Machine learning models for predicting survival in patients with ampullary adenocarcinoma

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ABSTRACT

Objective: The aim of this study was to predict the long-term survival probability of patients with ampullary adenocarcinoma (AAC), which would provide a theoretical basis for the long-term care of these patients.

Methods: Data on patients with AAC during 2004–2015 were obtained from the Surveillance, Epidemiology, and End Results database, which were split at a 7:3 ratio into two independent cohorts: training and testing cohorts. Differences in survival between the two groups were tested using the Kaplan–Meier estimator and log-rank test methods. We constructed six survival analysis methods: the American Joint Committee on Cancer TNM stage, Cox Proportional Hazards regression, CoxTime, DeepSurv, XGBoost Survival Embeddings, and Random Survival Forest. The performances of these models were evaluated using the C-index, receiver operating characteristic (ROC), and calibration curves.

Results: This study included 2,935 patients with AAC. Univariate Cox regression analyses of the training cohort indicated that race, marital status at diagnosis, scope of regional lymph node surgery, tumor grade, summary stage, American Joint Committee on Cancer stage, TNM stage T, and TNM stage N were important factors affecting survival \( (P < 0.05) \). The results of the C-index indicated that DeepSurv performed the best among the six models, with the highest C-index of 0.731. The areas under the ROC curves of the DeepSurv model at the 1-year, 3-year, 5-year, and 10-year time points were 0.823, 0.786, 0.803, and 0.813, respectively. The calibration curve indicated that DeepSurv performed well, with good calibration.

Conclusions: Machine learning models such as DeepSurv have a stronger performance in the survival analysis of patients with AAC.

Introduction

Ampullary adenocarcinoma (AAC), which constitutes approximately 0.2% of gastrointestinal cancers, is an uncommon but aggressive type of periampullary cancer that originates in biliary, duodenal, or pancreatic ductal epithelial cells.1–2 The incidence of AAC is estimated to be 0.5, 0.73, and 0.96 per 100,000 persons per year in the US, Japan, and the Netherlands, respectively.2–4 Despite its rarity, the occurrence of AAC has increased worldwide over the past few decades.2–5 Patients with AAC tend to present typical symptoms of biliary obstruction at relatively early stages, but these symptoms are mostly non-specific and are therefore often detected incidentally during examinations.5,6 Although the early detection of symptoms helps to improve the resection rates in radical surgery, which is the standard treatment for AAC, high risks of recurrence, and postoperative mortality are major concerns.7,8 Different centers have reported a wide range of 5-year overall survival (OS) rates after AAC resection: 32%–69.1%, with a median survival time of 28–70 months, while the 10-year OS rate ranged from 26% to 48%.9,10,11 High-quality evidence from clinical trials of AAC is currently inadequate, and relevant data are mostly collected from subgroup analyses of pancreaticobiliary malignancies or retrospective analyses.12 Specific treatment decisions and prognoses of AAC are under discussion including the construction of the American Joint Committee on Cancer (AJCC) TNM staging system.13 Knowledge of the prognostic factors associated with different survival outcomes among patients with AAC is important for survival predictions and nursing planning.4,14,15

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Previous research has used various types of prediction models to assess the short-term survival rates of AAC, including Kaplan–Meier survival analysis, logistic regression, and the Cox proportional hazards (CoxPH) model.\(^1\)–\(^15\)\(^-\)\(^23\) Kaplan–Meier survival analysis is the most commonly used method to investigate the prognostic factors for AAC, which does not allow adjustments for confounders and has a restrictive assumption of non-informative censoring.\(^14\)\(^-\)\(^26\) Logistic regression models aim to estimate the relationship between potential factors and survival outcomes as well as adjust for confounders.\(^26\)\(^-\)\(^27\) However, this method does not consider survival time, which might affect prediction accuracy.\(^27\) The CoxPH model is commonly used to explore the effects of joint covariates on OS, but it is based on hazard ratios (HRs) being constant over time and linear effects of covariates on hazards, which might not be applicable to real-life applications.\(^29\) It is therefore necessary to develop a new and more accurate model for predicting the survival rate in AAC.

With the rapid development of computer technology and increasing focus on personalized treatment, machine learning\(^30\) techniques can process large volumes of patient medical records or data without overly restrictive conditions, which can improve the accuracy and reliability of survival predictions.\(^31\) Deep learning is a new machine learning technique that utilizes artificial neural networks to extract patterns and make predictions from high-dimension data.\(^32\) It shows a great potential in the healthcare field, with good performance in the early detection of cancer.\(^33\) Although machine learning techniques are widely used for survival predictions in various cancers, few studies have applied them to determining the diagnosis, prognosis, or treatment in AAC. In this study, a traditional survival analysis method was constructed and compared with several common machine learning models. An optimal model for predicting the survival outcome of patients with AAC was established, which might help specific treatment decisions and personalized nursing planning for AAC.

### Methods

#### Data source

Data from 2004 to 2015 were collected from the Surveillance, Epidemiology, and End Results (SEER)\(^4\)\(^-\)\(^13\)\(^,\)\(^24\)^ 17 database using the SEER*Stat software (version 8.4.0.1), which was submitted in November 2021 and published in April 2022.\(^24\) The SEER 17 database collects and publishes cancer incidence and survival data from population-based cancer registries that cover approximately 26.5% of the US population. This study collected information of patients diagnosed with AAC after receiving permission to access the SEER 17 database through a multiple-step request process.

#### Study population and inclusion criteria

The study investigated patients diagnosed with AAC during 2004–2015 as defined by the International Classification of Diseases for Oncology, third edition. Patients with AAC were identified using a primary site code (ampulla of vater (C24.1)) and morphology code (adenocarcinoma, NOS [8140/3]). Among these patients, the exclusion criteria included having no data on tumor grade, diagnostic confirmation, AJCC TNM stage, surgery information, or marital status at diagnosis. The information of 2,935 patients with AAC were collected, including age, sex, race, marital status at diagnosis, scope of regional lymph node surgery, tumor grade, summary stage, AJCC TNM stage, surgery status, radiotherapy, chemotherapy, tumor extent, regional lymph node involvement and metastasis, primary indicator of malignancy, vital status, and survival time. These patients were subsequently randomly divided into the training and testing cohorts with a ratio of 7:3. Steps in this study to select AAC cases under these criteria and screening procedure are illustrated in Fig. 1.

#### Survival analysis models

The AJCC TNM staging system is a conventional diagnostic model that was used as the baseline model in this study. We performed univariate analyses of patient indicators using the traditional CoxPH regression model,\(^26\) screened out meaningful indicators (\(P < 0.05\)), and then used multivariate analysis to determine the ability of survival predictive of the Cox model. The four other survival analysis models used in this study included two learning models based on decision tree ensembles (XGBoost Survival Embeddings (XGBSE)\(^37\) and random survival forest (RSF)\(^38\)) and two deep learning models based on neural network structures (CoxTime\(^39\) and DeepSurv\(^40\)). All of the models were simulated using Python (version 3.9) software, and the Bayesian optimizer\(^41\) (Bayesian-optimization version 1.2.0) was used to optimize the model parameters. Among them, XGBSE and RSF used the XGBSE (version 0.2.3) and random survival forest (version 0.8.0) packages, respectively, and both CoxTime and DeepSurv were implemented using pycox (version 0.2.3).

![Flow diagram of patients with ampullary adenocarcinoma selection. AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.](image)
| Variables                                      | Overall N (%) | Train cohort N (%) | Test cohort N (%) | P-value |
|-----------------------------------------------|---------------|--------------------|------------------|---------|
| Patients                                      | 2935 (100.0%) | 2054 (70.0%)       | 881 (30.0%)      | 0.593   |
| Age (years)                                   |               |                    |                  |         |
| Median (IQR)                                  | 69.0 [59.0, 77.0] | 69.0 [59.0, 77.0] | 69.0 [59.0, 77.0] | 0.593   |
| Gender                                        |               |                    |                  |         |
| Male                                          | 1,683 (57.3%) | 1,170 (57.0%)      | 513 (58.2%)      | 0.551   |
| Female                                        | 1,252 (42.7%) | 884 (43.0%)        | 368 (41.8%)      |         |
| Race                                          |               |                    |                  | 0.618   |
| White                                         | 2,322 (79.1%) | 1,632 (79.5%)      | 690 (78.3%)      |         |
| Black                                         | 211 (7.2%)    | 149 (7.3%)         | 62 (7.0%)        |         |
| Others                                        | 402 (13.7%)   | 273 (13.3%)        | 129 (14.6%)      |         |
| Marital status at diagnosis                   |               |                    |                  | 0.138   |
| Married                                       | 1,841 (62.7%) | 1,269 (61.8%)      | 572 (64.9%)      |         |
| Single                                        | 381 (13.0%)   | 265 (12.9%)        | 116 (13.2%)      |         |
| DSW                                           | 713 (24.3%)   | 520 (25.3%)        | 193 (21.9%)      |         |
| Scope of regional lymph node surgery          |               |                    |                  | 0.771   |
| None                                          | 688 (23.4%)   | 491 (23.9%)        | 197 (22.4%)      |         |
| 1 to 3                                        | 172 (5.9%)    | 121 (5.9%)         | 51 (5.8%)        |         |
| 4 or more                                     | 2,037 (69.4%) | 1,417 (69.0%)      | 620 (70.4%)      |         |
| Unknown or not applicable                     | 38 (1.3%)     | 25 (1.2%)          | 13 (1.5%)        |         |
| Grade                                         |               |                    |                  | 0.882   |
| Grade I                                       | 332 (11.3%)   | 228 (11.1%)        | 104 (11.8%)      |         |
| Grade II                                      | 1,579 (53.8%) | 1,101 (53.6%)      | 478 (54.3%)      |         |
| Grade III                                     | 999 (34.0%)   | 707 (34.4%)        | 292 (33.1%)      |         |
| Grade IV                                      | 25 (0.9%)     | 18 (0.9%)          | 7 (0.8%)         |         |
| Summary stage                                 |               |                    |                  | 0.207   |
| Localized                                     | 394 (13.4%)   | 290 (14.1%)        | 104 (11.8%)      |         |
| Regional                                      | 1,944 (66.2%) | 1,355 (66.0%)      | 589 (66.9%)      |         |
| Distant                                       | 597 (20.3%)   | 409 (19.9%)        | 188 (21.3%)      |         |
| AJCC                                          |               |                    |                  | 0.765   |
| I                                             | 828 (28.2%)   | 589 (28.7%)        | 239 (27.1%)      |         |
| II                                            | 1,066 (36.3%) | 748 (36.4%)        | 318 (36.1%)      |         |
| III                                           | 720 (24.5%)   | 496 (24.1%)        | 224 (25.4%)      |         |
| IV                                            | 321 (10.9%)   | 221 (10.8%)        | 100 (11.4%)      |         |
| T                                             |               |                    |                  | 0.110   |
| T1                                            | 522 (17.8%)   | 386 (18.8%)        | 136 (15.4%)      |         |
| T2                                            | 749 (25.5%)   | 504 (24.5%)        | 245 (27.8%)      |         |
| T3                                            | 799 (27.2%)   | 564 (27.5%)        | 235 (26.7%)      |         |
| T4                                            | 810 (27.6%)   | 559 (27.2%)        | 251 (28.5%)      |         |
| TX                                            | 55 (1.9%)     | 41 (2.0%)          | 14 (1.6%)        |         |
| N                                             |               |                    |                  | 0.863   |
| N0                                            | 1,541 (52.5%) | 1,076 (52.4%)      | 465 (52.8%)      |         |
| N1                                            | 1,331 (45.3%) | 932 (45.4%)        | 399 (45.3%)      |         |
| NX                                            | 63 (2.1%)     | 46 (2.2%)          | 17 (1.9%)        |         |
| M                                             |               |                    |                  | 0.685   |
| M0                                            | 2,614 (89.1%) | 1,833 (89.2%)      | 781 (88.6%)      |         |
| M1                                            | 321 (10.9%)   | 221 (10.8%)        | 100 (11.4%)      |         |
| Surgery performed                             |               |                    |                  | 0.560   |
| Yes                                           | 2,314 (78.8%) | 1,613 (78.5%)      | 701 (79.6%)      |         |
| No                                            | 621 (21.2%)   | 441 (21.5%)        | 180 (20.4%)      |         |
| Radiotherapy                                  |               |                    |                  | 0.615   |
| Yes                                           | 621 (21.2%)   | 429 (20.9%)        | 192 (21.8%)      |         |
| No/Unknown                                    | 2,314 (78.8%) | 1,625 (79.1%)      | 689 (78.2%)      |         |
| Chemotherapy                                  |               |                    |                  | 0.954   |
| Yes                                           | 1,270 (43.3%) | 890 (43.3%)        | 380 (43.1%)      |         |
| No/Unknown                                    | 1,665 (56.7%) | 1,164 (56.7%)      | 501 (56.9%)      |         |
| CS extension                                  |               |                    |                  | 0.118   |
| Localized                                     | 522 (17.8%)   | 386 (18.8%)        | 136 (15.4%)      |         |
| Regional                                      | 2,062 (70.3%) | 1,427 (69.5%)      | 635 (72.1%)      |         |
| Distant                                       | 296 (10.1%)   | 200 (9.7%)         | 96 (10.9%)       |         |
| Unknown                                       | 55 (1.9%)     | 41 (2.0%)          | 14 (1.6%)        |         |
| CS lymph nodes involvement                    |               |                    |                  | 0.863   |
| Yes                                           | 1,331 (45.3%) | 932 (45.4%)        | 399 (45.3%)      |         |
| No/Unknown                                    | 1,604 (54.7%) | 1,122 (54.6%)      | 482 (54.7%)      |         |
| CS Mets at DX                                 |               |                    |                  | 0.685   |
| Yes                                           | 321 (10.9%)   | 221 (10.8%)        | 100 (11.4%)      |         |
| No                                            | 2,614 (89.1%) | 1,833 (89.2%)      | 781 (88.6%)      |         |
| First malignant primary indicator             |               |                    |                  | 0.361   |
| Yes                                           | 2,425 (82.6%) | 1,688 (82.2%)      | 737 (83.7%)      |         |
| No                                            | 510 (17.4%)   | 366 (17.8%)        | 144 (16.3%)      |         |
| Status                                        |               |                    |                  | 0.453   |
| Alive                                         | 764 (26.0%)   | 526 (25.6%)        | 238 (27.0%)      |         |
| Death                                         | 2,171 (74.0%) | 1,528 (74.4%)      | 643 (73.0%)      |         |

AJCC, American Joint Committee on Cancer.
Data analysis

Statistical analysis of patient data in this study was performed using Python software. The Kruskal–Wallis rank-sum or Mann–Whitney U tests were used to assess the distributions of the variables. Continuous variables that were not normally distributed were expressed as medians and 25th–75th percentiles, and categorical variables were expressed as percentages of the population. The Kaplan–Meier method was used to draw survival curves, and group survival differences were compared using the log-rank test. The C-index and area under the receiver operating characteristic (ROC) curve (AUC) were used to evaluate the predictive abilities of the models. Calibration plots were used to assess the relationship between follow-up outcomes and predicted survival probability.

Results

Baseline characteristics of the patients

The sample population comprised 2,935 patients with AAC, of which 1,683 (57.3% of the sample population) patients were male and 1,252 (42.7%) were female. The mean age was 69 years, males accounted for about 14% more of the population than did females (57.0% vs 43.0%), and 1,632 (79.5%) patients were white. Patients were followed for a maximum of 190 months, with a mean of 42 months. The overall patient follow-up mortality rate was 74.0%.

Table 1 lists the basic characteristics and variance analysis results for the total study population as well as in the training and testing cohorts. The training cohort consisted of 2,054 patients (70%). The log-rank test used to assess the difference between the two cohorts yielded \( P = 0.736 \), and the survival curves did not differ significantly between the two cohorts. Kaplan–Meier analysis curves of the training and testing cohorts are shown in Fig. 2.

Risk factors identified by Cox model

All variables in Table 1 were subjected to univariate Cox analyses, which revealed that race, marital status at diagnosis, scope of regional lymph node surgery, tumor grade, summary stage, AJCC stage, TNM stage T, and TNM stage N were risk factors for patients with AAC. These factors were subsequently included in a multivariate Cox analysis. Table 2 lists the results of univariate and multivariate analyses. Combined with Table 1, it can be seen that the mortality risk of patients with AAC was not related to age or sex, but was related to race. Compared with white patients, black patients had a higher mortality risk (HR = 1.25, 95% confidence interval [CI] = 1.01–1.55, \( P = 0.042 \)), while other races had lower mortality risks than whites (HR = 0.73, 95% CI = 0.61–0.87, \( P = 0.001 \)). Patients with Divorced/Separated/Widowed had a higher mortality risk than patients who were married (HR = 1.24, 95% CI = 1.08–1.41, \( P = 0.002 \)). Regardless of its degree, lymph node surgery reduced the mortality risk relative to no surgery (\( P > 0.05 \)). The cancer status of the patient, including tumor grade, summary stage, and AJCC TNM stage, were consistent with the basic understanding. The risk of mortality increased with the tumor grade and stage.

Model comparison of survival analysis

We used the training cohort to construct six survival analysis models and adjust the parameters to their best states. Model performance was then evaluated using a testing cohort that was completely isolated from the training cohort. Harrell’s C-index was first used to measure the relationship between model-predicted risk profiles and actual patient survival, reflecting the predictive power of the models. The AJCC TNM stage model had the worst result in predicting the survival of patients with AAC, with a C-index of only 0.606, followed by the CoxPH model (0.693) and then XGBSE (0.709) and RSF (0.716). The C-indexes of the deep learning model based on the neural network were 0.714 for Cox-Time and 0.731 for DeepSurv.

We calculated the 1-year, 3-year, 5-year, and 10-year ROC curves of all models to verify the recognition ability of the models. Fig. 3 shows the ROC assessments of the survival analysis model at different time points, representing the overall performance of the model. The AJCC TNM stage model had the worst performance in predicting patient survival, with AUCs of only 0.622, 0.664, 0.674, and 0.655 at 1 year, 3 years, 5 years, and 10 years, respectively, but the ROC curve of the DeepSurv model
DeepSurv and CoxTime. DeepSurv model has better classification and discriminative abilities; the AUCs for 1-year, 3-year, 5-year, and 10-year survival probabilities were 0.823, 0.786, 0.803, and 0.813, respectively. This indicates that the DeepSurv model had the largest total AUC, and the predicted survival to not change over time. It ignores the impact of some non-linear factors on patient survival outcomes. However, tumor development and its changes are affected by many different factors, and traditional strictly linear models are unlikely to accurately predict the prognoses of patients with cancer. It is therefore necessary to develop new methods to incorporate both linear and non-linear factors, and so in this study, we constructed and validated a deep learning model for predicting the mortality risk of patients with AAC by comparing multiple different types of survival analysis models.

According to the analysis results of the CoxPH regression model, race, marital status at diagnosis, scope of regional lymph node surgery, tumor grade, summary stage, and AJCC TNM stage are the main factors affecting patient survival. Racial disparities in patients with cancer have always been one of the focuses of research. Among patients with AAC in the US population of this study, black patients had a higher mortality risk. Because cancer treatment is expensive, this finding might be related to the medical insurance or financial status of the patient.

AJCC, American Joint Committee on Cancer.

### Table 2
Survival predictors in Cox PH model.

| Analysis variables | Univariate analysis | Multivariate analysis |
|--------------------|---------------------|----------------------|
|                    | HR                  | 95% CI               | P-value | HR                  | 95% CI               | P-value |
| Race               |                     |                      |         |                     |                      |         |
| White              | Reference           |                      |         | Reference           |                      |         |
| Black              | 1.22                | 0.98–1.51            | 0.069   | 1.25                | 1.01–1.55            | 0.042   |
| Others             | 0.72                | 0.60–0.86            | < 0.001 | 0.73                | 0.61–0.87            | 0.001   |
| Marital status at diagnosis |                     |                      |         |                     |                      |         |
| Married            | Reference           |                      |         | Reference           |                      |         |
| Single             | 1.07                | 0.90–1.28            | 0.459   | 1.06                | 0.89–1.27            | 0.506   |
| DSW                | 1.41                | 1.24–1.60            | < 0.001 | 1.24                | 1.08–1.41            | 0.002   |
| Scope of regional lymph node surgery |                     |                      |         |                     |                      |         |
| None               | Reference           |                      |         | Reference           |                      |         |
| 1 to 2             | 0.43                | 0.34–0.55            | < 0.001 | 0.39                | 0.30–0.51            | < 0.001 |
| 4 or more          | 0.26                | 0.23–0.30            | < 0.001 | 0.21                | 0.18–0.25            | < 0.001 |
| Unknown or not applicable | 0.27               | 0.16–0.46            | < 0.001 | 0.21                | 0.12–0.36            | < 0.001 |
| Grade              |                     |                      |         |                     |                      |         |
| Grade I            | Reference           |                      |         | Reference           |                      |         |
| Grade II           | 1.16                | 0.96–1.4             | 0.126   | 1.13                | 0.93–1.37            | 0.231   |
| Grade III          | 1.64                | 1.35–2.00            | < 0.001 | 1.54                | 1.26–1.88            | < 0.001 |
| Grade IV           | 1.03                | 0.54–1.96            | 0.924   | 1.04                | 0.55–2.00            | 0.897   |
| Summary stage      |                     |                      |         |                     |                      |         |
| Localized          | Reference           |                      |         | Reference           |                      |         |
| Regional           | 1.01                | 0.85–1.20            | 0.897   | 1.01                | 0.68–1.49            | 0.974   |
| Distant            | 2.14                | 1.76–2.60            | < 0.001 | 1.01                | 0.64–1.59            | 0.982   |
| AJCC                |                     |                      |         |                     |                      |         |
| I                  | Reference           |                      |         | Reference           |                      |         |
| II                 | 1.29                | 1.11–1.49            | 0.001   | 1.39                | 1.04–1.87            | 0.025   |
| III                | 1.90                | 1.62–2.23            | < 0.001 | 1.84                | 1.15–2.94            | 0.011   |
| IV                 | 4.60                | 3.79–5.59            | < 0.001 | 1.76                | 1.15–2.71            | 0.010   |
| T                  |                     |                      |         |                     |                      |         |
| T1                 | Reference           |                      |         | Reference           |                      |         |
| T2                 | 0.67                | 0.56–0.81            | < 0.001 | 0.94                | 0.69–1.30            | 0.726   |
| T3                 | 1.06                | 0.90–1.26            | 0.491   | 1.18                | 0.89–1.56            | 0.247   |
| T4                 | 1.43                | 1.21–1.68            | < 0.001 | 1.12                | 0.76–1.65            | 0.569   |
| TX                 | 3.81                | 2.58–5.63            | < 0.001 | 1.08                | 0.67–1.73            | 0.758   |
| N                  |                     |                      |         |                     |                      |         |
| N0                 | Reference           |                      |         | Reference           |                      |         |
| N1                 | 1.25                | 1.12–1.41            | < 0.001 | 1.31                | 1.13–1.53            | 0.001   |
| NX                 | 4.21                | 2.99–5.94            | < 0.001 | 1.25                | 0.85–1.83            | 0.254   |

AJCC, American Joint Committee on Cancer.

Fig. 4 compares the results of the six models in predicting patient survival with actual survival at 1 year, 3 years, 5 years, and 10 years. The closer to the standard 45-degree diagonal, the better the prediction. The results indicated that the AJCC and CoxPH models were significantly different. RSF and XGBSE fitted the 45-degree diagonal best, followed by DeepSurv and CoxTime.

### Discussion

AAC is gastrointestinal cancer with a high mortality rate. Although rare, its incidence has increased in recent decades. High recurrence and postoperative mortality risks are major prognostic issues in patients with AAC. Various genotypes and tumor stages that affect the prognosis of patients with AAC have recently been found. However, the available prediction models have both advantages and disadvantages. The CoxPH model is currently the most widely used predictive model in the field of survival analysis. This model requires each predictor to be a linear factor and for the effect of covariates on survival to not change over time. It ignores the impact of some non-linear factors on patient survival outcomes. However, tumor development and its changes are affected by many different factors, and traditional strictly linear models are unlikely to accurately predict the prognoses of patients with cancer. It is therefore necessary to develop new methods to incorporate both linear and non-linear factors, and so in this study, we constructed and validated a deep learning model for predicting the mortality risk of patients with AAC by comparing multiple different types of survival analysis models.

According to the analysis results of the CoxPH regression model, race, marital status at diagnosis, scope of regional lymph node surgery, tumor grade, summary stage, and AJCC TNM stage are the main factors affecting patient survival. Racial disparities in patients with cancer have always been one of the focuses of research. Among patients with AAC in the US population of this study, black patients had a higher mortality risk. Because cancer treatment is expensive, this finding might be related to the medical insurance or financial status of the patient.
Fig. 3. ROC plot. Comparison of ROC in six models at (a) 1-year, (b) 3-years, (c) 5-years, and (d) 10-years in testing cohort population. AJCC, American Joint Committee on Cancer; ROC: receiver operating characteristic; AUC: area under curve.

Fig. 4. Calibration plot. AJCC, American Joint Committee on Cancer.
The CoxPH model identified the main factors affecting patient outcomes. Adding these factors as covariates resulted in the model performing better than models using only AJCC TNM staging. However, due to too many constraints, the predictive ability cannot be further improved. In contrast, the decision-tree-based ensemble machine learning models (XGBoost and RSF) can automatically deal with a series of problems caused by the restrictive assumption of CoxPH and had achieved better evaluation results and a stronger ability to predict the survival of patients with AAC (with a higher C-index). The deep learning models (CoxTime and DeepSurv) also obtained the best prediction results due to the powerful non-linear fitting ability of their multilayer neuron-like structures. Comparing ROC curves at different time points revealed that these models also performed well, which was consistent with the performance of DeepSurv in predicting other diseases. The calibration of DeepSurv was no better than that of RSF or XGBoost. Compared with previous research, it was assumed that this was due to there being insufficient data. Deep learning involves data-driven models, and a larger amount of data results in better model performance.

At the same time, we believe that less data are available than in this study, the RSF model may be a better choice. In this study, the calibration curve of DeepSurv was acceptable. DeepSurv had a good predictive ability for the survival outcomes of patients with AAC.

This study had certain limitations. First, the SEER database does not contain detailed information about the views of a patient related to treatment types, such as whether the tumor was surgically removed, the type of chemotherapy, religious beliefs, and education. This undisclosed information may affect the prognosis of a patient. Second, the developed model needs to be verified externally in different centers. Validating the model in different regions and hospital centers can increase the robustness of the model. Finally, deep learning survival analysis models are difficult to interpret since it is difficult to accurately understand the internal computing process of these models. Future research should strive to address these issues.

Conclusions

In this study, CoxPH regression analysis was used to determine the risk factors affecting the prognosis of patients with AAC. These factors included race, marital status at diagnosis, scope of regional lymph node surgery, tumor grade, summary stage, AJCC stage, TNM stage T, and TNM stage N. We compared six survival prediction models and found that DeepSurv is most accurate at predicting the prognoses and survival intervals of patients with AAC.

Author contributions

**Conceived and designed the analysis:** Tao Huang, Liying Huang, Rui Yang.

**Collected the data:** Liying Huang.

**Experimental results and manuscripts review and medical guidance:** Rui Yang.

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Declaration of competing interest

None declared.

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Ethics statement

The data of this study comes from the SEER database. The SEER database is a tumor-related database developed by the National Cancer Institute of the United States, providing research data for researchers free of charge. All patients participating in the study received the ethical approval sought by the National Cancer Institute. The informed consent was obtained from all patients or, if patients are under 18, from a parent and/or legal guardian. The use of all data in the study follows the National Cancer Institute's data use statement. The research content follows the statement of the National Cancer Institute guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.japjon.2022.100141.

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