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Original Article

Surgical outcome and risk scoring to predict survival after hepatic resection for hepatocellular carcinoma with portal vein tumor thrombosis

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Backgrounds/Aims: The hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is classified as the advanced stage (BCLC stage C) with extremely poor prognosis, and in current guidelines is recommended for systemic therapy. This study aimed to evaluate the surgical outcomes and long-term prognosis after hepatic resection (HR) for patients who have HCC combined with PVTT.

Methods: We retrospectively analyzed 332 patients who underwent HR for HCC with PVTT at ten tertiary referral hospitals in South Korea.

Results: The median overall and recurrence-free survival after HR were 32.4 and 8.6 months, while the 1-, 3-, and 5-year overall survival rates were 75%, 48%, and 39%, respectively. In multivariate analysis, tumor number, tumor size, AFP, PIVKA–II, neutrophil-to-lymphocyte ratio, and albumin–bilirubin (ALBI) grade were significant prognostic factors. The risk scoring was developed using these seven factors–tumor, inflammation and hepatic function (TIF), to predict patient prognosis. The prognosis of the patients was well stratified according to the scores (log-rank test, $p < 0.001$).

Conclusions: HR for patients who have HCC combined with PVTT provided favorable survival outcomes. The risk scoring was useful in predicting prognosis, and determining the appropriate treatment strategy for those patients who have HCC with PVTT.

Key Words: Hepatocellular carcinoma; Tumor thrombosis; Portal vein; Hepatectomy; Prognosis

INTRODUCTION

Hepatocellular carcinoma (HCC) frequently invades the surrounding liver vasculature, with portal vein tumor thrombosis (PVTT) being the most common form of macrovascular invasion. At the time of HCC diagnosis, PVTT is detected in approximately 10%–40% of patients, and is associated with an extremely poor prognosis [1,2].

In most staging systems and guidelines, HCC with PVTT, regardless of the extent of the tumor, is classified as an advanced stage, and surgical resection is not recommended as the first-line treatment. Instead, consensus guidelines, such as those from the American Association of Study of Liver Disease (AASLD), the Asian Pacific Association for the Study of Liver (APASL), and the European Association for the Study of Liver (EASL), recommend systemic and targeted therapy for these patients [3,4]. Despite these recommendations, experienced liver centers in Asia have been attempting surgical resection for some patients with HCC exhibiting PVTT, and in selected patients, the outcomes are favorable [5-10]. However, most of the studies were conducted in only one center, had a small sample size, and in most of the patients, obtained undesirable surgical treatment outcomes. Thus, surgical resection has yet to be widely accepted as an effective treatment for patients with HCC and PVTT. In addition, a prognostic index that can indicate which surgical resection is beneficial in comparison with nonsurgical treatment remains unestablished. While a randomized controlled trial might be the best way to compare the outcomes of surgical resection and nonsurgical treatments, it is difficult to conduct, because of difficulties in ethical approval and allocation concealment. Therefore, adequate studies with large sample sizes are needed to clarify the benefits of surgical resection in patients with HCC and PVTT, and a prognostic index, which can specify the criteria for surgical resection in these patients, is required.

Accordingly, this study aimed to investigate the clinical outcomes and prognostic factors after hepatic resection in patients with HCC exhibiting PVTT, and to develop a prognostic index that can be helpful in determining the treatment strategy.

PATIENTS AND METHODS

Patients

This retrospective multicenter study enrolled patients who underwent surgical resection of HCC with PVTT at 10 university-affiliated hospitals in Korea between January 2005 and December 2019. The institutional review board of each study center approved the study protocol (IRB No. 2022-03-065-003). The inclusion criteria were as follow: 1) HCC with PVTT found on preoperative imaging, and proven by postoperative histology to be viable; 2) Child–Pugh class A liver function; 3) no extrahepatic metastasis and concomitant malignant tumors, other than HCC; 4) no previous hepatic resection for HCC; and 5) available medical records and/or imaging studies. We included 332 patients from 10 centers in Korea, and retrospectively reviewed their medical records.

Clinicopathological variables

Clinicopathological data were collected from each study center. The data included patient age, sex, body mass index, liver disease etiology, preoperative alpha–fetoprotein (AFP) level, preoperative proteins induced by vitamin K antagonist or absence II (PIVKA–II) level, preoperative indocyanine green retention test at 15 minutes (ICG R–15) level, albumin–bilirubin (ALBI) score, and serology. Tumor data included tumor number, maximum tumor size, PVTT classification, and detailed pathological findings (bile duct invasion, hepatic vein invasion, microvascular invasion, satellite nodule, and viable PVTT). PVTT was classified into four grades, according to the classification system of the Liver Cancer Study Group of Japan [11]. These grades, also known as Vp grades, were defined as follow: Vp0, no PVTT; Vp1, invasion or tumor thrombus distal to the second branch of the portal vein (PV); Vp2, invasion or tumor thrombus in the second branch of the PV; Vp3, invasion or tumor thrombus in the first branch of the PV; and Vp4, invasion or tumor thrombus in the PV trunk, or extending to a branch on the contralateral side. Surgery-related data included surgery type, extent of surgery, thrombectomy, surgical margin status, postoperative complications, and operative mortality.

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Statistical analysis

Clinicopathological data are summarized as number (percentage) for categorical variables, and median (range) or mean ± standard deviation for continuous variables. The cutoff values for continuous variables, including tumor size, AFP, PIVAK–II, and neutrophil–lymphocyte ratio (NLR), were chosen using receiver operating characteristic (ROC) curve analysis. Overall survival (OS) and recurrence-free survival (RFS) were calculated using the Kaplan–Meier method, and significance was determined using the log-rank test. Moreover, univariate and multivariate analyses were used to determine significant clinical factors predicting prognosis after surgical resection, using the Cox proportional hazards model. All statistical data were analyzed using SPSS version 25.0 program (IBM Co.).

Scoring system

After the first analysis, we developed a scoring system that could predict the prognosis of patients who underwent surgical resection for HCC with PVTT. We used a simple integer scoring system, which has already been reported and used successfully to predict outcomes in various disciplines [12,13], based on the frequency and hazard ratio of each risk factor analysis for tumor recurrence (overall and early), and patient survival (overall and early). Points were allocated to the patients according to the presence of these factors, with the score for each patient being derived from the sum of these points. Patients were classified into three groups according to the prognostic score: low-risk (total score: 0–4), intermediate-risk (total score: 5–8), and high-risk (total score: 9–11). OS and RFS were compared between these risk groups using Kaplan–Meier curves and the log-rank test.

RESULTS

Clinical features and pathological findings

Table 1 summarizes the clinical features and pathological findings of 332 patients. Among these patients, 291 (87.7%) were male, 267 (80.4%) had chronic hepatitis B, 74 (22.3%) had multiple tumors, and 172 (51.8%) had tumors with a maximal diameter over 6.5 cm. The mean age was 53.9 years. The median AFP level was 144.5 ng/mL, whereas the median PIVKA–II level was 424.0 mAU/mL. The grades of PVTT were Vp1, Vp2, Vp3, and Vp4 in 79, 94, 122, and 37 patients (23.8%, 28.3%, 36.7%, and 11.1%), respectively. Furthermore, 139 patients (41.9%) received the following HCC therapies preoperatively: transarterial chemoembolization (TACE) (70, 21.1%); radiofrequency ablation (RFA) (14, 4.2%); external beam radiotherapy (8, 2.4%); systemic chemotherapy (2, 0.6%); and combined therapy (45, 13.6%). On the Pathological examination, microscopic margin involvement, microvascular invasion, satellite nodules, viable PVTT, hepatic vein invasion, and bile duct invasion were identified in 41, 269, 103, 245, 18, and 24 patients (12.3%, 81.0%, 31.0%, 73.8%, 5.4%, and 7.2%), respectively.

Table 1. Clinicopathological features of the 332 patients who underwent surgical resection for hepatocellular carcinoma with PVTT

Clinical parameter	Value
Sex (male/female)	291 (87.7)/41 (12.3)
Age (yr)	53.9 ± 9.8
BMI (kg/m^2)	23.9 ± 3.1
Underlying liver disease	
Hepatitis B	267 (80.4)
Hepatitis C	18 (5.4)
Combined B & C	5 (1.5)
Alcoholic hepatitis	11 (3.3)
Autoimmune	15 (4.5)
NASH/cryptogenic	7 (2.1)/9 (2.7)
AFP	144.5 (0.9–705,233.0)
PIVKA-II	424.0 (11.7–76,397.0)
Preoperative ICG R-15	12.7 ± 6.6
Tumor number	
Solitary	258 (77.7)
Multiple	74 (22.3)
Tumor size	
< 6.5 cm	160 (48.2)
≥ 6.5 cm	172 (51.8)
PVT classification	
Vp 1	79 (23.8)
Vp 2	94 (28.3)
Vp 3	122 (36.7)
Vp 4	37 (11.1)
ALBI (Grade I/II)	158 (47.6)/174 (52.4)
NLR	3.8 (0.7–66.4)
Length of stay (day)	16.2 ± 12.5
Median follow-up (mon)	26.9 (0.3–205.7)
Type of surgery	
Open	314 (94.6)
Minimal invasive	18 (5.4)
Surgical complication	97 (29.2)
C-D grade I	37 (11.1)
C-D grade II	22 (6.6)
C-D grade IIIa	23 (6.9)
C-D grade IIIb	9 (2.7)
Surgical mortality	6 (1.8)
Recurrence	226 (68.1)
Intrahepatic (marginal)	60 (18.1)
Intrahepatic (multicentric)	60 (18.1)
Extrahepatic	30 (9.0)
Intra-, extrahepatic	76 (22.9)
Preoperative treatment	
No treatment	193 (58.1)
TACE	70 (21.1)
RFA	14 (4.2)
Radiotherapy	8 (2.4)
Systemic chemotherapy	2 (0.6)
Combined therapy	45 (13.6)

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Table 1. Continued

Clinical parameter	Number
Pathologic results	
Bile duct invasion	24 (7.2)
Hepatic vein invasion	18 (5.4)
Microvascular invasion	269 (81.0)
Satellite nodule	103 (31.0)
Microscopic margin (+)	41 (12.3)
Viable PVTT	245 (73.8)

Values are presented as number (%), mean ± standard deviation, or median (range).
PVTT, portal vein tumor thrombosis; BMI, body mass index; NASH, nonalcoholic steatohepatitis; AFP, alpha–fetoprotein; PIVKA-II, preoperative proteins induced by vitamin K antagonist or absence II; ICG R-15, indocyanine green retention test at 15 min; PVT, portal vein thrombosis; ALBI, albumin–bilirubin; NLR, neutrophil–leukocyte ratio; C-D, Clavien–Dindo classification; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

Surgical and survival outcomes in the overall cohort

Table 1 summarizes the surgical outcomes. We found 314 patients (94.6%) who underwent open liver resection, with a mean length of stay of 16.2 days postoperatively. Serious postoperative complications classified as Clavien–Dindo grade III or above occurred in 38 patients (11.4%), and perioperative mortality occurred within 3 months in six patients (1.8%). For the entire cohort of 332 patients, the 1-, 3-, and 5-year OS rates were 75%, 48%, and 39% (Fig. 1A), while the RFS rates were 45%, 34%, and 28%, respectively (Fig. 1B). The expected median OS was 32.4 months, and the expected median RFS was 8.6 months.

During a median follow-up of 26.9 months, tumor recurrence occurred in 226 patients (68.1%), and the median time to recurrence was 6.2 months postoperatively. Among the 226 patients who developed tumor recurrence, 120 (53.1%) had intrahepatic recurrence, 30 (13.3%) had extrahepatic recurrence, and 76 (33.6%) had both intrahepatic and extrahepatic recurrence. After recurrence, various treatment modalities, such as TACE, RFA, repeated resection, external beam radiotherapy, and systemic therapies, were applied according to the recurrence pattern, tumor number and size, liver function status, and patient tolerability.

Risk factors for tumor recurrence and patient survival

Univariate analysis showed that PVTT grade, tumor number, tumor size, AFP level, PIVKA–II level, ALBI grade, and NLR were significant preoperative risk factors for tumor recurrence and OS (Table 2). Microvascular invasion, satellite nodule presence, and positive resection margins also showed statistical significance as pathologic risk factors. In the multivariate analysis, multiple tumors, tumor size > 6.5 cm, PIVKA–II > 400, NLR > 3.5, and ALBI grade 2 were independent preoperative risk factors for RFS; those for OS were multiple tumors, tumor size > 6.5 cm, NLR > 3.5, and ALBI grade 2 (Table 3). We also analyzed independent preoperative risk factors for early recurrence (within 6 months), and early patient death (within 1 year). In multivariate analysis, multiple tumors, tumor size > 6.5 cm, AFP > 200, and NLR > 3.5 were independent preoperative risk factors for early recurrence, while those for early patient death were tumor size > 6.5 cm, AFP > 200, and NLR > 3.5 (Table 3).

Development of a scoring system for predicting prognosis

Based on risk factor analyses, we developed a scoring system that we named as the TIF score for predicting prognosis, which system comprised tumor factors (T), immunologic and inflammatory factors (I), and hepatic functional factors (F). Six prognostic factors, namely, tumor number, tumor size, AFP, PIVKA–II, NLR, and ALBI grade, were included, and allocated 0 to 3 points, according to the risk factor analyses. Patients were risk-stratified according to the sum of these points. Those with scores of 0–4, 5–8, and 9–11 belonged to the low-, intermedi-

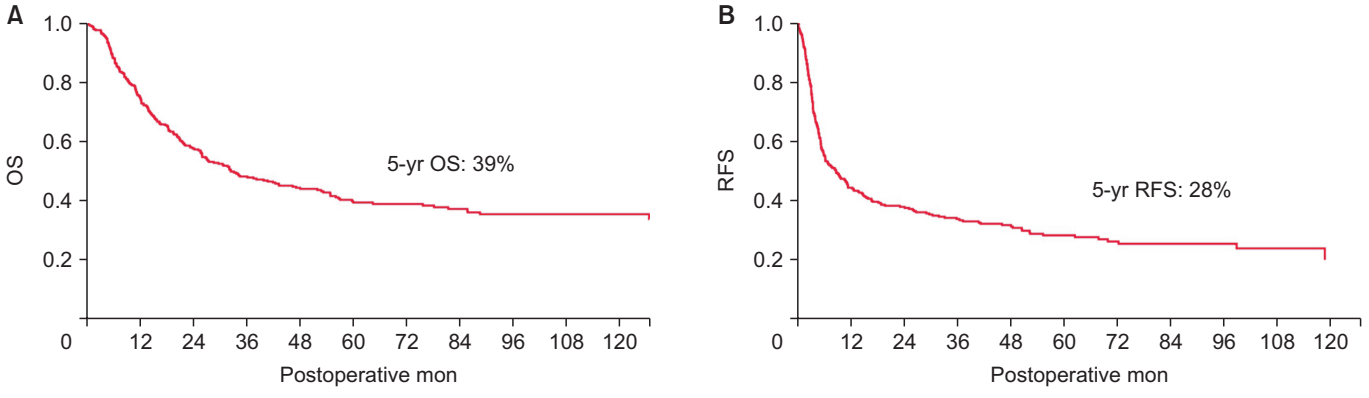

Fig. 1. OS and RFS curves of patients undergoing hepatic resection for hepatocellular carcinoma with portal vein tumor thrombosis. (A) OS curve. For the entire cohort of 332 patients, the 1-, 3-, and 5-year OS rates were 75%, 48%, and 39%, respectively. (B) The 1-, 3-, and 5-year RFS rates were 45%, 34%, and 28%, respectively. OS, overall survival; RFS, recurrence-free survival.

Table 2. Univariate analysis for prognostic factors associated with recurrence and survival

Variable	Recurrence		Survival	
	p-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)
Vp class (Vp1&2/3&4)	0.026	1.348 (1.037–1.751)	0.004	1.503 (1.135–1.989)
Multiple tumor	0.034	1.388 (1.025–1.879)	0.04	1.398 (1.016–1.924)
Tumor size ≥ 6.5 cm	0.001	1.559 (1.197–2.031)	< 0.001	1.75 (1.317–2.327)
PIVKA-II 400	0.001	1.624 (1.233–2.140)	0.011	1.464 (1.093–1.961)
AFP 200	0.025	1.353 (1.039–1.762)	0.099	1.265 (0.957–1.672)
Preoperative treatment (no treatment)	0.011	1.419 (1.082–1.860)	0.582	1.083 (0.816–1.438)
NLR > 3.5	< 0.001	1.64 (1.251–2.150)	0.001	1.646 (1.230–2.202)
ALBI grade	0.001	1.576 (1.208–2.055)	0.001	1.659 (1.247–2.209)
Resection margin (+)	0.001	1.894 (1.294–2.774)	< 0.001	2.035 (1.392–2.974)
Satellite nodule (+)	0.014	1.414 (1.072–1.863)	0.05	1.342 (1.000–1.800)
Microvascular invasion (+)	0.001	1.886 (1.307–2.720)	0.016	1.603 (1.092–2.353)

Vp, portal vein tumor thrombosis; PIVKA-II, preoperative proteins induced by vitamin K antagonist or absence II; AFP, alpha–fetoprotein; NLR, neutrophil–lymphocyte ratio; ALBI, albumin–bilirubin; CI, confidence interval.

ate-, and high-risk groups, respectively (Table 4). OS and RFS were compared using the Kaplan–Meier method and log-rank test. Fig. 2 depicts the OS and RFS of the three risk groups, and the differences between them were statistically significant. The 1-, 3-, and 5-year OS in the low-risk group was 88%, 63%, and 54%; in the intermediate-risk group, 71%, 42%, and 35%; and in the high-risk group, 50%, 20%, and 15%, respectively (log-rank $p < 0.05$, for all comparisons). Furthermore, the 1-, 3-, and 5-year RFS in the low-risk group was 60%, 48%, and 43%; in the intermediate-risk group, 40%, 28%, and 25%; and in the high-risk group, 11%, 6%, and 3%, respectively (log-rank $p < 0.05$, for all comparisons). In the low-, intermediate-, and high-risk groups, the expected median OS was 126.6, 27.4, and 11.8 months, respectively, while the expected median RFS was 30.3, 6.3, and 2.3 months, respectively.

Survival differences between the risk groups according to the grade of PVTT

Moreover, the survival differences between the risk groups were investigated in each PVTT grade subgroup. The Vp1/2 subgroup showed better OS and RFS than the Vp3/4 subgroup (Fig. 3A). Fig. 3B illustrates the OS and RFS of the three different risk groups of patients with Vp1/2. In the Vp1/2 group, both OS and RFS were significantly different between the risk groups (OS: low-risk vs. intermediate-risk, $p = 0.014$; intermediate-risk vs. high-risk, $p = 0.026$; low-risk vs. high-risk, $p < 0.001$; RFS: low-risk vs. intermediate-risk, $p = 0.005$; intermediate-risk vs. high-risk, $p = 0.002$; and low-risk vs. high-risk, $p < 0.001$). Significant differences in OS and RFS between the risk groups were also observed in the Vp3/4 group (Fig. 3C). The Vp3/4 group showed significant differences in OS between risk groups (low-risk vs. intermediate-risk, $p = 0.047$; intermediate-risk vs. high-risk, $p = 0.009$; low-risk vs. high-risk, $p < 0.001$). The RFS values in the low-risk and intermediate-risk groups were also significantly different from that in the high-risk group ($p < 0.001$), but the difference between the low-risk and intermediate-risk groups was not significant ($p = 0.165$).

Table 3. Multivariate analysis for prognostic factors associated with recurrence and survival

Variable	Recurrence		Early recurrence (< 6 mon)		Death		Early death (< 1 yr)	
	p-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)
Multiple tumor	0.002	1.677 (1.210–2.323)	0.011	1.668 (1.122–2.481)	0.008	1.582 (1.127–2.219)	0.230	1.370 (0.820–2.292)
Tumor size ≥ 6.5 cm	0.03	1.384 (1.031–1.857)	0.002	1.757 (1.224–2.522)	0.001	1.674 (1.239–2.263)	0.004	2.218 (1.273–3.558)
AFP > 200	0.261	1.181 (0.884–1.579)	0.005	1.65 (1.159–2.348)	0.535	1.102 (0.811–1.498)	0.046	1.62 (1.009–2.600)
PIVKA-II > 400	0.011	1.467 (1.093–1.970)	0.450	1.154 (0.796–1.675)	0.248	1.207 (0.877–1.661)	0.287	1.322 (0.791–2.209)
NLR > 3.5	0.001	1.671 (1.232–2.265)	0.001	1.88 (1.293–2.732)	0.022	1.462 (1.055–2.025)	0.022	1.799 (1.090–2.970)
ALBI grade	0.037	1.367 (1.019–1.832)	0.083	1.385 (0.958–2.002)	0.036	1.405 (1.023–1.931)	0.093	1.543 (0.930–2.561)

AFP, alpha–fetoprotein; PIVKA-II, preoperative proteins induced by vitamin K antagonist or absence II; NLR, neutrophil–lymphocyte ratio; ALBI, albumin–bilirubin; CI, confidence interval.

Table 4. Scoring system development

Factor	Point
Tumor number	
Solitary	0
Multiple	2
Tumor size	
< 6.5 cm	0
≥ 6.5 cm	3
AFP	
AFP ≤ 200	0
AFP > 200	1
PIVKA-II	
PIVKA-II ≤ 400	0
PIVKA-II > 400	1
NLR	
NLR ≤ 3.5	0
NLR > 3.5	3
ALBI grade	
Grade 1	0
Grade 2	1

Low-risk group: total score 0–4; intermediate-risk group: total score 5–8; high-risk group: total score 9–11.
AFP, alpha–fetoprotein; PIVKA-II, preoperative proteins induced by vitamin K antagonist or absence II; NLR, neutrophil–lymphocyte ratio; ALBI, albumin–bilirubin.

DISCUSSION

PVTT is common among patients with HCC, but is highly associated with poor prognosis. The most recent Barcelona Clinic Liver Cancer (BCLC) staging system strategy recommends systemic therapy based on atezolizumab plus bevacizumab as the first-line treatment for patients with HCC manifesting PVTT, who were classified as being in the advanced stage, and in recent clinical trials, expected to have a median survival rate of over 2 years, approximately [3]. However, in several recently published studies, surgical resection has been shown to have better survival outcomes in selected patients than in the non-liver resection group or other treatment modalities, including systemic therapy or TACE [6,14-17]. In the present study, the expected median OS and RFS after surgical resection for patients with HCC and PVTT was 32.4 and 8.6 months, respectively. The median follow-up period was 26.9 months, which seems a little short; however, it could be acceptable, because it is longer than the expected survival of 24 months with systemic treatment, which is targeted in the BCLC guideline. This result is comparable to the median survival of other studies, which is 8.9–33 months [18-22], and better than the results of recently updated systemic treatments, including the IMbrave150 clinical trial (19.2 months) [23], and the HIMALAYA clinical trial (16.4 months) [24]. In our study, tumor recurred after surgical resection in 68.1% of patients, with a median recurrence time of 6.2 months. Despite early recurrence after surgical resection, OS was considerably better than the results of primary systemic treatment for the heavy tumor burden reported by Hwang et al. [25]. This better result could be attributed to less aggressiveness by the absent or reduced tumor burden after complete removal of the advanced tumors. However, because of the retrospective analysis and heterogeneous characteristics of the patients, most previous studies, including our study, had a potential selection bias. Hence, most past studies have demonstrated the survival benefit of surgical treatment compared with nonsurgical treatment in only selected patients, while the suitability of surgical resection for such patients remains controversial [5,26,27]. Furthermore, definite criteria or recommendations for surgical resection in patients with HCC manifesting as PVTT are still unavailable.

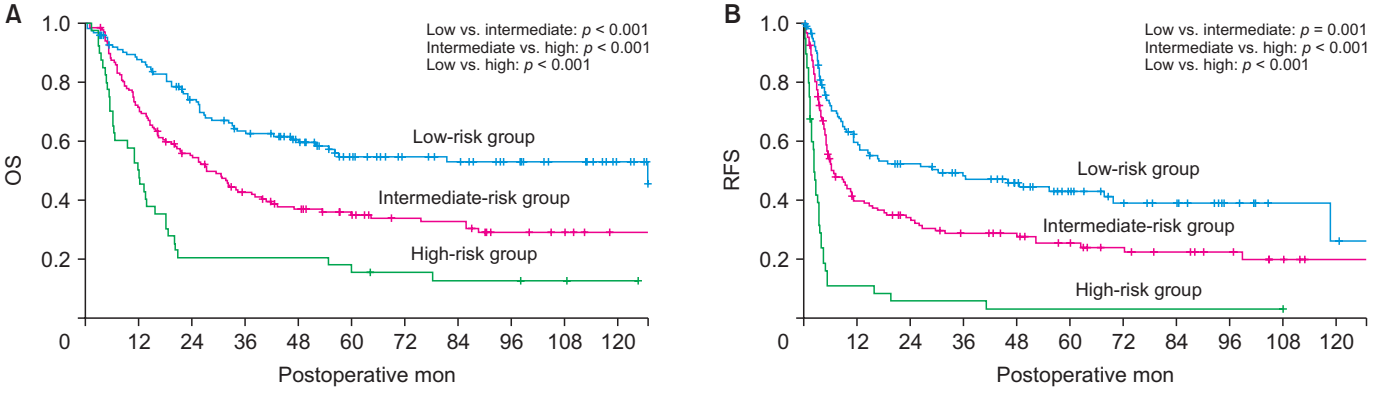

Fig. 2. RFS and OS curves of patients undergoing hepatic resection for hepatocellular carcinoma with portal vein tumor thrombosis according to the risk group by the TIF scoring system. (A) OS curve. The 1-, 3-, and 5-year OS in the low-risk group was 88%, 63%, and 54%; in the intermediate-risk group, 71%, 42%, and 35%; and in the high-risk group, 50%, 20%, and 15%, respectively (log-rank $p < 0.05$) for all comparisons. (B) RFS curve. The 1-, 3-, and 5-year RFS in the low-risk group was 60%, 48%, and 43%; in the intermediate-risk group, 40%, 28%, and 25%; and in the high-risk group, 11%, 6%, and 3%, respectively (log-rank $p < 0.05$, for all comparisons). OS, overall survival; RFS, recurrence-free survival.

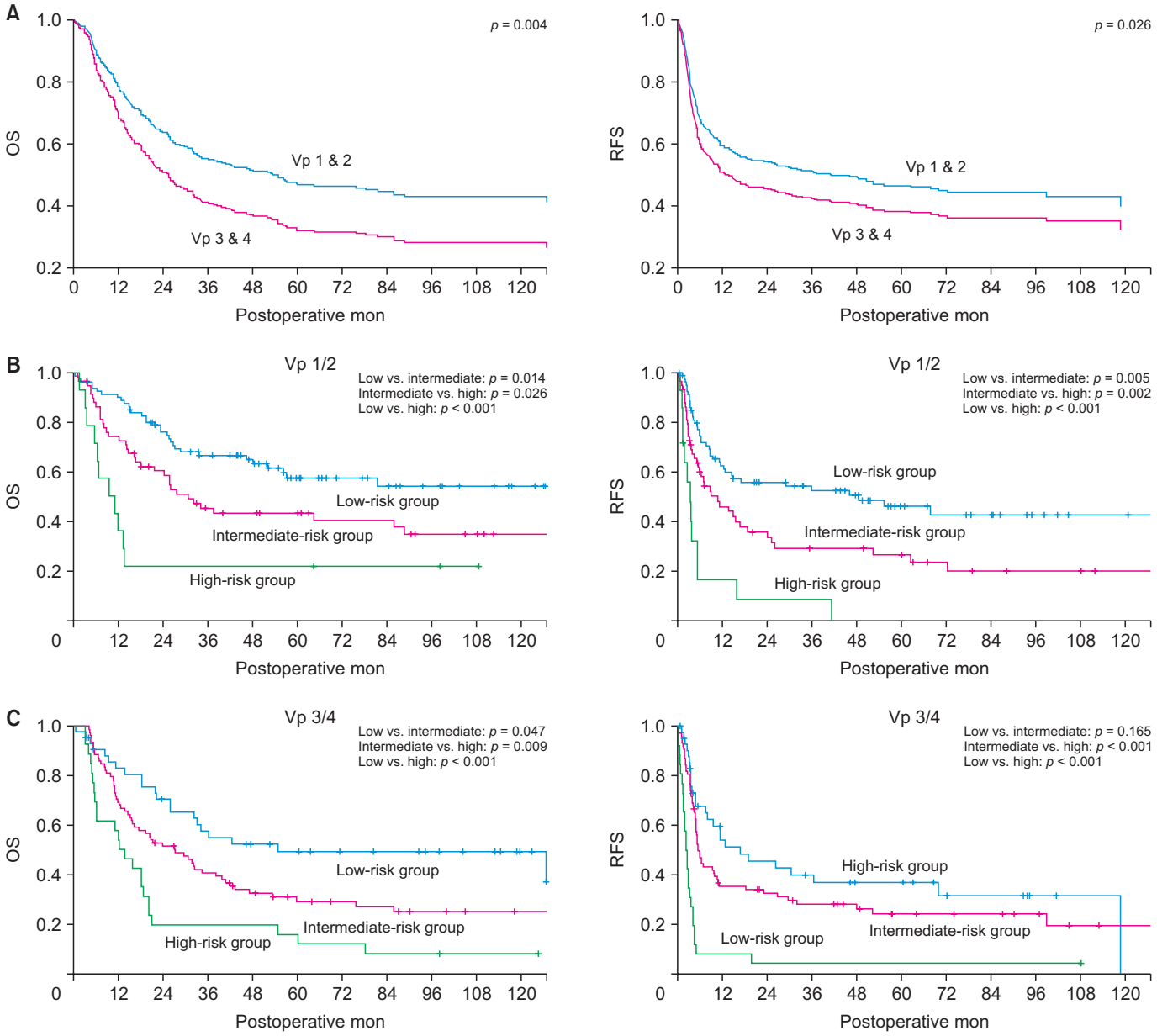

Fig. 3. Overall and RFSs of patients undergoing hepatic resection for hepatocellular carcinoma with portal vein tumor thrombosis at different grades according to the risk group by the TIF scoring system. (A) The Vp1/2 subgroup showed better OS and RFS than the Vp3/4 subgroup. (B) The OS and RFS of the three different risk groups of patients with Vp1/2. In the Vp1/2 group, both OS and RFS were significantly different between the risk groups. (C) Significant differences in OS and RFS between the risk groups in the Vp3/4 group. The Vp3/4 group showed significant differences in OS among the risk groups. The RFS values in the low-risk and intermediate-risk groups were also significantly different from that in the high-risk group ($p < 0.001$), but the difference in RFS between the low-risk and intermediate-risk groups was not significant ($p = 0.165$). OS, overall survival; RFS, recurrence-free survival; Vp, portal vein tumor thrombosis.

Meta-analyses by Liang et al. [28] and Zhang et al. [29] reported the difference in the survival outcomes of surgical treatment according to the PVTT grade, and indicated that surgical resection should be considered as a first-line treatment for patients with PVTT limited to the first-order branch or peripheral branches. In addition, Kokudo et al. [6] and Giannini et al. [30] demonstrated that surgical resection is associated with a longer OS than nonsurgical treatment. Our study also showed a better prognosis in patients with PVTT grades 1 and 2, than in those with grades 3 and 4. However, our multivariate analysis did not include the PVTT type as an independent risk factor for survival and recurrence. Therefore, the prognosis

after surgical resection might not be determined solely by the extent of PVTT; various factors that can influence prognosis should be considered when deciding the surgical treatment for patients with HCC experiencing PVTT.

Prediction of the post-treatment prognosis in these patients is difficult, given the extremely heterogeneous tumor extent and biology. In this study, we focused on identifying appropriate criteria for surgical resection in these patients. We revealed several factors that can impact prognosis after surgical resection in patients with HCC experiencing PVTT. The risk factors determined by the multivariate analysis differed slightly in surgical outcomes in terms of OS, early death, recurrence, and early recurrence. This difference is caused by the various treatment modalities and disease progression after recurrence. In our analysis, the scoring system was designed to predict surgical outcomes, and to suggest criteria for surgical resection in patients with HCC and PVTT. Our scoring system comprises various factors (tumor factors, biological factors, and hepatic functional factors) that can be easily determined preoperatively; thus, the overall prognosis can be predicted before surgery. Patients were categorized into three risk groups (of low, intermediate, and high), according to the sum of scores. The 1-, 3-, and 5-year OS rates in the low-risk group were 88%, 63%, and 54%; in the intermediate-risk group, 71%, 42%, and 35%; and in the high-risk group, 50%, 20%, and 15%, respectively ($p < 0.05$ for all comparisons). Therefore, the current scoring system can stratify the outcomes of patients undergoing surgical resection for HCC with PVTT. Previously, Ikai et al. [21] proposed a prognostic index that consisted of ascites, prothrombin activity, and maximal diameter for patients with HCC complicated with PVTT, which was then validated using a Japanese database by Hatano et al. [8]. However, that index was provided and validated only in patients with HCC with PVTT grades 3 and 4; it did not include those with PVTT grades 1 and 2. In comparison, our scoring system showed good stratification of the outcomes in grades 1 and 2, as well as grades 3 and 4 in the subgroup analysis, indicating that the current scoring system can be applied to all grades of PVTT.

In the current study, the expected median survival times in the low-, intermediate-, and high-risk groups were 126.6, 27.4, and 11.8 months, respectively. These results reveal that better survival after surgical resection could be expected in the low- and intermediate-risk groups, especially in the low-risk group, compared with the expected survival (over 2 years) presented in the BCLC strategy, and even better survival than updated systemic treatments, including the IMbrave150 clinical trial (19.2 months) [23], and the HIMALAYA clinical trial (16.4 months) [24]. Moreover, the perioperative mortality rate was 1.8%, which is within the acceptable range. Therefore, surgical resection should be considered as a first-line treatment for patients with HCC complicated by PVTT in the low- and intermediate-risk groups.

This large-scale multicenter study focused on the survival outcome after surgical resection, and the surgical indications for patients with HCC experiencing PVTT. However, this study has some limitations. First, these data were collected and analyzed retrospectively, implying the possibility of a selection bias in surgical indications. Second, this study was conducted in South Korea, and the etiology of HCC was mainly hepatitis B. However, the etiology of HCC was not considered a risk factor for poor prognosis, indicating the applicability of this result to other etiologies. Third, this study was not a comparative study; thus, prognosis after treatment could not be directly compared between the treatment modalities. Fourth, although we conducted a nationwide study that included large volume centers, we had only limited data for analysis and to develop the scoring system, because there were not enough patients who underwent surgical resection for HCC with PVTT. For this reason, we could not perform external validation to increase the reliability of this new scoring system.

In conclusion, surgical resection proved beneficial in patients with HCC complicated by PVTT, even in those with grades 3 and 4 PVTT. We proposed a scoring system that is composed of independent prognostic factors specifically for these patients, which showed good stratification between the risk groups. Thus, it can be helpful in determining the treatment strategy for these patients, regardless of the PVTT grade. However, this scoring system needs to be validated using a worldwide multicenter database.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y, et al. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a japanese nationwide survey. Cancer 2004;101:796-802.
2. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol 2006;12:7561-7567.
3. Reig M, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado Á, et al. Bclc strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681-693.
4. Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 2010;4:439-474.
5. Peng ZW, Guo RP, Zhang YJ, Lin XJ, Chen MS, Lau WY. Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. Cancer 2012;118:4725-4736.
6. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65:938-943.
7. Lee JM, Jang BK, Lee YJ, Choi WY, Choi SM, Chung WJ, et al. Survival outcomes of hepatic resection compared with transarterial chemoembolization or sorafenib for hepatocellular carcinoma with portal vein tumor thrombosis. Clin Mol Hepatol 2016;22:160-167.
8. Hatano E, Uemoto S, Yamaue H, Yamamoto M; Japanese Society of Hepato-Biliary-Pancreatic S. Significance of hepatic resection and adjuvant hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombus in the first branch of portal vein and the main portal trunk: a project study for hepatic surgery of the japanese society of hepato-biliary-pancreatic surgery. J Hepatobiliary Pancreat Sci 2018;25:395-402.
9. Zhang ZY, Dong KS, Zhang EL, Zhang LW, Chen XP, Dong HH. Resection might be a meaningful choice for hepatocellular carcinoma with portal vein thrombosis: a systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e18362.
10. Chok KS, Cheung TT, Chan SC, Poon RT, Fan ST, Lo CM. Surgical outcomes in hepatocellular carcinoma patients with portal vein tumor thrombosis. World J Surg 2014;38:490-496.
11. Kudo M, Kitano M, Sakurai T, Nishida N. General rules for the clinical and pathological study of primary liver cancer, nationwide follow-up survey and clinical practice guidelines: the outstanding achievements of the liver cancer study group of Japan. Dig Dis 2015;33:765-770.
12. Malik HZ, Prasad KR, Halazun KJ, Aldoori A, Al-Mukhtar A, Gomez D, et al. Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. Ann Surg 2007;246:806-814.
13. Halazun KJ, Najjar M, Abdelmessih RM, Samstein B, Griesemer AD, Guarrera JV, et al. Recurrence after liver transplantation for hepatocellular carcinoma: a new moral to the story. Ann Surg 2017;265:557-564.
14. Wei Z, Zhao J, Bi X, Zhang Y, Zhou J, Li Z, et al. Neoadjuvant radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a systematic review. Hepatobiliary Surg Nutr 2022;11:709-717.
15. Famularo S, Donadon M, Cipriani F, Giuliante F, Ferri S, Celsa C, et al. Hepatectomy versus sorafenib in advanced nonmetastatic hepatocellular carcinoma: a real-life multicentric weighted comparison. Ann Surg 2022;275:743-752.
16. Komatsu S, Ueshima K, Kido M, Kuramitsu K, Tsugawa D, Yanagimoto H, et al. Hepatectomy versus sorafenib for advanced hepatocellular carcinoma with macroscopic portal vein tumor thrombus: a bi-institutional propensity-matched cohort study. J Hepatobiliary Pancreat Sci 2023;30:303-314.
17. Tsilimigras DI, Bagante F, Moris D, Hyer JM, Sahara K, Paredes AZ, et al. Recurrence patterns and outcomes after resection of hepatocellular carcinoma within and beyond the barcelona clinic liver cancer criteria. Ann Surg Oncol 2020;27:2321-2331.
18. Konishi M, Ryu M, Kinoshita T, Inoue K. Surgical treatment of hepatocellular carcinoma with direct removal of the tumor thrombus in the main portal vein. Hepatogastroenterology 2001;48:1421-1424.
19. Pawlik TM, Poon RT, Abdalla EK, Ikai I, Nagorney DM, Belghiti J, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery 2005;137:403-410.
20. Kondo K, Chijiiwa K, Kai M, Otani K, Nagaike K, Ohuchida J, et al. Surgical strategy for hepatocellular carcinoma patients with portal vein tumor thrombus based on prognostic factors. J Gastrointest Surg 2009;13:1078-1083.
21. Ikai I, Hatano E, Hasegawa S, Fujii H, Taura K, Uyama N, et al. Prognostic index for patients with hepatocellular carcinoma combined with tumor thrombosis in the major portal vein. J Am Coll Surg 2006;202:431-438.
22. Le Treut YP, Hardwigsen J, Ananian P, Saïsse J, Grégoire E, Richa H, et al. Resection of hepatocellular carcinoma with tumor thrombus in the major vasculature. A European case-control series. J Gastrointest Surg 2006;10:855-862.
23. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022;76:862-873.
24. Abou-Alfa GK, Chan SL, Kudo M, Lau G, Kelley RK, Furuse J, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (PTS) with unresectable hepatocellular carcinoma (uHCC): Himalaya. JCO 2022;40:379.

25. Hwang S, Lee YJ, Kim KH, Ahn CS, Moon DB, Ha TY, et al. Long-term outcome after resection of huge hepatocellular carcinoma ≥ 10 cm: single-institution experience with 471 patients. World J Surg 2015;39:2519-2528.
26. Jiang JF, Lao YC, Yuan BH, Yin J, Liu X, Chen L, et al. Treatment of hepatocellular carcinoma with portal vein tumor thrombus: advances and challenges. Oncotarget 2017;8:33911-33921.
27. Wang HL, Cucchetti A, Zhong JH, Ye XP, Gu JH, Ma L, et al. Should hepatic resection be recommended to patients with hepatocellular carcinoma and portal vein invasion? J Hepatol 2016;65:1057-1058.
28. Liang L, Chen TH, Li C, Xing H, Han J, Wang MD, et al. A systematic review comparing outcomes of surgical resection and non-surgical treatments for patients with hepatocellular carcinoma and portal vein tumor thrombus. HPB (Oxford) 2018;20:1119-1129.
29. Zhang XP, Wang K, Li N, Zhong CQ, Wei XB, Cheng YQ, et al. Survival benefit of hepatic resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a systematic review and meta-analysis. BMC Cancer 2017;17:902.
30. Giannini EG, Bucci L, Garuti F, Brunacci M, Lenzi B, Valente M, et al. Patients with advanced hepatocellular carcinoma need a personalized management: a lesson from clinical practice. Hepatology 2018;67:1784-1796.