 | 0.385–0.986 | .044    |
| Local surgery (excision/destruction/curettage) |       | 0.526                 | 0.396–0.986 | .001    |
| Appendectomy                                | 0.526               | 0.396–0.986           |            | .001    |
| Segmental colectomy                         | 0.526               | 0.396–0.986           |            | .001    |
| Colectomy plus resection of contiguous organ|                     |                       |            |        |
| Unknown                                     | 0.707               | 0.539–0.927           |            | .012    |
| Radiotherapy                                | .49                 | NA                    |            |        |
| Chemotherapy                                |                     | Reference             |            |        |
| No                                          | 0                   | 1.215                 | 1.044–1.413 | .012    |
| Yes                                         |                     |                       |            |        |
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...
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 affect 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 node metastases, 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. 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 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. investigated the impact of these 2 factors on DSS and the interactions between them, and the effect of histological 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.

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, González-Moreno et al. 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. 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. 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 to 1 and the prediction is best without lymph node metastasis. Nash et al. 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. However, in 2004, Gonzalez-Moreno and Sugarbaker 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. proved that the correct hemicolectomy should be performed when the tumor cannot be removed, meaning that not

### Table 4

| 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 | | |
| Married (including common law) | 0.000 | |
| Single | 1.880 | |
| Gender | | |
| Female | 0.000 | NA |
| 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) | | |
| N0 | NA | |
| N1 | 0.000 | |
| N2 | 5.000 | |
| N3 | 10.000 | |
| Regional lymph nodes examined positive | 10.000 | |
| Less than 8 | 4.210 | 0.740 |
| More than 8 | 0.000 | 0.000 |
| Regional nodes positive | | |
| 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 | 2.900 |
| 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 | |
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 multifacto 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.

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.

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