Article

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Predictive Value of Preoperative MRI Combined With Serum PIVKA-II Detection for Recurrence of Hepatocellular Carcinoma After TACE

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Background: Primary hepatocellular carcinoma (HCC) is a prevalent and aggressive malignancy with a high mortality rate. Transarterial chemoembolisation (TACE) is a widely used non-surgical treatment, but post-procedural recurrence remains a major challenge. Magnetic resonance imaging (MRI) offers a detailed assessment of tumor morphology and perfusion, while serum Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) has emerged as a sensitive HCC-specific biomarker. This study focused on analyzing the predictive value of preoperative MRI combined with serum PIVKA-II for recurrence after TACE in primary HCC.

Methods: A total of 101 patients with primary HCC undergoing TACE between January 2018 and March 2021 were enrolled. Patients were divided into a recurrence group (n = 52) and a non-recurrence group (n = 49), followed by comparison of MRI parameters and serum PIVKA-II levels. Variables demonstrating significant differences underwent logistic regression analysis, and the diagnostic value of the parameters with significant differences was dissected using a receiver operating characteristic (ROC) curve area under the curve (AUC).

Results: Compared with the non-recurrence group, the recurrence group exhibited a higher proportion of localized protrusions and diffuse "target sign", lower arterial phase values, portal venous phase values, and arterial phase enhancement rates, and higher PIVKA-II levels ($p < 0.05$). Logistic regression analysis revealed statistically significant differences in arterial phase values, portal venous phase values, and PIVKA-II levels ($p < 0.05$). ROC curves demonstrated AUC values of 0.872, 0.766, 0.895, and 0.939 for arterial phase values, portal venous phase values, PIVKA-II levels, and combined prediction of post-TACE recurrence in primary HCC, respectively ($p < 0.05$).

Conclusions: Preoperative MRI combined with serum PIVKA-II testing holds significant predictive value for post-TACE recurrence in patients with primary HCC. Low arterial- and portal venous-phase enhancement values, together with elevated serum PIVKA-II levels, were identified as independent risk factors for recurrence. The combined use of these parameters can improve the accuracy of recurrence prediction, providing a basis for individualized postoperative management and follow-up strategies to optimize patient outcomes.

Keywords: Protein Induced by Vitamin K Absence or Antagonist-II; magnetic resonance imaging; hepatocellular carcinoma; postoperative recurrence; transarterial chemoembolisation; predictive value

Introduction

Hepatocellular carcinoma (HCC), a highly prevalent malignancy of the digestive system worldwide, ranks among the most common malignancies in China and is associated with a high mortality rate, posing a serious threat to public health [1,2]. Due to the latent onset and a lack of specific early clinical symptoms, most patients are diagnosed at an advanced stage, missing the optimal window for radical surgical resection [3]. Besides, in patients with multiple lesions, poor liver functional reserve, or combined vascular invasion, the indications for surgical resection are often difficult to meet, complicating clinical treatment [4,5].

Transarterial chemoembolisation (TACE) is currently the primary non-surgical treatment method for HCC [6]. TACE can block the blood supply to the lesion and provide localized chemotherapy through precisely delivering chemotherapy drugs and embolic agents to the tumor-feeding arteries. In virtue of its advantages, including minimal trauma, strong targeting, and definite short-term ef-

ficacy [7,8], it has been widely used in clinical practice. However, TACE is not a curative intervention; the post-procedure high incidence of local recurrence and distant metastasis of tumors remains a major bottleneck restricting the long-term survival of patients [9,10]. Even worse, patients who experience recurrence typically require multiple sessions of TACE treatments. The cumulative toxicity of chemotherapy agents and embolization-related complications are highly likely to precipitate liver failure, further deteriorating the prognosis of patients [8,11]. Therefore, there is an urgent need to identify efficient and reliable preoperative predictive indicators that can accurately stratify patients at high risk of recurrence after TACE, providing a basis for clinical formulation of individualized treatment plans.

Magnetic Resonance Imaging (MRI), with its ultra-high soft tissue resolution and multi-parameter imaging capabilities, can clearly display the size, boundaries, blood supply characteristics and infiltration range of tumors [12]. It has unique advantages in evaluating tumor microcirculation and histological features, making it a valuable tool for preoperative prediction of TACE efficacy [13,14]. The Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) is a liver cancer-specific marker that has attracted much attention in recent years, and its upregulation is closely related to the malignant proliferation and angiogenesis of liver cancer cells. PIVKA-II can accelerate tumor progression by promoting the secretion of vascular endothelial growth factor, and its diagnostic sensitivity and specificity are superior to those of the traditional marker alpha-fetoprotein (AFP) [15–17].

To date, few studies have explored the prognostic value of combining preoperative MRI with serum PIVKA-II levels in patients undergoing TACE. Based on this, this study evaluated preoperative MRI parameters combined with serum PIVKA-II detection in patients with/without post-TACE recurrence, aiming to explore the clinical utility of this combined approach and to provide reference and guidance for improving the diagnostic efficacy of TACE after HCC recurrence in clinical practice.

Methods

Study Design and Ethical Declaration

This was a single-center retrospective clinical study. This study recruited HCC patients who had received TACE treatment at Taizhou First People's Hospital from January 2018 to March 2021. According to the follow-up results for tumor recurrence as of June 2023, the 101 patients who met the inclusion criteria were divided into the recurrence group (n = 52) and the non-recurrence group (n = 49). Recurrence was defined as the appearance of new enhanced lesions in the original lesion area on postoperative imaging, or a significant increase in tumor marker levels after excluding other interfering factors. The follow-up protocol was as follows: All patients underwent the first enhanced MRI re-examination 1 month after TACE, followed by regular re-examinations every 3–6 months, including imaging examinations and tumor marker tests. Follow-up was completed in June 2023, with a median duration of 24 months (range: 12–36 months). To ensure the independence of the evaluation, all follow-up images were blindly evaluated by two radiologists who had no access to the patients' detailed preoperative data and were aware only that the patients had received re-examinations after TACE. In case of disagreement, a third senior physician adjudicated to reach a consensus diagnosis.

The study protocol has been approved by the Medical Ethics Committee of Taizhou First People's Hospital (Approval number: 2020-KY002-01). The entire research process strictly adhered to the ethical principles outlined in the Declaration of Helsinki. All clinical data of the included patients were anonymized to protect patients' privacy and data security. Informed consent was waived by the ethics committee for this retrospective study.

Study Population

The inclusion criteria were as follows: (1) Pathologically diagnosed HCC [18]; (2) First-time TACE treatment and absence of other anti-tumor systemic treatments such as surgery resection, targeted therapy, or radiotherapy; (3) Liver function classified as Child-Pugh A or B grade [19], and sufficient liver functional reserve to tolerate TACE treatment; (4) Age between 30 and 80 years, without gender restriction; (5) Voluntary participation and cooperation to complete all required examinations and postoperative follow-up.

Patients with any of following criteria should be excluded: (1) Contraindications to MRI examination (e.g., presence of implanted metallic objects); (2) Complicated with other malignant tumors; (3) Presence of distant metastasis; (4) Immune dysfunction; (5) Coagulation dysfunction; (6) Dysfunction of important organs, such as the heart and kidneys; (7) Mental disorders with poor compliance; (8) Incomplete clinical data; (9) Pregnant or lactating women.

Baseline Data Comparison

The baseline data were collected and compared between the two groups, including core demographic and clinical characteristics such as gender, age, whether the maximum tumor diameter exceeded 5 cm, Child-Pugh classification, Barcelona Clinic Liver Cancer (BCLC) stage, number of tumors, whether presence of cirrhosis, Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV), and Eastern Cooperative Oncology Group Performance Status (ECOG) scores.

Methods of Detection

MRI Examination and Image Analysis

All patients underwent MRI examination within 1 week before TACE. A 1.5T magnetic resonance imaging system equipped with a 32-channel body phased-array coil (Avanto, Siemens, Erlangen, Germany) was used for examination. The patient was positioned in the supine position, and the scanning was completed in the normal breathing state. The scanning sequence included axial T1-weighted imaging (T1WI), axial T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), and three-phase liver dynamic enhancement scan.

The parameters of each sequence were set as follows: (1) T1WI: repetition time (TR) of 186 ms, echo time (TE) of 1.23 ms in phase and 2.46 ms out of phase, 30 slices, slice thickness of 6.0 mm, slice spacing of 1.2 mm, field of view (FOV) of 380 mm $\times$ 300 mm, matrix of 200 $\times$ 256; (2) T2WI: TR of 1100 ms, TE of 87 ms, 30 slices, slice thickness of 6.0 mm, slice spacing of 1.2 mm, FOV of 380 mm $\times$ 300 mm, matrix of 200 $\times$ 320; (3) DWI: TR of 7100 ms, TE of 63 ms, 30 slices, slice thickness of 6.0 mm, slice spacing of 1.2 mm, FOV of 380 mm $\times$ 300 mm, matrix of 108 $\times$ 134, b values of 50, 400, 800 s/mm^2; (4) Dynamic enhanced scanning: Gadopentetate dimeglumine (HY-A0167, MCE, USA) administered by bolus injection via the cubital vein (dose 0.1 mmol/kg, flow rate 2.0 mL/s). The scan parameters were TR of 4.31 ms, TE of 2.1 ms, slice number of 72, slice thickness of 3.0 mm, slice spacing of 0.6 mm, FOV of 400 mm $\times$ 340 mm. The matrix was 200 $\times$ 380, and the scanning was performed at 20–30 s (arterial phase), 60–90 s (portal venous phase) and 120–180 s (delayed phase) after injection of contrast agent.

The imaging results were interpreted and recorded by three physicians with over 5 years of clinical experience. In cases of disagreement, the majority consensus was adopted. The parameters recorded included local protrusion, capsule, diffuse "target sign", apparent diffusion coefficient (ADC) value, plain scan, arterial phase value, portal venous phase value, arterial phase enhancement rate, portal venous phase enhancement rate, and portal venous phase clearance rate. Enhancement rate in arterial phase = (intensity value in arterial phase – signal intensity value in plain scan) / signal intensity value in plain scan $\times$ 100%; Enhancement rate in portal venous phase = (intensity value in portal venous phase – signal intensity value in plain scan) / signal intensity value in plain scan $\times$ 100%; Portal clearance rate = (arterial phase intensity value – portal venous phase intensity value) / (arterial phase intensity value – plain scan signal intensity value) $\times$ 100% [20].

Detection of Serum PIVKA-II Levels

5 mL fasting blood samples (5 mL) were drawn from the peripheral vein of each patient on the morning of the MRI examination and placed in a vacuum collection vessel without anticoagulant (YA1363, Solarbio, China). The blood samples were allowed to clot for 30–60 min at room temperature, and then centrifuged at 3000 r/min for 10 min. The upper serum was separated and immediately stored in a refrigerator at –20 ℃ to avoid repeated freezing and thawing affecting the test results.

The serum PIVKA-II level was detected using colloidal gold immunochromatography with the detection kit (ELK8570, ELK Biotechnology, Wuhan, China). Briefly, 100 µL of each standard or serum sample was added to the antibody-precoated wells of the microplate and incubated at 37 ℃ for 80 min. After washing three times with the wash buffer, 100 µL of biotin-labeled detection antibody working solution was added and incubated at 37 ℃ for 50 min, followed by an additional wash step. Then, samples were cultivated with 100 µL of horseradish peroxidase (HRP)-conjugated streptavidin working solution at 37 ℃ for 50 min, washed five times, and stained with 90 µL of 3,3′,5,5′-Tetramethylbenzidine (TMB) substrate in the dark at 37 ℃ for 20 min. The reaction was terminated by 50 µL of stop solution, and the absorbance was immediately measured at 450 nm using a microplate reader (Synergy H1 microplate reader, BioTek, Winooski, VT, USA). All procedures were performed by professionally trained laboratory technicians with strict adherence to specified reaction time, temperature, and wash cycles. Each batch of testing was performed simultaneously with standard calibration and quality control procedures to ensure the accuracy and reliability of the results.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software (IBM, Chicago, IL, USA). Categorical data were expressed as case (n), and compared between the two groups using χ^2 test. The Shapiro-Wilk test was applied for testing the normality of continuous variables. Normally distributed data were presented in mean $\pm$ standard deviation ($\bar{x} \pm s$) and compared using the independent sample t test, while non-normally distributed data were expressed in the quartile method and compared with the Mann-Whitney U test. The diagnostic value of each parameter was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC), where an AUC of 0.5–0.7 indicated low accuracy, and an AUC $>$0.7 indicated good accuracy. A $p < 0.05$ was considered statistically significant.

Results

Results of Baseline Data Comparison

There were no significant differences in gender (male/female: 48/4 vs 39/10), age (61.00 (52.00, 69.25) vs 60.00 (54.00, 68.00)), the proportion of tumors $>$5 cm (13/39 vs 5/44), Child-Pugh classification (28/24 vs 26/23), BCLC stage (45/7 vs 41/8), number of tumors (39/13 vs 36/13), presence of cirrhosis (44/8 vs 39/10), HBV/HCV (48/4 vs 44/5), ECOG scores (2.00 (1.00, 2.00) vs 1.00

Table 1. Comparison of two groups of general data.

Index	Recurrence group (n = 52)	Non-recurrence group (n = 49)	χ^2/Z	p
Gender [male/female (n)]	48/4	39/10	3.416	0.065
Age (years)	61.00 (52.00, 69.25)	60.00 (54.00, 68.00)	–0.133	0.895
Tumor >5 cm [yes/no (n)]	13/39	5/44	3.771	0.052
Child-Pugh classification [A/B (n)]	28/24	26/23	0.006	0.937
BCLC stage [B/C (n)]	45/7	41/8	0.164	0.686
Number of tumors [single/multiple (n)]	39/13	36/13	0.031	0.860
Presence of cirrhosis [yes/no (n)]	44/8	39/10	0.435	0.510
HBV/HCV (n)	48/4	44/5	0.009	0.926
ECOG scores	2.00 (1.00, 2.00)	1.00 (1.00, 2.00)	–0.950	0.342

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; ECOG, Eastern Co-operative Oncology Group Performance Status.

Table 2. Comparison of MRI Indicators and PIVKA-II Levels between the two groups.

Index	Recurrence group (n = 52)	Non-recurrence group (n = 49)	$\chi^2/t/Z$	p
Local protrusion [yes/no (n)]	28/24	15/34	5.570	0.018
Capsule [yes/no (n)]	39/13	34/15	0.397	0.529
Diffusion “target sign” [yes/no (n)]	20/32	8/41	6.169	0.013
ADC value [n (10^{-3} mm^2/s)]	0.83 ± 0.10	0.87 ± 0.09	–1.978	0.051
Plain scan	212.50 (178.25, 256.50)	225.00 (198.00, 272.00)	–1.560	0.119
Arterial phase value	322.94 ± 88.38	483.00 ± 108.18	–8.163	0.000
Portal venous phase value	380.90 ± 98.49	481.37 ± 88.58	–5.379	0.000
Arterial-phase enhancement rate [n (%)]	61.78 (32.10, 118.42)	103.18 (78.57, 147.95)	–3.537	0.000
Portal venous phase enhancement rate [n (%)]	83.27 (54.72, 114.31)	98.86 (71.17, 135.90)	–1.896	0.058
Portal venous phase clearance rate [n (%)]	–0.94 (–88.20, 28.02)	12.38 (–16.77, 27.46)	–1.305	0.192
PIVKA-II (mAU/mL)	2122.81 (609.04, 5146.55)	27.76 (20.19, 158.22)	–6.843	0.000

Abbreviations: ADC, apparent diffusion coefficient; PIVKA-II, Protein Induced by Vitamin K Absence or Antagonist-II.

(1.00, 2.00)) (Table 1, $p > 0.05$), suggesting that the baseline characteristics of the two groups were comparable.

Results of MRI Examination and PIVKA-II Detection

The proportion of capsule, ADC value, plain scan, portal venous phase enhancement rate and clearance rate did not differ significantly between the two groups (Table 2, $p > 0.05$). Compared with the non-recurrence group, the recurrence group exhibited a higher proportion of local protrusion and diffuse “target sign”, lower arterial- and the portal venous-phase values, a lower arterial phase enhancement rate, and higher PIVKA-II levels (Table 2, $p < 0.05$).

Logistic Regression Analysis

The variables with differences between the recurrent group and the non-recurrent group in Table 2 were analyzed by Logistic regression, and the values in the arterial phase, portal venous phase and PIVKA-II levels of the two groups were statistically significant (Table 3, $p < 0.05$).

ROC Analysis

The AUC values of arterial phase value, portal venous phase value and PIVKA-II levels in predicting the recurrence of HCC after TACE were 0.872, 0.766 and 0.895, respectively, which were greater than 0.7 (Table 4, Fig. 1, $p < 0.05$). The AUC value of the combined diagnosis of HCC recurrence after TACE was 0.939, which was greater than 0.7 (Table 4 and Fig. 1, $p < 0.05$).

Discussion

In order to improve the diagnostic efficiency for post-TACE recurrence and the prognosis of HCC, the diagnostic value of preoperative MRI combined with serum PIVKA-II detection was explored. The results showed that the combined diagnosis of preoperative MRI and serum PIVKA-II levels exhibited a certain predictive value and could provide a basis for predicting the prognosis of HCC patients after TACE.

PIVKA-II, a precursor protein of prothrombin primarily produced by liver cancer tissues, has levels that are closely related to the pathological characteristics of liver cancer [21,22]. A previous study focused on the prediction of early therapeutic efficacy through the dynamic changes after treatment, and found that the decrease in PIVKA-II levels one month after TACE was associated with the objective response observed at three months [23]. The tumor marker PIVKA-II has higher sensitivity than AFP in the detection of early HCC. The combined detection of AFP and

Table 3. Logistic regression analysis.

Index	B	SE	*p*	OR	95% CI (Lower)	95% CI (Upper)
Local protrusion [yes/no (n)]	–0.116	0.714	0.871	0.890	0.220	3.607
Diffusion target sign [yes/no (n)]	0.794	0.790	0.315	2.213	0.471	10.402
Arterial phase value	–0.015	0.005	0.002	0.985	0.976	0.994
Portal venous phase value	–0.009	0.004	0.011	0.991	0.984	0.998
Arterial phase enhancement rate [n (%)]	–0.010	0.008	0.234	0.991	0.975	1.006
PIVKA-II (mAU/mL)	0.001	0.000	0.003	1.001	1.000	1.001

Abbreviations: PIVKA-II, Protein Induced by Vitamin K Absence or Antagonist-II; B, Regression Coefficient; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

Table 4. ROC curve parameters.

Index	Cut-off value	Sensitivity	Specificity	AUC	*p*	95% CI (Lower)	95% CI (Upper)
Arterial phase value	405.500	0.846	0.714	0.872	0.000	0.807	0.937
Portal venous phase value	479.000	0.885	0.531	0.766	0.000	0.675	0.858
PIVKA-II (mAU/mL)	164.170	0.942	0.755	0.895	0.000	0.834	0.957
Combined diagnosis	0.491	0.885	0.878	0.939	0.000	0.895	0.983

Abbreviations: PIVKA-II, Protein Induced by Vitamin K Absence or Antagonist-II; CI, Confidence Interval; AUC, Area Under the Curve.

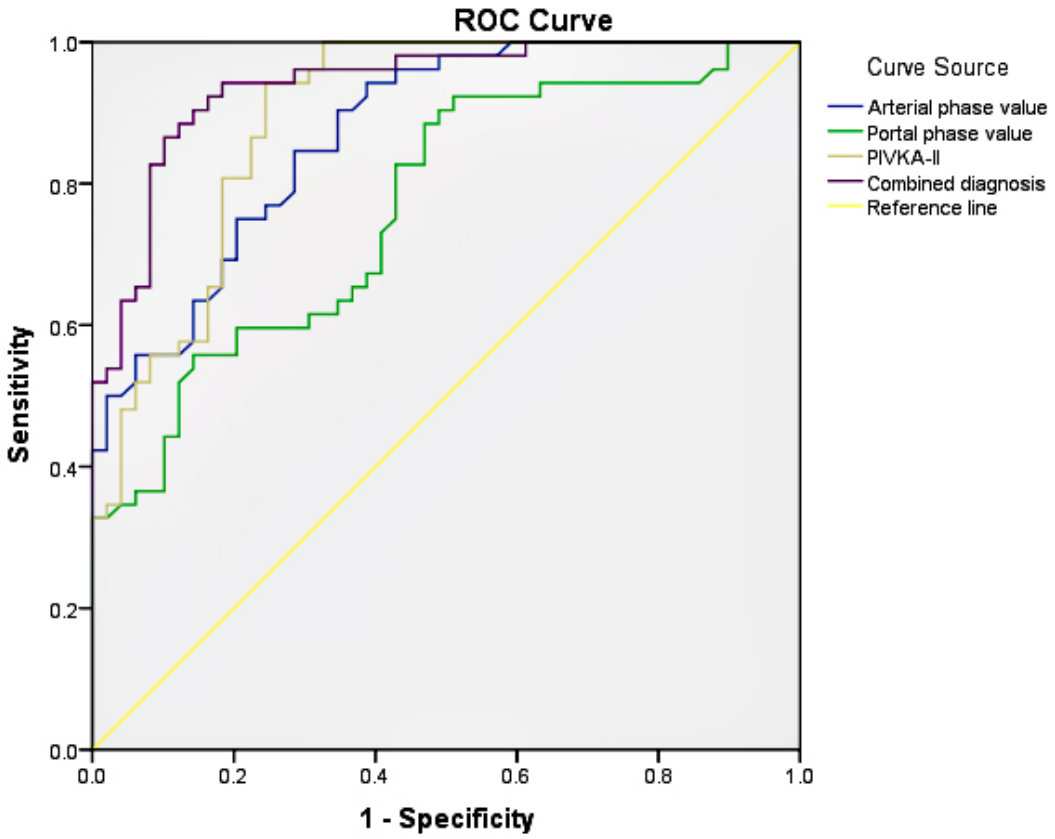

Fig. 1. Receiver operating characteristic (ROC) curve of magnetic resonance imaging (MRI) and Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) alone or in combination to predict the recurrence of hepatocellular carcinoma (HCC) after transarterial chemoembolisation (TACE).

PIVKA-II demonstrated superior sensitivity and specificity compared to either marker used alone. In addition, combining these biomarkers with ultrasound can improve the detection rate of early HCC in clinical practice [24]. However, different from the starting points of previous studies, this study showed elevated PIVKA-II level and decreased

values of arterial phase and portal venous phase in patients with postoperative recurrence relative to patients without postoperative recurrence, suggesting a relationship between elevated PIVKA-II levels and the recurrence of HCC after TACE. As a routine diagnostic and prognostic indicator of HCC, higher PIVKA-II levels indicate a more serious tumor burden and a greater possibility of recurrence and metastasis of residual tumor cells, consequently increasing the risk of post-TACE relapse [25,26]. Consistently, we found that the recurrent tumor after surgery showed increased invasiveness (with portal vein tumor thrombus) and greater resistance to TACE, as well as augmented serum PIVKA-II levels. After effective radiotherapy, the levels of PIVKA-II can diminish to the normal range and remain stable during long-term recurrence-free follow-up [27]. These findings not only confirm the value of PIVKA-II as a marker for recurrence risk but also suggest that its dynamic monitoring can be used to evaluate treatment responses.

These findings highlight the complementary role of biomarker assessment in managing HCC. Similarly, imaging biomarkers derived from serial scans have been explored for prognostic evaluation. Meanwhile, after the first TACE procedure, dynamic changes in quantitative functional MRI parameters, such as DWI, have been proven to strongly predict the long-term survival, and can monitor early response to TACE [28]. Notably, recent radiomics studies have confirmed that the functional MRI parameters after TACE, such as changes in the volume of ADC and venous enhancement, correlate significantly with the histopathological grading of HCC [29]. However, the aforementioned studies either focus on post-treatment imaging changes or rely on special functional imaging sequences. In contrast, this study explored the prognostic value of easily obtainable quantitative parameters (absolute signal intensity in the arterial phase and portal venous phase) derived from preoperative, clinically widespread, conventional dynamic contrast-enhanced MRI scans. This preoperative, conventional imaging-based approach aims to identify high-risk patients earlier in the clinical workflow, at the point of initial therapeutic decision-making. The blood supply of lesions in patients with liver cancer mainly derives from the hepatic artery [30], and its characteristics can be clearly visualized on three-phase dynamic contrast-enhanced MRI [31]. Surrounding liver tissue was not obviously enhanced, and generally produced high signal in the portal vein. Tumor thrombus presented with low signal intensity and obvious arterial phase enhancement. Lower arterial- and portal venous-phase enhancement values suggest a higher degree of tumor invasion and an increased risk of recurrence [32]. In addition, low preoperative arterial phase values may indicate insufficient arterial blood supply to the tumor, which may be related to microvascular invasion of the tumor, and is one of the important factors affecting the recurrence of liver cancer [33,34]. Low portal venous phase values may be indicative of the uneven blood perfusion of the tumor, promoting tumor cell quiescence under ischemia and hypoxia conditions, thereby increasing the risk of postoperative HCC relapse [35]. Therefore, arterial- and portal venous-phase values and PIVKA-II levels are closely related to the recurrence of HCC after TACE. Low arterial- and portal venous-phase values and high PIVKA-II levels are independent risk factors for recurrence after TACE.

Furthermore, in this study, all patients with HCC after TACE were examined by MRI and serum PIVKA-II before operation. The values of arterial phase, portal venous phase, PIVKA-II level and combined prediction of postoperative recurrence were obtained by ROC curve, and the accuracy of combined prediction was higher than that of a single predictor.

However, this study has several limitations. First, the retrospective design may introduce potential selection bias, as data were collected based on existing medical records rather than prospective enrollment. Second, the single-center setting restricted the generalizability of the results. Third, the sample source and size in this study were limited, and the results may not fully represent all patients with HCC after TACE. Therefore, the diagnostic efficacy of preoperative MRI combined with serum PIVKA-II detection should be further validated in large and multi-center studies to strengthen the relevant evidence and theoretical framework.

Conclusions

In conclusion, preoperative MRI combined with serum PIVKA-II detection may exhibit a high predictive value for post-TACE recurrence of HCC. Low arterial- and portal venous-phase values, together with high PIVKA-II levels, are independent risk factors for recurrence after TACE.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

SW and YJ designed the research study; SW, YJ, SZ and JF performed the experiments; JF, RC, XH and PJ collected and analyzed the data. SW, YJ and XH have been involved in drafting the manuscript and all authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity are addressed.

Ethics Approval and Consent to Participate

The study protocol had been approved by the Medical Ethics Committee of Taizhou First People's Hospital, and the ethics approval number was 2020-KY002-01. The entire research process strictly adhered to the ethical principles outlined in the Declaration of Helsinki. All clinical data of the included patients were anonymized to protect patients' privacy and data security. Informed consent was waived by the ethics committee for this retrospective study.

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Conflict of Interest

The authors declare no conflict of interest.

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