International Journal of Clinical Oncology (2024) 29:1182–1190
https://doi.org/10.1007/s10147-024-02553-9

ORIGINAL ARTICLE

New predictors of microvascular invasion for small hepatocellular carcinoma ≤ 3 cm

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Received: 5 March 2024 / Accepted: 7 May 2024 / Published online: 20 May 2024

Abstract

Background Microvascular invasion (MVI) is a risk factor for postoperative recurrence of hepatocellular carcinoma (HCC), even in early-stage HCC. In small HCC ≤ 3 cm, treatment options include anatomical resection or non-anatomical resection, and MVI has a major effect on treatment decisions. We aimed to identify the predictors of MVI in small HCC ≤ 3 cm.

Methods We retrospectively studied 129 patients with very early or early-stage HCC ≤ 3 cm who had undergone ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and subsequent hepatic resection from January 2016 to August 2023. These patients were divided into the derivation cohort (n = 86) and validation cohort (n = 43). We examined the risk factors for MVI using logistic regression analysis, and established a predictive scoring system in the derivation cohort. We evaluated the accuracy of our scoring system in the validation cohort.

Results In the derivation cohort, a Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3), prothrombin induced by vitamin K deficiency or antagonist-II (PIVKA-II), and metabolic tumor volume (MTV) were independent predictors of MVI. We established the scoring system using these three factors. In the validation test, there were no MVI-positive cases with a score of 0 and 1, and all cases were MVI-positive with a score of 4. Moreover, with a score ≥ 2, the sensitivity, specificity, and accuracy of our scoring system were 100%, 71.4%, and 81.4%, respectively.

Conclusions Our scoring system can accurately predict MVI in small HCC ≤ 3 cm, and could contribute to establishing an appropriate treatment strategy.

Keywords AFP-L3 · ^{18}F-FDG-PET/CT · Hepatocellular carcinoma · Microvascular invasion · Metabolic tumor volume

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. With recent improvements in surgical techniques, radiofrequency ablation (RFA), and systemic chemotherapy, treatment algorithms have been established according to the staging of HCC, and they have contributed to improved outcomes in HCC [1, 2]. However, even in very early and early-stage HCC, a high recurrence rate after treatment is still an ongoing issue [3, 4].

RFA is one of the first-line treatment options for very early and early-stage HCC. RFA is a minimally invasive local treatment for HCC compared with hepatic resection, and has comparable efficacy in patients with the largest tumor ≤ 3 cm in diameter and those with ≤ 3 nodules [5]. Hepatic resection is also a first-line treatment for HCC, and is one of the most effective and curative treatments in very early and early-stage HCC. To date, several risk factors for recurrence after resection have been reported, and microvascular invasion (MVI) was found to be a major risk factor [6, 7]. The presence of MVI implies local extension and is a risk factor for intrahepatic metastasis. In patients

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with HCC and MVI, anatomical resection of the liver may eradicate MVI confined to tumor-bearing portal territories and may be superior to partial resection in terms of a radical cure. In fact, anatomical resection for HCC with MVI results not only in the prevention of local recurrence but also in the long-term prognosis of recurrence-free survival and overall survival, compared with non-anatomical resection of the liver [8–10]. Therefore, MVI has a major effect on the decision between performing anatomical resection and non-anatomical resection for HCC. RFA is also a local treatment, and anatomical resection is theoretically reasonable for HCC with MVI. Therefore, MVI is a crucial factor regarding the decision between performing RFA and anatomical resection.

On the basis of the clinical question that small HCC ≤ 3 cm is an important borderline for treatment decisions such as anatomical or non-anatomical resection or RFA, we believe that the presence of MVI should be evaluated preoperatively. Information on MVI is only obtained from post-resection specimens, but some studies have predicted MVI preoperatively. Several studies have reported that ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake reflects tumor aggressiveness, and the standardized uptake value (SUV) is associated with the presence of MVI [11, 12]. Moreover, we have focused on metabolic parameters shown by ^{18}F-FDG-PET/CT, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG). These are metabolic parameters that take into account the metabolic activity of the entire tumor. We have reported that these parameters more accurately predicted tumor aggressiveness [13, 14]. We considered that these metabolic parameters would be useful in HCC. However, studies on early HCC with a small tumor size are limited. Therefore, this retrospective study aimed to identify predictors of MVI in very early and early-stage HCC, especially with tumor diameters ≤ 3 cm, which could be important for optimal treatment decisions.

Materials and methods

Patients

We retrospectively analyzed the data of 227 patients with HCC who underwent preoperative ^{18}F-FDG-positron emission tomography/computed tomography (PET/CT) and surgical resection from January 2016 to August 2023 in the Division of Hepatobiliary and Pancreatic Surgery at Gunma University Hospital. The inclusion criteria were as follows: (a) Barcelona Clinic Liver Cancer (BCLC) staging of very early stage or early-stage HCC; (b) patients with the largest HCC diameter ≤ 3 cm; (c) patients with initial hepatic resection; and (d) patients with curative resection. The exclusion criteria were as follows: (a) patients with macroscopic vascular invasion and extrahepatic spread in preoperative imaging; (b) patients with preoperative treatment, such as systemic chemotherapy, RFA, and transcatheter arterial chemoembolization (TACE); (c) patients who take vitamin K or warfarin; and (d) patients with poorly controlled diabetes. On the basis of the above-mentioned criteria, 129 patients were included in the analysis. In the first 86 patients (patients who underwent surgery in the first two thirds of the study period: derivation cohort), independent risk factors for MVI were examined. The remaining 43 patients (patients who underwent surgery in the last one third of the study period: validation cohort) who later underwent hepatic resection were examined to determine the accuracy of our scoring system.

The clinical characteristics and treatment-related details of all patients were collected from the medical records. Clinical laboratory data, including the tumor markers alpha-fetoprotein (AFP), a Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), and prothrombin induced by vitamin K deficiency or antagonist-II (PIVKA-II), were collected within 1 month prior to hepatic resection. HCC lesions were preoperatively diagnosed by several imaging modalities, including dynamic CT, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI), and abdominal ultrasonography (US). All imaging was performed within 1 month prior to surgery.

The final diagnosis of HCC was confirmed by a pathological examination of resected specimens. Pathological tumor characteristics were evaluated in accordance with the criteria of the Liver Cancer Study Group of Japan [15]. MVI was defined as the presence of tumor cells forming thrombi in the portal veins, intracapsular vessels, or vascular spaces lined by endothelial cells.

The study was approved by the Gunma University Ethics Committee (HS2023-017) and complied with institutional guidelines and the Declaration of Helsinki.

^{18}F-FDG-PET and image analysis

Details of the ^{18}F-FDG-PET/CT procedures have been previously reported [14]. We routinely performed ^{18}F-FDG-PET/CT in all patients with HCC preoperatively. All PET imaging was performed within 1 month prior to surgery using a ^{18}F-FDG-PET/CT scanner (Discovery STE, GE Healthcare, CA, USA; or Biograph 64, Siemens Medical Solutions, Knoxville, TN, USA) with a 700-mm field of view at Gunma University Hospital. The patients fasted for at least 6 h before ^{18}F-FDG-PET imaging, and the peripheral blood glucose levels were < 120 mg/dl. Two experienced nuclear medicine physicians interpreted the PET images without using any patient's clinical history or data. Any discrepancies were resolved by consensus.

To analyze ^{18}F-FDG uptake, the region of interest (ROI) was manually defined. In patients who did not show a high uptake, the ROI was drawn based on images from abdominal CT scans. The SUV was defined as follows: SUV = radioactive concentration in the ROI (kBq/ml)/injected dose (kBq)/patient's body weight (kg). Siemens Syngo.via software VB60A (Siemens Healthcare Solutions, Erlangen, Germany) was used at Gunma University Hospital on a workstation to automatically calculate the metabolic tumor volume (MTV) (cm^3) and total lesion glycolysis (TLG) (SUV x cm^3). MTV was defined as the tumor volume inside the tumor boundaries using SUV thresholds that were 50% of the tumor maximum SUV (SUVmax). TLG was calculated by multiplying the MTV by the mean SUV determined in a selected contouring volume of interest. In multiple cases, tumors with the highest ^{18}F-FDG uptake were selected, and MTV and TLG were calculated (Fig. 1).

Treatment and follow-up strategy

We performed a dynamic CT scan, Gd-EOB-DTPA-enhanced MRI, and abdominal US in all surgical cases to evaluate the number of tumors, tumor diameter, and tumor localization. The optimal operative procedure and extent of resection were determined by consensus through team conferences. After surgery, all patients were examined for recurrence every month by tumor markers, US, and a CT scan every 6 months after discharge. When recurrence was suspected, multiple image-based modalities were performed as indicated. Recurrent cases were treated by repeated hepatectomy, RFA, TACE, systemic chemotherapy or radiotherapy, depending on the situation of recurrence.

Statistical analysis

We analyzed the associations between continuous and categorical variables and MVI using the Student t-tests and the chi-square tests, as appropriate. We also performed a logistic regression analysis using variables with p-values of < 0.05 in the univariate analysis to predict independent predictors of MVI. To avoid the problem of collinearity, factors with strong correlations, such as tumor SUVmax, MTV, and TLG, were excluded and analyzed in a multivariate analysis. In addition, to determine the optimal cut-off values for predicting MVI, receiver operating characteristic (ROC) curves were created, and the area under the curve (AUC) was calculated. The cut-off value for the probability of MVI was determined using the Youden index in the derivation set. The Akaike information criteria (AIC) statistic was used to show the most appropriate metabolic parameter as predictor of MVI among tumor SUVmax, MTV, and TLG [16]. All statistical analyses were carried out using JMP software, version 15 (SAS Institute, Cary, NC, USA). A p-value < 0.05 was considered to show statistical significance.

Results

Patient's characteristics

According to the study criteria, we included 129 patients, with 86 in the derivation cohort and 43 in the validation cohort. Clinicopathological features in the overall cohort are shown in Table 1. According to the Child–Pugh classification, 128 (99.2%) patients were classified as A. According to BCLC staging, 47 (36.4%) patients were very early stage and 82 (63.6%) patients were early stage.

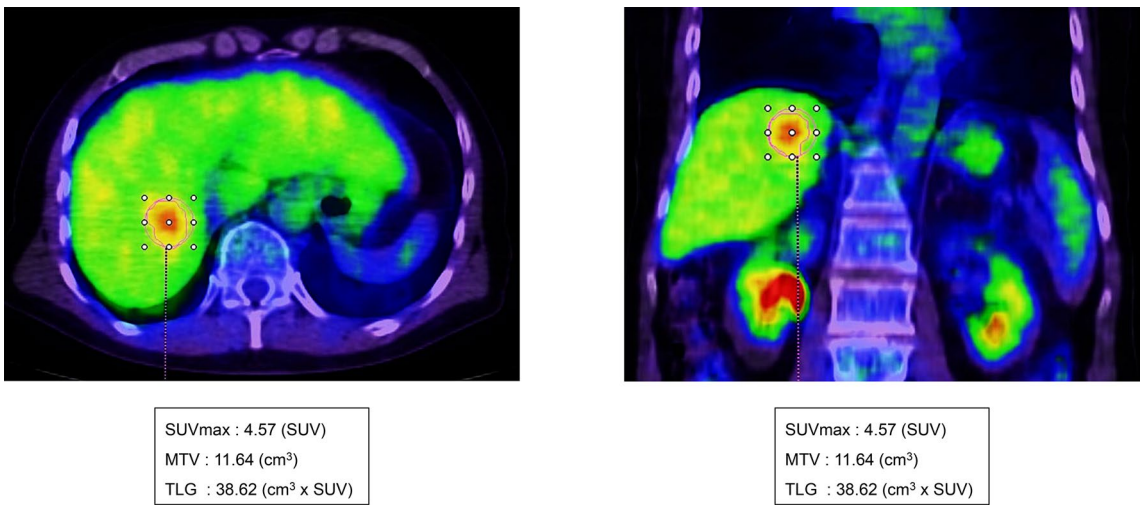

Fig. 1 The representative figure of tumor SUVmax, MTV, and TLG

Table 1 Clinicopathological features in the overall cohort

	Overall cohort (N = 129)
Host-related factor	
Age	72 (35–90)
Male (%)	108 (83.7%)
HBs Ab (%)	22 (17.1%)
HCV Ab (%)	54 (41.9%)
Child–Pugh score (A:B:C)	128 (99.2%): 1 (0.8%): 0 (0%)
Liver damage (A:B:C)	123 (95.3%): 6 (4.7%): 0 (0%)
BCLC staging (very early stage: early stage)	47 (36.4%): 82 (63.6%)
Diabetes mellitus (%)	49 (37.9%)
Albumin (g/dl)	4.2 (3.3–5.3)
Total bilirubin (mg/dl)	0.8 (0.3–3.1)
Platelet count (/μL)	15.6 (5.7–37.9)
Prothronbin time (%)	95 (43–136)
ICGR15 (%)	15.4 (2.8–56.9)
M2BPGi (c.o.i)	1.01 (0.22–8.8)
Tumor-related factor	
Tumor size (cm)	2.4 (0.6–3.0)
Multiple tumor number (%)	19 (14.7%)
AFP (ng/ml)	6.3 (0.5–5212)
AFP-L3 (%)	0.5 (0.5–86.3)
PIVKA-II (mAU/ml)	30.0 (11–2839)
Microvascular invasion (+)	40 (31.0%)
Poorly differentated type (+)	19 (14.7%)
Metabolic parameter	
SUVmax	3.19 (2.04–16.8)
MTV	3.49 (0.5–37.9)
TLG	8.94 (1.16–144.3)
Surgery-related factor	
Anatomical resection (%)	44 (34.1%)
Laparoscopic approach (%)	73 (56.6%)
Operative time (min)	281 (105–682)
Blood loss (g)	73 (0–3410)
Postoperative complications (+) (Clavien-Dindo ≥ III)	9 (6.9%)

Data are expressed as median (interquartile range), or number of patient (%)

HBs Ab hepatitis B surface antigen, *HCV Ab* hepatitis C virus antibody, *BCLC staging* Barcelona Clinic Liver Cancer staging, *ICGR15* indocyanine green dye retention test at 15 min, *M2BPGi* Mac-2 binding protein glycan isomer, *AFP* alpha-fetoprotein, *AFP-L3* lens culinaris agglutinin-reactive fraction of AFP, *PIVKA-II* prothrombin induced by vitamin K deficiency or antagonist-II, *SUVmax* maximum standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

Regarding the operative procedures, anatomical resection was performed in 49 (37.9%) patients and non-anatomical resection in 80 (62.1%) patients.

Identification of predictors for MVI

Clinicopathological features in the derivation cohort and validation cohort are shown in Supplementary Table 1. We examined the predictors of MVI in 86 patients in the derivation cohort (Table 2). In the derivation cohort, 24 (27.9%) patients had MVI. The univariate analysis revealed some univariate factors. About tumor-related factor, preoperative AFP-L3 ($p = 0.0004$) and PIVKA-II ($p = 0.013$) values were significantly higher in the MVI-positive group than in the MVI-negative group. Moreover, the rate of the poorly differentiated type was significantly higher in the MVI-positive group than in the MVI-negative group ($p = 0.0008$). Regarding metabolic parameters, tumor SUVmax ($p = 0.0003$), MTV ($p < 0.0001$), and TLG ($p < 0.0001$) values in the MVI-positive group were significantly higher than those in the MVI-negative group (Fig. 2). There were no other significant potential predictive factors for MVI.

We then performed multivariate analysis by a logistic regression model. Independent predictors of MVI were preoperative AFP-L3, PIVKA-II, tumor SUVmax, MTV, and TLG (Table 3). Regarding metabolic parameters as predictors of MVI, each parameter was compared based on the AUC and AIC. MTV showed the highest AUC and the lowest AIC statistic value (AUC 0.87, AIC 66.4), which indicated that it had the best ability to predict MVI compared with the other metabolic parameters (Fig. 3, Table 4). These results suggested that preoperative AFP-L3, PIVKA-II, and MTV were predictors of MVI for small HCC ≤ 3 cm.

To determine the optimum values for predicting MVI, the ROC curve was plotted. The best cut-off value of AFP-L3 was 9.9% (area under the curve [AUC] 0.68), and the best cut-off value of PIVKA-II was 50.0 mAU/ml (AUC 0.71). The best cut-off of MTV was 4.17 cm^3 (AUC 0.87) (Supplementary Fig. 1).

Predictive scoring system for MVI

The predictive scoring system was determined according to the number of positive MVI predictors in each case. Points were assigned according to odds ratio in the multivariate analysis. (AFP-L3 ≥ 9.9%, score = 1; PIVKA-II ≥ 50.0 mAU/ml, score = 1; MTV ≥ 4.17 cm^3, score = 2, with a total prediction score of 0 to 4 points). In addition, we examined 43 patients in the validation cohort to determine the accuracy of our scoring system (Fig. 4). There were 15 (34.9%) MVI-positive cases. No patients with a score of 0 (0/15) and score of 1 (0/5) were MVI-positive. More importantly, all (6/6) patients with a score of 4 were MVI-positive. Moreover, with a score ≥ 2, the sensitivity, specificity, and accuracy of our scoring system were 100%, 71.4%, and 81.4%, respectively.

Table 2 Predictor of microvascular invasion in Hepatocellular carcinoma

	MVI positive (N = 24)	MVI negative (N = 62)	p-values
Host-related factor			
Age	72 (35–88)	72 (56–87)	p = 0.714
Male (%)	17 (70.8%)	54 (87.1%)	p = 0.166
HBs Ab (%)	4 (16.7%)	14 (22.6%)	p = 0.769
HCV Ab (%)	13 (54.2%)	21 (33.9%)	p = 0.225
Child–Pugh score A	24 (100%)	61 (98.4%)	p = 1.000
Liver damage (A:B)	22 (91.7%): 2 (8.3%)	58 (93.5%): 4 (6.5%)	p = 0.670
BCLC staging (very early stage: early stage)	7 (29.2%): 17 (70.8%)	27 (43.5%): 35 (56.5%)	p = 0.325
Diabetes mellitus (%)	9 (37.5%)	25 (40.3%)	p = 0.768
Albumin (g/dl)	4.1 (3.5–5.0)	4.3 (3.4–5.3)	p = 0.534
Total bilirubin (mg/dl)	0.7 (0.4–1.7)	0.8 (0.3–3.1)	p = 0.528
Platelet count (/μL)	17.0 (7.7–28.9)	15.0 (5.7–37.9)	p = 0.541
Prothronbin time (%)	92 (46–111)	95.5 (68–120)	p = 0.647
ICGR15 (%)	14.6 (4.8–28.5)	15.8 (3.3–56.9)	p = 0.548
M2BPGi (c.o.i)	1.12 (0.22–5.15)	1.0 (0.25–8.8)	p = 0.732
Tumor-related factor			
Tumor size (cm)	2.5 (0.8–3.0)	2.2 (0.7–3.0)	p = 0.317
Multiple tumor number (%)	5 (20.8%)	5 (8.1%)	p = 0.296
AFP (ng/ml)	11.3 (1.6–4683)	4.7 (1.2–5212)	p = 0.221
AFP-L3 (%)	18.7 (0.5–84.9)	0.5 (0.5–70.1)	p = 0.0004*
PIVKA-II (mAU/ml)	158.0 (15–2839)	26.4 (11–2743)	p = 0.013*
Metabolic parameter			
SUVmax	3.48 (2.07–16.8)	3.09 (2.04–8.65)	p = 0.0003*
MTV	7.70 (0.56–37.9)	2.45 (0.5–11.9)	p < 0.0001*
TLG	23.7 (4.06–144.3)	6.1 (1.16–31.5)	p < 0.0001*

Data are expressed as median (interquartile range), or number of patient (%)

*p value < 0.05

MVI microvascular invasion, *HBs Ab* hepatitis B surface antigen, *HCV Ab* hepatitis C virus antibody, *BCLC staging* Barcelona Clinic Liver Cancer staging, *ICGR15* indocyanine green dye retention test at 15 min, *M2BPGi* Mac-2 binding protein glycan isomer, *AFP* alpha-fetoprotein, *AFP-L3* lens culinaris agglutinin-reactive fraction of AFP, *PIVKA-II* prothrombin induced by vitamin K deficiency or antagonist-II, *SUVmax* maximum standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

In addition, we examined the Kaplan–Meier curves for recurrence-free survival (RFS) and overall survival (OS) by the classifications of scoring: 0 to 4 in the total cohort (Supplementary Fig. 3). These curves showed that patients with a score of 4 had significantly worse RFS (p = 0.022) and OS (p = 0.024) than those with a score of 0.

Discussion

In this study, we showed that high AFP-L3 and PIVKA-II values, and a high MTV were independent predictors of MVI in patients with small HCC ≤ 3 cm. Moreover, the predictive scoring system created from these factors could accurately identify MVI. In addition to tumor markers, this scoring system incorporated MTV with ^{18}F-FDG-PET/CT, which was able to accurately evaluate tumor aggressiveness, and is considered to be more reliable. Currently, the treatment options are anatomical resection, non-anatomical resection, and RFA for small HCC ≤ 3 cm, and the presence of MVI is a major factor in determining the treatment strategy. Our novel scoring system could be useful for predicting MVI in very early or early-stage HCC ≤ 3 cm.

Among tumor markers, AFP-L3 and PIVKA-II are important factors in predicting the recurrence of HCC, but they are also important for predicting MVI [17]. Pote et al. reported the high diagnostic performance of PIVKA-II for MVI in early-stage HCC with BCLC staging [18]. Imura et al. found that high AFP-L3 values were an independent risk factors among tumor markers for MVI in HCC within the

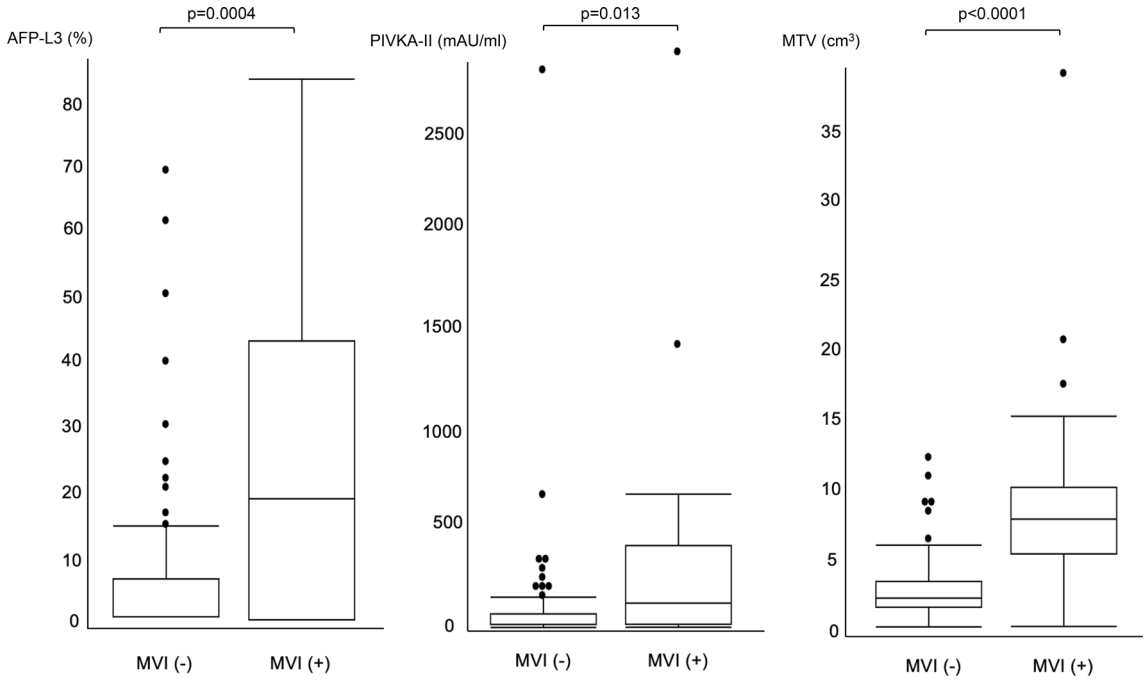

Fig. 2 Box plots of AFP-L3, PIVKA-II, and MTV values in the derivation cohort

Table 3 Multivariate analysis by logistic regression for independent predictor of microvascular invasion

	OR	95% CI	p-value
AFP-L3 (%)	1.04	1.00–1.08	p = 0.004*
PIVKA-II (mAU/ml)	1.01	1.00–1.01	p = 0.024*
MTV (cm3)	1.49	1.19–1.85	p < 0.001*

*p value < 0.05

OR Odds ratio, *95% CI* 95% confidence interval, *AFP-L3* lens culinaris agglutinin-reactive fraction of AFP, *PIVKA-II* prothrombin induced by vitamin K deficiency or antagonist-II, *MTV* metabolic tumor volume

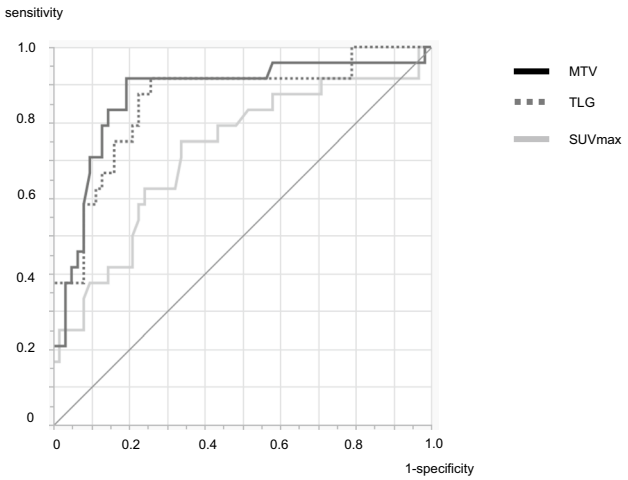

Fig. 3 Receiver operating characteristic (ROC) curve analysis for each metabolic parameter. Area under the curve (AUC) for MTV, SUVmax, and TLG were 0.87, 0.72, and 0.85, respectively

Milan criteria [19]. Furthermore, Hirokawa et al. reported that high AFP-L3 and PIVKA-II values were independent predictors of MVI, and the recurrence rate in patients with MVI was worse when these values were high [20]. Although these previous studies support the validity of our study, the cut-off values of tumor markers for predicting MVI are not constant. This variation may be due to the background liver or the tumor size in HCC. We limited the target HCC to the very early or early stage of BCLC staging and a tumor size ≤ 3 cm in our study. We believe that a strength of our study is that we established cut-off values of AFP-L3 and PIVKA-II, which are considered useful for predicting MVI in very early and early-stage HCC, and also created an accurate scoring system.

Regarding the association between tumor size and MVI, the incidence of MVI increases as the tumor size increases [21, 22]. Wang et al. confirmed this finding in a large analysis [23]. However, in very early or early-stage HCC in BCLC staging, the relationship between tumor size and MVI is controversial. Yamashita et al. found that, even in patients with HCC with a tumor size ≤ 3 cm, a larger tumor size was related to the incidence of MVI, and a tumor size ≥ 2 cm was an independent predictor of MVI [9]. However, Wang et al. reported no relationship between tumor size and the presence of MVI in HCC with a tumor size ≤ 2 cm [24]. In

Table 4 Comparison of prognostic performance of tumor SUVmax, tumor MTV, tumor TLG as a predictor of microvascular invasion

Metabolic parameter	MVI positive AIC
SUVmax	81.4
MTV	66.4
TLG	67.1

MVI microvascular invasion, *AIC* The Akaike information criteria, *SUVmax* maximum standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

our study, we included HCC with a tumor size ≤ 3 cm, and the tumor size was not an independent predictor of MVI. Therefore, we believe that an unclear borderline of MVI exists between tumor diameters of 2 cm and 3 cm, even in early stage HCC of BCLC staging, and MVI should not be determined only by the tumor diameter. Instead of the tumor diameter, the usefulness of tumor volume has also been evaluated. The ADV score, which is composed of AFP, PIVKA-II, and tumor volume, is an accurate prognostic indicator for HCC and a useful predictor of MVI [25].

We focused on MTV as an alternative and accurate factor to tumor size. Some reports have shown that metabolic parameters shown by ^{18}F-FDG-PET/CT are useful for reflecting tumor aggressiveness [13, 14, 26]. Additionally, ^{18}F-FDG accumulation is associated with a poor prognosis of HCC [27]. Shirabe et al. have focused on the usefulness of ^{18}F-FDG-PET/CT in evaluating histological differentiation and found that SUVmax was an independent predictor of MVI [11]. They also created a new scoring system for the prediction of MVI. In our study, among the metabolic parameters, MTV was the best predictor with the lowest AIC value, and one of the criteria in the accurate predicting scoring system. SUVmax is an index that represents only one point of the highest concentration of ^{18}F-FDG in the malignancy. Furthermore, this single point represents the value for one voxel in the ROI (normally < 0.1 ml); therefore, it has limited value for evaluating malignancy of the entire tumor. In this context, MTV has recently been used as a more accurate metabolic parameter of FDG uptake in the whole tumor. The association between ^{18}F-FDG uptake and MVI has already been demonstrated, and tumor volume has also been shown to be an important factor in predicting MVI [11, 12, 25, 27]. Our results that MTV represented ^{18}F-FDG uptake and tumor volume and was valid for predicting MVI are strongly supported by the conclusions of these studies.

We established a novel predictive scoring system that was useful for predicting MVI, but this was a single-center, retrospective, observational study. We used a validation cohort to confirm the accuracy of this scoring system, but total sample size was not enough because the study was limited to HCC ≤ 3 cm. It was difficult to plan multi-institutional study due to institutional differences in the measurement of metabolic parameters. Instead, future prospective studies at our institution could report more reliable results. We would like to consider prospective studies in the future.

In conclusion, we identified independent factors that predict MVI with very early or early-stage HCC ≤ 3 cm. Preoperative AFP-L3, PIVKA-II, and MTV values are strong predictors of MVI, and a novel scoring system using these factors is able to predict MVI. MVI-positive HCC recurs at a high rate. Therefore, anatomical resection is recommended over local therapy, such as RFA or non-anatomical resection, even for very early or early-stage HCC with a tumor diameter ≤ 3 cm. Our scoring system can accurately identify the presence or absence of MVI preoperatively and could be used to establish an appropriate treatment strategy, which may contribute to improving the outcome of HCC.

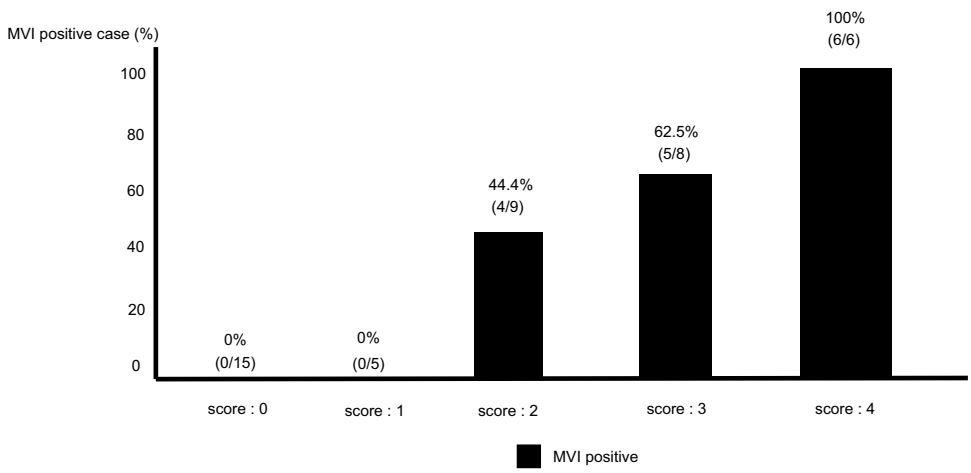

Fig. 4 Distribution of MVI-positive patients according to total scores from the predictive scoring system in the validation cohort. Black area, patients who were MVI-positive

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-024-02553-9.

Acknowledgements We thank Ellen Knapp, PhD, from Edanz (http://jp.edanz.com/ac) for editing a draft of this manuscript.

Authors contribution R.F., N.H., and K.S. contributed to the conception and design of this study. R.F., T.O., T.S., K.H., S.K., K.H. and H.T. contributed to the acquisition of data. R.F., N.H., N.I., M.T., T.I., and M.S. contributed to the analysis and interpretation of data. R.F., N.H., K.A., and K.S. contributed to the drafting of the manuscript. R.F., N.H., K.A., H.T., T.H., M.S., and K.S. contributed to the revision of the manuscript. All authors contributed to the final approval of the manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of interest The authors declare that they have no conflict of interest. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Ethical approval The study was approved by the Gunma University Ethics Committee (HS2023-017) and complied with institutional guidelines and the Declaration of Helsinki. Patient consent for participation was obtained using the opt-out method.

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