Original Article

Development and validation of an XGBoost model to predict 5-year survival in elderly patients with intrahepatic cholangiocarcinoma after surgery: a SEER-based study

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Background: Nomograms have been established to predict survival in postoperative or elderly intrahepatic cholangiocarcinoma (ICC) patients. There are no models to predict postoperative survival in elderly ICC patients. Extreme gradient boosting (XGBoost) can adjust the errors generated by existing models. This retrospective cohort study aimed to develop and validate an XGBoost model to predict postoperative 5-year survival in elderly ICC patients.

Methods: The Surveillance, Epidemiology, and End Results (SEER) program provided data on elderly ICC patients aged 60 years or older and undergoing surgery. The median follow-up time was 20 months. Totally 1,055 patients were classified as training (n=738) and testing (n=317) sets at a ratio of 7:3. The outcome was postoperative 5-year survival. Demographic, tumor-related and treatment-related variables were collected. Variables were screened using the XGBoost model. The predictive performance of the model was assessed by the area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Kaplan-Meier curve. Cox regression analysis was conducted to estimate the risk of death in the predicted populations. The predictive abilities of the XGBoost model and the American Joint Commission on Cancer (AJCC) system (7th edition) were compared.

Results: The XGBoost model achieved an AUC of 0.811, a sensitivity of 0.573, a specificity of 0.890, and a PPV of 0.849 in the training set. In the testing set, the model had an AUC of 0.713, a sensitivity of 0.478, a specificity of 0.814, and a PPV of 0.726. The 5-year mortality risk of patients predicted to die was 2.91 times that of patients predicted to survive [hazard ratio (HR) =2.91, 95% confidence interval (CI): 2.42–3.50]. The XGBoost model showed a better predictive performance than the AJCC staging system both in the training and testing sets. AJCC stage, multiple (satellite) tumors/nodules, tumor-node-metastasis (TNM) stage, more than one lobe invaded, direct invasion of adjacent organs, tumor size, and radiotherapy were relatively important features in survival prediction.

Conclusions: The XGBoost model exhibited some predictive capacity, which may be applied to predict postoperative 5-year survival for elderly ICC patients.

Keywords: XGBoost; postoperative survival; elderly; intrahepatic cholangiocarcinoma; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Intrahepatic cholangiocarcinoma (ICC), the second most common primary liver cancer, is a highly fatal hepatobiliary neoplasm originating from the epithelial cells of the intrahepatic bile ducts (1,2). The incidence and mortality rates of ICC continue to increase worldwide (3,4). Although surgery remains the optimal modality to extend survival in ICC patients, their prognosis remains unfavorable, with a 5-year overall survival after surgery of 30–35% (5-7). Notably, the incidence of ICC increases with age, as the incidence in older patients is almost twice as high as that in younger patients (8). Most patients are between 55 and 75 years old (2), suggesting that the elderly account for the majority of cases. Hence, effective tools to predict the postoperative prognosis of elderly patients with ICC are urgently needed.

Currently, the American Joint Commission on Cancer (AJCC) system (9,10) is the most frequently used staging system for ICC. However, it is more applicable to a cohort of patients as opposed to individual patients, and many other factors, such as age, tumor number, margin status, and treatment, should be considered in addition to tumor size, lymph node metastasis, and distant metastasis (5,11-14). Older age, larger tumor size, multiple tumors, lymph node metastasis, and vascular invasion were reported as predictors for shorter overall survival in ICC (6). Sahara *et al.* included sum of the number and largest tumor size >7, N1 disease, R1 resection, poor/undifferentiated tumor grade, major vascular invasion, and adjuvant chemotherapy to establish an online calculator to estimate 5-year survival following hepatectomy in ICC patients, with a concordance index (C-index) of 0.696 in the training set and 0.672 in the testing set (15). A prediction model of overall survival in resectable ICC was constructed with an immune signature for ICC, exhibiting a C-index of 0.719 in the derivation cohort and 0.667 in the validation cohort (16). A clinical-radiologic-radiomics (CRR) model was used to predict postsurgical overall survival in mass-forming ICC (C-index =0.71) (17). Nomograms have been established to predict survival in individual ICC patients after surgical resection or in elderly patients (18-20), with C-indexes around 0.7. However, these prediction tools had limited predictive abilities, and there are no models that predict survival following surgery in the elderly with ICC. Besides, Sahara *et al.* (15) indicated that nomograms had limited applicability and clinical utility because they are cumbersome and cannot be easily utilized in a simple, real clinical setting with varying clinical and pathological factors. Recently, artificial intelligence models on the basis of machine learning (ML) algorithms have attracted increasing attention in clinical practice. Extreme gradient boosting (XGBoost), a typical boosting algorithm, is an integrated technology that can be applied to adjust the errors generated by existing models (21,22). XGBoost models have been used for effective and precise survival prediction in several cancers, including breast cancer (23), osteosarcoma (24), and non-small-cell lung cancer (25); however, their applicability to ICC is unknown.

This study intended to develop and validate an XGBoost model to predict 5-year survival in elderly ICC patients after surgery, utilizing data in the Surveillance, Epidemiology, and End Results (SEER) program. Moreover, predictive performances of the XGBoost model and the AJCC staging system were compared. We present the following article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1238/rc).

Highlight box

Key Findings

- The developed XGBoost model exhibited some predictive capacity, and performed better than the AJCC system in predicting the postoperative 5-year survival of elderly ICC patients.

What is known and what is new?

- The AJCC system is the most frequently used staging system for ICC, but it is more applicable to a cohort of patients as opposed to individual patients.
- Compared with the AJCC system, the XGBoost model exhibited a better predictive performance.

What is the implication, and what should change now?

- The XGBoost model may be employed to predict 5-year survival in elderly patients with ICC after surgery, and may subsequently be used to promote individualized treatment.

Methods

Data source and study population

Data on elderly patients with ICC were collected from the SEER database [SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying)], which comprises 18 population-based registries and covers approximately 30% of the US population (26). Institutional review board approval was exempted for this

study as data from the SEER database are publicly available. This retrospective cohort study only involved patients with microscopically confirmed primary ICC aged 60 years or older and undergoing cancer-directed surgery (surgery of primary site codes 20–80). Patients who had missing data on lymphadenectomy, the pathologic examination of lymph nodes, AJCC stage, tumor size, and follow-up were excluded. The median follow-up time was 20 (Q_1, Q_3: 8, 39) months. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study variables

The outcome variable was 5-year survival after surgery in elderly ICC patients. Other variables included the primary site labeled, age, gender, race, marital status, tumor size (mm), multiple (satellite) tumors/nodules (no/yes), more than one lobe invaded (no/yes), major vascular invasion (no/yes), gallbladder invasion (no/yes), direct invasion of adjacent organs (extrahepatic bile ducts, gallbladder, ligament, diaphragm; no/yes), AJCC (7th edition) stage, T stage, N stage, M stage, resection and transplant (wedge or segmental resection, (extended) lobectomy without transplant, transplant), lymph nodes removed, radiotherapy (no/unknown/yes), chemotherapy (no/unknown/yes), and survival months.

Multiple (satellite) tumors/nodules included satellitosis, multifocal tumors and intrahepatic metastases. Major vascular invasion referred to an invasion of the branches of the main portal vein (right or left portal vein, excluding sectoral or segmental branches) or an invasion of one or more of the three hepatic veins (right, middle or left) [https://staging.seer.cancer.gov/cs/input/02.05.50/liver/extension/?breadcrumbs=(~schema_list~),(~view_schema~,~liver~)].

Construction and evaluation of the XGBoost model

The study population was classified as training and testing sets at a ratio of 7:3 in a random manner. The training set was utilized to develop a model, and the testing set was employed to internally validate the model. XGBoost (21), a gradient tree boosting algorithm, was adopted to construct a prediction model for 5-year survival after surgery in elderly ICC patients in the training set. The variables were directly screened using the XGBoost model via multivariate analysis.

The predictive performance of the model was assessed by the area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The patients were grouped in accordance with their 5-year survival predicted by the XGBoost model, and the Kaplan-Meier curve was constructed and compared using the log-rank test to assess the model's ability to distinguish survival status. Cox regression analysis was carried out to assess the risk of death in the predicted populations, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Furthermore, the predictive ability of the XGBoost model and the AJCC system (7th edition) were also compared.

Statistical analysis

Continuous data with normal distribution were illustrated as the mean ± standard deviation (SD); the independent sample t-test was applied to make inter-group comparisons. Continuous data with skewed distribution were reported by the median and quartiles [M (Q_1, Q_3)]; between-group comparisons were subject to the Mann-Whitney U rank sum test. Categorical data were presented as the number of cases and the composition ratio [n (%)]; inter-group comparisons was conducted using the Chi-square test or the Fisher's exact test. Samples with missing values were deleted. The threshold value of AUC for a good prediction model was 0.8. Feature importance analysis was conducted in the XGBoost model. All statistical tests were two-sided. $P<0.05$ denoted statistical significance. XGBoost modeling was conducted with Python 3.8 (Python Software Foundation, Delaware, USA), and other analyses were completed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Totally 1,055 elderly patients with ICC who underwent cancer-directed surgery were enrolled in this study after excluding patients without data on follow-up (n=1), AJCC stage (n=98), and tumor size (n=97). The patient selection flow chart is shown in *Figure 1*. The average age was 70.49 years. White people (83.22%) accounted for the majority of cases. Based on their vital status, these patients were classified into a survival group (n=512) and a death group (n=543). The median follow-up times of the death and survival groups were 15 and 30 months, respectively.

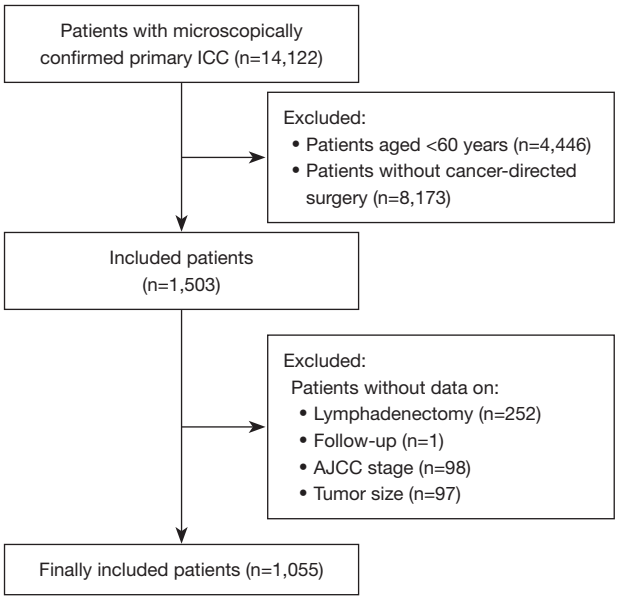

Figure 1 Patient selection flow chart. ICC, intrahepatic cholangiocarcinoma; AJCC, the American Joint Commission on Cancer.

Tumor size in the death group was significantly greater than that in the survival group (P<0.001). Patients in the survival group had fewer multiple (satellite) tumors/nodules than those in the death group (P<0.001). The following factors were markedly better in the survival group compared to the death group: more than one lobe invaded, major vascular invasion, direct invasion of adjacent organs, AJCC stage, T stage, N stage, and M stage (all P<0.05). *Table 1* presents the basic characteristics of the enrolled patients.

Construction of the XGBoost model

The study population was randomly divided into 738 patients in the training set and 317 patients in the testing set. Feature importance analysis was performed in the XGBoost model, as illustrated in *Figure 2*. AJCC stage III, N1 stage, multiple (satellite) tumors/nodules, T4 stage, AJCC stage IV, M1 stage, T3 stage, T2 stage, more than one lobe invaded, direct invasion of adjacent organs, tumor size, radiotherapy, and AJCC stage II were found to be features of relative importance. This model was tested and adjusted repeatedly, and the best parameters were determined. The parameter settings of this XGBoost model were as follows: n_estimators =2,000, learning_rate =0.0001, subsample =0.5, and colsample_bytree =0.3.

Evaluation of the XGBoost model

The predictive performance of the XGBoost model was assessed by the AUC, sensitivity, specificity, PPV, NPV, and Kaplan-Meier curve using a cutoff value of 0.507. The XGBoost model exhibited an AUC of 0.811 (95% CI: 0.781–0.841), a sensitivity of 0.573 (95% CI: 0.524–0.623), a specificity of 0.890 (95% CI: 0.858–0.923), and a PPV of 0.849 (95% CI: 0.805–0.893) in the training set. For internal validation in the testing set, the model showed an AUC of 0.713 (95% CI: 0.656–0.769), a sensitivity of 0.478 (95% CI: 0.401–0.555), a specificity of 0.814 (95% CI: 0.753–0.875), and a PPV of 0.726 (95% CI: 0.642–0.811) (*Table 2*). These findings indicated that the XGBoost model showed some predictive ability. Moreover, there was a significant difference between the survival curves of patients predicted to survive and those predicted to die (P<0.01), and the 5-year mortality risk of patients predicted to die was 2.91 times that of patients predicted to survive (HR =2.91, 95% CI: 2.42–3.50, P<0.01) (*Figure 3*), suggesting that the XGBoost model exhibited a good capacity to distinguish survival status.

Comparison of the XGBoost model and AJCC staging system

To evaluate the advantages of the XGBoost model, we compared it to the AJCC staging system (7th edition). According to *Table 2*, the cutoff value of the AJCC system was 0.633, and it had an AUC of 0.696 (95% CI: 0.640–0.751), a specificity of 0.795 (95% CI: 0.732–0.858), and a PPV of 0.733 (95% CI: 0.654–0.812) in the training set. In the testing set, the AUC, specificity, and PPV of the AJCC system were 0.651 (95% CI: 0.613–0.689), 0.722 (95% CI: 0.675–0.768), and 0.659 (95% CI: 0.604–0.713), separately. Compared with the AJCC staging system, the XGBoost model had a better predictive performance in terms of the AUC, specificity, and PPV, both in the training and testing sets.

Discussion

At present, there is a pressing need to accurately predict the 5-year survival of elderly ICC patients after surgery, as it may affect treatment planning and patient decision-making. This study established and validated an XGBoost model to predict the postoperative 5-year survival of elderly ICC patients. This XGBoost model achieved an AUC

Table 1 Basic characteristics of the enrolled patients

Variable	Total (n=1055)	Survival group (n=512)	Death group (n=543)	χ^2/t/Z	P
Primary site labeled, n (%)				2.699	0.100
C22.0-liver	218 (20.66)	95 (18.55)	123 (22.65)		
C22.1-intrahepatic bile duct	837 (79.34)	417 (81.45)	420 (77.35)		
Age, mean ± SD	70.49±6.42	70.16±6.30	70.79±6.52	−1.60	0.109
Gender, n (%)				2.813	0.094
Female	518 (49.10)	265 (51.76)	253 (46.59)		
Male	537 (50.90)	247 (48.24)	290 (53.41)		
Race, n (%)				0.545	0.762
Asian	112 (10.62)	56 (10.94)	56 (10.31)		
White	878 (83.22)	422 (82.42)	456 (83.98)		
Other	65 (6.16)	34 (6.64)	31 (5.71)		
Marital status, n (%)				4.524	0.210
Separated	232 (21.99)	108 (21.09)	124 (22.84)		
Married	681 (64.55)	328 (64.06)	353 (65.01)		
Unmarried	102 (9.67)	59 (11.52)	43 (7.92)		
Other	40 (3.79)	17 (3.32)	23 (4.24)		
Tumor size, M (Q_1, Q_3)	51.00 (33.00, 75.00)	48.00 (30.00, 70.00)	55.00 (35.00, 76.00)	−3.690	<0.001
Multiple (satellite) tumors/nodules, n (%)				27.240	<0.001
No	908 (86.07)	470 (91.80)	438 (80.66)		
Yes	147 (13.93)	42 (8.20)	105 (19.34)		
More than one lobe invaded, n (%)				6.644	0.010
No	1,035 (98.10)	508 (99.22)	527 (97.05)		
Yes	20 (1.90)	4 (0.78)	16 (2.95)		
Major vascular invasion, n (%)				4.861	0.027
No	1,024 (97.06)	503 (98.24)	521 (95.95)		
Yes	31 (2.94)	9 (1.76)	22 (4.05)		
Gallbladder invasion, n (%)				0.072	0.789
No	1,031 (97.73)	501 (97.85)	530 (97.61)		
Yes	24 (2.27)	11 (2.15)	13 (2.39)		
Direct invasion of adjacent organs, n (%)				16.243	<0.001
No	924 (87.58)	470 (91.80)	454 (83.61)		
Yes	131 (12.42)	42 (8.20)	89 (16.39)		
AJCC stage, n (%)				93.765	<0.001
I	390 (36.97)	256 (50.00)	134 (24.68)		
II	255 (24.17)	125 (24.41)	130 (23.94)		
III	196 (18.58)	54 (10.55)	142 (26.15)		
IV	214 (20.28)	77 (15.04)	137 (25.23)		

Table 1 *(continued)*

Table 1 *(continued)*

Variable	Total (n=1,055)	Survival group (n=512)	Death group (n=543)	χ^2/t/Z	P
T, n (%)				82.860	<0.001
T1	440 (41.71)	277 (54.10)	163 (30.02)		
T2	343 (32.51)	157 (30.66)	186 (34.25)		
T3	171 (16.21)	55 (10.74)	116 (21.36)		
T4	101 (9.57)	23 (4.49)	78 (14.36)		
N, n (%)				33.802	<0.001
N0	860 (81.52)	454 (88.67)	406 (74.77)		
N1	195 (18.48)	58 (11.33)	137 (25.23)		
M, n (%)				8.140	0.004
M0	1,001 (94.88)	496 (96.88)	505 (93.00)		
M1	54 (5.12)	16 (3.13)	38 (7.00)		
Resection and transplant, n (%)				3.413	0.182
Wedge or segmental resection	370 (35.07)	184 (35.94)	186 (34.25)		
(Extended) lobectomy without transplant	503 (47.68)	251 (49.02)	252 (46.41)		
Transplant	182 (17.25)	77 (15.04)	105 (19.34)		
Lymph nodes removed, n (%)				1.382	0.501
0	503 (47.68)	249 (48.63)	254 (46.78)		
1–3	313 (29.67)	155 (30.27)	158 (29.10)		
>3	239 (22.65)	108 (21.09)	131 (24.13)		
Radiotherapy, n (%)				0.539	0.463
No/unknown	921 (87.30)	443 (86.52)	478 (88.03)		
Yes	134 (12.70)	69 (13.48)	65 (11.97)		
Chemotherapy, n (%)				0.019	0.891
No/unknown	676 (64.08)	327 (63.87)	349 (64.27)		
Yes	379 (35.92)	185 (36.13)	194 (35.73)		
Survival months, M (Q_1, Q_3)	20.00 (8.00, 39.00)	30.00 (13.00, 63.00)	15.00 (5.00, 28.00)	10.192	<0.001

SD, standard deviation; AJCC, the American Joint Commission on Cancer.

of 0.811, specificity of 0.890, and a PPV of 0.849 in the training set, and an AUC of 0.713, specificity of 0.814, and a PPV of 0.726 in the internal validation set, indicating some predictive capacity. In contrast to the AJCC system (7^{th} edition), our model exhibited a better predictive performance, which may be employed to predict 5-year survival in elderly patients with ICC after surgery, and may subsequently be used to promote individualized treatment.

As far as we know, this study developed a prognostic model for elderly ICC patients after surgery based on an ML algorithm in a large-scale cohort for the first time. Previous studies focused on the survival prediction of ICC patients undergoing surgery (15,18,19). Hyder *et al.* (18) proposed a nomogram to estimate the long-term survival of ICC patients following resection, with a C-index of 0.692. The C-index of the nomogram developed by Wang *et al.* (19) for predicting survival among patients with ICC receiving partial hepatectomy was 0.74. Another prognostic tool on the basis of the metro-ticket paradigm was used to predict the 5-year overall survival following liver resection for ICC, with C-indexes of 0.725 and 0.724 in the training and validation sets, respectively (15). Regarding older adults

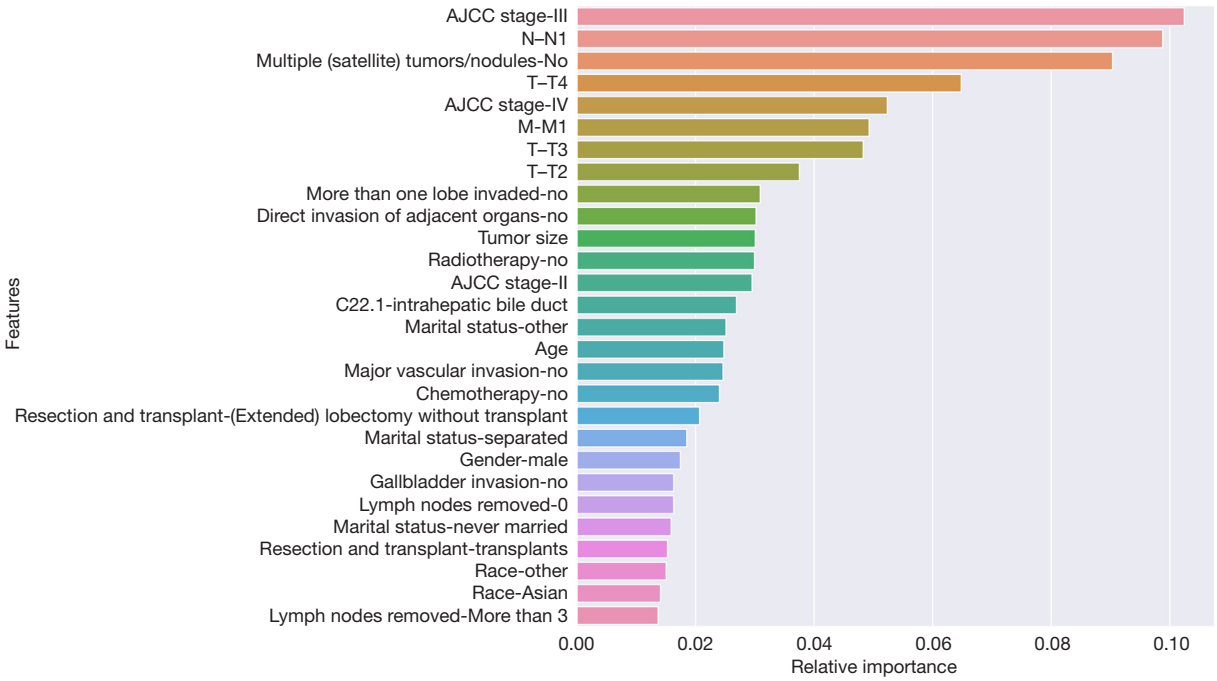

Figure 2 Feature importance analysis in the XGBoost model. AJCC, the American Joint Commission on Cancer.

Table 2 Predictive performance of the XGBoost model and AJCC staging system in the training and testing sets

Dataset	AUC	Sensitivity	Specificity	PPV	NPV	Cut-off
Our model						
Training set	0.811 (0.781–0.841)	0.573 (0.524–0.623)	0.890 (0.858–0.923)	0.849 (0.805–0.893)	0.660 (0.618–0.703)	0.507
Testing set	0.713 (0.656–0.769)	0.478 (0.401–0.555)	0.814 (0.753–0.875)	0.726 (0.642–0.811)	0.602 (0.536–0.668)	–
AJCC system						
Training set	0.696 (0.640–0.751)	0.547 (0.470–0.623)	0.795 (0.732–0.858)	0.733 (0.654–0.812)	0.629 (0.562–0.697)	0.633
Testing set	0.651 (0.613–0.689)	0.500 (0.450–0.550)	0.722 (0.675–0.768)	0.659 (0.604–0.713)	0.574 (0.528–0.619)	–

AJCC, the American Joint Commission on Cancer; AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value.

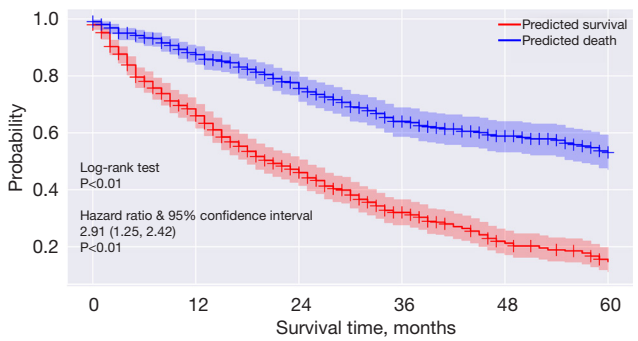

Figure 3 Survival curves of patients predicted to survive and die.

suffering from ICC, the predictive nomogram for OS by Zhu *et al.* (20) had C-indexes of 0.725 and 0.724 in the training and validation cohorts, respectively. Since most ICC patients are elderly, the number of elderly patients diagnosed with ICC is growing, and surgery remains the optimal treatment for ICC patients (2,7,27). Therefore, we focused on elderly ICC patients undergoing surgery. Notably, prior prediction models were developed with Cox regression or logistic regression (conventional algorithms) which are replaceable by more advanced algorithms. Recently, artificial intelligence models based on ML

algorithms have attracted increasing attention in clinical practice. Most models, such as random forests (RF), support vector machines (SVM), Bayesian networks and XGBoost, are developed on the basis of traditional ML algorithms (28). XGBoost, a typical boosting algorithm, can adjust the errors generated by existing models, which is efficient, flexible and portable (22). These advantages ensure the superior performance of XGBoost to other models in ML competitions (29). Thus, an XGBoost model was constructed in this study and showed some predictive ability in both the training and validation sets. Its performance in predicting the 5-year survival after surgery in elderly ICC patients was also confirmed by comparison with the AJCC system. Likewise, Ali *et al.* (30) reported that the AJCC (7^{th} edition) did not make a precise prediction for survival in ICC patients.

In the current study, AJCC stage, multiple (satellite) tumors/nodules, tumor-node-metastasis (TNM) stage, more than one lobe invaded, direct invasion of adjacent organs, tumor size, and radiotherapy were relatively important features for survival prediction in elderly ICC patients after surgery. The effect of tumor number on the postoperative survival of ICC patients was corroborated by prior studies, and multiple (satellite) tumors/nodules were associated with a greater risk of death in ICC (31-34). TNM stage was also identified as an independent predictor for survival in patients with ICC undergoing surgery and in elderly ICC patients (20,35). Consistently, direct invasion of adjacent organs was related to 5-year survival following ICC resection (36). Greater tumor size was related to malignant pathological factors, like worse tumor differentiation and vascular invasion, and tumor size was an independent prognostic factor for solitary ICC following resection (6,37,38). In this study, tumor size and age were expressed as continuous variables rather than categorical variables, which meant that 5-year survival could be predicted for a specific patient instead of a group of patients, indicating personalized prediction. Additionally, all of the variables in the basic characteristics of elderly ICC patients were considered in the survival prediction, which may help to provide accurate predictions.

Several limitations need to be considered in interpreting our results. Firstly, this was a retrospective study. Missing data could not be obtained at the time of the study. Some variables that may affect prognosis, such as nutritional status and comorbidities, were not available in the SEER database. Secondly, the prediction model had some predictive ability based on its AUC, specificity and PPV in the training and testing sets despite low sensitivity values, which necessitates more studies to improve the model in 5-year survival prediction of elderly ICC patients after surgery. Thirdly, although our model was developed and internally verified in the American population, external validation is required for applicability assessment.

Conclusions

The XGBoost model was developed to predict the postoperative 5-year survival of elderly ICC patients and exhibited some predictive performance based on the SEER database. Compared with the AJCC staging system, this model had a better predictive ability. Future studies are warranted to externally validate the applicability of our model.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1238/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1238/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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