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ORIGINAL RESEARCH

Development and Validation of Artificial Neural Networks for Survival Prediction Model for Patients with Spontaneous Hepatocellular Carcinoma Rupture After Transcatheter Arterial Embolization

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Background: Spontaneous rupture bleeding is a fatal hepatocellular carcinoma (HCC) complication and a significant determinant of survival outcomes. This study aimed to develop and validate a novel artificial neural network (ANN)-based survival prediction model for patients with spontaneous HCC rupture after transcatheter arterial embolization (TAE).

Methods: Patients with spontaneous HCC rupture bleeding who underwent TAE at our hospital between January 2010 and December 2018 were included in our study. The least absolute shrinkage and selection operator (LASSO) Cox regression model was used to screen clinical variables related to prognosis. We incorporated the above clinical variables identified by LASSO Cox regression into the ANNs model. Multilayer perceptron ANNs were used to develop the 1-year overall survival (OS) prediction model for patients with spontaneous HCC ruptured bleeding in the training set. The area under the receiver operating characteristic curve and decision curve analysis were used to compare the predictive capability of the ANNs model with that of existing conventional prediction models.

Results: The median survival time for the whole set was 11.8 months, and the 1-year OS rate was 47.5%. LASSO Cox regression revealed that sex, extrahepatic metastasis, macroscopic vascular invasion, tumor number, hepatitis B surface antigen, hepatitis B e antigen, tumor size, alpha-fetoprotein, fibrinogen, direct bilirubin, red blood cell, and γ-glutamyltransferase were risk factors for OS. An ANNs model with 12 input nodes, seven hidden nodes, and two corresponding prognostic outcomes was constructed. In the training set and the validation set, AUCs for the ability of the ANNs model to predict the 1-year OS of patients with spontaneous HCC rupture bleeding were 0.923 (95% CI, 0.890–0.956) and 0.930 (95% CI, 0.875–0.985), respectively, which were higher than that of the existing conventional models (all $P < 0.0001$).

Conclusion: The ANNs model that we established has better survival prediction performance.

Keywords: hepatocellular carcinoma spontaneous rupture bleeding, HCC spontaneous rupture bleeding, least absolute shrinkage and selection operator regression, LASSO regression, artificial neural networks, ANNs, survival, prognosis

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide.[1] The incidence of HCC is rising worldwide because of the increasing prevalence of viral hepatitis and nonalcoholic steatohepatitis.[2–4] The Asia–Pacific region, particularly China, has a high incidence of HCC.[5] Spontaneous

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tumor rupture bleeding is one of the most severe and life-threatening complications of HCC, with an occurrence rate of approximately 3–15% and high mortality rates.[6–8] The initial symptoms of these patients are mainly abdominal pain, bloating, and shock. According to previous research reports, the incidence of spontaneous rupture of HCC shows significant geographical differences. The incidence of spontaneous HCC rupture in Asia–Pacific region is higher than in Western countries.[9–11] Spontaneous HCC rupture might be related to the rapid growth of the tumor leading to intratumor necrosis and tumor vascular hyperplasia, with vascular dysfunction caused by the degeneration of the vessel structure composition (elastin, collagen IV).[12,13]

The current treatment strategy for patients with spontaneous HCC rupture remains controversial. At present, surgical treatments such as emergent liver resection, injection of absolute alcohol, hepatic artery ligation, and transcatheter arterial embolization (TAE) are available for HCC patients with spontaneous rupture bleeding. Considering the continuous improvement of surgical techniques and perioperative management, some doctors believe that resection of tumor lesions might be the best treatment, given that it can fully restore hemostasis and improve clinical prognosis.[6,14,15] However, the general condition and liver function of HCC patients are relatively poor; the tumor is usually unresectable, large, or multifocal and might be accompanied by invasion of major intrahepatic vessels and extrahepatic metastasis; surgical treatment could not bring curative resection to the patient, and the chance of severe complications after surgery might be significantly increased.

Owing to its relative safety and effectiveness for hemostasis, TAE was introduced as a method that can be widely used for hemostasis and the treatment of spontaneous HCC rupture. Notably, increasing evidence supports the application of TAE in patients with advanced-stage HCC or patients with Child-Pugh grade C liver function.[16–18] A recent study showed that TAE might bring a long-term survival benefit similar to open surgery to HCC patients with spontaneous rupture.[19] To date, most previous studies have mainly focused on comparing the safety of all kinds of treatment methods in patients during the perioperative period, and there is no prognostic model for predicting the prognosis of HCC patients with spontaneous rupture bleeding after TAE.

As a type of machine learning, artificial neural networks (ANNs), which are essentially mathematical tools driven by the biological nervous system, have been widely used in the risk assessment of disease prognosis.[20] In this study, we first evaluated the efficacy and safety of TAE treatment on spontaneous HCC rupture. Then we used the ANNs model to develop a simple, specific, and reliable prognostic model to predict the long-term survival outcomes based on large-sample preoperative data from a single center, which was further validated using internal validation sets. This study helps predict prognosis in patients with spontaneous HCC rupture after TAE and identifies optimal candidates for whom TAE treatment can help achieve tumor downgrade and obtain the opportunity for radical surgical resection.

Patients and Methods

A retrospective study was conducted on spontaneous HCC rupture patients who underwent TAE therapy between January 2010 and December 2018. The diagnosis of HCC followed the criteria recommended by the American Association for the Study of Liver Diseases (AASLD) of conclusive contrast-enhanced ultrasonography and magnetic resonance imaging without biopsy.[21] The diagnosis of spontaneous HCC ruptured bleeding relies on enhanced computed tomography (CT) of the abdomen to show that the integrity of the tumor is disrupted and that there is hematoma around the liver. Abdominal paracentesis is also a reliable procedure used to confirm the diagnosis.[9] The patient selection criteria for our study included the following (1) patients with unresectable spontaneous HCC rupture bleeding who were initially treated with TAE therapy; and (2) patients with detailed clinical characteristics. The exclusion criteria for this study were as follows: (1) the patients had another concurrent malignancy or severe nonmalignant illness; (2) patients with severe cardiopulmonary, renal, or cerebral dysfunction; and (3) patients with poor clinical data integrity. In this study, the whole set was randomly divided into two sets, 225 (70%) were included in the training set, and 97 (30%) were included in the validation set. The flowchart of the present study selection is shown in Figure 1, and the clinicopathologic characteristics of patients in the training and validation sets are listed in Table 1. Written informed consent was obtained from all patients to use their data for research purposes. This retrospective study was approved by the Ethics Committee of West China Hospital of Sichuan University and was performed in accordance with the 1975 Declaration of Helsinki.

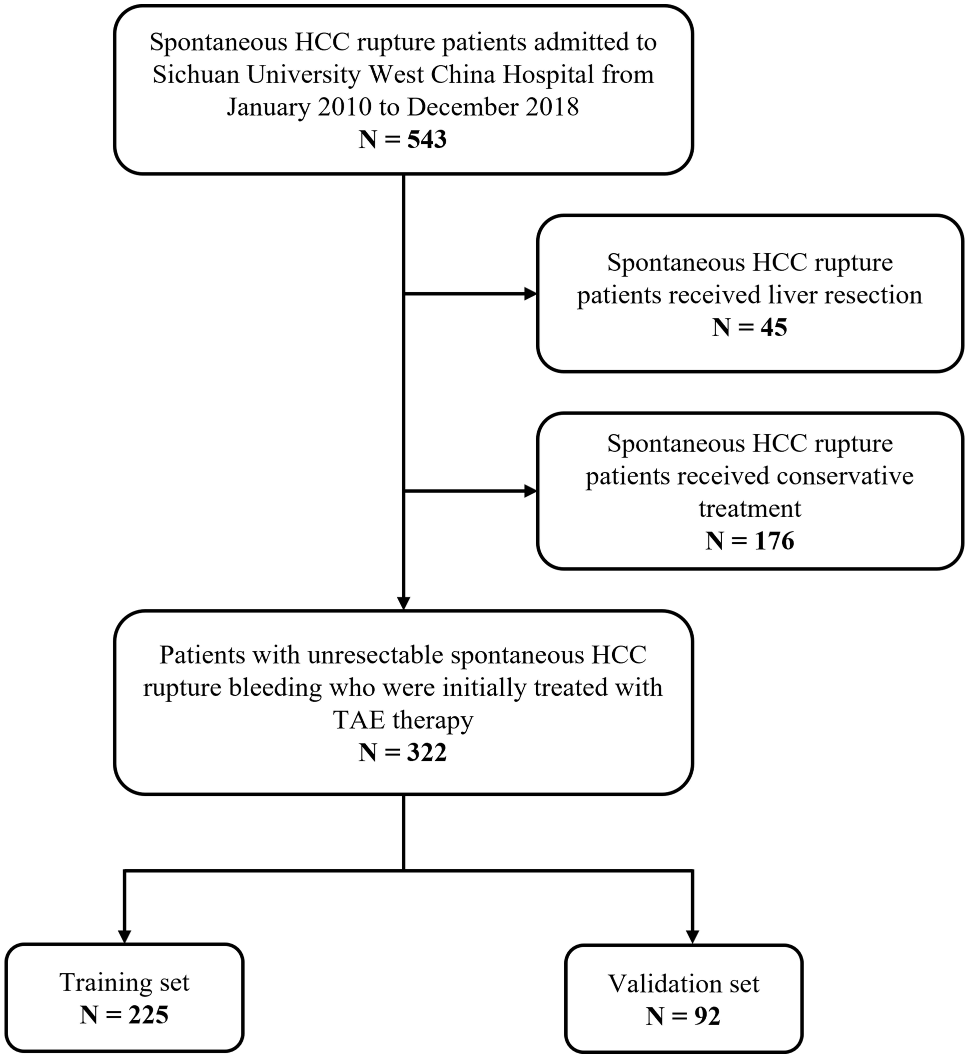

Figure 1 The flowchart of the present study selection.
Abbreviations: HCC, hepatocellular carcinoma; TAE, transcatheter arterial embolization.

Data Collection

The clinical data of patients with spontaneous HCC rupture were gathered from the electronic medical records, including demographics, liver cirrhosis, portal hypertension, Child-Pugh score, preoperative serum biochemistry data, preoperative coagulation parameters, preoperative serum tumor markers, imaging characteristics of tumors, complications after TAE, clinical data required for conventional staging systems and the corresponding clinical staging of each patient.[22–29] Unresectable HCC was defined as liver malignancy not suitable for liver surgery due to the extent of malignant tumor invasion or the refusal to undergo surgical liver resection. Portal hypertension was defined by the presence of either esophageal varices or splenomegaly with a decreased platelet count (100 × 10^9/L or less). Liver failure was defined using the International Study Group of Liver Surgery (ISGLS) score.[30]

The liver reserve of all the patients was evaluated using the albumin-bilirubin (ALBI) classification (ALBI = log10 bilirubin × 0.66–0.085 × albumin). The ALBI score was stratified into 3 classifications: ALBI grade I (≤−2.60), grade II (>−2.60 to ≤−1.39), and grade III (> −1.39).[29]

Treatment and Follow-Up

The initial treatment was rapid infusion to maintain circulation stability and correct the shock state promptly. Given that patients with HCC usually have a background of liver cirrhosis and poor blood coagulation, it is necessary to transfuse plasma and provide fresh blood promptly to ensure that the patients have normal signs of life. Experienced interventional radiologists performed all TAE procedures. In the emergency embolization treatment, the patient was required to be in a supine position with the knee flexed, and the Seldinger intubation

Table 1 Baseline Characteristics of Patients with Spontaneous Hepatocellular Carcinoma Rupture in the Different Sets

Variables	Training Set (n=225)	Validation Set (n=97)	*P* value
Age (years), median (IQR)	53(42.5–62.5)	48(38–60.5)	0.054
Gender, (male/ female)	207/18	88/9	0.872
BMI (kg^2/m^2), median (IQR)	23.4(20.6–25.6)	23.1(20.5–25.2)	0.766
Child-Pugh score			0.612
A	179(79.6%)	74(76.3%)	
B	46(20.4%)	23(23.7%)	
Portal hypertension, n (%)			0.577
Yes	86(38.2%)	41(42.3%)	
No	139(61.8%)	56(57.7%)	
HBsAg positive, n (%)	174/51	82/15	0.187
HBV-DNA positive, n (%)	63/162	31/66	0.560
Baseline laboratory investigations			
RBC count ×10^9/L, median (IQR)	3.6(3.0–4.3)	3.5(3.0–4.3)	0.767
HGB(g/L), median (IQR)	109(89–131)	109(87.5–131)	0.765
WBC count ×10^9/L, median (IQR)	9.2(6.5–12.6)	8.6(6.5–13.0)	0.866
NEUT count ×10^9/L, median (IQR)	7.2(4.9–10.6)	7.0(5.0–11.3)	0.955
PLT count ×109/L, median (IQR)	141(101–207)	140(100–195)	0.302
ALT (U/L), median (IQR)	43(28–77.5)	44(31–79.5)	0.455
AST (U/L), median (IQR)	59(36–118.5)	68(37–134)	0.586
ALP (U/L), median (IQR)	96(74–145)	96(69.5–152)	0.889
GGT (U/L), median (IQR)	89(54.5–164)	93(53–185)	0.815
DBIL ((μmol/L), median (IQR)	7.3(5.3–11.4)	7.5(5.6–12.2)	0.453
ALB (g/L), median (IQR)	35.5(31.4–40)	35.3(30.9–40.2)	0.638
INR, median (IQR)	1.15(1.07–1.26)	1.19(1.02–1.31)	0.057
FIB(g/L), median (IQR)	2.43(1.77–3.35)	2.36(1.82–3.10)	0.954
AFP, ng/mL median (IQR)	178.5(11.2–1210)	162.9(13.98–1210)	0.829
CA19-9 level(U/mL) median (IQR)	16.3(6.8–31.8)	16.8(6.8–30.9)	0.868
CEA, ng/mL median (IQR)	1.53(0.89–2.70)	1.59(1.02–2.53)	0.907
Tumor size (cm), median (range)	8.3(6.5–11.2)	8.1(6.4–10.6)	0.460
Tumor number, (Multiple/solitary)			0.865
Multiple	75(33.3)	34(35.1%)	
Solitary	150(66.7%)	63(64.9%)	
MCI			0.758
Yes	138(61.3%)	57(58.8%)	
No	87(38.7%)	40(41.2%)	
Extrahepatic metastasis			0.823
Yes	31(13.8%)	15(15.5%)	
No	194(86.2%)	82(84.5%)	
BCLC stage			0.912
A	55(24.5%)	22(22.7%)	
B	25(11.1%)	12(12.4%)	
C	145(64.4%)	63(64.9%)	
Repeated TACE			0.967
With	12(5.3%)	6(6.2%)	
Without	213(94.7%)	91(93.8%)	

Abbreviations: BMI, body mass index; HBsAg, hepatitis B surface antigen; RBC, red blood cell; HGB, hemoglobin; WBC, white blood cell; NEU, neutrophil; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; DBIL, direct bilirubin; ALB, albumin; INR, international normalized ratio; FIB, fibrinogen; AFP, alpha fetoprotein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; MCI, macroscopic vascular invasion; BCLC stage, Barcelona clinic liver cancer stage.

technique was used to insert the hepatic artery from the right femoral artery into the abdominal trunk or superior mesenteric artery and then perform the tumor-feeding arteries for selective embolization. After embolization, angiography was performed to determine the extent of vascular occlusion and to assess blood flow in other arterial vessels. All patients received liver protection, anti-infection and anti-shock treatments after surgery. Transarterial chemoembolization (TACE) is recommended to be carried out every 2 months after surgery, depending on the patient's physical status and liver function. All patients were followed up after discharge through outpatient clinic visits or phone calls. The primary endpoint of the study was overall survival (OS), which was defined as the period between discharge from the hospital and death.

Statistical Analysis

Continuous data are expressed as medians and interquartile ranges (IQR25-75) and were compared by the Mann–Whitney *U*-test, and categorical variables are expressed as frequencies and percentages and were compared by the chi-squared test and two-tailed Fisher's exact test. We identified the optimal structure of input layer parameters using a penalized Cox regression model with the least absolute shrinkage and selection operator (LASSO) penalty based on minimal criteria. ANNs model uses a multilayer perceptron (MLP) structure, including the input, hidden, and output layers. The input layer is the clinical variables identified by the LASSO Cox regression, and the output layer is the corresponding prognosis outcome. We used SPSS statistical software version 25.0 (IBM Corporation, Armonk, NY) to train the ANNs model. The discriminative ability of the ANNs model was assessed using the area under the receiver operating characteristic (ROC) curve (AUC), which was further compared with the results from conventional scoring systems, including the TNM (8th edition), Okuda,[22] Barcelona Clinic Liver Cancer (BCLC),[23] Cancer of the Liver Italian Program (CLIP),[24] Chinese University Prognostic Index (CUPI),[25] Japan Integrated Staging (JIS),[26] China integrated score (CIS),[27] ALBI grade,[29] and Child-Pugh score systems. Decision curve analysis (DCA) was used to determine the clinical net benefits and performance of the ANNs models and the above-mentioned conventional staging systems at each risk threshold probability.[31] All patients were stratified into 3 groups according to the tertiles of risk prediction values. OS was calculated with the Kaplan-Meier method. In addition, histogram and density plots were plotted in the training set and validation set. R version 4.0.0 (http://www.r-project.org/) was used for data analysis, LASSO Cox regression, C-index assessment, DCA, Kaplan-Meier curve analysis, and histogram and density plot construction. In all analyses, $P < 0.05$ was considered to indicate statistical significance.

Results

Patient Characteristics

After rigorous review, we enrolled a total of 322 patients who underwent TAE for patients in spontaneous HCC ruptured bleeding between January 2012 and December 2018 at West China Hospital. All patients were followed up until June 2020. All patients were randomly divided into a training set (n = 225, 75%) and a validation set (n = 97, 25%). A total of 114 (50.7%) patients died within 1 year in the training set, and 56 (57.7%) patients died within 1 year in the validation set. The demographic and clinical characteristics of the patients in the training and validation sets are listed in Table 1. The baseline demographic and clinical characteristics of the patients in the training and validation sets were similar ($P > 0.05$). Among the entire set, the median OS of the 322 patients with spontaneous HCC ruptured bleeding was 11.8 months. There was no statistically significant difference in the OS rate between the training set and validation set in the Kaplan-Meier analysis (all log-rank P=0.6), as shown in Supplementary Figure S1.

The Safety and Effectiveness of TAE Treatment

The common adverse reactions after TAE included fever, abdominal pain, nausea, and vomiting. Twenty-three patients had serious complications, including respiratory failure (n=4), liver and kidney failure (n=6), heart failure (n=2), pulmonary embolism (n=2), and gastrointestinal hemorrhage (n=5). In addition, four patients had recurrent tumor rupture. Two patients died due to severe complications and shock during the hospitalization period. All the remaining patients recovered and were discharged after symptomatic and supportive treatment.

Development of the ANNs Model for Predicting the 1-Year OS

In the training set, we used the LASSO Cox regression model to identify the clinical variables for predicting OS (Figure 2). The identified clinical variables included the following: sex, extrahepatic metastasis, MCI, tumor number, hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), tumor size, alpha-fetoprotein (AFP), fibrinogen (FIB), direct bilirubin (DBIL), red blood cell (RBC), γ-glutamyltransferase (γ-GGT). Then, these variables were included and used to

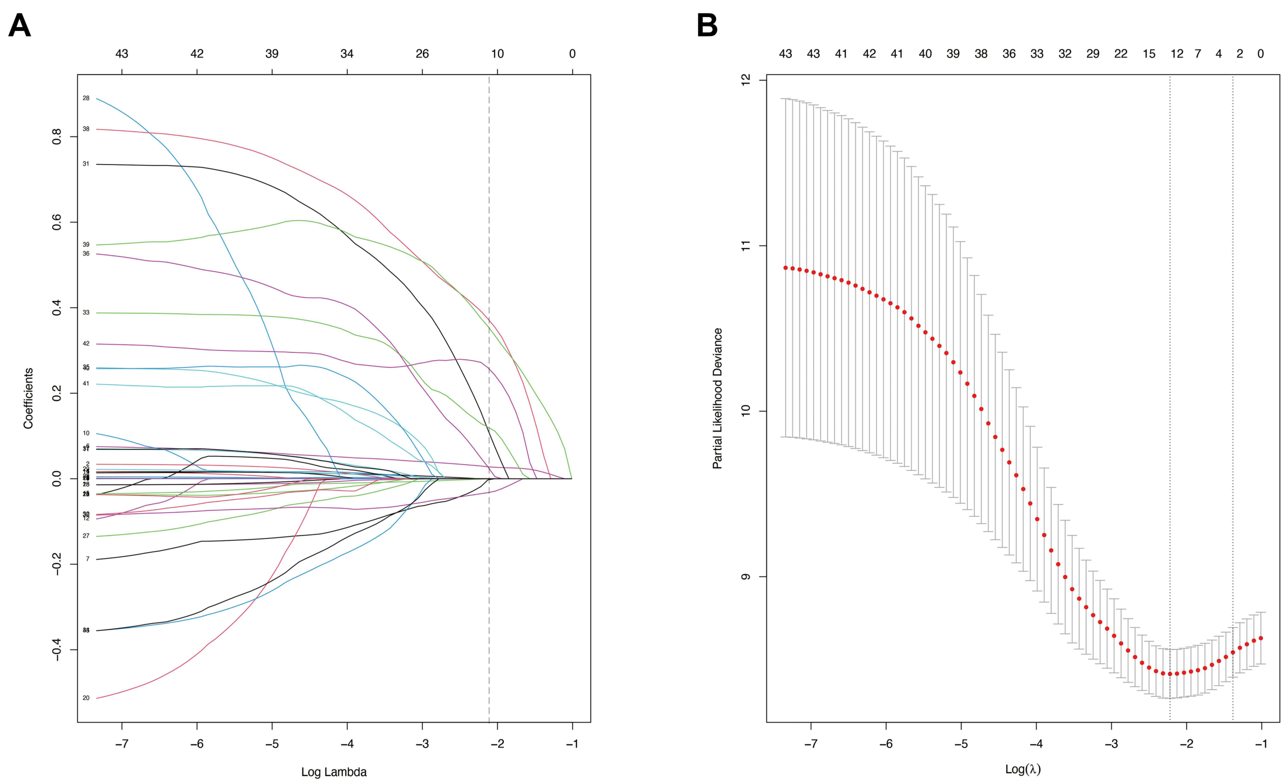

Figure 2 Screening significant prognosis-related clinical variables by likelihood-based survival using the least absolute shrinkage and selection operator (LASSO) cox regression model in the training set. (**A**) LASSO coefficient profiles of the 12 selected clinical features. A dashed vertical line is drawn at the value (logγ=−2.2) chosen by 10-fold cross-validation. (**B**) Partial likelihood deviance for the LASSO coefficient profiles. A light dashed vertical line (left line) indicates the minimum partial likelihood deviance.

construct the ANNs model. In the end, the ANNs model was constructed with a three-layer neural network including 12 input nodes, seven hidden nodes, and two corresponding prognosis outcomes (output nodes). The importance of the 12 relevant clinical variables was standardized (Figure 3). The corresponding clinical variables with the most and least importance were AFP with 100% importance and HBeAg with 14.7% importance, respectively.

Comparison of the Diagnostic Accuracy of the ANNs Model and Other Conventional Scoring Systems for 1-Year OS

In the training set, ROC analysis revealed that the predictive performance of the ANNs model for predicting 1-year OS was very high, with an AUC value of 0.880 (95% confidence interval [CI] 0.836–0.925), which was significantly higher than all the conventional scoring systems in predicting the 1-year OS of patients with spontaneous HCC rupture (ANNs: 0.923 vs CLIP: 0.717, JIP: 0.629, Liver Cancer Study Group of Japan (LCSGJ): 0.644, Okuda: 0.622, CUPI: 0.577, CIS: 0.626, TNM: 0.626; ALBI: 0.567, BCLC stage: 0.648, and Child-Pugh score: 0.506, $P< 0.05$ for all). In the validation set, the ANNs model was still superior to the conventional staging systems and had similar results as those obtained in the training set (Figure 4 and Table 2). In DCA, the ANNs model that we established demonstrated superior clinical usefulness in both the training set and validation set, compared with the existing conventional staging systems (Figure 5). This finding indicates that the ANNs model has superior clinical practicability compared with other models.

Application of the ANNs Model for Risk Stratification

According to the tertiles of the risk prediction values obtained from the ANNs model in the training set (low risk: 0.262, intermediate risk: 0.262–0.736, and high risk: 0.736). The clinicopathologic characteristics of patients with spontaneous HCC rupture according to risk stratification are shown in Table 3. The Kaplan–Meier OS curves revealed significant differences in the OS rate between different risk groups in both the training and validation sets (P <0.001 for all, as shown in Figure 6). In the training set, taking the low-risk group as the reference, the hazard ratios (HRs) of OS of the intermediate-risk

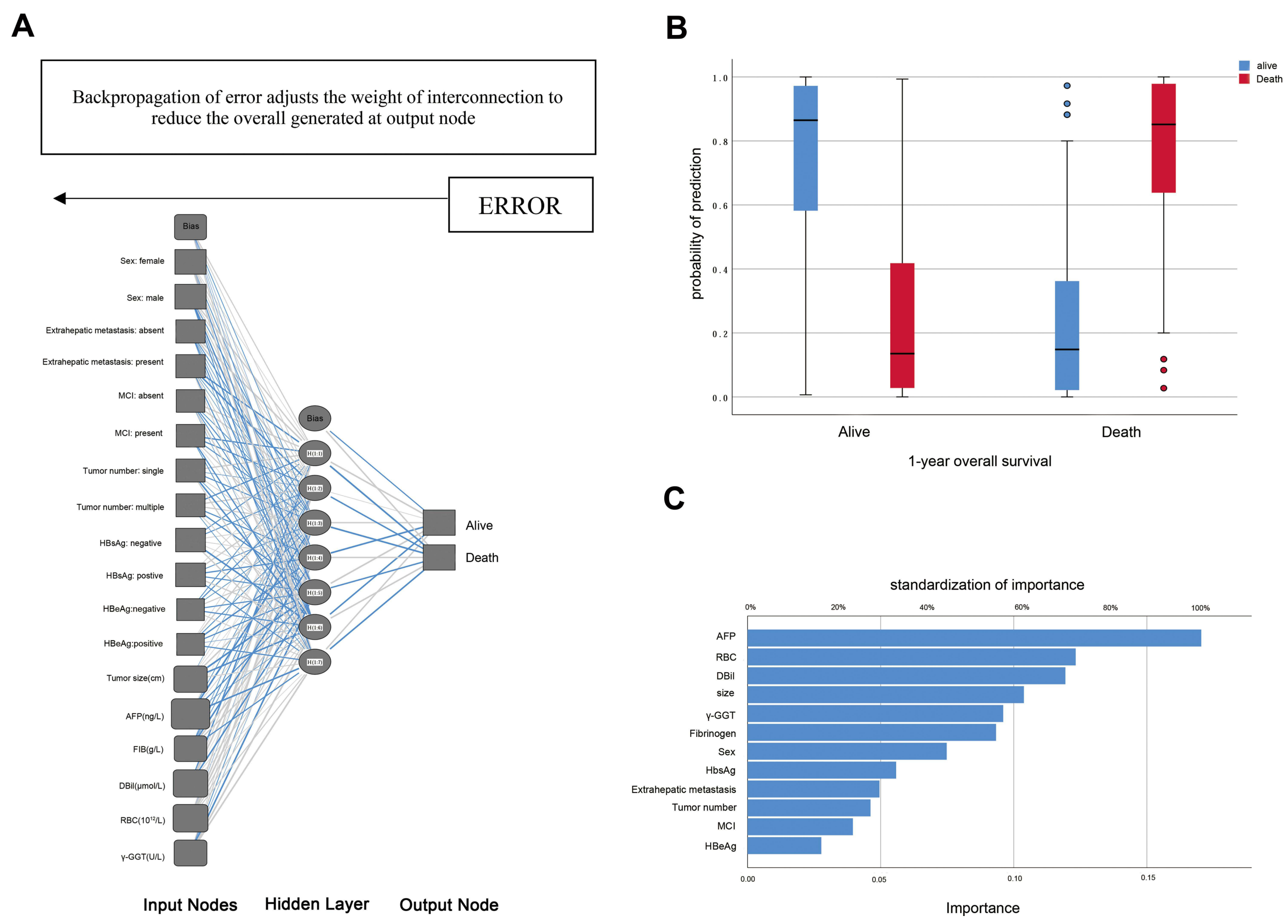

Figure 3 ANNs model was constructed to predict the prognosis for patients with spontaneous HCC ruptured bleeding. (**A**) The framework of the ANN model including one input layer with twelve nodes, one hidden layer with seven nodes, and one output layer with two nodes. (**B**) The relative importance of the twelve risk factors to the ANNs model. (**C**) Prediction probability histograms for the ANN model in patients with spontaneous HCC ruptured bleeding.

group and the high-risk group were 2.565 (95% CI, 1.819–3.617) and 8.623 (95% CI, 5.898–12.607) (P < 0.0001), respectively. In the validation set, the HRs for OS of the intermediate-risk and high-risk groups were 3.655 (95% CI, 2.080–6.421) and 12.903 (95% CI, 6.591–25.259) (P<0.0001), respectively, compared with the low-risk group. In addition, the high-risk group had a noticeably increased possibility of the 1-year probability of death in the training set and validation set. Density plots of the 1-year probability of death predicted by the ANNs model illustrated significant differences among the high-, intermediate-, and low-risk groups in the training and validation sets (Figure 7).

Discussion

Spontaneous tumor rupture is an essential factor related to the poor prognosis of HCC patients, and its incidence ranges from 34% to 71%.[32,33] According to the LCSG) staging (the 5th edition), the spontaneous HCC rupture is classified into stage IV regardless of the size and number of tumors.[32] However, not all patients with liver cancer rupture and bleeding have a poor prognosis after effective therapy.[34] There is no consistent conclusion about the optimal treatment approach for spontaneous HCC rupture.[35] Studies have reported that liver resection is an essential treatment for spontaneous HCC rupture patients.[36] However, spontaneous tumor rupture usually occurs in patients with advanced HCC. For unresectable patients, radical liver resection is not feasible due to severe liver cirrhosis and poor liver function, and palliative liver resection will bring considerable trauma. Moreover, whether palliative liver resection can bring a survival benefit to patients with unresectable liver cancer rupture remains controversial. It has been reported that TAE effectively achieves immediate hemostasis for spontaneously ruptured HCC.[19,37] Previous research suggested that TAE conferred similar acceptable tolerability and favorable survival rate as liver resection.[19] In our study, all patients

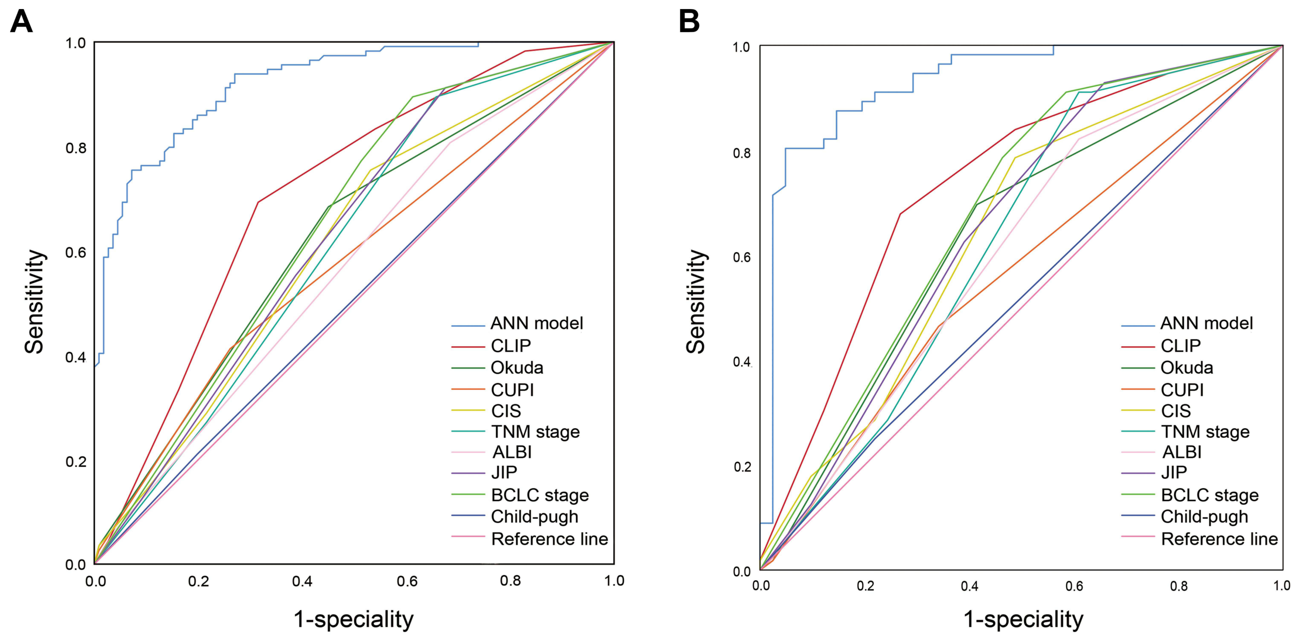

Figure 4 ROC curves for the ANN model and other existing conventional staging systems to predict the 1-year overall survival of patients with spontaneous HCC ruptured bleeding in the (**A**) training set and (**B**) validation set.

tolerated TAE treatment well. The general adverse reactions following TAE were minor and self-limiting.

TAE can achieve hemostasis effectively and create the possibility of downstaging the treatment of tumors and even regaining the opportunity for surgical treatment. To date, many clinical predictive staging systems have been used to predict the survival outcomes of advanced-stage HCC patients. However, few specifically designed predictive models have been reported on the prognosis of patients with spontaneous HCC rupture following TAE treatment and related factors affecting the prognosis. Furthermore, the prognosis of patients with spontaneous unresectable HCC rupture is likely to be determined based on the nonlinear regression of numerous clinical variables rather than simply using the clinical features described in the current clinical stage. Therefore, our research established an ANNs predictive model using machine learning to predict the 1-year OS rate of spontaneous HCC rupture patients for the first time. We wanted to determine which patients with spontaneous HCC rupture would benefit the most from TAE. Using a LASSO Cox regression model to reduce high dimensionality, twelve variables were selected for the ANNs model, including sex, extrahepatic metastasis, MCI, tumor number, HBsAg, HBeAg, tumor size, AFP, FIB, DBIL, RBC, and γ-GGT. Our results showed that the predictive power of the ANNs model, which is a nonlinear model, was significantly superior to that of existing prediction staging systems in predicting the 1-year OS of spontaneous HCC rupture patients.

The TNM staging and BCLC staging systems, usually used to guide patients in choosing the best treatment strategy, have been widely used in clinical practice.[38] The ALBI grade and Child-Pugh score also have a specific value in predicting the prognosis of HCC patients.[39,40] However, the above staging systems are usually applied to patients undergoing surgical resection, and their predictive ability in patients with spontaneous HCC rupture is poor. Our study found that they are not suitable for predicting the prognosis of patients with spontaneous HCC rupture because they are usually used to assess liver reserve function. In addition, the above staging systems did not contain some critical factors that affect the prognosis, such as tumor size and number. The ALBI grade or Child-Pugh score alone can hardly accurately predict the prognosis of patients with spontaneous HCC rupture. The CLIP score incorporated the characteristics of the tumor, Child-Pugh score, AFP, and MCI variables into a quantifiable system. The CLIP score has good predictive ability in both the training and validation sets, with C-indexes of 0.717 and 0.737, respectively. CLIP score was second only to the ANNs model in predicting the 1-year OS of spontaneous HCC rupture patients.

Table 2 Predictive Accuracy of ANNs Model and Existing Staging System for 1-Year OS Status in the Training Set and Validation Set

Group	Models	AUC/C-Index	*P* value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Training set	ANNs model	0.923 (95% CI, 0.890–0.956)	-	75.44%	92.79%	91.49%	78.63%
	JIP	0.629(95% CI, 0.560–0.699)	<0.001	91.23%	32.43%	58.10%	78.26%
	Okuda staging	0.622(95% CI, 0.549–0.695)	<0.001	68.42%	54.95%	60.94%	62.89%
	CUPI	0.577(95% CI, 0.516–0.638)	<0.001	41.23%	73.87%	61.84%	55.03%
	CIS	0.626(95% CI, 0.557–0.695)	<0.001	75.44%	46.85%	59.31%	65.00%
	TNM staging	0.626(95% CI,0.559–0.693)	<0.001	89.47%	34.23%	58.29%	76.00%
	BCLC staging	0.648(95% CI,0.588–0.709)	<0.001	89.47%	38.74%	60.00%	78.18%
	ALBI	0.567(95% CI,0.506–0.628)	<0.001	80.70%	31.53%	54.76%	61.40%
	Child-Pugh score	0.506(95% CI,0.453–0.559)	<0.001	21.05%	50.22%	52.17%	49.72%
	CLIP	0.717(95% CI, 0.651–0.783)	<0.001	69.30%	68.47%	69.30%	68.47%
Validation set	ANNs model	0.930 (95% CI, 0.875–0.985)	-	80.36%	95.12%	95.74%	78.00%
	JIP	0.666(95% CI, 0.559–0.773)	<0.001	92.86%	34.15%	65.82%	77.78%
	Okuda staging	0.646(95% CI, 0.547–0.744)	<0.001	67.86%	60.98%	70.37%	58.14%
	CUPI	0.565(95% CI, 0.466–0.665)	<0.001	44.64%	68.29%	65.79%	47.46%
	CIS	0.677(95% CI, 0.573–0.781)	<0.001	67.86%	63.41%	71.70%	59.09%
	TNM staging	0.676(95% CI, 0.573–0.779)	<0.001	91.07%	39.02%	67.11%	76.19%
	BCLC staging	0.682(95% CI, 0.586–0.778)	<0.001	91.07%	41.46%	68.00%	77.27%
	ALBI	0.609(95% CI, 0.510–0.707)	<0.001	82.14%	39.02%	64.79%	61.54%
	Child-Pugh	0.508(95% CI, 0.391–0.626)	<0.001	25.00%	78.05%	60.87%	43.24%
	CLIP	0.737(95% CI, 0.637–0.837)	<0.001	67.86%	73.17%	77.55%	62.50%

Abbreviations: OS, overall survival; ANNs, artificial neural networks; JIP, Japan Integrated Staging; CUPI, Chinese University Prognostic Index; CIS, China integrated score; BCLC stage, Barcelona clinic liver cancer stage; ALBI, albumin-bilirubin classification; CLIP, Cancer of the Liver Italian Program.

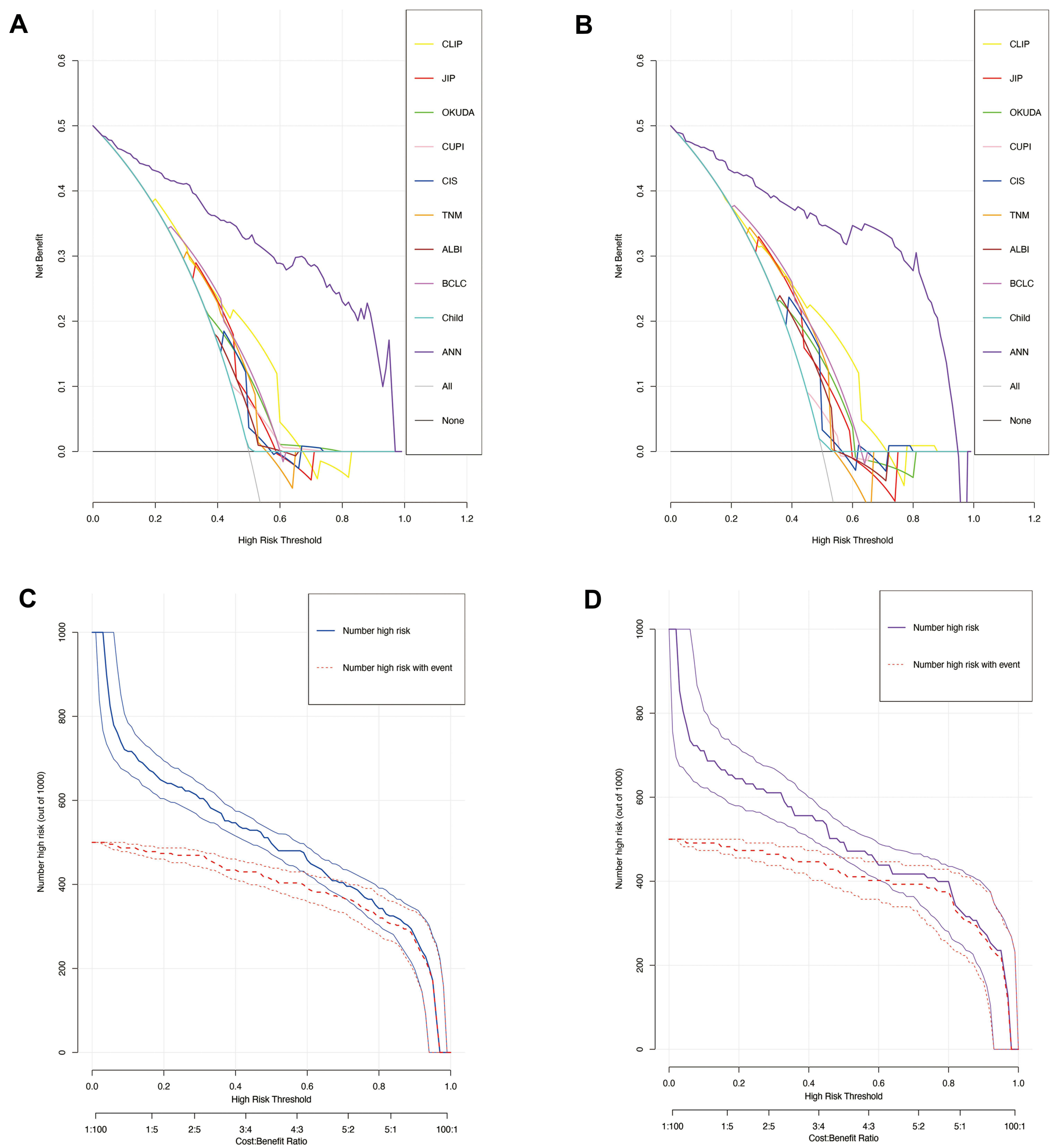

Figure 5 The decision curves of the 1-year overall survival in the training and validation sets (**A** and **B**). The Y-axis represents the net benefit. The X-axis shows the threshold probability. Clinical impact curves of the ANNs model for predicting 1-year overall survival of the patients with spontaneous HCC ruptured bleeding in the training and validation sets (**C** and **D**).

However, this staging system was not specifically designed for patients with spontaneous HCC rupture and did not contain essential serum indicators.

Large and multiple tumors are essential factors that reflect tumor burden, which is significantly associated with poor prognosis.[41] MCI can cause portal hypertension and damage the liver function of patients. In addition, portal vein involvement and increased intratumoral pressure caused by portal vein invasion were the main reasons for HCC recurrence and metastasis.[42] TAE treatment is generally prohibited for patients with PVTT in the main portal vein due to ischemic liver damage.[43] However, we can use the super-

Table 3 Clinicopathologic Characteristics of Patients with Spontaneous Hepatocellular Carcinoma Rupture According to Risk Stratification

Variables	Low Risk Group (n=102)	Intermediate Risk Group (n=110)	High Risk Group (n=110)	*P* value†
Age (years), median (IQR)	53(39–63)	51(42–61)	49(42–64)	1–2 0.944, 1–3 0.956, 2–3 0.981
Gender, (male/ female)	86/16	104/6	105/5	1–2 0.027, 1–3 0.007, 2–3 1.000
BMI (kg^2/m^2), median (IQR)	23.7(20.8–26.5)	23.6(21.3–25.3)	22.2(20.3–24.3)	1–2 0.780, 1–3 0.011, 2–3 0.012
Child-Pugh score, (A/B)	83/19	87/23	83/27	1–2 0.807, 1–3 0.380, 2–3 0.629
Portal hypertension, (Yes/No)	46/56	41/69	40/70	1–2 0.309, 1–3 0.248, 2–3 1.000
HBsAg positive, n (%)	65/37	94/16	97/13	1–2 0.001, 1–3 <0.001, 2–3 0.690
HBV-DNA positive, n (%)	26/76	36/74	32/78	1–2 0.247, 1–3 0.665, 2–3 0.662
Baseline laboratory investigations				
RBC count $\times 10^9$/L, median (IQR)	3.79(3.16–4.58)	3.35(2.92–4.22)	3.60(2.78–4.25)	1–2 0.019, 1–3 0.056, 2–3 0.802
HGB(g/L), median (IQR)	115(92–140)	104(86–124.5)	109(85–127)	1–2 0.017, 1–3 0.023, 2–3 0.940
WBC count $\times 10^9$/L, median (IQR)	10.13(6.21–13.10)	7.88(6.51–12.77)	9.12(6.72–11.80)	1–2 0.438, 1–3 0.956, 2–3 0.248
NEUT count $\times 10^9$/L, median (IQR)	7.36(4.36–11.35)	6.15(4.64–11.17)	7.59(5.31–10.25)	1–2 0.464, 1–3 0.743, 2–3 0.114
PLT count ×109/L, median (IQR)	132(95–197)	134(105–194)	155(116–221)	1–2 0.350, 1–3 0.005, 2–3 0.041
ALT (U/L), median (IQR)	37.5(23–56.25)	46.0(29.0–89.0)	47.0(33.8–92.0)	1–2 0.009, 1–3 0.001, 2–3 0.583
AST (U/L), median (IQR)	39.5(28.5–81.25)	68.0(40.0–134.5)	77.5(48.0–160.5)	1–2<0.001, 1–3<0.001, 2–3 0.190
ALP (U/L), median (IQR)	84.0(70.0–107.8)	93.0(69.0–146.3)	118.5(86.8–175.8)	1–2 0.054, 1–3<0.001, 2–3 0.002
GGT (U/L), median (IQR)	57.0(31.8–93.5)	107.0(62.25–216.0)	123.0(73.0–250.3)	1–2<0.001, 1–3<0.001, 2–3 0.126
DBIL (μmol/L), median (IQR)	6.9(4.7–9.5)	7.8(5.9–10.9)	8.45(5.6–13.2)	1–2 0.143, 1–3 0.057, 2–3 0.287
ALB (g/L), median (IQR)	37.8(32.6–42.1)	35.4(31.1–39.6)	33.5(30.9–38.0)	1–2 0.009, 1–3<0.001, 2–3 0.140
INR, median (IQR)	1.15(1.07–1.24)	1.16(1.08–1.29)	1.17(1.10–1.33)	1–2 0.076, 1–3 0.021, 2–3 0.509
FIB(g/L), median (IQR)	2.51(1.79–3.75)	2.32(1.75–3.29)	2.35(1.79–2.92)	1–2 0.156, 1–3 0.117, 2–3 0.853
AFP, ng/mL median (IQR)	24.50(5.60–334.10)	338.55(19.26–1210.00)	873.40(83.07–3471.75)	1–2 <0.001, 1–3 <0.001, 2–3 0.012
CA19-9 level(U/mL) median (IQR)	8.16(3.74–19.63)	18.76(8.99–33.55)	22.12(10.27–38.41)	1–2 <0.001, 1–3 <0.001, 2–3 0.347
CEA, ng/mL median (IQR)	1.41(0.89–2.89)	1.56(0.95–2.21)	1.73(1.15–2.73)	1–2 0.783, 1–3 0.414, 2–3 0.298
Tumor size (cm), median (range)	6.4(4.7–7.63)	8.3(6.95–10.7)	9.85(8.3–13.13)	1–2 <0.001, 1–3 <0.001, 2–3 <0.001
Tumor number, (Multiple/solitary)	18/84	29/81	62/48	1–2 0.173, 1–3 <0.001, 2–3 <0.001
MCI, (Yes/ No)	31/71	68/42	96/14	1–2 <0.001, 1–3 <0.001, 2–3 <0.001
Extrahepatic metastasis, (Yes/No)	12/90	7/103	27/83	1–2 0.256, 1–3 <0.001, 2–3 <0.001
BCLC stage, (A/B/C)	52/10/40	25/15/70	0/12/98	1–2 <0.001, 1–3 <0.001, 2–3 <0.001
Repeated TACE (with/without)	8/94	8/102	2/108	1–2 1.000, 1–3 0.039, 2–3 0.052

Notes: †Fisher's exact tests. 1–2 low risk group compared with intermediate risk group, 1–3 low risk group compared with high-risk group, 2–3 intermediate risk group compared with high-risk group.
Abbreviations: BMI, body mass index; HBsAg, hepatitis B surface antigen; RBC, red blood cell; HGB, hemoglobin; WBC, white blood cell; NEU, neutrophil; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; DBIL, direct bilirubin; ALB, albumin; INR, international normalized ratio; FIB, fibrinogen; AFP, alpha fetoprotein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; MCI, macroscopic vascular invasion; BCLC stage, Barcelona clinic liver cancer stage.

selective TAE method to achieve hemostasis as soon as possible and reduce the risk of postoperative liver failure. Our study found that the preoperative serum AFP level is an independent risk factor for poor short-term survival in patients with spontaneous HCC rupture. Increased serum AFP usually reflects poor cellular differentiation, biological aggressiveness, and tumor spread. FIB is a 340-KDa acute phase glycoprotein associated with increased fibrinogen deposits in tumor tissue, and it could lead to promoting the angiogenesis, metastasis, and proliferation of cancer cells.[44] Consistent with the findings of previous studies, in our study, preoperative GGT levels were found to be an essential risk factor,[45] and high serum GGT levels might reflect the severity of the liver injury status.

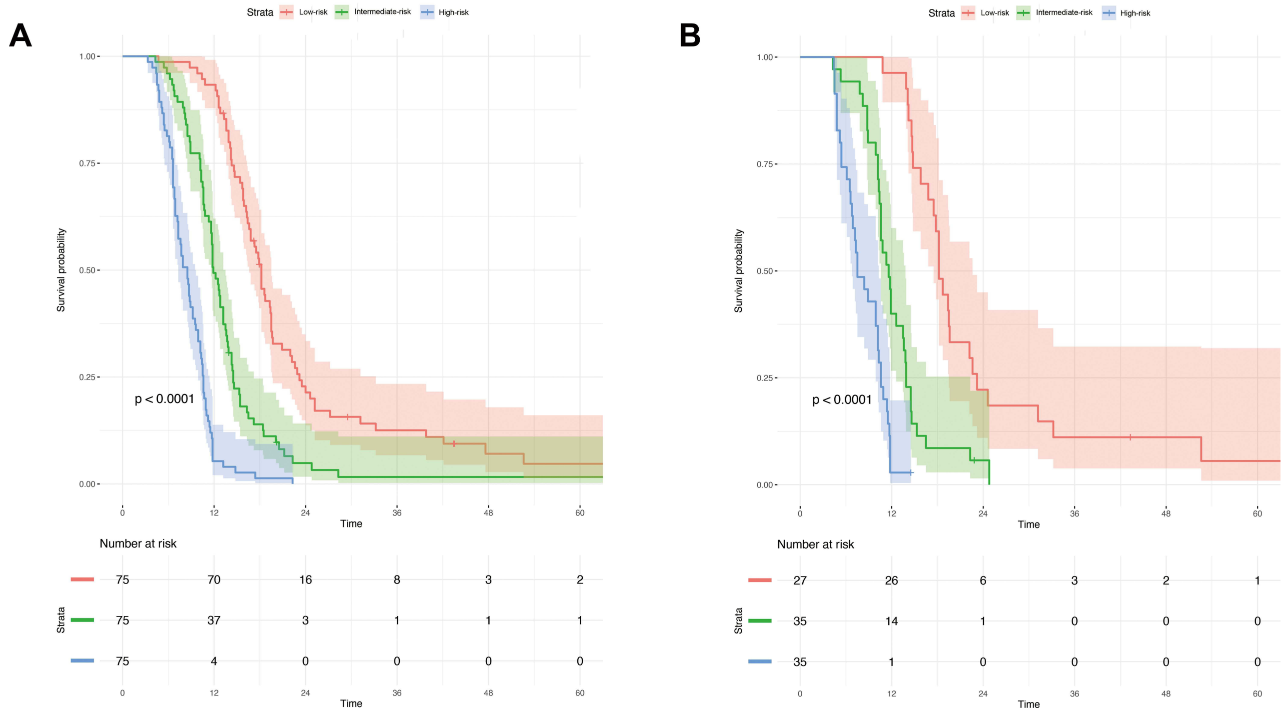

Figure 6 Kaplan–Meier survival analysis of overall survival according to risk stratification in the training set and validation set (**A** and **B**). The number at risk refers to the number of patients who have not relapsed at the corresponding time point.

Moreover, some studies have revealed that the elevated GGT expression could facilitate tumor progression, metastasis, cell apoptosis, and even DNA damage.[46,47] HBsAg-positive patients usually have severe liver cirrhosis, accompanied by more severe coagulation dysfunction. In contrast, HBeAg-positivity in patients indicates active viral replication and is closely related to the occurrence and development of HCC. Continuous active replication of the hepatitis B virus (HBV) may lead to the necrosis of hepatocytes, thereby causing the malignant transformation, which is not conducive to the prognosis of patients. HBeAg positivity could decrease p53 activity by interacting with NUMB, consequently leading to the progression of HCC.[47] We found that compared with patients who did not receive repeated TACE treatment, the prognosis of patients receiving repeated TACE treatment did not show a survival benefit, which might be related to the poor general condition of patients with spontaneous HCC rupture and their inability to tolerate regular repeated TACE treatment.

Several limitations should be taken into consideration when interpreting our findings. First, our research findings came from a single-center study. Due to the characteristics of retrospective studies, there inevitably might be potential inherent defects and selection bias, although a validation set was used to increase the reliability of our research. The relatively small sample size of this study will limit the full use of the predictive power of the ANNs model. Second, as most of the patients included in this study were hepatitis virus-infected, the established ANNs model warrants further investigation on its performance in patients with other etiologies.

Conclusion

In summary, we successfully developed and validated the ANNs model based on important clinical variables for predicting the 1-year OS of spontaneous HCC rupture patients who underwent TAE. Our established ANN model showed significantly better discriminative capability and a more accurate survival prediction ability than other prediction models; moreover, we could accurately identify low-risk, intermediate-risk, and high-risk patients.

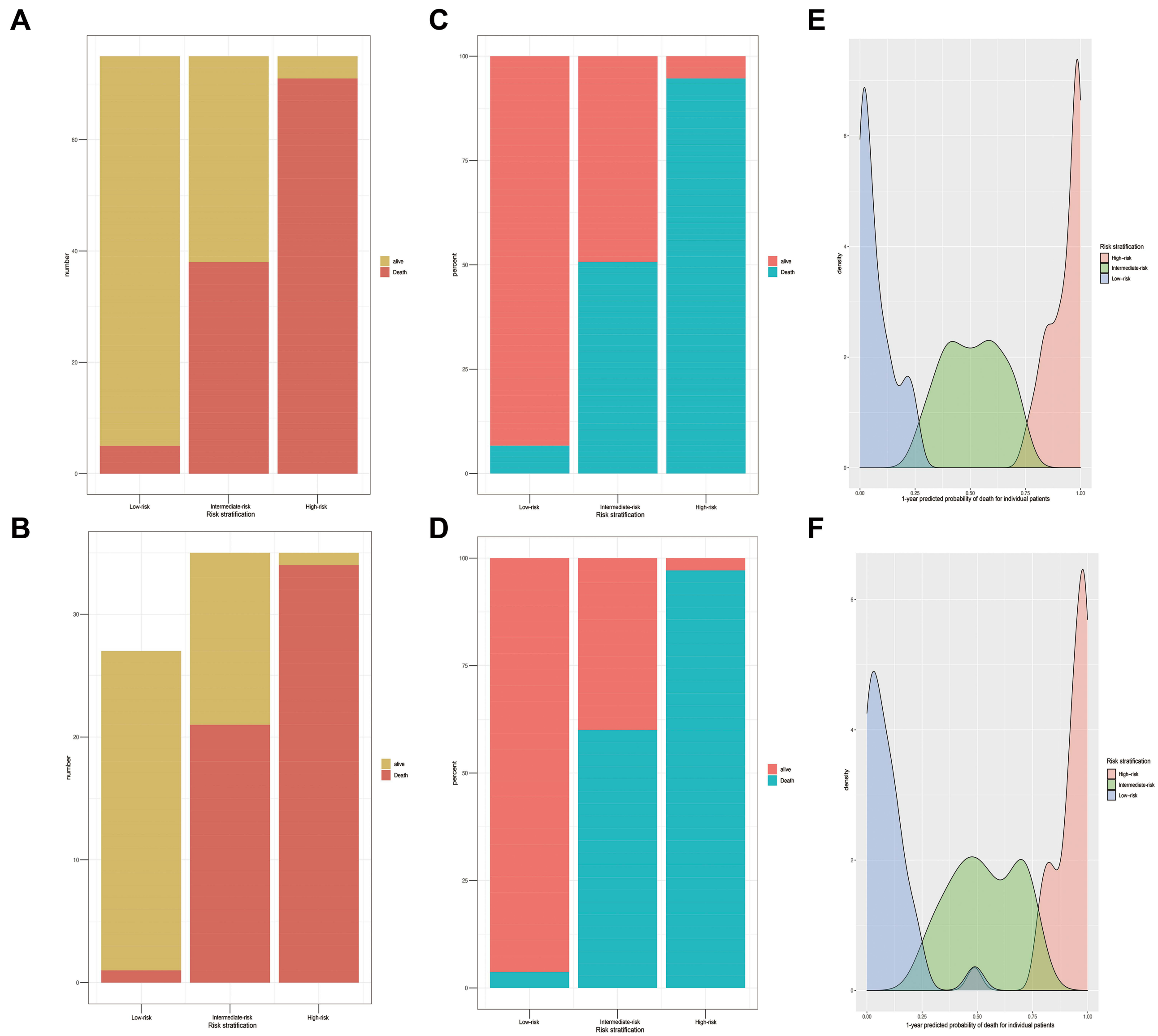

Figure 7 The discriminatory power of the ANNs model for 1-year overall survival with bar charts. Relationship of the 1-year mortality rate and risk group stratification assessed using the ANNs model in the training set and validation set (**A–D**). Density plot of the predicted 1-year mortality probability in the high- and low-risk groups of the training and validation sets (**E** and **F**).

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Ethical Statement

The study was approved by the ethics committee of Sichuan University, and informed consent was taken from all the patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published, have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors disclose no conflicts of interest for this work.

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