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Comparison of Liver Transplantation and Liver Resection for Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombus Type I and Type II

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Purpose: The aim of this study was to compare the efficacy of liver transplantation (LT) and liver resection (LR) for hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT) and to investigate risk factors affecting prognosis.

Materials and Methods: A total of 94 HCC patients with PVTT type I (segmental PVTT) and PVTT type II (lobar PVTT) were involved and divided into LR (n=47) and LT groups (n=47). Recurrence-free survival (RFS) and overall survival (OS) were compared before and after inverse probability of treatment weighting (IPTW). Prognostic factors for RFS and OS were explored.

Results: Two treatment groups were well-balanced using IPTW. In the entire cohort, LT provided a better prognosis than LR. Among patients with PVTT type I, RFS was better with LT (p=0.039); OS was not different significantly between LT and LR (p=0.093). In subgroup analysis of PVTT type I patients with α-fetoprotein (AFP) levels >200 ng/mL, LT elicited significantly longer median RFS (18.0 months vs. 2.1 months, p=0.022) and relatively longer median OS time (23.6 months vs. 9.8 months, p=0.065). Among patients with PVTT type II, no significant differences in RFS and OS were found between LT and LR (p=0.115 and 0.335, respectively). Multivariate analyses showed treatment allocation (LR), tumor size (>5 cm), AFP and aspartate aminotransferase (AST) levels to be risk factors of RFS and treatment allocation (LR), AFP and AST as risk factors for OS.

Conclusion: LT appeared to afford a better prognosis for HCC with PVTT type I than LR, especially in patients with AFP levels >200 ng/mL.

Key Words: Hepatocellular carcinoma, liver transplantation, liver resection, portal vein tumor thrombus

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer-associated deaths globally.[1] Portal vein tumor thrombus (PVTT) is a severe complication, posing high recurrence rates and poor prognosis, in HCC patients. HCC patients with PVTT are more likely to have extremely limited therapeutic options and shortened overall survival (OS) than HCC patients without PVTT.[2]

Lately, studies have demonstrated satisfactory prognosis after liver resection (LR) for HCC patients with PVTT in terms of long-term survival,[3-6] with a median survival time longer than 4 years for PVTT confined to the first-order branch.[7] Meanwhile, other studies have described survival benefits for liver transplantation (LT) in HCC patients with PVTT,[8-11] especially for segmental PVTT, with a 5-year OS rate of 50.3%.[12] Based on a number of studies, clinical practice guidelines from the European Association for the Study of Liver (EASL) have mentioned the possibility of therapeutic application of LR and LT for carefully-selected HCC patients with PVTT.[2] However, the efficacy of LT and LR for HCC patients with PVTT type I and PVTT type II remains controversial.

Accordingly, the aims of this study were to compare the efficacy of LT and LR for HCC patients with PVTT type I and PVTT type II and to analyze risk factors affecting recurrence-free survival (RFS) and OS.

MATERIALS AND METHODS

Data collection and patients

This study retrospectively analyzed HCC patients with PVTT who underwent LT or LR at two medical centers in China between December 2009 and August 2016. The diagnosis of HCC was made based on EASL standards.[2] The presence of PVTT was determined based on ultrasonography, enhanced computed tomography (CT), or magnetic resonance imaging (MRI) findings and was confirmed by pathology. The inclusion criteria were as follows: 1) newly diagnosed HCC patients with PVTT without previous treatment on admission; 2) HCC patients combined with PVTT without extending to the main trunk; 3) no metastasis or other malignancy; 4) Child-Pugh class A or B; and 5) no missing clinical parameters and follow up completion (follow up ≥3 years). A total of 94 patients were enrolled and classified into the LT group (n=47) or LR group (n=47). Additionally, we classified the HCC patients with PVTT into two groups: PVTT type I group (segmental PVTT), tumor thrombus occurring in segmental branches of portal vein or above, or PVTT type II group (lobar PVTT), tumor thrombus occurring in the right or/ and left portal vein.[12,13] Treatment allocation was performed following the recommendations from a multidisciplinary team and willingness or economical consideration from the patients' families. This retrospective cohort study was conducted with approval from Tianjin Medical University Cancer Institute and Hospital Medical Ethics Committee and the Tianjin First Central Hospital Medical Ethics Committee review board (approval number: 2016N075KY, bc2020080), and a waiver for informed consent was granted. Additionally, this study conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and no organs or tissues from prisoners were used.

The clinical variables of patient characteristics are summarized in Table 1. The severity of liver disease was assessed using albumin-bilirubin grade, Child-Pugh grade, aspartate aminotransferase-to-platelet ratio index grade, and model for end-stage liver disease grade.

LR

The operative procedures for hepatectomy were performed as described previously.[14] The location of the tumor, along with the invasion degree of the tumor thrombus, was detected using intraoperative ultrasonography. As for thrombectomy, the operation was determined according to the location of tumor and tumor thrombus as described by Shi, et al.[13]

LT

The possibility of unsatisfactory therapy outcomes and long waiting times were explained to patients, and informed consent was obtained before surgery. Transcatheter arterial chemoembolization (TACE) and/or sorafenib were used for patients on the waiting list for LT depending on the tumour characteristics, liver function, and patient willingness. The detailed operative procedures were identical to those introduced in previous studies.[12] After operation, tacrolimus, mycophenolate mofetil, and methylprednisolone were included as a conventional immunosuppressive regimen, and the medication regimen and dose were adjusted individually.

Follow-up and endpoints

The patients were generally evaluated using abdomen-pelvis multi-phase dynamic CT or MRI scans, chest radiography, α-fetoprotein (AFP), and liver function tests during follow-up at 1 month after the operation, every 2 to 3 months within the first year, and every 3 to 5 months thereafter. CT or MRI and a raised serum AFP level was used to identify relapse. Intrahepatic recurrence was defined as tumor recurrence initially detected in the liver and no additional extrahepatic lesions. Extrahepatic recurrence was defined as emergence of the tumor elsewhere outside the liver. Recurrent patients were considered for further treatment, such as LT, surgery, ablation, or chemotherapy, depending on the request of patient and multidisciplinary team discussion.

The primary endpoint of our study was RFS, which was defined as the period between initial treatment and tumor recurrence or death. The second endpoint was OS, which was defined as the time between initial treatment and the date of

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Table 1. Baseline Characteristics of LT and LR Groups Before and After IPTW

Covariates	Before IPTW adjustment		*p* value*	After IPTW adjustment		*p* value*
	LT (n=47)	LR (n=47)		LT (n=39)	LR (n=32)	
PVTT classification			0.828			1
Type I	30 (63.83)	32 (68.09)		26 (66.67)	22 (68.75)	
Type II	17 (36.17)	15 (31.91)		13 (33.33)	10 (31.25)	
Sex, male	43 (91.49)	39 (82.98)	0.355	35 (89.74)	26 (81.25)	0.626
Age (yr)			0.552			0.456
≤60	42 (89.36)	39 (82.98)		36 (92.31)	27 (84.38)	
>60	5 (10.64)	8 (17.02)		3 (7.69)	5 (15.63)	
Etiology			0.364			0.913
HBV	43 (91.49)	44 (93.62)		37 (94.87)	30 (93.75)	
HCV	2 (4.26)	0 (0)		1 (2.56)	0 (0)	
Alcohol-related	1 (2.13)	3 (6.38)		1 (2.56)	2 (6.25)	
Others	1 (2.13)	0 (0)		0 (0)	0 (0)	
Hypertension	0 (0)	4 (8.51)	0.117	0 (0)	2 (6.25)	0.430
Diabetes type 2	0 (0)	1 (2.13)	1	0 (0)	1 (3.13)	0.595
MELD grade			<0.001			0.084
<9	14 (29.79)	41 (87.23)		20 (42.55)	23 (71.88)	
9–15	18 (38.30)	6 (12.77)		11 (23.40)	9 (28.13)	
>15	15 (31.91)	0 (0)		8 (17.02)	0 (0)	
Child-Pugh grade			<0.001			0.152
A	21 (44.68)	41 (87.23)		24 (61.54)	27 (84.38)	
B	26 (55.32)	6 (12.77)		15 (38.46)	5 (15.63)	
ALBI grade			0.001			0.430
I	12 (25.53)	26 (55.32)		17 (43.59)	15 (46.88)	
II	27 (57.45)	21 (44.68)		18 (46.15)	17 (53.13)	
III	8 (17.02)	0 (0)		4 (10.26)	0 (0)	
APRI grade			0.002			0.453
≤0.5	5 (10.64)	19 (40.43)		6 (15.38)	10 (31.25)	
>0.5	42 (89.36)	28 (59.57)		33 (84.62)	22 (68.75)	
HCC liver lobe			0.009			0.264
Left	4 (8.51)	14 (29.79)		3 (7.69)	8 (25)	
Right	31 (65.96)	29 (61.70)		30 (76.92)	22 (68.75)	
Left and right	12 (25.53)	4 (8.51)		6 (15.38)	2 (6.25)	
Cirrhosis	41 (87.23)	39 (82.98)	0.773	33 (84.62)	28 (87.50)	0.850
Tumor size (cm)			0.520			0.873
≤5	19 (40.43)	15 (31.91)		11 (28.21)	10 (31.25)	
>5	28 (59.57)	32 (68.09)		28 (71.79)	22 (68.75)	
Tumor number			0.205			0.500
Solitary	25 (53.19)	32 (68.09)		22 (56.41)	22 (68.75)	
Multiple	22 (46.81)	15 (31.91)		17 (43.59)	10 (31.25)	
Differentiation			<0.001			0.084
Well	22 (46.81)	1 (2.13)		11 (28.21)	1 (3.13)	
Moderate	17 (36.17)	25 (53.19)		16 (41.03)	18 (56.25)	
Poor	8 (17.02)	21 (44.68)		12 (30.77)	13 (40.63)	
ln (AFP) (ng/mL)	5.48 (2.93)	6.44 (3.22)	0.167	6.25 (2.88)	6.74 (3.12)	0.595
PLT (10^9/L)	114.23 (77.3)	173.87 (83.46)	<0.001	121.17 (66.67)	155.91 (83.13)	0.130
ALB (g/L)	35.5 (5.97)	40.3 (5.11)	<0.001	37.80 (5.87)	39.4 (5.19)	0.418
ln (AST) (U/L)	4.31 (0.84)	3.82 (0.81)	0.002	4.16 (0.85)	3.92 (0.86)	0.595

Table 1. Baseline Characteristics of LT and LR Groups Before and After IPTW (continued)

Covariates	Before IPTW adjustment		*p* value*	After IPTW adjustment		*p* value*
	LT (n=47)	LR (n=47)		LT (n=39)	LR (n=32)	
ln (ALT) (U/L)	3.94 (0.79)	3.60 (0.72)	0.030	3.74 (0.85)	3.62 (0.74)	0.036
ln (TBIL) (umol/L)	3.57 (1.01)	2.75 (0.51)	<0.001	3.34 (0.9)	2.86 (0.57)	0.430
ln (GGT) (U/L)	4.93 (0.86)	4.70 (0.82)	0.090	4.82 (0.95)	4.59 (0.89)	0.418
ln (Cr) (umol/L)	3.56 (0.17)	3.69 (0.13)	<0.001	3.62 (0.16)	3.67 (0.13)	0.405
ln (INR)	0.28 (0.24)	0.04 (0.09)	<0.001	0.20 (0.22)	0.07 (0.1)	<0.001

IPTW, inverse probability of treatment weighting; PVTT, portal vein tumor thrombus; HCC, hepatocellular carcinoma; LT, liver transplantation; LR, liver resection; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; ALBI, the albumin-bilirubin; APRI, the aspartate aminotransferase-to-platelet ratio index; PLT, blood platelet; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; GGT, γ-glutamyl transpeptidase; Cr, creatinine; INR, international normalized ratio; AFP, α-fetoprotein.
Data are presented as mean (SD) or n (%).
*Categorical variables were compared using Fisher's exact test. Continuous variables were compared using Wilcoxon tests in the original data and weighted Student's t-tests after IPTW. To deal with multiple testing, we applied the Benjamini Hochberg method to obtain adjusted *p* values for tests after IPTW.

Table 2. Recurrence and Treatment Details of the LT and LR Groups

Characteristics	Total	According to treatment group		
		LT	LR	*p* value*
Total recurrence	64 (68.09)	24 (51.06)	40 (85.11)	0.001
Time to recurrence (month), median (range)	4.22 (2.13, 12.98)	8.71 (3.11, 15.23)	4.06 (1.92, 11.65)	0.138
Recurrence patterns				0.002
Intrahepatic only	27 (42.18)	4 (16.67)	23 (57.50)	0.002
Extrahepatic only	20 (31.25)	13 (54.17)	7 (17.50)	0.005
Concurrent	17 (26.56)	7 (29.17)	10 (25.00)	0.774
Recurrence in PVTT types				0.436
I	39 (60.94)	13 (54.17)	26 (65.00)	0.436
II	25 (39.06)	11 (45.83)	14 (35.00)	0.436
Treatments after recurrence				
LT	1 (1.56)	0 (0)	1 (2.50)	1.000
Surgery	4 (6.25)	1 (4.17)	3 (7.50)	1.000
Ablation	2 (3.13)	1 (4.17)	1 (2.50)	1.000
Chemotherapy (targeted or cytotoxic)	35 (54.69)	9 (37.50)	26 (65.00)	0.041
Radiotherapy	7 (10.94)	5 (20.83)	2 (5.00)	0.093
Sorafenib	5 (7.81)	5 (20.83)	0 (0.00)	0.006
Best supportive care	7 (10.94)	1 (4.17)	6 (15.00)	0.241
Unknown	8 (12.50)	5 (20.83)	3 (7.50)	0.139

LT, liver transplantation; LR, liver resection; PVTT, portal vein tumor thrombus.
Data are presented as n (%).
*Categorical variables were compared using Fisher's exact test.

mortality or the last observation taken.

Statistical analysis

Baseline characteristics were computed with continuous variables summarized as means and standard deviations and with categorical variables summarized as counts and proportions. To control confounding effects, we applied the inverse probability of treatment weights (IPTW) based on the method of propensity score to weight for our data. IPTW is defined as the probability of treatment assignment conditional on the observed baseline variables to overcome treatment selection bias. Following the procedure of IPTW, we built a multinomial logistic regression model, obtaining propensity scores for each subject. The statistical tests used for categorical variables were Fisher's exact tests. Continuous variables in the two groups were compared using Wilcoxon tests in the original data and weighted Student's t-tests after IPTW. To address multiple testing, we used the Benjamini Hochberg method to gain adjusted P values for tests after IPTW.

To conduct nonparametric analyses of RFS and OS for PVTT and treatment groups, Kaplan-Meier estimators were used to obtain Kaplan-Meier survival curves. Log-rank tests were used to compare curves for the two treatments, and Cox proportional hazards models were used to compare curves for data after IPTW. Univariate Cox proportional hazards models were used to examine associations for responses with each covari-

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ate. Variables that achieved significance at a 10% significance level in the univariate Cox proportional hazards model were included in multivariate analysis. Stepwise selection in both directions was used to eliminate non-significant covariates from the multivariate regression model. Statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), and $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics, recurrence, and survival

The clinicopathologic features of the LT (n=47) and LR (n=47) groups are shown in Table 1. Treatment groups were well-balanced at baseline using IPTW adjustment to address treatment selection bias.

After a median follow-up of 18.1 months (mean 26.2; range 6.6–37.1), 64 patients (68.1%) experienced recurrence. The recurrence patterns differed between the two treatment groups ($p=0.002$): In the LT group, 4 patients (16.7%) had only intrahepatic recurrence, 13 patients (54.2%) had only extrahepatic recurrence, and 7 patients (29.2%) had concurrent recurrence. In the LR group, intrahepatic recurrence occurred in 23 patients (57.5%), extrahepatic recurrence in 7 patients (17.5%), and concurrent recurrence in 10 patients (25.0%). Of these 64 recurrent patients, 1 patient received SLT, and 4 patients received a repetitive LR. The treatments after recurrence are listed in Table 2.

In addition, 69 (73.4%) died during the follow-up period. The causes of death were HCC recurrence (n=59; 85.5%), sepsis (n=2; 2.9%), biliary complication (n=1; 1.4%), graft malfunc-

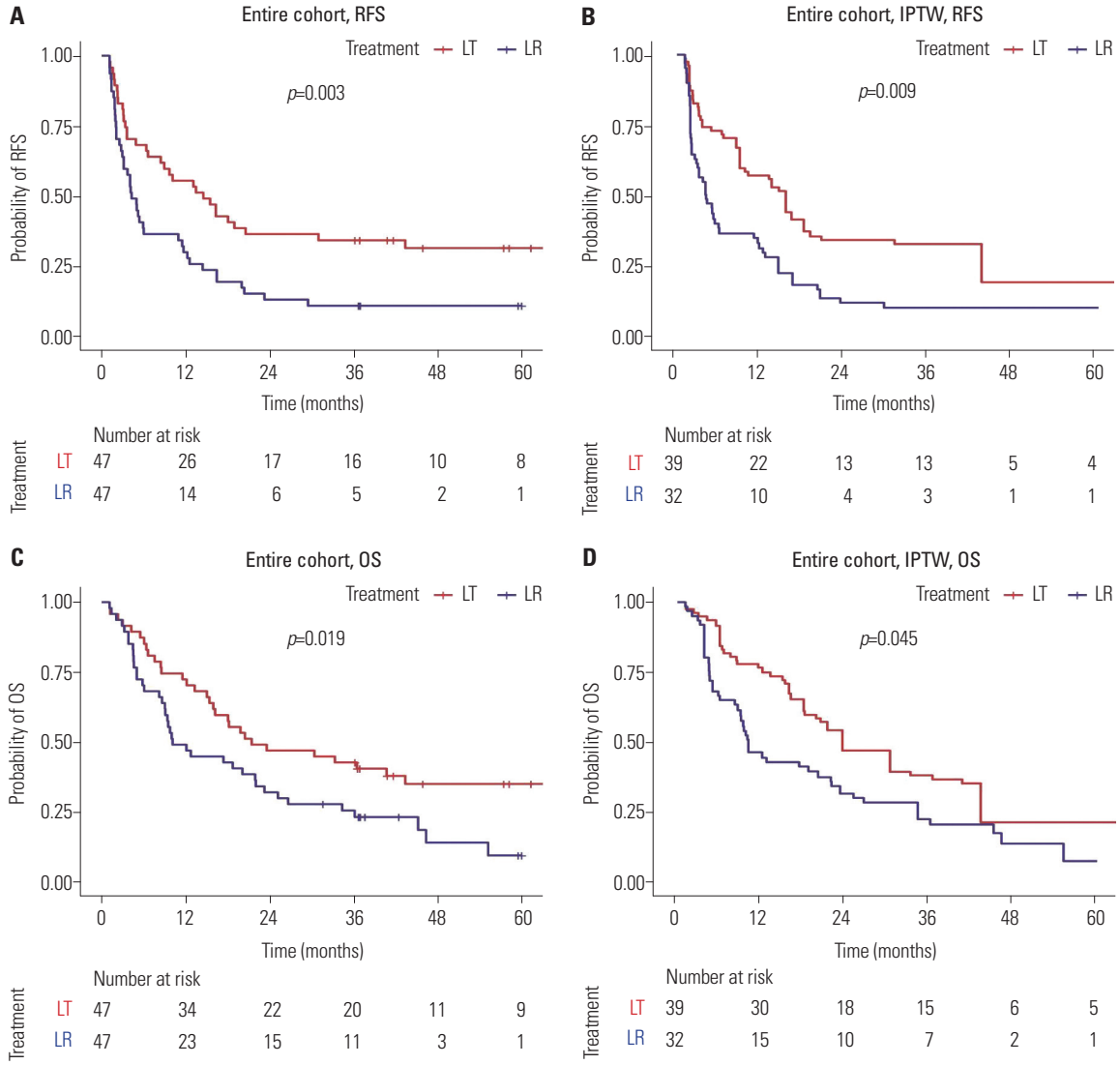

Fig. 1. Comparison of RFS and OS between LT and LR group in entire cohort before and after IPTW. Comparison of RFS between LT and LR group in entire cohort before (A) and after IPTW (B). Comparison of OS between LT and LR group in entire cohort before (C) and after IPTW (D). LT, liver transplantation; LR, liver resection; RFS, recurrence-free survival; OS, overall survival; IPTW, inverse probability of treatment weighting.

tion (n=1; 1.4%), drug-induced liver injury (n=1; 1.4%), postoperative liver failure (n=1; 1.4%), and others.

Outcomes analysis of LT and LR groups before and after IPTW

In the original data, the median RFS times of the LT and LR groups were 14.5 and 4.3 months, respectively, and the median OS times of the LT and LR groups were 21.4 and 10.1 months. The LT group had a significantly better RFS rate than the LR group (1-year: 55.3% vs. 29.8%; 2-year: 36.2% vs. 12.8%; 3-year: 34.0% vs. 10.6%; p=0.003) (Fig. 1A), as well as a more favorable OS rate (1-year: 72.3% vs. 48.9%; 2-year: 46.8% vs. 31.9%; 3-year: 42.6% vs. 25.4%; p=0.019) (Fig. 1C).

After IPTW adjustment, the median RFS times of the LT and LR groups were 15.5 and 4.1 months, respectively, and the median OS times were 23.6 and 10.1 months. The 3-year RFS and OS rates were 32.2% and 38.0% in the LT group and 9.3% and 22.2% in LR group, respectively. Results of RFS and OS followed similar trends with p=0.009 and 0.045, respectively (Fig. 1B and D).

Outcomes analysis in subgroups before and after IPTW

Among patients with PVTT type I, the median RFS and OS times in the original data were significantly longer in the LT group than in the LR group (RFS: 17.2 months vs. 4.8 months; OS: 30.0 months vs. 15.1 months) and 3-year RFS and OS rates were better in the LT group than those in the LR group (RFS: 40.0% vs. 15.6%, p=0.020; OS: 50.0% vs. 31.3%, p=0.047) (Fig. 2A and C). After IPTW adjustment, the median RFS times of the LT and LR groups were 18.0 and 3.0 months, respectively, and the median OS times were 23.6 and 10.1 months. The

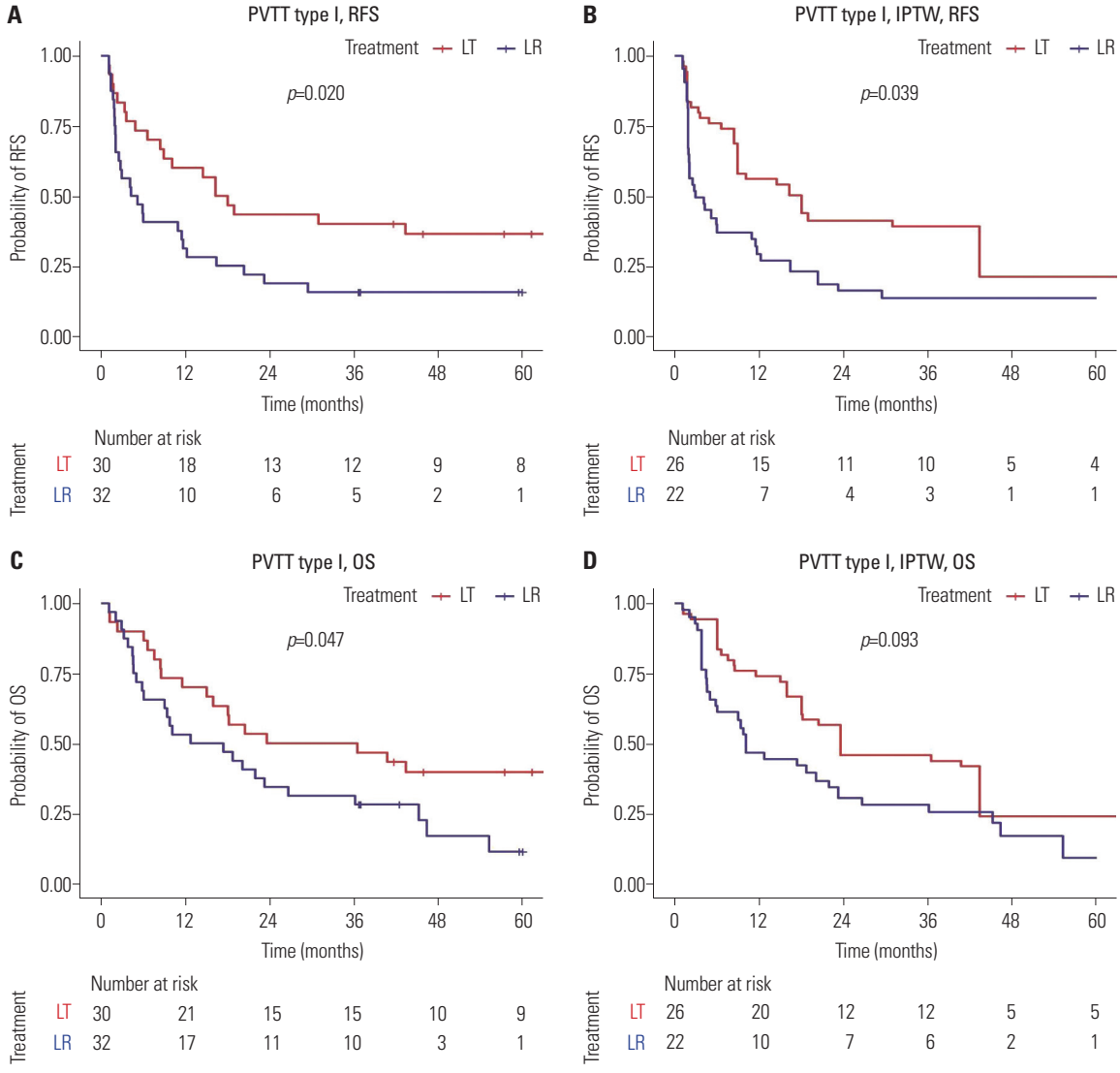

Fig. 2. Comparison of RFS and OS between LT and LR group in PVTT type I before and after IPTW. Comparison of RFS between LT and LR group in PVTT type I before (A) and after IPTW (B). Comparison of OS between LT and LR group in PVTT type I before (C) and after IPTW (D). LT, liver transplantation; LR, liver resection; RFS, recurrence-free survival; OS, overall survival; IPTW, inverse probability of treatment weighting; PVTT, portal vein tumor thrombus.

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3-year RFS and OS rates were 39.1% and 45.7% in the LT group and 13.5% and 28.1% in the LR group, respectively. Similar results were found in RFS rate (p=0.039), but not in OS rate (p=0.093) (Fig. 2B and D). Further analysis after IPTW indicated that LT and LR afforded similar median RFS (16.33 months vs. 23.26 months, p=0.876) and OS (36.47 months vs. 36.17 months, p=0.944) in PVTT type I patients with AFP levels ≤200 ng/ml (Fig. 3B and D). Meanwhile, in PVTT type I patients with AFP levels >200 ng/mL, LT elicited significantly longer median RFS (18.0 months vs. 2.1 months, p=0.022) and relatively longer median OS time (23.6 months vs. 9.8 months, p=0.065) than LR (Fig. 4B and D).

Among patients with PVTT type II, 3-year RFS and OS rates in the original data were 23.5% and 29.4% in the LT group and 0.0% and 10.0% in the LR group, respectively. After IPTW adjustment, the 3-year RFS and OS rates were 18.0% and 21.9% in the LT group and 0.0% and 6.2% in the LR group, respectively. There were no significant differences in RFS and OS between the two treatments before and after IPTW adjustment (Fig. 5).

Predictive factors of RFS and OS

Univariate and multivariate analyses for the entire cohort are outlined in Table 3. The multivariate analysis suggested that treatment allocation, AFP, aspartate aminotransferase (AST), and tumour size (>5 cm vs. ≤5 cm) were independent prognostic factors of RFS, whereas treatment allocation, AFP, and AST were independent prognostic factors of OS.

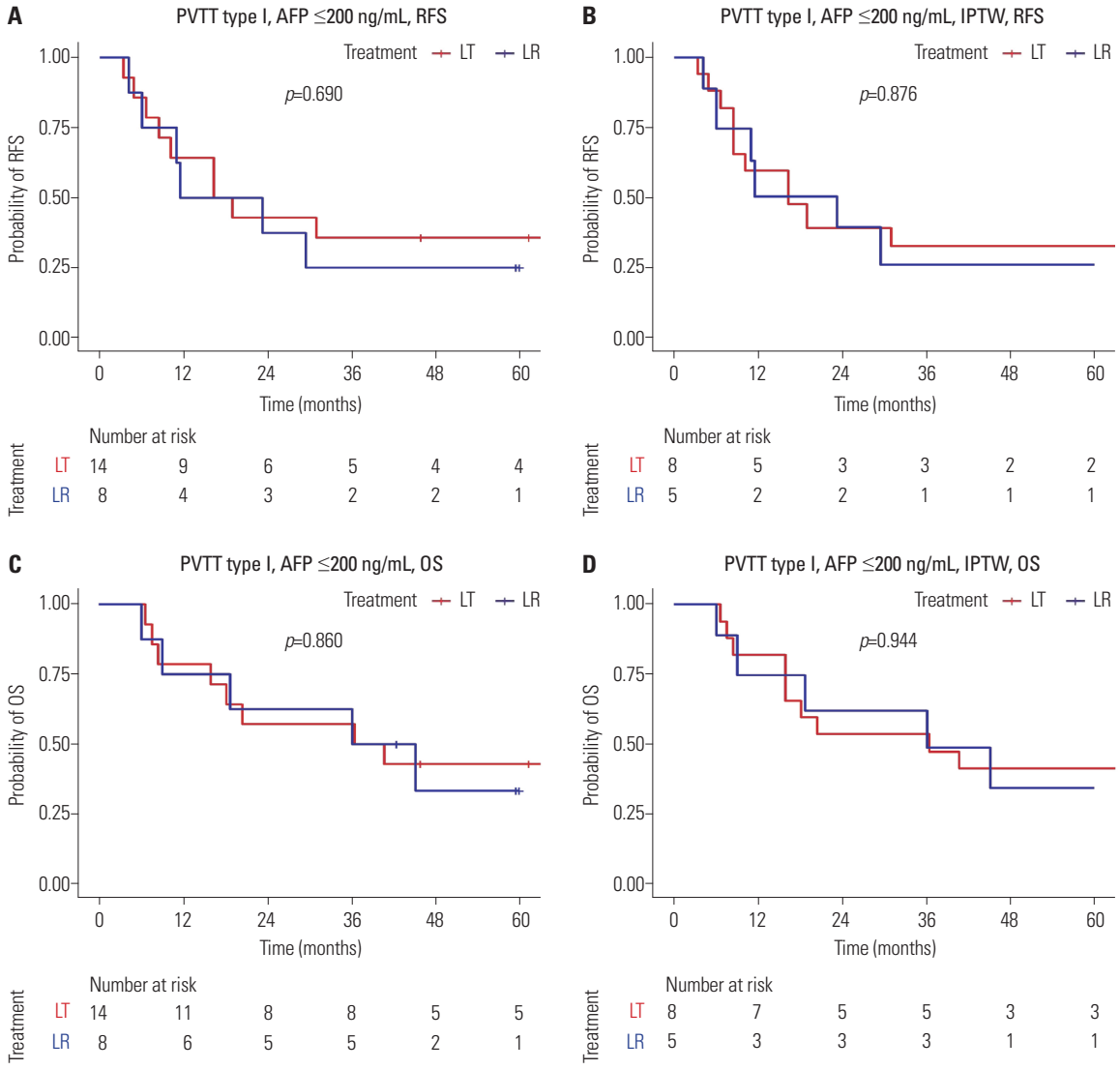

Fig. 3. Comparison of RFS and OS between LT and LR group in PVTT type I with AFP ≤200 ng/mL before and after IPTW. Comparison of RFS between LT and LR group in PVTT type I with AFP ≤200 ng/mL before (A) and after IPTW (B). Comparison of OS between LT and LR group in PVTT type I with AFP ≤200 ng/mL before (C) and after IPTW (D). LT, liver transplantation; LR, liver resection; RFS, recurrence-free survival; OS, overall survival; IPTW, inverse probability of treatment weighting; PVTT, portal vein tumor thrombus; AFP, α-fetoprotein.

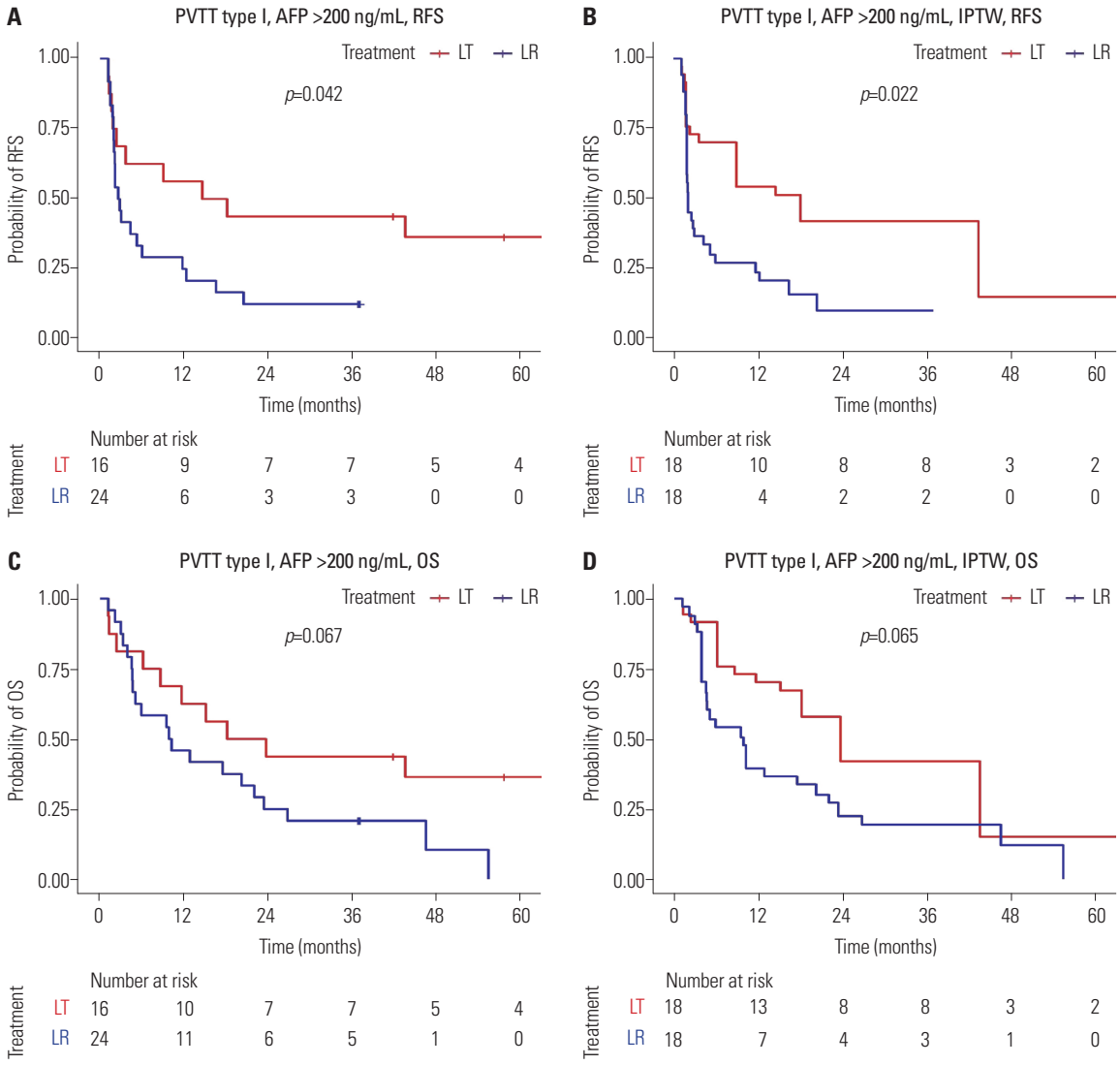

Fig. 4. Comparison of RFS and OS between LT and LR group in PVTT type I with AFP >200 ng/mL before and after IPTW. Comparison of RFS between LT and LR group in PVTT type I with AFP >200 ng/mL before (A) and after IPTW (B). Comparison of OS between LT and LR group in PVTT type I with AFP >200 ng/mL before (C) and after IPTW (D). LT, liver transplantation; LR, liver resection; RFS, recurrence-free survival; OS, overall survival; IPTW, inverse probability of treatment weighting; PVTT, portal vein tumor thrombus; AFP, α-fetoprotein.

DISCUSSION

PVTT is a severe complication with extremely limited therapeutic options. However, with the improvement of surgical techniques and comprehensive treatment of HCC, the understanding of PVTT therapy has improved. In recent studies, researchers indicated that some HCC patients with PVTT could benefit from LR[3-7] and that PVTT is not an absolute contraindication for LT.[8,9,11,12] Nevertheless, an optimal therapy protocol of HCC patients with PVTT has not been established, and the therapeutic allocation of PVTT is controversial. Previous studies have documented the results of comparing LR with TACE, radiotherapy, and sorafenib, but rarely with LT.[5,14-18] To our knowledge, this is the first report to focus on comparing treatment outcomes in HCC patients with PVTT type I and PVTT type II treated with LT or LR after IPTW analysis.

A few studies have evaluated the efficacy of LT for HCC patients with PVTT and demonstrated that PVTT is acceptable as an absolute contraindication for LT. However, recently, Lee, et al.,[9] Han, et al.,[11] and Choi, et al.[12] separately reported single center retrospective studies on the survival benefits of LT in HCC patients with PVTT. Moreover, reports have also indicated a favorable prognosis after LT for HCC patients with PVTT.[8,10] In the entire cohort of our study, LT afforded good prognosis with a 3-year cumulative OS rate of 42.6%, and patients with PVTT undergoing LT exhibited a better prognosis than those undergoing LR (p=0.019) (Fig. 1C), which is similar to the previous study published by the team of Shu-Sen Zheng.[8]

In subgroup analysis, LT yielded better RFS than LR in PVTT type I (Fig. 2). There was no significant difference in OS between LT and LR after IPTW adjustment (p=0.093), which perhaps may be related to small sample size of the current study,

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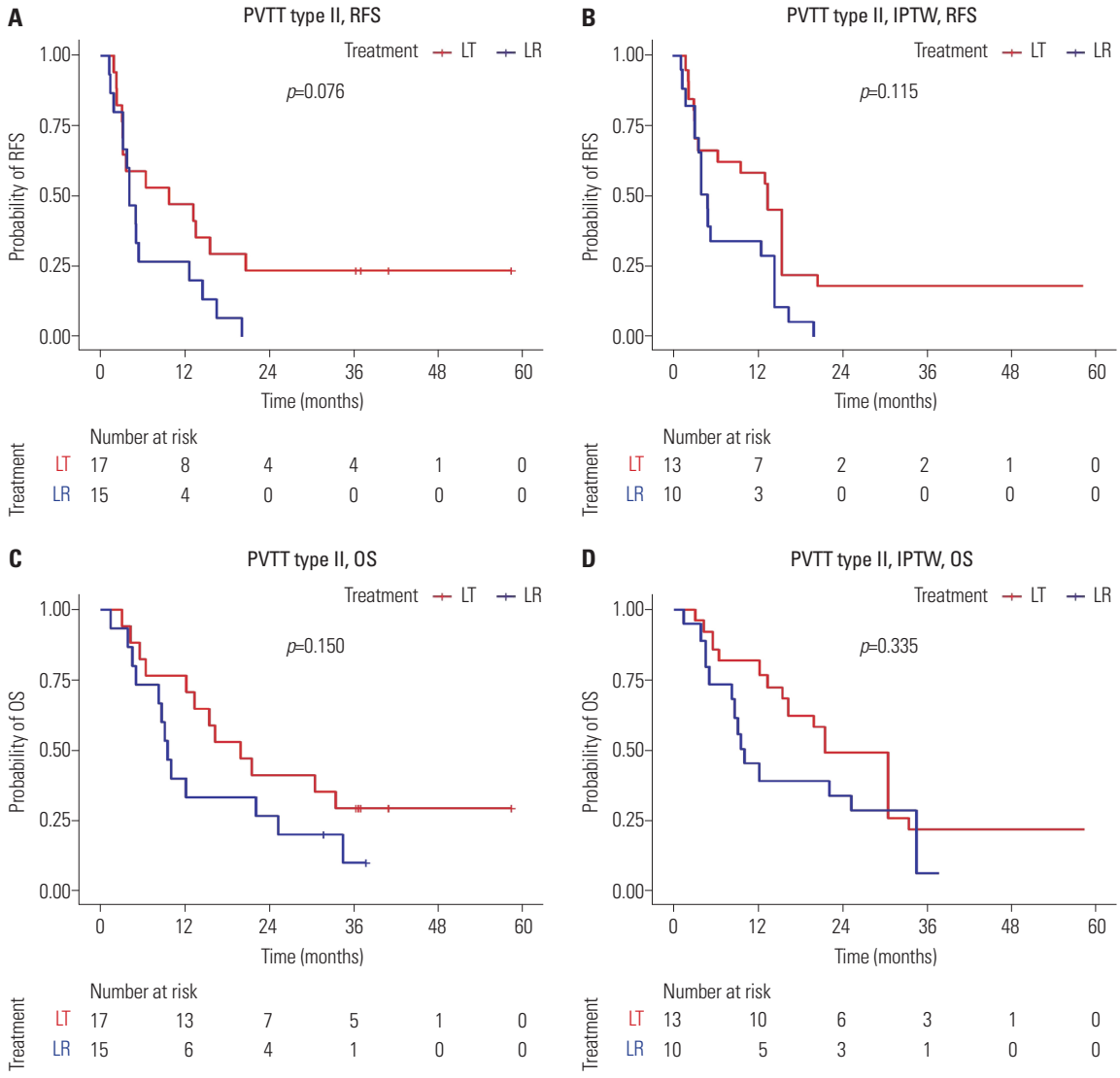

Fig. 5. Comparison of RFS and OS between LT and LR group in PVTT type II before and after IPTW. Comparison of RFS between LT and LR group in PVTT type II before (A) and after IPTW (B). Comparison of OS between LT and LR group in PVTT type II before (C) and after IPTW (D). LT, liver transplantation; LR, liver resection; RFS, recurrence-free survival; OS, overall survival; IPTW, inverse probability of treatment weighting; PVTT, portal vein tumor thrombus.

and multicenter study with a larger number of cases is needed for further validation. Further analysis also showed that PVTT type I patients with AFP levels >200 ng/mL, had better prognosis with LT than with LR (Fig. 4): AFP level is an important indicator related to the biological behavior of HCC and therefore prognosis. Altogether, our results suggested that HCC patients with PVTT type I could be indicated for LT therapy after careful assessment of comprehensive prognostic factors. Analysis of PVTT type II patients revealed no significant differences in prognosis between LT and LR, which may imply that LT offers no obvious superiority to LR for these patients (Fig. 5). However, more cases would be required to validate our conclusion.

It is worth noting that only some patients may be suitable for LT treatment. In our study, the 3-year RFS and OS rates of PVTT type I patients who underwent LT were 40.0% and 50.0%, respectively; while those for PVTT type II patients who underwent LT were 23.5% and 29.4%. LT for PVTT type II showed weaker therapeutic efficacy than for PVTT type I, thus LT may not appropriate in PVTT type II patients. Similarly, Ho Joong Choi, et al.[12] reported that while segmental PVTT was acceptable for LT, lobar PVTT may be contraindicated for LT, with 5-year OS rate of only 14.3%. On the whole, the therapeutic efficacy of treatments for HCC with PVTT type II is still suboptimal, and the best management for HCC patients with PVTT type II requires further investigation.

So far, many treatment modalities have been used in the clinical treatment of HCC patients with PVTT. According to previous reports, the 3-year OS achieved with TACE was 7.3%, and that for radiotherapy was 18%.[5,17] The median survival time with sorafenib was 6.2 months.[15] Compared with the efficacy of other treatments reported in other studies, LT and LR in our study afforded relatively good prognosis (LT: 3-year OS

Table 3. Univariate and Multivariate Analyses for RFS and OS

Covariates	Univariate analysis				Multivariate analysis			
	RFS		OS		RFS		OS	
	HR (95% CI)	*p* value*	HR (95% CI)	*p* value*	HR (95% CI)	*p* value†	HR (95% CI)	*p* value†
PVTT classification (Type II vs. Type I)	1.44 (0.89, 2.31)	0.136	1.33 (0.81, 2.20)	0.259				
Operation (LR vs. LT)	1.99 (1.25, 3.16)	0.004	1.76 (1.09, 2.85)	0.021	2.25 (1.36, 3.71)	0.002	1.73 (1.03, 2.89)	0.038
Sex	0.70 (0.36, 1.38)	0.304	0.78 (0.40, 1.52)	0.458				
Age (yr) (>60 vs. ≤60)	0.82 (0.42, 1.59)	0.553	0.68 (0.34, 1.37)	0.276				
Etiology								
HCV vs. HBV	0 (0, Inf)	0.995	0 (0, Inf)	0.996				
Alcohol-related vs. HBV	0.73 (0.23, 2.33)	0.600	0.99 (0.31, 3.15)	0.985				
Others vs. HBV	1.40 (0.19, 10.15)	0.741	3.43 (0.46, 25.42)	0.228				
Hypertension	0.76 (0.24, 2.42)	0.642	0.84 (0.27, 2.69)	0.774				
Diabetes type 2	1.22 (0.17, 8.83)	0.844	1.38 (0.19, 9.98)	0.752				
ln (AFP), ng/mL	1.19 (1.10, 1.29)	<0.001	1.19 (1.09, 1.29)	<0.001	1.11 (1.02, 1.21)	0.012	1.11 (1.02, 1.22)	0.020
PLT, 10^9/L	1.00 (1.00, 1.01)	0.072	1.00 (1.00, 1.00)	0.177				
ALB, g/L	1.00 (0.96, 1.04)	0.891	1.00 (0.96, 1.04)	0.908				
ln (AST), U/L	1.46 (1.10, 1.93)	0.009	1.52 (1.13, 2.05)	0.005	1.56 (1.15, 2.12)	0.004	1.47 (1.07, 2.02)	0.019
ln (ALT), U/L	1.19 (0.91, 1.57)	0.209	1.28 (0.96, 1.70)	0.092				
ln (TBIL), umol/L	1.04 (0.76, 1.43)	0.786	1.07 (0.79, 1.44)	0.660				
ln (GGT), U/L	1.05 (0.81, 1.35)	0.711	1.03 (0.79, 1.35)	0.830				
ln (Cr), umol/L,	0.90 (0.22, 3.65)	0.886	0.89 (0.21, 3.79)	0.875				
ln (INR)	0.33 (0.09, 1.13)	0.078	0.35 (0.09, 1.27)	0.110				
MELD grade								
9–15 vs. <9	0.75 (0.43, 1.31)	0.308	0.85 (0.48, 1.50)	0.576				
>15 vs. <9	0.71 (0.36, 1.40)	0.321	0.68 (0.33, 1.41)	0.302				
Child-Pugh grade (B vs. A)	0.80 (0.49, 1.30)	0.372	0.83 (0.50, 1.37)	0.461				
ALBI grade								
II vs. I	0.92 (0.57, 1.49)	0.733	0.88 (0.54, 1.46)	0.628				
III vs. I	1.51 (0.66, 3.44)	0.325	1.42 (0.62, 3.24)	0.409				
APRI grade (>0.5 vs. ≤0.5)	0.92 (0.55, 1.52)	0.738	1.07 (0.63, 1.84)	0.795				
HCC liver lobe								
Right vs. left	0.89 (0.50, 1.60)	0.697	0.82 (0.45, 1.47)	0.499				
Left and right vs. left	0.83 (0.39, 1.77)	0.627	0.77 (0.35, 1.68)	0.509				
Cirrhosis	1.27 (0.65, 2.47)	0.488	1.10 (0.56, 2.15)	0.786				
Tumor size (>5 cm vs. ≤5 cm)	2.40 (1.42, 4.04)	0.001	1.99 (1.16, 3.43)	0.013	2.23 (1.31, 3.81)	0.003	1.70 (0.97, 2.98)	0.062
Tumor number (multiple vs. solitary)	0.86 (0.54, 1.38)	0.539	0.78 (0.48, 1.28)	0.328				
Differentiation								
Moderate vs. well	2.31 (1.22, 4.38)	0.010	1.94 (1.00, 3.78)	0.051				
Poor vs. well	2.59 (1.33, 5.07)	0.005	2.43 (1.22, 4.88)	0.012				

RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PVTT, portal vein tumor thrombus; LR, liver resection; LT, liver transplantation; HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, α-fetoprotein; PLT, blood platelet; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; GGT, γ-glutamyl transpeptidase; Cr, creatinine; INR, international normalized ratio; MELD, model for end-stage liver disease; ALBI, the albumin-bilirubin; APRI, the aspartate aminotransferase-to-platelet ratio index; HCC, hepatocellular carcinoma.
*Univariate Cox proportional hazards models were used, †Multivariate regression was used with stepwise selection.

of 42.6%, median OS time of 21.4 months; LR: 3-year OS of 25.4%, median OS time of 10.1 months), especially in PVTT type I (LT: 3-year OS of 50.0%, median OS time of 30.0 months; LR: 3-year OS of 31.3%, median OS time of 15.1 months). Nevertheless, we suggest that surgery, including LT and LR, might be better suited for HCC patients with PVTT type I, not PVTT type II.

Previous studies have analyzed prognostic factors in HCC patients with PVTT and have indicated that liver function, AFP, tumor size, extent of PVTT, and so on are risk factors affecting survival. Multivariate analysis in our study showed similar results in that tumor size, AFP, and AST were risk factors for prognosis. Tumor size has been treated as a crucial prognostic factor for HCC patients with PVTT.[12,19] Similarly, in our data,

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compared with patients with smaller tumors, those with large tumors were more likely to recur. Also, in our study, AST was found to be an independent prognosticator predictive of both RFS and OS in HCC patients with PVTT. Advanced HCC is related to mitochondrial damage, and this can directly release AST into the blood, resulting in a sharp increase in serum levels. In support of our results, previous studies have reported that AST was an valuable prognosticator for predicting HCC recurrence and was indicative of liver damage and an inflammatory microenvironment that accelerates recurrence and invasion of HCC.[20-22]

Since a randomized controlled trial comparing LT and LR would be difficult to conduct, our study used applied IPTW adjustment analysis to overcome potential bias between the two treatments. IPTW adjustment can compensate for the nonrandomized design of retrospective research, using adjustment for a great quantity of pretreatment covariates to improve the reliability of findings.[23] After IPTW adjustment, most baseline parameters were no longer different in our study, except alanine aminotransferase and international normalized ratio. Nevertheless, these two parameters were not prominent factors affecting the outcome events in multivariate analysis, and thus, the significant differences therein between patient groups likely would not weaken the statistical power or reduce the accuracy of our results.

Several limitations of the present study should be considered. First, it was designed as a retrospective, non-randomized study. Second, the analyses were limited by the relatively small size cohort. Third, other treatments, such as TACE, radiotherapy, and sorafenib should been evaluated in this study, which would help with understanding the effects thereof on survival outcomes. Finally, our conclusions need to be verified in a prospective study with a large sample size.

In conclusion, LT showed better prognosis for HCC patients with PVTT type I than LR, especially in patients with AFP levels >200 ng/mL. HCC patients with PVTT type I could be chosen for LT therapy after careful assessment of comprehensive prognostic factors. No difference in prognosis between LT and LR was found for HCC patients with PVTT type II in our study, and the prognosis of LT achieved a less than ideal therapeutic effect, suggesting it should be contraindicated for these patients.

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