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A preoperative model based on gadobenate-enhanced MRI for predicting microvascular invasion in hepatocellular carcinomas (< 5 cm)

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Purpose: The present study aimed to develop and validate a preoperative model based on gadobenate-enhanced magnetic resonance imaging (MRI) for predicting microvascular invasion (MVI) in patients with hepatocellular carcinoma (HCC) size of \leq 5 cm. In order to provide preoperative guidance for clinicians to optimize treatment options.

Methods: 164 patients with pathologically confirmed HCC and preoperative gadobenate-enhanced MRI from July 2016 to December 2020 were retrospectively included. Univariate and multivariate logistic regression (forward LR) analyses were used to determine the predictors of MVI and the model was established. Four-fold cross validation was used to verify the model, which was visualized by nomograms. The predictive performance of the model was evaluated based on discrimination, calibration, and clinical utility.

Results: Elevated alpha-fetoprotein (HR 1.849, 95% CI: 1.193, 2.867, P=0.006), atypical enhancement pattern (HR 3.441, 95% CI: 1.523, 7.772, P=0.003), peritumoral hypointensity on HBP (HR 7.822, 95% CI: 3.317, 18.445, P<0.001), and HBP hypointensity (HR 3.258, 95% CI: 1.381, 7.687, P=0.007) were independent risk factors to MVI and constituted the HBP model. The mean area under the curve (AUC), sensitivity, specificity, and accuracy values for the HBP model were as follows: 0.830 (95% CI: 0.784, 0.876), 0.71, 0.78, 0.81 in training set; 0.826 (95% CI:0.765, 0.887), 0.8, 0.7, 0.79 in test set. The decision curve analysis (DCA) curve showed that the HBP model achieved great clinical benefits.

Conclusion: In conclusion, the HBP imaging features of Gd-BOPTA-enhanced MRI play an important role in predicting MVI for HCC. A preoperative model,

mainly based on HBP imaging features of gadobenate-enhanced MRI, was able to excellently predict the MVI for HCC size of \leq 5cm. The model may help clinicians preoperatively assess the risk of MVI in HCC patients so as to guide clinicians to optimize treatment options.

KEYWORDS

gadobenate dimeglumine, hepatocellular carcinoma, microvascular invasion, magnetic resonance imaging, nomogram

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third leading cause of death from cancer in the world (1, 2). While numerous treatment strategies have been developed, HCC patients remain at a high risk of tumor recurrence (3, 4). Microvascular invasion (MVI) is an important prognostic factor in patients with HCC and is associated with early recurrence and poor survival (5, 6). However, MVI diagnosis currently requires histopathological analysis of the surgical specimens, which can only be performed postoperatively (7). Previous study demonstrated that enlarged surgical margin (usually over 1cm) could reduce postoperative tumor recurrence rates in MVI-positive patients with HCC (8). And postoperative adjuvant transarterial chemoembolization could improve the overall survival and disease-free survival for patients who have HCC with MVI (9). Therefore, the preoperative prediction of MVI in patients with HCC is necessary for clinicians to optimize treatment options and improve long-term survival (10). Some evidence shows that tumor size is correlated to the incidence of MVI (11). This implies tumor size may be a potential confounding factor in predicting MVI. Meanwhile, early diagnosis of MVI in patients with HCC, especially patients with HCC size of ≤ 5 cm, will help clinicians choose more appropriate therapeutic regimens to improve prognosis.

Gadobenate dimeglumine (Gd-BOPTA) is a hepatobiliaryspecific agent, it can be selectively taken up into function hepatocytes by the specific organic anion transporting polypeptides (OATP1B1, OATP1B3) located on the surface of hepatocytes (12–14). In addition to dynamic contrast-enhanced MRI of the liver, this agent may also assist with specific imaging in the hepatobiliary phase (HBP) within 40–120 min after injection (15). Compared to gadoxetate disodium-enhanced MRI, Gd-BOPTA-enhanced MRI have a true delayed phase (DP), instead of a transitional phase (TP) (15). Previous studies have reported some models for predicting MVI using gadoxetate disodium-enhanced MRI (16, 17), but no previous literature has reported the use of gadolinate-enhanced MRI to build a model to predict MVI. The present investigation used the true DP and HBP imaging features based on gadobenate-enhanced MRI to preoperatively predict MVI in patients with HCC.

Accordingly, the present study aims to develop and validate a preoperative model based on gadobenate-enhanced MRI for predicting MVI in patients with HCC size of ≤ 5 cm. In order to provide preoperative guidance for clinicians to optimize treatment options.

Materials and methods

Patients

The present study was approved by the ethics committee of the Eastern Hepatobiliary Surgery Hospital, the Third Affiliated Hospital of Shanghai Naval Military Medical University, China. The requirement for written informed consent was waived.

Between July 2016 and December 2020, a total of 164 pathologically confirmed HCC patients (138 males and 26 females; 55.13 \pm 10.52 years) after preoperative Gd-BOPTA-enhanced MRI met the following inclusion criteria (Figure 1): (a) tumor size with the longest diameter of \leq 5 cm; (b) complete histopathologic HCC description; (c) Gd-BOPTA-enhanced MR examination was performed within two months before the operation, including complete scanning phase images (arterial phase, portal phase, DP, and HBP); and (d) no previous treatment history of HCC, such as liver transplantation, transarterial chemoembolization, radiofrequency ablation.

Laboratory examinations and histopathology

Preoperative laboratory indexes (Table 1) comprised protein induced by vitamin K absence/antagonist-II (PIVKA-II), serum alpha-fetoprotein (AFP), AFP-L3, carbohydrate antigen 19-9, carcinoembryonic antigen, hepatitis B virus (HBV), HBV-DNA



loads, anti-hepatitis C virus, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, cholinesterase (CHE), r-glutamyltransferase, α -L-fucosidase, total protein, albumin (ALB), total cholesterol, prothrombin time, activated partial thromboplastin time.

The histopathological characteristics (tumor size, MVI status, and Edmondson-Steiner) were assessed by a consensus of two experienced pathologists. Until recently, MVI was defined as the presence of a tumor in a portal vein, hepatic vein, or large capsular vessel of the surrounding hepatic tissue lining the endothelium (17–20). The grades of MVI are classified as M0 (no MVI), M1 (invasion of microvessels up to five times at the peritumoral parenchyma within 1 cm of the tumor surface), and M2 (MVI at >5 sites or >1 cm away from the tumor surface) (11, 20). The cases were divided into the MVI (M1-2) (n=55) and non-MVI (M0) (n=109) groups.

Gd-BOPTA-enhanced MR

MR images were acquired using a GE Optima MR360 1.5T (Optima MR360, GE Healthcare, USA) equipped with an eightchannel abdominal coil. Patients fasted for 4 h before the scan. Gd-BOPTA (MultiHance, Bracco) with a total dose of 0.1 mmoL/kg was injected into the median cubitus vein at a rate of 2.0 mL/s with a high-pressure syringe, followed by washing with 20 mL of normal saline. The arterial phase (AP), portal venous phase, DP, and HBP scans were performed 20–30 s, 50– 60 s, 90–120 s, and 60 min after the injection of Gd-BOPTA, respectively. HBP scans were performed 120 min after injection of the contrast agent in patients with impaired liver function. Detailed scanner and scan parameters can be found in Supplementary Table S1.

MR imaging analysis

MR imaging analysis was performed by two radiologists (with more than 10 years of abdominal imaging experience) who were blinded to the clinical and laboratory information. If their opinions were not consistent, a consensus decision was made after discussion. Two radiologists independently evaluated 10 imaging features defined in Liver Imaging Reporting and Data System (LI-RADS) v2018 (21): (a) tumor size, the longest axis diameter measured on HBP images; (b) radiological capsule enhancement; (c) restricted diffusion; (d) non-rim arterial phase hyperenhancement (APHE); (e) rim APHE; (f) non-peripheral washout; and (g) hepatobiliary phase hypointensity. The definition of LI-RADS features can be found in Supplementary Table S2.

Non-LI-RADS imaging features comprised (a) tumor number (b) shape (c) non-smooth margin (15); (d) enhancement pattern; (e) arterial peritumoral enhancement (17, 22); (f) peritumoral hypointensity on HBP (23, 24). The TABLE 1 Clinicoradiological characteristics for predicting MVI.

Chical fastres Siz Siz Siz Siz Siz Siz Siz Mac 156 (S14) 89 (B27) 49 (92 19) 0.263 Fernale 26 (L590) 20 (B27) 49 (92 19) 0.263 Fernale 15 (S190) 20 (B27) 49 (92 19) 0.263 Lord desate 11 (S19) 8 (C190) 21 (C190) 21 (C190) 0.264 (C190) 0.274 (C190)	Characteristic	Total (n = 164)	Non-MVI (n = 109)	MVI (n = 55)	P value
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InterfactUnit of the set of	Female	26 (15.9%)	20 (18.3%)	6 (10.9%)	
<table-container>HAYIQ 000000000000000000000000000000000000</table-container>	Liver disease				
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Instruct	Negative	110 (67 1%)	77 (70.6%)	33 (60.0%)	0 171
APP (ngl) Pa (48,1857) Fa (18,118,18) Ga (13,341.1) Quart APP (ngl) 146 (0.68,2.27) 1.18 (0.51.207) 178 (1.09,2.53) 0.002 PIVKA-II (mAU/mL) 56 (28,257.8) 56 (24,239.5) 94 (3.41.0) 0.432 PIVKA-II (mAU/mL) 1.63 (7.830.2) 17.1 (7.92.8.4) 163 (7.3.30.0) 0.713 CAI 09 (U/mL) 2.4 (1.6.3.2 2.3 (1.6.3.21) 2.5 (1.6.3.4) 0.52 ALT (U/L) 2.4 (1.6.3.2 2.4 (1.6.3.2) 2.5 (1.6.3.4) 0.52 ALT (U/L) 2.5 (20.0.3.68) 2.6 (1.9.3.1) 0.22,4(8.3.4) 0.24 ALB (g/L) 2.4 (3.9.9.4) 2.4 (3.9.4) 0.24 0.53 TBIL (umol/L) 4.5 (12.0.18.6) 1.54 (12.1.8.6) 1.34 (11.6.18.6) 0.47 DBIL (umol/L) 4.4 (3.9.9.4) 2.4 (3.9.2) 0.53 0.53 0.53 DBIL (umol/L) 4.7 (3.9.6.6.25.3) 1.54 (12.18.6) 1.44 (1.6.18.6) 0.47 DBIL (umol/L) 4.7 (3.9.6.6.25.3) 2.6 (1.6.3.2) 0.53 0.53 DBIL (umol/L)	Positive	54 (32.9%)	32 (29 4%)	22 (40.0%)	011/1
Arr legit properties Arr legit propertiesArr legit properties propertiesArr legit propertiesArr legit properties	AFP (ng/I)	29.4 (4.8 185.7)	151 (331188)	60.3(12.3.341.1)	0.023
Integration Interfactor Interfactor Interfactor Interfactor Interfactor PIVKA-II (mAU/mL) 56 (28,257) 56 (24,235) 97 (37410) 0.432 PIVKA-II (mAU/mL) 163 (7,830.2) 171 (7.92.8.4) 1.63 (7.73.0) 0.713 CEA (ng/mL) 24 (1.6,3.2) 23 (1.6,3.2) 25 (1.6,3.4) 0.529 ALT (U/L) 28 (19.30.8) 26 (19.35) 03 (22,48) 0.290 AST (U/L) 25 (50.03.68) 26 (19.35) 63 (64.57.3.7) 0.52 ALE (g/L) 68.4 (65.17.3.3) 68.5 (65.67.32) 68.3 (64.57.3.7) 0.52 ALE (g/L) 68.4 (65.17.3.3) 68.5 (65.67.32) 68.3 (64.57.3.7) 0.52 ALE (g/L) 42.8 (39.94.57) 42.7 (39.64.56.0) 43.2 (40.54.60.0) 0.52 ALE (g/L) 14.5 (12.0.18.6) 15.6 (12.2.18.6) 13.4 (11.6.18.6) 0.47 DBIL (umol/L) 54 (43.7.2) 65 (44.7.2) 40 (30.8.6) 0.63 GCT (U/L) 43 (29.84) 41 (28.0) 40 (30.8.6) 0.57 GCT (U/L) 3.9	AFP lg10 (ng/L)	1.46(0.682.27)	1 18 (0 51 2 07)	1 78 (1 09 2 53)	0.002
Interfact (unifying) Interfact (unifyingi (unifying) Interfact (unifyingi (unifying)	$\frac{\text{PIVK} A_{\text{II}} (\text{m} A_{\text{II}}/\text{m} I)}{\text{PIVK} A_{\text{II}} (\text{m} A_{\text{II}}/\text{m} I)}$	56 (28 257 8)	56 (24 239 5)	94 (37 410)	0.432
Interlagion Instruction Instruction <thinstruction< th=""> <thinstruction< th=""></thinstruction<></thinstruction<>	PIVKA-II [a10	1 85 (1 39 2 57)	1.73(1.362.47)	1 98 (1 45 2 61)	0.452
Chrony Control Dis (1,6,5,0,5) Dis (1,6,5,0,5) Dis (1,6,5,0,5) CEA (ng/mL) 24 (1,6,3,2) 23 (1,6,3,2) 25 (1,6,3,4) 0,529 ALT (U/L) 28 (19,3,0,8) 28 (19,3) 0 (22,48) 0,294 AST (U/L) 255 (20,3,68) 685 (65,67,3,2) 68,3 (64,5,7,3,7) 0,688 ALB (g/L) 42.8 (39,9,45,7) 42.7 (39,6,45,6) 32 (40,5,46,0) 0,678 TBL (µmol/L) 14.5 (12,0,18,6) 156 (12,2,18,6) 34 (11,6,18,6) 0,479 DBL (µmol/L) 44 (3,7,2) 56 (44,7,2) 49 (41,6,9) 0,574 GGT (U/L) 378 (596,68,258) 715 (533,98,226) 40 (30,86) 0,630 GGT (U/L) 43 (29,4) 41 (28,80) 04 (30,86) 0,574 AFU (U/L) 21 (14,12,6) 12 (11,412,9) 12,01 (11,312,5) 0,579 CHO (mmol/L) 39 (3,41,438) 396 (34,24,45) 381 (3,39,4,30) 0,580 AFMOSONSTEINER 12 (11,412,6) 12 (11,412,6) 12,01 (11,12,5) 0,581 ILI (INC) 39 (3,31,40 13 (3,63,91	CA199 (II/mI)	1.63(7.8.30.2)	1.75(1.50.2.47)	1.93(1.43,2.01) 16.3(7.7,33,0)	0.407
Cla (upine) Def (Upine) Def (Upine) Def (Upine) Def (Upine) Def (Upine) ALT (U/L) 28 (19,340.8) 28 (19,39) 0 (22,48) 0.249 AST (U/L) 25,5 (20,0,36,8) 26 (19,35) 25 (21,37) 0.628 ALB (g/L) 68.4 (65.1,73.3) 68.5 (65.67.3.2) 68.3 (64.57.37) 0.628 ALB (g/L) 42.8 (39.9,45.7) 42.7 (39.6,45.6) 3.2 (40.5,46.0) 0.57 DBL (umol/L) 14.5 (12.0,18.6) 15.6 (12.2,18.6) 3.4 (11.6,18.6) 0.147 DBL (umol/L) 14.5 (12.0,18.6) 15.6 (12.2,18.6) 49.4 (1.6,91 0.254 CHE (U/L) 3.78 (596.68.258) 5.6 (4.4,72) 49.4 (1.6,90 0.633 GGT (U/L) 43 (29.4) 41 (28.80) 40 (30.86) 0.633 PT (S) 12 (11.4.12.6) 12 (11.4.12.9) 2.0 (11.3,12.5) 0.593 CHOL (mmol/L) 24 (19.3) 39.6 (34.24.45) 3.81 (3.9.4.34) 0.580 PT (S) 12 (11.4.12.6) 12 (11.4.12.9) 2.0 (11.3,12.5) 0.581 ILINT 39	CEA (ng/mL)	24(1632)	(1, 3, 20, 4)	25(1634)	0.529
All (12) 26 (15.3, 80.5) 26 (15.3) 36 (12.40) 62.40 AST (U/L) 25 (20.3, 80.5) 26 (19, 35) 25 (21, 37) 0.290 TP (g/L) 68.4 (65.1, 73.3) 68.5 (65.6, 73.2) 68.3 (64.5, 73.7) 6.628 ALB (g/L) 42.8 (39.9, 45.7) 42.7 (39.6, 45.6) 43.2 (40.5, 46.0) 0.058 TBLI (µmol/L) 42.6 (39.9, 45.7) 56 (4.4, 7.2) 49 (4.1, 6.9) 0.254 CHE (U/L) 54 (4.3, 7.2) 56 (4.4, 7.2) 49 (4.1, 6.9) 0.254 GGT (U/L) 31.3 (29.8, 40 44 (28.80) 40 (30.86) 0.574 AFU (U/L) 13 (11.41.2.6) 12.1 (11.41.2.9) 24 (18.32) 0.653 PT (S) 12 (11.41.2.6) 12.0 (11.3, 12.5) 0.259 CHO (µmol/L) 39 (33.41.4.38) 396 (34.24.45) 3.81 (3.39.4.34) 0.580 Pathologic factors II-I 13.91 (3.53) 18.1 1.91 0.580 II-IV 139 (85.3%) 18 (16.5%) 6 (11.1%) 0.483 0.580 II-IV 139 (85.3%) 16 (57	ALT (II/I)	2.4(1.0, 3.2)	2.5 (1.0,5.2)	2.5(1.0, 5.4)	0.329
AT (24) 2.5 (260,900) 2.6 (19,7) 62.90 TP (g/L) 68.4 (65.1,73.3) 68.5 (65.6,73.2) 68.3 (64.5,73.7) 66.28 ALB (g/L) 42.8 (39,945.7) 42.7 (39,645.6) 32.2 (40.5,46.0) 0.50 TBL (µmol/L) 15.4 (12,01.8.6) 15.6 (12,2,18.6) 13.4 (11.6,18.6) 0.147 DBLL µmol/L) 5.4 (4.3,7.2) 5.6 (4.4,7.2) 4.9 (41,6.9) 0.254 CHE (U/L) 7378 (5966,8258) 7153 (5339,8226) 7487 (6715,8297) 0.003 GGT (U/L) 43 (29,84) 44 (28,80) 40 (30,86) 653 AFU (U/L) 23 (19,29) 23 (19,28) 21.0 (11.3,12.5) 0.259 CHO (µmol/L) 3.94 (3.41-4.38) 3.96 (3.42,455) 3.81 (3.39,434) 0.580 Pathogic factors 12.0 (11.3,12.5) 0.580 0.580 5.560	AST (U/L)	25(19.3,40.8)	26 (19,59)	25 (21 37)	0.249
IP (gr) 064 (05.1/.5.) 06.3 (05.1/.5.) 06.3 (05.1/.5.) 06.3 (05.1/.5.) ALB (gr) 42.8 (39.9.45.7) 42.7 (39.6.45.6) 43.2 (40.5,4.0.) 0.54 BIL (µmol/L) 14.5 (12.0,18.6) 15.6 (12.2,18.6) 13.4 (11.6,18.6) 0.254 DBIL (µmol/L) 5.4 (4.3,7.2) 5.6 (4.4.7.2) 49 (41.6.59) 0.003 GGT (U/L) 43 (29.84) 44 (28.80) 40 (30.86) 0.574 AFU (U/L) 23 (19.29) 23 (19.28) 24 (18,32) 0.633 GGT (U/L) 3.9 (3.41.4.38) 3.96 (3.42,4.45) 3.81 (3.3.9,4.34) 0.590 CHOL (mmol/L) 3.9 (3.41.4.38) 3.96 (3.42,4.45) 3.81 (3.3.9,4.34) 0.590 Patholgic factors - - - 1.21 (11.4-12.9) 1.20 (11.3,12.5) 0.590 II-IV 3.94 (3.41.4.38) 3.96 (3.42,4.55) 3.81 (3.3.9,4.34) 0.590 II-IV 13.9 (5.3.%) 18 (16.5%) 4.8 (8.9%) . . Microscopic cirrhosis - - - . . <td< td=""><td>$TD(\alpha/L)$</td><td>68 4 (65 1 72 2)</td><td>20(19,55)</td><td>23(21,37)</td><td>0.290</td></td<>	$TD(\alpha/L)$	68 4 (65 1 72 2)	20(19,55)	23(21,37)	0.290
ALB (gr) 42.6 (35,46.7) 42.7 (35,63.6) 43.2 (40.3,40.0) 60.58 TBIL (µmol/L) 14.5 (12.01.8.6) 15.6 (12.2,18.6) 13.4 (11.6,18.6) 0.147 DBIL (µmol/L) 5.4 (4.3,7.2) 5.6 (4.2,7.2) 4.9 (4.1,6.9) 0.254 CHE (U/L) 312 (32,84) 4 (28,80) 40 (30,86) 0.574 GGT (U/L) 312 (0,29) 23 (19,28) 24 (18,32) 0.653 PT (S) 12 (11.4-12.6) 12.0 (11.3,12.5) 0.254 CHOL (mmol/L) 3.9 (3.41-4.38) 3.9 (3.42,44.5) 3.81 (3.39,4.34) 0.580 Ptologic factors	IF(g/L)	42.8 (20.0.45.7)	(3.5, (3.6, 7.5.2))	43.2 (40.5.46.0)	0.028
F13. (12.4,18.0) 13.8 (12.4,18.0) 13.8 (11.6,18.0) 0.147 DBIL (µmol/L) 54 (4.3,7.2) 56 (4.4,7.2) 4.9 (4.1,6.9) 0.254 CHE (U/L) 7378 (596,8258) 7153 (5339,8226) 7487 (6715,8297) 0.033 GGT (U/L) 43 (29,84) 44 (28,80) 40 (30,86) 0.574 AFU (U/L) 23 (19,29) 23 (19,28) 24 (18,32) 0.533 PT (S) 12 (11.4-12.6) 12.1 (11.4-12.9) 12.0 (11.3,12.5) 0.580 Pt (blogic factors 3.81 (3.39,4.34) 0.580 0.580 0.580 Pathologic factors 11.1 13.9 (85.3%) 9.6 (3.42,4.45) 3.81 (3.39,4.34) 0.580 Pt II 3.94 (3.41-4.38) 3.96 (3.42,4.45) 3.81 (3.39,4.34) 0.580 Pathologic factors 11.1 13.9 (85.3%) 9.16 (3.5%) 0.483 III-IV 24 (14.7%) 18 (16.5%) 6 (11.1%) 0.483 Microsopic cirrhosis 11.1 13.9 (85.1%) 0.139 0.735 Present 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 MIR features 11.1% 12.9 (20.5	TPH (umol/L)	145(120186)	42.7 (39.0, 43.0)	43.2 (40.3,40.0)	0.038
DBL (µnb) (1) 3.4 (4.3, 2) 3.6 (4.4, 2) 4.9 (4.16.9) 0.234 CHE (U/L) 7378 (5966,8258) 7153 (5339,8226) 7487 (6715,8297) 0.003 GGT (U/L) 43 (29,84) 44 (28,80) 40 (30,86) 0.574 AFU (U/L) 23 (19,29) 23 (19,28) 24 (18,32) 0.533 PT (S) 12 (11.4-12.6) 12.1 (11.4-12.9) 12.0 (11.3,12.5) 0.259 CHD (µmol/L) 3.94 (3.1-4.38) 3.96 (3.4,4.45) 3.81 (3.39,4.34) 0.580 Pathologic factors 5.7 5.8 (4.4, 7.2) 1.1 (1.4-12.9) 1.20 (11.3,12.5) 0.580 Pathologic factors 5.7 5.9 (6.4, 4.5) 3.81 (3.39,4.34) 0.580 Pathologic factors 5.7 5.8 (6.4, 4.5) 5.8 (6.4, 4.5) 5.8 (6.4, 4.5) 5.8 (6.4, 4.5) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) 5.8 (7.4, 6.7) <td>DPIL (µmol/L)</td> <td>54(4272)</td> <td>5.6(12.2,18.0)</td> <td>13.4 (11.0,18.0)</td> <td>0.147</td>	DPIL (µmol/L)	54(4272)	5.6(12.2,18.0)	13.4 (11.0,18.0)	0.147
Chi (Off) 737 (3960,228) 738 (3930,228) 7487 (6/13,227) 0.003 GGT (U/L) 43 (29,84) 44 (28,80) 0 (30,86) 0.574 AFU (U/L) 23 (19,29) 23 (19,28) 24 (18,32) 0.653 PT (\$) 12 (11.4-12.6) 12.1 (11.4-12.9) 12.0 (11.3,12.5) 0.259 CHOL (mmol/L) 394 (3.41-4.38) 396 (3.42,4.45) 381 (3.39,4.34) 0.580 Pathologic factors 5.59 Edmondson-Steiner grade II-IV 24 (14.7%) 18 (16.5%) 6 (11.1%) 0.483 Microscopic cirrhosis Present 93 (58.1%) 61 (57.0%) 22 (60.4%) 0.735 Microscopic cirrhosis MRI features </td <td></td> <td>5.4 (4.5, 7.2)</td> <td>5.0 (4.4,/.2)</td> <td>4.9 (4.1,0.9)</td> <td>0.254</td>		5.4 (4.5, 7.2)	5.0 (4.4,/.2)	4.9 (4.1,0.9)	0.254
GGT (0/L) 45 (25,84) 44 (25,60) 40 (30,86) 0.574 AFU (1/L) 23 (19,29) 23 (19,28) 24 (18,32) 0.653 PT (S) 12 (11.4-12.6) 12.1 (11.4-12.9) 12.0 (11.3,12.5) 0.259 CHOL (nmol/L) 3.94 (3.41-3.3) 3.96 (3.42,45) 3.81 (3.39,4.34) 0.580 Pathologic factors Edmondson-Steiner grade 5.81 (3.39,4.34) 0.580 III-IV 24 (14.7%) 18 (16.5%) 6 (11.1%) 0.483 Microscopic cirrhosis 319 (85.3%) 91 (83.5%) 48 (88.9%) 0.483 Present 93 (58.1%) 6 (157.0%) 32 (60.4%) 0.735 Present 93 (58.1%) 6 (43.0%) 21 (39.6%) 0.735 MRI features 21 (39.6%) 1.28 Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 1.28 Multiple 16.8%) 102 (93.6%) 16.6%) 1.28	CRE (U/L)	(20, 84)	(135 (5559,8220)	/48/ (8/15,829/)	0.003
AFO (0/L) 25 (19,29) 25 (19,29) 24 (18,52) 0.653 PT (S) 12 (11.4-12.6) 12.1 (11.4-12.9) 12.0 (11.3,12.5) 0.259 CHOL (mmol/L) 3.94 (3.41-4.38) 3.96 (3.42,445) 3.81 (3.39,4.34) 0.580 Pthologic factors Edmondson-Steiner grade -<	GGI (U/L)	45(29,84)	44(28,80)	40 (30,88)	0.574
P1 (S) 12 (11.4-12.6) 12.1 (11.4-12.9) 12.0 (11.3,12.5) 0.259 CHOL (mmol/L) 3.94 (3.41-4.38) 3.96 (3.42,445) 3.81 (3.39,4.34) 0.580 Pathologic factors Edmondson-Steiner grade I-II 24 (14.7%) 18 (16.5%) 6 (11.1%) 0.483 III-IV 39 (85.3%) 91 (83.5%) 48 (88.9%) 0.483 Microscopic cirrhosis 32 (60.4%) 0.735 Present 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 Present 67 (41.9%) 46 (43.0%) 21 (39.6%) 12 MRI features Tumor number 11 12 (93.6%) 128 Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (98.%) 7 (64.%) 9 (16.4%) 128		25 (19,29)	23(19,28)	24 (18,52)	0.055
CHOL (mmol/) 3.94 (3.41-4.38) 3.96 (3.42,4.45) 3.81 (3.39,4.34) 0.580 Pathologic factors Edmondson-Steiner grade Edmondson-Steiner grade 5.91 (3.9,4.34) 0.483 I-II 24 (14.7%) 18 (16.5%) 6 (11.1%) 0.483 III-IV 139 (85.3%) 91 (83.5%) 48 (88.9%) Microscopic cirrhosis Absent 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 Present 67 (41.9%) 46 (43.0%) 21 (39.6%) MIT fatures Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 169.8%) 7 (6.4%) 9 (16.4%) 128		12 (11.4-12.6)	12.1 (11.4-12.9)	12.0 (11.3,12.5)	0.259
Pathologic factors Edmondson-Steiner grade I-II 24 (14.7%) 18 (16.5%) 6 (11.1%) 0.483 III-IV 139 (85.3%) 91 (83.5%) 48 (88.9%) 1 Microscopic cirrhosis 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 Present 93 (58.1%) 61 (30.0%) 21 (39.6%) 0.735 Present 67 (41.9%) 46 (43.0%) 21 (39.6%) 0.735 MIr features Tumor number Tumor number 11 (10.1%) 11 (10.1%) Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 169.8%) 7 (64%) 9 (16.4%) 11 (10.1%)		3.94 (3.41-4.38)	3.96 (3.42,4.45)	3.81 (3.39,4.34)	0.580
I-II 24 (14.7%) 18 (16.5%) 6 (11.1%) 0.483 III-IV 139 (85.3%) 91 (83.5%) 48 (88.9%) Microscopic cirrhosis 32 (60.4%) 0.735 Present 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 MIt features 67 (41.9%) 46 (43.0%) 21 (39.6%) 0.735 MIt features 51 (57.0%) 102 (93.6%) 46 (83.6%) 0.128 Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%) 128	Pathologic factors				
1-11 24 (14.7%) 18 (16.5%) 6 (11.1%) 0.483 III-IV 139 (85.3%) 91 (83.5%) 48 (88.9%) Microscopic cirthosis 32 (60.4%) 0.735 Absent 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 Present 67 (41.9%) 46 (43.0%) 21 (39.6%) 1 MRI features Tumor number 5 102 (93.6%) 46 (83.6%) 0.128 Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%) 128	Edmondson-Steiner grade				
III-IV I39 (85.3%) 91 (83.5%) 48 (88.9%) Microscopic cirrhosis Microscopic cirrhosis 32 (60.4%) 0.735 Absent 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 Present 67 (41.9%) 46 (43.0%) 21 (39.6%) 1 MRI features Tumor number 51 51 102 (93.6%) 46 (83.6%) 0.128 Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%)	1-11	24 (14.7%)	18 (16.5%)	6 (11.1%)	0.483
Microscopic cirrhosis 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 Absent 67 (41.9%) 46 (43.0%) 21 (39.6%)	111-1V	139 (85.3%)	91 (83.5%)	48 (88.9%)	
Absent 93 (58.1%) 61 (57.0%) 32 (60.4%) 0.735 Present 67 (41.9%) 46 (43.0%) 21 (39.6%) MRI features Tumor number 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%) 0.128	Microscopic cirrhosis	/>	/>	()	
Present 67 (41.9%) 46 (43.0%) 21 (39.6%) MRI features Tumor number 102 (93.6%) 46 (83.6%) 0.128 Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%)	Absent	93 (58.1%)	61 (57.0%)	32 (60.4%)	0.735
MRI features Tumor number Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%)	Present	67 (41.9%)	46 (43.0%)	21 (39.6%)	
Tumor number Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%)	MRI features				
Single 148 (90.2%) 102 (93.6%) 46 (83.6%) 0.128 Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%)	Tumor number				
Multiple 16 (9.8%) 7 (6.4%) 9 (16.4%)	Single	148 (90.2%)	102 (93.6%)	46 (83.6%)	0.128
	Multiple	16 (9.8%)	7 (6.4%)	9 (16.4%)	

(Continued)

TABLE 1 Continued

Characteristic	Total (n = 164)	Non-MVI (n = 109)	MVI (n = 55)	P value
MRI Tumor diameter (cm)	2.7 (2.0,3.7)	2.6 (2.1,3.6)	2.9 (1.9,4.0)	0.559
Shape				
Regular	111 (67.7%)	77 (70.6%)	34 (61.8%)	0.290
Irregular	53 (32.3%)	32 (29.4%)	21 (38.2%)	
Margin				
Smooth	88 (53.7%)	65 (59.6%)	23 (41.8%)	0.032
Non-smooth	76 (46.3%)	44 (40.4%)	32 (58.2%)	
Radiological capsule				
Present	127 (77.4%)	90 (82.6%)	37 (67.3%)	0.029
Absent	37 (22.6%)	19 (17.4%)	18 (32.7%)	
Radiological capsule enhancement				
Complete	64 (39.0%)	52 (47.7%)	12 (21.8%)	0.002
Incomplete/Absent	100 (61.0%)	57 (52.3%)	43 (78.2%)	
Rim APHE				
Absent	123 (75.0%)	90 (82.6%)	33 (60.0%)	0.002
Present	41 (25.0%)	19 (17.4%)	22 (40.0%)	
Non-peripheral washout				
Present	105 (64.0%)	80 (73.4%)	25 (45.5%)	0.001
Absent	59 (36.0%)	29 (26.6%)	30 (54.5%)	
Enhancement pattern				
Typical	106 (64.6%)	81 (74.3%)	25 (45.5%)	< 0.001
Atypical	58 (35.4%)	28 (25.7%)	30 (54.5%)	
Arterial peritumoral enhancement				
Absent	126 (76.8%)	90 (82.6%%)	36 (65.5%)	0.016
Present	38 (23.2%)	19 (17.4%)	19 (34.5%)	
Restricted diffusion				
Absent	10 (6.1%)	9 (8.3%)	1 (1.8%)	0.139
Present	154 (93.9)	100 (91.7)	54 (98.2)	
Hepatobiliary phase hypointensity				
Atypical	67 (40.9%)	55 (50.5%)	12 (21.8%)	0.001
Typical	97 (59.1%)	54 (49.5%)	43 (78.2%)	
Peritumoral hypointensity on HBP				
Absent	119 (72.6%)	95 (87.2%)	24 (43.6%)	< 0.001
Present	45 (27.4%)	14 (12.8%)	31 (56.4%)	

MVI, microvascular invasion; HBV, hepatitis B virus; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; CA199, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; CHE, cholinesterase; ALB, albumin; GLOB, globulin; GGT, r-glutamyl transferase; AFU, a-fucosidase; PT, prothrombin time; CHOI, total cholesterol; APHE, arterial phase hyperenhancement; HBP, hepatobiliary phase.

definition of Non-LI-RADS imaging features can be found in Supplementary Table S3.

Model development, validation, and evaluation

Multivariate logistic regression (forward LR) was used to identify independent predictors of MVI and the HBP model was established. Four-fold cross validation (123 patients in the training set and 41 patients in test set) was used to verify the model, which was visualized by nomograms (25). The predictive performance of the model was evaluated based on discrimination, calibration, and clinical utility. The discrimination for the prediction model was quantified using the area under receiver operating characteristic (ROC) curve, sensitivity, specificity, and accuracy. The calibration curve analysis was conducted to evaluate the consistency between the MVI model prediction and the actual MVI state. Decision curve analysis (DCA) was conducted to determine the clinical utility of the model by quantifying the net benefits at different threshold probabilities. Net reclassification improvement (NRI) and Integrated discrimination improvement (IDI) were used to compare the diagnostic accuracy improvement level and overall improvement level between models.

Statistical analysis

IBM SPSS Statistics (version 25; IBM) or R (version 3.6.0; http://www.r-project.org) were used for statistical analyses. Continuous variables conforming to the normal distribution and homogeneity of variance were represented as the means \pm standard deviations. Inconsistent continuous variables were represented using the median (range) and compared with the Mann-Whitney U test. Categorical variables were compared using the χ 2 test. Interobserver agreement between two radiologists were compared with the Kappa test, variables with kappa value < 0.75 were removed. In light of the large gradient variance, logarithmical conversion (log AFP grad and log PIVKA-II grad) was performed and used for analysis. The radiological, clinical, and pathological factors with P<0.1 in the univariate logistic regression analysis were included in multivariate logistic regression analysis (forward LR) to establish the model.

Results

Clinicoradiological characteristics for predicting MVI

Among the 164 patients (138 men; 55.13 ± 10.52 years), only 55 patients suffered from MVI, and 109 patients had no MVI. The comparison of Clinicoradiological characteristics is shown in Table 1. Using comparative analysis of the clinicopathological parameters of the MVI (n = 55) and non-MVI (n = 109) groups, it was found that the AFP_lg10 (P=0.002) and CHE (P=0.003) levels in the MVI group were higher than those in the non-MVI group.

Among the MRI features, non-smooth margin (58.2% vs. 40.4%, P=0.032), absent radiological capsule (32.1% vs. 17.4%, P=0.029), incomplete or absent radiological capsule enhancement (78.2% vs. 52.3%, P=0.002), atypical enhancement pattern (54.5% vs. 25.7%, P<0.001), rim APHE (40.0% vs. 17.4%, P=0.002), arterial peritumoral enhancement (34.5% vs. 17.4%, P=0.016), HBP hypointensity (78.2% vs. 49.5%, P=0.001), and peritumoral hypointensity on HBP (56.4% vs. 12.8%, P<0.001) had a higher probability in the MVI group than in the non-MVI group.

Univariate and multivariate analysis factors predictive of MVI

A total of 12 features were related to MVI at a test level of P<0.1 in univariate analysis (Table 2). All of the above 12 variables were included in multivariate logistic regression analysis (forward LR), which determined that elevated AFP_lg10 (hazard ratio (HR) 1.849, 95% confidence interval (CI): 1.193, 2.867, P=0.006), atypical enhancement pattern (HR 3.441, 95% CI: 1.523, 7.772, P=0.003), peritumoral hypointensity on HBP (HR 7.822, 95% CI: 3.317, 18.445, P<0.001), and homogeneous HBP hypointensity (HR 3.258, 95% CI: 1.381, 7.687, P=0.007) were independent risk factors of MVI. Therefore, the above four risk factors constituted the HBP model (Table 3). The representative images of MVI cases are displayed in Figures 2, 3, and non-MVI cases are displayed in Figure 4.

Model development, validation and comparison

The above four risk factors constituted the HBP model (Table 3), and a nomogram established based on the HBP model for predicting MVI in HCC is shown in Figure 5A.

TABLE 2 Univariate analysis factors predictive of MVI.

Variable	HR (95%CI)	P Value
AFP_lg10 (ng/L)	1.784 (1.233,2.581)	0.002
Atypical enhancement pattern	3.471 (1.754,6.872)	< 0.001
Arterial peritumoral enhancement	2.500 (1.188,5.262)	0.016
Radiological capsule enhancement	3.269 (1.556,6.866)	0.002
Peritumoral hypointensity on HBP	8.765 (4.043,19.003)	< 0.001
Hepatobiliary phase hypointensity	3.650 (1.738,7.664)	0.001
Margin	2.055 (1.064,3.970)	0.032
Radiological capsule	2.304 (1.089,4.877)	0.029
Rim APHE	3.158 (1.519,6.566)	0.002
Non-peripheral "washout"	3.310 (1.677,6.533)	0.001
ALB (g/L)	1.049 (0.988,1.102)	0.058
CHE (U/L)	1.000 (1.000,1.000)	0.003

P Value is the p value of univariate Logistic regression analysis; HR, Hazard Ratio; Abbreviations can be found in the notes of Table 1.

	HBP model			
Variable	β	HR (95%CI)	P Value	
AFP_lg10 (ng/L)	0.615	1.849 (1.193,2.867)	0.006	
Atypical enhancement pattern	1.236	3.441 (1.523,7.772)	0.003	
Peritumoral hypointensity on HBP	2.057	7.822 (3.317,18.445)	< 0.001	
Hepatobiliary phase hypointensity	1.181	3.258 (1.381,7.687)	0.007	

TABLE 3 Multivariate analysis factors predictive of MVI.

P Value is the p value of univariate Logistic regression analysis; HR, Hazard Ratio; Abbreviations can be found in the notes of Table 1.

Four-fold cross validation was used to verify the model, the results showed that the mean area under the curve (AUC), sensitivity, specificity, and accuracy values for the HBP model were as follows: 0.830 (95% CI: 0.784, 0.876), 0.71, 0.78, 0.81 in training set; 0.826(95% CI:0.765, 0.887), 0.8, 0.7, 0.79 in test set (Figures 5C, D; Table 4). It was further evaluated using calibration curves (Supplementary Figure S1), which showed that the predicted MVI probability from the HBP nomogram is consistent with the estimated value of the actual MVI probability. The DCA curve for the HBP model showed that the model obtained a good net clinical benefit (Figure 5B). To further demonstrated the HBP model has an excellent prediction efficiency, we also established a no-HBP model after removing HBP imaging features, which constituted with elevated AFP_lg10, atypical enhancement pattern, arterial peritumoral enhancement, and capsule enhancement. Comparison between models with or without HBP imaging features determined that the NRI was 0.182 (95% CI: 0.069, 0.295, P=0.002) (Supplementary Figure S2), while the IDI was 0.098 (95% CI: 0.044, 0.151, P<0.001), indicating that the prediction efficiency of the HBP model is significantly improved. Therefore, the HBP model has stable and excellent prediction performance.

Discussion

For clinicians, MVI is essential for assessing patient prognosis and implementing appropriate treatment strategies, which has an important impact on patient survival (26, 27). The study results demonstrated that elevated AFP levels, atypical enhancement pattern, HBP hypointensity, and peritumoral hypointensity on HBP were independent risk factors for MVI. The above four risk factors constituted the HBP model. By verifying and evaluating the HBP model, the results showed that



FIGURE 2

Representative images of MVI positive cases: A 71-year-old male with elevated AFP, Gd- BOPTA MRI detected a solid lesion in hepatic segment VI (A), restricted diffusion (B), atypical enhancement pattern without "wash-in" (C–E), with the architectures of peritumoral enhancement on arterial phase images (C), incomplete capsule enhancement on portal venous phase and transitional phase images (D, E), and peritumoral hypointensity on hepatobiliary phase (F).



FIGURE 3

Representative images of MVI positive cases: A 60-year-old male with elevated AFP, Gd-BOPTA MRI detected a solid lesion in hepatic segment V (A), restricted diffusion (B), atypical enhancement pattern without "wash-in" (C-E), incomplete capsule enhancement on portal venous phase and transitional phase images (D, E), and homogeneous HBP hypointensity (F).

the HBP model has stable and excellent prediction performance. By comparing between models with or without HBP imaging features, the results showed that HBP model improved the prediction efficiency. Therefore, a preoperative HBP model, mainly based on HBP imaging features of Gd-BOPTAenhanced MRI, was able to excellently predict the MVI for HCC size of \leq 5cm. Previous study demonstrated that enlarged surgical margin (usually over 1cm) could reduce postoperative tumor recurrence rates in MVI-positive patients with HCC (8). The results of our study may help clinicians preoperatively assess the risk of MVI in HCC patients to provide preoperative guidance for clinicians to optimize treatment options.



FIGURE 4

Representative images of MVI negative case: A 61-year-old male, the lesion located at hepatic segment VIII (A), restricted diffusion (B), but showed a well-circumscribed smooth tumor edge and complete capsule enhancement (D, E), typical enhancement pattern with "wash-in" and "wash-out" (C–E), without peritumoral enhancement on arterial phase images (C) and mild HBP hypointensity (F).



In the present study, peritumoral hypointensity on HBP was a significant independent risk factor for predicting MVI in the HBP model, which was consistent with other research (7, 19, 20). Peritumoral hypointensity on HBP might be a result of impaired functions of peritumoral hepatocyte organic anion-transporting polypeptide transporters due to perfusion alterations in the hepatocytes around the HCC (28). It may be caused by impaired hepatocyte function (29) or Kupffer cell damage in neoplastic arterial portal shunts, as portal vein branches are blocked by cancer embolus (30). HBP hypointensity is a prominent imaging feature of HCC based on Gd-BOPTA-enhanced MRI, indicating a lack of

functional hepatocytes in the tumor (31). In our study, compared with MVI-negative cases, the hepatobiliary phase was more likely to show homogeneous hypointensity rather than mild hypointensity in MVI-positive cases.

Atypical enhancement pattern was also an independent predictor of MVI, but it has been rarely reported in previous studies. HCC is unique since a non-invasive diagnosis can be achieved *via* imaging features when specific clinical criteria and imaging characteristics are met (32). However, HCC is a highly heterogeneous neoplasm (33). The atypical enhancement pattern may be attributed to different pathological subtypes (34). Atypical

TABLE 4	Predictive	performance	for the	HBP mod	el.
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HBP model		
Fraining set	Test set	
330 (0.784, 0.876)	0.826 (0.765, 0.887)	
0.71	0.8	
0.78	0.7	
0.81	0.79	
	Fraining set 330 (0.784, 0.876) 0.71 0.78 0.81	

AUC, the area under the mean receiver operating characteristic curve.

HCC subtypes vary widely in morphology, which can be attributed to specific histological and molecular features and may lead to atypical imaging features (35). Previous studies have shown that clear cell HCC lacks the tendency to hyperenhancement in the arterial phase and classic enhancement pattern when the proportion of clear cells was 100% (34, 35); the most common enhancement patterns in scirrhous HCC are peripheral, rim-like enhancement and late-phase progressive central enhancement (34, 35). In addition, Elevated AFP level has been reported to be independent predictors of MVI, which is in agreement with the present results (7, 15).

Arterial peritumoral enhancement and incomplete or absent capsule enhancement have been reported as independent risk factors for MVI (5, 6). However, in the present study, these imaging features were significantly susceptible to MVI but were not independent risk factors for MVI. A variety of studies have suggested that arterial peritumoral enhancement may be a result of compensatory arterial hyperperfusion leading to a reduced portal blood flow, which possibly results in occlusion of the tiny portal vein branches *via* microtumor thrombus formation around the tumor (35, 36). Some studies showed that intact capsules may protect against the dissemination and progression of HCC (33, 37). However, if cancerous cells breach the capsule, the image will show an incomplete or absent capsule enhancement and infiltrative border (non-smooth margin) (37). The present data showed that intact capsules are more common in patients without MVI.

The strengths of this study include the use of the hepatobiliaryspecific contrast agent Gd-BOPTA, which obtained HBP imaging features. Previous studies have reported some models for predicting MVI using gadoxetate disodium-enhanced MRI (16–18), but no previous literature has reported the use of gadolinate-enhanced MRI to build a model to predict MVI for HCC. Furthermore, the present study focused on the HCC size within 5 cm, which reduced the confounding effect from tumor size. At present, the radical treatment rate of patients with HCC size of \leq 5 cm has been significantly improved, which has become a practical problem that urgently needs to be solved in hepatic surgery.

The study has several limitations. First, the retrospective single-center nature of the study might have introduced selection biases. Second, because few hospitals are using Gd-BOPTA hepatobiliary-specific contrast agent, external validation was not conducted. Third, the enrolled cases were mainly concentrated in tumors with sizes of ≤ 5 cm, resulting in a slightly lower frequency of MVI in the study population. Therefore, the reliability and robustness of these findings should be validated in future studies with larger HCCs.

In conclusion, the HBP imaging features of Gd-BOPTAenhanced MRI play an important role in predicting MVI for HCC. A preoperative HBP model, mainly based on HBP imaging features of Gd-BOPTA-enhanced MRI, was able to successfully predict the MVI for HCC size of \leq 5cm. The model may help clinicians preoperatively assess the risk of MVI in HCC patients so as to guide clinicians to optimize treatment options.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by The Eastern Hepatobiliary Surgery Hospital, the Third Affiliated Hospital of Shanghai Naval Military Medical University, China. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SZ conceived the project and designed the study. LH, YF, YL, JZ, and YW performed the data extraction and collection. WL and SZ performed the data analysis. SZ, WL, and NJ wrote and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/ fonc.2022.992301/full#supplementary-material

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