

RESEARCH ARTICLE

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Platelet-to-Lymphocyte Ratio and Large Tumor Size Predict Microvascular Invasion after Resection for Hepatocellular Carcinoma

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Abstract

Background: Recurrence after curative resection of hepatocellular carcinoma (HCC) is associated with early death and poor prognosis. Microvascular invasion (mVI) is strongly associated with disease recurrence. Although many studies have examined the relationship between various serum inflammatory indices and post-treatment prognosis, little is known about preoperative predictors of microvascular invasion in HCC. **Methods:** Patients who underwent curative hepatic resection for HCC at our institute from January 2006 to December 2016 were retrospectively reviewed. The associations between mVI and various potential risk factors, including tumor size, hepatitis B and C virus infection, Child–Pugh scores, platelet-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio, were analyzed. Optimal cut-off values were determined using receiver operating characteristic curves. **Results:** A total of 330 HCC patients were enrolled in this study, of whom 74 (22.4%) had tumors with mVI. After univariate analysis, two parameters were significantly associated with mVI after hepatic resection: platelet-to-lymphocyte ratio ≥ 102 (odds ratio [OR] 2.385, $p = 0.001$) and tumor size ≥ 5 cm (OR 4.29, $p < 0.001$). Both variables remained significant risk factors for mVI after multivariate analysis: platelet-to-lymphocyte ratio ≥ 102 (OR 1.831, $p = 0.034$) and tumor size ≥ 5 cm (OR 3.791, $p < 0.001$). **Conclusions:** Large tumor size (≥ 5 cm) and high platelet-to-lymphocyte ratio (≥ 102) are independent predictive factors for mVI in HCC.

Keywords: Hepatocellular carcinoma- risk factors- platelet-to-lymphocyte- prognosis- microvascular

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide (Torre et al., 2015). Many treatment options are available for HCC, depending on the stage of disease and the presence of liver cirrhosis (Bruix et al., 2016), but liver transplantation is considered the optimal approach because it treats both the tumor and background liver disease simultaneously. However, in Thailand, resection is the main treatment option because of the limited availability of donor organs. Although the overall morbidity and mortality associated with surgical treatment of HCC have declined in recent years, the rate of cancer recurrence remains high (Fan et al., 1999; Imamura et al., 2003; Regimbeau et al., 2004; Liu et al., 2015). Indeed, recurrent intrahepatic disease is the most common cause of death from HCC (Lim et al., 2012; Bruix et al., 2016).

Microvascular invasion (mVI), large tumor size, multifocality, high serum alpha-fetoprotein (AFP)

concentration, and liver cirrhosis are among the known risk factors for poor prognosis in HCC (Poon et al., 2000b; Cha et al., 2003; Regimbeau et al., 2004; Kaibori et al., 2009; Kamiyama et al., 2012). Of these, mVI is the most commonly reported predictor of poor prognosis of HCC after curative resection (Poon et al., 2000a; Lim et al., 2011; Rodriguez-Peralvarez et al., 2013). The American Joint Committee on Cancer Staging manual, 7th edition (Compton Cc, 2006), classifies HCC with mVI as T2, regardless of the tumor size. A second form of vascular invasion is macrovascular (Sumie et al., 2014), which is defined as tumor growth into a major vessel that can be identified by macroscopic examination or preoperative radiological imaging. According to the Barcelona Clinic Liver Cancer Classification system, macrovascular invasion is a contraindication for liver transplantation due to very high recurrence rate (Bruix et al., 2016). In contrast, mVI, which is defined as the presence of tumor emboli in a portal pedicle vein, a large capsule vessel, or a vascular space lined by endothelial cells, does not preclude

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transplantation (Rodriguez-Peralvarez et al., 2013).

Various predictors of mVI in HCC have been reported, including tumor size, tumor capsule, tumor multifocality, and smooth tumor margin in computed tomography (Pawlik et al., 2005; Kim et al., 2008; Eguchi et al., 2010; Suh et al., 2012; Rodriguez-Peralvarez et al., 2013; Yamamura et al., 2014; Pote et al., 2015; Xia et al., 2015; Goh et al., 2016; Yang et al., 2017). In addition, several recent studies have identified several serum inflammatory factors associated with post-treatment prognosis of HCC, including platelet-to-lymphocyte ratio (PLR) (Tian et al., 2016; Huang et al., 2017; Yang et al., 2017), neutrophil-to-lymphocyte ratio (NLR) (Goh et al., 2016; Jin et al., 2017; Urabe et al., 2017), and prognostic nutritional index (PNI) (Chan et al., 2015; Wu et al., 2016). However, only a few studies have examined the relationship between inflammatory indices and mVI (Gomez et al., 2008; Chan et al., 2015; Zheng et al., 2017). The aim of this study was to identify preoperative predictors of mVI by evaluating the correlation between preoperative clinicopathological features, including serum inflammatory indices, and mVI.

Materials and Methods

Patients and methods

This was a retrospective study of 330 consecutive patients who underwent liver resection for pathologically proven HCC at the Department of Surgery at our hospital between January 2006 and December 2016. The Institutional Review Board of Ramathibodi Hospital approved the study.

Patient demographic and clinicopathological data collected included age, gender, indocyanine green retention value at 15 min (ICG-R15), AFP, alcohol consumption, and Child–Pugh score. All patients underwent preoperative cross-sectional dynamic imaging using either triple-phase computed tomography or magnetic resonance imaging. Liver biopsy was not routinely performed, except in cases with an inconclusive diagnosis after preoperative imaging. The tumor size was derived from preoperative imaging. Routine blood examinations included complete blood count, coagulogram, liver and kidney function tests, hepatitis B and C virus (HBV, HCV) infection, and serum AFP concentration. A preoperative ICG-R15 was also performed. NLR was calculated as neutrophil count divided by the lymphocyte count. PLR was calculated as the platelet count divided by the lymphocyte count. PNI was calculated as $([\text{albumin } \{\text{g/L}\} + 0.005] \times [\text{total lymphocyte count } \{\mu\text{L}\}])$. HCC was diagnosed preoperatively based on characteristic findings on computed tomography or magnetic resonance imaging. In our center, patients are selected for curative resection based on the Makuuchi criteria (Miyagawa et al., 1995). The extent of liver resection was individualized according to the patient's liver functional reserve, which was mainly assessed using the Makuuchi criteria, including preoperative ascites volume, Child–Pugh score, ICG-R15, and, occasionally, volumetric computed tomography analysis.

Surgery was performed laparoscopically or by open

laparotomy. Prophylactic antibiotics were routinely injected up to 30 min before skin incision. The incision type depended on the surgeon's preference. The Pringle maneuver was performed using intermittent clamping (clamp for 15 min, de-clamp for 5 min). Intraoperative ultrasound was routinely used to stage the disease and to guide parenchymal transection, which was performed using a Cavitron ultrasonic aspirator or the clamp crushing technique, depending on the surgeon's preference. Blood loss was estimated by an anesthesiologist, who also assessed the need for blood transfusion. The operative time was defined as the period from the start of incision until closure of the abdominal wound.

Pathological specimens were reviewed by a pathologist to confirm the diagnosis of HCC. Patients with combined cholangiocarcinoma, other kinds of malignancies, or with incomplete data were excluded from the study. mVI was defined as the presence of tumor cells in the microvasculature.

Statistical analysis

Categorical and numerical variables were analyzed using Pearson's χ^2 test and the Mann–Whitney test, respectively. Univariate and multivariate analyses were conducted using the logistic regression model. Odds ratios (OR) and 95% confidence intervals (CI) were computed to assess the strength of the associations between the various factors and the outcome. A p value of <0.05 was considered statistically significant. Analyses were performed using STATA program version 14 (StataCorp, College Station, TX, USA). The cut-off value for high and low PLR, 102, was determined by receiver operating characteristic (ROC) curve analysis.

Results

Patient characteristics

A total of 330 patients underwent curative resection for HCC from January 2006 to December 2016, of whom 74 (22.4%) had mVI. For analyses, the patients were divided into mVI+ ($n = 74$) and mVI– ($n = 256$) groups. The clinicopathological characteristics of the two groups are shown in Table 1. The mVI+ group had significantly higher median platelet counts than the mVI– group ($2.07 \times 10^5/\mu\text{L}$ [range 0.94–8.5] vs $1.92 \times 10^5/\mu\text{L}$ [0.14–6.90], $p = 0.009$) and median PLR (129.2 vs 94.1, $p = 0.001$). The median tumor size was also higher in the mVI+ group than the mVI– group (6.8 vs 4.0 cm, $p < 0.001$). In the mVI+ group ($n = 74$), there was a significant difference in the number of patients with tumor size <5 cm compared with ≥ 5 cm (19 vs 55, $p < 0.001$) and in the number of patients with PLR <102 compared with PLR ≥ 102 (47 vs 27, $p = 0.001$; Table 1). There were no significant differences between the two groups with respect to age, gender, HBV, HCV, ICG-R15, AFP, international normalized ratio (INR), NLR, PNI, alcohol consumption, Child–Pugh score, number of tumors, or multifocality.

Univariate and multivariate analyses

The results of the univariate and multivariate analyses of potential predictors of mVI are shown in Table 2.

Table 1. Preoperative Characteristics of Patients Stratified by Microvascular Invasion

Characteristics	Total (n=330)	mVI- (n=256)	mVI+ (n=74)	p value
Age (years), mean±sd ^a	58.12 (10.65)	58.32 (10.31)	57.44 (11.76)	0.536
Platelets ($\times 10^5$ / μ L)	1.95 (0.14–8.50)	1.92 (0.14–6.90)	2.07 (0.94–8.5)	0.009
INR (U/L)	1.06 (0.06–1.70)	1.06 (0.06–1.70)	1.04 (0.84–1.28)	0.238
AFP (ng/mL)	15.20 (0.89–82392)	13.56 (0.89–60500)	33.5 (0.9–82392)	0.09
ICG-R15 (%)	14.70 (0.10–51.60)	14.90 (0.50–51.60)	13.95 (0.10–33.80)	0.247
Tumor size (cm)	4.5 (0.1–26.5)	4 (0.10–19)	6.80 (1.50–26.50)	0
Lymphocytes (/ μ L)	1,900.8 (480–21060)	1,938.4 (480–21060)	1,803 (630–4893)	0.266
PLR	101.7 (6.89–536.83)	94.1 (6.9–536.8)	129.2 (38.6–370.5)	0.001
Neutrophils (/ μ L)	3,451 (1064–11620)	3,440 (1064–10600)	3,583 (1575–11620)	0.476
PNI	95.37 (24.4–1053.3)	97.3 (24.4–1053.3)	90.6 (31.8–245.0)	0.272
NLR	1.81 (0.33–10.62)	1.78 (0.50–10.62)	2.03 (0.33–6.38)	0.162
PNI, n (%) (n = 312)				
<95	153 (49.04)	114 (47.30)	39 (54.93)	0.259
>95	159 (50.96)	127 (52.70)	32 (45.07)	
NLR, n (%) (n= 310)				
<1.8	153 (49.35)	122 (50.62)	31 (44.93)	0.404
>1.8	157 (50.65)	119 (49.38)	38 (55.07)	
Tumor size, n (%)				
<5 cm	172 (52.12)	153 (59.77)	19 (25.68)	0
>5 cm	158 (47.88)	103 (40.23)	55 (74.32)	
PLR, n (%)				
<102	175 (53.03)	148 (57.81)	27 (36.49)	0.001
>102	155 (46.97)	108 (42.19)	47 (63.51)	
Gender, n (%)				
Male	127 (38.48)	101 (39.45)	26 (35.14)	0.501
Female	203 (61.52)	155 (60.55)	48 (64.86)	
HBV, n (%)				
Negative	147 (44.55)	109 (42.58)	38 (51.35)	0.181
Positive	183 (55.45)	147 (57.72)	36 (48.65)	
HCV, n (%)				
Negative	271 (82.12)	212 (82.81)	59 (79.73)	0.542
Positive	59 (17.88)	44 (17.19)	15 (20.27)	
Alcohol consumption, n (%) (n=299)				
None	167 (55.85)	132 (51.56)	35 (47.30)	0.572
Occasional	70 (23.41)	51 (19.92)	19 (25.68)	
Alcoholism	62 (20.74)	47 (18.36)	15 (20.27)	
Child–Pugh, n (%) (n = 309)				
A	293 (94.82)	229 (95.02)	64 (94.12)	0.767
B	16 (5.18)	12 (4.98)	4 (5.88)	
Multifocal tumor, n (%)				
Single	255 (77.27)	200 (78.13)	55 (74.32)	0.492
Multiple	75 (22.73)	56 (21.88)	19 (25.68)	

^a, Age is presented as the mean \pm standard deviation (sd). All other data are presented as the median (range) or number (%) of patients; AFP, alpha-fetoprotein; CI, confidence interval; HCV, hepatitis C virus; ICG, indocyanine green retention; INR, international normalized ratio; mVI-/+ , microvascular invasion absent/present; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI prognostic nutritional index, PTT, partial thromboplastin time; sd, standard deviation.

Univariate analysis identified two variables significantly associated with mVI after hepatic resection: PLR ≥ 102 (OR 2.385, $p = 0.001$) and tumor size ≥ 5 cm (OR 4.29, $p < 0.001$). In multivariate analysis, these variables

remained significant predictive indicators of mVI: PLR ≥ 102 (OR 1.831, $p = 0.034$) and tumor size ≥ 5 cm (OR 3.791, $p < 0.001$).

Table 2. Univariate and Multivariate Analysis of Predictors of Microvascular Invasion

Variables	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	0.992 (0.96–1.02)	0.535		
INR	0.418 (0.04–4.15)	0.457		
AFP (<400 ng/mL)				
>400 ng/mL	1.557 (0.91–2.65)	0.102		
PLR (<102)				
>102	2.385 (1.39–4.07)	0.001	1.831(1.05–3.21)	0.034
PNI (<95)				
>95	0.736 (0.43–1.25)	0.259		
NLR (<1.8)				
>1.8	1.167 (0.96–1.42)	0.121		
Tumor size (<5cm)				
>5 cm	4.299 (2.41–7.66)	0	3.791(2.1–6.84)	0
Gender (Male)				
Female	1.202 (0.70–2.06)	0.502		
HBV (Negative)				
Positive	0.702 (0.42–1.18)	0.182		
HCV (Negative)				
Positive	1.224 (0.64–2.35)	0.543		
Alcohol (None)				
Occasional	1.405 (0.74–2.68)	0.302		
Alcoholism	1.203 (0.60–2.40)	0.599		
Child–Pugh score (A)				
B	1.193 (0.37–3.82)	0.767		
Multifocal tumor (Single)				
zMultiple	1.233 (0.68–2.25)	0.492		

AFP, alpha-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

Discussion

The presence of mVI is strongly associated with HCC recurrence and early disease-related death (Poon et al., 2000a; Poon et al., 2007; Lim et al., 2011). Several studies have shown that mVI+ patients have poorer prognosis than mVI– patients (Pawlik et al., 2005; Yamamoto et al., 2015; Hirokawa et al., 2016; Shimoda et al., 2016). Although there is currently no consensus definition of mVI, Rodriguez-Peralvarez (2013) recently proposed the following criteria: (i) the presence of tumor cells forming plug or polyp and (ii) tumor thrombus partially or totally covered by endothelial cells in either the portal vein or hepatic vein branches. They also suggested that tumor cells or small clusters of tumor cells free-floating inside isolated vessels but not covered by endothelium should not be considered part of the criteria (Rodriguez-Peralvarez et al., 2013). In the present study, we defined mVI according to these criteria. The rate of mVI in this study was 22.4%, comparable to that seen in previous studies (Kim et al., 2008; Eguchi et al., 2010; Rodriguez-Peralvarez et al., 2013; Shimoda et al., 2016). Since mVI cannot be identified preoperatively, knowledge

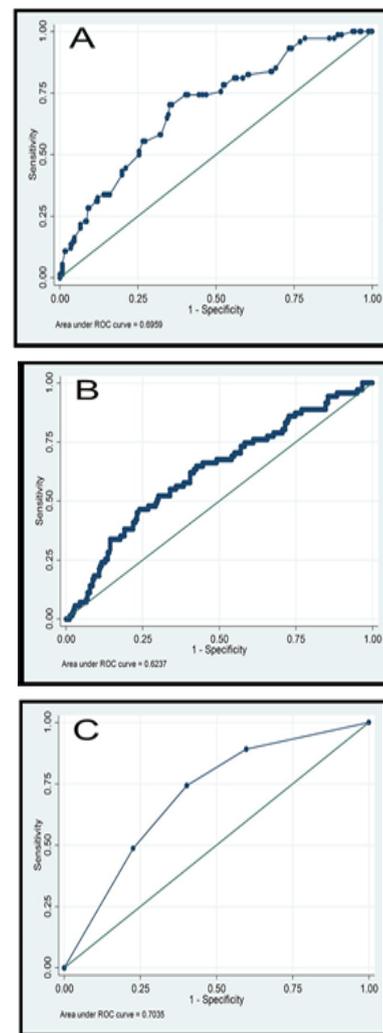


Figure 1. Receiver Operating Characteristic Curves for Predicting Microvascular Invasion. (A) Tumor size. (B) Platelet-to-lymphocyte ratio. (C) Tumor size ≥ 5 cm and platelet-to-lymphocyte ratio ≥ 102 .

of significant risk factors could be of great help to the surgeon for preoperative preparation. From univariate and multivariate analyses, we identified tumor size ≥ 5 cm and PLR ≥ 102 as preoperative predictors of mVI.

Angiogenesis is the main mechanism of mVI in HCC. Rodriguez-Peralvarez (2013) reported that vascular invasion results when tumor cells develop a sufficiently evolved phenotype to invade blood vessels and potentially begin to metastasis. The production of proteases and reduced expression of E-cadherin result in loss of tissue integrity and further facilitate tumor invasion (Wu et al., 2011; Rodriguez-Peralvarez et al., 2013). Pawlik (2005) reported that the incidence of mVI positively correlated with increasing tumor size, and that mVI was twice as common in patients with tumors ≥ 5 cm vs < 5 cm.

Although it is well-established that tumor size is associated with the outcome after resection in HCC (Shirabe et al., 2014; Hwang et al., 2015; Lei et al., 2016) and that large tumor size is associated with mVI, there is some controversy about the optimal tumor size for risk stratification (Pawlik et al., 2005; Shindoh et al., 2013). In the present study, we identified a cut-off value of 5 cm

for predicting mVI. Chen et al. reported that patients with smaller HCC tumors (<5 cm) have better prognosis (Chen et al., 2011). In addition, several large population studies in HCC have identified a relationship between mVI and >5 cm tumors (Pawlik et al., 2005; Kaibori et al., 2009; Huang et al., 2015; Hwang et al., 2015). In the Barcelona Clinic Liver Cancer staging system, patients with tumor sizes <5 cm are classified as having early stage HCC (Bruix et al., 2016). A single tumor of size ≤5 cm is one of the Milan criteria for liver transplantation (Mazzaferro et al., 2008). In accordance with these findings, we suggest a cut-off value of 5 cm for the association between tumor size and mVI.

Systemic inflammatory responses play critical roles in the pathogenesis and progression of cancer (Grivennikov et al., 2010). Inflammation promotes tumor angiogenesis, invasion, and metastasis through regulation of a subset of regulatory T lymphocytes and chemokines (Mantovani et al., 2008; Fan et al., 2015). Recently, Zhou and Templeton (Templeton et al., 2014; Zhou et al., 2014) reported that PLR is a significant biomarker of poor prognosis for many cancers, including HCC. Moreover, in patients who underwent hepatic resection, transplantation, and transarterial chemoembolization, high PLR levels were associated with poor prognosis and disease recurrence (Suh et al., 2012; Xue et al., 2015; Goh et al., 2016; Song et al., 2016; Yang et al., 2017).

Few studies have investigated the relationship between PLR and mVI (Ma et al., 2016; Zheng et al., 2017). Ma (2016) performed a meta-analysis of the prognostic value of PLR in HCC and found no association with vascular invasion; however, this conclusion was based on only three eligible studies, and vascular invasion was defined as including both macrovascular invasion and mVI. The Memorial Sloan Kettering Center group (Zheng et al., 2017) investigated the utility of serum inflammatory markers as predictors of mVI. They found that the mVI+ group had higher mean PLR values than the mVI-, but univariate and multivariate analyses identified significant associations between mVI and AFP, albumin, and radiologic tumor size, but not PLR. In contrast, PLR was significantly higher in the mVI+ group than mVI- group in our study, and univariate and multivariate analysis demonstrated that PLR >102 was an independent prognostic factor for mVI. These apparently discrepant results could be due to the higher proportion of HBV-infected patients (55.5% vs 25%) and alcoholic patients (44.3% vs 11%) in our study vs the Memorial Sloan Kettering Center study (Zheng et al., 2017). Inflammation plays a role in the severity of chronic HBV infection through antigen-nonspecific inflammatory cell enhancement of cytotoxic T lymphocyte-mediated liver damage, and platelets facilitate intrahepatic accumulation of cytotoxic T lymphocytes (Iannacone et al., 2005; Seki and Schwabe, 2015). In two studies examining inflammatory indices in patients with chronic HBV infection, Zhao and Wang (Wang et al., 2015; Zhao et al., 2017) both reported an association between PLR and liver fibrosis and disease severity.

Although the relationship between PLR and mVI has previously been investigated, no consensus cut-off value

was obtained (Yamamura et al., 2014; Spolverato et al., 2015; Goh et al., 2016; Ma et al., 2016; Yang et al., 2017). Our finding that PLR >102 is an independent risk factor for mVI is consistent with previous studies, most of which identified PLR cut-off values of >100 (Ma et al., 2016). Notably, we showed that the combination of tumor size ≥5 cm and PLR ≥102 had superior predictive sensitivity and specificity compared with either measure (Figure 1).

This study has some limitations. First, because of its retrospective nature, the study design could have some selection bias. Second, some preoperative inflammatory indices, such as the Glasgow Prognostic Score, could not be included because our center does not routinely measure C-reactive protein, which is a component of the Glasgow Prognostic Score.

In conclusions in this study, we demonstrated that large tumor size and high PLR are independent predictive risk factors for mVI. The suggested cut-off values are >5 cm for tumor size and 102 for PLR. When used in combination, these factors showed better discriminatory performance than either measure alone for predicting mVI. These findings may be helpful for surgeons in preoperative counselling for the patients undergoing HCC resection.

Author contributions

NR: study design, data collection and interpretation, writing and drafting of the manuscript; SM: data collection and analysis; PT: data collection and analysis; PM: data collection; WS: data collection; SA: data collection and analysis.

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