Development and validation of a machine learning-based model to predict survival in patients with cirrhosis after transjugular intrahepatic portosystemic shunt

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Summary

Background Although numerous prognostic scores have been developed for patients with cirrhosis after Transjugular intrahepatic portosystemic shunt (TIPS) placement over years, an accurate machine learning (ML)-based model remains unavailable. The aim of this study was to develop and validate a ML-based prognostic model to predict survival in patients with cirrhosis after TIPS placement.

Methods In this retrospective study in China, patients diagnosed with cirrhosis after TIPS placement from 2014 to 2020 in our cohort were included to develop a ML-based model. Patients from the other two tertiary hospitals between 2016 and 2022 were as external validation cohort. The random forest (RF) model was built using 7 selected features via the least absolute shrinkage and selection operator (LASSO) regression, and subsequent 10-fold cross-validation was performed.

Findings A total of 400 patients in our cohort were included (median age and interquartile range, 59 (50, 66); 240 men). Two hundred and eighty patients made up the training set and 120 were in the testing set, and 346 patients were included in the external validation cohort. Seven attributes were selected: Na, ammonia (Amm), total bilirubin (Tb), albumin (Alb), age, creatinine (Cr), and ascites. These parameters were included in a new score named the RF model. The accuracy, precision, recall, and F1 Score of the RF model were 0.84 (95% CI: 0.76, 0.91), 0.84 (95% CI: 0.77, 0.91), 0.99 (95% CI: 0.95, 1.00), 0.91 (95% CI: 0.81, 0.10) in the testing set, and 0.88 (95% CI: 0.84, 0.91), 0.89 (95% CI: 0.85, 0.92), 0.99 (95% CI: 0.97, 1.00), 0.93 (95% CI: 0.85, 0.97) in the validation cohort, respectively. The calibration curve showed a slope of 0.875 in the testing set and a slope of 0.778 in the external validation cohort, suggesting well calibration performance. The RF model outperformed other scoring systems, such as the (Child-Turcotte-Pugh score) CTP, (model for end-stage liver disease) MELD, (sodium MELD) MELD-Na, (Freiburg index of post-TIPS survival) FIPS and (Albumin-Bilirubin) ALBI, showing the highest (area under the curve) AUC of 0.82 (95% CI: 0.72, 0.91) and 0.7 (95% CI: 0.60, 0.79) in predicting 1-year survival across the testing set and external validation cohort.

Interpretation This study developed a RF model that better predicted 1-year survival for patients with cirrhosis after TIPS placement than the other scores.

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Keywords: Random forest model; Prediction; Survival; Cirrhosis; Transjugular intrahepatic portosystemic shunt

Research in context

Evidence before this study

We searched PubMed with the search terms "Ammonia" [Mesh] AND "Liver Cirrhosis" [Mesh] AND "Portasystemic Shunt, Transjugular Intrahepatic" [Mesh], for publications from database inception to November 20, 2024. We have identified eighteen studies, the majority of which demonstrate a significant correlation between hyperammonemia and hepatic encephalopathy. Only one study, published by our team, provided an external validation of the modified CTP score based on ammonia (Amm) to predict survival in patients with cirrhosis after transjugular intrahepatic portosystemic shunt (TIPS) placement. It is important to note that this study did not employ a machine learning (ML) model in its analysis.

Added value of this study

To our knowledge, this is the first study to develope and validate a ML model, incorporating plasma Amm as a predictive factor, to predict survival in patients with cirrhosis after TIPS placement. At the same time, the discrimination and calibration of the ML model are better than other traditional systems, such as the (Child-Turcotte-Pugh score) CTP, (the model for end-stage liver disease) MELD, (MELD with Sodium) MELD-Na, (Freiburg index of post-TIPS survival) FIPS and (Albumin-Bilirubin) ALBI.

Implications of all the available evidence

This ML model may assist in identifying high-risk patients after TIPS placement and facilitating timely interventions in clinical practice. Further prospective researches are needed to evaluate the effectiveness of this model.

Introduction

In patients with cirrhosis, the progression to portal hypertension is associated with a notable reduction in their quality of life and a sharp rise in the risk of hospitalization and mortality.[1,2] The transjugular intrahepatic portosystemic shunt (TIPS) procedure, known for its low frequency of procedural and shunt-related issues, is recognized as a proficient treatment for alleviating portal hypertension and managing its associated complications, including variceal bleeding (VB) and refractory ascites (RA).[3,4] However, not all patients derive survival benefits from the TIPS procedure, it is crucial to develop a precise and sensitive model to more effectively select suitable candidates.

Several risk scoring systems such as the Child-Turcotte-Pugh (CTP),[5] the model for end-stage liver disease (MELD)[6] and sodium MELD (MELD-Na),[7] albumin-bilirubin (ALBI),[8] and Freiburg index of post-TIPS survival (FIPS),[9] have been developed to predict survival and ascertain the individuals who exhibit susceptibility to mortality after TIPS implantation. However, the increasing application of multiple machine learning (ML) algorithms, along with improvements in computational power, has significantly heightened interest in enhancing the predictive accuracy of medical diagnoses and prognostic evaluations. Compared with the conventional ML algorithms such as logistic regression, random forest (RF) model is an ensemble learning method based on decision tree, which can handle more complex data structures and analysis non-linear relationships.

Ammonia (Amm), as a critical mediator of neuronal dysfunction, is central to the progression of hepatic encephalopathy (HE).[10] A recent study has proven that Amm was an independent predictor of the development of overt HE (OHE) and a ML model was developed to predict the probability of OHE in outpatients with cirrhosis.[11] Another study reveals that elevated Amm levels are significantly associated with 28-day mortality in patients with acute-on-chronic liver failure, particularly those with hepatitis B virus reactivation, highlighting Amm is a strong prognostic factor and potential therapeutic target in these patients.[12] Our previous study has shown that Amm is correlated with the probability of mortality in patients with decompensated cirrhosis after TIPS.[13] Therefore, adding plasma Amm to the ML model might provide potential prognostic value for patients with cirrhosis after TIPS implantation.

This multi-center study aims to develop and validate a RF model, incorporating plasma Amm as a predictive factor, to predict 1-year transplant-free survival in patients with cirrhosis after TIPS placement.

Methods

Patient selection

Fig. 1 presents the flowchart of the study design and statistical analysis. This retrospective cohort study reviewed 771 consecutive patients who underwent elective TIPS placement in Drum Tower Hospital between January 2014 and August 2020. All patients were followed up for at least 1 year. Written informed consent from all subjects included in this study was obtained. For all patients, the guidelines of the 1975 Declaration of Helsinki and Istanbul were followed. All procedures

have been approved by the institutional review boards of the Drum Tower Hospital (2024-410-02). The inclusion criteria were as follows: (1) patients with cirrhosis undergoing TIPS procedure; (2) patients aged ≥18 years. The exclusion criteria were as follows: (1) patients without plasma Amm measurement before TIPS; (2) patients who had TIPS history; (3) patients who had HCC or extrahepatic malignancy; and (4) patients who were lost to follow-up within 1 year. To further validate the RF model, patients from two additional tertiary hospitals were included as an external validation cohort: the First Affiliated Hospital of Wenzhou Medical University and Mengchao Hepatobiliary Hospital of Fujian Medical University, with data collected from January 2016 to June 2022. The inclusion criteria, exclusion criteria and follow-up period were identical to our cohort. The external validation cohort was authorized by the Institutional Review Board of the First Affiliated Hospital of Wenzhou Medical University and Mengchao Hepatobiliary Hospital of Fujian Medical University, which approved waiving informed consent considering that the data used in this study have no personally identifiable information of patients.

Data collection

The cirrhosis diagnosis was formulated by a thorough synthesis of the patient's medical history, radiological findings, and laboratory parameters, with biopsy confirmation applied when necessary. All patients with cirrhosis received treatment targeting the underlying etiologies. The definition of RA is referred to EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis.[14] To enhance promotion in different hospitals, the ratio of baseline plasma Amm levels to the upper limit of normal range (Amm-ULN) was utilized. All scoring systems were derived from clinical and laboratory results obtained within 72 h before TIPS placement (Supplementary Table S1). Outpatient monitoring was set at 1, 3, 6, and 12 months after TIPS implantation, or as needed. Monitoring of patients undergoing liver transplantation was discontinued on the date of the transplantation. The clinical primary endpoint was the 1-year transplant-free survival after TIPS creation.

Construction and evaluation of the RF model

The study population was divided into the training set and testing set with a ratio of 7:3 using completely random sampling. The training set was used to build the RF model to predict 1-year survival, and the testing set was used for internal validation. All variables were included in the least absolute shrinkage and selection operator (LASSO) regression for variable selection. The selected variables were then incorporated into the RF algorithm to construct the prediction model. The predictive performance of the RF model was evaluated via the area under the curve (AUC), calibration curve, accuracy, precision, recall, F1 score, and confusion matrix.

Statistical analysis

Data adhering to a normal distribution are characterized by the mean ± standard deviation (mean ± SD) and are compared using the t-test. Data distributions that are skewed are noted as the median and the first and third quartiles (M (Q1, Q3)), and are analyzed with the Wilcoxon rank sum test. Data were assessed for normality using the Kolmogorov–Smirnov test. Categorical data are shown as numerical counts and percentages (n (%)), with the chi-square test or Fisher's exact test used for statistical evaluation. LASSO regression was applied for multivariate analysis to select variables. The importance ranking of these variables was provided by a random forest algorithm. The cutoff values for these variables were determined using the receiver operating characteristic (ROC) curve analysis, with the maximum Youden index indicating the optimal threshold. Kaplan–Meier (K-M) survival curves were used to assess the cumulative survival rates among groups, and differences between the curves were compared using the log-rank tests. The calibration curve was applied to evaluate the calibration ability. The discriminative performance of the risk scoring systems in predicting the 1-year survival rate was compared by AUC, and the DeLong test was used for comparing different AUC values. R studio (version 4.3.0) was used for all analyses. Statistical significance was set at a P value < 0.05.

Role of the funding source

The funder had no role in data collection, study design, preparation of the manuscript, and decision to publish. No authors received payment from any pharmaceutical company or other agency for the writing of this article. All authors had full access to all the data in the study and take responsibility for the decision to submit for publication.

Results

Characteristics of the study population

A total of 771 patients who underwent TIPS implantation for RA and/or secondary prophylaxis of VB from January 2014 to August 2020 were screened from our center. One hundred and one patients did not meet the inclusion criteria because of non-cirrhotic portal hypertension (5 Budd-Chiari syndrome, and 96 hepatic sinusoidal obstruction syndromes). One hundred and ninety-four patients were excluded due to the absence of plasma Amm before TIPS creation, 17 patients due to the history of the TIPS placement, 34 patients due to the HCC or extrahepatic malignancy, and 25 patients lost to follow-up within 1 year. In summary, 400 patients were included in our cohort (Fig. 1). The median age was 59 (50, 66) years, and 240 (60%) were male. The main

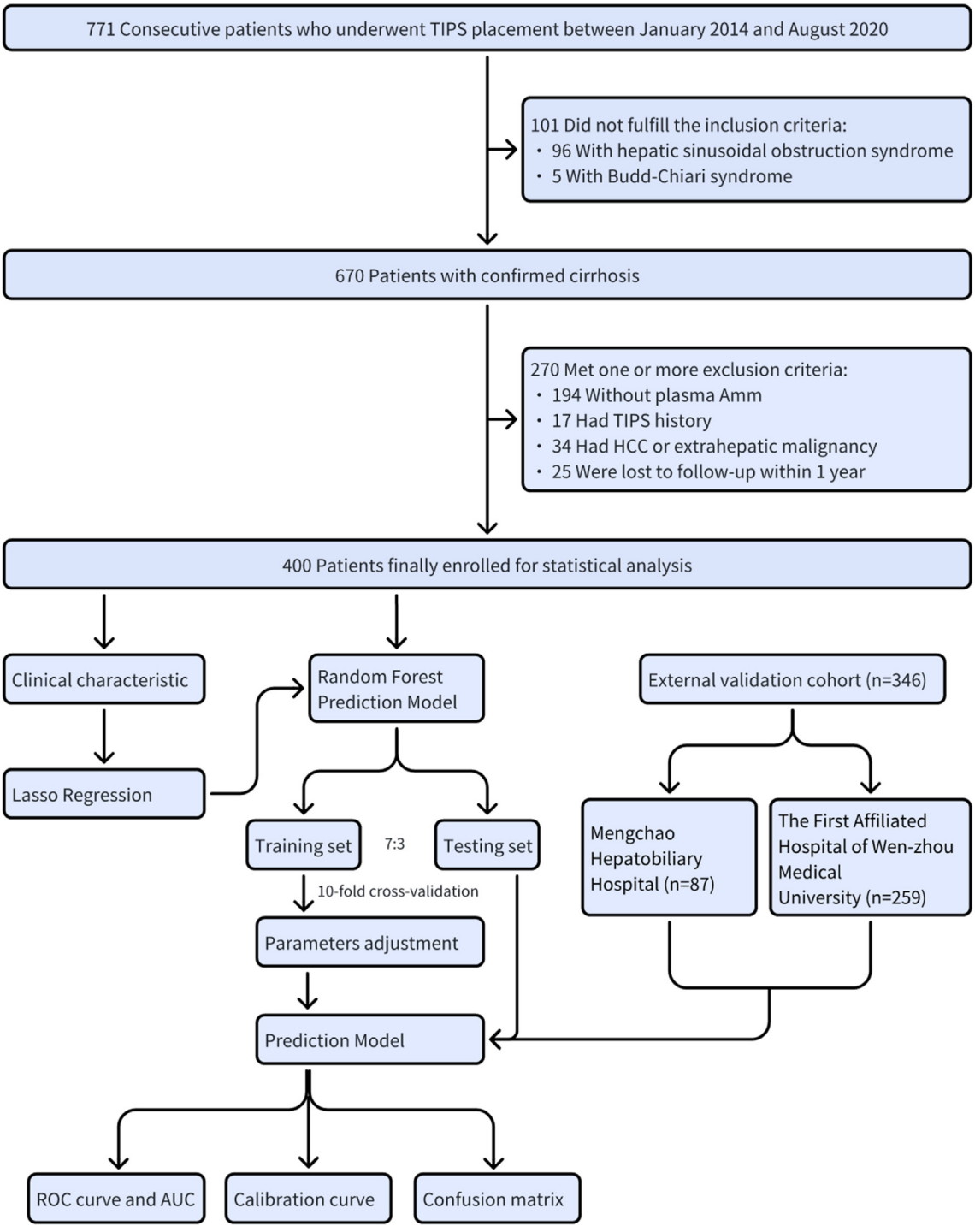

Fig. 1: The flowchart describes the process of conducting the study and statistical analysis. ROC, curve receiver operating characteristic curve; AUC, area under the curve.

etiologies for liver cirrhosis were hepatitis virus infection (49.5%), alcohol use (11%), primary biliary cirrhosis (PBC) (9%), autoimmune hepatitis (AIH) (4.8%), and others (25.8%). TIPS implantation was performed on 338 (84.5%) individuals for secondary prophylaxis of VB, 27 (6.8%) for RA, and 35 (8.8%) for both of them.

Seventy-nine (19.8%) patients had portal vein thrombosis (PVT). Two hundred and forty-nine (62.3%) patients had moderate-severe ascites. According to the 1-year survival, our cohort patients were divided into the Survival group (n = 346) and the Death group (n = 46). Of the 46 patients (11.5%) who experienced either death or undergone liver transplantation within 1 year, 36 (78.3%) died from liver-related complications, 7 (15.2%) died from other causes and 3 (6.5%) underwent liver transplantation. The baseline characteristics of the two groups are presented in Table 1. The two groups were significantly different in age, indication for TIPS, ascites, total bilirubin (TB), international normalized ratio (INR), creatinine (Cr), Na, albumin (Alb), and the risk scoring systems (CTP, MELD, MELD-Na, ALBI, and FIPS) (all $p < 0.05$). The baseline characteristics according to the training set, testing set, and external validation cohort were shown in Supplementary Table S2. Patients from our cohort were randomly split (7:3) into a training set (280 patients total, 28 death or liver transplantation, and 252 survival) and a testing set (120 patients total, 18 death or liver transplantation,

	Total (n = 400)	Survival (n = 354)	Death (n = 46)	p
Age (years)	59 (50, 66)	58 (49, 65)	61 (53, 70)	0.016
Gender (Male)	240 (60%)	210 (59%)	30 (65%)	0.443
Etiology of cirrhosis				0.538
Hepatitis B	184 (46.0%)	161	23	
Hepatitis C	14 (3.5%)	11	3	
Alcohol-related	44 (11.0%)	41	3	
PBC	36 (9.0%)	34	2	
AIH	19 (4.8%)	16	3	
Others	103 (25.8%)	91	12	
Indication for TIPS				0.006
Variceal bleeding	373 (93.3%)	335	38	
Refractory ascites	27 (6.8%)	19	8	
PVT	79 (19.8%)	72 (20.3%)	7 (15.2%)	0.412
Ascites				<0.001
No	89 (22.3%)	85	4	
Mild-moderate	249 (62.3%)	223	26	
Refractory	62 (15.5%)	46	16	
History of HE	6 (1.5%)	5	1	0.784
ALT (U/L)	20 (14, 31)	20 (14, 31)	21 (13, 35)	0.749
AST (U/L)	27 (21, 39)	27 (21, 39)	28 (21, 42)	0.977
TB (μmol/L)	18.4 (12.9, 25.8)	17.6 (12.7, 24.6)	22.9 (17.0, 34.9)	0.001
INR	1.2 (1.2, 1.4)	1.2 (1.2, 1.4)	1.3 (1.2, 1.5)	0.014
Creatinine (μmol/L)	61 (52, 73)	61 (51.7, 71.0)	70 (54.8, 96.0)	0.007
Na (mmol/L)	140.8 (138.0, 142.5)	141.0 (138.4, 142.7)	138.1 (133.9, 141.6)	<0.001
Alb (g/L)	32.7 ± 4.3	32.9 ± 4.2	30.8 ± 4.3	0.001
PLT ($\times 10^9$/L)	63 (44, 112)	63 (44, 117.5)	60.5 (44, 88)	0.600
WBC ($\times 10^9$/L)	2.9 (1.9, 5.0)	2.9 (1.9, 4.8)	3.1 (2.1, 6.6)	0.378
Diameter of TIPS stent				0.467
6 mm	88 (22.0%)	80 (22.6%)	8 (17.4%)	
7 mm	45 (11.2%)	40 (11.3%)	5 (10.9%)	
8 mm	264 (66.0%)	231 (65.3%)	33 (71.7%)	
10 mm	3 (0.8%)	3 (0.8%)	0 (0%)	
Amm-ULN	0.93 (0.57, 1.43)	0.93 (0.53, 1.43)	1.03 (0.7, 2.04)	0.074
PPG drop (mmHg)	9 (6, 12)	9 (6, 12)	9 (6.75, 12)	0.827
CTP	7 (6, 8)	7 (6, 8)	8 (7, 9)	<0.001
MELD	9 (8, 11)	9 (7, 11)	11 (9, 14)	<0.001
MELD-Na	9.2 (7.6, 11.3)	8.9 (7.4, 10.8)	11.7 (9.6, 15.7)	<0.001
ALBI	−1.9 ± 0.4	−2.0 ± 0.4	−1.7 ± 0.4	<0.001
FIPS	−1.1 ± 0.8	−1.2 ± 0.8	−0.6 ± 0.8	<0.001

PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; PVT, portal vein thrombosis; HE, hepatic encephalopathy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Tb, total bilirubin; INR, international normalized ratio; Alb, albumin; PLT, platelet; WBC, white blood cells; Amm, ammonia; PPG, portosystemic pressure gradient.

Table 1: **Baseline characteristics of the cohort.**

and 102 survival). Three hundred and forty-six patients from the external validation cohort were included.

Ranking of feature importance

After LASSO regression, seven features are selected based on the 1 Standard Error (SE) (Fig. 2). These features were Na, Amm, Tb, Alb, age, Cr, and ascites, according to the feature importance given in the random forest algorithm (Fig. 3A). ROC curves were used to evaluate the prediction effect of these variables on post-TIPS 1-year survival. The optimal cutoff of Na was identified at 136.25 mmol/L (sensitivity: 0.887, specificity: 0.435) and the AUC was 0.676 (95% CI: 0.52, 0.70). For Amm-ULN, the cutoff was 1.85 (sensitivity: 0.893, specificity: 0.283), with an AUC of 0.581 (95% CI: 0.49, 0.67). For Tb, the cutoff was 18.85 mmol/L (sensitivity: 0.554, specificity: 0.717), with an AUC of 0.652 (95% CI: 0.57, 0.74). For Alb, the cutoff was 30.85 g/L (sensitivity: 0.729, specificity: 0.522), with an AUC of 0.628 (95% CI: 0.54, 0.72). For age, the cutoff was 69.5 years (sensitivity: 0.876, specificity: 0.348), with an AUC of 0.609 (95% CI: 0.58, 0.77). For Cr, the cutoff was 69.5 mmol/L (sensitivity: 0.720, specificity: 0.522), with an AUC of 0.621 (95% CI: 0.53, 0.71) (Table 2). The K-M survival analysis revealed significant differences between the two groups, based on the cutoff values of the variables. Specifically, the Na, Tb, Alb, age, and Cr showed highly significant associations with survival ($p < 0.0001$ for Na, $p = 0.0055$ for Tb, $p = 0.00016$ for Alb, $p < 0.0001$ for age, and $p = 0.036$ for Cr). The Amm-ULN did not reach statistical significance ($p = 0.068$), which exceeds the conventional threshold of 0.05 for statistical significance. Notably, in the LASSO regression analysis, Amm-ULN ranked second, suggesting that despite not reaching statistical significance, it still holds considerable weight in the model and may be a significant predictor that warrants further investigation. Meanwhile, there was a significant difference in K-M survival curves in different grades of the ascites ($p = 0.0057$) (Fig. 3B–H).

Predictive performance of the RF model

The individuals who died during the 1-year follow-up period exhibited significantly higher scores across the risk scores compared to the survivors: CTP scores were notably higher (8 vs. 7, $p < 0.001$), as were MELD scores (11 vs. 9, $p < 0.001$), MELD-Na scores (11.7 vs. 8.9, $p < 0.001$), ALBI scores (–1.7 vs. –2.0, $p < 0.001$) and FIPS scores (–0.6 vs. –1.2, $p < 0.001$) (Table 1). Among these risk scores, the discriminative performances in predicting the 1-year transplant-free survival rate were the best for the RF model according to the AUC in the testing set and external validation cohort (Fig. 4A and B). In the testing set, the p-values for the comparison of the AUCs between the RF model and the CTP, MELD, MELD-Na, FIPS, and ALBI models using the DeLong test are as follows: RF vs. CTP ($p = 0.22$), RF vs. MELD ($p = 0.11$), RF vs. MELD-Na ($p = 0.23$), RF vs. FIPS ($p = 0.30$), and RF vs. ALBI ($p = 0.07$). In the external validation cohort, the p-values for the comparison of the AUCs between the RF model and the CTP, MELD, MELD-Na, FIPS, and ALBI models using the DeLong test are as follows: RF vs. CTP ($p = 0.05$), RF vs. MELD ($p = 0.07$), RF vs. MELD-Na ($p = 0.09$), RF vs. FIPS ($p = 0.04$), and RF vs. ALBI ($p = 0.02$). The calibration curve of the RF model showed a slope of 0.875, with an intercept of 0.446 in the testing set and a slope of 0.778, with an intercept of –0.449 in the external validation cohort, suggesting well calibration performance compared with other scores (Fig. 4C and D and Supplementary Fig. S1). In summary, the RF model demonstrates superior discrimination and calibration compared to other scoring systems, both in the testing set and the external validation cohort.

Youden's index was used to determine the cut-off value from the ROC curve analysis. Using the

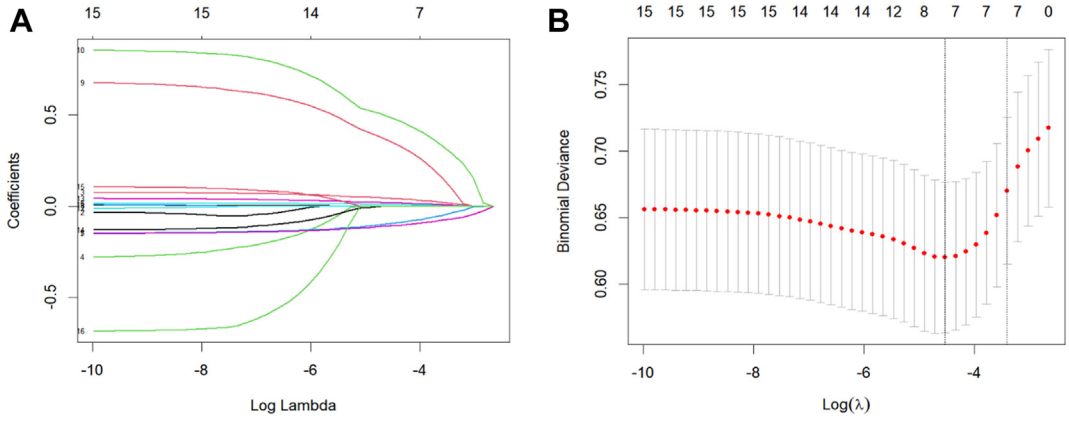

Fig. 2: LASSO feature selection for model construction. A The path of coefficients in a LASSO regression model as the regularization parameter - lambda. B The binomial deviance as a function of the log of the lambda parameter for LASSO regression. LASSO, least absolute shrinkage and selection operator; RF, random forest.

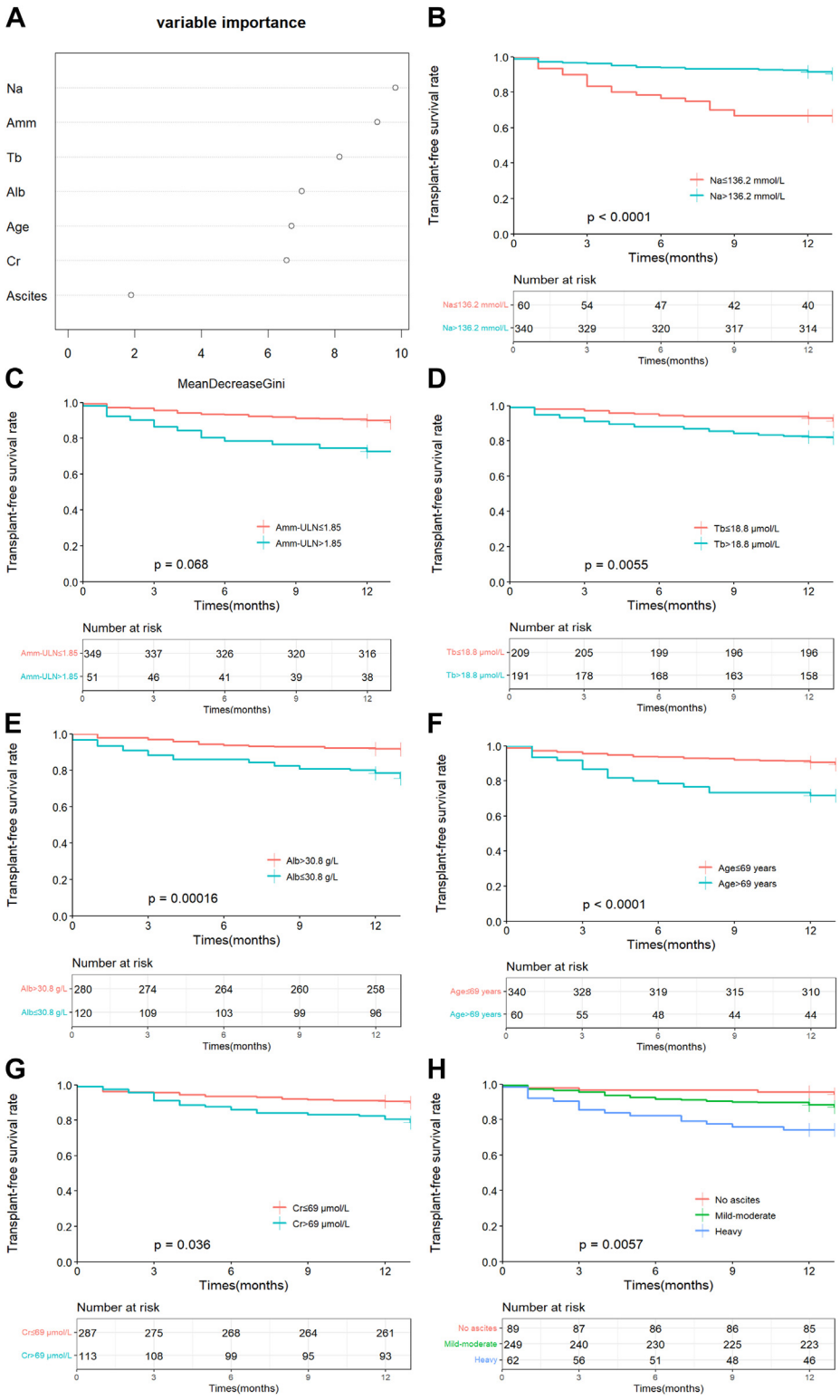

Fig. 3: Importance ranking of variables for RF model construction and K-M survival curves for each variable. Na, sodium; Amm, ammonia; Tb, total bilirubin; Alb, albumin; Cr, creatine. A Important ranking of features for the RF model construction. B 1-year transplant-free survival stratified according to the cutoff value of serum Na. C 1-year transplant-free survival stratified according to the cutoff value of plasma Amm. D 1-year transplant-free survival stratified according to the cutoff value of Tb. E 1-year transplant-free survival stratified according to the cutoff value of Alb. F 1-year transplant-free survival stratified according to the cutoff value of Age. G 1-year transplant-free survival stratified according to the cutoff value of Cr. H 1-year transplant-free survival stratified according to the grade of ascites.

	cutoff value	sensitivity	specificity	AUC
Na (mmol/L)	136.25	0.887	0.435	0.676 (95% CI: 0.52, 0.70)
Amm-ULN	1.85	0.893	0.283	0.581 (95% CI: 0.49, 0.67)
Tb (μmol/L)	18.85	0.554	0.717	0.652 (95% CI: 0.57, 0.74)
Alb (g/L)	30.85	0.729	0.522	0.628 (95% CI: 0.54, 0.72)
Age (years)	69.5	0.876	0.348	0.609 (95% CI: 0.58, 0.77)
Cr (μmol/L)	69.5	0.720	0.522	0.621 (95% CI: 0.53, 0.71)

Amm-ULN the ratio of plasma ammonia to the upper limit of the normal range. Tb, total bilirubin; Alb, albumin; Cr, creatinine.

Table 2: **The cutoff values and AUC values for each variable predict 1-year survival.**

established cut-off values 0.28 for the testing set and 0.22 for the external validation cohort, the patients were divided into the low- and high-risk subgroups. The results showed a significant difference in transplant-free survival rate between the two subgroups, with the high-risk subgroup exhibiting a markedly lower survival rate (Fig. 5).

In the testing set, the RF model had the accuracy, precision, recall, and F1 Score of 0.84 (95% CI: 0.76, 0.91), 0.84 (95% CI: 0.77, 0.91), 0.99 (95% CI: 0.95, 1.00), 0.91 (95% CI: 0.81, 0.10), respectively. In the external validation cohort, the RF model had the accuracy, precision, recall, and F1 Score of 0.88 (95% CI: 0.84, 0.91), 0.89 (95% CI: 0.85, 0.92), 0.99 (95% CI: 0.97, 1.00), 0.93 (95% CI: 0.85, 0.97), respectively. Then, the confusion matrixes for the testing set and external validation cohorh are shown in Fig. 6. In general, our RF model behaved efficiently and successfully.

Discussion

Although many risk scoring systems have been proposed, the present study for the first time proposes a ML-based prognostic model including plasma Amm in predicting poor survival for patients with cirrhosis after TIPS placement. This study developed a RF model by considering patients' basic features, and laboratory test

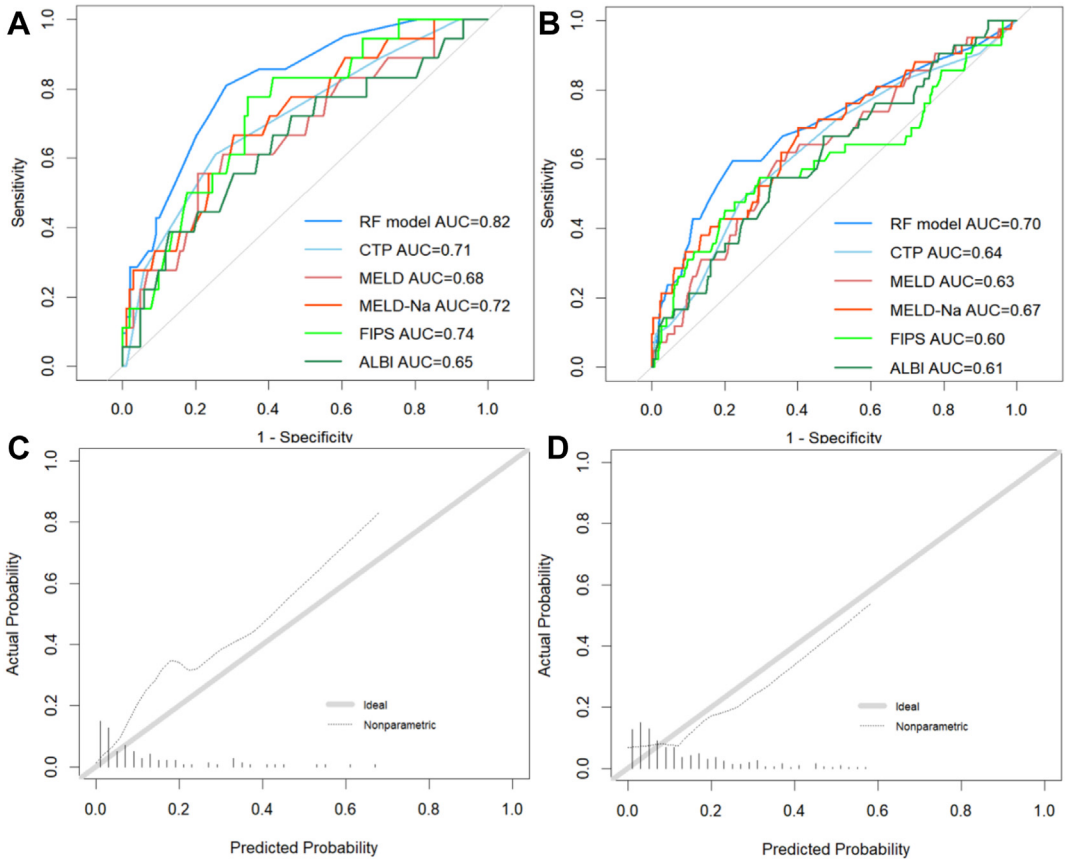

Fig. 4: The RF model performance in predicting post-TIPS 1-year transplant-free survival in the testing set and external validation cohort TIPS, Transjugular intrahepatic portosystemic shunt. A ROC curve of the RF model, CTP, MELD, MELD-Na, ALBI, and FIPS scores for 1-year transplant-free survival in the testing set: the AUC of the RF model was greater than that of the other scores. B ROC curve of the RF model, CTP, MELD, MELD-Na, ALBI, and FIPS scores for 1-year transplant-free survival in the external validation cohort: the AUC of the RF model was greater than that of the other scores. C Calibration curve of RF model in the testing set: a slope of 0.875 with an intercept of 0.446. D Calibration curve of RF model in the external validation cohort: a slope of 0.788 with an intercept of −0.449.

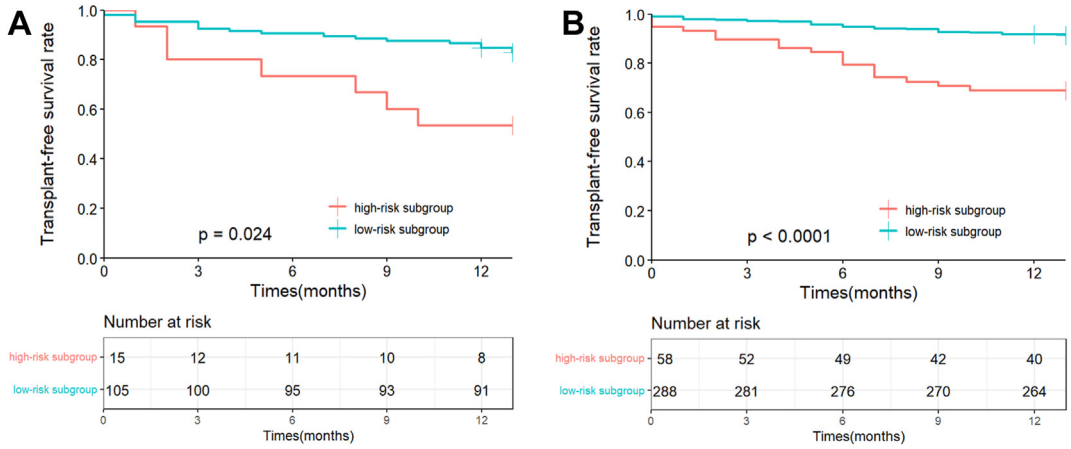

Fig. 5: The Kaplan–Meier survival curves for the low- and high-risk subgroups from the testing set and external validation cohort. A Kaplan–Meier survival curves in the testing set. B Kaplan–Meier survival curves in the external validation cohort.

indicators before TIPS implantation according to LASSO regression, with the accuracy, precision, recall, and F1 Score of 0.86, 0.86, 0.99, and 0.92 in the testing set, and 0.88, 0.89, 0.99, and 0.93 in the validation cohort, respectively, indicating a good predictive capacity in predicting poor survival after TIPS. At the same time, the RF model showed superior discrimination than the CTP, MELD, MELD-Na, ALBI, and FIPS scores via AUC in the testing set and external validation cohort.

TIPS placement is a proficient medical intervention for the management of portal hypertension along with its associated complications.[15–17] Several risk scoring systems have been proposed for risk stratification, including the CTP, MELD, MELD-Na, ALBI, and FIPS scores. The CTP score has been employed over decades to evaluate liver function and is currently the most frequently applied in clinical practice.[6] However, the CTP score incorporates highly subjective parameters such as the degree of ascites and the severity of HE, leading to considerable variability among observers. In the year 2000, the MELD score was initially formulated to predict early death after elective TIPS.[18] Then it was modified in 2001 by multiplying each coefficient by ten and rounding to the closest whole number.[6] In 2006, Biggins and colleagues introduced the sodium MELD (MELD-Na) score, integrating serum sodium levels into the MELD formula. This enhancement demonstrated superior predictive accuracy for the survival of end-stage liver disease patients awaiting liver transplantation, outperforming the traditional MELD score.[7] Our findings were consistent with this, indicating that MELD-Na possesses a heightened predictive power compared to MELD. The

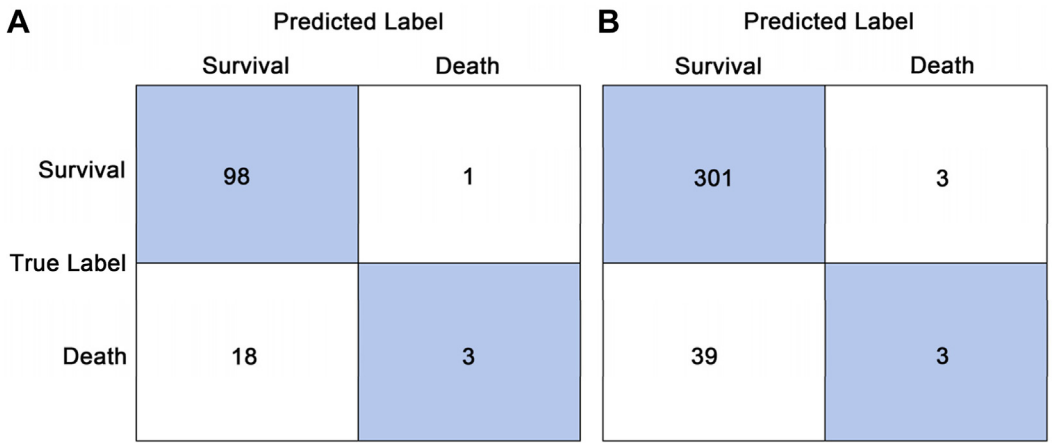

Fig. 6: Confusion matrix of the RF model predicted 1-year transplant-free survival in the testing set and external validation cohort. A Confusion matrix in the testing set. B Confusion matrix in the external validation cohort.

ALBI score, developed in 2015, serves to gauge liver function specifically among individuals with hepatocellular carcinoma.[8] In 2021, a novel scoring system known as the Freiburg index of post-TIPS survival (FIPS) was developed by Bettinger et al. in a German cohort. It was confirmed that FIPS surpasses the CTP, MELD, and MELD-Na scores in predicting poor outcomes for high-risk patients undergoing TIPS placement.[9] The ROC curve and AUC in our cohort showed that FIPS did have a stronger predictive power for 1-year survival after TIPS than other established scores in our cohort.

ML algorithms, an innovative approach for personalized risk assessment, can discern patterns within the complex, multi-dimensional datasets of numerous patients, thereby enabling the delivery of tailored predictive insights.[19] The RF model can uncover non-linear relationships between outcomes and variables, whereas Logistic regression (LR) is limited to identifying linear relationships. In this study, we identified Na, Amm, Tb, Alb, age, Cr, and ascites as significant predictors of 1-year transplant-free survival in patients with cirrhosis after TIPS placement according to LASSO regression analysis. Na, Tb, Alb, Cr, and the presence of ascites are significant predictors of survival in patients with cirrhosis,[20–23] which is confirmed by our research. Age has been also recognized as a critical prognostic indicator for patients after TIPS implantation. So, it has been incorporated into the FIPS score to enhance its predictive accuracy.[9] Our RF model encompasses nearly all the variables of existing risk scoring systems, which also explains why the performance of the RF model is superior to that of existing scores.

The breakdown and removal of plasma Amm primarily depend on the urea cycle and glutamine synthetase. In cirrhosis, impaired liver function diminishes the capacity of the two clearance mechanisms. Concurrently, these patients with cirrhosis also suffer from portal hypertension and portosystemic shunts, which contribute to hyperammonemia. As a result, they may experience episodic or persistent HE, or minimal HE, which is not clinically overt but can be diagnosed through psychometric testing and advanced brain imaging techniques.[24–26]

Studies also have shown that hyperammonemia can upset the skeletal muscle's protein homeostasis by diminishing the rate of protein production and enhancing autophagy, subsequently causing sarcopenia, linked to a higher risk of long-term mortality.[27] In 2022, a prospective study was undertaken to assess the link between plasma Amm and adverse outcomes in cirrhotic patients who are in a stable condition, finding that plasma Amm was reported as a crucial indicator of detrimental outcomes, including the likelihood of hospitalization, liver-related issues, and death.[28] The elevated ammonia level was linked to liver-related complications and predicted 30-day mortality in individuals with acute-on-chronic liver failure.[29] However, whether there is a correlation between plasma Amm and the clinical outcomes of patients with cirrhosis undergoing TIPS placement needs to be revealed. In the present study, we tried to put plasma Amm into a ML-based predicting model for the first time. The result showed that in the importance ranking of the seven features according to the random forest algorithm, Amm ranks second. Nevertheless, with additional attention to Amm, the RF model performed well in predicting poor survival in patients with cirrhosis after TIPS implantation and outperformed the CTP, MELD, MELD-Na, ALBI, and FIPS scores. This improvement allowed for a more precise prediction of poor survival and effective risk stratification in cirrhotic patients after TIPS placement.

In this study, we developed a RF model with strong predictive capabilities by incorporating plasma Amm levels. This model may assist in identifying high-risk patients after TIPS placement and facilitating timely interventions in clinical practice. Of course, the present study had several potential limitations. First, many patients had to be excluded because of baseline plasma Amm deficiency and lost to follow-up within 1 year, which resulted in potential bias in patient selection. Second, the study was a retrospective study with all its inherent limitations. Third, the comprehensive statistical methods we employed strengthened the reliability of our findings, yet there remains the possibility that unaccounted variables could affect clinical outcomes.

In conclusion, a RF model was developed and validated to have superior predictive performance than established scoring systems for poor survival in patients with cirrhosis undergoing elective TIPS placement, which might provide additional assistance for clinicians to identify the high-risk patients with a worse prognosis after elective TIPS placement. However, more studies are essential to evaluate the effectiveness of this model on other populations.

Contributors

BD, LW, MZ, YZ, and FZ was responsible for developing the models and drafting the manuscript. BD, HC, WW, WG, AZ, QY, JG, JX, and JC undertook data collection and curation. LW, MZ, YZ, and FZ contributed expertise in clinical study design and provided primary oversight of the analyses. BD participated in the literature review and validation of statistical results. The initial draft was reviewed by all the authors, who subsequently approved the final manuscript. All authors had access to and verify the underlying study data. And all authors read and approved the final manuscript.

Data sharing statement

The datasets used during the current study are available from the corresponding author upon reasonable request.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103001.

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