Original Article

Impact of splenomegaly and splenectomy on prognosis in hepatocellular carcinoma with portal vein tumor thrombus treated with hepatectomy

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Background: Hepatocellular carcinoma (HCC) commonly occurs in patients with splenomegaly. This study aimed to investigate the impact of splenomegaly with or without splenectomy on long-term survival of HCC patients with portal vein tumor thrombus (PVTT) treated with liver resection (LR).

Methods: HCC patients with PVTT who underwent LR from 2005 to 2012 from 6 hospitals were retrospectively studied. The long-term overall survival (OS) and recurrence-free survival (RFS) were compared between patients with or without splenomegaly, and between patients who did or did not undergo splenectomy for splenomegaly. Propensity score matching (PSM) analysis was performed to match patients in a 1:1 ratio.

Results: Of 716 HCC patients with PVTT who underwent LR, 140 patients had splenomegaly (SM group) and 576 patients had no splenomegaly (non-SM group). The SM group was further subdivided into 49 patients who underwent splenectomy (SPT group), and 91 patients who did not received splenectomy (non-SPT group). PSM matched 140 patients in the SM group, and 49 patients in the SPT group. Splenomegaly was an independent risk factor of poor RFS and OS. The OS and RFS rates were significantly better for patients in the non-SM group than the SM group (OS: P<0.001; RFS: P<0.001), and for patients in the SPT group than the non-SPT group (OS: P<0.001; RFS: P<0.001).

Conclusions: Patients who had splenomegaly had significantly worse survival in HCC patients with PVTT. Splenectomy for splenomegaly significantly improved long-term survival in these patients.

Keywords: Hepatocellular carcinoma (HCC); portal vein tumor thrombus (PVTT); splenomegaly; splenectomy

Submitted Mar 06, 2020. Accepted for publication Oct 16, 2020.

doi: 10.21037/atm-20-2229

View this article at: http://dx.doi.org/10.21037/atm-20-2229

Introduction

Worldwide, hepatocellular carcinoma (HCC) is one of the most common cancers and the third leading cause of cancer-related death (1). In excess of 80% of HCC occur in Africa and Asia due to the prevalence of hepatitis B virus (HBV) infection in these regions. Portal vein tumor thrombus (PVTT) occurs in 44% to 62% of HCC patients and, without treatment, the median survival time (MST) is dismal, ranging from 2.7 to 4.0 months (2,3). Because PVTT complicating HCC often indicates more aggressive disease, reduced liver function, and elevated recurrence rates following treatment, it is considered a strong negative prognostic risk factor.

The best treatment strategy for HCC patients with PVTT remains controversial. HCC with PVTT is considered an advanced stage disease by the Barcelona Clinic Liver Cancer (BCLC) Staging System, and the American Association for the Study of Liver Diseases (AASLD). In most HCC staging classifications, sorafenib is considered the standard of care (4,5). However, the MST of HCC patients with advanced stage disease treated with sorafenib is only approximately 6.5 months (6-8). Recently, increasing evidence has shown R0 liver resection (LR) can yield better survival compared to nonoperative treatments, especially for patients whose PVTT involves first or second order portal vein branches (2,3,9).

Patients with HCC commonly have portal hypertension and splenomegaly with associated hypersplenism (defined as pathologic spleen) (10). A pathologic spleen in a patient with HCC was once considered a contraindication to hepatectomy (11-13) due to increased surgical risks and poor long-term survival. Splenectomy for patients with pathologic spleen is recommended by the AASLD (14) as it can improve liver fibrosis, restore immune function, improve low platelet and white blood cell counts and reduce portal venous pressure (10,15,16). Synchronous splenectomy and hepatectomy has been reported to improve survival in patients with HCC and cirrhotic hypersplenism (17-19). Because a high splenic volume (a measure of splenomegaly/pathologic spleen) is a predictor of poor survival in HCC patients, Takeishi *et al.* found that combined splenectomy and hepatectomy in such patients should be the appropriate treatment (20). Similarly, the PVTT in HCC patients may obstruct blood flow through the portal venous system, inducing portal hypertension and pathologic spleen, with consequent negative impact on survival. However, the specific influence of pathologic spleen in HCC patients with PVTT and the impact of splenectomy remain unclear.

The aim of this study was to investigate the long-term survival of surgically treated patients with HCC and PVTT, and to compare long-term survival when treated either with or without splenectomy in the subset of these patients having a pathologic spleen.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-2229).

Methods

Patients

The study comprised 716 consecutively accrued HCC patients with PVTT, who underwent LR from 2005 to 2012 in 6 hospitals. Clinicopathologic, demographic, and pathology data were recorded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committees of the Eastern Hepatobiliary Surgery Hospital. (NO.: EHBHKY-2015-01-028) and informed consent was taken from all the patients.

The diagnostic criteria to verify PVTT included both imaging examinations [ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI)], and intraoperative and postoperative histopathology. Based on the classification proposed by Cheng to describe the specific site of portal vein involvement (21), the categories are I, segmental/sectoral branches of the portal vein; II, left or right portal vein; III, main portal vein (MPV); and IV, thrombus in MPV extending to involve the superior mesenteric vein.

Inclusion and exclusion criteria

The inclusion criteria were (I) resectable HCC; (II) verification of PVTT; (III) patients with PVTT that was limited to Cheng type I and II PVTT; (IV) absence of macroscopic hepatic vein tumor thrombus, macroscopic bile duct tumor, local extrahepatic spread or distant metastases; (V) no other associated malignancies. Exclusion criteria included (I) liver function of Child-Pugh class C; (II) operative contraindications to splenectomy; or (III) incomplete data. HCC patients with PVTT were divided into two groups according to whether they had splenomegaly. Those patients who had splenomegaly were further subdivided into two subgroups according to whether they had undergone splenectomy prior to hepatectomy.

Diagnosis of splenomegaly and the criteria of splenectomy

Splenomegaly was diagnosed by physical examination and imaging studies. Splenomegaly with hypersplenism was defined as a pathological spleen. Patients underwent splenectomy on the basis of the following criteria: splenomegaly with hypersplenism classified as greater than class I (spleen enlarged beyond left subcostal margin and palpable); hypersplenism with a concurrent white blood cell count (WBC) count of less than 3.0×10^9/L and PLT count less than 80×10^9/L (18); or splenomegaly of grade 1 or greater with a WBC count of less than 2.0×10^9/L or a PLT count below 50×10^9/L (22).

Follow-up

All patients were followed every 2 to 3 months until death or if they drop out of the follow-up program. Specifically included was the thickness of the splenic hilum (which reflects the extent of splenomegaly) as defined by CT or MRI, measured in the central part of the hilum, perpendicular to the long axis of the spleen (23). When tumor recurrence was diagnosed, patients were treated with percutaneous ethanol injection, radiofrequency ablation, transhepatic arterial chem therapy and embolization, or LR, depending on the general condition of the patient, the functional liver reserve, and the pattern of tumor recurrence.

Statistical analysis

Continuous data was reported as medians with interquartile range (IQR) and were compared using the Mann-Whitney test. Normally distributed variables was reported as mean and standard deviation and were compared using the Student's t test. Categorical variables was presented as numbers or frequencies (%), and were compared using the Chi-square test or the Fisher's exact test. Survival curves were generated using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analyses were analyzed using the Cox proportional hazards stepwise model. Factors with statistical significance on univariate analysis were incorporated into multivariate analysis. Propensity score matching (PSM) was used in this study as there was heterogeneity in the study populations between the splenomegaly group (SM) and the non-splenomegaly group (non-SM) and between the splenectomy group (SPT) and the non- splenectomy group (non-SPT). Patients in the SM and non-SM groups were matched to the non-SM group using a matching ratio of 1:1, with the closest estimated propensity score (PS) within 0.1 of the standard deviation of the logit of PS. Patients in the SPT and non-SPT groups were similarly matched. A P value <0.05 was considered statistically significant. Following completion of PSM, univariate, multivariate logistic regression and Kaplan-Meier analyses were performed. The data analyses were performed using the SPSS software version 22.0 (Chicago IL, USA).

Results

Patient characteristics

The flowchart in *Figure 1* shows the selection details of the 716 HCC patients with PVTT enrolled in this study. The baseline characteristics of the patients in the SM and non-SM groups are shown in *Table 1*, and the patients in the SPT and non-SPT groups are shown in *Table 2*. After PSM, these clinicopathological features were well-balanced (Tables S1,S2).

Risk factors of poor recurrence-free survival (RFS) and overall survival (OS) for patients in the SM and non-SM groups

Univariate and multivariate analyses before PSM demonstrated that incomplete tumor encapsulation (P<0.001), aspartate aminotransferase level (AST, P<0.001), and thickness of splenic hilum (P=0.006) were independent risk factors of poor RFS (*Table 3*). Furthermore, α-fetoprotein level (P<0.001), carcinoembryonic antigen level (CEA, P<0.001) incomplete tumor encapsulation (P<0.001) and thickness of splenic hilum (P=0.004) were independent risk factors of poor OS (*Table 4*). In contrast, sex, age, HBV infection, hepatitis C virus infection, gastroesophageal varices, cirrhosis, histopathological grading, carcinoembryonic antigen (CEA), carbohydrate Atigen 19-9 (CA199), prothrombin time (PT), α-fetoprotein (AFP), alanine aminotransferase (ALT), total bilirubin (TBIL), albumin (ALB), tumor diameter, number of tumors, PVTT, and BCLC staging were not significant factors influencing RFS or OS.

Survival Analysis of patients in the SM and non-SM groups

Before PSM, the median RFS (MRFS 95% CI) was 6.5 (6.3–7.8) months for the non-SM group, and 4.3 (3.8–5.3) months

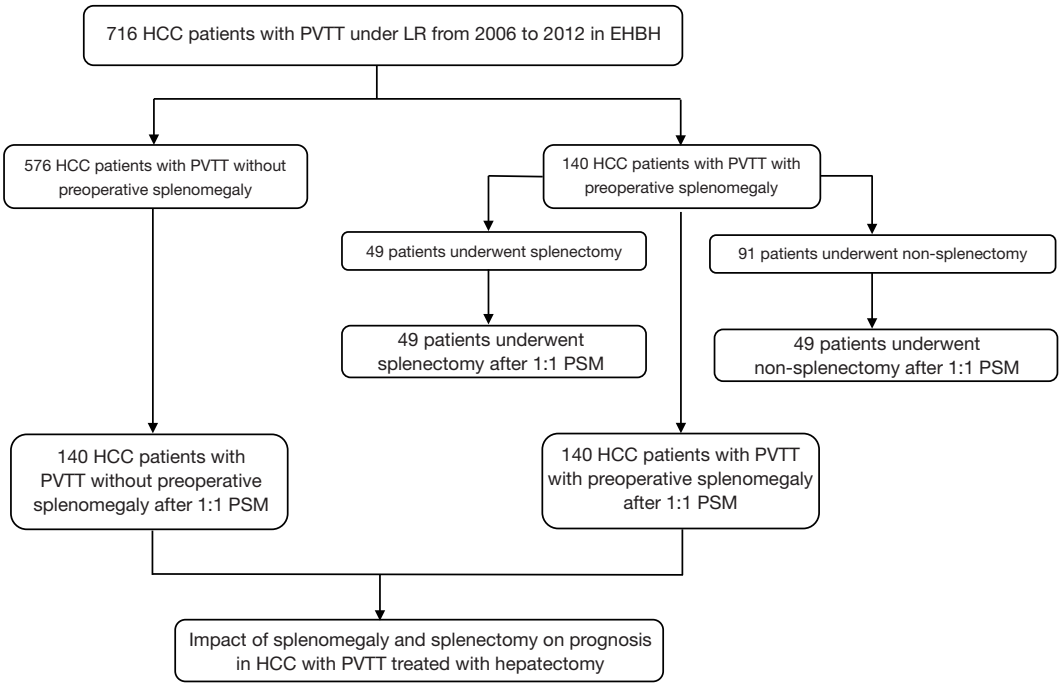

Figure 1 Flow chart for the selection of HCC patients enrolled in this study. HCC, hepatocellular carcinoma.

Table 1 The clinicopathological features of patients with or without splenomegaly before PSM

Clinical variables	Splenomegaly (n=140)	Non-splenomegaly (n=576)	P
Age, year	48.0 (32.0–75.0)	48.0 (10.0–78.0)	0.489
Sex			0.948
Male	126 (90.0%)	522 (90.6%)	
Female	14 (10.0%)	54 (9.4%)	
Hepatitis B virus infection			0.799
No	33 (23.6%)	164 (28.5)	
Yes	107 (76.4%)	412 (71.5%)	
HBsAg			0.912
No	14 (10%)	62 (10.8%)	
Yes	126 (90%)	514 (89.2%)	
Tumor diameter	8.0 (0.0–18.0)	8.0 (0.0–32.0)	0.078
No# of tumor			0.940
Single	122 (87.1%)	498 (86.5%)	
Multiple	18 (12.9%)	78 (13.5%)	
PVTT			0.963
I	46 (32.9%)	193 (33.5%)	
II	94 (67.1%)	383 (66.5%)	

Table 1 (*continued*)

Table 1 (*continued*)

Clinical variables	Splenomegaly (n=140)	Non-splenomegaly (n=576)	P
Encapsulation			0.026
No	87 (62.1%)	341 (59.2%)	
Incomplete	9 (6.4%)	85 (14.8%)	
Complete	44 (31.5%)	150 (26.0%)	
Liver Cirrhosis			<0.001
No	21 (15.0%)	189 (32.8%)	
Yes	119 (85.0%)	387 (67.2%)	
Ascites			0.368
No	120 (85.7%)	512 (88.9%)	
Yes	20 (14.3%)	64 (11.1%)	
Esophageal and gastric varices			0.458
No	109 (77.9%)	467 (81.1%)	
Yes	31 (22.1%)	109 (18.9%)	
Child-Pugh			0.750
A	138 (98.6%)	562 (97.6%)	
B	2 (1.4%)	14 (2.4%)	
Satellite lesions			0.011
None	11 (7.9%)	34 (5.9%)	
Same lobe	117 (83.6%)	432 (75.0%)	
Different lobe	12 (8.6%)	110 (19.1%)	
Thickness of splenic hilum	5.0 (4.1–15.0)	3.2 (1.0–4.0)	<0.001
TBIL	15.0 (5.3–32.0)	14.0 (4.0–251.0)	0.768
DBIL	6.0 (2.1–16.0)	6.6 (1.0–174.0)	0.215
ALB	41.50 (30.0–52.0)	41.7 (30.0–52.0)	0.637
ALT	47.0 (11.0–262.0)	43.0 (10.0–523.0)	0.947
PT	12.5 (0.0–112.0)	12.1 (0.0–212.5)	0.928
GGT	119.0 (0.0–1052.0)	125.0 (0.0–1052.0)	0.508
ALP	107.5 (46.0–372.0)	109.5 (0.0–595.0)	0.673
AFP	1,210.0 (0.0–1,210.0)	1,210.0 (0.0–3,400.0)	0.297
CA199	17.2 (0.0–235.6)	23.0 (0.0–1,000.0)	0.045
CEA	2.0 (0.0–12.0)	2.2 (0.0–75.2)	0.048
AST	47.0 (14.9–390.0)	48.0 (14.9–389.0)	0.628
PLT	141.0 (40.0–400.0)	158.0 (0.0–495.0)	<0.001

Data were presented as n (%) or medians with interquartile range (IQR). PSM, propensity score matching; HBsAg, Hepatitis B surface antigen; PVTT, portal vein tumor thrombus; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; ALT, Alanine Aminotransferase; PT, Prothrombin time; GGT, γ-Glutamyltransferase; ALP, Alkaline phosphatase; AFP, α-fetoprotein; CA199, Carbohydrate Atigen 19-9; CEA, Carcinoembryonic antigen; AST, Aspartate Aminotransferase; PLT, Platelet.

Table 2 The clinicopathological features of patients with or without splenectomy before PSM

Clinical variables	Splenectomy (n=49)	Non-splenomegaly (n=91)	P
Age, year	49.0 (33.0–69.0)	47.0 (32.0–75.0)	0.647
Sex			0.408
Male	46 (93.9%)	80 (87.9%)	
Female	3 (6.1%)	11 (12.1%)	
Hepatitis B virus infection			0.983
No	11 (22.4%)	22 (24.2%)	
Yes	38 (77.6%)	69 (75.8%)	
HBsAg			0.379
No	3 (6.1%)	11 (12.1%)	
Yes	46 (93.9%)	80 (87.9%)	
Tumor diameter	8.0 (1.2–15.0)	8.0 (0.0–18.0)	0.252
No# of tumor			0.916
Single	47 (85.7%)	80 (87.9%)	
Multiple	2 (14.3%)	11 (12.1%)	
PVTT			1.000
I	16 (32.7%)	30 (33.0%)	
II	33 (67.3%)	61 (67.0%)	
Encapsulation			1.000
No	31 (63.3%)	56 (61.5%)	
Incomplete	3 (6.1%)	6 (6.6%)	
Complete	15 (30.6%)	29 (31.9%)	
Liver cirrhosis			1.000
No	7 (14.3%)	14 (32.8%)	
Yes	42 (85.7%)	77 (67.2%)	
Ascites			0.448
No	44 (89.8%)	76 (83.5%)	
Yes	5 (10.2%)	15 (16.5%)	
Esophageal and gastric varices			0.565
No	40 (81.6%)	69 (75.8%)	
Yes	9 (18.4%)	22 (24.2%)	
Child-Pugh			0.121
A	47 (95.9%)	91 (100.0%)	
B	2 (4.1%)	0 (0.0%)	
Satellite lesions			0.827
None	4 (8.2%)	7 (5.9%)	

Table 2 (*continued*)

Table 2 (*continued*)

Clinical variables	Splenectomy (n=49)	Non-splenomegaly (n=91)	P
Same lobe	42 (85.7%)	75 (75.0%)	
Different lobe	3 (6.1%)	9 (19.1%)	
Thickness of splenic hilum	5.0 (4.1–10.0)	5 (4.1–15.0)	0.725
TBIL	15.6 (6.0–29.0)	14.4 (5.3–32.0)	0.426
DBIL	6.0 (3.0–16.0)	5.9 (2.1–19.0)	0.426
ALB	41.0 (30.0–50.0)	42.0 (30.0–52.0)	0.538
ALT	47.0 (18.0–262.0)	47.0 (11.0–208.0)	0.603
PT	12.5 (0.0–112.0)	12.4 (0.0–15.5)	0.382
GGT	122.0 (36.0–1052.0)	114.0 (0.0–584.0)	0.108
ALP	107.0 (60.0–372.0)	108.0 (46.0–255.0)	0.104
AFP	1000.0 (1.0–1210.0)	1210.0 (0.0–1210.0)	0.788
CA199	15.6 (0.0–91.6)	21.0 (0.0–235.0)	0.025
CEA	2.0 (0.0–7.2)	2.0 (0.0–12.0)	0.235
AST	41.0 (17.1–263.0)	54.0 (14.9–390.0)	0.022
PLT	141.0 (42.0–384.0)	141.0 (40.0–400.0)	0.202

Data were presented as n (%) or medians with interquartile range (IQR). PSM, propensity score matching; HBsAg, Hepatitis B surface antigen; PVTT, portal vein tumor thrombus; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; ALT, Alanine Aminotransferase; PT, Prothrombin time; GGT, γ-Glutamyltransferase; ALP, Alkaline phosphatase; AFP, α-fetoprotein; CA199, Carbohydrate Atigen 19-9; CEA, Carcinoembryonic antigen; AST, Aspartate Aminotransferase; PLT, Platelet.

for the SM group (Table S3). The RFS of patients in the non-SM group was significantly better than the SM group (1 year, 32.3% *vs.* 17.6%; 2 years, 21.1% *vs.* 6.8%; 3 years, 16.1% *vs.* 5.4%; P<0.001, *Figure 2A*). The median OS (MOS 95% CI) for patients in the SM compared to non-SM groups were 7.4 (6.7–13.9) months *vs.* 12.4 (11.7–13.5) months (Table S4). The OS in the non-SM group was significantly better than that of the SM group (1 year, 51.7% *vs.* 25.7%; 2 years, 28.0% *vs.* 10.2%; 3 years, 18.6% *vs.* 7.2%; P<0.001, *Figure 2B*).

After PSM, the MRFS (95% CI) was 6.3 (5.4–7.3) months for the non-SM group and 4.3 (3.8–5.3) months for the SM group (Table S5). The RFS in the non-SM group was significantly better than that of the SM group (1 year, 22.8% *vs.* 17.6%; 2 years, 18.3% *vs.* 6.8%; 3 years, 7.2% *vs.* 5.4%; P<0.001, *Figure 2C*). The MOS (95% CI) was 12.4 (10.3–13.8) months for the non-SM group and 7.4 (6.7–9.6) months for the SM group (Table S6). The OS in the non-SM group was significantly better than that of the SM group (1 year, 51.4% *vs.* 25.7%; 2 years, 21.4% *vs.* 10.2%; 3 years, 10.1% *vs.* 7.2%; P<0.001, *Figure 2D*).

Survival analysis for patients in the SPT and non-SPT groups

Before PSM, the MRFS (95% CI) was 11.1 (9.0–15.3) months for the non-SPT group and 3.5 (2.9–4.2) months for the SPT group (Table S5). The RFS in the SPT group was significantly better than that of the non-SPT group (1 year, 42.9% *vs.* 3.3%; 2 years, 18.3% *vs.* 0%; 3 years, 14.6% *vs.* 0%; P<0.001, *Figure 3A*). The MOS (95% CI) in the SPT *vs.* the non-SPT groups was 14.0 (12.1–23.7) months *vs.* 6.2 (5.4–6.7) months (Table S5). The OS of patients in the SPT group was significantly better than that of the non-SPT group (1 year, 59.2% *vs.* 6.6%; 2 years, 38.9% *vs.* 0%; 3 years, 13.2% *vs.* 0%; P<0.001, *Figure 3B*).

After PSM, the MRFS (95% CI) was 11.1 (9.0–15.3) months for the SPT group and 3.6 (2.7–4.6) months for the non-SPT group (Table S6). The RFS of patients in the SPT group was significantly better than that of the non-

Table 3 Univariate and multivariable analysis for recurrence-free survival of patients with or without splenomegaly before PSM

Clinical variable	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	P	β	HR (95% CI)	P
Age, year	–2.071	0.991 (0.983–1)	0.038	0.813	1.004 (0.995–1.013)	0.416
Sex, male *vs*. female	0.654	1.096 (0.833–1.44)	0.513			
HBsAg	–0.576	0.926 (0.713–1.203)	0.565			
TBIL	0.201	1.001 (0.99–1.012)	0.841			
DBIL	0.222	1.002 (0.985–1.02)	0.824			
ALB	–0.623	0.994 (0.974–1.014)	0.533			
ALT	0.34	1 (0.999–1.002)	0.734			
PT	–0.453	0.998 (0.991–1.005)	0.65			
AFP	3.273	1 (1.0–1.0)	0.001	0.108	1 (1.0–1.0)	0.914
Tumor diameter	2.425	1.022 (1.004–1.04)	0.015	1.554	1.017 (0.995–1.04)	0.12
Esophageal and gastric varices	0.851	1.093 (0.891–1.341)	0.395			
Ascites	–0.644	0.92 (0.713–1.186)	0.52			
Liver cirrhosis	2.3	1.232 (1.031–1.472)	0.021	–1.633	0.851 (0.701–1.033)	0.102
No# of tumor	–1.171	0.867 (0.682–1.101)	0.242			
PVTT	3.353	1.346 (1.131–1.601)	0.001	–0.144	0.986 (0.809–1.2)	0.885
Tumor capsule	–6.057	0.753 (0.687–0.825)	<0.001	–5.157	0.283 (0.175–0.457)	<0.001
CA199	0.4	1 (0.999–1.002)	0.689			
CEA	0.85	1.008 (0.989–1.027)	0.396			
AST	4.18	1.004 (1.002–1.006)	<0.001	3.818	1.004 (1.002–1.006)	<0.001
Thickness of splenic hilum	4.595	1.185 (1.102–1.275)	<0.001	2.739	1.117 (1.032–1.209)	0.006
PLT	1.445	1.001 (1–1.002)	0.149			

PSM, propensity score matching; HBsAg, Hepatitis B surface antigen; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; ALT, Alanine Aminotransferase; PT, Prothrombin time; AFP, α-fetoprotein; PVTT, portal vein tumor thrombus; CA199, Carbohydrate Atigen 19-9; CEA, Carcinoembryonic antigen; AST, Aspartate Aminotransferase; PLT, Platelet.

SPT group (1 year, 42.9% *vs*. 2.0%; 2 years, 18.3% *vs*. 0%; 3 years, 14.6% *vs*. 0%; P<0.001, *Figure 3C*). The MOS was 14.0 (12.1–23.7) months for the SPT group and 6.3 (5.6–7.2) months for the non-SPT group (Table S6). The OS in the SPT group was significantly better than that of the non-SPT group (1 year, 59.2% *vs*. 4.1%; 2 years, 38.9% *vs*. 0%; 3 years, 13.2% *vs*. 0%; P<0.001, *Figure 3D*).

Discussion

PVTT has been recognized as one of the most significant prognostic factors of poor survival in HCC patients (2,24). While many therapeutic modalities have been used to treat these patients, their effectiveness remains unsatisfactory. However, advances in both surgical treatment and perioperative management have rendered feasible R0 LR for the complex combination of HCC with types I and II PVTT (3,9,25). To our knowledge, there have been no prior studies that have assessed survival of HCC patients with PVTT and pathologic spleen, comparing treatment with or without splenectomy following LR.

Macrovascular invasion of the portal venous system presenting as PVTT is virtually always classified as advanced HCC (26,27). However, the specific factors impacting survival of HCC patients with PVTT remain elusive. A recent study reported that HBV infection and activity of

Table 4 Univariate and Multivariable Analysis for Overall Survival of Patients with or without Splenomegaly before PSM

Clinical variable	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	P	β	HR (95% CI)	P
Age, year	–1.648	0.993 (0.985–1.001)	0.099			
Sex, male *vs*. female	0.137	1.019 (0.776–1.34)	0.891			
HBsAg	–1.269	0.844 (0.65–1.097)	0.204			
TBIL	–0.407	0.998 (0.99–1.006)	0.684			
DBIL	–0.472	0.997 (0.985–1.01)	0.637			
ALB	–0.518	0.995 (0.975–1.015)	0.605			
ALT	–0.333	1 (0.998–1.001)	0.739			
PT	–0.838	0.997 (0.99–1.004)	0.402			
AFP	3.965	1 (1.0–1.0)	<0.001	1.971	1 (1.0–1.0)	<0.001
Tumor diameter	2.985	1.027 (1.009–1.045)	0.003	1.963	1.021 (1–1.043)	0.05
Esophageal and gastric varices	–0.092	0.99 (0.807–1.215)	0.927			
Ascites	–0.405	0.949 (0.736–1.224)	0.686			
Liver cirrhosis	1.863	1.184 (0.991–1.415)	0.062			
No# of tumor	–0.383	0.954 (0.751–1.213)	0.702			
PVTT	1.233	1.116 (0.938–1.327)	0.218			
Tumor capsule	–6.288	0.739 (0.673–0.812)	<0.001	–4.253	0.809 (0.734–0.892)	<0.001
CA199	1.013	1.001 (0.999–1.002)	0.311			
CEA	2.913	1.026 (1.008–1.044)	0.004	3.619	1.03 (1.013–1.046)	<0.001
AST	4.003	1.004 (1.002–1.006)	<0.001	1.838	1.002 (1–1.004)	0.066
Thickness of splenic hilum	5.219	1.22 (1.132–1.315)	<0.001	2.894	1.129 (1.04–1.226)	0.004
PLT	0.268	1 (0.999–1.001)	0.789			

PSM, propensity score matching; HBsAg, Hepatitis B surface antigen; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; ALT, Alanine Aminotransferase; PT, Prothrombin time; AFP, α-fetoprotein; PVTT, portal vein tumor thrombus; CA199, Carbohydrate Atigen 19-9; CEA, Carcinoembryonic antigen; AST, Aspartate Aminotransferase; PLT, Platelet.

the TGF-b-miR-34a-CCL22 axis might be related to the development of PVTT (28). Others have shown that liver fibrosis, severity of PVTT, and proteins induced by vitamin K absence or antagonist II (PIVKA-II) were independent prognostic factors for survival of HCC patients with PVTT (29). In contrast, a low serum concentration of des-γ-carboxy prothrombin combined with curative resection of HCC with main portal vein PVTT was associated with improved 5-year survival (30). Multiple tumours, tumour rupture and macrovascular invasion have been identified as independent risk factors for recurrence and reduced survival in operated HCC patients with PVTT (31). In the current study, incomplete tumor encapsulation, AST, and thickness of splenic hilum were independent risk factors of poor RFS. Additionally, independent risk factors for poor OS included α-fetoprotein level, CEA, incomplete tumor encapsulation, and thickness of splenic hilum. Notably, the thickness of splenic hilum has reportedly been an indicator for splenomegaly, an independent risk factor for poor survival, and should be considered a novel prognostic factor for poor survival in patients with HCC and PVTT. Not surprisingly we found that RFS and OS in the non-SM group were significantly better than that of the SM group. Splenomegaly negatively impacted RFS and OS in

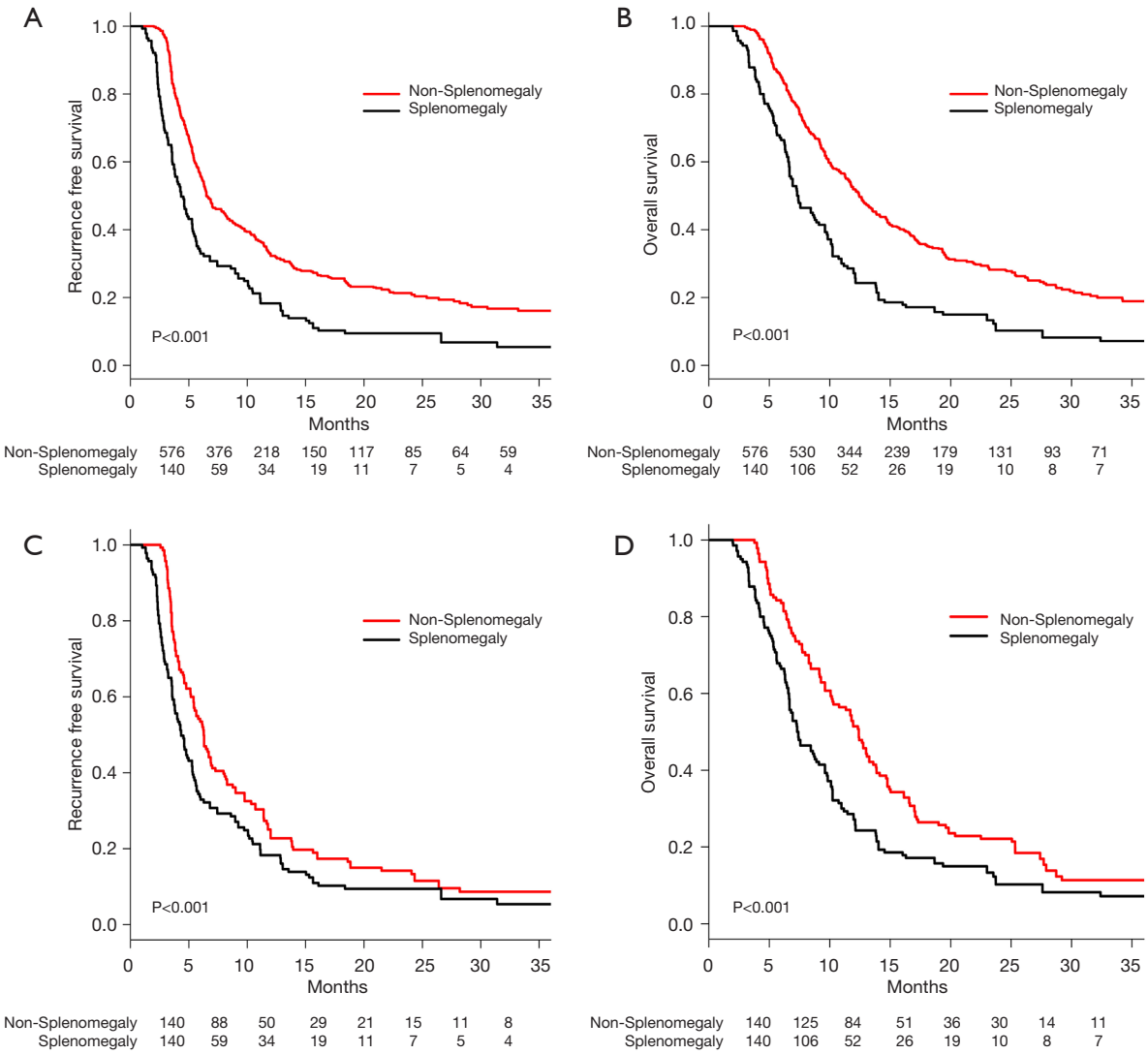

Figure 2 The survival analysis of patients with or without splenomegaly. (A) Kaplan-Meier analysis of RFS in patients with or without splenomegaly before PSM (P<0.001). (B) Kaplan-Meier analysis of OS in patients with or without splenomegaly before PSM (P<0.001). (C) Kaplan-Meier analysis of RFS in patients with or without splenomegaly after PSM (P<0.001). (D) Kaplan-Meier analysis of OS in patients with or without splenomegaly after PSM (P<0.001). PSM, propensity score matching.

HCC patients with PVTT treated with LR. The reason appears to be directly related to hypersplenism (32,33). HCC with PVTT is always complicated by decompensated liver function caused by liver cirrhosis. Decompensated liver function is accompanied by portal hypertension, splenomegaly with hypersplenism, all of which compromise the outcome of curative treatment (34,35). Furthermore, hypersplenism decreases WBC and platelet counts, increasing risk of coagulopathy and infection. Ultimately it increases the risks of tumour recurrence and metastasis (36).

Due to the frequent potential postoperative complications associated with splenomegaly, splenectomy was performed prior to LR in these HCC patients. Reports have demonstrated that splenectomy has improved thrombocytopenia and leukopenia and decreased portal venous pressure (15,37). Additionally, splenectomy may help to improve liver function, nutritional metabolism, and Child–Pugh scores which have expanded the indications for

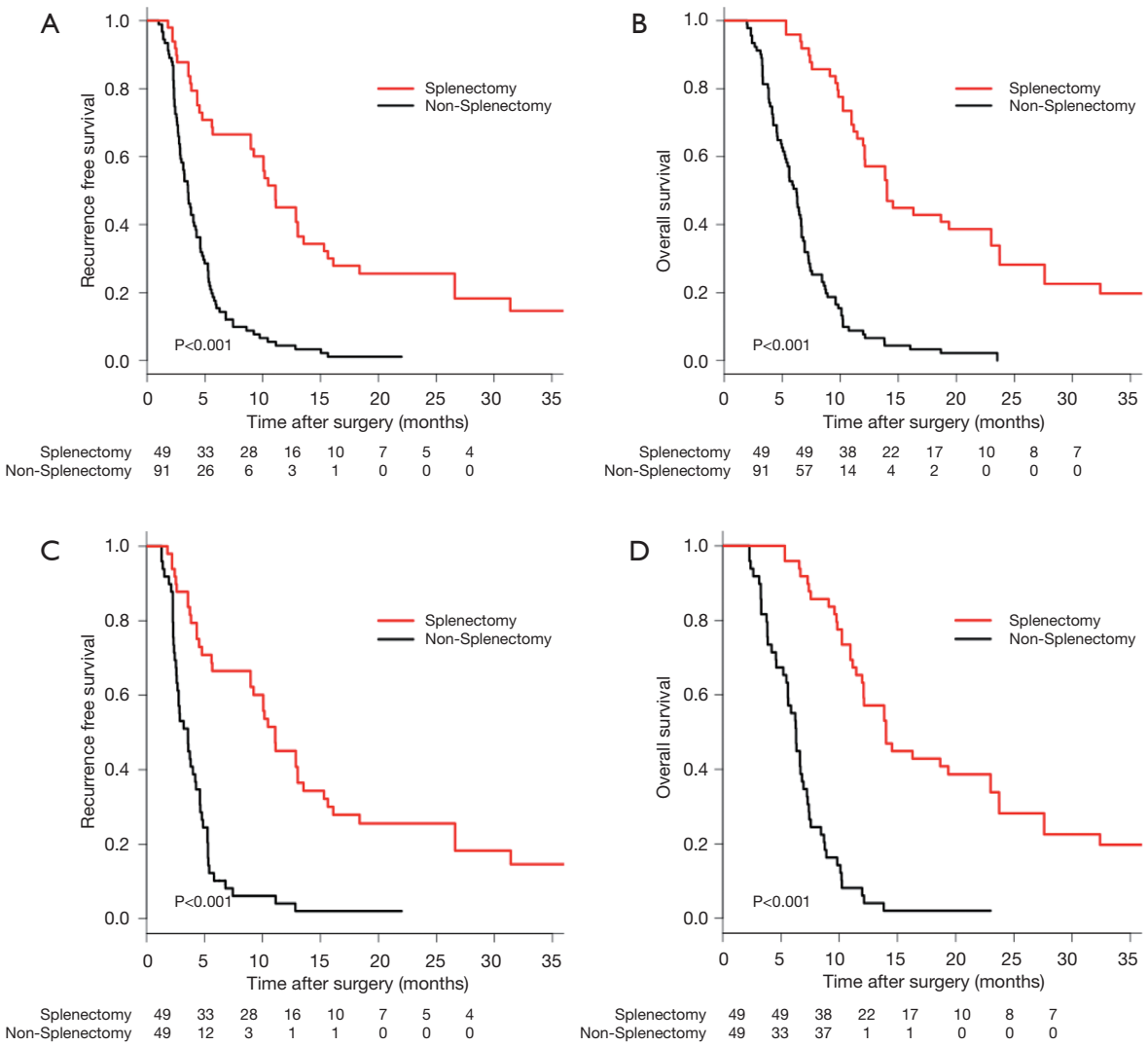

Figure 3 The survival analysis of patients with or without splenectomy. (A) Kaplan-Meier analysis of RFS in patients treated with or without splenectomy before PSM (P<0.001). (B) Kaplan-Meier analysis of OS in patients treated with or without splenectomy before PSM (P<0.001). (C) Kaplan-Meier analysis of RFS in patients treated with or without splenectomy after PSM (P<0.001). (D) Kaplan-Meier analysis of OS in patients treated with or without splenectomy after PSM (P<0.001). PSM, propensity score matching.

LR and increased RFS (10,15,16,38-40). Some researchers advise synchronous hepatectomy and splenectomy in patients with HCC and a pathologic spleen (41). In this study, the long-term survival of HCC patients with PVTT in the SPT group was significantly better than the non-SPT group (P<0.001 for OS and DFS). Studies suggest that splenectomy can restore lymphocyte function and induce tumour regression, perhaps due to increased number of natural killer (NK) cells, reduced transforming growth factor (TGF)-β1 expression, and alteration of the immune response against cancer due to modulation of CD4+ and CD8+ T cells (17,19,42,43). Splenectomy may even play a prophylactic role against HCC recurrence following LR (18). Taken together, these studies support our findings that splenectomy is beneficial for HCC patients with PVTT.

Our study has several limitations. First, it is a retrospective study with the usual attendant potential biases. Second, most patients enrolled in this study had a background of HBV infection. Whether the results of our study can be applied

to patients with HCV or alcohol-related HCC remain to be determined.

In conclusion, HCC patients with PVTT but without splenomegaly had better long-term survival, but in patients with splenomegaly, splenectomy resulted in improved survival.

Acknowledgments

Funding: This work was supported by the grants of the National Natural Science Foundation of China [81702335].

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-2229

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-2229

Peer Review File: Available at http://dx.doi.org/10.21037/atm-20-2229

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-2229). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committees of the Eastern Hepatobiliary Surgery Hospital. (NO.: EHBHKY-2015-01-028) and informed consent was taken from all the patients.

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Cite this article as: Chai ZT, Zhang XP, Shao M, Ao JY, Chen ZH, Zhang F, Hu YR, Zhong CQ, Lin JH, Fang KP, Wu MC, Lau WY, Cheng SQ. Impact of splenomegaly and splenectomy on prognosis in hepatocellular carcinoma with portal vein tumor thrombus treated with hepatectomy. Ann Transl Med 2021;9(3):247. doi: 10.21037/atm-20-2229

Supplementary

Table S1 the clinicopathological features of patients with or without splenomegaly after PSM

Clinical variables	Splenomegaly (n=140)	Non-Splenomegaly (n=140)	P
Age, year	48.0 (32.0–75.0)	49.0 (10.0–75.0)	0.791
Sex			1.000
Male	126 (90.0%)	125 (89.3%)	
Female	14 (10.0%)	15 (10.7%)	
Hepatitis B virus infection			1.000
No	33 (23.6%)	33 (23.6%)	
Yes	107 (76.4%)	107 (76.4%)	
HBsAg			0.675
No	14 (10%)	11 (7.9%)	
Yes	126 (90%)	129 (92.1%)	
Tumor diameter	8.0 (0.0–18.0)	8.0 (1.2–20.0)	0.440
No# of tumor			1.000
Single	122 (87.1%)	121 (86.4%)	
Multiple	18 (12.9%)	19 (13.6%)	
PVTT			0.615
I	46 (32.9%)	51 (36.4%)	
II	94 (67.1%)	89 (63.6%)	
Encapsulation			0.057
No	87 (62.1%)	87 (62.1%)	
Incomplete	9 (6.4%)	20 (14.3%)	
Complete	44 (31.5%)	33 (23.6%)	
Liver Cirrhosis			0.870
No	21 (15.0%)	23 (16.4%)	
Yes	119 (85.0%)	117 (83.6%)	
Ascites			1.000
No	120 (85.7%)	119 (85.0%)	
Yes	20 (14.3%)	21 (15.0%)	
Esophageal and gastric varices			0.770
No	109 (77.9%)	112 (80.0%)	
Yes	31 (22.1%)	28 (20.0%)	
Child-Pugh			0.684
A	138 (98.6%)	136 (97.1%)	
B	2 (1.4%)	4 (2.9%)	
Satellite lesions			0.951
None	11 (7.9%)	12 (8.6%)	
Same lobe	117 (83.6%)	115 (82.1%)	
Different lobe	12 (8.6%)	13 (9.4%)	
Thickness of splenic hilum	5.0 (4.1–15.0)	4.0 (4.0–4.0)	<0.001
TBIL	15.0 (5.3–32.0)	13.0 (4.0–34.0)	0.054
DBIL	6.0 (2.1–16.0)	5.0 (1.0–13.0)	0.139
ALB	41.50 (30.0–52.0)	42.2 (33.0–50.1)	0.170
ALT	47.0 (11.0–262.0)	39.0 (14.0–303.0)	0.291
PT	12.5 (0.0–112.0)	11.9 (0.0–15.5)	0.179
GGT	119.0 (0.0–1052.0)	121.5 (23.0–810.0)	0.324
ALP	107.5 (46.0–372.0)	107.5 (0.0–595.0)	0.274
AFP	1210.0 (0.0–1210.0)	940.1 (0.6–1210.0)	0.053
CA199	17.2 (0.0–235.6)	21.0 (0.0–114.0)	0.287
CEA	2.0 (0.0–12.0)	2.3 (0.0–14.9)	0.594
AST	47.0 (14.9–390.0)	51.0 (15.7–359.0)	0.602
PLT	141.0 (40.0–400.0)	139.0 (0.0–495.0)	0.460

Data were presented as n (%) or medians with interquartile range (IQR). PSM, propensity score matching; HBsAg, Hepatitis B surface antigen; PVTT, portal vein tumor thrombus; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; ALT, Alanine Aminotransferase; PT, Prothrombin time; GGT, γ-Glutamyltransferase; ALP, Alkaline phosphatase; AFP, α-fetoprotein; CA199, Carbohydrate Atigen 19-9; CEA, Carcinoembryonic antigen; AST, Aspartate Aminotransferase; PLT, Platelet.

http://dx.doi.org/10.21037/atm-20-2229

Table S2 The clinicopathological features of patients with or without splenectomy after PSM

Clinical variables	Splenectomy (n=49)	Non-splenectomy (n=49)	P
Age, year	49.0 (33.0–69.0)	47.0 (32.0–75.0)	0.607
Sex			1.000
Male	46 (93.9%)	47 (95.9%)	
Female	3 (6.1%)	2 (4.1%)	
Hepatitis B virus infection			0.814
No	11 (22.4%)	13 (26.5%)	
Yes	38 (77.6%)	36 (73.5%)	
HBsAg			0.912
No	3 (6.1%)	3 (6.1%)	1.000
Yes	46 (93.9%)	46 (93.9%)	
Tumor diameter	8.0 (1.2–15.0)	7.3 (0.0–14.4)	0.855
No# of tumor			1.000
Single	42 (85.7%)	42 (86.5%)	
Multiple	7 (14.3%)	7 (13.5%)	
PVTT			0.827
I	16 (32.7%)	14 (28.6%)	
II	33 (67.3%)	35 (71.4%)	
Encapsulation			1.000
No	31 (63.3%)	30 (61.2%)	
Incomplete	3 (6.1%)	3 (6.1%)	
Complete	15 (30.6%)	16 (32.7%)	
Liver Cirrhosis			1.000
No	7 (14.3%)	8 (16.3%)	
Yes	42 (85.7%)	41 (83.7%)	
Ascites			0.715
No	44 (89.8%)	46 (93.9%)	
Yes	5 (10.2%)	3 (6.1%)	
Esophageal and gastric varices			1.000
No	40 (81.6%)	40 (81.6%)	
Yes	9 (18.4%)	9 (18.4%)	
Child-Pugh			0.495
A	47 (95.9%)	49 (100.0%)	
B	2 (4.1%)	0 (0.0%)	
Satellite lesions			1.000
None	4 (8.2%)	4 (8.2%)	
Same lobe	42 (85,7%)	41 (83.6%)	
Different lobe	3 (6.1%)	4 (8.2%)	
Thickness of splenic hilum	5.0 (4.1–10.0)	5 (4.1–15.0)	0.842
TBIL	15.6 (6.0–29.0)	15.0 (5.3–32.0)	0.458
DBIL	6.0 (3.0–16.0)	5.9 (2.1–14.0)	0.545
ALB	41.0 (30.0–52.0)	30.0 (30.0–49.0)	0.858
ALT	47.0 (18.0–262.0)	52.0 (13.3–138.0)	0.880
PT	12.5 (0.0–112.0)	12.4 (0.0–14.4)	0.316
GGT	122.0 (36.0–1052.0)	133.0 (43.0–584.0)	0.445
ALP	107.0 (60.0–372.0)	112.0 (62.0–255.0)	0.418
AFP	1000.0 (1.0–1210.0)	1210.0 (0.0–1210.0)	0.906
CA199	15.6 (0.0–91.6)	19.8 (0.0–193.3)	0.185
CEA	2.0 (0.0–7.2)	2.0 (0.0–5.0)	0.700
AST	41.0 (17.1–263.0)	42.0 (17.1–184.0)	0.740
PLT	141.0 (42.0–384.0)	145.0 (40.0–400.0)	0.336

Data were presented as n (%) or medians with interquartile range (IQR). PSM, propensity score matching; HBsAg, Hepatitis B surface antigen; PVTT, portal vein tumor thrombus; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; ALT, Alanine Aminotransferase; PT, Prothrombin time; GGT, γ-Glutamyltransferase; ALP, Alkaline phosphatase; AFP, α-fetoprotein; CA199, Carbohydrate Atigen 19-9; CEA, Carcinoembryonic antigen; AST, Aspartate Aminotransferase; PLT, Platelet.

http://dx.doi.org/10.21037/atm-20-2229

Table S3 Comparison of RFS and OS rate among HCC patients with PVTT with or without splenomegaly before PSM

Indexes	n	1-year	2-year	3-year	Median survival time (95% CI)	Log-rank	P value
OS							
Non-splenomegaly	576	51.7 (47.8–56.0)	28.0 (24.5–31.9)	18.6 (15.5–22.4)	12.4 (11.7–13.5)	40.0	<0.001
Splenomegaly	140	25.7 (19.4–34.1)	10.2(6.1–17.2)	7.2 (3.7–13.9)	7.4 (6.7–9.6)		
RFS							
Non-Splenomegaly	576	32.3 (28.6- 36.4)	21.1 (17.9–24.8)	16.1 (13.1–19.7)	6.5 (6.3–7.8)	35.1	<0.001
Splenomegaly	140	17.6 (12.2–25.2)	6.8 (3.4–13.6)	5.4 (2.4–12.3)	4.3 (3.8–5.3)		

RFS, recurrence-free survival; OS, overall survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; PSM, propensity score matching.

Table S4 Comparison of RFS and OS rate among HCC patients with PVTT with or without splenectomy before PSM

Indexes	n	1-year	2-year	3-year	Median survival time (95% CI)	Log-rank	P value
OS							
Non-splenomegaly	91	6.6 (3.0–14.2)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	6.2(5.4–6.7)	66.4	<0.001
Splenomegaly	49	59.2 (46.9–74.7)	38.9 (36.8–56.2)	13.2(4.8–36.3)	14.0 (12.1–23.7)		
RFS							
Non-Splenomegaly	91	3.3 (1.1–10.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	3.5 (2.9–4.2)	43.8	<0.001
Splenomegaly	49	42.9 (30.8–59.7)	18.3 (9.3–36.0)	14.6 (6.5–32.8)	11.1 (9.0–15.3)		

RFS, recurrence-free survival; OS, overall survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; PSM, propensity score matching.

Table S5 Comparison of RFS and OS rate among HCC patients with PVTT with or without splenomegaly after PSM

Indexes	n	1-year	2-year	3-year	Median survival time (95% CI)	Log-rank	P value
OS							
Non-splenomegaly	140	51.4 (43.8–60.4)	21.4 (15.6–29.4)	10.1 (5.9–17.1)	12.4 (10.3–13.8)	12.1	<0.001
Splenomegaly	140	25.7 (19.4–34.1)	10.2(6.1–17.2)	7.2 (3.7–13.9)	7.4 (6.7–9.6)		
RFS							
Non-splenomegaly	140	22.8 (16.7- 31.0)	18.3 (8.6–20.6)	7.2 (3.6–14.2)	6.3 (5.4–7.3)	7.6	<0.001
Splenomegaly	140	17.6 (12.2–25.2)	6.8 (3.4–13.6)	5.4 (2.4–12.3)	4.3 (3.8–5.3)		

RFS, recurrence-free survival; OS, overall survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; PSM, propensity score matching.

Table S6 Comparison of RFS and OS rate among HCC patients with PVTT with or without splenectomy after PSM

Indexes	n	1-year	2-year	3-year	Median survival time (95% CI)	Log-rank	P value
OS							
Non-splenectomy	49	4.1 (1.1–15.9)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	6.3 (5.6–7.2)	58.5	<0.001
Splenectomy	49	59.2 (46.9–74.7)	38.9 (36.8–56.2)	13.2 (4.8–36.3)	14.0 (12.1–23.7)		
RFS							
Non-splenectomy	49	2.0 (0.3–14.2)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	3.6 (2.7–4.6)	36.6	<0.001
Splenectomy	49	42.9 (30.8–59.7)	18.3 (9.3–36.0)	14.6 (6.5–32.8)	11.1 (9.0–15.3)		

RFS, recurrence-free survival; OS, overall survival; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; PSM, propensity score matching.

http://dx.doi.org/10.21037/atm-20-2229