Intraoperative portal venous pressure and long-term outcome of curative resection for hepatocellular carcinoma

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Running head: Influence of portal pressure on hepatectomy for HCC

Abbreviations

HCC, hepatocellular carcinoma, ICG-R15, indocyanine green retention at 15 minutes

LHL 15, liver to heart uptake ratio at 15 minutes

PVP, portal venous pressure

Key words: hepatocellular carcinoma, liver resection, portal venous pressure

ABSTRACT

Background: Outcomes of liver resection for hepatocellular carcinoma (HCC) have improved due to better surgical techniques and patient selection. Portal hypertension may influence outcome but the preoperative definition and role of portal hypertension are far from clear. The aim of this study was to elucidate the influence of intraoperative directly measured portal venous pressure (PVP) on outcomes of liver resection in patients with HCC.

Methods: Patients who underwent resection of their HCC between 1997 and 2009 and who underwent direct measurement of PVP immediately after laparotomy were enrolled. These patients were divided into two groups according to PVP; PVP≥ 20 cmH_2O (high PVP group) or PVP < 20 cmH_2O (low PVP group). The influence of PVP on survival rates and recurrence free survival rates was analyzed and prognostic factors were identified.

Results: A total of 177 patients were enrolled, 129 in low PVP group and 48 in high PVP group. The 5-year survival rate and recurrence free survival rate were significantly higher in patients with low PVP 63.7% vs. 31.4%, (P < 0.001) and 52.5% vs. 12.1% (P < 0.001), respectively. In multivariate analysis, tumor number≥2, tumor diameter ≥5cm, high PVP, liver damage of class B, hepatic activity index (HAI) grading≥7 and AFP

≥100 ng/ml were significant predictors of poorer survival after liver resection. **T**umor number ≥2, tumor diameter ≥ 5cm and HAI grading ≥7 were significant predictors of a poorer recurrence.

Conclusion: Portal venous pressure is associated with the long term outcome of liver resection for HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide (1). Outcomes of liver resection for HCC have improved significantly in recent years because of improved surgical techniques and better perioperative management (2, 3). Adequate estimation of preoperative liver function and tailoring the extent of hepatectomy based on liver function have reduced postoperative mortality and morbidity rates (2-4).

The degree of portal hypertension probably reflects the severity of liver fibrosis in patients with liver cirrhosis (LC). Patients with LC often have portal hypertension preoperatively, and currently are not candidates for liver resection, especially major hepatectomy, according to USA and European guidelines (5, 6). Several reports have shown that the preoperatively estimated portal hypertension was associated with the prognosis of HCC (7, 8). Major hepatic resection increases portal venous pressure (PVP) in cirrhotic and non-cirrhotic livers, this increase in PVP after hepatectomy however does not seem to have a direct effect on early postoperative morbidity and mortality (10). On the other hand, directly measured high PVP during hepatectomy was associated with complications after hepatectomy in cirrhotic patients with HCC (11).

The aim of the present study was to clarify whether PVP reflects prognosis of

patients with HCC after hepatic resection and to identify factors affecting recurrence and survival.

METHODS

Patients

All patients with HCC, who underwent curative hepatic resection between January 1997 and December 2009 in the Department of Surgery, Nagasaki University Hospital and in whom PVP was measured were eligible for the study. Curative resection was defined as an operation in which all tumors were macroscopically resected during surgery. Hepatic resection was performed based on preoperative tumor staging and liver function tests. The selection for minor resection (partial hepatectomy or segmentectomy) or major resection (bisegmentectomy and lobectomy) was based on the location and diameter of HCC and liver function test (10). Tumor staging included preoperative ultrasonography (US), multidetector computed tomography (MDCT), and magnetic resonance imaging (MRI) in all patients. Preoperative liver function was assessed by liver function tests, indocyanine green retention for 15 minutes (ICG-R15), liver scintigraphy represented by liver to liver plus heart ratio at 15 minutes after 99mTc Galactosyl sialyl albumin (GSA) loading (LHL15) and Child-Pugh classification.

Patient data collected before surgery included age, sex, virus status, platelet count ($x10^4/mm^3$), prothrombin time (PT) (%), albumin (g/dL), total bilirubin (mg/dL), alanine aminotransferase(ALT) (IU/L), Child-Pugh class, liver damage defined by Liver Cancer Study Group of Japan (LCSGJ)(12), ICG R15 and LHL15.

Intra-operative PVP measurement was performed as described previously (10, 11). Briefly, a catheter was inserted into a jejunal mesenteric vein around 100cm to 120cm from Treitz's ligament before liver mobilization and resection. PVP was then measured using a water pressure gauge with saline. Patients with a history of upper abdominal surgery and mesenteric membrane adhesions were excluded because intubation could not be done easily after laparotomy. A high PVP was defined as pressure $\geq$ 20 cmH_2O (10, 11). Pressure over 15 mmHg was considered an indicator to avoid small for size graft syndrome after liver transplantation. Generally, A PVP of 15 mmHg was taken to be equal to 20 cmH_2O (conversion factor 1.36) (13). Patients were divided a high PVP group ($\geq$ 20.0 cm H_2O) and a low PVP group (< 20.0 cmH_2O) at the time of the operation. Liver dysfunction was defined as patients with hyper bilirubinemia, severe ascites, lower prothrombin time, and elevated sustained liver functional test after hepatectomy.

Postoperative follow up included serum alpha-fetoprotein (AFP) and serum

protein induced by vitamin K absence II (PIVKA-II) levels, and US, CT or MRI every 2 or 3 months. If indicated, chest CT or bone scintigraphy were performed. If tumor recurrence was found, the optimal treatment (transarterial chemoembolization for intrahepatic multiple recurrence, radio frequency ablation for single small recurrence, repeat hepatectomy for single intrahepatic recurrence) was selected for patients with preserved liver function.

Analyses and Statistics

Preoperative clinical data in the high PVP and low PVP groups were compared including age, sex, virus status, Child-Pugh classification, liver damages, ICG R15, LHL15, platelet count ($x10^4/mm^3$), prothrombin time (%), serum albumin (g/dL), total bilirubin (mg/dL), alanine aminotransferase (IU/L), AFP (ng/ml), PIVKA-II (mAU/ml) and pathological data including tumor number and diameter, vascular invasion, liver inflammation and fibrosis using the hepatic activity index (HAI) (14). Clinical and pathological factors related to the presence of high PVP were compared by Mann-Whitney U test and Chi square test. Survival was analyzed from day of surgery to most recent follow-up. Recurrence after surgery was determined by the image study. Survival and recurrence free survival rates between high PVP and low PVP were

assessed with the Kaplan-Meier method using the log-rank test. To clarify the prognostic factors for survival and recurrence, 14 clinical and pathological variables were determined. Factors on liver function included platelet count, Child-Pugh classification, liver damage, ICG R15. Tumor factors included AFP level, PIVKAII levels, maximum tumor size, number of tumor, type of resection, vascular invasion, HAI grading and staging. Univariate and multivariable analyses of prognostic factors were performed using the Cox proportional hazard model. Differences were considered statistically significant when the p-values were < 0.05. Statistical analyses were done using SPSS Version 18.0 software package (Tokyo, Japan).

RESULTS

Patient characteristics and differences between high and low PVP

Eighty-three percent of patients were male, and median age was 65 (20–81). Forty-seven patients (26.6%) were seropositive for hepatitis B antigen (HBs-Ag), three (1.7%) were seropositive HBs-Ag and hepatitis C antibody (HCV-Ab), 84 (47.4%) were seropositive for HCV and 43 (24.3%) were seronegative for both HBs-Ag and HCV-Ab.

There were 48 patients with high PVP and 129 patients with low PVP. The characteristics of patients with high PVP and low PVP, which was assessed along with

the parameters related to the PVP, are described in Table 1. Patients with a high PVP had a lower platelet count, a lower PT, lower albumin, higher ALT, higher CP class, higher liver damage class, higher ICG R15, lower LHL15, higher AFP level, and less frequent solitary tumors, resulting in fewer major hepatectomies, and a higher hepatic activity index (HAI) grading and staging. Eighteen patients had less than $10x10^4/mm^3$ platelets in the high PVP group (27.1%) and 13 (10%) in the low PVP group. Twenty patients (41.6%) in the high PVP group developed complications after hepatectomy, including ascites in 8 (16.6%), pleural effusion in 8 (16.6%), and infectious disease in 8 (16.6%) patients. Fifty-four patients (41.9%) with low PVP developed complications, with ascites in 18 (13.9%), pleural effusion in 23 (17.8%), and infectious disease in 9 (7%) respectively. There were no differences in postoperative incidence of the pleural effusion, ascites, and infection between the high and low PVP groups. However, patients with a high PVP had significantly more often liver dysfunction (n=7) compared to the low PVP group (n=2, p=0.01).

Patient survival and recurrence free survival

Median follow-up of all patients was 39.2 months (1.1-207). Five patients died due to liver failure and sepsis with multi-organ failure after hepatectomy. Recurrence

after resection developed in 37 patients (77.0%) in the high PVP group, and in 93 patients (72.1%) in the low PVP group. The one, 3- and 5-year survival rates of the low PVP group (n=129) were 92.0%, 78.2% and 63.7%, respectively. This was significantly better than the corresponding 72.9%, 48.5% and 31.4% survival rates in the high PVP group (n=48) ($p < 0.001$) Figure 1. The 1-year, 3-year and 5-year recurrence free survival rates of the low PVP group were 73.9%, 61.0% and 52.5%, respectively. This again was significantly better than the corresponding 47.7%, 27.0% and 12.1%, respectively in the high PVP group ($p < 0.001$) Figure 2.

Prognostic factors for survival and recurrence free survival

Univariate analysis identified 7 significant prognostic factors for survival in patients with high PVP. The presence of multiple tumors, tumor diameter≥ 5cm, high PVP, liver damage class B, HAI grading≥ 7, AFP ≥100 ng/ml, and vascular invasion were significant prognostic factors for poorer survival (Table 2).

A multivariable analysis was performed for survival based on the variables identified as significant in the univariate analysis. Presence of multiple tumors, tumor diameter ≥ 5cm, high PVP, liver damage, and a HAI grading≥ 7 were identified as independent prognostic indicators for survival.

Table 3 shows the results of the univariate analysis to identify factors related to recurrence. Poor prognostic factors were the presence of multiple tumors, tumor diameter ≥ 5cm, an HAI grading ≥ 7, high PVP, vascular invasion, and AFP ≥ 100ng/ml. The presence of multiple tumors, tumor diameter ≥ 5cm, and an HAI grading ≥ 7 were identified as significant prognostic indicators for recurrence based in the multivariable analysis.

DISCUSSION

Portal hypertension is considered to be a contraindication for liver resection according the EASL/AASLD guidelines (5, 6). However, in recent years liver resection for cirrhotic patients has been performed safely. According to these guideline, treatment for such patients with HCC should be local therapy, such as radio frequency ablation (RFA) or transarterial chemoembolization (TACE). Bruix et al. reported that a hepatic venous pressure gradient ≥10 mmHg was the most powerful predictor of postoperative liver failure in cirrhotic patients (7). Caupussoti et al. observed that survival was worse in patients with portal hypertension than in patients without portal hypertension, although the results were similar for patients with or without portal hypertension if only patients with Child-Pugh A disease were evaluated (9). On the other hand, Imamura et

al. analyzed 1056 consecutive liver resections (532 for HCC, 262 for other liver malignancies, 57 for biliary tract malignancy, 174 living donor and 31 for other disease) that did not result in mortality over a period of 8 years. They concluded that portal hypertension and liver cirrhosis did not affect overall postoperative complications in patients with HCC, and identified blood loss greater than or equal to 1000 mL as the major risk factor (3).

Cucchetti et al. performed a retrospective one-to-one matched analysis of 241 cirrhotic patients divided in 2 groups according to the presence or absence of portal hypertension. They identified the preoperative MELD score as the major determinant of postoperative outcome. Portal hypertension in this analysis did not affect postoperative complication rates in patients with HCC (15).

The present study demonstrated that a high PVP is related to of liver inflammation and fibrosis as evidenced by the incidence of lower platelets, PT, albumin, a higher Child Pugh score, HAI grading and staging. Partial hepatectomies or segmentectomies, i.e. limited hepatic resections of the liver, were deemed appropriate more often for patients with a high PVP **as** patients with a PVP $\geq$ 20 cm H_2O **are** more likely to develop hyperbilirubinemia after hepatectomy (11). Limited resections for patients with liver cirrhosis proved to be an effective treatment for HCC to avoid liver

dysfunction and mortality after hepatectomy in the author's unit (16).

HCC in patients with severe cirrhosis can arise anywhere in the cirrhotic liver as multicentric occurrence carcinogenesis. Minute and 'undetectable' HCC may be found in explant livers in patients with severe cirrhosis at liver transplantation (17). The differences between the present data and those of other reports may have resulted from the cut-off values of PVP that were used in the different studies. The BCLC group labeled patients as having hypertension based on the presence of esophageal varices, splenomegaly and a platelet count < 100,000/mm^3. This differs markedly from the direct measurement of portal vein pressure during surgery (7). Figueras reported that portal vein pressure at the beginning of surgery, hepatic venous pressure gradient (HVPG), high central venous pressure (CVP), and intraoperative blood loss were factors associated with complications after liver resection (18). In the current authors' indication CVP before liver resection was usually 5 mmHg, and it was assumed that a PVP of 20cmH_2O before liver resection would be equivalent to a PVP of 15mmHg and an HVPG of 10mmHg (HVPG = PVP – CVP). However detailed data concerning the CVP at the start of surgery in this study were not available.

Capussotti et al. showed that the presence of portal hypertension in patients with Child Pugh-A did not affect overall survival (9). Ripoll et al. showed that portal

hypertension, assessed via a hepatic venous pressure gradient, was an independent predictor of survival of patients (8). The present data support these results indicating that overall survival and recurrence free survival rates after hepatectomy were worse in patients with high PVP (assessed by direct portal venous pressure) > 20 cm H_2O. In this study, overall survival was lower in patients with high PVP because of their worse liver function. A high PVP may reflect inflammation and fibrosis in the liver, and may be associated with liver dysfunction because HAI grading of the background liver and staging was worse in the high PVP group than in the low PVP group. A multivariable analysis for recurrence revealed that the presence of multiple and huge tumors, and inflammation in the remnant liver, were associated with earlier recurrence of HCC after hepatectomy even after curative resection. Indeed high PVP was not associated with recurrence although RFS in high PVP group was significantly inferior to that in the low PVP group. High PVP was the fourth harvest associated with recurrence followed by high HAI Grading. High PVP may have the potential inflammation in the remnant liver and reflect the impaired liver function which caused to the potential multi-centric carcinogenesis in the liver.

HPVG measurement allows selection of patients pre-operatively and therefore, this may be more appropriate in the future.

Author Contributions

Study conception and design: Hidaka, Eguchi

Acquisition of data: Tanaka, Muraoka, Hara

Analysis and interpretation of data: Takatsuki, Soyama, Kuroki

Drafting of manuscript: Hidaka, Eguchi, Kanematsu

Critical revision: Kanematsu, Eguchi

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Figure legends

Figure 1. Comparison of survival in patients with an HCC and high PVP or low PVP after hepatectomy ($p < 0.001$). PVP, portal venous pressure

Figure 2. Comparison of the recurrence free survival in patients with an HCC and high PVP or low PVP after hepatectomy ($p < 0.001$). PVP, portal venous pressure

Table 1. Clinical characteristics of patients with high or low PVP under going hepatectomy for HCC

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; HAI, hepatic activity index; ICG R15, indocyanine green retention test at 15 minutes; LHL, liver to liver plus heart uptake ratio at 15 minutes; PIVKA II, protein induced by vitamin K absence II.

Table 2. Results of univariate and multivariable analyses of prognostic factors regarding survival after hepatectomy

AFP, alpha-fetoprotein; ICG R15, indocyanine green retention test at 15 minutes; LHL, liver to liver plus heart uptake ratio at 15 minutes; PIVKA II, protein induced by vitamin K absence II; PVP, portal venous pressure.

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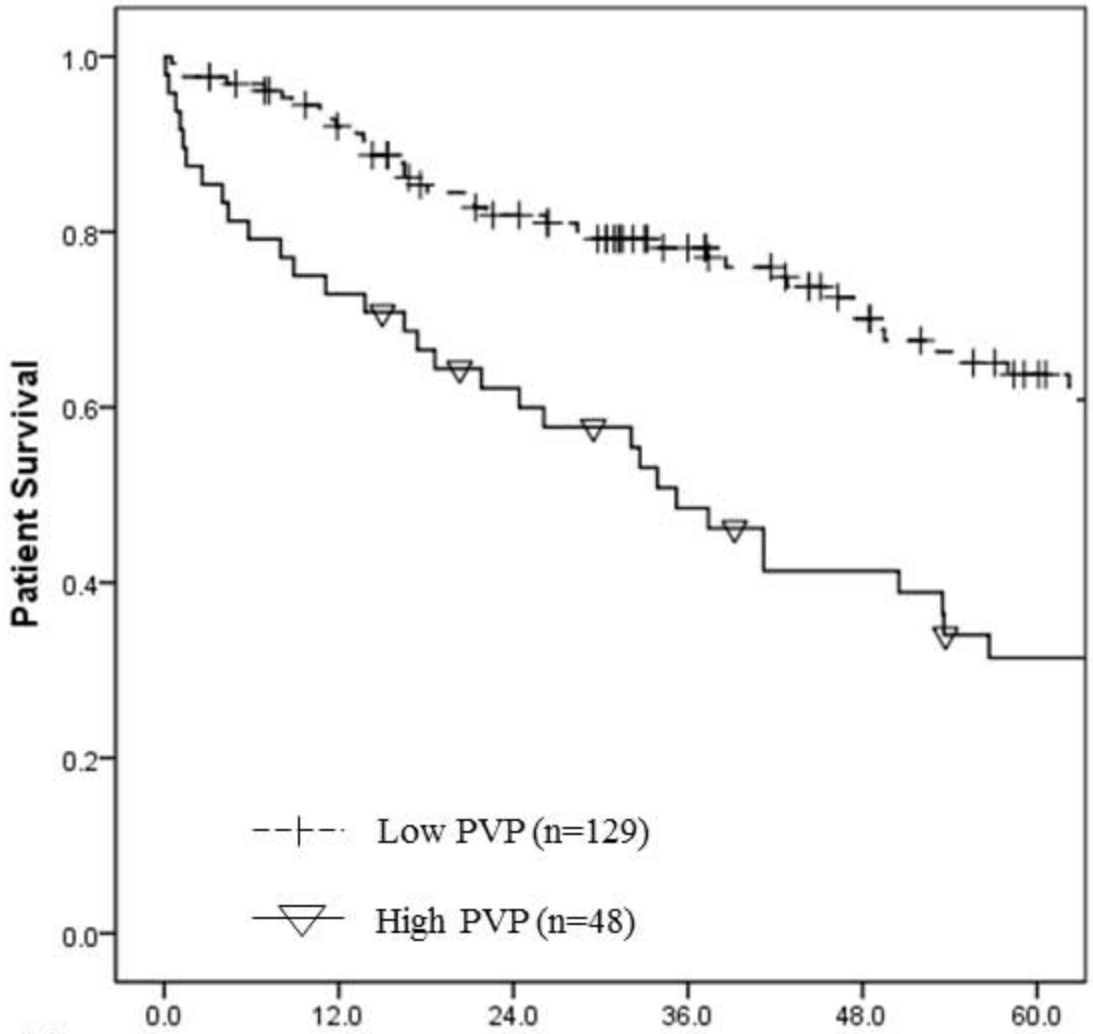

No. at risk

Low PVP	129	112	93	74	58	46
High PVP	48	35	28	21	17	12

Figure 1. Comparison of survival **in** patients **with an HCC** and high PVP **or** low PVP after hepatectomy ($p < 0.001$).

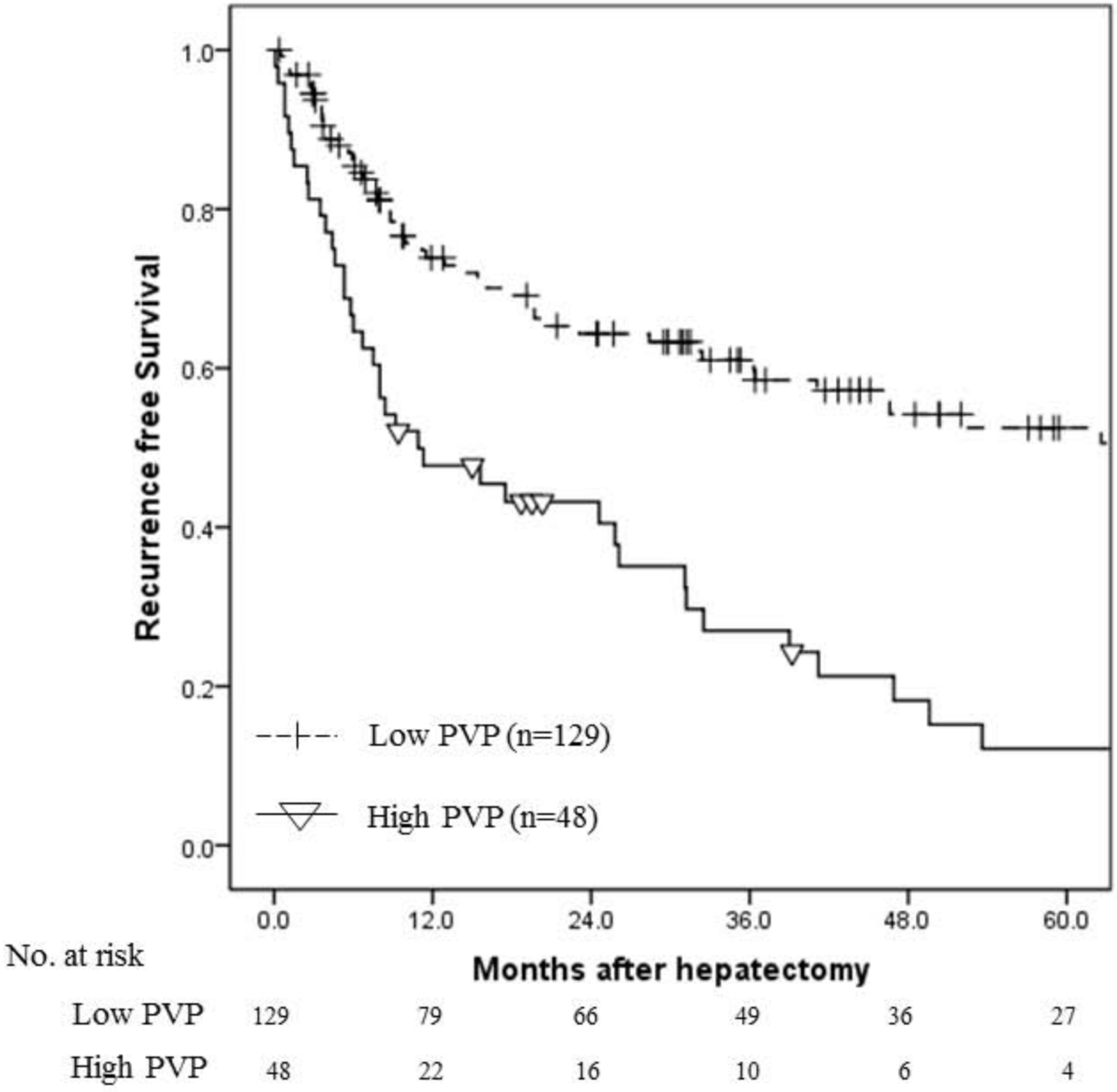

Figure 2. Comparison of the recurrence free survival in patients with **an HCC** and high PVP **or** low PVP after hepatectomy ($p < 0.001$).

Variables	High PVP ($\geq$ 20cmH_2O) (n = 48)	Low PVP (< 20 cmH_2O) (n = 129)	p-value
Ages (years)	63 (43 - 78)	66 (20 - 81)	0.162
Sex (M : F)	40 : 8	107 : 22	0.856
Etiology			0.347
Hepatitis B	14 (29.2%)	33 (25.6%)	
Hepatitis C	26 (54.2%)	58 (45.0%)	
Hepatitis B + C	1 (2.0%)	2 (1.5%)	
Negative	7 (14.6%)	36 (27.9%)	
Platelet count (x10^4/mm^3)	11.8 (4.1 - 35.6)	15.9 (2.6 - 47)	0.001
Prothrombin time (%)	83.7 (63 - 105)	91 (54 - 122)	0.002
Albumin (g/dl)	3.8 (2.5 - 4.7)	4.0 (2.8 - 4.8)	0.001
Total bilirubin (mg/dl)	0.9 (0.4 - 4.8)	0.7 (0.3 - 2.4)	0.06
ALT (IU/L)	55.5 (18 - 190)	34.5 (7 - 222)	0.002
Child Pugh classification			0.004
Class A	38 (79.2%)	122 (94.6%)	
Class B	10 (20.8%)	7 (5.4%)	
Liver damage			0.001
Class A	30 (62.5%)	109 (76.8%)	
Class B	18 (37.5%)	17 (13.2%)	
ICG R15 (%)	18 (3 - 39)	11 (1 - 40)	0.004
LHL15	0.89 (0.77 - 0.96)	0.93 (0.61 - 0.97)	0.001
AFP (ng/ml)	47.5 (4.2 - 454,300)	13.1 (1.2 - 151,367)	0.03
PIVKAII (mAU/ml)	73 (21 - 10,173)	133 (2 - 60,380)	0.52
Tumor diameter (cm)	2.9 (1.0 - 13.0)	4.0 (0.5 - 17.0)	0.08
Solitary tumor	29 (59.1%)	101 (78.3%)	0.01
Type of hepatectomy			
Minor hepatectomy	41 (85.4%)	76 (58.9%)	0.001
Major hepatectomy	7 (14.6%)	53 (31.1%)	
Vascular invasion	10 (26.3%)	40 (31.9%)	0.207
HAI			
Grading	9.1 (3 - 13)	4.8 (1 - 13)	0.001
Staging	3.8 (2 - 4)	2.1 (0 - 4)	0.001

Table 1. Clinical characteristics of patients with high or low PVP under going hepatectomy for HCC

		Univariate analysis			Multivariable analysis		
Variables	Category	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Tumor number	≥ 2	3.15	2.02 - 4.90	<0.001	2.52	1.58 - 4.02	<0.001
Tumor diameter (cm)	≥ 5	1.67	1.09 - 2.54	0.018	2.22	1.41 - 3.50	0.001
PVP	≥ 20cmH_2O	2.44	1.60 - 3.60	<0.001	1.74	1.24 - 3.03	0.004
Liver damage	B	1.91	1.19 - 3.07	0.007	1.74	1.07 - 2.82	0.026
HAI Grading	≥ 7	2.14	1.42 - 3.25	<0.001	1.65	1.04 - 2.63	0.034
AFP (ng/ml)	≥ 100	1.69	1.11 - 2.57	0.013			0.354
Vascular invasion	+	1.68	1.08 - 2.61	0.02			0.521
Platelet count (x10^4/mm^3)	≤ 10	0.99	0.60 - 1.63	0.985			
ICG R15 (%)	≥ 15	1.21	0.81 - 1.80	0.354			
LHL 15	≤ 0.9	0.6	0.34 - 1.07	0.79			
PIVKA II	≥ 100	0.85	0.53 - 1.37	0.515			
Child Pugh	B	1.49	0.83 - 2.70	0.177			
Partial hepatectomy	+	1.17	0.77 - 1.76	0.465			
HAI Staging	4	1.31	0.84 - 2.03	0.24			

Table 2. Results of univariate and multivariable analyses of prognostic factors regarding survival after hepatectomy

AFP, alpha-fetoprotein; HAI, hepatic activity index; ICG R15, indocyanine green retention test at 15 minutes; LHL, liver to liver plus heart uptake ratio at 15 minutes; PIVKA II, protein induced by vitamin K absence II; PVP, portal venous pressure.

		Univariate analysis			Multivariable analysis		
Variables	Category	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Tumor number	≥ 2	2.49	1.68 - 3.69	<0.001	2.3	1.49 - 3.54	<0.001
Tumor diameter (cm)	≥ 5	1.86	1.27 - 2.72	0.001	2.19	1.39 - 3.17	<0.001
HAI Grading	≥ 7	1.77	1.21 - 2.57	0.003	1.72	1.16 - 2.56	0.007
PVP	≥ 20cmH_2O	1.65	1.10 - 2.48	0.014			0.328
Vascular invasion	+	1.65	1.10 - 2.48	0.015			0.479
AFP (ng/ml)	≥ 100	1.49	1.01 - 2.23	0.047			0.189
Platelet count (x10^4/mm^3)	≤ 10	1.04	0.66 - 1.65	0.854			
ICG R15 (%)	≥ 15	1.3	0.94 - 1.96	0.1			
LHL 15	≤ 0.9	0.74	0.48 - 1.17	0.195			
PIVKA II	≥ 100	1.39	0.95 - 2.03	0.085			

Child Pugh	B	1.09	0.60 - 1.98	0.775
Liver damage	B	1.36	0.87 - 2.13	0.167
Partial hepatectomy	+	1.08	0.74 - 1.57	0.704
HAI Staging	4	1.01	0.66 - 1.55	0.957

Table 3. Results of the univariate and multivariable analyses of prognostic factors regarding recurrence after hepatectomy

AFP, alpha-fetoprotein; HAI, hepatic activity index; ICG R15, indocyanine green retention test at 15 minutes; LHL, liver to liver plus heart uptake ratio at 15 minutes; PIVKA II, protein induced by vitamin K absence II; PVP, portal venous pressure.