Construction of a prognostic nomogram for transarterial chemoembolization combined with ^{125}I seed implantation for hepatocellular carcinoma with portal vein tumor thrombus: a multicenter retrospective study

Xiao-Hui Zhao
The Affiliated Cancer Hospital of Zhengzhou University
Lei Zhao
Henan Red Cross Blood Center
Yan Zhao
The Affiliated Cancer Hospital of Zhengzhou University
Hai-Liang Li
The Affiliated Cancer Hospital of Zhengzhou University
Zhen Li
The First Affiliated Hospital of Zhengzhou University
Guang-Shao Cao
Henan Provincial People's Hospital, People's Hospital of Zhengzhou University
Hong-Le Li
The Affiliated Cancer Hospital of Zhengzhou University
Shi-Jun Xu
The Affiliated Cancer Hospital of Zhengzhou University
Hong-Tao Hu (huhongtaogy@163.com)
The Affiliated Cancer Hospital of Zhengzhou University

Research Article

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Abstract

Background: To investigate the efficacy of transhepatic arterial chemoembolization (TACE) combined with ^{125}I seed implantation in patients with first-branch portal vein tumor thrombus (PVTT) hepatocellular carcinoma (HCC), establish a prognostic nomogram to determine the prognosis for individual patients.

Methods: We retrospectively collected 102 cases of TACE combined with ^{125}I seed implantation in our hospital as the primary cohort. The main observation index of the results of the study was the median overall survival (mOS). Univariate analysis and LASSO regression with cross-validation were used to screen the variables. The selected variables were included in the multivariate Cox survival regression model, and a prognostic nomogram was developed. The performance of the nomogram was assessed with respect to calibration, discrimination, and clinical usefulness. The internal and external verifications were evaluated.

Results: The mOS of all patients was 13.5 months. The final determination was made using the Child-Pugh score, tumor burden, and PVTT types to establish a nomogram prediction model [C -index :0.740 (95% CI: 0.692-0.788), C-index: 0.732 through internal validation]. The model demonstrated good discrimination and calibration. Application of the nomogram to the external verification data still yielded good discrimination [C-index: 0.731(95% CI: 0.656–0.806)], and good calibration. The decision curve analysis demonstrated that the clinical validity of the model is clinically useful.

Conclusion: TACE combined with ^{125}I seed implantation indicated better long-term outcomes in patients with HCC combined with type II PVTT. This nomogram can be used to predict the prognostic survival time of such patients and help doctors make decisions in clinical practice.

1 Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors of the digestive tract. It is highly malignant and has a low survival rate (1–2). Portal vein tumor thrombus (PVTT) is a common vascular metastasis route for HCC, and 60–90% of patients with advanced HCC have PVTT (3). The Barcelona Clinic Liver Cancer (BCLC) system is the most widely adopted HCC management guideline (4). According to this system, HCC with PVTT is categorized as BCLC stage C. Although survival after systemic therapy for HCC has improved in recent years, it is still accompanied by poor prognosis of patients with PVTT. It still has a low median survival of 2.7–4.0 months for those who are untreated (5). According to the BCLC system, transarterial chemoembolization (TACE) is the standard treatment option for advanced HCC. However, PVTT is often accompanied by portal hypertension, intrahepatic metastasis, and liver function deterioration (6–7), making the effect of TACE treatment extremely limited. Other reported treatment methods, including ^{90}Y radioembolization, stereotactic body radiotherapy, systemic therapy, targeted therapy, and immunotherapy have shown some curative effects; however, there is no consensus on PVTT (8–11).

Currently, ^{125}I is widely used in the treatment of HCC and other malignant tumors (12–13). ^{125}I seed implantation exhibits strong targeting and high conformability. The radiation dose received by tumors increases significantly, while the radiation dose to normal tissues does not increase. This therapy has the advantages of minimal damage to normal tissue, high quality of life, and a short hospital stay (14). At the same time, ^{125}I seed implantation for PVTT significantly prolongs the median survival time of PVTT patients (15–17). A prospective study in China also showed that ^{125}I seed implantation therapy had a greater effect on type II PVTT than TACE combined with sorafenib (TACE-S) (18). Some HCC patients with PVTT can use the ^{125}I seed implantation method to achieve tumor reduction and obtain better curative effects and survival (19).

Despite clinical reports on the efficacy and safety of ^{125}I seed implantation in the treatment of PVTT, there is no nomogram for predicting the survival of patients with HCC and PVTT after ^{125}I seed implantation with TACE. Therefore, this study aimed to evaluate the tumor response and prognostic factors of 102 HCC patients with type II PVTT who received ^{125}I seed implantation. A nomogram was constructed and validated based on the clinical characteristics to predict the prognosis of individual patients.

2 Materials And Methods

2.1 Patient Information

This study retrospectively collected clinical data from HCC patients with type II PVTT who underwent TACE with ^{125}I seed implantation at the our hospital,and two other hospitals from June 1,2016 to December 31,2019.

The inclusion criteria were as follows: (1) 18–80 years old patients; (2) diagnosis of HCC based on the Practice Guidelines Committee, American Association for the Study of Liver Diseases (20). The diagnosis of PVTT is based on pathological diagnostic criteria or if the diagnosis of liver cancer is definite and there are imaging signs of PVTT; (3) Child-Pugh grade of A or B (score $\leq$ 7); (4) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; (5) patients who are unsuitable for surgery or are not eligible for resection; (6) no history of chemotherapy, radiotherapy, systemic therapy, targeted therapy, or immunotherapy; (7) no severe comorbidities, such as serious cardiac dysfunction, severe liver malfunction, and renal failure; and (8) no history of severe iodine allergy.

2.2 Classification of PVTT

This study adopted the Cheng's classification (21) and divided the patients into four types depending on the degree of PVTT invasion of the portal vein: I0: microscopic tumor thrombosis; type I: tumor thrombus involving secondary and above secondary portal vein branches; type II: cancer thrombus involving the first-level portal vein branch; type IIa: cancer thrombus involving one lobe and first-level portal vein branch, such as the left or right portal vein; type IIb: tumor thrombus involving the two-lobe first-level

portal vein branch, that is, involving the left and right portal vein stem; type III: cancer thrombus involving the main portal vein; and type IV: cancer thrombus involving the mesentery and superior mesenteric vein or inferior vena cava.

The imaging characteristics of PVTT include actual space-occupying lesions in the portal vein at each stage, enhancement in the arterial phase, and filling defect in the portal vein. At the same time, multi-phase enhanced computed tomography (CT) or dynamic enhanced Magnetic Resonance Imaging (MRI)is used to diagnose PVTT, where it is manifested as portal vein lumen thickening and intravascular low-density filling defect. Type II PVTT was mainly included in this study.

All patients provided written informed consent to receive treatment, and this retrospective study was approved by the ethics committee of each hospital.

2.3 TACE Procedure

After using a 5F RH catheter (Termao, Japan) with guide wire to guide routine angiography, the arterial cannula was super-selected to enter the blood supply branch of the tumor. As per previous reports, according to the liver function of the patient, tumor size, and body surface area, 30–50 mg/m^2 (Haizheng Pharmaceutical Co. Ltd., China) and 5–20 ml of super-liquid lipiodol (Guerbet, France)were used and then slowly passed through the catheter after mixing. Arterial infusion chemotherapy was injected, and gelatin sponge particles (500–700 um in diameter, Hangzhou Alikang Medical Technology Co., Ltd., China) were used to supplement the embolization for those who still had residual blood after embolization with iodized oil emulsion. Attention was given to possible participation during surgery. The artery supplying the tumor was embolized, and the endpoint of the embolization was the stagnation of blood flow in the artery supplying the tumor. If a hepatic artery-portal fistula was found during the operation, gelatin sponge particles of different sizes were selected to embolize the fistula according to the intraoperative angiography situation. If a hepatic artery-portal fistula was still found during the second angiography, a coil was used (China, Cook Medical Trading Co.) for mixed embolization.

2.4 ^{125}Iodine seed implantation procedure

Within 3–5 days after the first TACE, the patient's blood parameters, liver function, and coagulation indicators were re-examined. If the results demonstrated no contraindications to puncture, the patient was treated immediately with ^{125}I seed implantation in PVTT. First, a treatment planning system (TPS) (FTT Technology Ltd. Co, Beijing, China) was used to evaluate using the image results of preoperative CT examinations to preoperatively plan and determine the number of particles required, the total dose, the location of implanted particles, and the puncture route. Under CT guidance, following the angle and depth of the puncture needle track designed for the PVTT position, a special puncture needle for seed implantation was used for percutaneous PVTT puncture, and CT examination was performed. After the puncture needle entered the PVTT according to the predetermined route, the preoperative TPS plan was followed, and radioactive ^{125}I particles (Tianjin Xiehe Medical Technology Co., Ltd., China) were implanted. The particles were distributed with a spacing of 5 mm to ensure that the particles were evenly

distributed. The needle was removed after completion, the site was pressed for 3 min to stop the bleeding, and a bandage was applied, thereafter. A CT scan was performed to observe the position and quantity of the particles and to check for pneumothorax, hemorrhage, and exudation around the needle tract and the liver, after the implantation was completed. After seed implantation, TPS was used for evaluation. Seed replacement is required if the radiation dose distribution is poor.

2.5 Follow-up and evaluation

Patients were followed-up every 4–6 weeks after TACE. The follow-up included detailed evaluation of clinical manifestations, laboratory indicators, and imaging examinations. The imaging examination used was abdominal multi-phase enhanced CT or multi-phase dynamic enhanced MRI. The main goals of this study were to determine the survival rate of patients at 6, 12, and 18 months after surgery; the median overall survival (mOS); and the prognostic factors that affected the survival of the patients. The secondary goals were to determine were objective response rate (ORR) and treatment-related adverse reactions.

In this study, two associate radiology professors carefully observed the imaging data of patients and evaluated the efficacy of TACE followed by ^{125}I treatment on intrahepatic tumors and PVTT, based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Assessment results were categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (23, 24).

2.6 Statistical analysis

Chi-square and Mann–Whitney U tests were used to compare the differences among the three institutions in terms of baseline characteristics. The survival curve was calculated using the Kaplan–Meier method. All statistical tests were two-sided tests, and the P value < 0.05 indicated statistical significance.

The R program was used (version 4.1.2, Foundation for Statistical Computing, Vienna, Austria) in this program. Univariate Cox regression and LASSO regression with cross-validation were used to initially select variables, and a multivariate Cox survival regression model was used to establish two predictions models built from the different variables. The best model based on the time area under the curve (AUC), Akaike information criterion (AIC) were determined. The AIC value is the standard for measuring the goodness of fit of the statistical model. Thereafter, a prognostic nomogram was established. The performance of the nomogram was assessed by calculating the concordance index (C-index) with 1000 bootstrap resamples. The value of the c index ranged from 0.5 to 1. The higher the c index, the higher the prediction performance. Decision curve analysis (DCA) was used to evaluate the accuracy of the model and net clinical benefits. The flowchart of the analysis is shown in Fig. 1.

3 Results

3.1 Baseline Characteristics

A total of 102 patients were enrolled from June 1, 2016, to December 31, 2019. Of all enrolled patients, 56 had type IIa PVTT and 46 had type IIb PVTT. The detailed baseline characteristics, including sex, age, ECOG score, Child-Pugh score, tumor number, maximum tumor diameter, tumor burden, type of PVTT, AFP level, and blood test results are shown in Table 1. There was no statistical difference in baseline characteristics between the different types of PVTT.

Table 1
Baseline characteristics of patients with type IIa and IIb PVTT in the primary cohort

Variable	IIa type PVTT (n = 56)	IIb type PVTT(n = 46)	SMD(*t*)	*P*-value
Sex (M/F)	51/5	41/5	0.065	1.000
Age	57.00 ± 10.61	57.28 ± 9.46	0.028	0.889
ECOG (0/1–2)	52/4	39/7	0.258	0.323
Child-Pugh score(5/6/7)	29/20/7	16/23/7	0.351	0.222
Tumor number	3.45 ± 2.38	3.54 ± 2.30	0.041	0.836
Maximum diameter	6.79 ± 3.48	7.29 ± 4.12	0.132	0.504
Tumor burden	10.24 ± 4.30	10.84 ± 5.26	0.125	0.527
Tumor distribution (Right or Left/Bilobar)	27/29	24/22	0.079	0.842
Preoperative AFP	316.28 ± 463.80	428.06 ± 479.72	0.237	0.236
Ascities(none/have)	38/18	25/21	0.280	0.233
TBL(umol/L)	18.71 ± 9.44	21.17 ± 12.75	0.219	0.268
Albumin(g/L)	39.42 ± 5.03	39.39 ± 4.20	0.007	0.971
WBC($\times 10^9$/L)	5.05 ± 1.75	5.34 ± 2.08	0.152	0.442
RBC($\times 10^{12}$/L)	4.22 ± 0.56	4.34 ± 0.55	0.218	0.277
HGB (g/L)	132.48 ± 16.30	130.87 ± 17.46	0.0.95	0.631
Unless otherwise indicated, data are presented as numbers of patients.				
Data are presented as mean (standard deviation)				
Abbreviations: AFP = alpha fetoprotein, ECOG, Eastern Cooperative Oncology Group; HGB = hemoglobin, PT = prothrombin time, PVTT, portal vein tumor thrombosis; RBC = red blood cell, TACE = transarterial chemoembolization; TBL = total bilirubin, WBC = white blood cell				

3.2 Evaluation of the efficacy of intrahepatic lesions and PVTT

The objective response rate (ORR) of intrahepatic lesions in type IIa PVTT and type IIb PVTT group were 57.78% and 77.19%, respectively. The ORR of intrahepatic lesions in the type IIa PVTT group was significantly higher than that in the type IIb PVTT group (χ^2 = 4.403, P = 0.036). The ORRs of the two types of PVTT were 46.67% and 75.44%, respectively, with a statistical difference between the two (χ^2 = 8.906, P = 0.003) (Table 2).

Table 2
The objective response rate of intrahepatic lesions and portal vein tumor thromboses

	Intrahepatic lesions		**PVTT**	
	IIa type PVTT	IIb type PVTT	IIa type PVTT	IIb type PVTT
CR	4	1	5	0
PR	40	25	38	21
SD	9	13	10	16
PD	4	6	4	8
ORR	77.19%	57.78%	75.44%	46.67%
Unless otherwise indicated, data are numbers of patients.				
Abbreviations: CR = complete response, ORR = objective response rate, PD = progressive disease, PR = partial response, PVTT = portal vein tumor thrombosis, SD = stable disease				

3.3 Survival analysis

As of June 30,2021, the mOS of all patients was 13.5 months; the survival rates at 6, 12, and 18 months were 85.3%, 53.3%, and 27.9%, respectively; and the mOS of type IIa and type IIb were 15.3 and 7.9 months, respectively. The OS curve, PVTT type, and survival curves of the three centers are shown in Fig. 2.

3.4 Preliminary screening of variables

As shown in Fig. 3, the univariate Cox regression and LASSO regression with cross-validation were used as preliminary screening variables. The results showed that the variables for univariate Cox regression screening were Child-Pugh score, tumor number, maximum diameter, tumor burden, and PVTT type. LASSO regression with cross-validation showed that the screening variables were the Child-Pugh score, tumor burden, and PVTT type.

3.5 Build different models and compare them

The multivariate Cox survival regression model and stepwise backward regression were used to determine the final model variables with the minimum AIC. These variables were then modelled using a multivariate Cox survival regression.

The results showed that the variables (model 1) from univariate Cox regression screening to be analyzed by multivariate Cox survival regression model were Child Pugh score, tumor number, maximum diameter, and PVTT type. The variables selected by LASSO regression with cross-validation did not change after multivariate Cox survival regression model analysis (model 2), including the Child-Pugh score, tumor burden, and PVTT type.

The time AUC curve showed that the AUC values of models 1 and 2 were very close majority of the time (Fig. 4). Although the AIC values of Model 2 were smaller than of Model 1, both models were further analyzed for verification; hence, Model 2 were chosen.

3.6 Development and validation of an individualized prediction model

The independent predictors related to the two models identified by multivariate Cox regression analysis are shown in Table 3. A model that incorporated these independent predictors was developed and presented as a nomogram (Fig. 5). The calibration curve for median survival probability showed a moderate level of consistency between the predicted and observed results.

Table 3
Risk Factors Affecting Survival in Two Models

	Model 1			Model 2		
Intercept and Variable	β	Odds Ratio (95% CI)	P	β	Odds Ratio (95% CI)	P
Intercept	5.14		< 0.001	5.139		< 0.001
Child-Pugh Score	-0.227	1.602(1.143–2.245)	< 0.001	-0.227	2.566(1.306–5.044)	0.006
PVTT types	-0.463	2.973(1.874–4.715)	< 0.001	-0.459	2.974(1.868–4.736)	< 0.001
Tumor burden	-0.044	1.115(1.059–1.174)	< 0.001	-0.048	NA	
Tumor number		NA		-0.042	1.543(1.086–2.193)	0.016
Maximum diameter		NA		-0.896	1.515(1.191–1.928)	< 0.001
C-index						
Primary cohort		0.740 (0.692–0.788)			0.727(0.653–0.801)	
Validation cohort		0.731(0.656–0.806)			0.735(0.661–0.809)	
AIC		627.3532			629.3473	
BIC		637.2169			641.6768	
NOTE. b is the regression coefficient.						

For internal validation, the C-index for the prediction nomogram was 0.740 (95% CI: 0.692–0.788) for the primary cohort, which was confirmed to be 0.732 via bootstrapping validation. Independent validation with good calibration was observed for the prediction of mOS in the validation cohort. The C-index of the nomogram for the prediction of mOS was 0.731(95% CI: 0.656–0.806).

3.7 Clinical usefulness

The DCA results for the nomogram are shown in Fig. 6. The decision curve demonstrated that if the threshold probability of a patient or physician was 12.5%, using the developed nomogram to predict median survival was more beneficial than using treat-all-patients or treat-none schemes.

3.8 Adverse reactions related to TACE and ^{125}I seed implantation

Most patients experienced mild adverse reactions related to TACE, including abdominal pain, nausea, and vomiting. After 3–7 days of symptomatic treatment, the patient's symptoms were relieved. No serious adverse reactions related to TACE was observed. Six patients (6/102) developed pneumothorax due to ^{125}I seed implantation. Among them, two patients with large intrathoracic gas were treated with closed thoracic drainage, and the other four patients received no special treatment. All patients with pneumothorax were re-examined at 1–2 weeks after the operation, which showed that the pleural air was absorbed. Ten (10/102) patients had minor subcapsular hepatic hemorrhage, in which the bleeding stopped after medication was administered. None of the patients experienced any adverse reactions related to surgery.

4 Discussion

4.1 Analysis of the curative effect of TACE combined with ^{125}I seed implantation

Previous studies have shown that the prognosis of patients with advanced HCC with PVTT is generally poor, and PVTT is a risk factor that affects the survival of patients with HCC (25). In this study, TACE combined with ^{125}I seed implantation was used to treat HCC patients with type II PVTT, and the mOS reached 13.2 months, which is similar to previous reports (15–18).

It has been reported that surgical resection may be a treatment for HCC with PVTT (26–28). However, most patients already lose the opportunity to undergo surgical resection by the time the tumor is discovered. Although TACE alone has a certain effect on patients with HCC and PVTT, its effect is often unsatisfactory, with a median survival time of only 7.1 months (29). Owing to obstruction of the portal vein caused by PVTT, reperforming TACE greatly reduces the blood supply to the liver, leading to liver tissue necrosis and liver function failure. Therefore, it is particularly important to control PVTT progression and reduce the occurrence of complete portal vein obstruction. In our study, ^{125}I seed implantation largely controlled the progress of PVTT, with an ORR of 65%. When PVTT is well controlled, the patient's liver function can be restored to a certain extent. At the same time, a prospective study reported that TACE combined with ^{125}I seed implantation has a certain effect on maintaining liver function (18). Therefore, for HCC patients with PVTT, it is particularly important to actively control PVTT.

Radiotherapy is also an important local treatment for PVTT (8). ^{125}I seed implantation is as effective as Stereotactic Body Radiation Therapy (SBRT) and Three Dimensional Conformal Radiation Therapy (3DCR) as IR therapy. A randomized, open-label clinical trial to compare the efficacy and safety of TACE combined with radiotherapy and sorafenib in the treatment of liver cancer and large vessel invasion (30) showed that, compared with sorafenib, the former can prolong progression-free survival and overall survival of patients, with an mOS of 13.1 months.

The PVTT classification is closely related to the prognosis and therapeutic effects of HCC. In our study, we conducted a subgroup analysis of type IIa and type IIb PVTT and compared the difference in survival. The results showed that the mOS of patients with type IIa PVTT was significantly higher than those with

type IIb PVTT. This may be because when only one branch of the portal vein is blocked by a tumor thrombus, the liver function is better, and the portal vein pressure is maintained relatively low compared to when both branches of the portal vein are blocked. Patients with type IIa PVTT have better liver function and lower portal pressure than patients with type IIb PVTT; therefore, they can withstand more treatment. Previous studies have shown that type III PVTT is an independent predictor of poor prognosis in such patients. The higher the degree of PVTT (31–33), the worse the treatment effect, which is similar to the results of the present study.

4.2 Analysis and clinical significance of predictive models

In this study, the results showed that Child-Pugh score, tumor burden, and PVTT Alpha fetoprotein (AFP) level were significant risk factors for OS. The prognostic factors of HCC have been shown to include maximum tumor diameter, tumor type, tumor stage, cirrhosis, Child-Pugh score, AFP level, and serological indicators of liver function (34–36), which are similar to the results of our study.

The “Six and Twelve” model proposed in the previous study is an excellent model for HCC treatment with TACE (37). This model indicates that patients with cumulative tumor size > 12 cm have a poor prognosis, and the mOS is only 15.8 months. This study also used the sum of tumor size (cm) and tumor number to evaluate the tumor burden. According to the characteristics of the enrolled patients, the standard deviation of the patient’s tumor burden was 10.51, indicating that the tumor burden was relatively large. However, it is worth noting that the "Six and Twelve" model does not evaluate vascular metastasis, and the appearance of PVTT undoubtedly increases the tumor burden and patient survival also deteriorate. We found that tumor size and number in model 1 were components of tumor burden, and their sum was equal to the tumor burden. Model 1 predicted the prognosis from tumor size and number, whereas Model 2 predicted the prognosis from the perspective of tumor burden, and the results are relatively inferior. The models established by the variables screened by different methods are not the same; however, the best model can be selected only on the basis of rigorous statistics based on previous research and practical clinical significance. This shows that even in patients with portal vein metastasis, the use of the sum of tumor size and number to evaluate intrahepatic lesions, combined with the treatment of PVTT, can be used for HCC patients with type II PVTT who undergo TACE combined with ^{125}I seed implantation therapy. According to the prediction model of this study, it is feasible to predict the prognosis of such patients.

A unique feature of this study was the development of a personalized predictive model to predict the prognosis of each patient. From the perspective of tumor burden, we constructed a nomogram to predict the mOS and combined the Child-Pugh score to predict the prognosis of type II PVTT from more perspectives. Previous studies and discussions have also illustrated the impact of the Child-Pugh score on HCC patients with type II PVTT.

Simultaneously, we evaluated the model from different angles, conducted external verifications, and obtained good results. In statistical analysis, the general model usually focuses only on the AUC value

when it is of interest, such as one or two years, or mOS. This study drew the time AUC curve and observed the AUC value at different time points. It can be more intuitive to compare the advantages and disadvantages of different models at different times.

Research based on TNM staging only focuses on the change in the size of the patient's tumor and whether it has metastasized (38) while ignoring the impact of clinical indicators and the overall patient survival. It is undoubtedly one-sided to consider the survival of patients solely based on tumor status, and the development of the nomogram provides a more comprehensive basis for judgment. At present, the nomogram has been shown to have a certain role in evaluating the prognosis of many cancer patients, including those with HCC and PVTT (39–41). It reflects the characteristics of the tumor and the patient's state, including additional clinical parameters. Therefore, the nomogram is considered more advantageous than the traditional staging method. Some researchers have proposed it as an alternative method or a new standard for guiding cancer treatment (42).

4.3 Security and limitations

In terms of safety, TACE combined with ^{125}I seed implantation for PVTT is well tolerated, consistent with the results of other studies (15–18).

This study has certain limitations. First, it is a retrospective study with a small sample size, which may have led to selection bias. The results need to be further confirmed in prospective, multicenter, randomized controlled trials. Although the Child-Pugh score, tumor burden, and PVTT type were included in the nomogram as predictors, they showed a good predictive ability. Owing to the small number of indicators included in this study, more effective indicators may not be included. Therefore, the prediction efficiency of the model must be further improved.

In conclusion, there are still controversies about the treatment of PVTT, but most of the current research and clinical practice showed that for HCC patients with PVTT, combined treatment should be used to obtain better treatment results. This study showed that TACE combined with ^{125}I seed implantation is an effective method for the treatment of HCC with PVTT. Based on the "Six and Twelve" model, combined with the Child-Pugh score and PVTT type, it is a predictive model that can be used to predict mOS in patients with HCC and PVTT receiving treatment.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Conception and design: HTH

Patient selection and treatment: XHZ, HLL, LZ, GSC,

Data collection, analysis and interpretation: XHZ, YZ, SJX, HLL

Data interpretation: HTH, XHZ, YZ, SXJ, HLL

Undertook steering committee activities and critical statistical processing: HTH, YZ

Manuscript writing:XHZ, YZ

Manuscript reviewing: HTH

Ethics approval

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki, and was approved by the Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University review board.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent to participate

All of the patients sign in the informed consent form.

Consent for publication

None.

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Figures

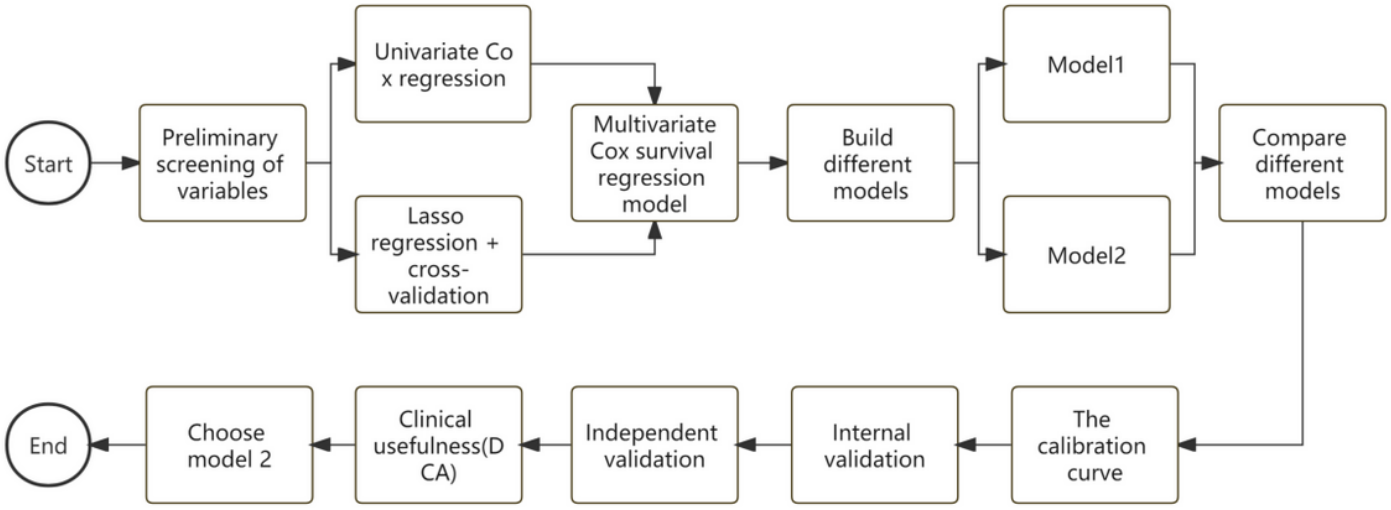

Fig1. Statistical analysis flow chart

Figure 1

See image above for figure legend.

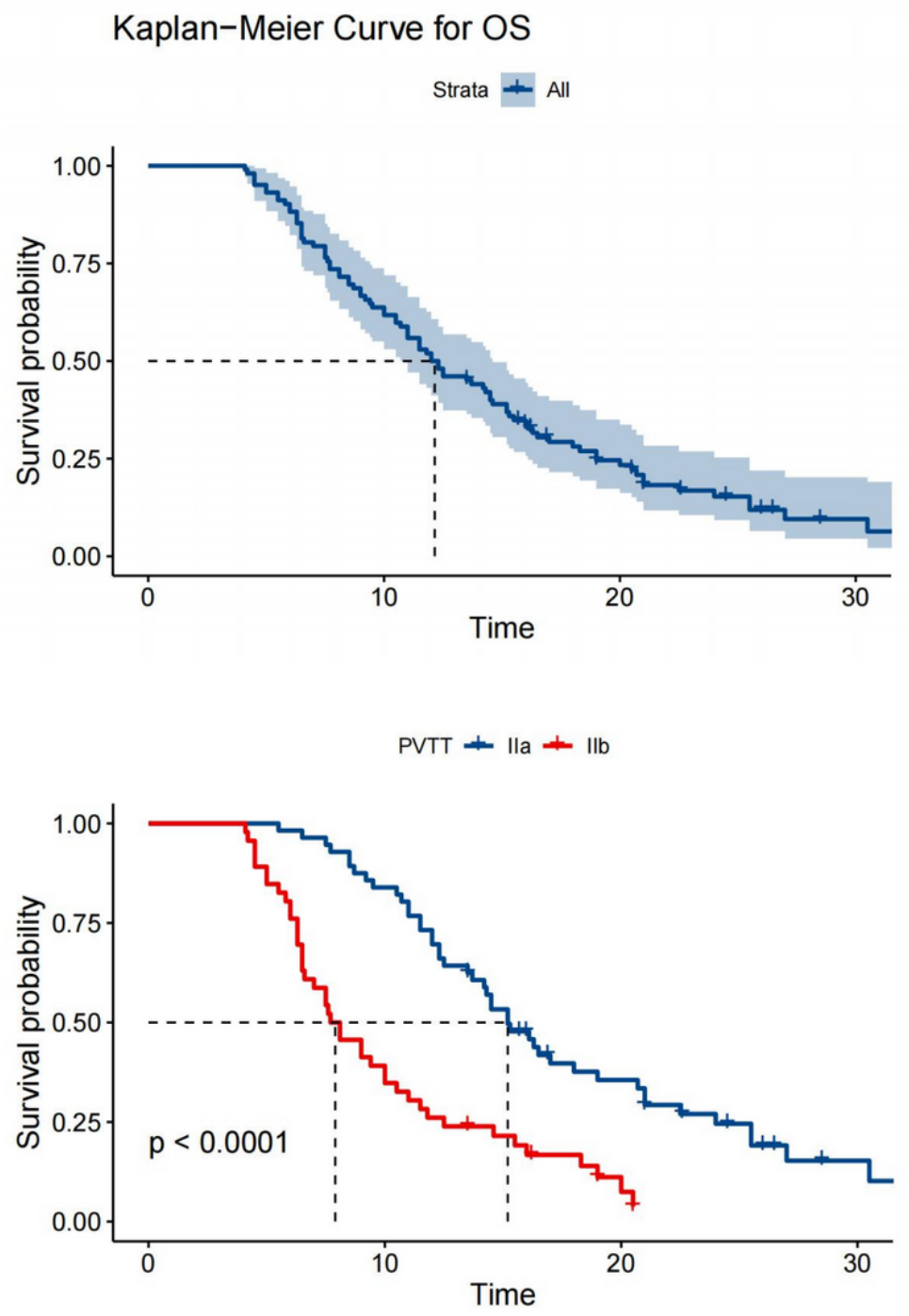

Fig. 2. Overall survival curve, PVTT type and survival curve of the three centers.(P < 0.001, log-rank test)

Figure 2

See image above for figure legend.

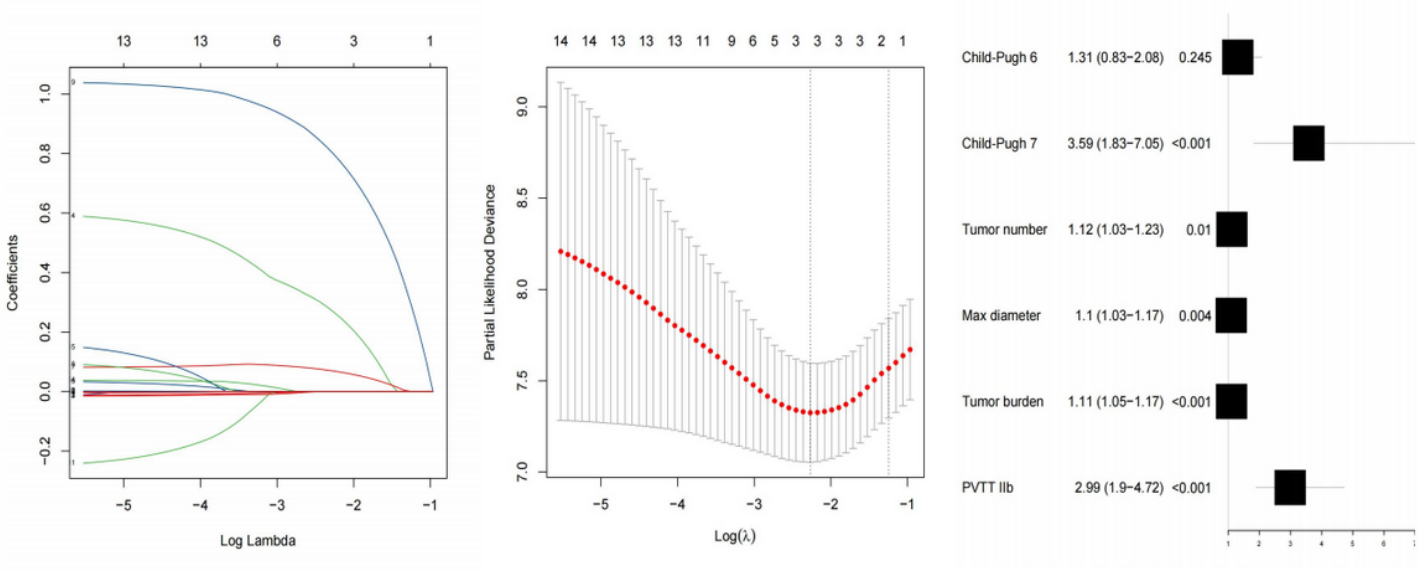

Fig3. Two ways (Univariate analysis and Lasso regression + cross-validation) to filter variables

Figure 3

See image above for figure legend.

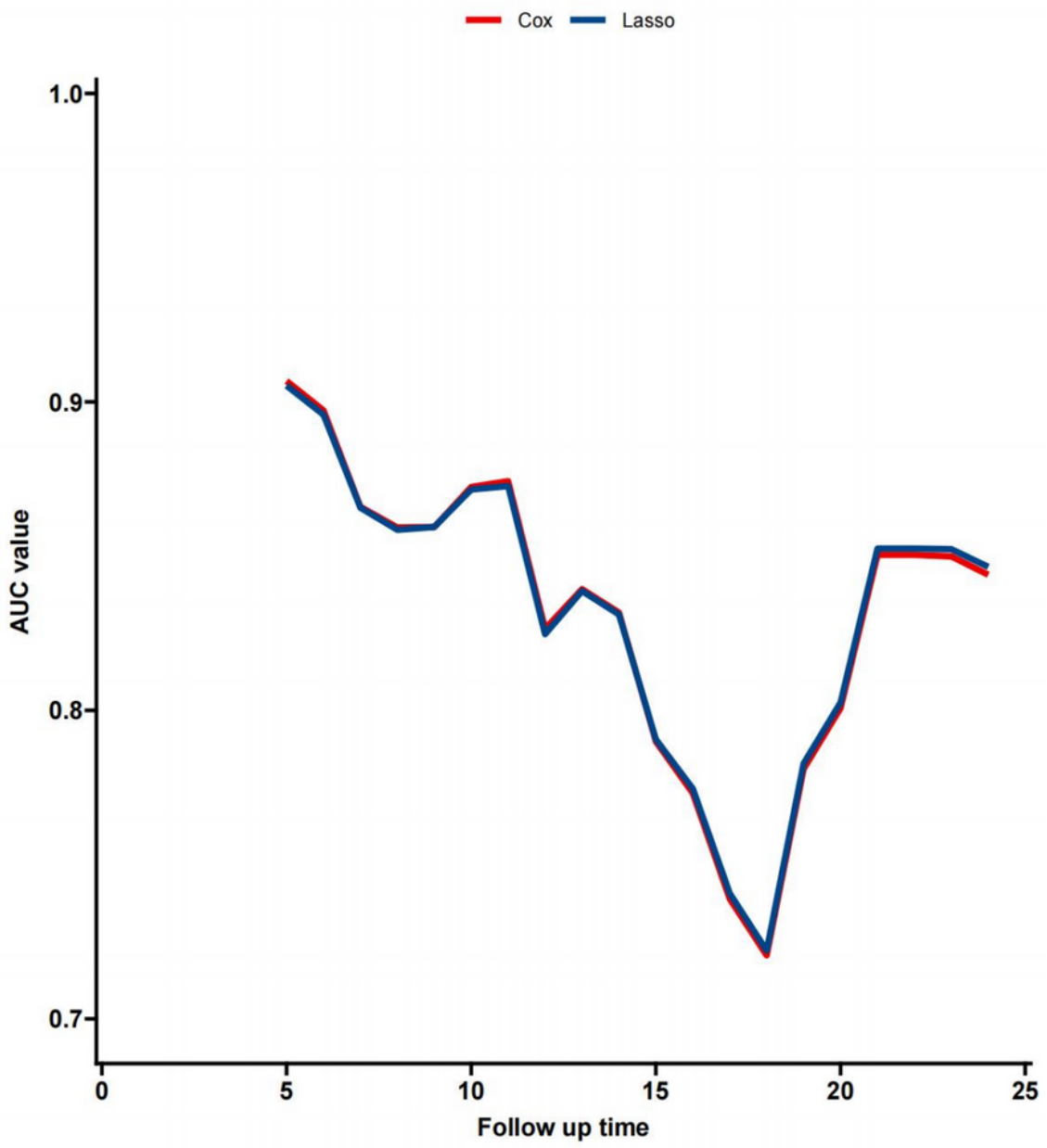

Fig 4. The time AUC (The model AUC changes over time. The time AUC curve represents the beginning of the first month to the end of 24 months, with an interval of 1 month)

Figure 4

See image above for figure legend.

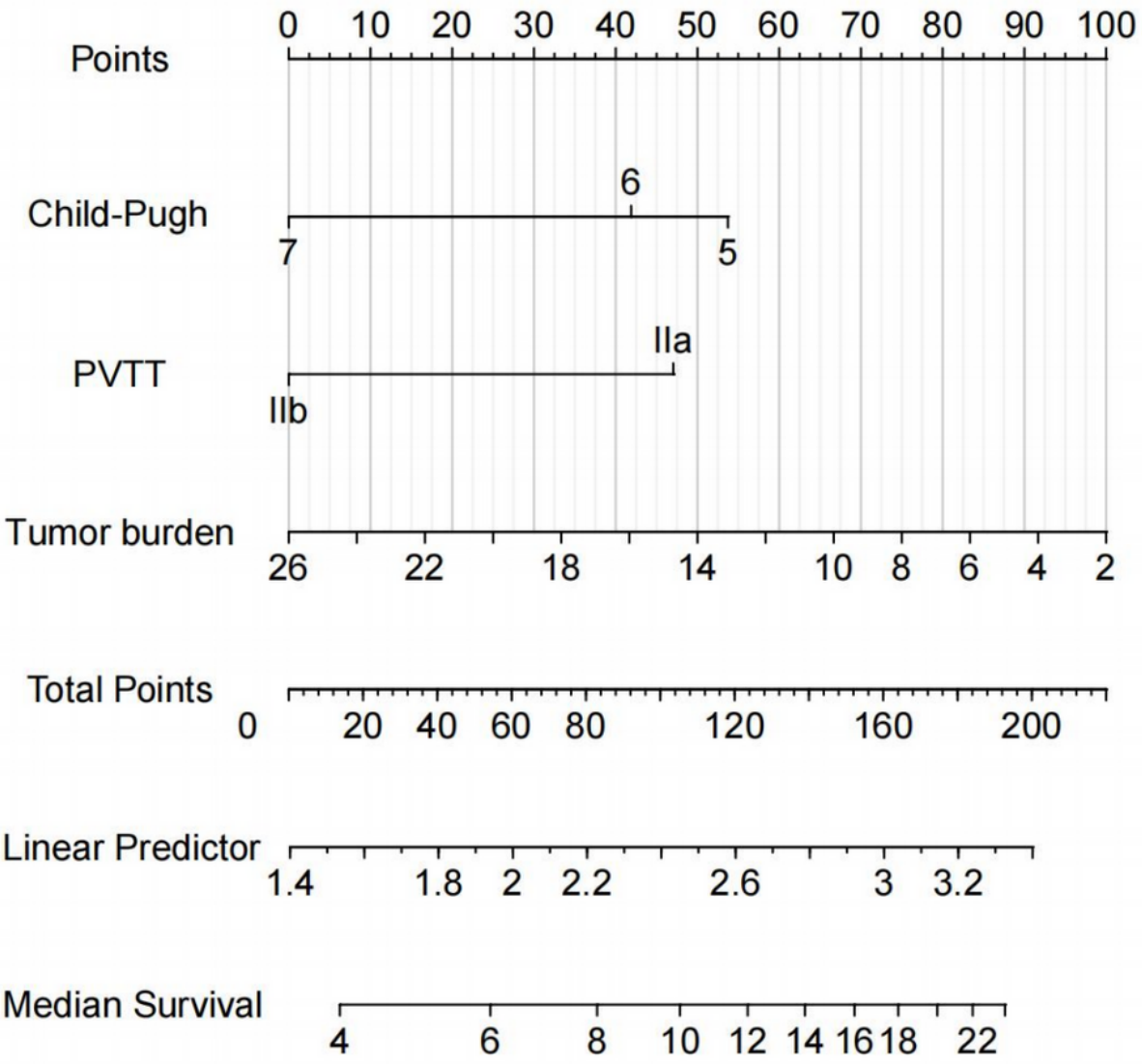

Fig 5.A nomogram for the prediction of median survival was established based on the multivariate Cox survival regression model.

Figure 5

See image above for figure legend.

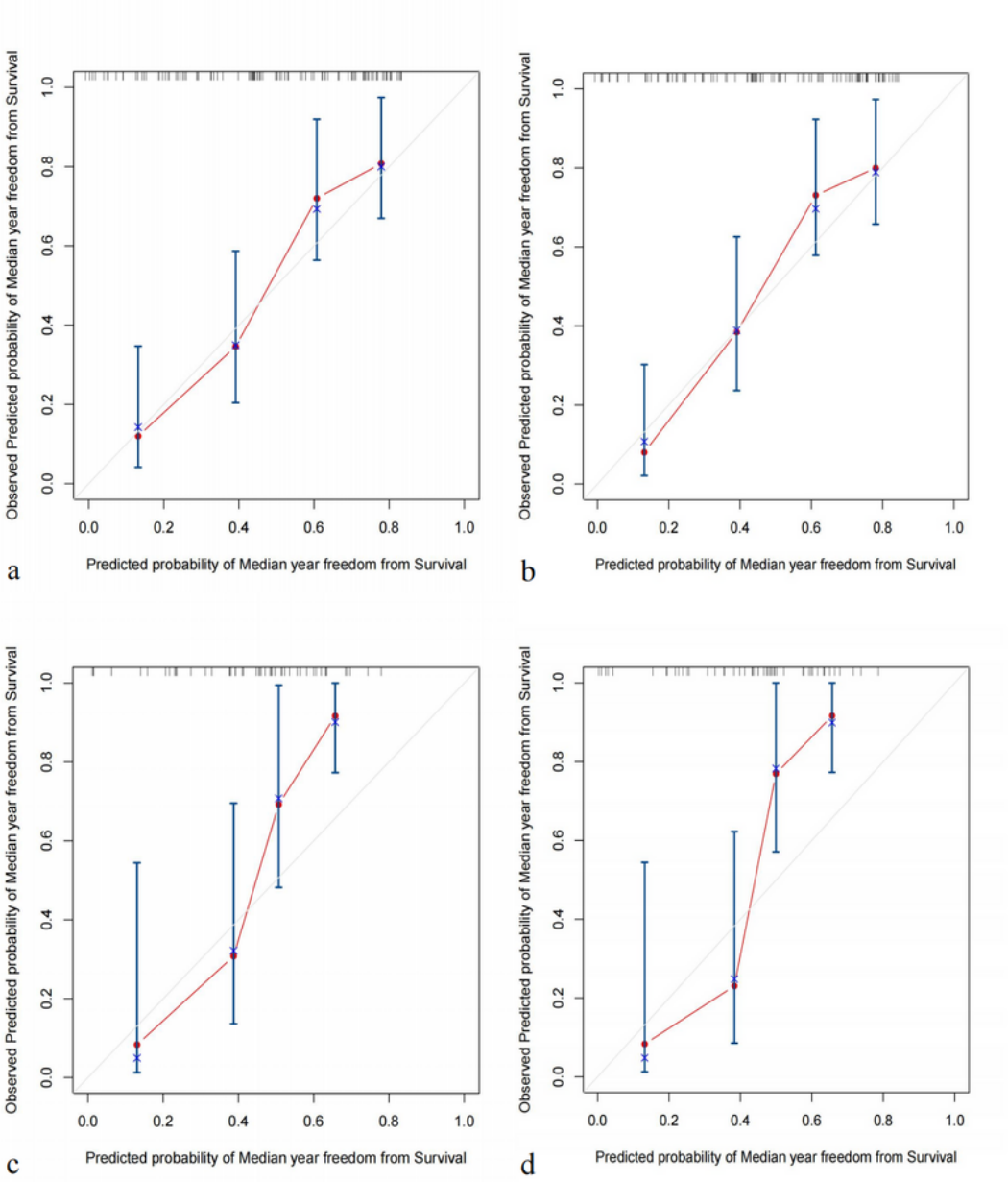

Fig 6. Nomograms for each cohort and calibration curves for the two prediction models. (a) Calibration curve of Model 1 nomogram in the main cohort. (c) Calibration curve of the Model 1 nomogram in the validation cohort. (b) Calibration curve of the Model 2 nomogram in the main cohort. (d) Calibration curve for Model 2 in the validation cohort. The calibration curves describe the calibration of each model in terms of the agreement between the predicted and observed mOS of mOS.

Figure 6

See image above for figure legend.

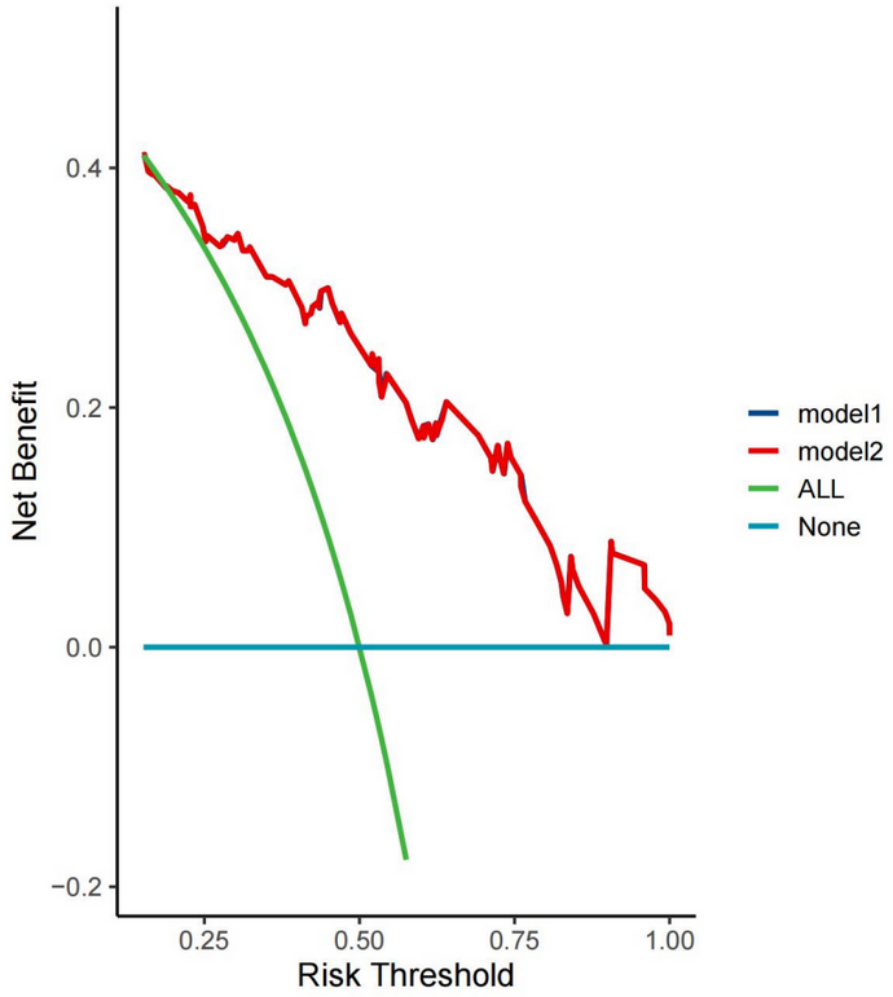

Fig 7. Decision curve analysis for the nomogram based on clinical characteristics. The broken line represents the nomogram. The thick line represents all negative samples. These participants received no interventions. The fine line represents all positive samples, and these participants received interventions

Figure 7

See image above for figure legend.