Journal of Hepatocellular Carcinoma Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Prognostic Prediction and Risk Stratification of Transarterial Chemoembolization Combined with Targeted Therapy and Immunotherapy for Unresectable Hepatocellular Carcinoma: A Dual-Center Study

Wendi Kang[1,*], Huafei Zhao[2,*], Qicai Lian[3,*], Hang Li[1], Xuan Zhou[4], Hao Li[5], Siyuan Weng[1], Zhentao Yan[5], Zhengqiang Yang[1]

[1]Department of Interventional Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, People's Republic of China; [2]Department of Radiology, Guangdong 999 Brain Hospital, Guangzhou, 510080, People's Republic of China; [3]Department of Interventional Radiology, the Affiliated Cancer Hospital of Guizhou Medical University, Guiyang, 550000, People's Republic of China; [4]Department of Radiology, Third Xiangya Hospital, Central South University, Changsha, 410013, Hunan, People's Republic of China; [5]Department of Interventional Radiology, The First Hospital of China Medical University, Shenyang, 110001, Liaoning, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhengqiang Yang, Email yangzq@cicams.ac.cn

Purpose: The combination of transarterial chemoembolization, molecular targeted therapy, and immunotherapy (triple therapy) has shown promising outcomes in the treatment of unresectable hepatocellular carcinoma (HCC). This study aimed to build a prognostic model to identify patients who could benefit from triple therapy.

Patients and Methods: This retrospective study encompassed 242 patients with HCC who underwent triple therapy from two centers (Training cohort: 158 patients from the Center 1; External validation cohort: 84 patients from the Center 2). Independent predictors of overall survival (OS) and progression-free survival (PFS) were identified through Cox regression analyses, and prognostic models based on Cox proportional hazards models were developed. Prognosis was assessed using Kaplan – Meier curves.

Results: In the training cohort, independent predictors of PFS included vascular invasion and the C-reactive protein and alpha-fetoprotein in immunotherapy (CRAFITY) score. Independent predictors of OS were the CRAFITY score, extrahepatic metastasis, and the neutrophil-to-lymphocyte ratio. Prognostic prediction models were constructed based on these variables. The prognostic model for OS demonstrated a C-index of 0.715 (95% confidence interval (CI), 0.662–0.768) in the training cohort and 0.701 (95% CI, 0.628–0.774) in the validation cohort. Patients were divided into low- and high-risk categories using the predictive model ($P<0.001$). These findings were corroborated by the external validation cohort.

Conclusion: The developed prognostic model serves as a reliable and convenient tool to predict outcomes in patients with unresectable HCC undergoing triple therapy. It aids clinicians in making informed treatment decisions.

Keywords: hepatocellular carcinoma, combined regimen, transarterial chemoembolization, prognostic model, risk stratification, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is the third most prevalent cause of cancer-related death globally and the sixth most common type of cancer overall.[1] Radical surgical resection remains the primary curative approach for HCC. However, most patients are diagnosed with unresectable disease, leading to a poor prognosis.[2] The advent of targeted and

Received: 15 July 2024
Accepted: 23 October 2024
Published: 7 November 2024

immunotherapy has significantly transformed the treatment landscape for unresectable HCC.[3–5] Combining local therapies with systemic treatments offer a more comprehensive approach to managing the disease. Specifically, transarterial chemoembolization (TACE) combined with molecularly targeted therapy and immunotherapy has emerged as a crucial treatment modality for unresectable HCC.[6–8]

TACE is the cornerstone treatment for unresectable HCC.[9] When combined with molecularly targeted therapy and immunotherapy, TACE can yield synergistic antitumor effects.[10,11] A national multicenter study has demonstrated that TACE, in combination with molecularly targeted therapies and immunotherapy, offers superior efficacy in patients with HCC compared to TACE alone.[12] Numerous other studies have corroborated these findings, showing that the combination of TACE with targeted and immunotherapy is more effective compared to monotherapy with either TACE or tyrosine kinase inhibitors.[13–17] Despite the proven safety and efficacy of this triple therapy, identifying which patients will benefit most from it before treatment remains unclear, making the rational selection of triple therapy challenging. Currently, there is a lack of prognostic prediction models for patients with unresectable HCC undergoing triple therapy.

In this study, the prognosis of patients with HCC undergoing triple therapy was evaluated. The objective was to construct and validate a prognostic model to identify, prior to treatment, which patients would benefit from combined therapy, thereby guiding clinical treatment decisions more effectively.

Material and Methods

Patients

This study was approved by the Ethics Committee of the Cancer Hospital Chinese Academy of Medical Sciences and complied with the Declaration of Helsinki 1975 (Ethical number: 24/336-4616). Informed consent was waived in consideration of its retrospective nature and simultaneous confirmation that the data was anonymized or maintained with confidentiality. This retrospective study included patients who received triple therapy for HCC from January 2019 to August 2023 at two centers. The training cohort comprised patients from Cancer Hospital Chinese Academy of Medical Sciences, while the independent external validation cohort comprised patients from the Affiliated Cancer Hospital of Guizhou Medical University.

Inclusion criteria for this study encompassed: (1) age ≥18 years; (2) histologically or clinically confirmed diagnosis of Barcelona Clinical Cancer stage B or C HCC; (3) Child–Pugh classification of A or B; (4) Eastern Cooperative Oncology Group performance status of 0 or 1; and (5) initiation of triple therapy as first-line treatment. Exclusion criteria encompassed: (1) incomplete clinical data; (2) history of other malignancies; (3) receipt of other antitumor therapies before or after the initiation of combination therapy; and (4) incomplete follow-up information.

Treatment Procedures

All patients received standard conventional TACE treatment.[18] The entire TACE procedure was performed by an interventional radiologist with over 10 years of experience. The procedure began with puncturing the right femoral artery under local anaesthesia using the Seldinger technique. Subsequently, the number, position, size, and feeding arteries of the target lesion were then ascertained by performing a standard hepatic or celiac arteriogram. A microcatheter was then inserted superselectively into the artery supplying the tumor, through which a mixed emulsion of iodine oil (5–20 mL) and epirubicin was administered. This was followed by selective embolization using gelatine sponge particles to occlude blood flow in the feeding arteries. TACE treatment was repeated every 4–6 weeks based on ongoing assessments of the target tumor and liver function.

Patients received targeted therapy and immunotherapy within 30 days before or after the first TACE treatment, depending on the patient's overall health status and liver function recovery. Standard doses of molecularly targeted agents and immune checkpoint inhibitors were administered as detailed in the Table S1. Decisions regarding treatment interruptions, dose adjustments, or discontinuations were based on disease progression or the onset of intolerable adverse events.

Follow-Up

All patients underwent scheduled follow-up assessments. They underwent abdominal contrast-enhanced magnetic resonance imaging and computed tomography (CT), as well as chest CT, every 60 days (±7 days) after the start of combination therapy. Tumor response evaluations were conducted by two experienced radiologists with over 5 years of expertise, adhering to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Patient follow-up was maintained until death occurred or until the study's conclusion on 1 July 2024.

Research Endpoints

The primary endpoints of the study included overall survival (OS) and progression-free survival (PFS). OS was defined as the duration from the initiation of triple therapy to death from any cause or the last follow-up. PFS was defined as the duration from the initiation of triple therapy to the first occurrence of tumor progression or death. Secondary endpoints included the objective response rate and disease control rate.

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation or median (interquartile range) and were compared using Student's *t*-test or Mann–Whitney *U*-test. Categorical variables are expressed as percentages and compared using the chi-square or Wilcoxon rank sum test. Survival analyses were performed using the Kaplan–Meier method, and group comparisons were performed using the Log rank test. Univariate and multivariate Cox regression analyses were performed to identify independent predictors of PFS and OS. The discriminatory power of the prognostic model was assessed using the C-index and the area under the curve (AUC) of the receiver operating characteristic curve (ROC). Calibration curves were used to evaluate the model's performance, and a nomogram was constructed to visualize the model. External validation of the prognostic models was conducted using an independent external validation cohort. Statistical significance was set at $P<0.05$. Statistical analyses were performed using R software (version 3.6.1).

Results

Patient Characteristics

This study enrolled 242 patients with HCC who underwent triple therapy at two centers from January 2019 to August 2023, with 158 patients assigned to the training cohort and 84 to the external validation cohort. Table 1 presents the baseline characteristics of the included patients. In the training cohort, the median age was 55.2±10.8 years, and 140 (88.6%) patients were males. Between the two groups, there were no statistically significant differences in clinical variables ($P>0.05$).

Treatment Response and Survival Analysis

Table 2 presents the outcomes of the best tumor response. Among the patients, 12 (7.6%) patients achieved a complete response, 93 (58.8%) showed partial response, 39 (24.7%) had stable disease, and 14 (8.9%) experienced progressive disease. The disease control rate and objective response rate were highest at 91.1% and 66.4%, respectively. The training cohort's median OS and PFS were 27.6 months (95% CI, 24.6–32.8) and 12.0 months (95% CI, 10.6–14.6), respectively (Figure 1A and B).

Independent Prognostic Factors

Tables 3 and 4 summarize the findings of the univariate and multivariate Cox regression analyses identifying independent predictors of PFS and OS. In the multivariate analyses for PFS, the C-reactive protein (CRP) and alpha-fetoprotein (AFP) in immunotherapy (CRAFITY) score ($P<0.001$) and vascular invasion ($P=0.035$) emerged as independent prognostic factors. Similarly, the multivariate analysis for OS revealed that the CRAFITY score ($P=0.004$), neutrophil-to-lymphocyte ratio (NLR) ($P=0.003$), and presence of extrahepatic metastasis ($P=0.009$) were independent prognostic factors of OS.

Table 1 Baseline Characteristics of Patients in the Training Cohort and Independent Validation Cohort

Characteristic	Training cohort (n = 158)	Validation cohort (n=84)	P value
Age (years), mean ± SD	55.2±10.8	54.6±10.5	0.680
Sex			0.601
Female	18 (11.4)	7 (8.3)	
Male	140 (88.6)	77 (91.7)	
HBV			0.923
Negative	26 (16.5)	15 (17.9)	
Positive	132 (83.5)	69 (82.1)	
ECOG PS			0.892
0	110 (69.6)	57 (67.9)	
1	48 (30.4)	27 (32.1)	
Child-Pugh class			0.420
A	127 (80.4)	63 (75.0)	
B	31 (19.6)	21 (25.0)	
BCLC stage			0774
B	67 (42.4)	38 (45.2)	
C	91 (57.6)	46 (54.8)	
ALBI grade			0.809
1	60 (38.0)	34 (40.5)	
2 and 3	98 (62.0)	50 (59.5)	
NLR			0.862
<3	87 (55.1)	48 (57.1)	
≥3	71 (44.9)	36 (42.9)	
AFP (ng/mL)			0.615
<400	93 (58.9)	53 (63.1)	
≥400	65 (41.1)	31 (36.9)	
Vascular invasion			0.342
No	96 (60.8)	57 (67.9)	
Yes	62 (39.2)	27 (32.1)	
Extrahepatic metastasis			0.922
No	104 (65.8)	54 (64.3)	
Yes	54 (34.2)	30 (35.7)	
Tumor number			0.584
Single	52 (32.9)	24 (28.6)	
Multiple	106 (67.1)	60 (71.4)	
Tumor size (cm)			0.310
<5	35 (22.2)	26 (31.0)	
5–10	67 (42.4)	33 (39.2)	
>10	56 (35.4)	25 (29.8)	
CRAFITY score			0.243
0	54 (34.2)	35 (41.7)	
1	59 (37.3)	33 (39.3)	
2	45 (28.5)	16 (19.0)	

Abbreviations: SD, standard deviation; HBV, hepatitis B virus; ECOG PS, Eastern cooperative oncology group performance status; BCLC, Barcelona Clinic Liver Cancer; ALBI albumin-bilirubin; NLR: neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; CRAFITY, C-reactive protein and alpha-fetoprotein in immunotherapy.

Table 2 Radiological Tumor Responses mRECIST and Clinical Efficacy in the Training Cohort

Best response, n (%)	Training cohort (n = 158)
Complete response	12 (7.6)
Partial response	93 (58.8)
Stable disease	39 (24.7)
Progressive disease	14 (8.9)
Objective response rate, n (%)	105 (66.4)
Disease control rate, n (%)	144 (91.1)

Abbreviation: mRECIST, modified response evaluation criteria in solid tumors.

Development and Validation of the Prognostic Model

Two independent prognostic factors for PFS were used to develop a Cox proportional hazards prognostic model. The C-index was 0.682 (95% CI, 0.629–0.735) for the training cohort and 0.690 (95% CI, 0.610–0.770) for the validation cohort. ROC analyses indicated that the AUC values for predicting 1-year and 2-year PFS were 0.721 and 0.732 for the training cohort, respectively (Figure 2A), and 0.709 and 0.730 for the validation cohort, respectively (Figure 2B). Three independent prognostic factors for OS were combined to establish a Cox proportional hazards model. The C-index was 0.715 (95% CI, 0.662–0.768) for the training cohort and 0.701 (95% CI, 0.628–0.774) for the validation cohort. ROC analyses demonstrated AUC values of 0.717, 0.741, and 0.798 for predicting 1-, 2-, and 3-year OS in the training cohort, respectively (Figure 2C), and AUC values of 0.699, 0.736, and 0.795, in the validation cohort, respectively (Figure 2D), indicating strong discriminative ability.

Prognostic Assessment

In both the training and validation cohorts, the calibration curves demonstrated strong agreement between the predicted 1-year and 2-year PFS and actual outcomes (Figure S1). Similarly, calibration curves for predicted 2-, and 3-year OS values showed excellent alignment with the actual OS (Figure S2), confirming the accuracy of the prognostic model.

Risk Stratification

Nomograms were constructed to visualize prognostic models for PFS and OS based on independent prognostic factors (Figure 3). These nomograms effectively stratified all patients into low-risk and high-risk groups based on risk scores. For PFS, a risk score of >32.6 indicated a high-risk group, while a score of ≤32.6 indicated a low-risk group. For OS, a score of >70.4 classified patients into a high-risk group, with a score of ≤70.4 indicating a low-risk group. In both

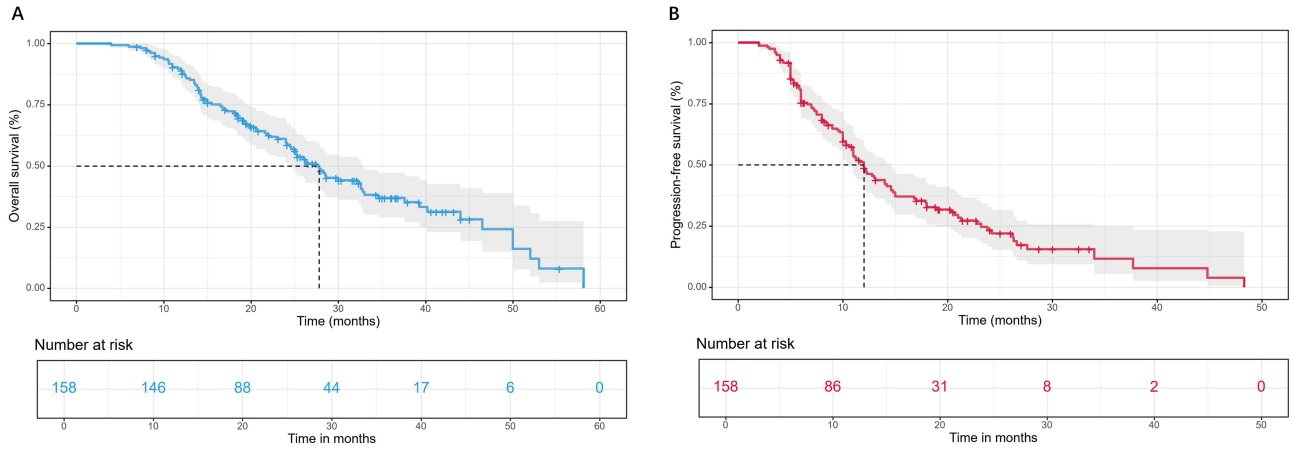

Figure 1 Kaplan–Meier curves for overall survival (**A**) and progression-free survival (**B**) of patients with hepatocellular carcinoma in the training cohort.

Table 3 Univariate and Multivariate Analysis of Factors Associated with PFS in the Training Cohort

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.00 (0.98–1.02)	0.823		
Sex (male/female)	0.94 (0.50–1.76)	0.846		
HBV (yes/no)	1.40 (0.82–2.38)	0.218		
ECOG PS (1/0)	1.04 (0.69–1.56)	0.850		
Child–Pugh class (B/A)	1.31 (0.82–2.10)	0.257		
BCLC stage (C/B)	1.22 (0.83–1.80)	0.308		
ALBI grade (2 and 3 vs 1)	0.95 (0.65–1.40)	0.811		
NLR (≥3/<3)	1.97 (1.34–2.88)	0.001	1.38 (0.93–2.06)	0.113
AFP (≥400/<400)	1.13 (0.77–1.66)	0.521		
Vascular invasion (yes/no)	1.91 (1.31–2.80)	0.001	1.54 (1.03–2.29)	0.035
Extrahepatic metastasis (yes/no)	1.63 (1.11–2.39)	0.014	1.17 (0.77–1.78)	0.470
Tumor size (5–10 and >10 vs <5)	1.23 (0.95–1.60)	0.115		
Tumor number (multiple/single)	1.45 (0.96–2.20)	0.080		
CRAFITY score (1 and 2 vs 0)	2.06 (1.63–2.62)	<0.001	1.81 (1.38–2.37)	<0.001

Abbreviations: HR, hazard ratio; HBV, hepatitis B virus; ECOG PS, Eastern cooperative oncology group performance status; BCLC, Barcelona Clinic Liver Cancer; ALBI albumin-bilirubin; NLR: neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; CRAFITY, C-reactive protein and alpha-fetoprotein in immunotherapy.

Table 4 Univariate and Multivariate Analysis of Factors Associated with OS in the Training Cohort

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.00 (0.98–1.02)	0.869		
Sex (male/female)	1.13 (0.54–2.35)	0.743		
HBV (yes/no)	0.92 (0.54–1.56)	0.763		
ECOG PS (1/0)	1.44 (0.93–2.21)	0.102		
Child–Pugh class (B/A)	1.39 (0.82–2.34)	0.217		
BCLC stage (C/B)	1.39 (0.91–2.14)	0.130		
ALBI grade (2 and 3 vs 1)	1.22 (0.80–1.88)	0.357		
NLR (≥3/<3)	2.60 (1.68–4.01)	<0.001	1.95 (1.24–3.08)	0.003
AFP (≥400/<400)	0.86 (0.56–1.33)	0.507		
Vascular invasion (yes/no)	1.54 (1.02–2.34)	0.041	1.30 (0.84–2.02)	0.237
Extrahepatic metastasis (yes/no)	2.22 (1.46–3.36)	<0.001	1.80 (1.16–2.80)	0.009
Tumor size (5–10 and >10 vs <5)	1.51 (1.12–2.04)	0.007	1.11 (0.80–1.53)	0.527
Tumor number (multiple/single)	1.47 (0.91–2.36)	0.113		
CRAFITY score (1 and 2 vs 0)	2.05 (1.57–2.69)	<0.001	1.55 (1.15–2.10)	0.004

Abbreviations: HR, hazard ratio; HBV, hepatitis B virus; ECOG PS, Eastern cooperative oncology group performance status; BCLC, Barcelona Clinic Liver Cancer; ALBI albumin-bilirubin; NLR: neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; CRAFITY, C-reactive protein and alpha-fetoprotein in immunotherapy.

cohorts, when compared to patients in the low-risk group, individuals in the high-risk group had noticeably lower OS and PFS probability (P<0.05) (Figure 4).

Discussion

Numerous studies have highlighted the efficacy and safety of triple therapy for treating patients with unresectable HCC,[12,19–24] underscoring its increasing significance in future treatment paradigms. Therefore, developing robust prognostic models capable of identifying biomarkers in patients likely to benefit from triple therapy, predicting prognosis

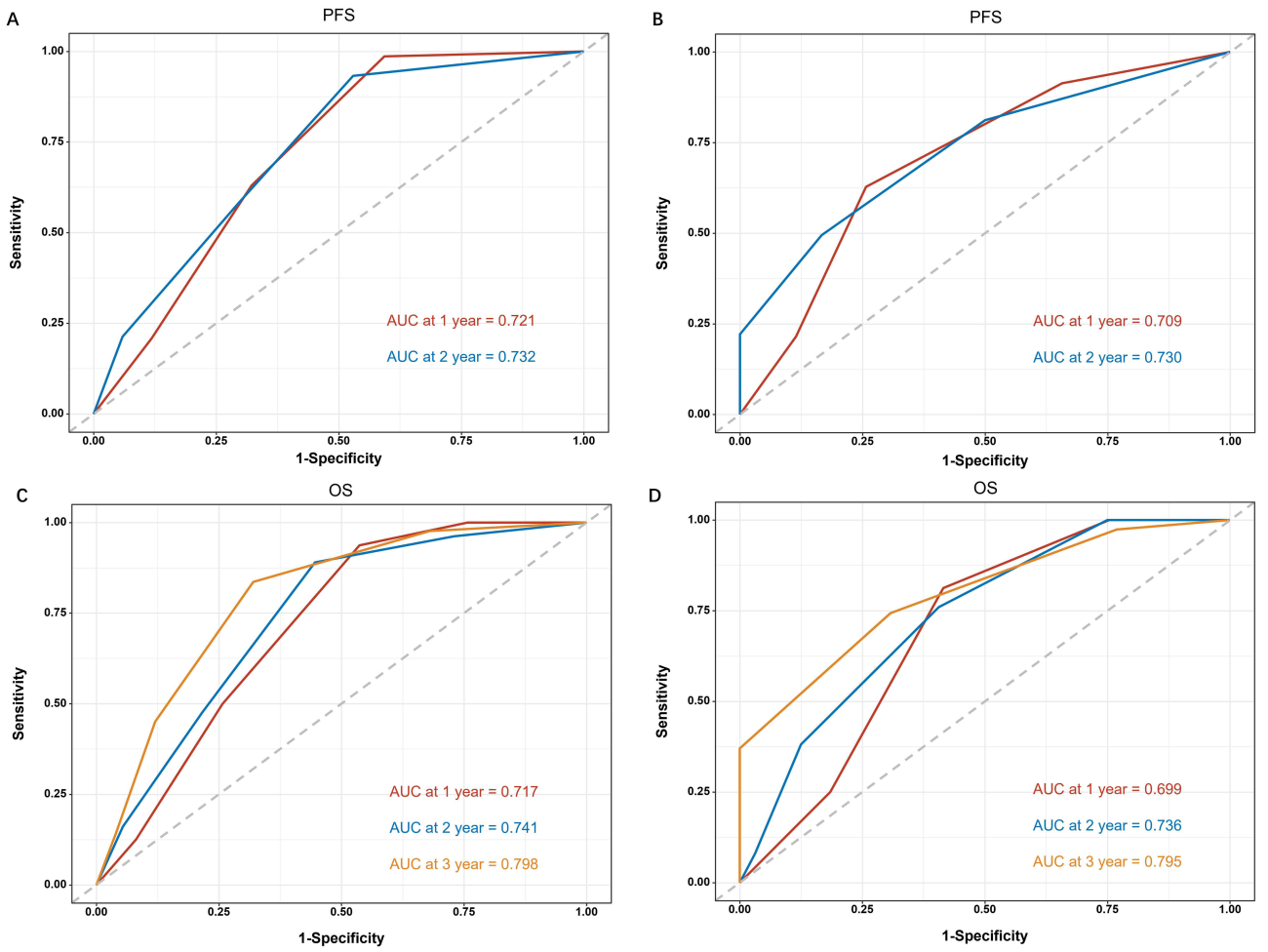

Figure 2 Receiver operating characteristic (ROC) curves (**A** and **B**) for predicting 1- and 2-year progression-free survival (PFS) in the training and validation cohorts. ROC curves (**C** and **D**) for predicting the 1-, 2-, and 3-year overall survival (OS).

before treatment, and guiding clinical decisions is crucial. However, there remains a lack of prognostic models for patients with unresectable HCC undergoing triple therapy. In this study, a prognostic model incorporating several independent predictors to accurately predict outcomes for patients with HCC receiving triple therapy was constructed.

In the multivariate analysis for PFS, two clinical factors (vascular invasion and the CRAFITY score) emerged as independent predictors. For OS, three clinical factors (the CRAFITY score, extrahepatic metastasis, and NLR) emerged as independent predictors. The CRAFITY score has demonstrated effective prognostic utility in predicting the prognosis of patients with HCC undergoing immunotherapy and combination therapy.[25–30] Specifically, the CRAFITY score categorizes patients as follows:[25] CRAFITY 0 indicates an AFP level of <100 ng/mL or a CRP level of < 1 mg/dL, CRAFITY 1 indicates an AFP level of ≥100 ng/mL or a CRP level of ≥1 mg/dL, and CRAFITY 2 indicates an AFP level of >100 ng/mL and a CRP level of >1 mg/dL. Consistent with previous findings, our study reaffirms the significance of the CRAFITY score as a critical prognostic indicator for OS and PFS in patients receiving triple therapy. Moreover, Extrahepatic metastases have been demonstrated to be an independent prognostic factor affecting outcomes in patients with unresectable HCC receiving triple therapy,[31,32] a conclusion supported by our study. Qu et al[33] identified NLR as a predictive marker for determining patients with HCC who would benefit from the triple therapy, a finding which our study also corroborates.

However, there is a lack of prognostic models for patients with HCC undergoing triple therapies. Hu et al[28] demonstrated the predictive potential of the CRAFITY score in assessing prognosis among patients with HCC receiving TACE in combination with immunotherapy and targeted therapies. Similarly, Zhang et al[29] demonstrated that the

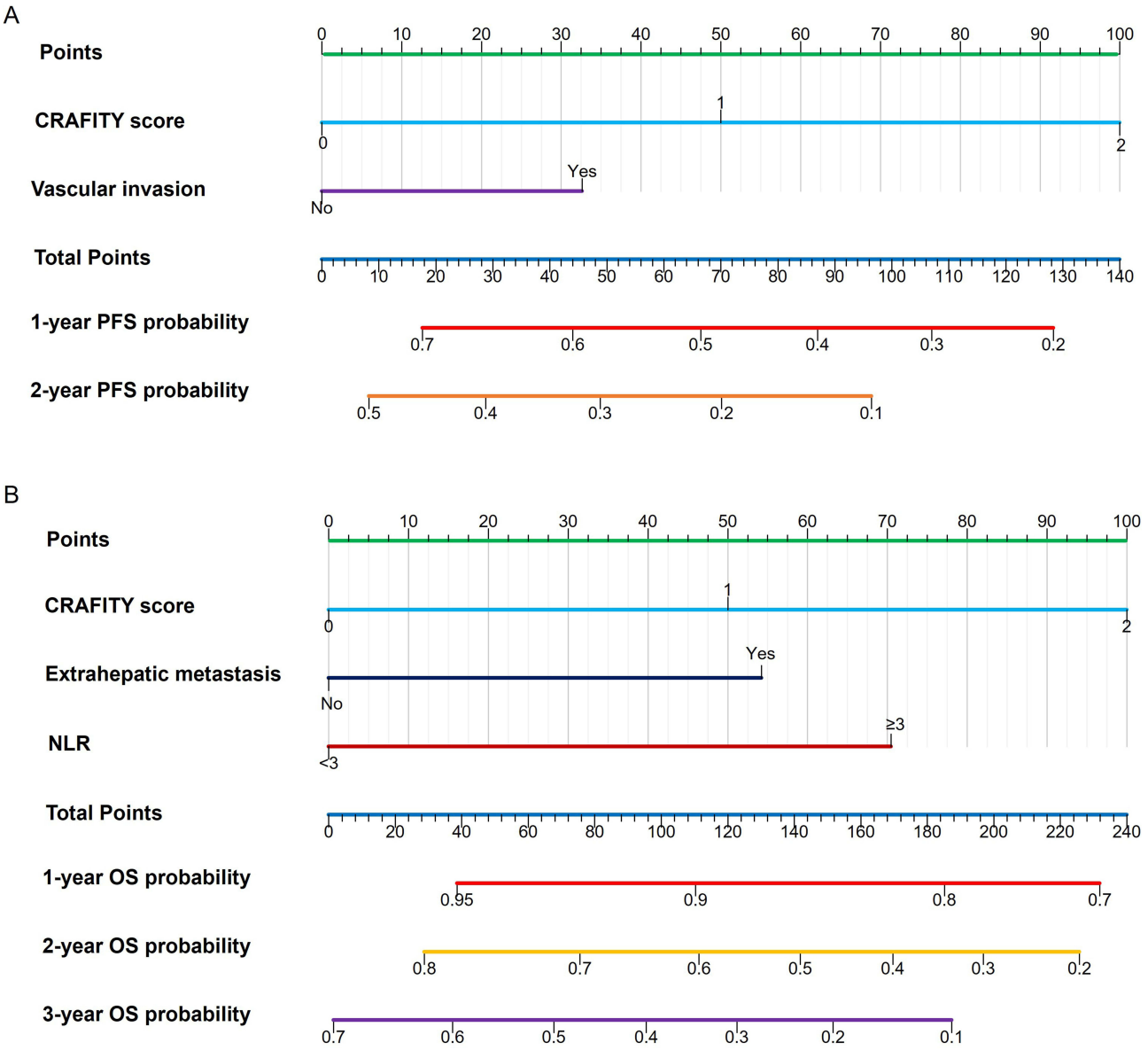

Figure 3 The nomogram predicting progression-free survival (**A**) and overall survival (**B**) in patients with hepatocellular carcinoma receiving triple therapy in the training cohort.

CRAFITY score can be used to predict the outcome, and tumor response in patients treated with TACE combined with targeted and immunotherapy. Their studies underscored the significant role of the CRAFITY score in the context of triple therapy. However, they focused only on the CRAFITY score and did not combine it with other clinical factors to develop a comprehensive prognostic model. In contrast, Zeng et al[32] used three pre-treatment variables (total bilirubin, AFP, and extrahepatic metastasis) to a TAE score to predict the prognosis of patients with unresectable HCC treated with TACE plus lenvatinib and programmed cell death 1 inhibitor. However, their study did not incorporate the critical CRAFITY score, nor did it evaluate the performance of their model, potentially affecting its predictive accuracy. In our study, independent prognostic factors relating to PFS and OS were used to build the Cox proportional hazards predictive model. This prognostic model demonstrated strong discriminatory power and consistency. The prognostic model was used to stratify the patients into low-risk and high-risk categories, revealing significant differences in OS and PFS between the two cohorts, which were confirmed in an external validation cohort. The prognostic model in the study is an easy and reliable way to predict prognosis and identifying patients most likely to benefit from triple therapy. Furthermore, it assists

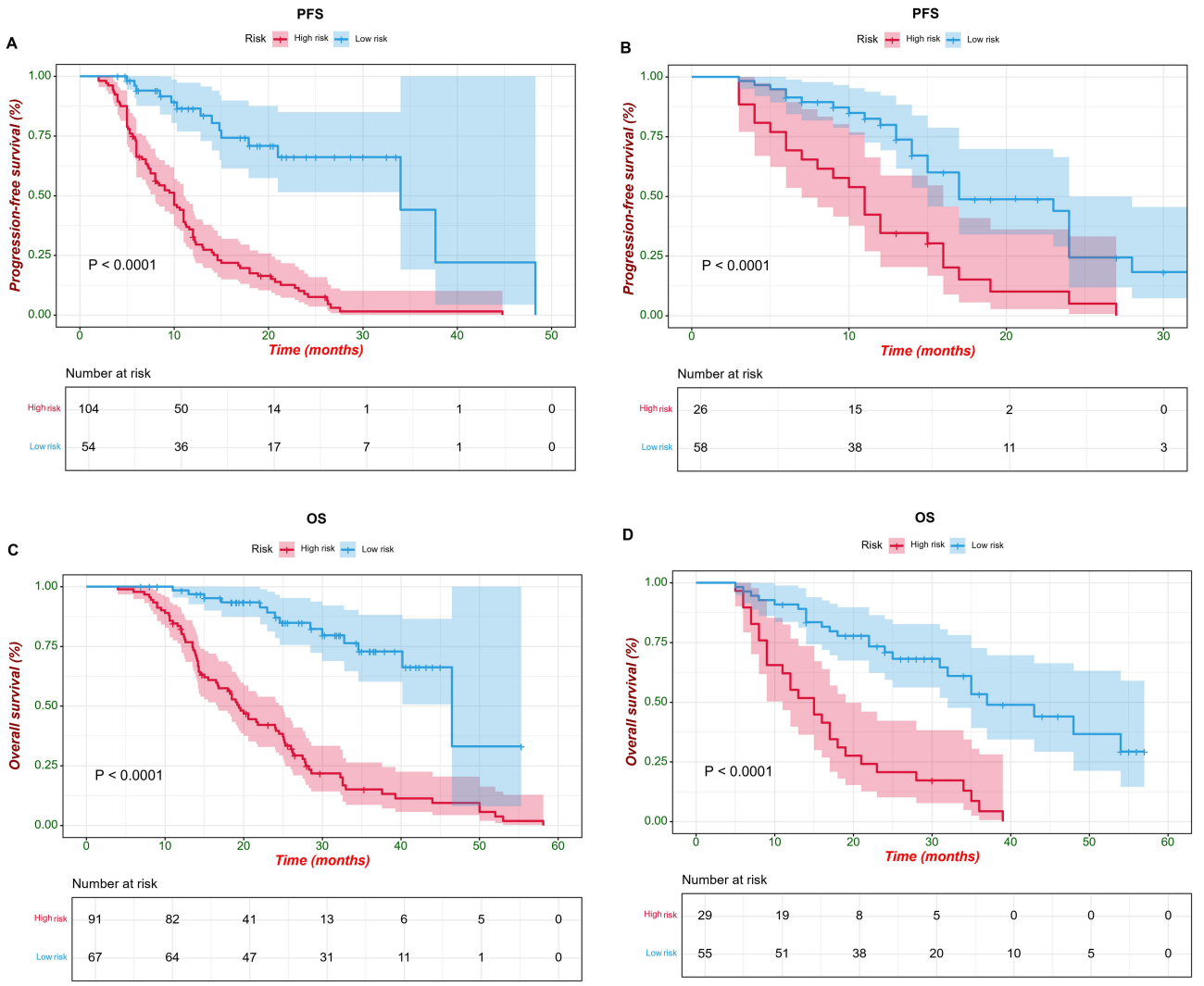

Figure 4 Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in patients with hepatocellular carcinoma receiving triple therapy in the low-risk and high-risk groups in the training and validation cohorts. (**A**) Kaplan–Meier curves for PFS risk stratification in the training cohort. (**B**) Kaplan–Meier curves for PFS risk stratification in the validation cohort. (**C**) Kaplan–Meier curves for OS risk stratification in the training cohort. (**D**) Kaplan–Meier curves for OS risk stratification in the validation cohort.

clinicians in selecting the appropriate treatment before initiation and enables the personalization of treatment plans for individual patients.

This study has several limitations. First, as a two-center retrospective study, there might be selection bias. Therefore, further validation in a large, multicenter prospective cohort is needed. Second, the main aetiology of the patients in this study was hepatitis B virus-related HCC. Given the heterogeneity of patients with HCC with different aetiologies,[34] studies focusing on other aetiologies are necessary to validate the performance of the prognostic model for triple therapy. Third, this study lacked the effect of HBV viral load on the prognosis of triple therapy, and there is a need to further analyze the effect of HBV viral load on the prognosis of triple therapy in future studies. Fourth, different molecular targeted agents and immune checkpoint inhibitors were used in the study population, potentially increasing treatment variability. Currently, studies on TACE combined with molecular targeted therapy and immunotherapy have involved multiple agent combinations, and the sample size of patients treated with single-agent therapy remains limited. Therefore, future research should explore larger sample sizes of patients treated with single-agent therapy in combination with TACE. Additionally, this study did not incorporate genomics, transcriptomics, radiomics, pathomics, or other multiomics

data to establish prognostic models from different dimensions. Future research will aim to include these approaches to develop more robust prognostic models.

Conclusion

In conclusion, the prognostic models developed in this study can predict prognosis and perform risk stratification before treatment initiation. It can effectively identify patients who are most likely to benefit from this combination regimen and provide crucial guidance for clinical decision-making.

Abbreviations

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; CT, computed tomography; mRECIST, modified Response Evaluation Criteria in Solid Tumors; OS, overall survival; PFS, progression-free survival; AUC, area under the curve; ROC, receiver operating characteristic curve; CI, confidence interval; CRP, C-reactive protein; AFP, alpha-fetoprotein; CRAFITY, the C-reactive protein and alpha-fetoprotein in immunotherapy; NLR, neutrophil-to-lymphocyte ratio.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the Cancer Hospital Chinese Academy of Medical Sciences (Ethics number: 24/336-4616) and was conducted in strict accordance with the principles of the Declaration of Helsinki. Informed consent was waived in consideration of its retrospective nature and simultaneous confirmation that the data was anonymized or maintained with confidentiality.

Acknowledgments

We thank Bullet Edits Limited for the linguistic editing of the manuscript.

Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76(3):681–693. doi:10.1016/j.jhep.2021.11.018
3. Foerster F, Gairing SJ, Ilyas SI, Galle PR. Emerging immunotherapy for HCC: a guide for hepatologists. *Hepatology*. 2022;75(6):1604–1626. doi:10.1002/hep.32447
4. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular Carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
5. Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, Phase 3 trial. *Lancet Oncol*. 2021;22(7). doi:10.1016/S1470-2045(21)00151-0
6. Kudo M. Immune Checkpoint Inhibitors plus Anti-VEGF/Tyrosine Kinase Inhibitors Combined with TACE (Triple Therapy) in Unresectable Hepatocellular Carcinoma. *Liver Cancer*. 2024;13(3):227–234. doi:10.1159/000538558
7. Sun Y, Zhang W, Bi X, et al. Systemic Therapy for Hepatocellular Carcinoma: Chinese Consensus-Based Interdisciplinary Expert Statements. *Liver Cancer*. 2022;11(3):192–208. doi:10.1159/000521596
8. Zhang J-X, Hua H-J, Cheng Y, Liu S, Shi H-B, Zu -Q-Q. Role of Transarterial Chemoembolization in the Era of Tyrosine Kinase Inhibitor and Immune Checkpoint Inhibitor Combination Therapy for Unresectable Hepatocellular Carcinoma: a Retrospective Propensity Score Matched Analysis. *Acad Radiol*. 2024;31(4):1304–1311. doi:10.1016/j.acra.2023.09.001
9. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6. doi:10.1038/s41572-020-00240-3
10. Fu Y, Zeng CH, An C, Liu Y, Shin JH, Li X. How Biology Guides the Combination of Locoregional Interventional Therapies and Immunotherapy for Hepatocellular Carcinoma: cytokines and Their Roles. *Cancers*. 2023;15(4). doi:10.3390/cancers15041324
11. Ben Khaled N, Seidensticker M, Ricke J, et al. Atezolizumab and bevacizumab with transarterial chemoembolization in hepatocellular carcinoma: the DEMAND trial protocol. *Future Oncol*. 2022;18(12):1423–1435. doi:10.2217/fon-2021-1261
12. Zhu H-D, Li H-L, Huang M-S, et al. Transarterial chemoembolization with PD-(L)1 inhibitors plus molecular targeted therapies for hepatocellular carcinoma (CHANCE001). *Signal Transduct Target Ther*. 2023;8(1):58. doi:10.1038/s41392-022-01235-0
13. Jin Z-C, Chen -J-J, Zhu X-L, et al. Immune checkpoint inhibitors and anti-vascular endothelial growth factor antibody/tyrosine kinase inhibitors with or without transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma (CHANCE2201): a target trial emulation study. *EClinicalMedicine*. 2024;72:102622. doi:10.1016/j.eclinm.2024.102622

14. Yuan Y, He W, Yang Z, et al. TACE-HAIC combined with targeted therapy and immunotherapy versus TACE alone for hepatocellular carcinoma with portal vein tumor thrombus: a propensity score matching study. *Int J Surg*. 2023;109(5):1222–1230. doi:10.1097/JS9.0000000000000256
15. Liu J, Wang P, Shang L, et al. TACE plus tyrosine kinase inhibitors and immune checkpoint inhibitors versus TACE plus tyrosine kinase inhibitors for the treatment of patients with hepatocellular carcinoma: a meta-analysis and trial sequential analysis. *Hepatol Int*. 2024;18(2):595–609. doi:10.1007/s12072-023-10591-0
16. Li J, Li Y, Song J, Zhao L. Efficacy and Safety Analysis of Transarterial Chemoembolization Plus Donafenib With or Without Immune Checkpoint Inhibitors for Unresectable Hepatocellular Carcinoma: a Prospective, Single-Arm, Single-Center, Phase II Clinical Study. *J Hepatocell Carcinoma*. 2024;11:1207–1219. doi:10.2147/JHC.S473617
17. Wang -Y-Y, Yang X, Wang Y-C, et al. Clinical outcomes of lenvatinib plus transarterial chemoembolization with or without programmed death receptor-1 inhibitors in unresectable hepatocellular carcinoma. *World J Gastroenterol*. 2023;29(10):1614–1626. doi:10.3748/wjg.v29.i10.1614
18. Zhou J, Sun H, Wang Z, et al. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). *Liver Cancer*. 2020;9(6):682–720. doi:10.1159/000509424
19. Huang J-T, Zhong B-Y, Jiang N, et al. Transarterial Chemoembolization Combined with Immune Checkpoint Inhibitors Plus Tyrosine Kinase Inhibitors versus Immune Checkpoint Inhibitors Plus Tyrosine Kinase Inhibitors for Advanced Hepatocellular Carcinoma. *J Hepatocell Carcinoma*. 2022;9:1217–1228. doi:10.2147/JHC.S386672
20. Jin Z-C, Zhong B-Y, Chen -J-J, et al. Real-world efficacy and safety of TACE plus camrelizumab and apatinib in patients with HCC (CHANCE2211): a propensity score matching study. *Eur Radiol*. 2023;33(12):8669–8681. doi:10.1007/s00330-023-09754-2
21. Li S-Q, Wu J-Y, Wu J-Y, et al. Transarterial Chemoembolization Plus Lenvatinib and PD-1 Inhibitors for Hepatocellular Carcinoma with Main Trunk Portal Vein Tumor Thrombus: a Multicenter Retrospective Study. *J Hepatocell Carcinoma*. 2023;10:1799–1811. doi:10.2147/JHC.S428980
22. Wu J-Y, Zhang Z-B, Zhou J-Y, et al. Outcomes of Salvage Surgery for Initially Unresectable Hepatocellular Carcinoma Converted by Transcatheter Arterial Chemoembolization Combined with Lenvatinib plus Anti-PD-1 Antibodies: a Multicenter Retrospective Study. *Liver Cancer*. 2023;12(3):229–237. doi:10.1159/000528356
23. Liu J, Li Z, Zhang W, et al. Comprehensive Treatment of Trans-Arterial Chemoembolization Plus Lenvatinib Followed by Camrelizumab for Advanced Hepatocellular Carcinoma Patients. *Front Pharmacol*. 2021;12:709060. doi:10.3389/fphar.2021.709060
24. Llovet JM, Vogel A, Madoff DC, et al. Randomized Phase 3 LEAP-012 Study: transarterial Chemoembolization With or Without Lenvatinib Plus Pembrolizumab for Intermediate-Stage Hepatocellular Carcinoma Not Amenable to Curative Treatment. *Cardiovasc Intervent Radiol*. 2022;45(4):405–412. doi:10.1007/s00270-021-03031-9
25. Scheiner B, Pomej K, Kirstein MM, et al. Prognosis of patients with hepatocellular carcinoma treated with immunotherapy - development and validation of the CRAFITY score. *J Hepatol*. 2022;76(2):353–363. doi:10.1016/j.jhep.2021.09.035
26. Yang Y, Ouyang J, Zhou Y, Zhou J, Zhao H. The CRAFITY score: a promising prognostic predictor for patients with hepatocellular carcinoma treated with tyrosine kinase inhibitor and immunotherapy combinations. *J Hepatol*. 2022;77(2):574–576. doi:10.1016/j.jhep.2022.03.018
27. Guan R, Mei J, Lin W, Deng M, Li S, Guo R. Is the CRAFITY score a superior predictor of prognosis and adverse events in hepatocellular carcinoma patients treated with locoregional-immunotherapy? *Hepatol Int*. 2023;17(5):1279–1288. doi:10.1007/s12072-023-10535-8
28. Hu Z-X, Xu X-Y, Wang Z, et al. Prognosis Prediction of CRAFITY Score in HCC Undergoing TACE Combined with PD-(L)1 Inhibitors and Molecular Targeted Therapy. *J Hepatocell Carcinoma*. 2023;10:2073–2082. doi:10.2147/JHC.S439660
29. Zhang L, Sun T, Sun B, et al. Utility and predictive value of the CRAFITY score in advanced hepatocellular carcinoma treated with transarterial chemoembolization plus tyrosine kinase inhibitors and PD-1 inhibitor. *BMC Cancer*. 2024;24(1):223. doi:10.1186/s12885-024-11936-0
30. Hatanaka T, Kakizaki S, Hiraoka A, et al. Prognostic impact of C-reactive protein and alpha-fetoprotein in immunotherapy score in hepatocellular carcinoma patients treated with atezolizumab plus bevacizumab: a multicenter retrospective study. *Hepatol Int*. 2022;16(5):1150–1160. doi:10.1007/s12072-022-10358-z
31. Cai M, Huang W, Huang J, et al. Transarterial Chemoembolization Combined With Lenvatinib Plus PD-1 Inhibitor for Advanced Hepatocellular Carcinoma: a Retrospective Cohort Study. *Front Immunol*. 2022;13:848387. doi:10.3389/fimmu.2022.848387
32. Zeng Z-X, Wu J-Y, Wu J-Y, et al. The TAE score predicts prognosis of unresectable HCC patients treated with TACE plus lenvatinib with PD-1 inhibitors. *Hepatol Int*. 2024;18(2):651–660. doi:10.1007/s12072-023-10613-x
33. Qu S, Wu D, Hu Z. Neutrophil-to-Lymphocyte Ratio and Early Tumor Shrinkage as Predictive Biomarkers in Unresectable Hepatocellular Carcinoma Patients Treated With Lenvatinib, PD-1 Inhibitors, in Combination With TACE. *Technol Cancer Res Treat*. 2023;22:15330338231206704. doi:10.1177/15330338231206704
34. Chidambaranathan-Reghupaty S, Fisher PB, Sarkar D. Hepatocellular carcinoma (HCC): epidemiology, etiology and molecular classification. *Adv Cancer Res*. 2021;149. doi:10.1016/bs.acr.2020.10.001