Original Article

Development and validation of a clinical factors and body fat distribution-based nomogram to predict refractoriness of transarterial chemoembolization in hepatocellular carcinoma

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Background: Transarterial chemoembolization (TACE) is an important treatment modality for hepatocellular carcinoma (HCC). However, some patients may develop TACE refractoriness during treatment. We aimed to construct a prediction model incorporating computed tomography (CT) body composition and clinical factors to preoperatively predict the risk of developing TACE refractoriness in patients with HCC, enabling the rapid identification of patients at high risk of TACE refractoriness.

Methods: This study included 128 HCC patients treated with TACE who were randomly assigned to the training (n=89) and validation groups (n=39) in a 7:3 ratio. Multiple body-composition parameters were outlined from CT images of the third lumbar vertebra level of each patient. Standardized values of body-composition parameters were calculated, such as visceral-to-subcutaneous adipose tissue area ratio (VSR). Multifactor logistic regression analysis was performed to identify independent predictors of TACE-refractoriness in patients and to develop predictive models. High- and low-risk subgroup analyses were performed for the predictive model.

Results: Alpha-fetoprotein (AFP) level (P=0.041), tumor size (P=0.001), and VSR (P=0.043) were independent risk factors for TACE refractoriness. The combined clinical-body composition model had an area under the curve (AUC) value of 0.875 in the training cohort and an AUC value of 0.837 in the validation cohort. Calibration curves and decision curves revealed the specific optimal performance and clinical utility of the combined model. Subgroup analysis showed differences in predicted TACE refractoriness between the high- and low-risk groups (P<0.001).

Conclusions: The combined clinical-body fat distribution model has the good performance in predicting a patient's risk of TACE refractoriness preoperatively and can help clinicians make the best clinical decisions in advance for the treatment of high-risk patients.

Keywords: Hepatocellular carcinoma (HCC); body composition; body fat distribution; transarterial chemoembolization refractoriness (TACE refractoriness); nomogram

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor worldwide and has the second highest mortality rate among malignant tumors (1). According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) is considered the standard treatment for patients with intermediate stage HCC (2). HCC usually requires multiple repetitions of TACE therapy to control tumor progression (3). The concept of TACE-refractory/failed was first introduced by the Japanese Society of Hepatology (JSH) and revised in 2014 and 2021 (4,5). The revised definition of TACE refractoriness by the JSH has been accepted in several Asian clinical treatment guidelines. The concept of TACE failure/refractory has been widely introduced in clinical trials of HCC (6,7).

Recently, several studies have begun to focus on the effect of body composition on the prognosis of patients with HCC (8-11). Computed tomography (CT) allows quantitative measurement and adequate differentiation of body composition, such as skeletal muscle (SM), subcutaneous fat, visceral fat, etc. and is considered an important technique for assessing body composition (12). The body composition parameters that have been studied more frequently are SM and adipose tissue, and changes in these body composition parameters have been associated with poor prognosis in patients with tumors, including HCC (13-15). To our knowledge, studies on the possible correlation between SM and adipose tissue and TACE refractoriness in patients with HCC are still lacking.

Repeated TACE therapy is associated with increased angiogenesis and embolization-related liver injury, and may even counteract the benefits achieved by TACE therapy in tumors and adversely affect overall survival (16,17). It may be undesirable for TACE-refractory patients to pursue repeated TACE to control tumor progression in clinical practice. Therefore, it is important to carefully assess the indications for TACE and appropriately identify TACE failure/refractoriness to prevent deterioration of liver function due to ineffective TACE.

In this study, we focused on the effect of body composition on refractoriness to TACE treatment for HCC. Our goal was to develop and validate a noninvasive and easily applied predictive model that can accurately predict the risk of TACE refractoriness preoperatively. We present this article in accordance with the TRIPOD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-963/rc).

Methods

Patients

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Hunan Cancer Hospital. Informed consent was waived because the data of patients were collected retrospectively. All patients' data were anonymized before analysis. This study retrospectively screened 745 patients diagnosed with HCC and treated with TACE between June 2013 and October 2021 in Hunan Cancer Hospital. Based on the inclusion and exclusion criteria, a total of 128 patients were finally included in the study, and the clinical data of all patients were collected. Inclusion criteria were as follows: (I) HCC diagnosed by pathological biopsy, cytology or imaging according to the diagnostic criteria for HCC established by the American College of Hepatology; (II) 18–75 years of age; (III) receiving TACE treatments; (IV) patients with BCLC stage A or B; (V) and enhanced CT examination within two weeks before the first TACE procedure.

Exclusion criteria were as follows: (I) incomplete clinical and imaging data; (II) initial treatment was not TACE; (III) time interval between the first and second TACE was more than 3 months; (IV) combination of other antitumor treatments; (V) extrahepatic metastasis or combination of malignant tumors from other sites; (VI) missed visits. The study flow is shown in *Figure 1*.

Treatment

TACE was performed within two weeks of the patient's diagnosis of HCC, and all patients were treated with conventional TACE. All procedures were performed by interventionalists with over 10 years of experience. Using the Seldinger technique, a 5 F arterial catheter was inserted into the femoral artery after local anesthesia. The catheter was then advanced into the hepatic artery, and digital subtraction angiography was performed. All patients underwent abdominal trunk and superior mesenteric artery angiography to assess hepatic vascular circulation prior to treatment. Tumor trophoblastic vessels were hyperselected using 2.7 F or 2.2 F microcatheters, if necessary, depending on liver involvement and vascular anatomy. TACE was performed using an oil iodide emulsion containing an

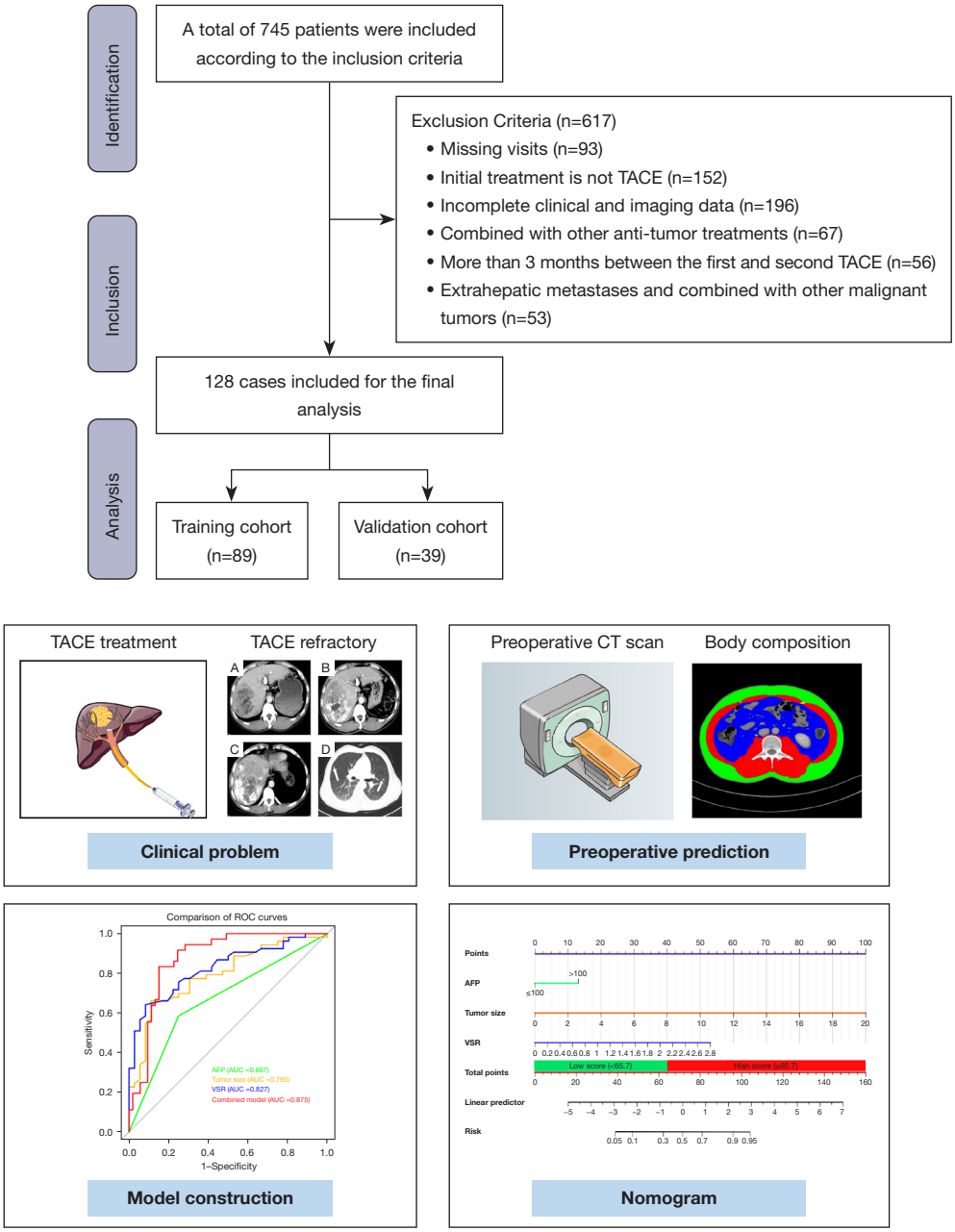

Figure 1 Inclusion and exclusion steps for patient selection and flow chart for this study. TACE, transarterial chemoembolization; CT, computed tomography; ROC, receiver operator characteristic; AUC, area under the curve; AFP, alpha-fetoprotein; VSR, visceral-to-subcutaneous adipose tissue area ratio.

epirubicin mix. TACE was performed using 20 mL of iodinated oil emulsion containing a mixture with epirubicin. Using the water-in-oil technique, the oil-epirubicin emulsion is prepared by mixing iodinated oil with a distilled water solution containing the dissolved epirubicin drug mixture in a 3:1 ratio. The dose of epirubicin in conventional TACE is 50–75 mg/m^2. in conventional TACE, after injection of epirubicin oil emulsion, gelatin sponge slurry is injected to embolize the proximal tumor vessels. The technical endpoint of TACE was defined as a decrease in tumor artery inflow and tumor vessel dissection and loss of tumor staining. When there was an inadequate

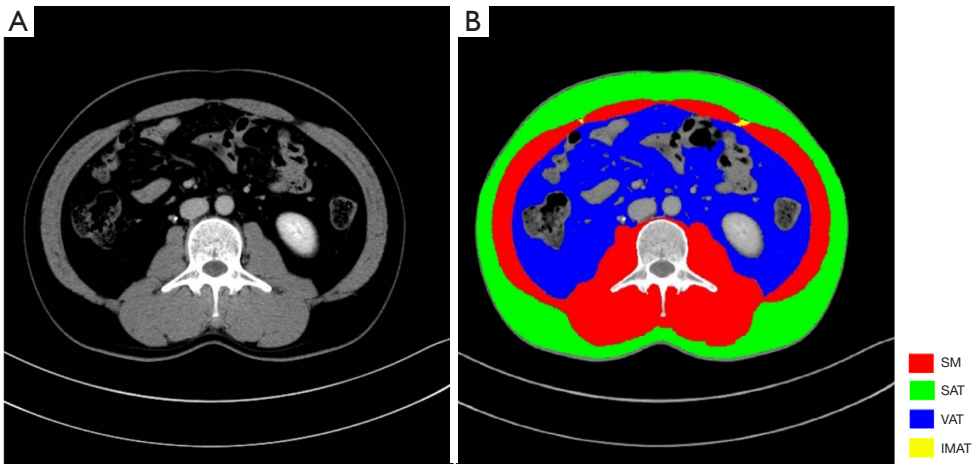

Figure 2 Schematic diagram of the body composition at the level of the L3 vertebra. (A) Original image; (B) schematic diagram of body composition. Red, green, blue and yellow represent the SM, SAT, VAT and IMAT, respectively. SM, skeletal muscle; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; IMAT, intermuscular adipose tissue.

response after the first TACE procedure, the embolic agent, chemotherapeutic agent or tumor donor artery was reselected in the second TACE procedure, and the protocol was adjusted according to liver function and peripheral leukocyte and platelet levels.

Definition and follow-up of TACE refractoriness

The JSH revised definition of TACE refractoriness in 2021 states the following (5): (I) 2 or more consecutive hepatic progressions with poor target tumor response (viable lesion >50%) or new tumor lesions at CT/magnetic resonance imaging (MRI) response assessment 1 to 3 months after elective TACE even with chemotherapy drug change and/or reconfirmation of tumor arteries; (II) extrahepatic metastases or vascular invasion; (III) a decrease in tumor marker level is not observed immediately after TACE, or only a minimal and transient decrease is observed, but a trend of increasing tumor marker levels immediately follows the procedure.

Enhanced CT or MRI images and clinical data were obtained for all patients before and after the first and second TACE treatments. Two abdominal radiologists with extensive experience who were not involved in body composition analysis evaluated all available follow-up CT or MRI images 1–3 months after TACE to determine the response to TACE treatment for HCC.

CT scan analysis of body composition

Enhanced CT scans of the abdomen were performed within two weeks before/after the first TACE treatment, pre-treatment images were used for analysis, and the abdominal CT image parameters were as follows: 5-mm layer thickness, 120 kVp, 250 mA, and 40 cm field of view. The CT image data of all patients were stored in the picture archiving and communication system and output in DICOM format.

All patients were randomly divided into a training cohort and a validation cohort. The areas of SM, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and intermuscular adipose tissue (IMAT) at the level of L3 on CT images in the venous phase were measured separately in this study using ImageJ software (https://imagej.nih.gov/ij/). The area of SM at the level of third lumbar vertebra included the psoas major, rectus abdominis internal and external oblique muscles as well as the transverse abdominis, lumbar square and erector spinae muscles. Heinz unit (HU) thresholds were used to differentiate body component tissues: −29 to +150 HU for SM, −190 to −30 HU for subcutaneous and intermuscular fat, and −150 to −50 HU for visceral fat (*Figure 2*). The cross-sectional area of each variable was then normalized by dividing by the square of the patient's height (m^2) to obtain an index (cm^2/m^2). The skeletal muscle index (SMI) was calculated as

the area of SM at the third lumbar vertebra level divided by the square of height (cm^2/m^2). The visceral adipose tissue index (VATI), subcutaneous adipose tissue index (SATI), and intermuscular adipose tissue index (IMATI) were defined as the adipose tissue area divided by the square of the height (cm^2/m^2). The total adipose tissue index (TATI) was defined as the sum of VATI and SATI, and visceral-to-subcutaneous adipose tissue area ratio (VSR) was defined as the ratio of VAT to SAT area.

Two trained radiologists measured and assessed SM, SAT, VAT, and IMAT together and discussed until agreement was reached on each assessment.

Statistical analysis

Continuous variables in patient clinical data were expressed as the mean and standard deviation or median and interquartile range, and categorical variables were expressed as percentages. Continuous variables between the two groups were tested using the *t*-test or the Mann-Whitney *U* test. Categorical variables were tested using the chi-square test. Univariate and multivariate analyses were performed to confirm clinical factors for TACE refractoriness. Clinical factors with P<0.05 in the univariate logistic regression analysis were included in the multivariate analysis, and independent predictors of TACE refractoriness were identified and modeled in the multivariate logistic regression analysis. Multiple model prediction accuracy in the training cohort and validation cohort was quantified by the area under the curve (AUC). Nomograms were used to visualize the prediction models and calculate the risk of occurrence for each patient, and calibration curves and decision curves were used to evaluate model performance. Patients were grouped into high- and low-risk groups for subgroup analysis based on the receiver operator characteristic (ROC) curve best cutoff values. Statistical analyses were performed using R software (version 3.6.3, http://www.r-project.org). All statistical tests were two-sided, and P<0.05 was considered statistically significant.

Results

Baseline characteristics of the patient's clinical and body composition

The 128 patients with HCC treated with TACE were randomly divided into training and validation cohorts, and all TACE procedures were technically successful. *Table 1* summarizes the training cohort (n=89) and the validation cohort (n=39) as well as patient clinical data and body composition characteristics. The mean age of all patients was 56 years, and the majority of patients were male (88.3%). There was no significant difference between the training and validation cohorts for the remaining variables except for the significant difference between the training and validation cohorts for satellite nodules on CT images (P=0.031). The total number of patients included 56 (43.8%) TACE-refractory patients and 72 (56.2%) non-TACE-refractory patients. The training and validation cohorts included 36 (40.4%) and 20 (51.3%) TACE-refractory patients, respectively, and there was no significant difference in the prevalence of TACE between the two groups (P=0.35).

Independent risk factors for TACE refractoriness

Figure 3 shows a case of a typical TACE-refractory patient. The results of univariate and multivariate logistic analyses of clinical data and body composition of the training cohort are shown in *Table 2*. The results of the univariate analysis showed the following factors with P<0.05: tumor size (P<0.001), alpha-fetoprotein (AFP) >100 (ng/mL) (P=0.002), cirrhosis (P=0.049), VATI (P=0.013), and VSR (P<0.001). Further multivariate logistic analysis revealed that tumor size [P=0.001; odds ratio (OR): 1.55, 95% confidence interval (CI): 1.2–2.01], AFP >100 ng/mL (P=0.041; OR: 3.31, 95% CI: 1.01–10.87), and VSR (P=0.043; OR: 4.04, 95% CI: 1.02–16.04) were independent predictors of TACE refractoriness in HCC patients.

Clinical and body composition model construction

AFP level, tumor size, and VSR were used as independent risk factors to construct prediction models and plot ROC curves separately. The AUC values for AFP in the training cohort and validation cohort were 0.667 (95% CI: 0.569–0.766) and 0.770 (95% CI: 0.634–0.905), respectively. The AUC values for tumor size in the training cohort and validation cohort were 0.827 (95% CI: 0.743–0.911) and 0.778 (95% CI: 0.620–0.935), respectively. The AUC values for VSR in the training cohort and validation cohort were 0.793 (95% CI: 0.699–0.887) and 0.733 (95% CI: 0.566–0.900), respectively.

Table 1 Baseline demographics of patients included in the study

Characteristic	All patients (N=128)	Training cohort (N=89)	Validation cohort (N=39)	P value
Age (years)	56±11	56±11	55±11	0.58
Gender				0.97
Female	15 (11.7)	11 (12.4)	4 (10.3)	
Male	113 (88.3)	78 (87.6)	35 (89.7)	
ALT (U/L)	38.9 (27.7–60.0)	37.3 (27.0–57.6)	47.2 (34.0–62.7)	0.06
AST (U/L)	49.4 (36.4–70.9)	46.0 (36.5–67.5)	56.2 (35.5–84.5)	0.14
Albumin (g/L)	38.1±4.8	38.5±4.6	37.2±5.3	0.17
TB (μmol/L)	15.5 (12.5–22.0)	15.8 (12.6–21.9)	15.3 (12.3–20.9)	0.66
PT (s)	13.2 (12.4–14.1)	13.2 (12.5–14.0)	13.3 (12.1–14.4)	0.84
NLR	2.8 (1.9–4.3)	2.9 (1.9–4.5)	2.8 (1.7–4.0)	0.47
Tumor size (cm)	6.5 (5.8–9.9)	7.3 (5.8–9.5)	6.0 (5.1–8.6)	0.25
Child-Pugh grade				0.73
A	115 (89.8)	81 (91.0)	34 (87.2)	
B	13 (10.2)	8 (9.0)	5 (12.8)	
ECOG				0.46
0	61 (47.7)	40 (44.9)	21 (53.8)	
1	67 (52.3)	49 (55.1)	18 (46.2)	
HBV				0.77
Negative	13 (10.2)	10 (11.2)	3 (7.7)	
Positive	115 (89.8)	79 (88.8)	36 (92.3)	
AFP (ng/mL)				0.64
≤100	60 (46.9)	40 (44.9)	20 (51.3)	
>100	68 (53.1)	49 (55.1)	19 (48.7)	
Satellite				0.035
Negative	98 (76.6)	63 (70.8)	35 (89.7)	
Positive	30 (23.4)	26 (29.2)	4 (10.3)	
Tumor number				0.10
Single	60 (46.9)	37 (41.6)	23 (59.0)	
Multiple	68 (53.1)	52 (58.4)	16 (41.0)	
Cirrhosis				0.38
Negative	65 (50.8)	48 (53.9)	17 (43.6)	
Positive	63 (49.2)	41 (46.1)	22 (56.4)	
BCLC				0.19
A	9 (7.0)	4 (4.5)	5 (12.8)	
B	119 (93.0)	85 (95.5)	34 (87.2)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	All patients (N=128)	Training cohort (N=89)	Validation cohort (N=39)	P value
VATI (cm^2/m^2)	29.7 (17.1–48.1)	29.0 (16.4–48.1)	31.6 (20.3–48.4)	0.73
SATI (cm^2/m^2)	31.9 (19.1–47.4)	30.0 (18.2–44.2)	35.0 (21.2–49.9)	0.43
VSR (cm^2/m^2)	0.92 (0.67–1.34)	0.93 (0.66–1.35)	0.91 (0.70–1.27)	0.77
TATI (cm^2/m^2)	64.4 (37.7–92.2)	62.2 (36.9–93.0)	68.8 (44.4–91.7)	0.55
SMI (cm^2/m^2)	47.6±7.4	47.7±7.4	47.4±7.5	0.82
IMATI (cm^2/m^2)	2.4 (1.5–4.0)	2.3 (1.6–3.7)	2.9 (1.4–4.3)	0.72
TACE refractoriness				0.35
No	72 (56.2)	53 (59.6)	19 (48.7)	
Yes	56 (43.8)	36 (40.4)	20 (51.3)	

Continuous variables are expressed as means (± standard deviations) or medians (interquartile ranges), and categorical variables are expressed as numbers (percentages). ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; PT, prothrombin time; NLR, neutrophil-to-lymphocyte ratio; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; VSR, visceral-to-subcutaneous adipose tissue area ratio; TATI, total adipose tissue index; SMI, skeletal muscle index; IMATI, intermuscular adipose tissue index; TACE, transarterial chemoembolization.

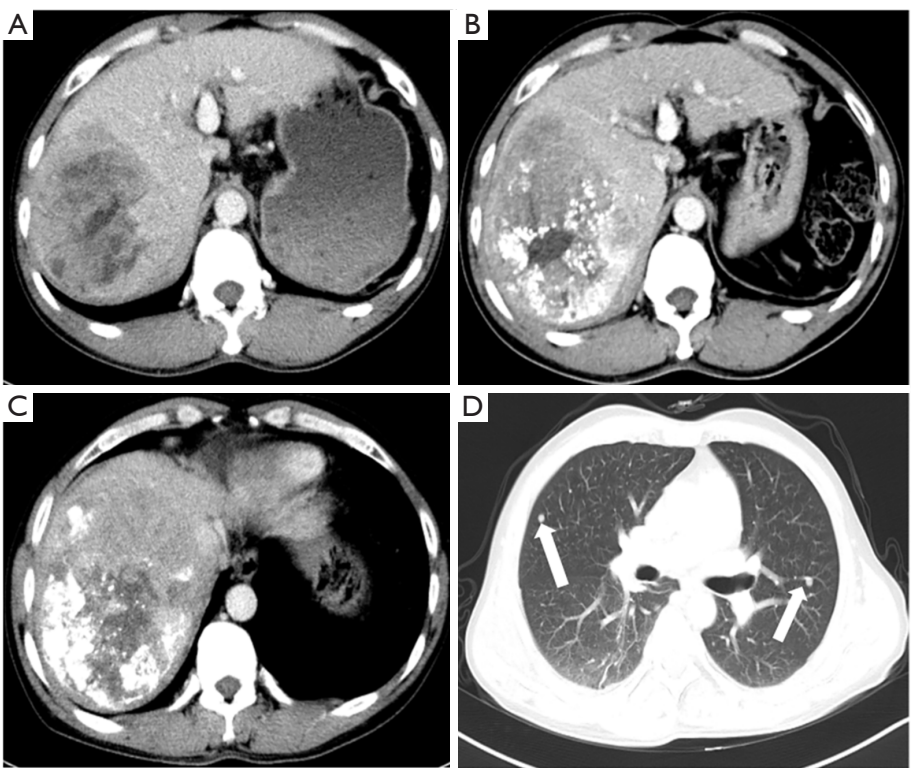

Figure 3 A 46-year-old male patient with hepatocellular carcinoma treated with TACE presented with TACE refractoriness after two consecutive TACE procedures. Baseline enhanced CT showed a 10.5-cm-sized tumor with heterogeneous enhancement (A). Follow-up enhancement CT after two TACE treatments showed a progressively larger and >50% surviving tumor (B,C) with bilateral lung metastases (D, white arrows). TACE, transarterial chemoembolization; CT, computed tomography.

Table 2 Univariate and multivariate logistic analysis in training cohort

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age (years)	0.99 (0.95–1.03)	0.61		
Gender				
Female	1			
Male	1.22 (0.33–4.51)	0.77		
Albumin	1.02 (0.93–1.11)	0.75		
ALT	1.00 (0.98–1.01)	0.54		
AST	0.99 (0.98–1.01)	0.33		
Tumor size (cm)	1.68 (1.32–2.13)	<0.001	1.55 (1.2–2.01)	0.001
AFP (ng/mL)				
≤100	1			
>100	4.23 (1.67–10.73)	0.002	3.31 (1.01–10.87)	0.041
Tumor number				
Single	1			
Multiple	2.19 (0.9–5.33)	0.08		
Cirrhosis				
Negative	1			
Positive	0.41 (0.17–1.00)	0.049	0.72 (0.22–2.28)	0.57
BCLC				
A	1			
B	0.67 (0.09–4.96)	0.69		
VATI	1.03 (1.01–1.05)	0.013	1.01 (0.98–1.04)	0.36
SATI	1 (0.98–1.03)	0.88		
VSR	9.87 (3.13–31.1)	<0.001	4.04 (1.02–16.04)	0.043
TATI	1.01 (1–1.02)	0.13		
SMI	1.01 (0.95–1.07)	0.84		
IMATI	0.98 (0.76–1.26)	0.86		

"1" means reference value. CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; VATI, visceral adipose tissue index; SATI, subcutaneous adipose tissue index; VSR, visceral-to-subcutaneous adipose tissue area ratio; TATI, total adipose tissue index; SMI, skeletal muscle index; IMATI, intermuscular adipose tissue index.

Construction and evaluation of a combined clinical-body composition model

The AFP level, tumor size, and VSR were combined to construct a combined clinical-body composition prediction model and plot ROC curves (*Figure 4A*,*4B*), and the combined model performed best in predicting TACE refractoriness in both the training and validation cohorts. The combined model had an AUC value of 0.875 (95% CI: 0.802–0.949) with a sensitivity of 83.3% and specificity of 89.5% in the training cohort and an AUC value of 0.837 (95% CI: 0.705–0.969) with a sensitivity of

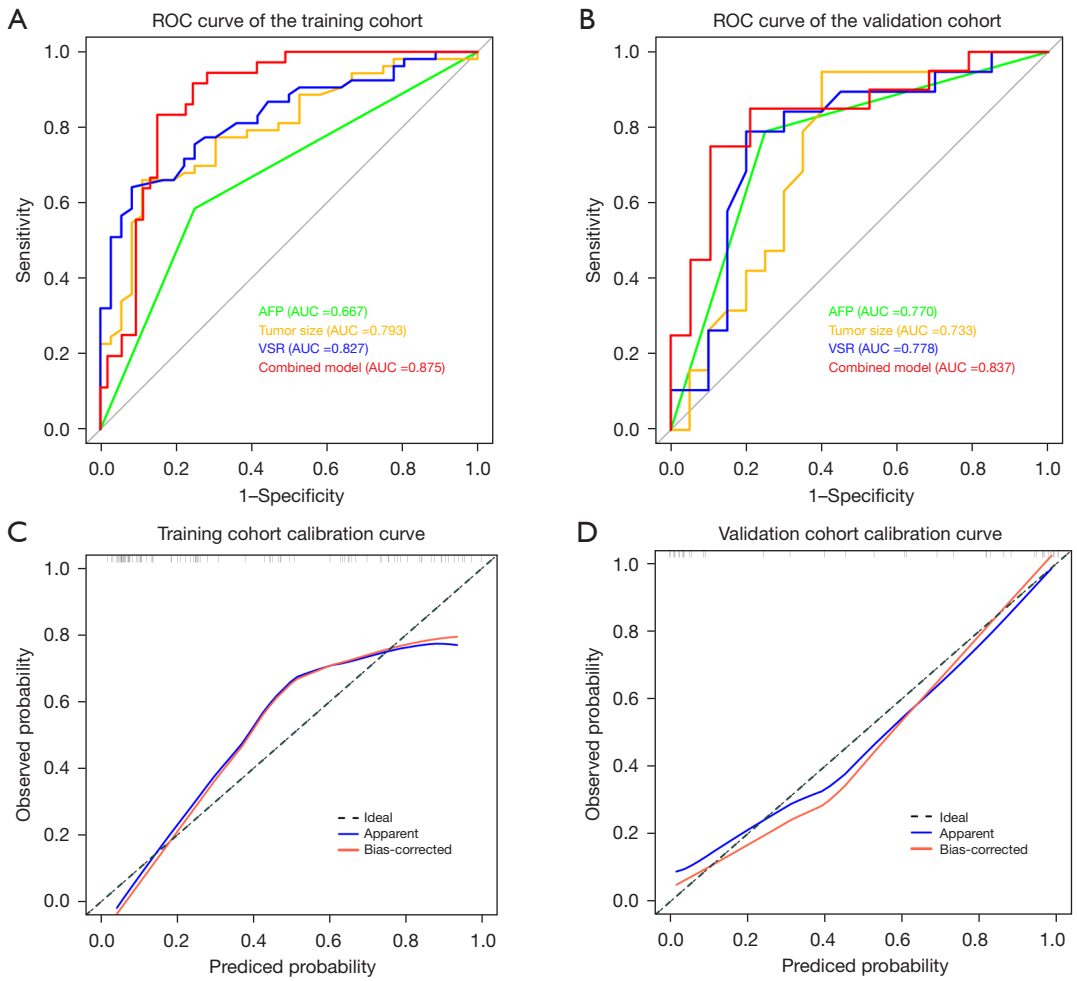

Figure 4 Construction and validation of the combined model for predicting transarterial chemoembolization refractoriness in hepatocellular carcinoma. ROC curves and the AUC values for the clinical model, the ratio of VSR model, and the combined model in the training cohort (A) and the validation cohort (B). Calibration curves for the combined clinical-body composition model in the training cohort (C) and validation cohort (D). ROC, receiver operating characteristic; AFP alpha-fetoprotein; AUC, area under the ROC curve; VSR, visceral adipose tissue to subcutaneous adipose tissue area.

75.0% and specificity of 84.9% in the validation cohort. The performance of the different models to predict TACE refractoriness in the training and validation cohorts is shown in *Table 3*. The calibration curve showed good agreement between the training and validation cohorts in predicting the occurrence of TACE refractoriness and the true situation (*Figure 4C*,*4D*). The nomogram visualized the prediction model (*Figure 5*), and the risk scores of the relevant variables can be calculated from the baseline situation of the patient before TACE treatment with the nomogram. Finally, the risk of refractory outcome after TACE treatment is determined from the total score. Decision curve analysis (DCA) showed that the net clinical benefit of the combined clinical-body composition model was higher than that of either the clinical model (AFP level and tumor size) or the body composition VSR model alone over a wide range of threshold probability intervals (*Figure 6*).

Subgroup analysis

The ROC based on the combined model of the training cohort determined the optimal cutoff value of 65.7 for the Youden index. The total score for each patient was determined and stratified to represent high- and low-

Table 3 Predictive performance of different models in the training and validation cohorts

Models	Cohort	Sensitivity	Specificity	Accuracy	AUC (95% CI)
AFP	Training cohort	0.75	0.789	0.652	0.667 (0.569–0.766)
	Validation cohort	0.75	0.585	0.763	0.770 (0.634–0.905)
Tumor size	Training cohort	0.917	0.789	0.795	0.827 (0.743–0.911)
	Validation cohort	0.8	0.642	0.753	0.778 (0.620–0.935)
VSR	Training cohort	0.889	0.860	0.769	0.793 (0.699–0.887)
	Validation cohort	0.6	0.717	0.724	0.733 (0.566–0.900)
Combined model	Training cohort	0.833	0.895	0.843	0.875 (0.802–0.949)
	Validation cohort	0.75	0.849	0.821	0.837 (0.705–0.969)

AUC, area under the curve; CI, confidence interval; AFP, alpha-fetoprotein; VSR, visceral-to-subcutaneous adipose tissue area ratio.

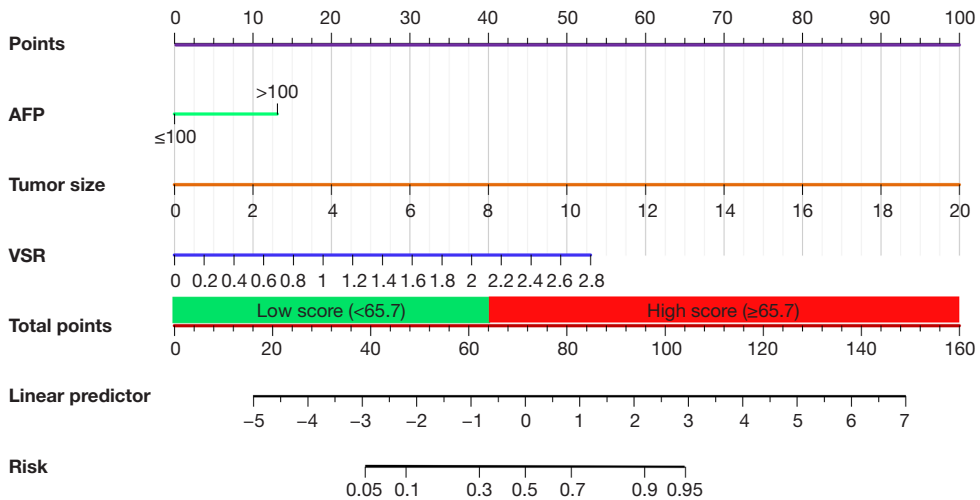

Figure 5 Nomogram incorporating clinical-body combined model predicts transarterial chemoembolization refractoriness in hepatocellular carcinoma. AFP, alpha-fetoprotein; VSR, visceral-to-subcutaneous adipose tissue area ratio.

risk groups based on the cutoff value. Patients with a total score <65.7 in both the training cohort and the validation cohort were considered the low-risk subgroup, and those with a score ≥65.7 were considered the high-risk subgroup. The difference in prevalence of TACE-refractoriness between the low-risk and high-risk subgroups was statistically significant in the training cohort (18.9% *vs.* 88.9%; P<0.001) and the validation cohort (30% *vs.* 94.7%; P<0.001) (*Table 4*). We found that the prevalence of TACE refractoriness was higher in all high-risk groups than in the low-risk group, suggesting that the combined prediction model can help identify and guide the clinical management of high-risk TACE-refractory patients.

Discussion

Our study constructed a noninvasive, convenient, and easy-to-use model to preoperatively predict the risk of TACE refractoriness in HCC patients after TACE. To the best of our knowledge, our study is the first to propose that TACE refractoriness in HCC patients is associated with body composition VSR. The prediction model performed better in both the training cohort and the validation cohort. Based on these results, our model can help to appropriately select patients for TACE treatment, and make more rational and scientific decisions about TACE treatment; making the decision to switch to molecular targeted therapy or

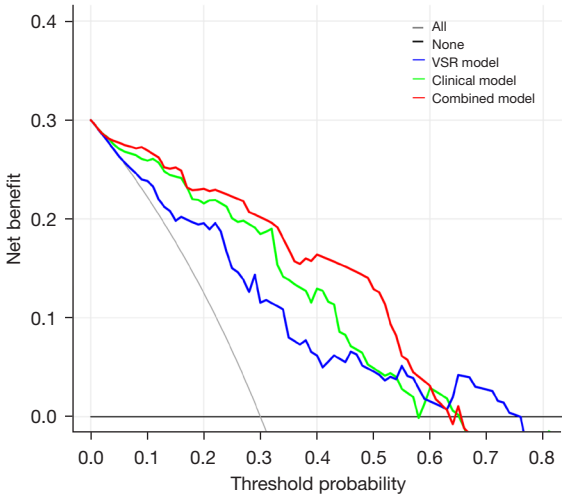

Figure 6 Decision curve analysis of different prediction models. The black solid line represented the use of the full no-intervention protocol for these patients. The solid gray line represented the use of the full intervention protocol for these participants. The blue line represented the VSR model, the green line represented the clinical model, and the red line represented the combined model. The threshold probability was defined as the point at which the expected benefit of the intervention was equal to the benefit of avoiding intervention. The results indicated that the combined model provided a greater net benefit than the clinical model and VSR model (range, 0.05–0.6). VSR, visceral-to-subcutaneous adipose tissue area ratio.

Table 4 The incidences of TACE refractoriness in the low- and high-risk groups

Groups	Without TACE refractoriness, n (%)	With TACE refractoriness, n (%)	P value
Training cohort			
High-risk group	10 (18.9)	32 (88.9)	<0.001
Low-risk group	43 (81.1)	4 (11.1)	
Validation cohort			
High-risk group	6 (30.0)	18 (94.7)	<0.001
Low-risk group	14 (70.0)	1 (5.3)	

TACE, transarterial chemoembolization.

combination therapy earlier for patients at risk of TACE refractoriness is facilitated.

TACE is the standard of care for intermediate-stage HCC. However, the effectiveness of this treatment may be limited by the possibility of patients developing TACE refractoriness (18). According to JSH recommendations, ineffective TACE should not be repeated in patients who develop TACE refractoriness, and it is recommended that these patients be treated with systemic therapy (4). Therefore, patients at high risk of TACE refractoriness can be rapidly identified for timely conversion to combination therapy or molecular targeted therapy. Several scoring systems have been developed to predict TACE refractoriness (19). One study established a scoring system called the Assessment for Retreatment with TACE (ART) score. The ART scores included the increase of aspartate aminotransferase by >25%, an increase of Child-Pugh score of 1 or ≥2 points from baseline, and the absence of radiologic tumor response. Patients with an ART score ≥ 2.5 before the second TACE have a poor prognosis and may not benefit from further TACE therapy. However, given that radiologic response is a parameter of the ART score, prospective studies are needed to validate the ART score and incorporate the Modified Response Evaluation Criteria In Solid Tumors into the study design (20). Another study also constructed an included BCLC and AFP (>200 ng/mL) at baseline, increase in Child-Pugh score ≥2 from baseline, and absence of radiological response (ABCR) score. ABCR scores were significantly associated with median overall survival. An ABCR score >4 before a second TACE identifies patients with a poor prognosis who may not benefit from further TACE treatment. However, the ABCR score has limitations and it should be tested in different populations and validated in prospective trials (21). However, one study noted that neither score is sufficient to support definitive clinical decision making and that further efforts are needed to assess TACE refractoriness (22). Therefore, preoperative quantitative prediction of the risk of TACE refractoriness can provide critical information to guide decision making regarding TACE treatment in HCC patients.

In recent years, high VAT seemingly correlating with a risk factor for HCC in male patients with cirrhosis and for recurrence after liver transplantation (23). Sarcopenia has been one of the most evaluated body composition-related conditions, and its presence has been shown to be associated with poor prognosis, recurrence and overall complications in patients with HCC (8,24,25). However, the influence of body composition on the disease process still needs to be further explored. To address this question, we combined clinical factors and measures of multiple body compositions in HCC patients to assess the risk of TACE refractoriness

occurring. Regarding clinical factors, AFP and tumor size were associated with TACE refractoriness. Previous studies have shown that neutrophil-to-lymphocyte ratio (NLR) is a widely validated indicator of prognostic information for patients with HCC (26). Although NLR did not lead to this conclusion in our study, we also need to recognize the important role of NLR in the treatment as well as prognosis of HCC. We need to further explore the importance of NLR in future studies.

For body composition, the results showed that VSR was an independent risk factor associated with TACE refractoriness. The prediction model based on three independent risk factors including VSR further improved the predictive performance of clinical factors, and the combined model of the three had the optimal predictive performance, with AUCs of 0.875 (95% CI: 0.802–0.949) and 0.837 (95% CI: 0.705–0.969) in the training and validation cohorts, respectively. The calibration curves indicated that the combined model was a robust prognostic model. The DCA indicated that the combined model had high clinical application. According to the cutoff values of the model risk scores, patients in the high-risk group were more likely to develop TACE refractoriness than those in the low-risk group, suggesting that the model contributes to the risk classification of patients with TACE refractoriness. Based on these results, both clinical and body composition factors are indispensable for predicting TACE refractoriness.

For patients who are refractory to TACE, we think that the subsequent treatment should be different for patients with different conditions. If the internal target lesion is still in progression disease after two TACE treatments, it may be necessary to discontinue TACE and switch to other treatments, including systemic therapies such as targeted therapies, immune checkpoint inhibitor therapies, and combinations of other local therapies such as hepatic arterial infusion chemotherapy, transarterial radioembolization (Y90), ablation, and ^{125}I particle implantation. If vascular invasion or extrahepatic spread occurs after TACE, systemic therapy, such as targeted therapy combined with immunotherapy, is required. If vascular invasion or extrahepatic spread occurs after TACE, continuation of TACE is important to control the intrahepatic lesions, and a combination of other local therapies including TACE, such as ablation, transarterial radioembolization (Y90), and particle therapy, may be used.

In our study, there was no significant effect of SMI on the response to TACE therapy in HCC, and studies in larger cohorts may be needed to validate the relationship between the two. Our results showed that a higher VSR was associated with TACE refractoriness in patients with HCC, whereas VATI and SATI were not. This finding suggests that the distribution of adipose tissue, rather than the absolute value, is the main determinant of TACE treatment response in patients with HCC. Adipose tissue controls the function of other organs by secreting adipokines. There are significant differences in cytokine production between VAT and SAT (27). The accumulation of visceral fat increases the secretion of proinflammatory adipokines such as tumor necrosis factor-α and interleukin 6 by visceral adipocytes and decreases the level of the anti-inflammatory adipokine lipocalin (28), whereas the anti-inflammatory cytokine lipocalin is secreted by subcutaneous adipocytes (29). These results suggest that the balance between visceral and SAT is more important than VATI itself. Since free fatty acids and adipokines released from visceral fat flow directly to the liver through the portal vein, the liver is substantially affected by such changes (30). In contrast, subcutaneous fat effectively stores excess lipids and fats to prevent them from entering other organs. However, the present study cannot yet address the question of causality, and further basic and clinical studies are needed.

Our study still has some limitations: (I) this is a retrospective study with a small sample size and, therefore, may be subject to selection and statistical bias. (II) Due to the small sample size of the study and the relatively low clinical incidence of TACE refractoriness, a more detailed analysis was not possible, and a subsequent multicenter, large sample size prospective study is needed for further validation before more convincing conclusions can be drawn. (III) This study was observational; therefore, we cannot infer a causal relationship between body composition and TACE refractoriness. (IV) Our patients and results may not be applicable to HCC patients in non-hepatitis B populations, while more validation is needed. (V) Our choice of AFP ≥100 ng/mL may have some limitations, so we need to further explore the effect of different AFP levels on HCC TACE refractoriness in future studies.

Conclusions

In summary, our study provides a reliable, and noninvasive method to predict TACE refractoriness in patients with HCC before TACE treatment. This will likely help clinicians select timely modalities such as combination therapy or molecular targeted therapy and, thereby, improve

the prognosis of patients with HCC after TACE therapy.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-963/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-963/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. This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Hunan Cancer Hospital. Informed consent was waived because the data of patients were collected retrospectively.

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