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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

A Novel Online Calculator to Predict Risk of Microvascular Invasion in the Preoperative Setting for Hepatocellular Carcinoma Patients Undergoing Curative-Intent Surgery

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ABSTRACT

Background. The presence of microvascular invasion (MVI) has been highlighted as an important determinant of hepatocellular carcinoma (HCC) prognosis. We sought to build and validate a novel model to predict MVI in the preoperative setting.

Methods. Patients who underwent curative-intent surgery for HCC between 2000 and 2020 were identified using a multi-institutional database. Preoperative predictive models for MVI were built, validated, and used to develop a web-based calculator.

Results. Among 689 patients, MVI was observed in 323 patients (46.9%). On multivariate analysis in the test cohort, preoperative parameters associated with MVI included α-fetoprotein (AFP; odds ratio [OR] 1.50, 95% confidence interval [CI] 1.23–1.83), imaging tumor burden score (TBS; hazard ratio [HR] 1.11, 95% CI 1.04–1.18), and neutrophil-to-lymphocyte ratio (NLR; OR 1.18, 95% CI 1.03–1.35). An online calculator to predict MVI was developed based on the weighted β-coefficients of these three variables (https://yutaka-endo.shinyapps.io/MVIrisk/). The c-index of the test and validation cohorts was 0.71 and 0.72, respectively. Patients with a high risk of MVI had worse disease-free survival (DFS) and overall survival (OS) compared with low-risk MVI patients (3-year DFS: 33.0% vs. 51.9%, $p < 0.001$; 5-year OS: 44.2% vs. 64.8%, $p < 0.001$). DFS was worse among patients who underwent an R1 versus R0 resection among those patients at high risk of MVI (R0 vs. R1 resection: 3-year DFS, 36.3% vs. 16.1%, $p = 0.002$). In contrast, DFS was comparable among patients at low risk of MVI regardless of margin status (R0 vs. R1 resection: 3-year DFS, 52.9% vs. 47.3%, $p = 0.16$).

Conclusion. Preoperative assessment of MVI using the online tool demonstrated very good accuracy to predict MVI.

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Hepatocellular carcinoma (HCC) is a major health concern, being the sixth most common cancer worldwide, and is a main cause of cancer-related deaths in the US, with

a 5-year survival rate of <20%.[1–3] Although liver resection is the principle therapeutic option for patients with resectable HCC and well-preserved liver function, long-term survival after curative-intent resection of HCC remains poor due to high rates of recurrence.[4] The impact of various clinicopathological factors on postoperative recurrence have been investigated.[5] In particular, the presence of microvascular invasion (MVI) has been highlighted as an important determinant of poor survival following resection.[6,7] Information on the presence or absence of MVI may also help inform decisions about optimal treatment options. For example, wider surgical margins may lead to better long-term outcomes among HCC patients with MVI given the higher risk of tumor satellites in portal tributaries.[8] Patients with MVI may also benefit from closer surveillance and consideration of adjuvant therapy.[9,10] Since detection of MVI is determined on pathological evaluation of surgical specimens, information on MVI is accessible only after resection, and as such, use of MVI in the preoperative setting has been very limited. In turn, there has been much interest in the accurate preoperative prediction of MVI to help stratify patient risk, guide therapeutic options, and estimate the potential benefit of resection.

To date, several investigators have proposed various risk models, including nomograms that combine blood biomarkers (i.e. serum α-fetoprotein [AFP], liver function, and systemic inflammatory score) with preoperative imaging patterns on computed tomography (CT) or magnetic resonance imaging (MRI) to estimate the risk of MVI in the preoperative setting.[11–16] However, the application and clinical utility of these predictive models have suffered from lack of reproducibility and high interrater variability relative to radiological findings.[17] In turn, most MVI models suffer from poor predictive performance, as well as an inability to interpret the models easily in a real clinical setting.[18] In addition, the association between MVI risk and oncologic outcomes, as well as MVI's role in informing choice of surgical procedure, have not been well-defined.[12,14]

Therefore, the objective of the current study was to build and validate a novel model to predict MVI in the preoperative setting. To facilitate clinical applicability of the model, an easy-to-use online calculator to predict MVI risk among patients with HCC prior to curative-intent surgery was developed. In addition, the potential role of MVI to inform choice of surgical procedure, as well as stratify patients relative to prognosis, were also examined.

METHODS

Study Population and Inclusion Criteria

Patients who underwent curative-intent liver resection for HCC between 2000 and 2020 were identified from an international multi-institutional database (The Ohio State University Wexner Medical Center, Columbus, OH, USA; Beaumont Hospital, Clichy, France; The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Ospedale San Raffaele, Milan, Italy; University of Verona, Verona, Italy; Curry Cabral Hospital, Lisbon, Portugal; APHP, Westhead Hospital, Sydney, NSW, Australia; Stanford University, Stanford, CA, USA; Fundeni Clinical Institute, Bucharest, Romania; University of Ottawa, Ottawa, ON, Canada; Keio University, Tokyo, Japan; The University of Sydney, School of Medicine, Sydney, NSW, Australia; University of Colorado, Denver, CO, USA; Yokohama City University, Yokohama, Japan). Patients who had missing information on MVI or laboratory data, as well as individuals who underwent palliative surgery, were excluded. The Institutional Review Boards (IRBs) of each participating institution approved the study.

Baseline Characteristics, Definition, and Outcomes

Variables of interest included patient demographics (i.e., age, sex, preoperative cirrhosis, infection with hepatitis B [HBV] or hepatitis C virus [HCV], Child–Pugh Classification), laboratory data (AFP, neutrophil-to-lymphocyte ratio [NLR], albumin-bilirubin [ALBI] score, and platelets count [PLTs]), and clinicopathological characteristics (imaging tumor burden score [TBS], tumor grade, MVI, macrovascular invasion, surgical margin status, perineural invasion, liver capsule involvement, pathological TBS, and tumor staging). MVI was defined as intraparenchymal vascular involvement identified on histological evaluation,[19] while TBS was calculated using the following formula: [TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2].[20] Margin status was classified as R0 and R1 for microscopically negative (>0 mm) and positive resection margins, respectively, and tumor staging was defined according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition.[19] The primary outcomes were disease-free survival (DFS) and overall survival (OS), defined as the time interval between the date of resection to the date of any recurrence, and death from any cause or last follow-up, respectively. Early recurrence was defined as recurrence within 8 months after surgery.[21] Recurrence patterns were classified as intrahepatic versus extrahepatic, and single site versus multiple sites.[22]

Statistical Analysis

Descriptive statistics were presented as median values (interquartile ranges [IQRs]) for continuous variables and frequency (%) for categorical variables. Continuous variables were compared using the Mann–Whitney U test and

categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Survival probabilities were compared using the log-rank test and estimated using the Kaplan–Meier method.

The study cohort was randomly assigned to test and validation cohorts in a 1:1 ratio. In the test cohort, preoperative variables were assessed relative to MVI using univariate and multivariate logistic regression analysis with backward exclusion. In the case of AFP, the distribution was markedly skewed to the right; therefore, natural logarithm transformation was conducted before analyzing the impact of this variable on the risk of MVI. Variables with a p-value <0.05 on univariate analysis were included in the multivariable analysis; odds ratio (ORs) and hazard ratios (HRs) were presented with 95% confidence intervals (CIs). The β-coefficients of the selected significant values on the final step of the multivariate analysis were used to develop a weighted risk score. The discrimination performance of the derived risk score was subsequently evaluated in the test and validation cohorts using the area under the receiver operating characteristic (ROC) curve (AUC). The cut-off values to estimate low and high risk for MVI were determined using the median value of the MVI risk score. The impact of different MVI risk on DFS and OS was analyzed using bivariate and multivariate Cox regression in the entire cohort. In addition, the impact of MVI risk on the incidence of early recurrence was assessed using logistic regression analysis. All statistical analyses were performed using SPSS software version 28.0 (IBM Corporation, Armonk, NY, USA) and R version 4.2.0 (The R Project for Statistical Computing, Vienna, Austria). All tests were two-sided and a p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics in the Entire Dataset

A total of 689 patients who underwent liver resection for HCC met prespecified inclusion and exclusion criteria and were enrolled in the analytic cohort. Median patient age was 64.5 years (IQR 55.3–72 years) and a majority of patients were male ($n = 547$, 79.4%). Nearly one-half of patients had liver cirrhosis ($n = 288$, 41.8%). An overwhelming majority of patients were classified as Child–Pugh A ($n = 659$, 95.6%). Median AFP and NLR were 14 ng/mL (IQR 4–244.5 ng/mL) and 2.41 (IQR 1.69–3.35), respectively. On preoperative imaging, median TBS was 5.10 (IQR 3.20–9.10), and median pathological TBS was 5.50 (3.50–9.50). On pathology, almost one-half of patients had MVI ($n = 323$, 46.9%), while only a small subset of patients had R1 margin status ($n = 94$, 13.6%); 212 (30.8%) patients had a poor or undifferentiated tumor, while 18 (2.6%) and 129 (18.7%) patients had perineural invasion or liver capsule involvement, respectively (electronic supplementary Table 1). The test and validation datasets were well-balanced with no significant differences for any variables between the two groups (electronic supplementary Table 1).

Prognostic Importance of Microvascular Invasion (MVI) on Disease-Free Survival (DFS) and Overall Survival (OS)

With a median follow-up of 24 months (IQR 11–42 months), 3-year DFS and 5-year OS were 42.8% and 54.5% in the entire cohort, respectively. Patients who underwent resection of an HCC with MVI had worse 3-year DFS and 5-year OS versus individuals without MVI (3-year DFS: 31.5% vs. 52.8%, $p < 0.001$; 5-year OS: 42.4% vs. 64.8%, $p < 0.001$) [electronic supplementary Fig. 1]. On multivariate analysis, pathological TBS (HR 1.02, 95% CI 1.00–1.04, $p = 0.02$), macrovascular invasion (HR 2.86, 95% CI 2.04–3.99, $p < 0.001$), margin status (HR 1.46, 95% CI 1.04–2.05, $p = 0.03$), and tumor grade (HR 1.44, 95% CI 1.11–1.88, $p = 0.006$) were associated with DFS. Of note, after controlling for these other pathologic factors, MVI remained independently associated with worse DFS (HR 1.35, 95% CI 1.01–1.80, $p = 0.04$). MVI was similarly associated with worse OS (HR 1.66, 95% CI 1.21–2.29, $p = 0.002$), as well was pathological TBS (HR 1.03, 95% CI 1.01–1.05, $p < 0.001$) and AJCC T category (HR 2.24, 95% CI 1.65–3.04, $p < 0.001$) [electronic supplementary Table 2].

Preoperative Characteristics for Prediction of MVI

On multivariate analysis of the test dataset, preoperative variables, including the natural logarithm of AFP (OR 1.50, 95% CI 1.23–1.83, $p < 0.001$), imaging TBS (OR 1.11, 95% CI 1.04–1.18, $p = 0.001$), and NLR (OR 1.18, 95% CI 1.03–1.35, $p = 0.02$), were associated with the presence of MVI (Table 1). A risk score was subsequently developed based on the β-coefficients of these independent variables. Specifically, the final weighted risk score was (Eq. 1):

$$\text{Probabilities} = 1/\left(1 + e^{-(-1.798 + 0.442 \times \text{a natural logarythm of AFP} + 0.102 \times \text{imaging TBS} + 0.158 \times \text{NLR})}\right) \quad (1)$$

The AUC for the risk score was 0.71 (95% CI 0.66–0.77) in the test dataset and 0.72 (95% CI 0.66–0.78) in the validation dataset, respectively (Fig. 1). Importantly, the AUC of the MVI risk score performed

TABLE 1 Multivariable analysis of predictors of microvascular invasion in the test dataset ($n = 349$)

Variable	Bivariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	0.99	0.97–1.00	0.12	–	–	–
Sex, male	0.93	0.55–1.57	0.79	–	–	–
Cirrhosis	0.97	0.64–1.48	0.90	–	–	–
HBV	1.74	1.08–2.81	0.02	–	–	–
HCV	0.65	0.41–1.03	0.07	–	–	–
Child–Pugh A	1.17	0.44–3.10	0.76	–	–	–
lnAFP	1.57	1.31–1.90	< 0.001	1.50	1.23–1.83	< 0.001
NLR	1.21	1.05–1.39	0.008	1.18	1.03–1.35	0.02
PLTs	1.00	1.00–1.01	0.01	–	–	–
ALBI score	1.18	0.73–1.92	0.50	–	–	–
Imaging TBS	1.13	1.07–1.20	< 0.001	1.11	1.04–1.18	0.001

HR hazard ratio, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ALBI* albumin-bilirubin, *AFP* α-fetoprotein, *NLR* neutrophil-to-lymphocyte count, *PLTs* platelets count, *TBS* tumor burden score

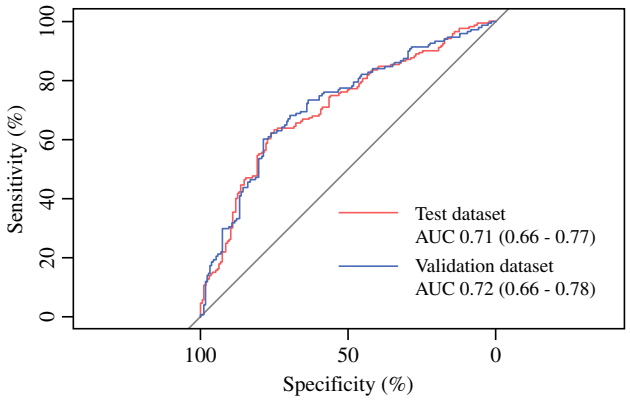


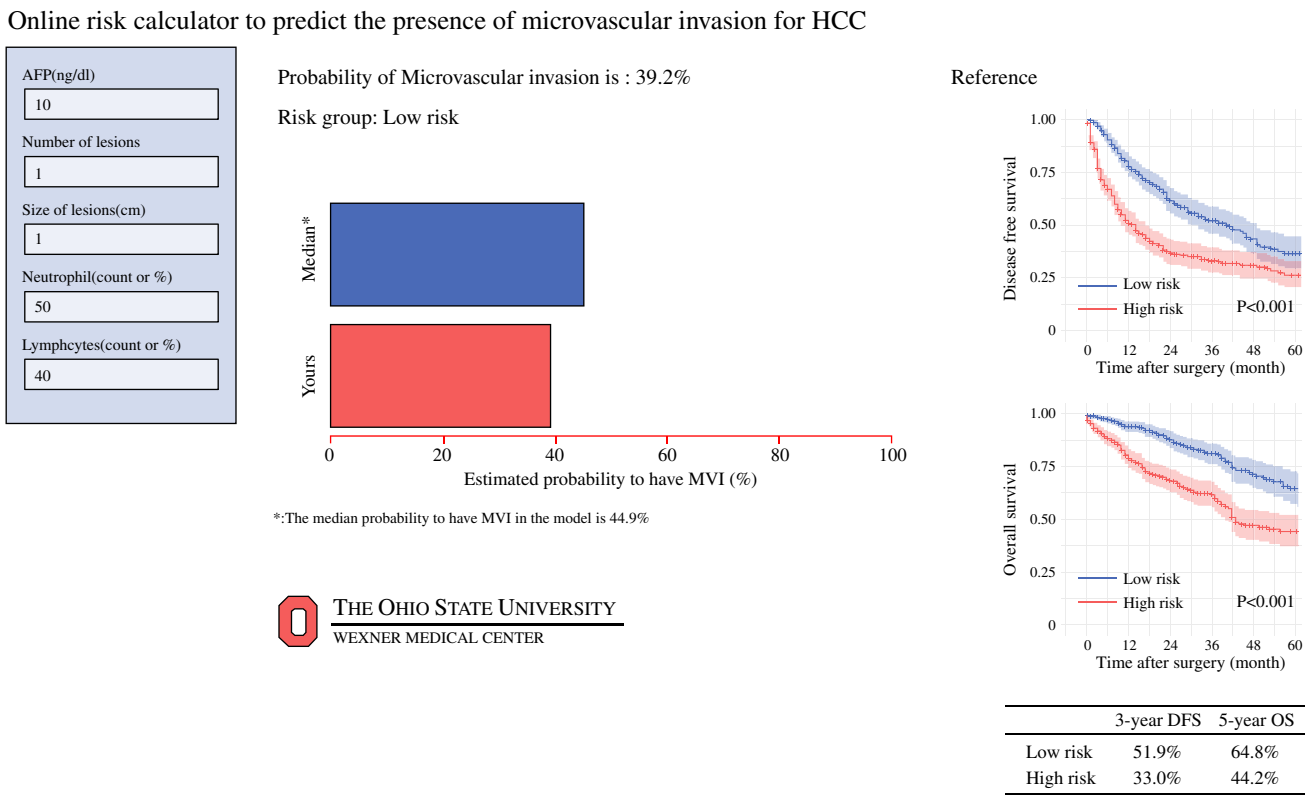
FIG. 1 Receiver operating characteristic curves of the risk model in the test and validation datasets. *AUC* area under the curve

well among patients with early-stage HCC within the Milan criteria (AUC 0.69, 95% CI 0.62–0.75) [electronic supplementary Fig. 2]. The online model to predict MVI among patients undergoing resection for HCC is available at https://yutaka-endo.shinyapps.io/MVIrisk/ (Fig. 2).

Survival Analysis of Patients with Different MVI Risk Score After Surgery

Based on the risk model, patients were categorized into risk groups relative to MVI: low risk ($n = 346$, 50.2%) versus high risk ($n = 343$, 49.8%) [median 0.450]. The MVI risk model was able to stratify patients relative to prognosis (high risk vs. low risk: 3-year DFS, 33.0% vs. 51.9%, $p < 0.001$; 5-year OS, 44.2% vs. 64.8%, $p < 0.001$) (Fig. 3), which was comparable with predictions based on actual pathological MVI. Of note, the MVI risk score remained independently associated with worse DFS (HR 1.44, 95% CI 1.13–1.84, $p = 0.004$) even after controlling for pathological TBS (HR 1.02, 95% CI 1.00–1.04, $p = 0.03$), macrovascular invasion (HR 2.74, 95% CI 2.06–3.63, $p < 0.001$), margin status (HR 1.43, 95% CI 1.07–1.92, $p = 0.02$), and tumor grade (HR 1.40, 95% CI 1.11–1.77, $p = 0.005$). In addition, on multivariable analyses after controlling for competing risk factors such as TBS (HR 1.03, 95% CI 1.01–1.05, $p = 0.006$), AJCC T category (HR 2.09, 95% CI 1.53–2.85, $p < 0.001$), and tumor grade (HR 1.37, 95% CI 1.02–1.86, $p = 0.04$), the MVI risk model was still able to stratify patients relative to postoperative OS (HR 1.49, 95% CI 1.06–2.07, $p = 0.02$) (Table 2). Importantly, the MVI high-risk group was associated with early recurrence (OR 2.90, 95% CI 1.74–4.84, $p < 0.001$), as well as macrovascular invasion (OR 5.05, 95% CI 2.82–9.03, $p < 0.001$), margin status (OR 1.94, 95% CI 1.06–3.55, $p < 0.001$), and tumor grade (OR 2.03, 95% CI 1.26–3.28, $p = 0.004$) [electronic supplementary Table 3]. For MVI high-risk patients, extrahepatic recurrence was more common compared with MVI low-risk patients (MVI high risk: $n = 95$, 27.7% vs. MVI low risk: $n = 22$, 6.4%, $p < 0.001$), as well as recurrence at multiple sites (MVI high risk: $n = 106$, 30.9% vs. MVI low risk: $n = 63$, 18.2%, $p = 0.01$).

Further analyses stratified by surgical margin status were then performed. Of note, DFS was markedly worse among patients who underwent an R1 versus R0 resection among those patients who were estimated to be at high risk



	3-year DFS	5-year OS
Low risk	51.9%	64.8%
High risk	33.0%	44.2%

FIG. 2 Illustration of the online calculator of the MVI predictive model. *AFP* α-fetoprotein, *HCC* hepatocellular carcinoma, *MVI* microvascular invasion, *DFS* disease-free survival, *OS* overall survival

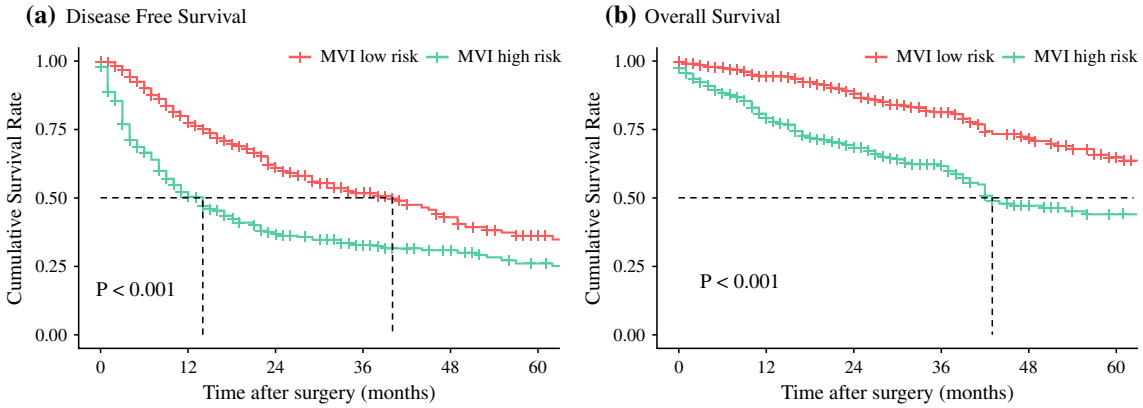


FIG. 3 Long-term survival of hepatocellular carcinoma patients with different MVI risk probabilities. Kaplan–Meier curve of high- versus low-risk MVI patients. (**a**) Disease-free survival; (**b**) overall survival. *MVI* microvascular invasion

of MVI based on the preoperative MVI calculator (R0 vs. R1 resection: 3-year DFS, 36.3% vs. 16.1%, $p = 0.002$). In contrast, DFS was comparable among patients estimated to be at low risk of MVI based on the preoperative calculator regardless of surgical margin status (R0 vs. R1 resection: 3-year DFS, 52.9% vs. 47.3%, $p = 0.16$) (Fig. 4). On multivariate analysis, margin status was an independent predictor of worse DFS among high-risk MVI patients (HR 1.87, 95% CI 1.24–2.82, $p = 0.003$), whereas R0 resection was not associated with DFS among low-risk MVI patients (electronic supplementary Table 4).

DISCUSSION

Among several known adverse pathological features associated with HCC, MVI has been particularly highlighted due to its association with poor oncological outcomes, as well as possible implications for

TABLE 2 Pathological factors associated with disease-free survival and overall survival in the entire cohort

Characteristics	Bivariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Disease-free survival						
MVI risk						
Low	Ref			Ref		
High	1.90	1.54–2.35	<0.001	1.44	1.13–1.84	0.004
Pathological TBS	1.03	1.02–1.05	<0.001	1.02	1.00–1.04	0.03
Macrovascular invasion						
No	Ref			Ref		
Yes	3.60	2.78–4.66	<0.001	2.74	2.06–3.63	<0.001
Perineural invasion						
No	Ref			–	–	–
Yes	1.33	0.73–2.44	0.36	–	–	–
Liver capsule involvement				–	–	–
No	Ref			–	–	–
Yes	1.34	1.02–1.77	0.04	–	–	–
AJCC T stage				–	–	–
T1a/T1b	Ref			–	–	–
T2/3/4	2.16	1.74–2.68	<0.001	–	–	–
Margin status						
No	Ref			Ref		
Yes	1.78	1.34–2.36	<0.001	1.43	1.07–1.92	0.02
Grade						
Well to moderate	Ref			Ref		
Poor to undifferentiated	1.80	1.44–2.23	<0.001	1.40	1.11–1.77	0.005
Overall survival						
MVI risk						
Low	Ref			Ref		
High	2.20	1.66–2.91	<0.001	1.49	1.06–2.07	0.02
Pathological TBS	1.04	1.03–1.06	<0.001	1.03	1.01–1.05	0.006
Macrovascular invasion						
No	Ref		–	–		
Yes	3.28	2.43–4.43	<0.001	–	–	–
Perineural invasion						
No	Ref		–	–		
Yes	0.59	0.19–1.84	0.36	–	–	–
Liver capsule involvement						
No	Ref		–	–		
Yes	1.73	1.26–2.37	<0.001	–	–	–
AJCC T stage						
T1a/T1b	Ref			Ref		
T2/3/4	2.52	1.92–3.30	<0.001	2.09	1.53–2.85	<0.001
Margin status						
No	Ref		–	–		
Yes	1.18	0.77–1.81	0.45	–	–	–
Grade						
Well to moderate	Ref			Ref		
Poor to undifferentiated	2.12	1.62–2.79	<0.001	1.37	1.02-1.86	0.04

MVI Microvascular invasion, *TBS* Tumor burden score, *AJCC* American Joint Committee on Cancer 8th edition

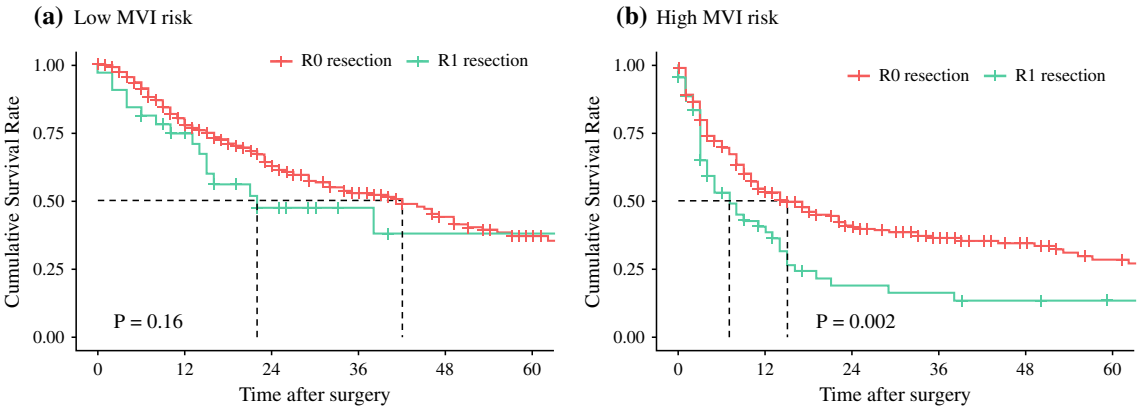


FIG. 4 Disease-free survival among hepatocellular carcinoma patients stratified by R0 versus R1 margin status. Kaplan–Meier curve of patients with high or low risk of MVI. *MVI* microvascular invasion

treatment.[11–14,23] In this regard, accurate preoperative prediction of MVI may be important to better identify which patients may benefit the most from surgical resection, plan the impact of surgical margin status, as well as stratify patients relative to prognosis. To date, several predictive models and nomograms using clinical and imaging parameters have been developed to determine the presence of MVI in HCC being resected or ablated;[13,23] however, previous risk models have had several shortcomings. Identification of imaging characteristics suffered from significant interrater variability.[24] The applicability of previous risk models was also often limited due to the inability to use these tools and lack of true clinical applicability, which is a well-known criticism of nomograms.[25,26] The current study was important because an MVI risk score calculator was built and validated using preoperative clinical information and this tool was made available as an easy-to-use online calculator (https://yutaka-endo.shinyapps.io/MVIrisk/) (Fig. 2). Of note, the MVI risk score incorporated a number of prognostic factors that involved tumor biology (i.e., AFP), tumor burden (i.e., TBS), and systemic inflammation markers (i.e., NLR). The model demonstrated good discrimination in both the test (AUC 0.71, 95% CI 0.66–0.77) and validation (AUC 0.72, 95% CI 0.66–0.78) datasets. In addition, the tool performed well even among patients with early-stage HCC within the Milan criteria (AUC 0.69, 95% CI 0.62–0.75). Importantly, when patients were stratified according to the MVI score, high-risk patients had worse long-term outcomes. Of particular note, R0 resection was associated with better DFS among patients at high risk for MVI, whereas margin status was not associated with prognosis among low-risk patients.

Recently, there has been a growing interest in the accessibility and utilization of risk scoring models to preoperatively predict the presence of MVI using radiological tumor features (i.e., non-smooth margin, peritumoral enhance, or radiomics).[27] However, interpretation of imaging can often be subjective and frequently requires specific proprietary computer software.[11,17,24] As such, to make assessment of preoperative risk more accessible, online calculators based on clinical factors may be preferred.[28] To this end, we developed an easy-to-use online MVI risk calculator that incorporated easily accessible clinical information such as AFP, TBS, and NLR. AFP has conventionally been considered an important tumor marker and predictor of HCC aggressiveness.[29] In addition, TBS, which incorporates tumor size and number, has been validated as a composite index of HCC tumor burden, which has been strongly associated with long-term outcomes.[20,30,31] The MVI risk score also included NLR, which is a marker of systemic inflammation.[32,33] Previous data had suggested that high inflammatory status may be associated with a higher prevalence of MVI and worse long-term outcomes.[34] Collectively, the proposed web-based calculator incorporated factors related to tumor biology, the extent of tumor, and systemic inflammation. The calculator was able to predict MVI with good accuracy and discrimination in both the test and validation datasets. In turn, such a tool may help identify patients at highest risk of MVI in the preoperative clinical setting.

The ability to predict MVI has important clinical implications as MVI has been strongly associated with prognosis among patients with HCC after resection or liver transplantation. For example, Rodriguez et al. reported that the presence of MVI resulted in an almost two- to three-fold increased likelihood of recurrence after surgical resection (3-year DFS: relative risk [RR] 1.82, 95% CI 1.61–2.07) or liver transplantation (3-year DFS: RR 2.41, 95% CI 2.05–5.70).[7] In turn, estimating MVI risk may enable providers to estimate long-term outcomes more accurately.[12–14] In the current study, the MVI risk model stratified patients relative to prognosis (high risk vs. low risk; 3-year DFS, 33.0% vs. 51.9%, $p < 0.001$; 5-year OS, 44.2% vs. 64.8%, $p < 0.001$) (Fig. 3). Importantly, the

ability of the preoperative MVI tool to stratify patients relative to long-term survival was comparable with prognostic stratification based on actual postoperative pathological MVI. In addition, even after controlling for other competing risk factors, the preoperative MVI risk calculator was still able to stratify patients relative to postoperative OS (HR 1.49, 95% CI 1.06–2.07, $p = 0.02$) (Table 2).

In addition to prognosis, identification of MVI preoperatively may inform the surgeon about the relative importance of intraoperative margin status. Previous data suggested that the presence or absence of MVI on pathology may differentially impact the survival benefit of an R0 margin. In particular, Zheng et al. noted that wider resection margins resulted in better long-term outcomes among patients with pathologic MVI, yet margin status did not impact patients with HCC tumors without MVI.[33] The authors postulated that MVI places patients at higher risk to develop micrometastasis with microvascular tumor thrombi at the liver transection plane; in turn, a narrower surgical margin width may result in tumor dissemination through larger vessels and higher subsequent recurrence.[35] Consistent with these findings, we noted in the current study that patients who were at high risk of MVI based on the preoperative calculator had worse outcomes when the surgical margin was close or positive. In contrast, surgical margin status did not impact outcomes among patients at low risk of MVI based on the calculator (electronic supplementary Table 4). In turn, the preoperative assessment of MVI risk may help surgeons to plan the appropriate intraoperative treatment strategy with a greater attempt to achieve a wide negative surgical margin for patients at high risk of MVI based on the preoperative calculator. Furthermore, in the current study, MVI risk score was associated with recurrence patterns (i.e. early recurrence, site of recurrence). Specifically, early recurrence (within 8 months) was almost three times as likely in high-risk patients compared with low-risk patients (electronic supplementary Table 3). Moreover, high-risk patients were more likely to develop extrahepatic recurrence or recurrence at multiple sites. Some data have even suggested that patients undergoing resection of HCC with MVI may benefit from adjuvant therapy.[9,10] In this regard, the MVI risk model may provide additional insights into risk of recurrence and the potential need for adjuvant therapy, especially as newer targeted therapies emerge.

The current study had several limitations that should be considered when interpreting the results. As with all retrospective studies, selection bias may have influenced which patients were treated with surgery. In addition, although the multi-institutional nature of the database was a strength, patient selection and choice of surgical procedures may have varied according to treatment institution. Since the correlation of pre- versus postoperative information of MVI was based on the calculator tool compared with findings on the pathologic specimen, the predictive ability could not be assessed among patients who did not undergo surgery (i.e., ablation, transplantation, or transarterial chemoembolization). Therefore, the results cannot be generalized to these patient populations.

CONCLUSION

A preoperative risk model to predict MVI was developed that incorporated AFP tumor marker, extent of tumor burden, and systemic inflammation data. The tool was made available as an easy-to-use online calculator and was validated using a separate cohort of HCC patients. Preoperative assessment of MVI using the online tool demonstrated very good accuracy and discrimination to predict MVI and was able to stratify patients relative to postoperative prognosis, as well as identified those patients at high risk of MVI who benefited the most from a margin-free resection. The proposed online calculator may help surgeons with preoperative MVI risk stratification, as well as planning optimal treatment strategies and surveillance of patients with HCC.

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