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MINIREVIEWS

Predicting the prognosis of hepatic arterial infusion chemotherapy in hepatocellular carcinoma

Qi-Feng Wang, Zong-Wei Li, Hai-Feng Zhou, Kun-Zhong Zhu, Ya-Jing Wang, Ya-Qin Wang, Yue-Wei Zhang

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Abstract

Hepatic artery infusion chemotherapy (HAIC) has good clinical efficacy in the treatment of advanced hepatocellular carcinoma (HCC); however, its efficacy varies. This review summarized the ability of various markers to predict the efficacy of HAIC and provided a reference for clinical applications. As of October 25, 2023, 51 articles have been retrieved based on keyword predictions and HAIC. Sixteen eligible articles were selected for inclusion in this study. Comprehensive literature analysis found that methods used to predict the efficacy of HAIC include serological testing, gene testing, and imaging testing. The above indicators and their combined forms showed excellent predictive effects in retrospective studies. This review summarized the strategies currently used to predict the efficacy of HAIC in middle and advanced HCC, analyzed each marker's ability to predict HAIC efficacy, and provided a reference for the clinical application of the prediction system.

Key Words: Hepatocellular carcinoma; Hepatic artery infusion chemotherapy; Prediction; Prognosis; Imaging; Biomarkers; Genomics

Core Tip: Hepatic artery infusion chemotherapy (HAIC) has good clinical efficacy and high safety, and it has become one of the main treatment options for patients with intermediate to advanced hepatocellular carcinoma (HCC). Through predicting the prognosis of HAIC, appropriate patients can be screened for HAIC, and the overall efficacy of HAIC in HCC patients can improve. This review summarized the strategies currently used to predict the efficacy of HAIC in middle and advanced HCC, analyzed each marker's ability to predict HAIC efficacy, and provided a reference for the clinical selection of an appropriate HAIC prediction modality.

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INTRODUCTION

Primary liver cancer is the sixth most common cancer worldwide and the third leading cause of cancer-related deaths. Hepatocellular carcinoma (HCC) accounts for 75%-85% of all primary liver cancer cases[1-4]. With recent advances in the treatment of HCC, patient survival can be improved using effective methods including surgical resection, radiofrequency ablation, microwave ablation, hepatic artery chemoembolization (TACE), hepatic artery infusion chemotherapy (HAIC), multimolecular targeted agents, immunotherapy, and liver transplantation[5,6]. However, due to the nonspecific symptoms of liver cancer, most patients are already in the middle and late stages when diagnosed. Therefore, TACE, HAIC, targeting, and immunization have become the main treatments for middle- and late-stage liver cancers[7]. Studies have shown that HAIC therapy increases local drug concentration in the tumor through selective hepatic artery perfusion, which can significantly improve antitumor treatment and reduce systemic adverse effects[8]. It has been included in guidelines for improving the prognosis of advanced HCC[5,9,10]. In addition, HAIC treatment has also shown good efficacy in biliary tract tumors, and metastatic tumors, such as liver metastases from breast cancer[11-14], liver metastases from gastric cancer, and liver metastases from colorectal cancer[9,15-20].

However, owing to the heterogeneity of tumors, the efficacy of HAIC may vary. To improve the efficacy of HAIC treatment, there is an urgent need for the predictive assessment of HAIC efficacy when selecting appropriate patients for treatment. Current prognostic prediction modalities for HAIC treatment include serological indicators, genomic sequencing, and imaging techniques (Figure 1). This review summarized the existing HAIC predictive indicators, provided a reference for the clinical selection of appropriate patients with HCC, and attempted to identify the direction of further development of predictive modalities.

BIOMARKERS FOR PREDICTING THE PROGNOSIS OF HAIC IN HCC

Many biomarkers are commonly used for the early diagnosis, monitoring, and outcome prediction in patients with HCC because of their high sensitivity, specificity, and accessibility[21]. Currently, inflammatory indicators and tumor-specific markers are used to predict the prognosis of HAIC, and we summarized and analyzed the impact of these markers on prognosis (Table 1).

Inflammatory markers

The inflammatory response plays a crucial role in the development and progression of various cancers[22]. Inflammatory factors, such as inflammatory cell levels, active oncogenes, reactive oxygen species, and necrotic substances present in cancerous tissues can promote cancer initiation and progression and affect patient survival[23-25]. Among them, absolute white blood cell count, lymphocyte-to-C-reactive protein ratio, neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and cytokines are readily available and have been suggested to correlate with the prognosis of patients with various malignancies[26,27]. For example, NLR is now widely recognized as a predictive marker for advanced melanoma, colorectal cancer with liver metastases, and breast cancer[28-30]. Terashima *et al*[31] analyzed the effect of NLR on the prognosis of HAIC in patients with advanced HCC in the HAIC form of 5-fluorouracil (5-FU) combined with interferon α-2b. The results showed that patients with high NLR have worse objective response rates [27.1 *vs* 37.6; hazard ratio (HR): 1.918; 95% confidence interval (CI): 1.092-3.369; $P = 0.024$], progression-free survival (PFS) (3.2 *vs* 5.6; HR: 1.363; 95%CI: 1.008-1.843; $P = 0.044$), and overall survival (OS) (8.0 *vs* 20.7; HR: 1.492; 95%CI: 1.106, 2.012; $P < 0.01$), which can be used as prognostic predictors for patients with HAIC treatment of advanced HCC (Figure 2). Meanwhile, Tajiri *et al*[32] also showed that lower NLR suggested better efficacy [odds ratio (OR): 0.49; 95%CI: 0.18-0.96; $P = 0.04$] and prolonged OS (HR: 3.24; 95%CI: 1.15-9.14; $P = 0.03$) of HAIC in advanced HCC patients, using HAIC modality of cisplatin combined with 5-FU. Further studies with larger groups of patients are needed to determine the most appropriate NLR threshold and provide better sensitivity and specificity as predictors (Table 1).

Table 1 Biomarkers for predicting hepatic artery infusion chemotherapy prognosis

Biomarker	PFS HR (95%CI)	OS HR (95%CI)	ORR HR (95%CI)	ORR (%)	Ref.
NLR	1.363 (1.008-1.843)	1.492 (1.106-2.012)	1.918 (1.092-3.369)	37.6	[31]
NLR	1.984 (1.111-3.545)			24.3	[39]
DCP	2.460 (1.434-4.220)	3.097 (1.728-5.551)		24.3	[39]
AFP		2.17 (1.23-3.92)		51.9	[52]
DCP		1.9 (1.06-3.42)		56.4	[52]
VEGF		2.42 (1.33-4.38)		35.2	[43]
Serum transferrin		1 (0.132-0.603)		46.9	[47]
IL-28B		1.720 (1.072-2.759)	2.620(1.124-6.107)	51.9	[73]

NLR: Neutrophil to lymphocyte ratio; DCP: Des-γ-carboxy prothrombin; AFP: Alpha-fetoprotein; VEGF: Vascular endothelial growth factor; IL-28B: Interleukin-28B; PFS: Progression-free survival; OS: Overall survival; ORR: objective response rate; CI: Confidence interval.

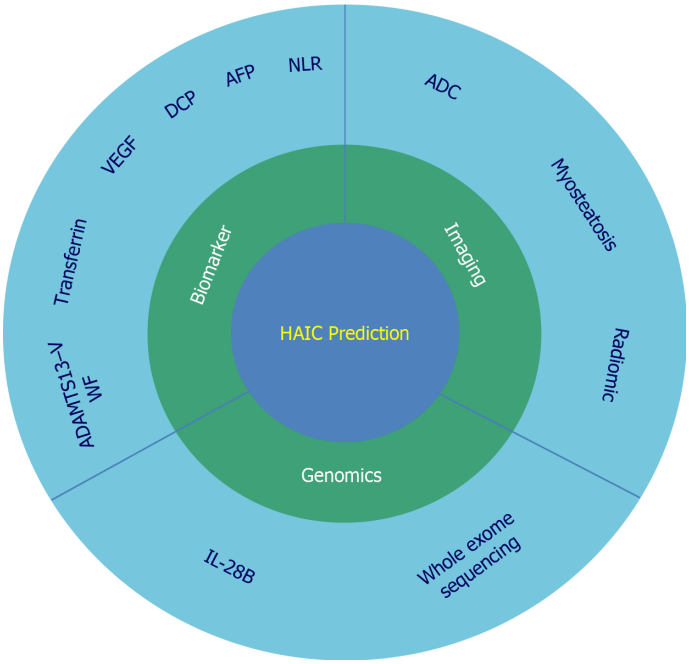


Figure 1 A simplified scheme for the hepatic artery infusion chemotherapy prediction strategy. Prognostic factors influencing hepatic arterial infusion chemotherapy for hepatocellular carcinoma, Such as biomarkers, imaging, and genomics. HAIC: Hepatic arterial infusion chemotherapy; NLR: Neutrophil to lymphocyte ratio; DCP: Des-γ-carboxy prothrombin; AFP: Alpha-fetoprotein; VEGF: Vascular endothelial growth factor; VWF: Willebrand factor; ADC: Apparent diffusion coefficient; IL-28B: Interleukin-28B.

Nonspecific tumor markers

Des-γ-carboxy prothrombin (DCP), known as a protein induced by vitamin K absence or antagonist-II, is an abnormal protein produced in HCC. Some studies have shown that DCP-elevated tumors in patients with HCC are more prone to microvascular infiltration, metastasis, and recurrence and can be used as a predictor of HCC prognosis[33,34]. The serum marker alpha-fetoprotein (AFP), the most widely used biomarker for diagnosing HCC, has a diagnostic yield of approximately 46%[35,36]. Whether combined AFP and DCP can improve the prediction effect in HCC diagnosis and prognostic prediction[37]. Yamamoto *et al*[38] used changes in AFP and DCP levels before and after treatment to evaluate the predictive performance of HAIC (sensitivity, 64% and 79%; specificity, 88% and 64%, respectively). On this basis, the combination of AFP and DCP showed a better predictive ability (sensitivity and specificity of 93% and 60%, respectively). Tsunematsu *et al*[39] used DCP combined with the NLR to predict the prognosis of cisplatin combined with 5-FU (HAIC) in patients with advanced HCC. It was found that patients with low NLR had significantly longer PFS (PFS: 8.4 *vs* 2.8; HR: 1.984; 95%CI: 1.111- 3.545; P = 0.021), and early decrease of DCP after HAIC was associated with better prognosis (PFS: 7.2 *vs* 2.3; HR: 2.460; 95%CI: 1.434-4.220; P = 0.001; OS: 18.5 *vs* 6.1; HR: 3.097; 95%CI: 1.728-5.551; P < 0.001). Thus, AFP and DCP are effective predictive indicators, and tumor markers, in combination with inflammatory indicators, can improve the prediction of HAIC.

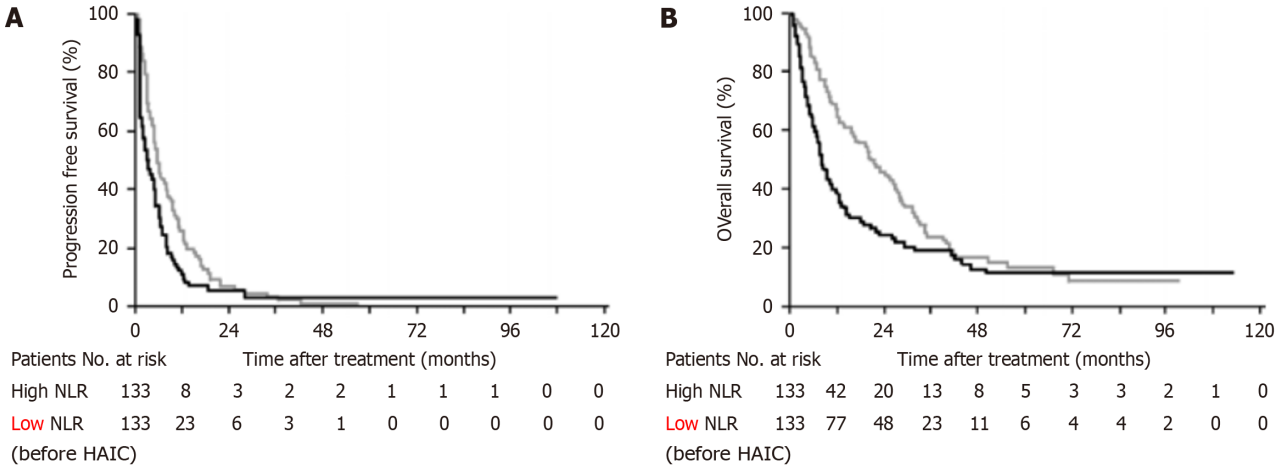


Figure 2 Kaplan-Meier plot of progression-free survival and overall survival since commencement of hepatic arterial infusion chemotherapy according to neutrophil to lymphocyte ratio[31]. A: Median progression-free survival of the patients with high neutrophil to lymphocyte ratio (NLR) was 3.2 months, which was significantly worse than that of the patients with low NLR, 5.6 months ($P < 0.01$); B: Median overall survival of the patients with high NLR was 8.0 months, which was significantly worse than that of the patients with low NLR, 20.7 months ($P < 0.01$). Image, High NLR; image, Low NLR. Citation: Terashima T, Yamashita T, Iida N, Yamashita T, Nakagawa H, Arai K, Kitamura K, Kagaya T, Sakai Y, Mizukoshi E, Honda M, Kaneko S. Blood neutrophil to lymphocyte ratio as a predictor in patients with advanced hepatocellular carcinoma treated with hepatic arterial infusion chemotherapy. *Hepatol Res* 2015; 45: 949-959. Copyright © 2014. Published by John Wiley and Sons. The authors have obtained the permission for figure using (Supplementary material).

Vascular endothelial growth factor

The secretion of VEGF by the tumor cells and the surrounding stroma stimulates endothelial cell proliferation, leading to structural abnormalities under neovascular and hypoxic conditions[40] and significantly correlates with the development, progression, and metastasis of HCC[26,41]. Matsui *et al*[42] found that a higher serum VEGF level was correlated with a poor prognosis for HAIC. Furthermore, Niizeki *et al*[43] observed that the serum level of VEGF was an independent predictor of HAIC treatment (cisplatin combined with 5-FU) (OR: 4.77; 95%CI: 1.21-18.90; $P = 0.026$), and the result indicated that patients with lower serum VEGF levels were more suitable for HAIC treatment.

Serum transferrin

Serum transferrin levels can predict survival in patients with various liver diseases[44,45]. In addition, it has been shown that serum transferrin, similar to deferoxamine, exerts antitumor effects[46]. Zaitsu *et al*[47] found that serum transferrin is an independent prognostic predictor of HAIC treatment (low-dose cisplatin combination with 5-FU) (HR: 0.282; 95%CI: 0.132-0.603; $P = 0.001$) and that patients with serum transferrin ≥190 mg/dL had better survival than those with serum transferrin < 190 mg/dL (median survival time 12.0 *vs* 4.9; HR: 1; 95%CI: 0.132-0.6030; $P = 0.001$). These results suggested that serum transferrin can predict the prognosis of HCC patients treated with HAIC and that elevated transferrin *in vivo* contributes to anti-tumor progression and improves patient survival.

ADAMTS13 and Willebrand factor

ADAMTS13 is a metalloprotease produced by the hepatic stellate cells, whose main function is to cleave vascular VWF into smaller multimers[48]. ADAMTS13–VWF imbalance is associated with hypercoagulability and cancer progression [48-50]. Takaya *et al*[51] found that the ratio of VWF to ADAMTS13 was an independent predictor for patients with HCC treated with HAIC (cisplatin combined with 5-FU) (OR: 0.176; 95%CI: 0.0493-0.631; $P = 0.00766$), with high specificity (87.1%), sensitivity (53.7%), and an AUC of 0.715. The above study used coagulation-related factors to predict the prognosis of HAIC based on the blood coagulation cascade related to cancer progression. Further studies are needed to explore the specific mechanism (Figure 3).

Combined biomarkers

In addition to using a single indicator to predict the efficacy of HAIC, many recent studies have improved predictive efficacy by combining indicators. Saeki *et al*[52] developed an Assessment for Continuous Treatment score composed of three independent indicators: Child-Pugh score, AFP, and DCP, which ranged from 0 to 3. Patients stratified into two groups according to this score showed significantly different prognoses (≤ 1 *vs* ≥ 2 points: median survival time, 15.1 *vs* 8.7 months; $P = 0.003$). Many HCC staging systems and other prognostic scoring criteria have been developed to predict the prognosis of patients with HCC. Mei *et al*[53] used six independent predictors, including C-reactive protein, albumin-bilirubin (ALBI) grade, AFP, extrahepatic metastasis, portal vein invasion, and tumor size to establish a nomogram to predict individualized OS in patients with unresectable HCC after HAIC. Compared with the predicted effect of conventional staging systems, such as the Barcelona Clinic Liver Cancer (BCLC), Japan Integrated Staging (JIS) score, American Joint Committee on Cancer (AJCC), and Hong Kong liver cancer (HKLC)[7,54-56], the nomogram showed a better C-index (0.71, Table 2), indicating its superior predictive ability. Furthermore, Wang *et al*[57] established two nomogram models to assess the survival prognosis of HAIC and HAIC combined therapies in patients with HCC. First, five

Table 2 C-index of the nomogram and conventional staging system[53]

Staging system	Training cohort (*n* = 308)			Validation cohort (*n* = 155)		
	C-index	95%CI	*P* value[1]	C-index	95%CI	*P* value[1]
The nomogram	0.710	0.674–0.746	NA	0.716	0.664–0.768	NA
BCLC staging system	0.562	0.523–0.602	< 0.001	0.613	0.558–0.668	0.005
HKLC staging system	0.626	0.594–0.658	< 0.001	0.659	0.616–0.702	0.043
CIS	0.631	0.596–0.666	< 0.001	0.658	0.610–0.707	0.044
AJCC eighth edition	0.637	0.603–0.672	< 0.001	0.634	0.588–0.680	0.015
JIS score	0.619	0.582–0.655	< 0.001	0.638	0.587–0.689	0.017
Okuda classification	0.634	0.600–0.668	< 0.001	0.631	0.585–0.676	0.011

[1]*P* value was calculated according to the difference between the nomogram and other staging systems.

BCLC: Barcelona Clinic Liver Cancer; HKLC: Hong Kong Liver Cancer; CIS: China integrated score; AJCC: American Joint Committee on Cancer; JIS: Japan Integrated Staging; HR: Hazard rate; CI: Confidence interval; NA: Not available. Citation: Mei J, Lin WP, Shi F, Wei W, Liang JB, Shi M, Zheng L, Li SH, Guo RP. Prognostic nomogram predicting survival of patients with unresectable hepatocellular carcinoma after hepatic arterial infusion chemotherapy. *Eur J Radiol* 2021; 142: 109890. Copyright © 2021, The Authors. Published by Elsevier. The authors have obtained the permission for table using (Supplementary material).

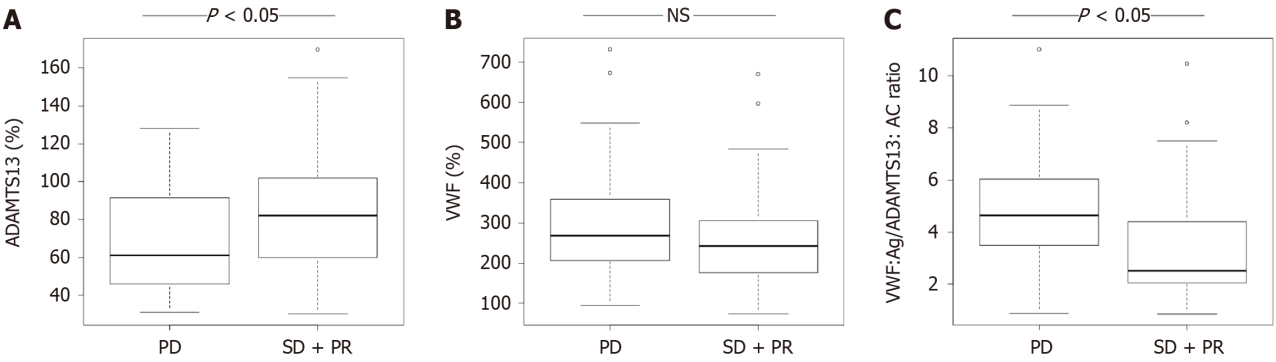


Figure 3 The prognostic in patients with hepatocellular carcinoma with different level of plasma ADAMTS13 and Von Willebrand factor receiving hepatic arterial infusion chemotherapy treatment[51]. A: ADAMTS13 levels were significantly higher in hepatocellular carcinoma patients receiving hepatic arterial infusion chemotherapy treatment with stable disease (SD) + partial response (PR) than in those with progressive disease (PD) ($P < 0.05$); B: Von Willebrand factor (VWF) antigen levels were not different between patients with SD + PR and PD; C: VWF/ADAMTS13 ratio was significantly lower in patients with SD + PR than in those with PD ($P < 0.05$). SD: Stable disease; PR: Partial response; PD: Progressive disease; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; ADAMTS13:AC: ADAMTS13 activity; VWF: Von Willebrand factor; VWF:Ag: VWF antigen; VWF:Ag/ADAMTS13:AC ratio: Ratio of VWF:Ag to ADAMTS13:AC. Citation: Takaya H, Namisaki T, Moriya K, Shimozato N, Kaji K, Ogawa H, Ishida K, Tsuji Y, Kaya D, Takagi H, Fujinaga Y, Nishimura N, Sawada Y, Kawaratani H, Akahane T, Matsumoto M, Yoshiji H. Association between ADAMTS13 activity-VWF antigen imbalance and the therapeutic effect of HAIC in patients with hepatocellular carcinoma. *World J Gastroenterol* 2020; 26: 7232-7241. Copyright © The Author(s) 2020. Published by Baishideng Publishing Group Inc. The authors have obtained the permission for figure using (Supplementary material).

independent indicators (tumor size, vascular invasion, metastasis, ALBI grade, and AFP level) were identified using multivariate analysis. The C-index value of this model was 0.701 (95%CI: 0.664-0.738) for the external test cohort. The predictive effect improved significantly in the HAIC combined model, including the abovementioned factors and the number of sessions, in combination with immune checkpoint inhibitors, tyrosine kinase inhibitors, and local therapy. The C-index values were 0.816 (95%CI: 0.789-0.843) in the external test cohort (Figure 4). Thus, nomogram models are essential for identifying patients with large HCC who are suitable for treatment with HAIC combination therapy and may potentially benefit personalized decision-making.

IMAGING PARAMETERS FOR PREDICTING THE PROGNOSIS OF HAIC TREATMENT FOR HCC

Apparent diffusion coefficient

Apparent diffusion coefficient (ADC), a magnetic resonance imaging technique, is established based on the diffusion-weighted imaging (DWI) modality, which quantitatively reflects the restriction of water molecule movement[58]. It has been shown that the ADC helps predict HCC with differentiation adverse, proliferative activity, and microvascular infilt-

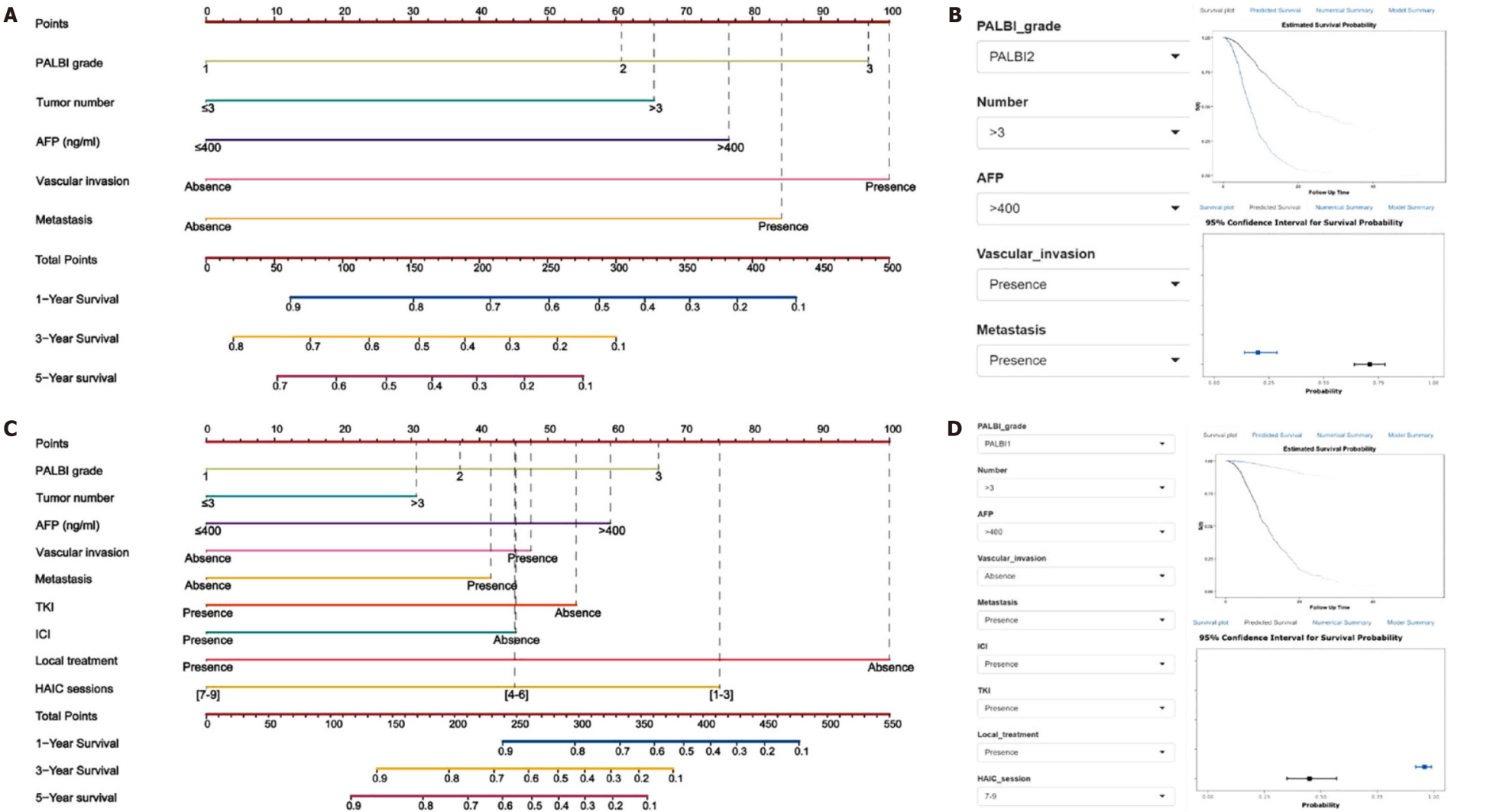


Figure 4 Development of prognostic models[57]. A: The Hepatic artery infusion chemotherapy (HAIC) nomogram was established using diagnostic factors for patients who had not received HAIC treatment and had preoperative HAIC data; B: The website for the pre-HAIC is available at https://prehaicnomogramforhcc.shinyapps.io/DynNomapp/; C: The post-HAIC nomogram was established using multiple factors for patients who had undergone HAIC treatment and had both preoperative and post-HAIC data; D: The website for post-HAICN is available at https://prehaicnomogramforhcc.shinyapps.io/postHAICN/. Citation: Yao W, Wei R, Jia J, Li W, Zuo M, Zhuo S, Shi G, Wu P, An C. Development and validation of prognostic nomograms for large hepatocellular carcinoma after HAIC. *Ther Adv Med Oncol* 2023; 15: 17588359231163845. Copyright © 2023. Published by SAGE Publications. The authors have obtained the permission for figure using (Supplementary material).

ration[59-62]. Therefore, the calculation of ADC values using DWI can be used to assess the tumor stage and predict the treatment outcome of liver cancer. Sung *et al*[63] found that the tumor ADC to liver ADC ratio (OR: 3.217; 95%CI: 1.264-8.187; $P = 0.014$) was correlated with the response to HAIC treatment for unresectable advanced HCC patients. A ratio < 0.741 suggests a good therapeutic effect of HAIC. In summary, analysis of the changes in the ratio of tumor ADC to liver ADC after HAIC treatment is helpful in predicting the efficacy in patients and can be used as an important predictor of HAIC treatment.

Computed tomography assessment of myosteatosis

In recent years, preoperative assessment of body composition has received increasing attention. Many studies have shown that the assessment of myosteatosis on computed tomography (CT) can predict the prognosis of patients with HCC. Yi *et al*[64] established a nomogram by measuring the value of myosteatosis combined with clinical variables (serum red blood cells, hemoglobin, creatinine, and mean CT value of visceral fat) to effectively predict the prognosis of combined anti-PD-1 and HAIC therapy. The AUC of the prediction model was 0.711 (95%CI: 0.75-0.95). However, large-scale multicenter prospective studies with standardized imaging protocols and body composition measurement tools are required to validate these results.

Combined imaging parameters

Recently, Zhao *et al*[65] developed a better prognostic score for predicting HAIC-treated HCC using a nomogram with a combined model of radiomics and albumin-bilirubin scores (Figure 5). The albumin-bilirubin score in this nomogram (AUC 0.69; 95%CI: 0.51-0.88) and the radiomic score (AUC 0.70; 95%CI: 0.58-0.82) were both independent indicators of HAIC treatment response. The result showed that the combined two indicators achieved better performance in the prediction, with AUC scores of 0.79 (95%CI: 0.68-0.90) and 0.75 (95%CI: 0.58-0.92) in the training and validation cohorts, respectively.

GENOMICS FOR PREDICTING THE PROGNOSIS OF HAIC TREATMENT FOR LIVER CANCER

HCC exhibits tumor heterogeneity[66]. It has been shown that HCC, which develops on HBV infection, HCV infection, alcohol abuse, and nonalcoholic fatty liver disease, have different molecular mutation profiles[67]. Schulze *et al*[68] and Gao *et al*[69] showed that *TP53, CTNNB1,* and *TERT* promoters are the most common mutations in HCC, and targeting these molecular mutations can improve patient outcomes. Therefore, the analysis of the mutational characteristics of patients and targeted treatment of genetic targets are beneficial for improving patient prognosis.

Single-nucleotide polymorphism as a predictor

The interleukin-28B (IL-28B) gene is a member of the IFN-related cytokine family[70]. Single-nucleotide polymorphisms in IL-28B are associated with the effectiveness of interferon therapy for chronic hepatitis C infection[60,71]. Whether IL-28B genotype affects the prognosis of patients with advanced HCC remains unknown[72]. Terashima *et al*[73] analyzed whether the IL-28B SNP (rs8099917) was correlated with the therapeutic efficacy and patient prognosis of HAIC in advanced HCC. Genotypes were divided into minor and major genotypes. Patients with minor genotypes had better objective response rates (51.9% *vs* 29.1%, $P = 0.022$) and significantly longer median OS (16.9 *vs* 14.1, $P = 0.027$) (Table 1). In addition, it has been shown that the SNP polypeptide N -acetylgalactosaminyltransferase14 (GALNT14-rs9679162) genotype "GG" is associated with prolonged overall survival after HAIC treatment using HAIC modality of cisplatin combined with 5-FU in patients with advanced HCC (HR: 0.187; 95%CI: 0.020-1.775; $P = 0.019$)[74,75].

Whole-exome sequencing and targeted region sequencing as a predictor

Furthermore, Ning *et al*[76] developed an exploratory model for predicting the efficacy of FOLFOX HAIC based on genomic sequencing of 96 patients (Figure 6A). A panel of 15 mutant genes (*PIK3CD, HNRNPCL4, NBPF20, TCHH, RAB3-GAP2, FGFR4, ARID1B, AGO2, PGR, KMT2A, SLX4, NF1, ERBB2, AXIN2, and PRKD2*) was derived from whole-exome sequencing of 90 patients to predict the efficacy of HAIC treatment (Figure 6B). The multivariate model indicated that the mutational panel was independent of clinical characteristics and could differentiate 83% of the patients who responded to HAIC treatment. HAIC responders had longer PFS and OS (PFS 14.3 *vs* 6.2 months, $P = 0.001$; OS 19.3 *vs* 10.6, $P = 0.002$; Figure 6C-E).

CONCLUSION

In conclusion, serological indicators, genetic testing, and imaging techniques can predict the prognosis of patients with HCC treated with HAIC and have shown excellent predictive value. Despite the apparent correlation with HAIC efficacy, there are shortcomings of the above markers for predicting the prognosis of HAIC treatment for HCC. First, this was a retrospective study. Second, they were conducted in a single center, and the number of cases in some studies was small, which may lead to potential prognostic bias; therefore, there is a need for validation using large-scale prospective studies of multiple centers. Finally, there is a need to improve prognostic accuracy by combining multiple markers and artificial intelligence to predict the prognosis of patients with HAIC-treated HCC. Although these are promising developments, there is still a need to standardize data for future studies to improve the veracity and accuracy of the results.

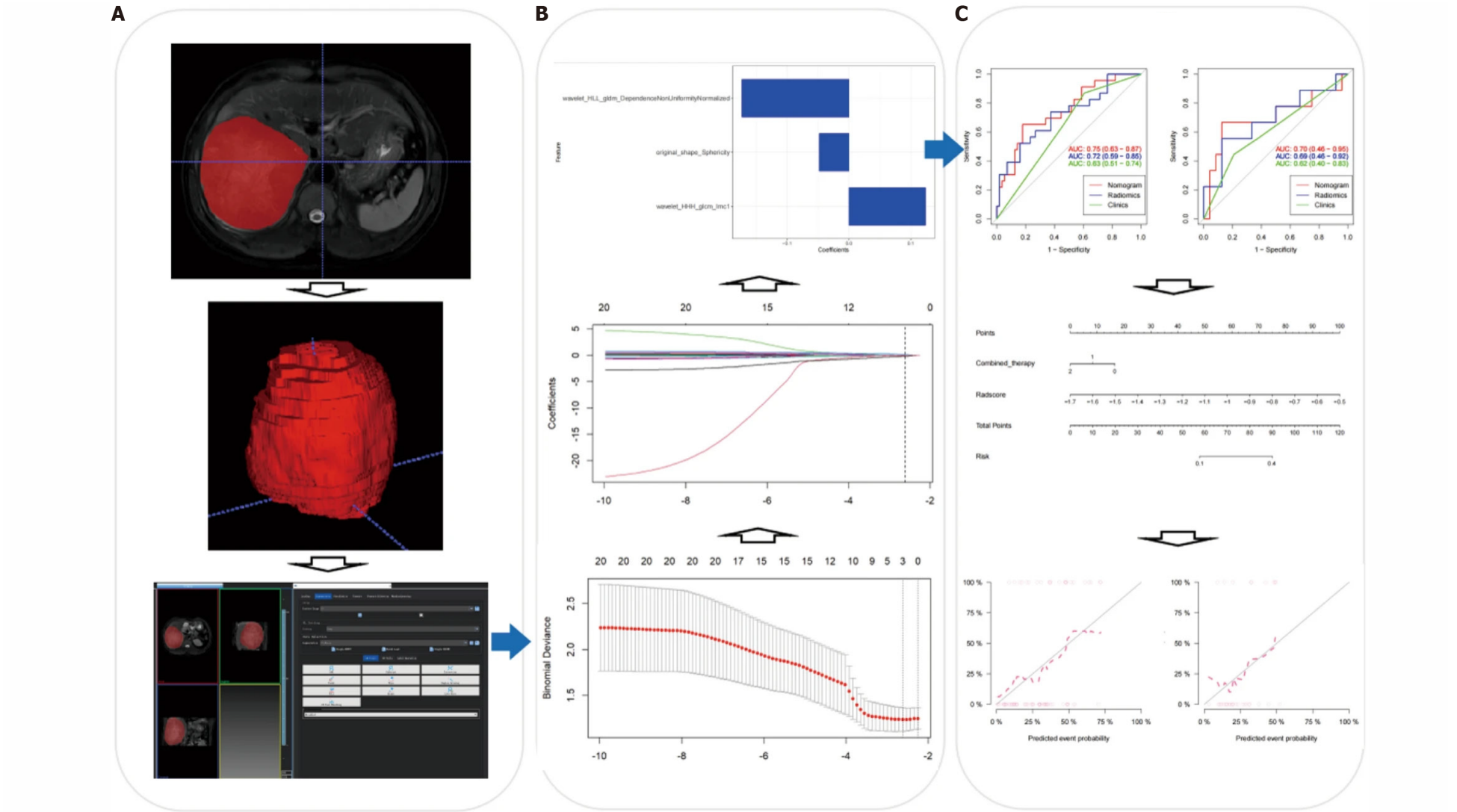
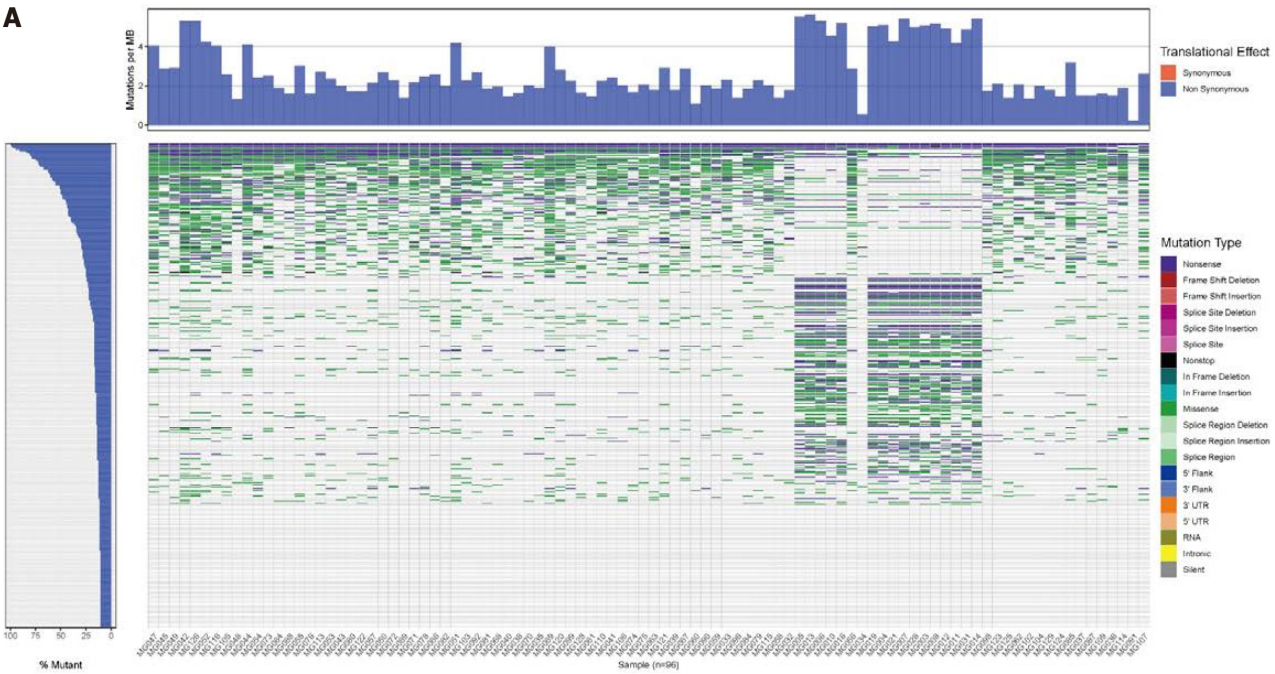


Figure 5 Workflow of the study[65]. A: Tumor segmentation on magnetic resonance images. Radiomic feature extraction from the volume of interest; B: The least absolute shrinkage and selection operator regression was applied to identify optimal radiomic features and construct the Rad-score; C: The nomogram model was established. The receiver-operator characteristic and calibration curves were constructed to assess the model performance. Citation: Zhao Y, Huang F, Liu S, Jian L, Xia X, Lin H, Liu J. Prediction of therapeutic response of unresectable hepatocellular carcinoma to hepatic arterial infusion chemotherapy based on pretherapeutic MRI radiomics and Albumin-Bilirubin score. *J Cancer Res Clin Oncol* 2023; 149: 5181-5192.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In Frame Deletion
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Splice Region Insertion
Splice Region
5' Flank
3' Flank
3' UTR
5' UTR
RNA
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Silent
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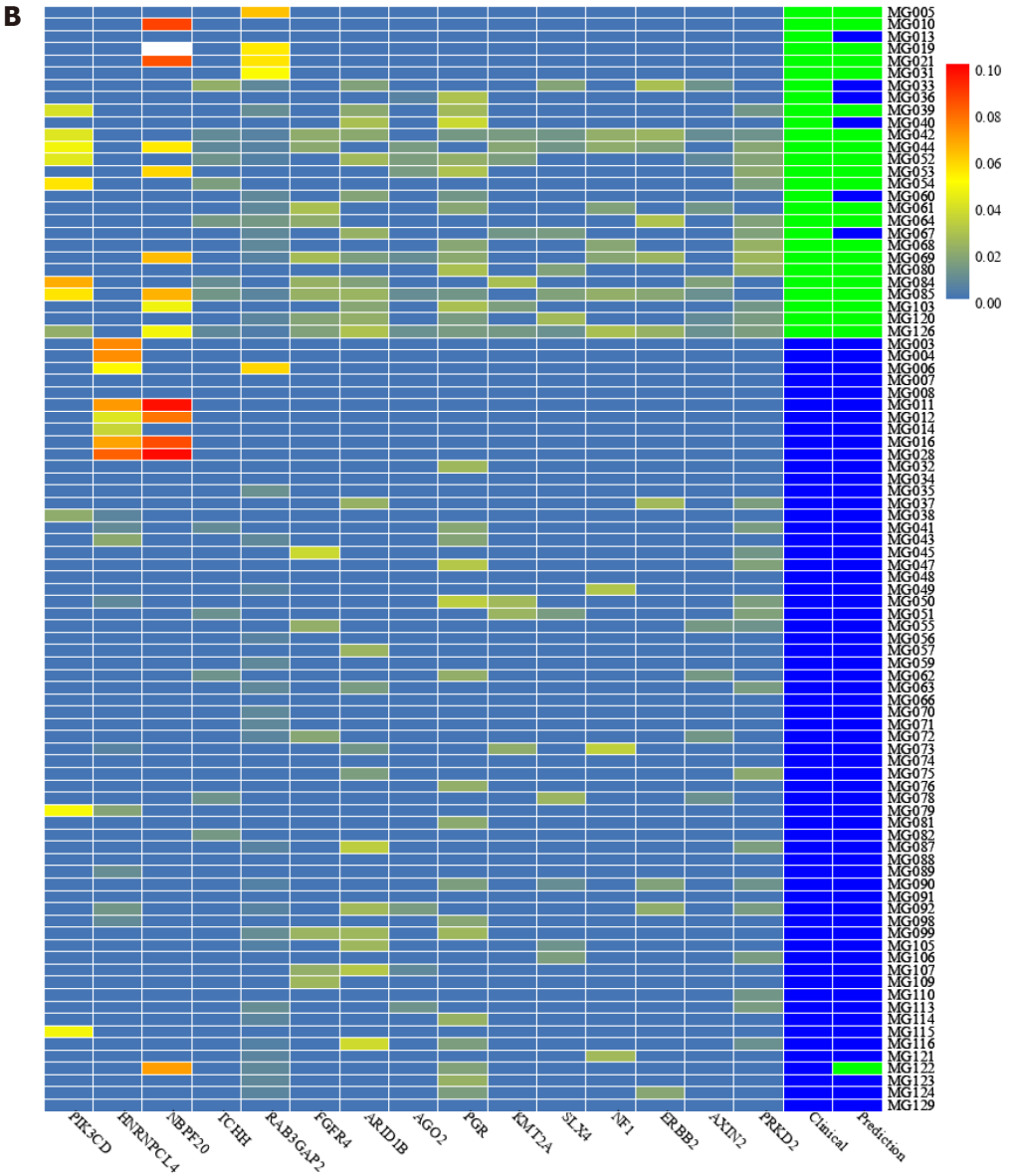
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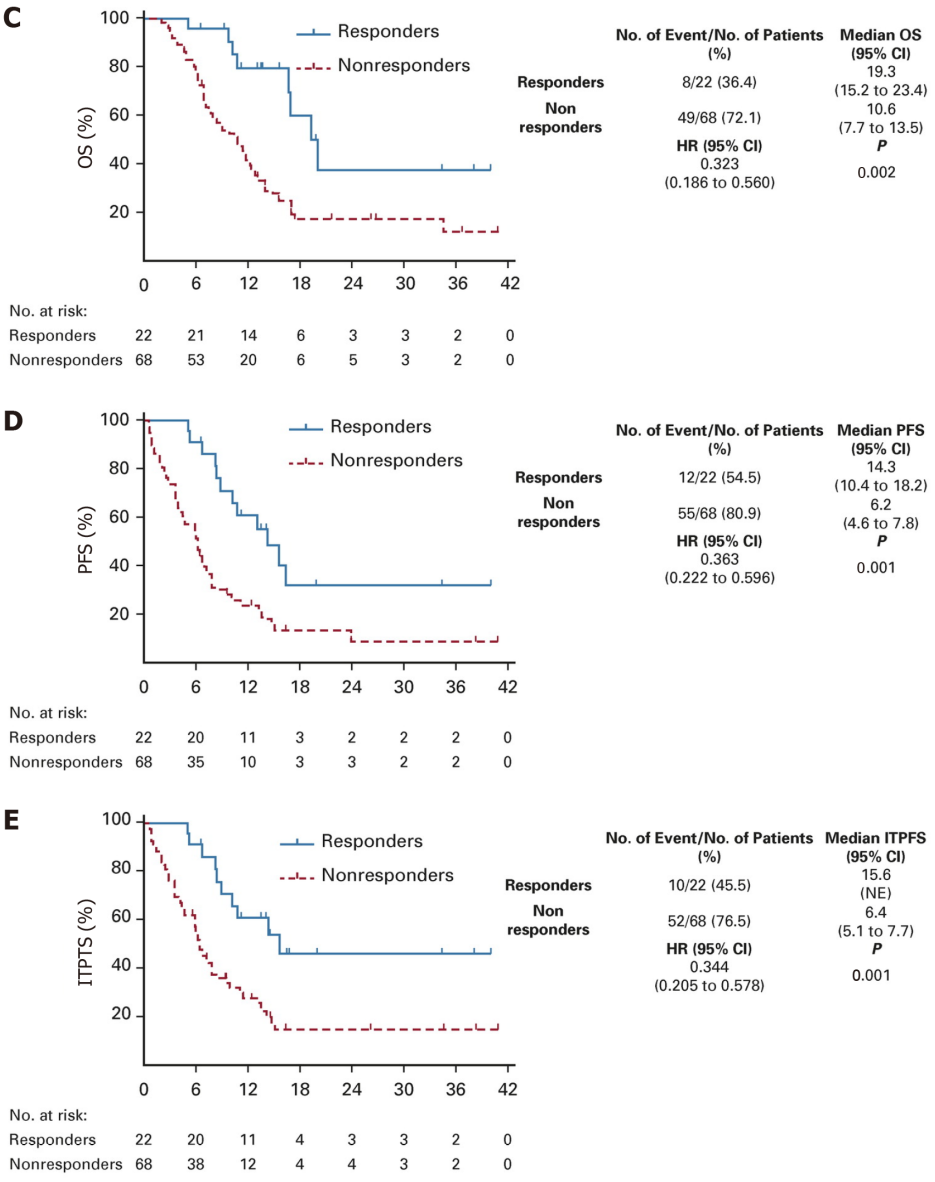

Figure 6 Gene signature set predicts hepatic artery infusion chemotherapy response[76]. A: Mutational landscape of the total 96 patients' sequence data by the next-generation sequencing analysis (Each row represents a gene, each column represents a sample, and different colors represent types of mutations); B: Heatmap of the correlation of 15-gene model and tumor response to the hepatic artery infusion chemotherapy (HAIC) treatment in the total 96 patients underwent genomic sequencing (Row: One sample of the mutation of the chosen 15 polymorphic sites, Column: One polymorphic site of the 90 samples). The right two columns show the tumor response to the HAIC treatment (green: response; blue: non-response); C: Survival outcomes between the HAIC responders and the HAIC nonresponders identified by the 15- mutant-gene prediction model; C-E: Kaplan-Meier estimates of (C) overall survival, (D) progression-free survival, and (E) intrahepatic tumor progression-free survival (ITPFS). Citation: Lyu N, Wang X, Li JB, Lai JF, Chen QF, Li SL, Deng HJ, He M, Mu LW, Zhao M. Arterial Chemotherapy of Oxaliplatin Plus Fluorouracil Versus Sorafenib in Advanced Hepatocellular Carcinoma: A Biomolecular Exploratory, Randomized, Phase III Trial (FOHAIC-1). *J Clin Oncol* 2022; 40: 468-480. Copyright © 2022. Published by American Society of Clinical Oncology. The authors have obtained the permission for figure using (Supplementary material).

FOOTNOTES

Author contributions: Wang QF drafted the manuscript and conception; Li ZW, Zhou HF, and Zhu KZ performed the literature search, and design; Wang YJ collected and assessed the data; Wang YQ and Zhang YW were contributed equally to this work responsible for the conception of the study, final editing, and review of the manuscript and as co-corresponding authors; all authors contributed to the article and approved the submitted version.

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