Scoring system for predicting postoperative pain after transarterial chemoembolization treatment in liver cancer

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Abstract

Purpose: Patients that experience severe postoperative pain are more reluctant to adhere the treatment. This study intends to identify the relevant risk factors and construct a scoring system for prediction.

Materials and methods: Liver cancer patients that underwent the first TACE treatment at the Second Affiliated Hospital of Chongqing Medical University from January 2019 to December 2020 were collected. The 11-point numerical rating scale (NRS-11) was utilized to evaluate the patient's pain level. The patients were randomly divided into a training and a validation cohort. In the training cohort, the correlation between each parameter and the pain level after TACE was evaluated through logistic regression, and a risk prediction model was established. Finally, the predictive power of the model was verified in the validation cohort.

Results: A total of 255 patients with liver cancer were included. In the training cohort, univariate analysis found postoperative pain was related to tumor number, tumor size, microsphere volume, and operation time. The above variables were then incorporated into the multivariate analysis to construct the prediction model. In the training and validation cohorts, the area under the curve (AUC) of the model used to predict moderate to severe pain response after TACE was 0.71 and 0.74, respectively. Additionally, we also created a nomogram for clinical use, patients with a total score greater than 72.90 are considered at a high risk of experiencing moderate to severe pain following TACE.

Conclusion: This study successfully constructed and validated a scoring system for predicting moderate to severe pain after an initial TACE treatment.

Introduction

Hepatocellular carcinoma (HCC) is currently considered the fifth most common cancer and the third leading cause of cancer mortality [1, 2]. Transarterial chemoembolization (TACE) has become the standard treatment for patients clinically diagnosed with intermediate and advanced liver cancer who are unable to receive radical treatment [3]. There are some risk factors associated with the prognosis of the patients undergoing TACE treatment, such as post-embolization syndrome (PES), this syndrome is characterized by a number of symptoms, notably pain [4-6].

There is increasing evidence that postoperative pain after TACE is associated with poorer outcomes, including longer hospital stays and higher readmission rates [7, 8]. Severe postoperative pain can cause significant physical and mental stress, making it more difficult for patients to adhere to and continue treatment. Therefore, screening for factors influencing postoperative pain after TACE, as well as prevent and manage them, is critical for avoiding postoperative pain and accelerating patients' postoperative recovery.

The main objectives of this study were to report the incidence of postoperative pain following TACE, identify the factors that influence postoperative pain following TACE, and develop and validate a pain

level prediction model following the first TACE treatment session for liver cancer.

Materials And Methods

Inclusion and Exclusion Criteria

From January 2019 to December 2020, patients with liver cancer who received their first TACE treatment session at the Second Affiliated Hospital of Chongqing Medical University were included in this retrospective study. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. The study was exempt from patient consent given the retrospective nature of the study and that data was stored anonymously.

The inclusion criteria were patients who underwent their first TACE session for treating liver cancer, diagnosis of liver cancer was primarily based on laboratory examinations and imaging data. Patients who had previously undergone TACE, or those with decompensated cirrhosis, serious cardiovascular and cerebrovascular diseases, renal insufficiency or dysfunction, preoperative infection (biliary tract infection, lung infection, urinary system infection, etc.), and a completely occluded portal vein with no collateral blood supply, were excluded from this study.

Pain Level Scoring

Postoperative pain levels were obtained based on the validated, verbally administered, 11-point (0 to 10 points) numerical rating scale (NRS-11) [9, 10]. Twenty-four hours before surgery, the nurse educated the patient on pain levels and taught the patient on how to use the NRS-11. Based on the patient's self-assessment, pain scores were incorporated into the nursing routine, monitored and recorded along with vital signs. After surgery, the patient was assessed for pain at least once a day. If the pain score was ≥ 4 , the frequency increased to four times per day.

The score was obtained before any treatments were made. If the score was between one and three, the patient was taught to relieve pain through distraction. If the score was between 4 and 6, the patient was prescribed a COX-2 inhibitor. If the pain score ≥ 7 , the doctor would modify the analgesic plan, this would usually include tramadol hydrochloride, dexocine or pethidine hydrochloride. We extracted the pain scores of each patient within 24 hours after operation and calculated the average value. Using the average value, the study subjects were divided into low score group (≤ 5 , no pain or slight pain) and high score group (> 5 , moderate to severe pain).

TACE Procedures

For femoral artery approach, the right femoral artery was punctured using the Seldinger puncture procedure through a 5F puncture sheath (American COOK). With the use of a contrast guide wire (150cm, US COOK), a contrast catheter (110cm, US COOK) was inserted to the abdominal trunk, common hepatic artery, or superior mesenteric artery, depending on tumor location. Then, a 2.4F micro catheter (28mc24130sn, MERIT) with the help of a micro guide wire (180cm, Meriton) was introduced into the

tumor target vessel for chemoembolization. Following the procedure, the puncture sheath was removed and a right femoral artery electronic compression hemostat (01-GF-A, RISING MEDICAL) was utilized to compress and halt bleeding.

For radial artery approach, the puncture site was selected to be approximately 1 cm from the patient's left hand to the proximal end of the radial process, i.e., the radial arterial pulse point. After local anesthesia, the site was punctured using a specialized single arm needle (PSI-4F-11-018, MERIT). The guide wire (LWSTDA35180, MERIT) and 4F vascular sheath (PSI-4F-11-018, MERIT) were then inserted and anticoagulant and antispasmodic (Heparin 2000u + Nitroglycerin 200ug + Normal saline 20ml) medicines were administered. Under fluoroscopy, a specialized 4F radial artery catheter (PV412538U1, MERIT) with the help of a guide wire was inserted into the phrenic artery, celiac trunk artery, common hepatic artery, superior mesenteric artery and renal artery, depending on tumor location. The micro catheter (Meriton 2.7f130cm) was then guided to the target vessel for chemoembolization with the help of a micro guide wire (28mc24150sn, MERIT). After the procedure was concluded, an arterial electronic compression hemostat (AP-S-180, RISING MEDICAL) was utilized to control the bleeding.

Statistical Analysis

SPSS Statistics 22.0 software and R software with “rms” and “nomogramEx” packages were used for statistical analysis. Continuous variables were expressed as mean $\pm$ standard deviation (SD), and independent sample t test was used for comparison between groups. Classification variables were expressed in terms of the number of cases and the corresponding proportion, and Fisher's test was used for comparison between groups. Logistic regression analysis was used to determine the risk factors for pain level after TACE treatment, and variables with $P < 0.1$ obtained from univariate analysis were included in multivariate analysis to build a predictive model. A nomogram was drawn based on the prediction model. The area under the receiver operating characteristic (ROC) curve was used to assess the predictive performance of various indicators for postoperative pain. The Youden index was used to judge the best nomogram score. The Hosmer-Lemeshow test and calibration plot were used to evaluate the consistency between the predicted and actual probability. To illustrate the clinical relevance of nomogram, decision curves are drawn to quantify the net benefit for patients at different threshold probabilities. A $P < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Data

A total of 255 patients who underwent initial TACE were screened for this study. Our study set the random number seed 20210101 and randomly divide the total cohort into training cohort ($n=170$) and verification cohort ($n=85$) in the ratio of 2:1. The general characteristics are shown in **Table 1**.

The patients in this study were 80.4 percent male, with an average age of 56 years. The liver function of most patients was classified as Child-Pugh A (85.5%), whereas 54.4 % had three or fewer tumors, while

45.6 % had more than 3 tumors. The average diameter of the largest tumor was 68.04mm, and 62.8% of patients had tumors diagnosed either as Barcelona stage C or D. The preoperative levels of alpha-fetoprotein (AFP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin (TBIL) of the patients were described in **Table 1**. In this study, 146 patients (57.3%) were treated with TACE through radial artery approach to alleviate postoperative discomfort induced by limb immobilization. Furthermore, most patients in this study received superselective embolization, with only 8 patients having no obvious tumor supply arteries therefore undergoing non-superselective embolization.

Before TACE, all patients have no presentation of pain. After TACE, we found that 20.1% of patients experienced moderate to severe pain. Personalized analgesic therapy based on the recommendations of members of a specialized pain team were implemented, and after appropriate pain management was attained using oral analgesics alone, the patients' pain could be relieved.

Univariate analysis and multivariate analysis in training cohort

In the training cohort, univariate analysis found potential correlation between tumor number [odds ratio (OR), 2.13; 95% confidence interval (CI): 0.94-4.81], tumor size of the largest tumor (OR, 1.01; 95%CI: 1.00-1.02), BCLC stage (OR, 3.72; 95%CI: 1.04-13.32), microspheres volume (OR, 1.05; 95%CI: 0.99-1.12), operation time (OR, 1.01; 95%CI: 1.00-1.02) and postoperative pain levels (all $P < 0.1$). Since the BCLC stage is associated with tumor number and tumor size of the largest tumor, the multivariate analysis only included tumor number, tumor size of the largest tumor, microspheres volume, and operation time. It was found that tumor size of the largest tumor (OR, 1.01; 95%CI: 1.00-1.02) was an independent risk factor for moderate to severe pain levels after TACE. The results of univariate and multivariate analysis are shown in **Table 2**.

Construction of prediction model and prediction efficiency analysis

The prediction model of postoperative pain levels after TACE consists of tumor number, tumor size of the largest tumor, microsphere volume and operation time and can be expressed using the following formula: $\text{logit}(p) = 0.702 \times \text{tumor number} + 0.011 \times \text{tumor size of the largest tumor} + 0.028 \times \text{microsphere volume} + 0.008 \times \text{operation time} - 3.447$. When these variables were applied, the area under the ROC curve for postoperative moderate to severe pain was 0.71 (0.62-0.80), suggesting that the model has a high degree of differentiation (**Figure 1A**). The Hosmer-Lemeshow test was performed to analyze the calibration of the prediction model, and it was discovered that the difference between the predicted and actual values of the model was not statistically significant, indicating that the predicting model had high calibration ability (Hosmer-Lemeshow test $\chi^2 = 10.963$, $P = 0.204$; **Figure 1B**).

Validation of the prediction model

The validation cohort was used for verification. When utilizing the previously identified four indicators, the area under the ROC curve for moderate to severe postoperative pain is 0.74 (0.62-0.85), indicating that this model has a high degree of differentiation (**Figure 2A**). The Hosmer-Lemeshow test was again used

to evaluate the calibration of this prediction model, and was shown that the difference between the predicted and actual values of the model was not statistically significant, suggesting that the prediction model had high calibration ability (Hosmer-Lemeshow test $X^2 = 8.516$, $P = 0.385$; **Figure 2B**).

Predictive effect of nomogram on the risk of postoperative pain after TACE

We developed a nomogram of the prediction model using the training cohort for better clinical application (**Figure 3**). The scores for each patient were calculated using the tumor number, tumor size of the largest tumor, microsphere volume, and operation duration, with a cut-off value of 72.90 being used as a threshold. Patients in the training and validation cohorts were divided into two groups based on the cut-off value: high risk or low risk group. The incidence rate of post-TACE pain in the training cohort was higher in the high-risk group (29/98, 29.59%) than in the low-risk group (1/52, 1.92%) ($P=0.001$), and the incidence rate in the validation cohort was higher in the high-risk group (19/57, 33.33%) than in the low-risk group (0/19, 0%), with a statistically significant difference ($P=0.002$). Furthermore, the decision curve analysis indicate that the model is capable of accurately predicting postoperative pain (**Figure 4**).

Discussion

TACE is used as a first-line treatment for intermediate and advanced hepatic malignancy [3]. The number of newly diagnosed hepatic malignancies is growing, especially within mainland China, with many patients being clinically diagnosed with intermediate or advanced tumors. TACE's primary purpose is to reduce tumor size, and a vast number of publications indicate that TACE is associated with a considerable increase in overall survival, as well as helping some patients achieve a lower tumor stage, allowing them an opportunity for radical resection or liver transplantation.

However, there is a high incidence of postoperative complications following TACE [11-13]. Pain is by far the most prevalent post-TACE complication, and it was often associated with a prolonged hospital stay [14, 15]. As a result, postoperative pain management for TACE is viewed as one of the most important aspects of perioperative care. The underlying pathophysiological mechanism of pain following TACE is still not completely clear at this point. Acute ischemia of the liver parenchyma, ischemia caused by accidental embolization of the gallbladder artery, increased tension of the liver capsule caused by temporary hepatic swelling, chemical injury of the hepatic artery, and biliary tract ischemia are considered as possible contributing factors of postoperative pain after TACE. With regard to these factors, there were numerous reports on how to improve pain tolerance and reduce the effects of post-embolization syndrome after treatment. For example, the use of glucocorticoids, n-acetylcysteine, and even super-selective embolization of tumor supplying arteries has been shown to lower the risk of postoperative embolism syndrome and relieve patients' postoperative pain [16-18]. However, there are still few studies on the risk factors of pain and poor tolerance after TACE. As far as we know, no one has constructed and verified a prediction scoring system for pain occurrence after TACE treatment for liver cancer.

In our study, we found pain levels after TACE treatment for hepatic malignancies was correlated with tumor number, tumor size, microsphere volume, and operative time. Our results suggest that the tumor size of the largest tumor and number of tumors appear to be closely related to the occurrence of abdominal pain following TACE, which are consistent with previous reports [11, 19]. Both Ichid et al. and Poon et al. found that tumor size and number were associated with a poorer long-term survival rate and higher TACE-related mortality [20, 21]. Some experts even proposed that total tumor diameter be included as a contraindication for TACE [22]. Liver enzymes and bilirubin were found to be significant predictors of other postoperative complications of TACE such as acute liver failure, nausea or vomiting [23, 24]. However, in our study, no significant association was seen between these serological indications and postoperative pain following TACE. This is mostly attributable to the fact that in our center, when liver enzymes and bilirubin levels were more than three times higher than normal, TACE therapy was not performed until these signs improved. It has been reported that postoperative pain following TACE is associated to the underlying condition of the liver parenchyma, and that severe pain occurs significantly more often in patients without chronic liver disease, however according to their study results, patients with hepatic malignancy without chronic liver disease also had a higher tumor load than those with chronic liver disease [15]. So, the effect of underlying condition of the liver parenchyma on pain levels might be indirectly caused by higher tumor load. Whether there was an association between underlying condition of the liver parenchyma and pain levels still needs to be explored in the further study.

The size of microsphere diameter was also proved to be related to post-treatment tolerance [25]. But in our study, we did not include the size of microsphere diameter for analysis. The main reason is that we used a mixture of 100 um microspheres to 300 um microspheres for each patient. Our results show that the volume of microspheres administered was associated with postoperative pain, which is consistent with prior studies, indicating that modifying the dosage had an influence on postoperative complications [25]. Furthermore, contrary to another study's conclusion [18], our study did not find that superselective interventional embolization of tumor vessels had an effect on postoperative pain, this may be due to the fact that there were only a few number of cases without superselective embolization. Since lesions and their vessels can now be diagnosed much more accurately by CT and MRI, superselective embolization could be successfully conducted in most instances, and very rarely, not performed. As a result, superselective embolization has little influence on the construction of a scoring system for prediction.

Furthermore, our study revealed a relation between operating time and pain following TACE, which we felt was mostly due to differences in the number and diameter of tumors in the liver, that were also identified as a risk factor in this study. Moreover, patients with more and larger tumors frequently have more blood vessels, requiring a longer operation time. At the same time, arteriovenous fistulas may occur in certain patients' tumors, necessitating arteriovenous fistula embolization prior to TACE therapy for hepatic malignant tumor, resulting in a much longer operation time.

Our center strongly advocates an enhanced recovery after surgery (ERAS) program and has routinely performed TACE surgery for liver tumors using the radial artery approach, where several studies have

demonstrated the safety and effectiveness in improving patients' postoperative comfort [26]. In our study, we found no evidence that different puncture paths affected patients' pain levels following TACE. We can explain this by looking at the following factors. First, these studies primarily focus on the impact of various puncture pathways on overall body comfort, while pain mentioned in this study mostly pertains to discomfort in the right upper abdomen following TACE, that is, pain caused directly by TACE. Second, all the procedures were carried out by the same skilled interventional surgeon. Even though the puncture pathways varied, the surgical procedures in the liver (including surgical duration and microsphere dosage, among other things) would be relatively the same.

The identification of predictors aids in patient risk assessment, and the variables listed above were used in multivariate analysis to develop prediction models. As this model proved effective at predicting pain levels after TACE, we created a nomogram for clinical usage. Patients with a total score of > 72.90 are thought to be at a higher risk of developing moderate to severe pain following TACE. As a result, physicians evaluated the risk of pain following TACE in these patients, paid more attention to perioperative pain therapy, improved postoperative comfort, enhanced patient compliance, integrated the concept of ERAS, and avoided additional medical expenses.

There were several limitations to the study as well. It used a limited sample size of 255 patients from a single center, which may limit the ability to detect significant differences. In this relatively small data set, the internal validation employed in our investigation was limited, which may necessitate external validation to confirm our findings. At the same time, due to its retrospective nature, the results would include some discrepancies. Since we employed the NRS-11 to assess patients' pain levels after TACE, the results were subjective, which meant that pain levels after TACE may be exaggerated or underestimated. These shortcomings are expected to be improved in future large-scale prospective studies. In conclusion, while there are certain limitations to this study, it is the first study to present a prediction model of pain intensity following TACE for liver cancer, which is important for assessing pain risk.

Declarations

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Author contributions

YBW: conceptualization, data curation, formal analysis, writing—original draft. HSZ: data curation. HS: writing—review and editing. LC: formal analysis, supervision. JGW: writing—original draft, writing—review and editing, supervision.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request

Ethics statement

The study was performed in accordance with the Declaration of Helsinki. The study was reviewed and approved by Institutional Review Board and the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. The data are collected retrospectively and anonymous, so the requirement for informed consent was waived by the ethics committee.

Conflict of interest

None.

Acknowledgements

None.

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Tables

Table 1. Demographic and Clinical Data

Variables	Group	Total (n=255)	Training cohort (n=170)	Validation cohort (n=85)	P value
Sex	Male	205 (80.39%)	142 (83.53%)	63 (74.12%)	0.094
	Female	50 (19.61%)	28 (16.47%)	22 (25.88%)	
Age (year)		56±13	56±12	55±13	0.768
Child pugh grade	A	218 (85.49%)	151 (88.82%)	67 (78.82%)	0.065
	B	35 (13.73%)	18 (10.59%)	17 (20%)	
	C	2 (0.8%)	1 (0.6%)	1 (1.18%)	
Tumor number	≤3	124 (48.63%)	83 (48.82%)	41 (48.24%)	0.888
	>3	104 (40.78%)	68 (40%)	36 (42.35%)	
Tumor size of the largest tumor (mm)		68.04±46.38	64.77±41.96	74.41±53.69	0.138
BCLC stage	A	52 (20.39%)	37 (21.76%)	15 (17.65%)	0.076
	B	32 (12.55%)	26 (15.29%)	6 (7.06%)	
	C	141 (55.29%)	89 (52.35%)	52 (61.18%)	
	D	1 (0.4%)	0 (0%)	1 (1.18%)	
AFP level	≤400	163 (63.92%)	106 (62.35%)	57 (67.06%)	0.482
	>400	86 (33.73%)	60 (35.29%)	26 (30.59%)	
Preoperative ALT (U/L)		49.34±45.48	46.85±49.41	54.36±35.98	0.216
Preoperative AST(U/L)		69.87±125.31	61.67±85.17	86.27±180.22	0.235
Preoperative TBIL (umol/L)		25.21±108.10	18.30±27.59	39.02±183.08	0.302
TACE routes	Radial artery	146 (57.25%)	98 (57.65%)	48 (56.47%)	0.894
	Femoral artery	109 (42.74%)	72 (42.35%)	37 (43.53%)	
Supers elective TACE	Yes	247 (96.86%)	166 (97.65%)	81 (95.29%)	0.447
	No	8 (3.14%)	4 (2.35%)	4 (4.71%)	
Lipiodol (ml)		10.07±4.13	10.13±4.14	9.95±4.12	0.748
Microspheres volume (ml)		3.6±5.6	3.9±6.0	3.0±4.6	0.216
Pirarubicin (ml)		37.92±19.70	37.59±19.51	38.59±20.19	0.703

Lobaplatin (ml)		17.54±19.96	16.88±19.80	18.85±20.35	0.460
NRS-11 score	≤5	203 (79.61%)	138 (81.18%)	65 (76.47%)	0.507
	>5	51 (20%)	32 (18.82%)	19 (22.35%)	
Operation time (min)		86.87±38.03	86.87±38.03	83.15±32.79	0.443

Note: AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBIL = total bilirubin; TACE = transarterial chemoembolization; NRS-11 = 11-point (0-10) numerical rating scale.

Table2. Univariate and Multivariate analysis

Variables	Group	Univariable analysis		Multivariable analysis	
		OR (95% CI)	P value	OR (95% CI)	P value
Sex	Male/female	0.82 (0.30-2.23)	0.700		
Age (year)		1.01 (0.98-1.04)	0.484		
Child pugh grade	A	1 (Reference)			
	B	1.26 (0.38-4.10)	0.707		
	C	0.00 (0.00-NA)	1.000		
Tumor number	≤3	1 (Reference)		1	
	≥3	2.13 (0.94-4.81)	0.069	2.02 (0.84-4.84)	0.115
Tumor size of the largest tumor (mm)		1.01 (1.00-1.02)	0.007	1.01 (1.00-1.02)	0.032
BCLC stage	A	1 (Reference)			
	B	2.70 (0.58-12.48)	0.204		
	C	3.72 (1.04-13.32)	0.043		
AFP level	≥400/≤400	1.71 (0.77-3.81)	0.188		
Preoperative ALT (U/L)		1.00 (0.99-1.01)	0.530		
Preoperative AST (U/L)		1.00 (1.00-1.01)	0.568		
Preoperative TBIL (umol/L)		1.00 (0.99-1.02)	0.804		
TACE Procedures	TRA/TFA	1.80 (0.79-4.07)	0.162		
Superselective TACE	Yes/No	3.86E+8 (0-NA)	1.000		
Lipiodol (ml)		1.06 (0.97-1.15)	0.208		
Microspheres volume (ml)		1.05 (0.99-1.12)	0.090	1.03 (0.97-1.10)	0.372

Pirarubicin (ml)	1.01 (0.99-1.03)	0.329		
Lobaplatin (ml)	1.00 (0.98-1.02)	0.844		
Operation time (min)	1.01 (1.00-1.02)	0.044	1.01 (1.00-1.02)	0.117

Note: OR = odds ratio; CI = confidence interval; AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBIL = total bilirubin; TACE = transarterial chemoembolization.

Figures

Figure 1

ROC curve and calibration curve in training cohort

Note: In the training cohort, we drew the ROC curve to judge the predictive value of our scoring system for postoperative pain level. The results showed that the area under the ROC curve was 0.71 (**Figure 1A**). Similarly, the results of the calibration curve suggest that there is a high correlation between the possibility of predicted pain and the possibility of actual pain ($r = 0.68$, $P = 0.03$; **Figure 1B**).

Figure 2

ROC curve and calibration curve in validation cohort

Note: In the validation cohort, we drew the ROC curve to judge the predictive value of our scoring system for postoperative pain level. The results showed that the area under the ROC curve was 0.74 (**Figure 2A**). Similarly, the results of the calibration curve suggest that there is a high correlation between the possibility of predicted pain and the possibility of actual pain ($r = 0.80$, $P < 0.01$; **Figure 2B**).

Figure 3

Nomogram for predicting postoperative pain after TACE

Note: Using the data from the training cohort, we created a nomogram based on four variables: tumor number, tumor size of the largest tumor, microsphere volume, and operation time. This nomogram is convenient for clinical use to assess the risk of moderate to severe pain after TACE.

Figure 4

Decision curve analysis of the nomogram

Note: Decision curve analysis was conducted in the training cohort. The gray line indicates the condition that all patients have moderate to severe postoperative pain. The horizontal solid line assumes the condition that no patient has moderate to severe postoperative pain. As can be seen from the figure, when the high-risk threshold is 0 to 0.35, the net benefit rate is greater than 0, which is of clinical significance. Moreover, the smaller the value, the higher the net benefit and the greater the clinical significance.