



Predictive value of random forest prediction model based on postoperative adjuvant transcatheter arterial chemoembolization therapy for survival of hepatocellular carcinoma patients with microvascular invasion: a retrospective cohort study

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Background: Microvascular invasion (MVI), as an important stage of tumor cell invasion of blood vessels, is a key step for hepatocellular carcinoma (HCC) to metastasize into the liver and remote organs. Transcatheter arterial chemoembolization (TACE) is currently the most widely used adjuvant treatment after HCC surgery, which is used to treat tumor micrometastasis, and can inactivate residual tumor foci and reduce the recurrence rate. However, there is still controversy concerning its efficacy. The objective of our clinical study is to use propensity score matching and random forest models to determine whether HCC patients with MVI can benefit from postoperative adjuvant TACE therapy. Additionally, based on adjuvant TACE treatment, we aim to develop individualized random forest prediction models for the 5-year disease-free survival (DFS) rate and overall survival (OS) rate in HCC patients with MVI.

Methods: Three hundred and twelve HCC patients with MVI and without MVI were divided into TACE and non-TACE (N-TACE) groups by propensity matching scoring method. Kaplan-Meier method was used to compare DFS and OS. Cox regression analysis evaluated the effect of adjuvant TACE on DFS and OS. The most influential characteristic variables of DFS and OS were used to construct the random forest prediction models.

Results: After matching, the 1-, 3-, and 5-year DFS and OS of HCC patients with MVI in the TACE group were significantly higher than those in the N-TACE group ($P < 0.05$). There was no significant difference in DFS and OS of HCC patients without MVI. Adjuvant TACE was an independent predictor of DFS and OS in HCC patients with MVI. Moreover, the random forest prediction models showed the key role of postoperative adjuvant TACE in DFS and OS of HCC patients with MVI.

Conclusions: Postoperative adjuvant TACE improves the survival of HCC patients with MVI. The random forest prediction model has a good value for predicting the survival of HCC patients with MVI.

Keywords: Adjuvant transcatheter arterial chemoembolization therapy (adjuvant TACE therapy); hepatocellular carcinoma (HCC); microvascular invasion (MVI); prognosis; random forest prediction model

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Introduction

Hepatocellular carcinoma (HCC) is the most common malignant tumor, ranking 6th among global malignancies, and 2nd among cancer-related deaths (1). There are more than 700,000 new cases of HCC each year (2). In China, there are approximately 4.66 million HCC patients and approximately 370,000 individuals die of HCC each year, accounting for 51% of the world's deaths from HCC (3). Radical resection and liver transplantation are effective treatments for HCC, but due to vascular invasion, patients have a low tumor-free survival rate, high recurrence rate, and poor long-term prognosis. It has been reported that the recurrence rate of HCC after radical resection is as high as 50% to 70% (4).

Microvascular invasion (MVI), as an important stage of tumor cell invasion of blood vessels, is a key step for HCC to metastasize into the liver and remote organs. Studies have shown that the risk of early recurrence of

HCC combined with MVI is significantly higher than that of patients without MVI (5,6). Generally, HCC patients with MVI have shorter tumor-free survival and overall survival (OS), and worse prognosis (6). The HCC staging system proposed by the American Joint Committee on Cancer (AJCC) focuses on the pathological factors that affect the prognosis of HCC after surgery, which includes the presence or absence of MVI (7). Therefore, effective adjuvant therapy has very important clinical significance for preventing recurrence and metastasis of HCC after surgery. The causes of intrahepatic recurrence include intrahepatic metastasis and multicentric occurrence. Intrahepatic metastasis is the primary mode of recurrence after liver resection for HCC. In previous studies, postoperative adjuvant transcatheter arterial chemoembolization (TACE) has been the most discussed and widely used adjuvant therapy, though its efficacy remains controversial (4-8). Most studies suggest that only patients with high-risk recurrence factors—such as multiple tumors, large tumor diameter, positive surgical margins, or positive vascular endothelial growth factor (VEGF)—may benefit from it (4-7). MVI is a critical step in intrahepatic and distant metastasis, and extensive research has confirmed that the presence of MVI is an independent risk factor affecting the prognosis of HCC patients (7). TACE is currently the most widely used adjuvant treatment after HCC surgery, which is used to treat tumor micrometastasis, and can inactivate residual tumor foci and reduce the recurrence rate (8). However, there is still controversy concerning its efficacy. Moreover, studies have confirmed that only patients with high-risk factors can benefit from postoperative adjuvant TACE therapy (7,8). The objective of our clinical study is to use propensity score matching and random forest models to determine whether HCC patients with MVI can benefit from postoperative adjuvant TACE therapy. Additionally, based on adjuvant TACE treatment, we aim to develop individualized predictive models for the 5-year disease-free survival (DFS) rate and OS rate in HCC patients with MVI.

At present, there is no evidence-based A-level evidence to evaluate whether postoperative adjuvant TACE therapy has an impact on the long-term prognosis of patients with HCC with MVI. Although prospective randomized controlled trials are currently the gold standard for evaluating the clinical efficacy of a certain treatment, in practice, such trials are limited due to factors such as research subjects, funding, and ethics. However, the propensity matching scoring system can make more effective use of clinical observation data and has the characteristics of low acquisition cost and relatively

Highlight box

Key findings

- Postoperative adjuvant transcatheter arterial chemoembolization (TACE) therapy significantly prolongs survival in hepatocellular carcinoma (HCC) patients with microvascular invasion (MVI); the constructed random forest prediction model based on adjuvant TACE therapy can accurately predict postoperative survival outcomes for HCC patients with MVI.

What is known and what is new?

- MVI is an independent risk factor affecting the prognosis of HCC patients. HCC patients with MVI have shorter tumor-free survival and overall survival, and worse prognosis. TACE is currently the most widely used adjuvant treatment after HCC surgery, which is used to treat tumor micrometastasis, and can inactivate residual tumor foci and reduce the recurrence rate. However, it remains controversial whether HCC patients with MVI can benefit from postoperative adjuvant TACE therapy.
- Our findings may provide a basis for the application of adjuvant TACE therapy after clinical operation in HCC. Moreover, it assists clinicians in early and accurate assessment of postoperative survival in HCC patients with MVI.

What is the implication, and what should change now?

- For patients with upregulated vascular endothelial growth factor (VEGF) expression, postoperative supplementation with molecular targeted drugs against VEGF may be necessary to enhance the efficacy of adjuvant TACE therapy and improve patient survival benefits. The specific selection of chemotherapeutic agents and the number of adjuvant TACE treatment sessions for HCC patients with MVI require further exploration through prospective studies.

small ethical restrictions (9,10). It can effectively reduce the confounding bias and selection bias of observational research, thus obtaining similar effects of prospective randomized controlled trials (11). Therefore, the propensity-matching scoring system is generally considered to be a practical, novel, and credible statistical method (10). In recent years, more and more studies have applied the method of propensity score matching in the analysis of lung cancer and colorectal cancer (10,11). However, there are few studies on HCC, especially the evaluation of the clinical efficacy of adjuvant TACE therapy in patients with HCC with MVI. The random forest prediction model, an algorithm that integrates multiple decision trees through the idea of ensemble learning, is mostly used in predicting disease risk and evaluating disease prognosis, with high accuracy and strong generalization ability. In recent years, with the rapid development of artificial intelligence, machine learning has played an increasingly important role in medical research. The random forest prediction model, a type of ensemble learning method in machine learning, employs bootstrapping to randomly sample the original data with replacement, creating subsets of the data. One-third of the data is excluded as out-of-bag data during the process of creating sample subsets, while the remaining two-thirds are used to construct decision tree models by randomly selecting feature variables. A large number of decision trees are trained, and the final prediction is determined through a weighted voting mechanism among these individual trees. Due to its high accuracy and strong generalization capability, the random forest model has been increasingly applied in various fields, including disease diagnosis, importance assessment of research factors, and prognostic evaluation (12).

In this study, the clinical efficacy of postoperative adjuvant TACE treatment in HCC patients with MVI was retrospectively analyzed. The subjects were matched by propensity score matching. The long-term DFS rate and OS rate of HCC patients with/without MVI and with/without TACE were evaluated, respectively. The random forest prediction model was established to evaluate the value of postoperative adjuvant TACE as the most influential characteristic variables of DFS and OS. Our findings may provide a basis for the application of adjuvant TACE therapy after clinical operation in HCC. Moreover, it assists clinicians in early and accurate assessment of postoperative survival in HCC patients with MVI, enabling the formulation of individualized and refined treatment strategies based on different risk stratifications. We present this article in accordance with the TRIPOD reporting

checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2585/rc>).

Methods

Patients

We recruited patients who underwent radical resection of HCC in the First Affiliated Hospital of Xinjiang Medical University (Urumqi, China) from January 2015 to June 2018. Sample size

calculation formula: $D = \frac{(z_{\alpha/2} + z_{\beta})}{(\ln(HR))^2 \times p(1-p)}$ (HR represents

the hazard ratio of death for HCC cases with MVI, p represents the proportion of HCC cases with MVI among all HCC cases, $\alpha = 0.05$, $\beta = 0.2$). All patients received standard clinical treatment. The inclusion criteria were: (I) patients with a confirmed diagnosis of HCC who underwent radical resection of HCC for the first time; (II) age between 30 and 70 years old, regardless of gender; (III) Child-Pugh classification was A or B; (IV) Barcelona Clinic Liver Cancer (BCLC) classification was stage A. The exclusion criteria included: (I) patients combined with extensive intrahepatic and extrahepatic metastasis and lymph node invasion; (II) patients combined with portal vein or vena cava tumor thrombus; (III) patients who received palliative resection; (IV) patients combined with other malignant tumors; (V) patients with Child-Pugh grade C; (VI) patients with a single tumor larger than 10 cm in diameter or the combined diameters of two or three tumors exceeding 10 cm; (VII) patients with more than three tumors; and (VIII) patients who were lost to follow up during the study period. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (No. K202103-04) and individual consent for this retrospective analysis was waived due to the retrospective nature of the study and the anonymous nature of patient information.

Laboratory measurements

On the morning of the second day of admission, 5 mL of upper limb venous blood was drawn from all patients on an empty stomach. The blood was anticoagulated with ethylenediaminetetraacetic acid (EDTA) and centrifuged at 3,000 r/min for 5 minutes. The separated supernatant

sample was stored in a low-temperature refrigerator until detection. Serum liver function indicators such as bilirubin and albumin were measured by using chemiluminescence, and coagulation function indicators were measured by using immunoturbidimetry prothrombin activity (PTA), enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of alpha-fetoprotein (AFP) and VEGF, and indocyanine green clearance test was used to measure liver function reserve indicators indocyanine green retention rate within 15 minutes (ICG-R15).

Radical surgery

According to the previous description (1,2), the criteria for radical resection (anatomical resection) of HCC included: (I) complete resection of the tumor during the operation; (II) no residual cancer at the resection margin; (III) no residual tumor on imaging examination 3 months after surgery; (IV) postoperative AFP dropped to normal within 2 months if it was positive before surgery.

MVI diagnosis

The diagnosis of MVI, which mainly relied on the pathological results of postoperative specimens, was defined as the presence of nests of cancer cells in the vascular cavity lined by endothelial cells under the microscope. It was more common in the small branches of the portal vein in the liver tissue adjacent to the cancer or the blood vessels in the tumor membrane. MVI was classified based on its quantity and distribution. M0: no involved vessels within 1 cm from the tumor edge; M1 (low-risk): 1–5 involved vessels within 1 cm from the tumor edge; M2 (high-risk): more than 5 involved vessels within 1 cm from the tumor edge, or involved vessels located more than 1 cm from the tumor edge. M0 was defined as having no MVI, while M1 and M2 were defined as having MVI (7).

TACE treatment

The patients received adjuvant TACE treatment 6–8 weeks after radical resection of HCC. Briefly, the right femoral artery was punctured using the modified Seldinger method, and a 5F catheter sheath was inserted. The Rosch hepatic (RH) catheter was guided to the superior mesenteric artery for indirect portal vein angiography. Then, the catheter was guided to the proper hepatic artery for digital subtraction angiography. Oxaliplatin (50 mg) and epirubicin (30 mg)

were infused separately into the proper hepatic artery. Following this, an emulsion mixture of 3 to 5 mL of lipiodol and 20 mg of epirubicin was injected into the proper hepatic artery for embolization. Following the “Guidelines for TACE Treatment of Hepatocellular Carcinoma in China”, the endpoints of embolization were defined as the dual embolization of both the tumor-feeding artery and portal vein. On post-embolization angiography, the cessation of blood flow in the tumor-feeding artery, complete devascularization of the tumor, and dense and uniform deposition of lipiodol within the tumor region and at the peritumoral portal vein branches suggested embolization. Evaluation of the necessity for additional TACE treatment was based on findings from contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) as well as tumor marker reassessment.

Follow-up and endpoints

Follow-up was performed on the enrolled 312 HCC patients and no patient was lost to follow up. Follow-up frequency: years 1–3 postoperation: re-exam every 3 months (high-risk patients may shorten to 2 months); years 3–5 postoperation: re-exam every 6 months. Follow-up examinations include: serological tests: AFP, complete blood count, liver function, and coagulation profile; imaging studies: abdominal ultrasound, contrast-enhanced abdominal CT, and contrast-enhanced MRI. The median follow-up time was 22 months. The follow-up endpoint was tumor recurrence, metastasis, and death within 5 years after HCC surgery. DFS was the survival time from HCC resection to the occurrence of HCC recurrence and metastasis, and OS was the survival time from HCC surgery to all-cause death.

Statistical analysis

SPSS 25.0 statistical software was used to analyze the data. According to whether TACE treatment was performed after surgery, the HCC patients with/without MVI were grouped into the TACE group and the non-TACE (N-TACE) group. The propensity score was estimated based on the Logistic regression model, which was constructed with postoperative TACE treatment as the dependent variable and various clinical-pathological factors as independent variables. The calculation formula for the propensity score was $e^x/(1+e^x)$, where e represents the base of the natural logarithm (approximately equal to 2.71828), and x is the sum of the weighted regression coefficients of the respective

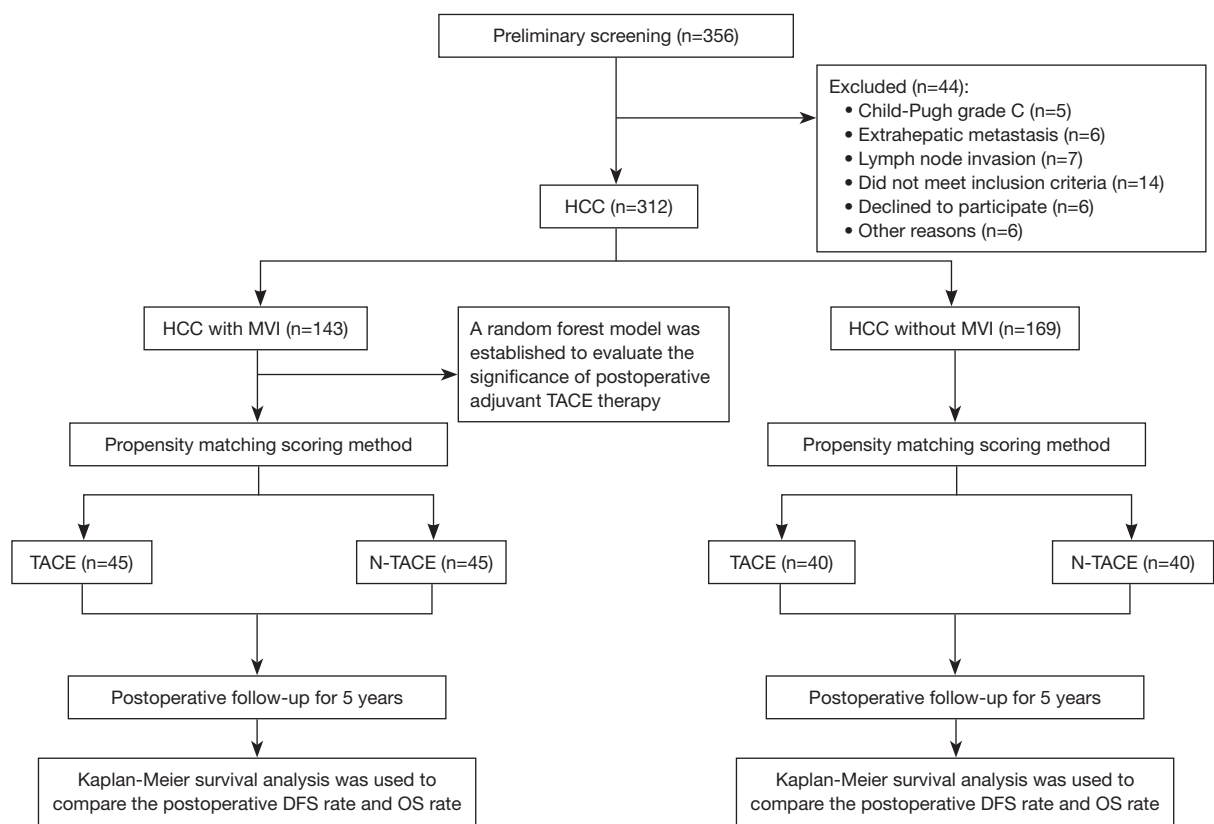


Figure 1 Experimental technical route. Experimental technical route delineated the clinical research design, encompassing patient enrollment criteria, group allocation strategies, follow-up protocols, experimental methodologies, and research objectives. DFS, disease-free survival; HCC, hepatocellular carcinoma; MVI, microvascular invasion; N-TACE, non-TACE; OS, overall survival; TACE, transcatheter arterial chemoembolization.

variables. The 1:1 nearest neighbor matching method was used to match the patients in the two groups based on their closely matched propensity scores. Each individual in the TACE group was matched with one individual in the N-TACE group who had the most similar propensity score. The caliper value was defined as 0.02 to ensure the goodness of the matching results, and the balance of the clinical-pathological indicators of the two groups before and after the matching was tested with a *t*-test or Chi-squared test. A smaller standard deviation approaching 0 after matching indicates a more satisfactory outcome, with a difference below 0.1 (10%) regarded as indicating a good balance in inter-group variables. Kaplan-Meier survival analysis was used to compare the postoperative DFS rate and OS rate of HCC patients with and without MVI in the TACE group and the N-TACE group. Univariate and multivariate Cox regression analysis was used to evaluate the effect of adjuvant TACE treatment before and after

matching on DFS and OS in HCC patients with MVI. A *P* value <0.05 was considered statistically significant. The most influential characteristic variables of DFS and OS were used to construct a random forest prediction model using the minimum depth method and R4.1.2 statistical analysis software (“randomForestSRC” package). The average Gini index was used to evaluate the importance of each variable in the random forest prediction model. The out-of-bag prediction error rate and the error prediction rate in validation group was used to assess the accuracy of the random forest prediction model (Figure 1).

Results

Comparison of baseline clinical and pathological data between patients with and without MVI

A total of 312 patients were enrolled in this study, including 180 males (57.7%) and 132 females (42.3%),

Table 1 Comparison of baseline clinical and pathological data between patients with and without MVI

Variables	Patients with MVI (n=143)	Patients without MVI (n=169)	t/ χ^2	P
Age (years)	56.8±9.5	56.3±9.9	t =0.447	0.66
Gender (male/female)	87 (60.8)/56 (39.2)	93 (55.0)/76 (45.0)	$\chi^2=1.071$	0.30
Body mass index (kg/m ²)	22.1±2.2	22.4±2.3	t =1.172	0.24
Smoking history (yes/no)	67 (46.9)/76 (53.1)	82 (48.5)/87 (51.5)	$\chi^2=0.086$	0.77
Drinking history (yes/no)	54 (37.8)/89 (62.2)	67 (39.6)/102 (60.4)	$\chi^2=0.116$	0.73
Cause of disease (hepatitis B/hepatitis C/NASH)	86 (60.1)/38 (26.6)/19 (13.3)	81 (47.9)/26 (15.4)/62 (36.7)	$\chi^2=23.221$	<0.001
Hypertension (yes/no)	91 (63.6)/52 (36.4)	96 (56.8)/73 (43.2)	$\chi^2=1.505$	0.22
Diabetes (yes/no)	20 (14.0)/123 (86.0)	24 (14.2)/145 (85.8)	$\chi^2=0.003$	0.96
Coronary heart disease (yes/no)	31 (21.7)/112 (78.3)	30 (17.8)/139 (82.2)	$\chi^2=0.759$	0.38
Cerebral infarction (yes/no)	28 (19.6)/115 (80.4)	31 (18.3)/138 (81.7)	$\chi^2=0.077$	0.78
Maximum tumor size (cm)	5.6±1.7	5.8±1.7	t =1.036	0.30

Data are presented as mean ± standard deviation or n (%). MVI, microvascular invasion; NASH, nonalcoholic steatohepatitis.

with an average age of 56.5±9.8 years. Their average body mass index was 22.3±2.3 kg/m². All patients had BCLC stage A and the tumor diameters were lower than 10 cm. Postoperative pathological examination showed that 143 patients (45.8%) were with MVI (M1, n=41 and M2, n=102) and 169 patients (54.2%) were without MVI (M0). The etiology between patients with MVI and those without MVI was significantly different (P<0.05) (Table 1). However, there was no statistically significant difference in terms of age, gender, body mass index, smoking history, drinking history, hypertension, diabetes, coronary heart disease, maximum tumor size, and cerebral infarction between the two groups (P>0.05).

Comparison of clinicopathological data between TACE group and N-TACE group of HCC patients with MVI before and after matching

To obtain comparable clinical and pathological indicators, the HCC patients with MVI were divided into the TACE group and the N-TACE group (Table 2). Before matching, there were 61 cases (42.7%) in the TACE group and 82 cases (57.3%) in the N-TACE group. The analysis showed that AFP, PTA, maximum tumor diameter, TBil, and ICG-R15 (indocyanine green retention rate within 15 minutes) were different between the two groups (P<0.05), while the other clinical signs were not statistically significant. We further optimized the clinical and pathological indicators of the two groups by using the propensity score 1:1 nearest neighbor matching method,

and finally successfully matched 45 pairs. After matching, the clinicopathological indicators between the two groups were consistent, with no statistical significance.

Comparison of clinicopathological data of the TACE group and N-TACE group of HCC patients without MVI before and after matching

The HCC patients without MVI were also divided into the TACE group and the N-TACE group. Before matching, there were 53 cases (31.4%) in the TACE group and 116 cases (68.6%) in the N-TACE group (Table 3). The analysis showed that AFP, PTA, maximum tumor diameter, TBil, ICG-R15, and VEGF were significantly different between the two groups (P<0.05). Similarly, we further optimized the clinicopathological data of the two groups by using the propensity score 1:1 nearest neighbor matching method, and finally successfully matched 40 pairs. After matching, the difference in clinicopathological data between the two groups was non-significant (P>0.05). After matching, the clinicopathological data of the TACE group and the N-TACE group of HCC patients without MVI became consistent.

Comparison of postoperative DFS rate and OS rate of TACE group and N-TACE group in HCC patients with MVI after matching

To evaluate the clinical efficacy of adjuvant TACE therapy in HCC with MVI, Kaplan-Meier survival analysis was

Table 2 Comparison of clinicopathological data between the TACE group and N-TACE group of HCC patients with MVI

Items	Before matching			After matching		
	TACE (n=61)	N-TACE (n=82)	P	TACE (n=45)	N-TACE (n=45)	P
Age (years)	55.5±9.4	57.8±8.2	0.12	56.0±8.3	56.4±8.3	0.82
Gender (male/female)	39 (63.9)/22 (36.1)	48 (58.5)/34 (41.5)	0.51	30 (66.7)/15 (33.3)	28 (62.2)/17 (37.8)	0.66
Cause of disease (hepatitis B/ hepatitis C/NASH)	36 (59.0)/14 (23.0)/11 (18.0)	50 (61.0)/24 (29.3)/8 (9.7)	0.31	25 (55.6)/11 (24.4)/9 (20.0)	26 (57.8)/12 (26.7)/7 (15.6)	0.86
AFP (ng/mL)	656.7±37.4	698.5±41.2	<0.001	615.9±35.2	608.3±39.2	0.34
TBil (μmol/L)	32.1±7.8	37.4±6.8	<0.001	34.1±7.3	35.7±7.2	0.30
PTA (%)	81.2±9.8	75.4±8.5	<0.001	78.7±7.2	76.2±7.1	0.10
Child-Pugh (grade A/grade B)	31 (50.8)/30 (49.2)	36 (43.9)/46 (56.1)	0.41	23 (51.1)/22 (48.9)	21 (46.7)/24 (53.3)	0.67
Cirrhosis (yes/no)	37 (60.7)/24 (39.3)	54 (65.9)/28 (34.1)	0.52	28 (62.2)/17 (37.8)	29 (64.4)/16 (35.6)	0.83
Maximum tumor diameter (cm)	5.8±1.9	5.2±1.6	0.04	5.6±1.6	5.4±1.5	0.54
Number of tumors (single/multiple)	41 (67.2)/20 (32.8)	51 (62.2)/31 (37.8)	0.54	29 (64.4)/16 (35.6)	30 (66.7)/15 (33.3)	0.82
Degree of differentiation (1–2/3–4)	26 (42.6)/35 (57.4)	40 (48.8)/42 (51.2)	0.46	20 (44.4)/25 (55.6)	21 (46.7)/24 (53.3)	0.83
ICG-R15 (%)	9.5±2.1	11.1±2.3	<0.001	9.9±1.8	10.3±2.1	0.33
VEGF (positive/negative)	34 (55.7)/27 (44.3)	35 (42.7)/47 (57.3)	0.12	28 (62.2)/17 (37.8)	26 (57.8)/19 (42.2)	0.67

Data are presented as mean ± standard deviation or n (%). AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; ICG-R15, indocyanine green retention rate at 15 minutes; MVI, microvascular invasion; NASH, nonalcoholic steatohepatitis; N-TACE, non-TACE; PTA, prothrombin activity; TACE, transcatheter arterial chemoembolization; TBil, total bilirubin; VEGF, vascular endothelial growth factor.

Table 3 Comparison of clinicopathological data of TACE group and N-TACE group of HCC patients without MVI

Items	Before matching			After matching		
	TACE (n=53)	N-TACE (n=116)	P	TACE (n=40)	N-TACE (n=40)	P
Age (years)	54.2±8.8	57.1±8.1	0.045	55.3±8.6	56.8±8.2	0.43
Gender (male/female)	33 (62.3)/20 (37.7)	60 (51.7)/56 (48.3)	0.20	25 (62.5)/15 (37.5)	27 (67.5)/13 (32.5)	0.64
Cause of disease (hepatitis B/ hepatitis C/NASH)	31 (58.5)/10 (18.9)/12 (22.6)	50 (43.1)/16 (13.8)/50 (43.1)	0.38	28 (70.0)/6 (15.0)/6 (15.0)	25 (62.5)/6 (15.0)/9 (22.5)	0.68
AFP (ng/mL)	671.2±46.5	613.7±56.7	<0.001	642.1±41.7	631.8±42.8	0.28
TBil (μmol/L)	30.8±9.2	35.7±8.8	0.002	32.7±7.3	33.6±7.5	0.59
PTA (%)	83.5±7.4	78.5±7.1	<0.001	81.8±7.2	80.6±6.5	0.44
Child-Pugh (grade A/grade B)	34 (64.2)/19 (35.8)	59 (50.8)/57 (49.2)	0.11	26 (65.0)/14 (35.0)	23 (57.5)/17 (42.5)	0.49
Cirrhosis (yes/no)	31 (58.5)/22 (41.5)	82 (70.7)/34 (29.3)	0.12	25 (62.5)/15 (37.5)	27 (67.5)/13 (32.5)	0.64
Maximum tumor diameter (cm)	6.1±1.8	5.5±1.6	0.04	5.8±1.6	5.7±1.4	0.77
Number of tumors (single/multiple)	33 (62.3)/20 (37.7)	80 (69.0)/36 (31.0)	0.39	26 (65.0)/14 (35.0)	25 (62.5)/15 (37.5)	0.82
Degree of differentiation (1–2/3–4)	26 (49.1)/27 (50.9)	71 (61.2)/45 (38.8)	0.14	13 (32.5)/27 (67.5)	16 (40.0)/24 (60.0)	0.49
ICG-R15 (%)	9.8±2.3	11.3±2.6	<0.001	10.4±2.1	10.7±2.3	0.54
VEGF (positive/negative)	35 (66.0)/18 (34.0)	30 (25.9)/86 (74.1)	<0.001	25 (62.5)/15 (37.5)	23 (57.5)/17 (42.5)	0.65

Data are presented as mean ± standard deviation or n (%). AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; ICG-R15, indocyanine green retention rate at 15 minutes; MVI, microvascular invasion; NASH, nonalcoholic steatohepatitis; N-TACE, non-TACE; PTA, prothrombin activity; TACE, transcatheter arterial chemoembolization; TBil, total bilirubin; VEGF, vascular endothelial growth factor.

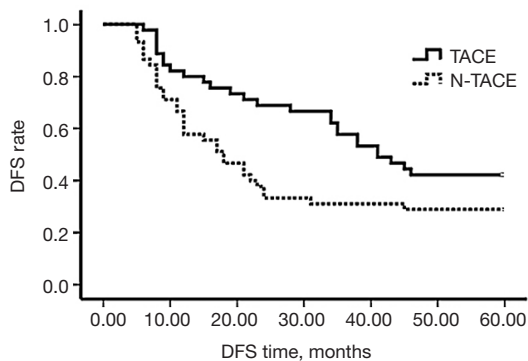


Figure 2 Comparison of postoperative DFS rates between the TACE group and the N-TACE group of hepatocellular carcinoma patients with MVI. Kaplan-Meier survival analysis showed that after matching, the DFS rates of hepatocellular carcinoma patients with MVI after matching at 1, 3, and 5 years in the TACE group were significantly higher than those in the N-TACE group [86.7% (39/45), 68.9% (31/45), and 42.2% (19/45) *vs.* 71.1% (32/45), 33.3% (15/45), and 26.7% (12/45), $P < 0.05$]. DFS, disease-free survival; MVI, microvascular invasion; N-TACE, non-TACE; TACE, transcatheter arterial chemoembolization.

conducted to compare the DFS rate and OS rate of the TACE group and the N-TACE group of HCC patients with MVI after matching. The results showed that the 1-, 3-, and 5-year DFS rate of the TACE group after matching was significantly higher than that in the N-TACE group [86.7% (39/45), 68.9% (31/45), and 42.2% (19/45) *vs.* 71.1% (32/45), 33.3% (15/45), and 26.7% (12/45), $P < 0.05$, *Figure 2*]. In addition, the 1-, 3-, and 5-year OS rate of the TACE group was significantly higher than that of the N-TACE group [100.0% (45/45), 88.9% (40/45), and 71.1% (32/45) *vs.* 93.3% (42/45), 57.8% (26/45), and 51.1% (23/45), $P < 0.05$, *Figure 3*].

Comparison of postoperative DFS rate and OS rate of TACE group and N-TACE group in HCC patients without MVI after matching

To evaluate the clinical efficacy of postoperative adjuvant TACE treatment for HCC patients without MVI, we compared the DFS rate and OS rate of the TACE group and the N-TACE group with Kaplan-Meier survival analysis. The results showed that the DFS rate of HCC patients without MVI after matching in the TACE group was higher than that of the N-TACE group at 1, 3, and 5 years in the TACE group, but the difference was not

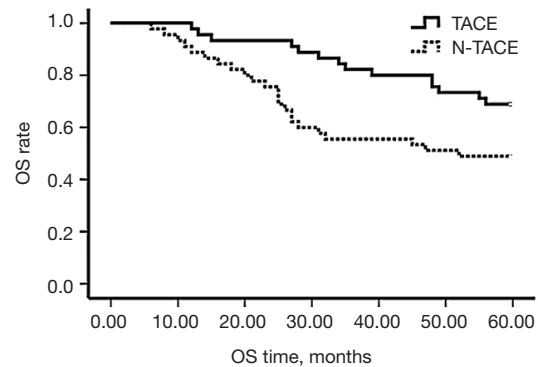


Figure 3 Comparison of postoperative OS rates between the TACE group and N-TACE group in hepatocellular carcinoma patients with MVI after matching. Kaplan-Meier survival analysis showed that after matching, there was a significant difference in OS rates between the TACE group and the N-TACE group of hepatocellular carcinoma patients with MVI after 1, 3, and 5 years [100.0% (45/45), 88.9% (40/45), and 71.1% (32/45) *vs.* 93.3% (42/45), 57.8% (26/45), and 51.1% (23/45), $P < 0.05$]. MVI, microvascular invasion; N-TACE, non-TACE; OS, overall survival; TACE, transcatheter arterial chemoembolization.

statistically significant [100.0% (40/40), 72.5% (29/40), and 62.5% (25/40) *vs.* 87.5% (35/40), 65.0% (26/40), and 48.9% (20/40), $P > 0.05$, *Figure 4*]. Similarly, although the OS rate of 1, 3, and 5 years in the TACE group was higher than that in the N-TACE group, the difference was not statistically significant [100.0% (40/40), 85.0% (34/40), and 75.0% (30/40) *vs.* 95.0% (38/40), 67.5% (27/40), and 62.5% (25/40), $P > 0.05$, *Figure 5*].

Cox regression analysis of the effects of adjuvant TACE treatment before and after matching on DFS and OS in HCC patients with MVI

To verify the clinical value of adjuvant TACE therapy in HCC patients with MVI after matching, we used Cox regression analysis to conduct sensitivity analysis to evaluate the effect of adjuvant TACE therapy before and after matching on DFS and OS. The postoperative recurrence and death of HCC patients with MVI were used as the dependent variable, and adjuvant TACE treatment was used as the independent variable to perform univariate and multivariate Cox regression analyses. In the univariate analysis, the only variable was adjuvant TACE treatment as a variable. The results showed that adjuvant TACE treatment had statistical significance (*Tables 4, 5*). Model

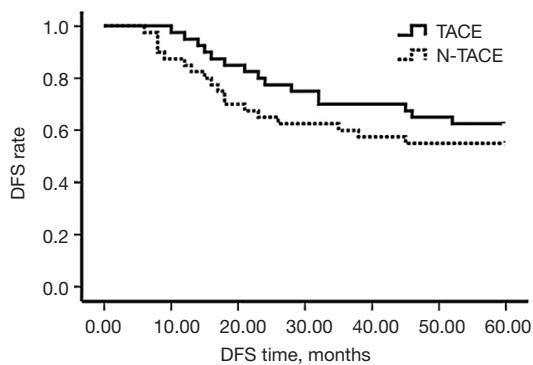


Figure 4 Comparison of postoperative DFS rates between the TACE group and N-TACE group of patients without MVI after matching. Kaplan-Meier survival analysis showed that after matching, although the 1-, 3-, and 5-year DFS rates of hepatocellular carcinoma patients without MVI in the TACE group were higher than those in the N-TACE group, the difference was not statistically significant [100.0% (40/40), 72.5% (29/40), and 62.5% (25/40) vs. 87.5% (35/40), 65.0% (26/40), and 48.9% (20/40), $P>0.05$]. DFS, disease-free survival; MVI, microvascular invasion; N-TACE, non-TACE; TACE, transcatheter arterial chemoembolization.

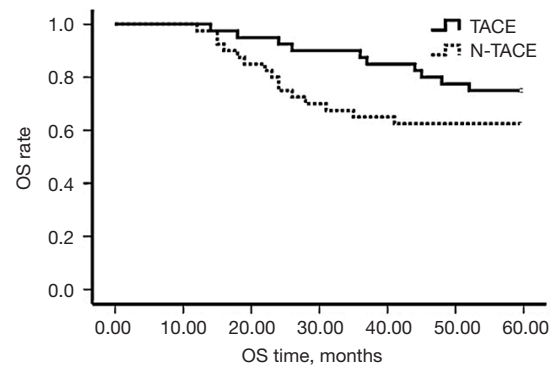


Figure 5 Comparison of postoperative OS rates between the TACE group and N-TACE group in hepatocellular carcinoma patients without MVI after matching. Kaplan-Meier survival analysis showed that after matching, the OS rate of hepatocellular carcinoma patients without MVI in the TACE group was higher than that in the N-TACE group at 1, 3, and 5 years, but there was no significant difference [100.0% (40/40), 85.0% (34/40), and 75.0% (30/40) vs. 95.0% (38/40), 67.5% (27/40), and 62.5% (25/40), $P>0.05$]. MVI, microvascular invasion; N-TACE, non-TACE; OS, overall survival; TACE, transcatheter arterial chemoembolization.

Table 4 Cox regression analysis of the effects of adjuvant TACE treatment on postoperative DFS and OS of HCC patients with MVI before matching

Cox regression analysis	DFS			OS		
	HR	95% CI	P	HR	95% CI	P
Univariate analysis	0.36	0.17–0.58	0.009	0.47	0.27–0.69	0.006
Model 1	0.42	0.21–0.68	0.01	0.51	0.31–0.75	0.01
Model 2	0.51	0.38–0.76	0.03	0.59	0.35–0.84	0.02

The two factors of age and gender are adjusted in model 1, and all the factors listed in *Table 1* are adjusted in model 2. CI, confidence interval; DFS, disease-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; MVI, microvascular invasion; OS, overall survival; TACE, transcatheter arterial chemoembolization.

Table 5 Cox regression analysis of the effect of adjuvant TACE treatment on postoperative DFS and OS of HCC patients with MVI after matching

Cox regression analysis	DFS			OS		
	HR	95% CI	P	HR	95% CI	P
Univariate analysis	0.41	0.22–0.61	0.01	0.50	0.31–0.73	0.03
Model 1	0.48	0.28–0.71	0.02	0.55	0.37–0.79	0.04
Model 2	0.57	0.41–0.79	0.03	0.64	0.49–0.86	0.048

The two factors of age and gender are adjusted in model 1, and all the factors listed in *Table 1* are adjusted in model 2. CI, confidence interval; DFS, disease-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; MVI, microvascular invasion; OS, overall survival; TACE, transcatheter arterial chemoembolization.

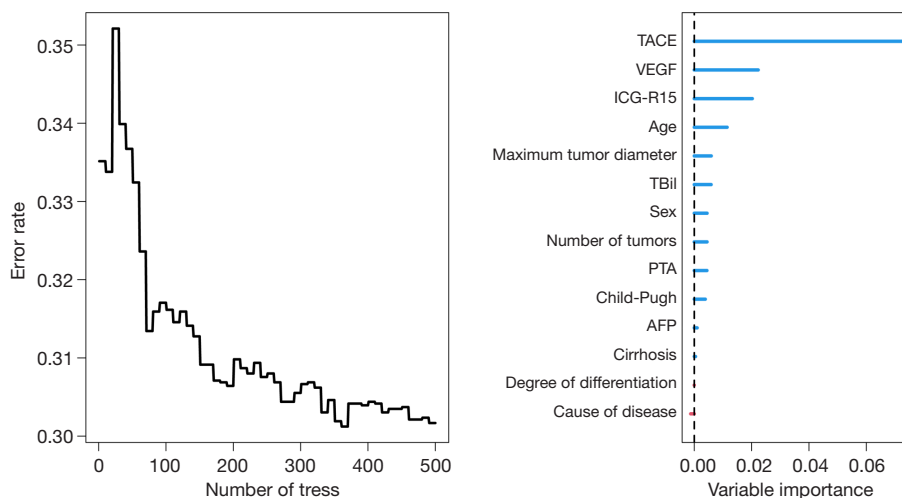


Figure 6 The out-of-bag prediction error rate curve and the average Gini index importance score of the random forest model for predicting postoperative disease-free survival in hepatocellular carcinoma patients combined with MVI. The prediction error rate gradually decreased. When 500 decision trees were generated, the out-of-bag prediction error rate in modeling group was at least 30.1%, the error prediction rate in validation group was 23.3%. The Gini index was used to calculate the influence of each variable on the heterogeneity of observations on all decision tree nodes in the forest. Then, the importance of the variables was compared. The larger the value, the greater the contribution of the variable to the model. It can be seen that postoperative adjuvant TACE therapy played a key role in postoperative disease-free survival of hepatocellular carcinoma patients with MVI. AFP, alpha-fetoprotein; ICG-R15, indocyanine green retention rate at 15 minutes; MVI, microvascular invasion; PTA, prothrombin activity; TACE, transcatheter arterial chemoembolization; TBil, total bilirubin; VEGF, vascular endothelial growth factor.

I was a multivariate COX regression model, in which the factors of age and gender were adjusted. Model 2 also involved a multivariate Cox regression analysis. In both Model 1 and Model 2, the adjuvant TACE treatment before and after matching was identified as an independent predictor of DFS and OS in HCC patients with MVI (Tables 4, 5). Before matching, the risk of postoperative recurrence in the TACE group was 0.51 times that of the N-TACE group [HR =0.51; 95% confidence interval (CI): 0.38–0.76; P=0.03], and the risk of death was 0.59 times that of the N-TACE group (HR =0.59; 95% CI: 0.35–0.84; P=0.02) (Table 4). After matching, the risk of postoperative recurrence in the TACE group was 0.57 times that of the N-TACE group (HR =0.57; 95% CI: 0.41–0.79; P=0.03). The risk of postoperative death in the TACE group was 0.64 times that of the N-TACE group (HR =0.64; 95% CI: 0.49–0.86; P=0.048) (Table 5).

Random forest prediction model

Random forest prediction models were established to predict the postoperative DFS of 143 HCC patients with MVI. One

hundred and forty-three HCC patients with MVI randomly divided into modeling group (n=100) and validation group (n=43) according to 7:3 ratio. Approximately 1/3 of the out-of-bag data was generated in the total sample during the model establishment. After repeated verification, the final out-of-bag prediction error rate in modeling group was stable at 30.1%, and the generated decision trees were 500, the error prediction rate in validation group was 23.3%, indicating that the model has high stability and scientificity. The average Gini index assessed the significance of each variable in the random forest model. The minimum depth method identified the characteristic variables with the most influential and generalizing ability for the outcome events (ntree =500, mtry =4). The results indicated a significant role of postoperative adjuvant TACE therapy in the DFS of HCC patients with MVI, with an importance score of 0.074 (Figure 6). Patients without postoperative adjuvant TACE treatment had a significantly higher risk of postoperative tumor recurrence and metastasis compared to those with postoperative adjuvant TACE treatment (Figure 7). Other categorical variables such as VEGF, gender, Child-Pugh classification, differentiation degree, cirrhosis, and

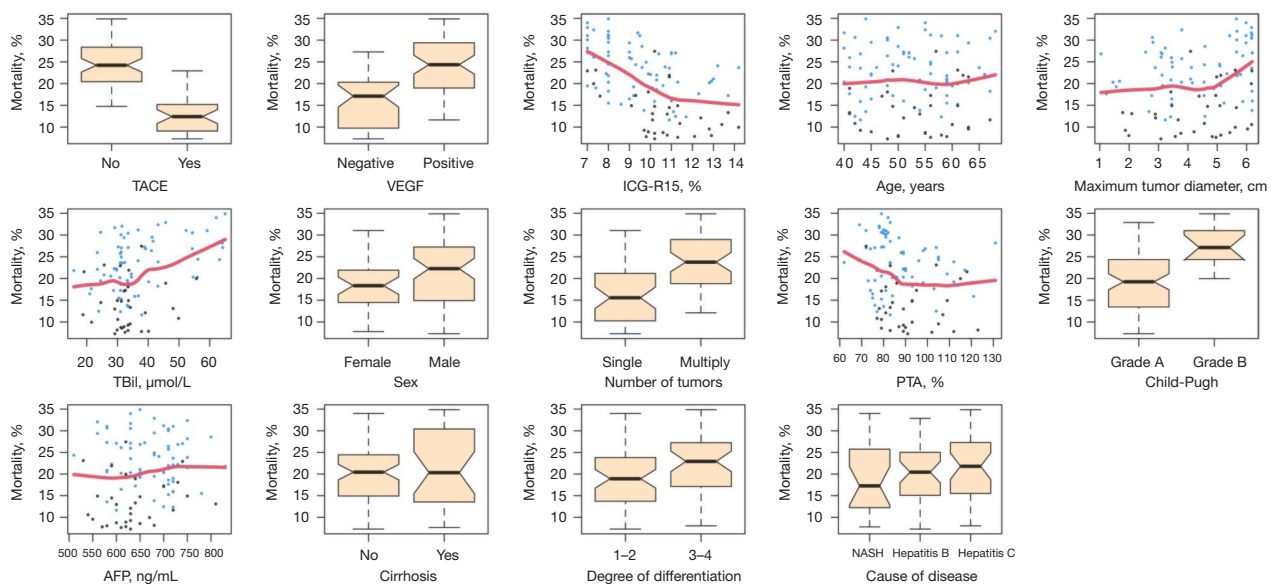


Figure 7 The relationship between each variable and the risk of tumor recurrence and metastasis in hepatocellular carcinoma patients with MVI. The risk of postoperative tumor recurrence and metastasis in patients without postoperative adjuvant TACE treatment was significantly higher than that in patients with postoperative adjuvant TACE treatment. AFP, alpha-fetoprotein; ICG-R15, indocyanine green retention rate at 15 minutes; MVI, microvascular invasion; NASH, nonalcoholic steatohepatitis; PTA, prothrombin activity; TACE, transcatheter arterial chemoembolization; TBil, total bilirubin; VEGF, vascular endothelial growth factor.

etiology were not characteristic variables in the random forest model. Continuous variables such as ICG-R15, age, total bilirubin, PTA, tumor diameter, and AFP showed no significant association with the risk of recurrence and metastasis in patients.

Random forest prediction models also predicted the postoperative OS of 143 HCC patients with MVI, respectively. The final out-of-bag prediction error rate in modeling group, after repeated verification, stabilized at 24.2%, with 480 generated decision trees, the error prediction rate in validation group was 20.9%, demonstrating the high stability and reliability of the model. The average Gini index was used to assess the importance of each variable in the random forest model, and the minimum depth method identified characteristic variables with the most influential and generalizing ability on the outcome events ($n_{tree}=480$, $m_{try}=4$). The results revealed associations between postoperative TACE therapy, PTA, VEGF, ICG-R15, tumor number, and age with postoperative OS in HCC patients with MVI, with respective importance scores of 0.087, 0.012, 0.022, 0.023, 0.015, and 0.019 (Figure 8). Patients without postoperative adjuvant TACE treatment had a significantly higher risk of postoperative mortality compared to those receiving

postoperative adjuvant TACE treatment (Figure 9). VEGF-positive patients had a significantly higher risk of death than VEGF-negative patients, and the risk of death in patients with multiple tumors was significantly higher than in those with single tumors. PTA and ICG-R15 were significantly negatively correlated with the risk of patient death, while patient age was significantly positively correlated. Other categorical variables such as gender, Child-Pugh classification, differentiation degree, cirrhosis, and etiology were not characteristic variables in the random forest model. Continuous variables such as total bilirubin, tumor diameter, and AFP showed no significant correlation with the risk of patient death.

Discussion

HCC resection and liver transplantation are still the main methods for radical cure of HCC, but because HCC cells can easily invade blood vessels, neither HCC resection nor liver transplantation can prevent its recurrence and metastasis (13). MVI is an independent risk factor that affects postoperative recurrence, metastasis, and long-term survival of HCC patients (14), and intervention in the occurrence and development of MVI has received much

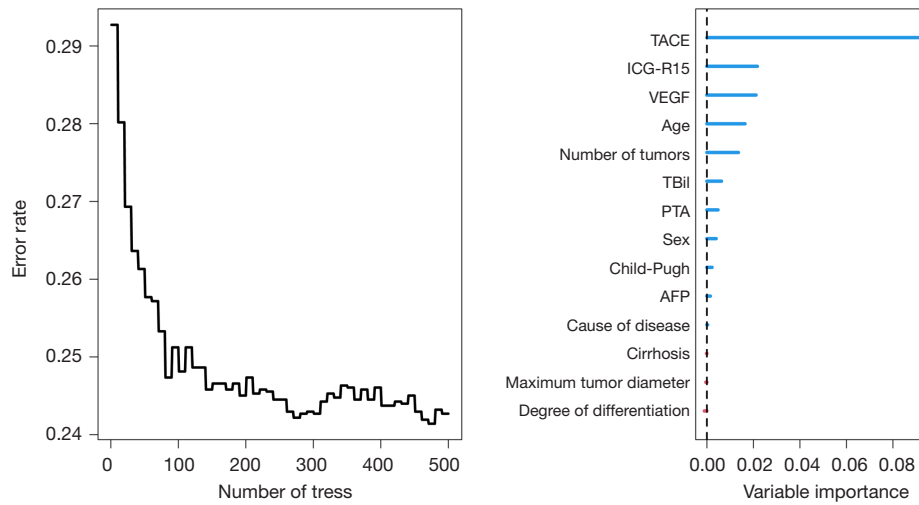


Figure 8 The out-of-bag prediction error rate curve and the average Gini index importance score of the random forest model for predicting the postoperative overall survival of patients with MVI-positive hepatocellular carcinoma. When 480 decision trees were generated, the minimum out-of-bag prediction error rate in modeling was 24.2%, the error prediction rate in validation group was 20.9%. The Gini index was used to calculate the influence of each variable on the heterogeneity of observations on all decision tree nodes in the forest. It can be seen that postoperative adjuvant TACE therapy, PTA, VEGF, ICG-R15, tumor number, and age played a key role in postoperative overall survival of hepatocellular carcinoma patients with MVI. AFP, alpha-fetoprotein; ICG-R15, indocyanine green retention rate at 15 minutes; MVI, microvascular invasion; PTA, prothrombin activity; TACE, transcatheter arterial chemoembolization; TBil, total bilirubin; VEGF, vascular endothelial growth factor.

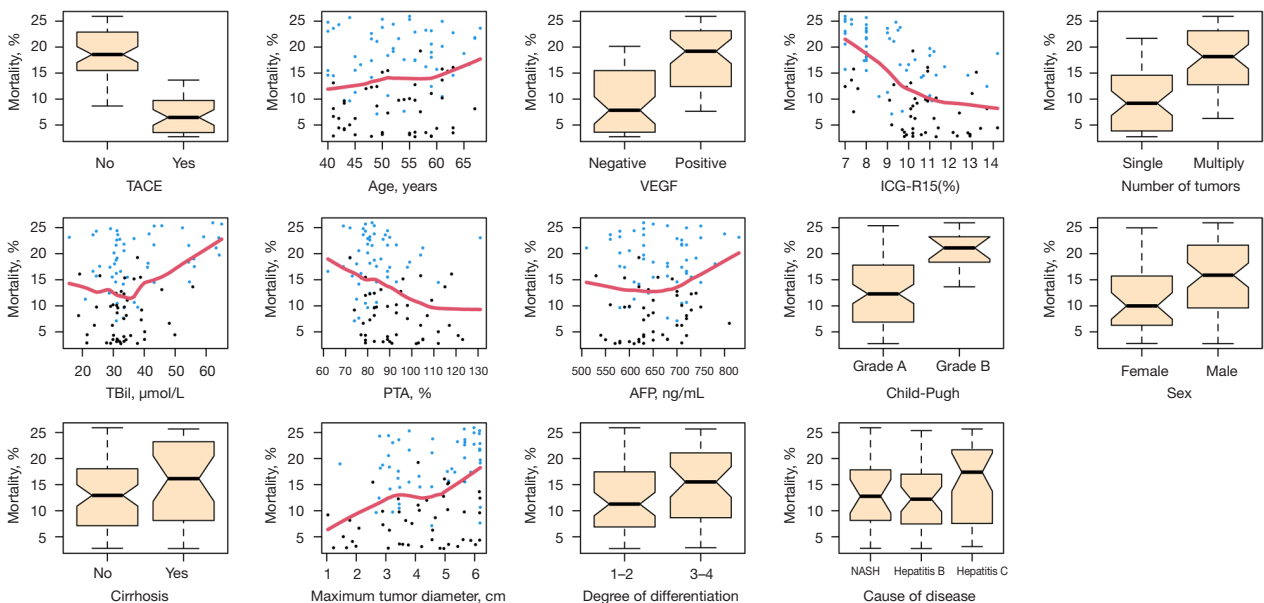


Figure 9 The relationship between each variable and the risk of postoperative mortality in hepatocellular carcinoma patients with MVI. The risk of postoperative mortality in patients without postoperative adjuvant TACE treatment was significantly higher than that in patients with postoperative adjuvant TACE treatment. AFP, alpha-fetoprotein; ICG-R15, indocyanine green retention rate at 15 minutes; MVI, microvascular invasion; NASH, nonalcoholic steatohepatitis; PTA, prothrombin activity; TACE, transcatheter arterial chemoembolization; TBil, total bilirubin; VEGF, vascular endothelial growth factor.

attention in the field of HCC. The current treatments for MVI mainly include postoperative adjuvant TACE, molecular targeted drugs (sorafenib, etc.), and local radiotherapy. Among them, postoperative adjuvant TACE therapy is the most commonly used treatment to prevent recurrence and metastasis of HCC, but its efficacy in improving the prognosis of HCC is still controversial. He *et al.* found that the tumor-free survival rate of HCC patients receiving TACE treatment at 4, 8, and 12 months after surgery was significantly higher than that of the surgery-alone group, suggesting that TACE treatment can reduce the early recurrence rate of HCC patients after surgery (4). Chen *et al.* retrospectively analyzed 278 HCC patients with MVI and found that the 3-year tumor-free survival rate and OS rate of the TACE group were significantly higher than those of the N-TACE group (15). Further stratified analysis of the included patients according to Milan criteria found that HCC patients with MVI who did not meet the Milan criteria could benefit from postoperative TACE treatment, while TACE treatment could not improve the survival rate of patients who met the Milan criteria. However, it has also been shown that patients with or without MVI cannot benefit from postoperative TACE (16).

In this study, according to whether TACE treatment was performed after surgery, the patients with MVI and without MVI were paired and grouped by propensity score matching method, which minimized the influence of confounding variables on the research results. After matching, the clinicopathological data of the TACE group and the N-TACE group with or without MVI were comparable. The results of the Kaplan-Meier survival analysis showed that the 1-, 3-, and 5-year DFS and OS rates of HCC patients with MVI after matching in the TACE group were significantly higher than those in the N-TACE group. However, there was no significant difference in the postoperative DFS rate and OS rate of HCC patients without MVI between the TACE group and the N-TACE group. Further Cox regression analysis of the effect of adjuvant TACE therapy on the long-term prognosis of HCC patients with MVI showed that adjuvant TACE therapy significantly prolonged the postoperative DFS and OS of HCC patients with MVI. After matching, the risk of postoperative recurrence and death in the TACE group was 0.57 times and 0.64 times that of the N-TACE group, respectively. Postoperative adjuvant TACE therapy can significantly reduce the risks of recurrence, metastasis, and mortality in HCC patients with MVI, thereby improving

survival outcomes in this population.

In summary, the above results indicate that TACE treatment can reduce the risk of postoperative recurrence and metastasis of HCC patients with MVI, and improve their DFS rate and OS rate, but it does not bring significant survival benefits to patients without MVI. Kaewdech *et al.* summarized the data of patients with hepatitis B-related HCC combined with MVI and found that the 2-year tumor-free survival rate (23.4%) after hepatectomy in the TACE group was significantly higher than that in the N-TACE group (12.9%) (17). Sun *et al.* retrospectively analyzed the data of HCC patients with MVI and found that the median recurrence time and median survival time in the TACE group were 26.4 and 51.2 months, respectively, which were significantly higher than those in the N-TACE group (10.6 and 26.9 months, respectively) (18). A further prospective analysis of 186 patients showed that even for MVI-positive HCC patients, early HCC could benefit from TACE. Here, our results are consistent with the above studies (17-19). In addition, using the propensity score matching method, we also paired HCC patients with and without MVI according to the TACE treatment. On this basis, we comprehensively evaluated the clinical value of TACE treatment for postoperative survival of HCC with and without MVI.

TACE treatment significantly improved the prognosis of HCC patients with MVI. We suppose that the underlying mechanism may be as follows: according to the principle of tumor cell proliferation kinetics, tumor burden decreases after tumor removal, and residual cancer cells grow faster (20,21). Most tumor cells may enter the proliferative phase and such cells are more sensitive to chemotherapeutic drugs (22,23). Thus, postoperative intervention with TACE allows chemotherapeutic drugs entering the hepatic artery to inhibit and remove tumor cells in the proliferation phase in the microvessels and eliminate micro-cancer thrombi in the microvessels more effectively (24). In addition, there are often small anastomotic branches between the hepatic artery and the portal vein, and TACE may directly eliminate the MVI in the small branches of the portal vein through this mechanism (25). However, it has been suggested that TACE may damage the neovascularization of tumors, reduce the body's immunity, and damage liver function, thereby increasing the risk of tumor cell proliferation (26,27). Another study has shown that the increase in microvessel density and VEGF in HCC patients after TACE treatment will accelerate the metastasis of tumor cells in microvessels (28). Therefore, postoperative adjuvant TACE therapy should not be abused. In clinical practice, it

should be determined according to the specific conditions of the patient.

Moreover, in this study, two random forest prediction models were established to predict postoperative DFS and OS of HCC patients with MVI, respectively, and the importance score of each characteristic variable reflected the contribution rate of each variable to the model. Among them, postoperative adjuvant TACE therapy played a key role in the accuracy and generalization ability of the model, which further indicates that postoperative adjuvant TACE therapy plays a crucial role in improving postoperative DFS and OS of HCC patients with MVI. In addition to confirming the significance of postoperative adjuvant TACE therapy for the postoperative survival of HCC patients, this study also found via the random forest model that the expression status of VEGF was also an important factor affecting the postoperative survival of HCC patients combined with MVI (29). This suggests that in cases where HCC patients combined with MVI have positive VEGF expression, molecular targeted drugs such as sorafenib, aimed at inhibiting the formation and growth of new tumor blood vessels, may be necessary in addition to adjuvant TACE therapy to achieve an optimal therapeutic outcome.

While postoperative adjuvant TACE treatment effectively controls residual cancer lesions and eliminates residual cancer cells, it has its limitations, especially in patients with positive VEGF expression (29). VEGF can induce the formation of new blood vessels in liver cancer tissue, promoting the progression and metastasis of residual tumors (29). Thus, besides postoperative adjuvant TACE treatment, such patients might require additional molecular targeted drugs, e.g., sorafenib, to counteract the effect of VEGF, thereby enhancing the efficacy of adjuvant TACE therapy and improving patient survival benefits.

Random forest is a supervised learning method designed to sample samples and variables, thus generating a large number of decision trees, constructing multiple prediction models, and summarizing the results of the models to improve accuracy. Moreover, random forest uses unbiased estimation, and the model has strong generalization ability. Additionally, during the operation of the random forest model, approximately 1/3 of the samples are generated as the model's validation set, and out-of-bag prediction error can be obtained by comparing it with the actual observations. Compared with studies without external validation, this is a major advantage of random forests. Therefore, the results of the random forest model

constructed in this study are relatively reliable, accurate, and effective. Nevertheless, the small sample size was one of the limitations of this study. Further studies are warranted.

In summary, our study utilized propensity score matching and random forest analysis to evaluate the clinical significance of postoperative adjuvant TACE in improving survival outcomes for HCC patients with MVI. The random forest prediction model was developed based on postoperative adjuvant TACE therapy to forecast postoperative survival in HCC patients with MVI. The model's accuracy was validated using out-of-bag data generated during the decision tree construction process and data in the validation group. The results demonstrated that: postoperative adjuvant TACE therapy significantly prolongs survival in HCC patients with MVI; the constructed random forest prediction model based on adjuvant TACE therapy can accurately predict postoperative survival outcomes for HCC patients with MVI. For patients with upregulated VEGF expression, postoperative supplementation with molecular targeted drugs against VEGF may be necessary to enhance the efficacy of adjuvant TACE therapy and improve patient survival benefits. There are some limitations to our study, the sample size is relatively small. In addition, this article did not explore the influencing factors and specific mechanisms of TACE treatment in improving the prognosis of HCC patients with MVI. Our conclusions still need to be further confirmed by prospective randomized controlled studies with larger samples.

Conclusions

Postoperative adjuvant TACE improves the survival of HCC patients with MVI. The random forest prediction model has a good value for predicting the survival of HCC patients with MVI.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2585/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2585/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (No. K202103-04) and individual consent for this retrospective analysis was waived due to the retrospective nature of the study and the anonymous nature of patient information.

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